

Product Class 13: Benzoxazoles and Other Annulated Oxazoles

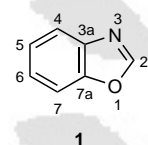
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General Introduction

Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. E 8a, pp 1020–1194. Benzoxazole (**1**) is also named benzo[d]oxazole or 1,3-benzoxazole, although the numbering can be omitted. Scheme 1 shows the basic structure and numbering of the benzoxazole ring system, as well as ^1H NMR^[1] and ^{13}C NMR^[2] spectroscopic data for the parent compound. UV data for benzoxazole are as follows: λ (ϵ): 231 (3.90; 3.97), 263 (3.38), 270 (3.53; 3.61), 276 (3.51; 3.64).^[3]

2-Methyl- and 2-phenylbenzoxazole were prepared in 1876 by Ladenburg and their structure was also correctly assigned.^[4]

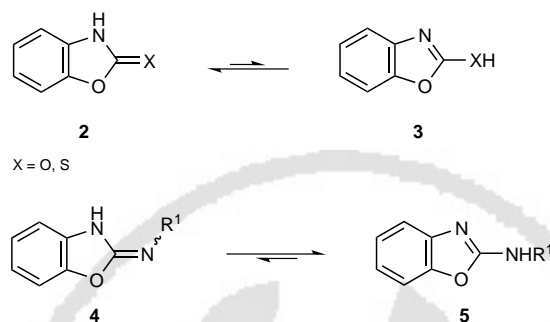
Scheme 1 Numbering of the Parent Ring System and NMR Shifts^[1,2]



Position	NMR (CDCl_3 , δ)		Ref
	^{13}C	^1H	
2	152.6	8.42	[1,2]
3a	140.1	–	[1,2]
4	120.5	7.41	[1,2]
5	125.4	7.77	[1,2]
6	124.4	7.70	[1,2]
7	110.8	7.41	[1,2]
7a	150.5	–	[1,2]

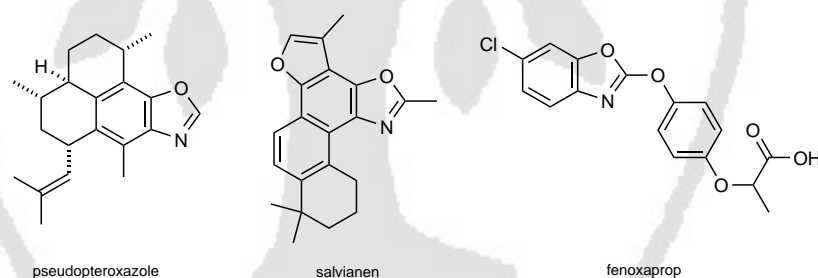
2-Heteroatom-substituted benzoxazoles may exist in two tautomeric forms (e.g., **2** and **3**, Scheme 2). The X-ray analysis of such compounds shows that benzoxazol-2(3H)-one (**2**, X=O), benzoxazole-2(3H)-thione (**2**, X=S), and *N*-benzylbenzoxazol-2(3H)-imine (**4**, R¹=Bn) exist with an exocyclic double bond in the crystalline form.^[5] For benzoxazol-2(3H)-ones and benzoxazole-2(3H)-thiones this is also true in solution (according to IR^[6,7] and ^{13}C NMR^[8]). In solution, benzoxazol-2-amines occur in their 2-amino form **5** but in the crystalline state it depends on the substituents; either only benzoxazol-2(3H)-imines **4** or a mixture of the imino and 2-amino form are present.^[9]

for references see p 50

Scheme 2 Tautomeric Equilibria in 2-Heteroatom-Substituted Benzoxazoles^[5-9]

Some reactions of benzoxazoles such as salt formation and quaternization occur, in analogy to oxazoles, at the ring nitrogen. Electrophilic substitutions, e.g. nitration or halogenation, take place at the 5- or 6-position of the benzene ring, with preference for the 6-position. Nucleophiles attack benzoxazoles, benzoxazolium salts, and *N*-alkylbenzoxazolium salts in the 2-position. As expected, nucleophilic substitutions of 2-halobenzoxazoles take place very easily, but the alkylsulfanyl group is also a useful leaving group. *N*-Alkyl-2-chlorobenzoxazolium salts are still more reactive and are therefore efficient dehydrating agents,^[10] e.g. for the synthesis of isocyanides from formamides,^[11] or the formation of ketones from α -hydroxycarboxylic acids.^[12]

The benzoxazole ring system occurs in a number of natural products, e.g. pseudopteroxazole and salvanen (Scheme 3).^[13] Additionally, some biologically active compounds containing the benzoxazole moiety, e.g. the herbicide fenoxaprop, have been described in the literature.^[13]

Scheme 3 Benzoxazole in Natural and Biologically Active Products^[13]

11.13.1 Synthesis by Ring-Closure Reactions

11.13.1.1 By Annulation to an Arene

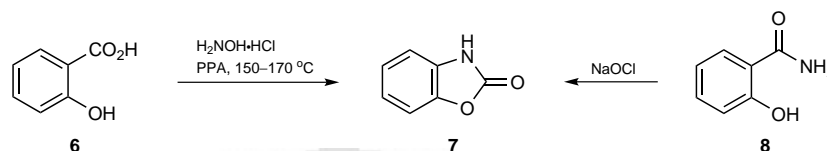
11.13.1.1.1 With Formation of One O—C and One N—C Bond

11.13.1.1.1.1 Fragment O—C—C—N

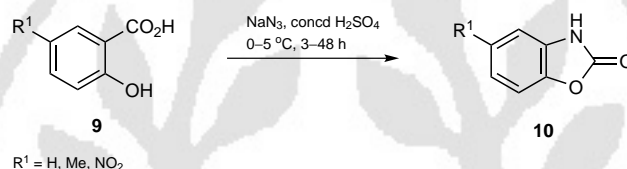
11.13.1.1.1.1 Method 1:

Synthesis from 2-Hydroxybenzoic Acids, Amides, or Azides

Lossen reaction of 2-hydroxybenzoic acid (**6**, salicylic acid) with hydroxylamine hydrochloride in the presence of polyphosphoric acid at 150–170 °C^[14] and Hofmann degradation of salicylamide (**8**) both lead to benzoxazol-2(3*H*)-one (**7**) (Scheme 4).^[15]

Scheme 4 Benzoxazol-2(3*H*)-one via Lossen Reaction and Hofmann Degradation^[15]

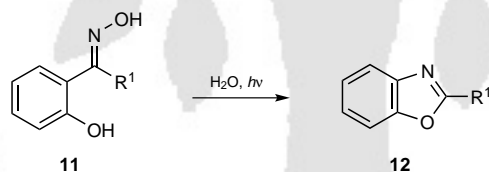
In the reaction of 2-hydroxybenzoic acids **9** with sodium azide in concentrated sulfuric acid at 0–5 °C, benzoxazol-2(3*H*)-ones **10** are again formed (Scheme 5).^[16]

Scheme 5 Benzoxazol-2(3*H*)-ones from Salicylic Acid via Schmidt Reaction^[16]

11.13.1.1.1.2

Method 2:**Synthesis from 1-(2-Hydroxyphenyl)alkanone Oximes and Derivatives Thereof (Beckmann Rearrangement)**

The photolysis of oximes **11** leads to benzoxazoles **12** via Beckmann rearrangement and cyclization. The reaction is carried out in protic solvents such as water, methanol, or ethanol (Scheme 6).^[17]

Scheme 6 Benzoxazoles via Photolytic Beckmann Rearrangement^[17]

R ¹	Yield (%)	Ref
H	75	[17]
Me	82	[17]

The reaction of 1-(2-hydroxyphenyl)alkanone oximes **13** under dehydrating reaction conditions leads either to 1,2-benzisoxazoles (see Section 11.10.1.1.3) or via Beckmann rearrangement and cyclization to benzoxazoles **12**. As expected, only *E*-oximes lead to benzoxazoles readily.^[18,19] Most acidic catalysts commonly used in the Beckmann rearrangement are applicable, including zeolites.^[20] Examples are presented in Scheme 7.

for references see p 50

Scheme 7 Beckmann Rearrangement of Oximes^[20–24]

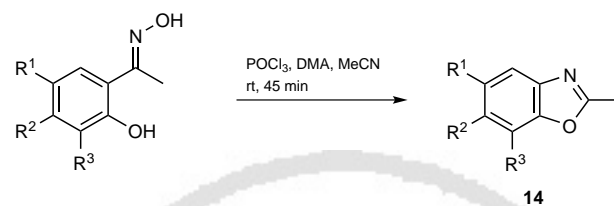
R ¹	R ²	R ³	Conditions	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
Me	Me	H	HY zeolite, 160 °C	92	83–85/20.25	[20]
Cl	Me	H	HY zeolite, 160 °C	90	52–53	[20]
H	Me	H	PPSE, ^a PPE, rt	75	–	[21]
Me		H	concd H ₂ SO ₄ , heat	81	144 (MeOH/H ₂ O)	[22]
Me		Ac	NaOH, 185 °C	54	144 (MeOH/H ₂ O)	[22]
Br	Ph	H	PPA, 110 °C, 35 min	93	111–112 (MeOH)	[23]

^a PPSE = polyphosphoric acid trimethylsilyl ester.



R ¹	Yield (%)	Ref
Ac	80	[24]
2,4-(O ₂ N)C ₆ H ₃	58	[24]

Hydroxy-substituted 2-methylbenzoxazoles **14** are best formed in the presence of phosphoryl chloride/dimethylacetamide in acetonitrile (62–92% yields) (Scheme 8).^[25] With this method, no concomitant formylation of the 2-methyl group is observed even at slightly elevated temperatures.

Scheme 8 Examples of the Preparation of Hydroxy-Substituted 2-Methylbenzoxazoles^[25]

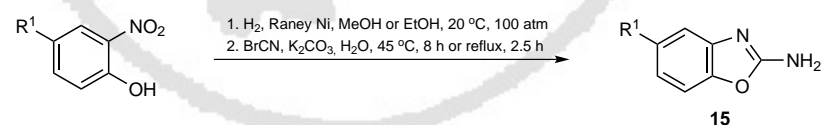
R ¹	R ²	R ³	Yield (%)	mp (°C)	Ref
H	OH	H	83	194–196	[25]
<i>t</i> -Bu	OH	Me	85	166–168	[25]
CEt ₂ Me	OH	H	87	217–218	[25]
OH	4-Tol	H	92	195–196	[25]
H	O(CH ₂) ₁₅ Me	H	76	56–57	[25]

6-Hydroxy-2-methylbenzoxazole (14, R¹ = R³ = H; R² = OH); Typical Procedure:^[25]

POCl₃ (2.4 mL, 26 mmol) was added dropwise (at <30 °C) to a stirred soln of 2,4-dihydroxyacetophenone oxime (4.20 g, 25 mmol) in DMA/MeCN (1:3; 20 mL) over 15 min. The mixture was stirred for 30 min at rt and then poured into a soln of NaOAc (6.0 g) in ice water (200 mL). The product precipitated and was collected by filtration; yield: 3.08 g (83%); mp 194–196 °C.

11.13.1.1.1.2 Fragments O—C—C—N and C**11.13.1.1.1.2.1 Method 1:****Synthesis from 2-Nitrophenols and Carbonic Acid Derivatives or Aldehydes**

2-Nitrophenols can be reduced to 2-aminophenols and then reacted with a C₁ component and cyclized to benzoxazoles **15** in some cases in situ. One example for such an application is reduction with Raney nickel. After filtration of the catalyst, the reaction mixture is immediately reacted with cyanogen bromide (Scheme 9).^[26]

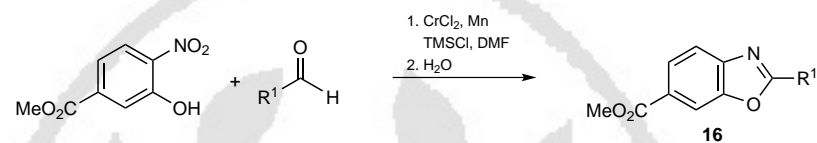
Scheme 9 Benzoxazol-2-amines from 2-Nitrophenols Using Raney Nickel/Cyanogen Bromide^[26]

R ¹	Yield (%)	mp (°C)	Ref
H	53	132	[26]
CO ₂ Me	78	235	[26]
CO ₂ Et	75	210	[26]

for references see p 50

Alternatively, this type of transformation can be carried out with chromium(II) chloride/manganese(0) and aldehydes in a redox-coupled reaction (Scheme 10). Both aliphatic and aromatic aldehydes can be converted into benzoxazoles **16** by this one-pot method.^[27] An electron-withdrawing group *para* to the nitro functionality is essential for a successful transformation.

Scheme 10 Benzoxazol-2-amines from a 2-Nitrophenol Using Chromium(II) Chloride/Manganese(0)^[27]



R ¹	Yield (%)	Ref
Ph	73	[27]
2,4-(MeO) ₂ C ₆ H ₃	47	[27]
4-MeOC ₆ H ₄	35	[27]
(CH ₂) ₇ Me	76	[27]
Pr	67	[27]
(CH ₂) ₄ Me	55	[27]
Cy	81	[27]
iPr	57	[27]
s-Bu	62	[27]
2-HOC ₆ H ₄	0	[27]

Benzoxazol-2-amines 15; General Procedure:^[26]

The 2-nitrophenol (1 mol) was dissolved in MeOH or EtOH (1.3 L) and hydrogenated under Raney Ni catalysis (15 g) at 20 °C and 100 atm H₂ in a shaking autoclave. The catalyst was then removed by filtration and BrCN (105.9 g, 1 mol) and K₂CO₃ (138.2 g, 1 mol) were added in portions [dissolved in H₂O (200–300 mL)]. During the addition the temperature rose to 45 °C. The mixture was stirred for 8 h or refluxed for 2.5 h. The resulting precipitate was then filtered, washed with H₂O, and purified by recrystallization.

Methyl 2-Phenylbenzoxazole-6-carboxylate (16, R¹ = Ph); Typical Procedure:^[27]

Methyl 3-hydroxy-4-nitrobenzoate (99 mg, 0.5 mmol), Mn chips (165 mg, 3 mmol), and CrCl₂ (13 mg, 0.1 mmol) were taken up in dry DMF (3 mL) in a flame-dried, N₂-purged round-bottomed flask. TMSCl (0.25 mL, 2 mmol) was slowly added dropwise (**CAUTION: on a larger scale, this step proceeds noticeably exothermically and should be carried out at 0 °C**). After allowing this mixture to stir at rt for 15 min, PhCHO (53 mg, 0.5 mmol) was added, and stirring was allowed to continue at rt for 18 h. The reaction was then quenched with H₂O (3 mL), and the mixture was allowed to stir for an additional 1 h. The resulting mixture was then poured into H₂O (10 mL) and extracted with EtOAc (3 × 15 mL). Care must be taken during the extraction procedure not to vigorously agitate the mixture, as intractable emulsions can result. The combined organic extracts were dried (Na₂SO₄) and filtered, and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (silica gel, hexane/EtOAc 4:1) provided a white solid; yield: 92 mg (73%).

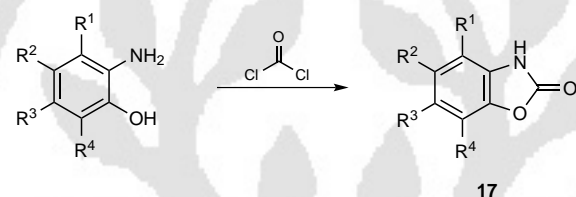
11.13.1.1.1.2.2 Method 2:
Synthesis from 2-Aminophenols and Carbonic Acid Derivatives

11.13.1.1.1.2.2.1 Variation 1:
Synthesis of 2-Alkoxybenzoxazoles or Benzoxazol-2(3H)-ones

2-Ethoxybenzoxazole is formed from 2-aminophenol by reaction with tetraethoxymethane (60% yield) or triethoxyacetonitrile (48%).^[28]

Benzoxazol-2(3H)-ones (e.g., **17**) are formed in the reaction of 2-aminophenols and phosgene,^[29–31] ethyl chloroformate,^[32] or urea.^[30,33,34] In the case of phosgene (Scheme 11) the reaction is mostly carried out in presence of a base (e.g., KOAc,^[30] pyridine,^[31,32] NaOH,^[35] or NaOAc^[36]).

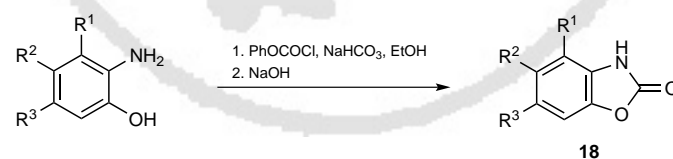
Scheme 11 Benzoxazol-2(3H)-ones from 2-Aminophenols and Phosgene^[30,31,35–37]



R ¹	R ²	R ³	R ⁴	Conditions	Yield (%)	Ref
H	Me	Me	H	KOAc, EtOAc, reflux	68	[30]
H	Me	H	Br	CHCl ₃ , reflux, 30 min	57	[37]
H	Br	H	H	NaOAc, EtOAc	90	[36]
NO ₂	H	H	H	4 M NaOH, toluene, 5 °C, 1 h, then 20 °C, 1 h	62	[35]
CO ₂ Me	H	H	H	toluene, pyridine	96	[31]

2-Aminophenols are cyclized easily with ethyl chloroformate in the presence of sodium ethoxide in ethanol to the corresponding benzoxazol-2(3H)-ones **18** in good yields.^[32] The use of phenyl chloroformate and sodium hydrogen carbonate has also been reported and good yields are usually obtained (Scheme 12).^[38]

Scheme 12 Benzoxazol-2(3H)-ones from 2-Aminophenols and Phenyl Chloroformate^[38]



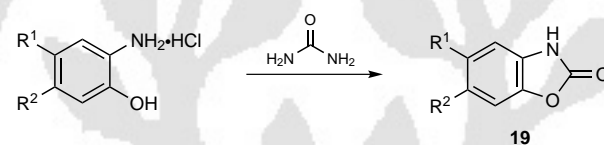
R ¹	R ²	R ³	Yield (%)	mp (°C)	Ref
H	H	H	83	139–140	[38]
H	Me	H	66	131–132	[38]
H	H	Me	80	145–146	[38]

for references see p 50

R ¹	R ²	R ³	Yield (%)	mp (°C)	Ref
H	NO ₂	H	76	229–230	[38]
NO ₂	H	H	78	229–231	[38]
H	CO ₂ Et	H	71	132–133	[38]
H	H	OMe	70	152–153	[38]

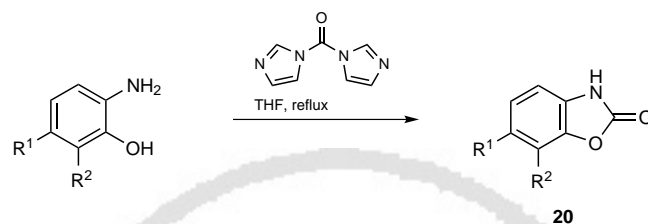
The reaction of 2-aminophenols^[30] (or their hydrochlorides)^[33,34] with urea is widely applied (Scheme 13). The synthesis can be carried out neat in the melt at an optimal temperature of 145 °C.

Scheme 13 Benzoxazol-2(3*H*)-ones from 2-Aminophenol Hydrochlorides and Urea^[30,34,39]



R ¹	R ²	Conditions	Yield (%)	Ref
Cl	H	140–150 °C, 2 h	92	[34]
H	OMe	180 °C, 2 h	26	[39]
H	H	180 °C, 2 h	88	[30]
Me	H	180 °C, 2 h	79	[30]
Pr	H	180 °C, 2 h	79	[30]
OMe	H	180 °C, 2 h	76	[30]
(CH ₂) ₄ Me	H	180 °C, 2 h	90	[30]
OH	H	145 °C, 3 h	47	[33]
H	OH	145 °C, 3 h	34	[33]

An alternative reagent, 1,1'-carbonyldiimidazole, has been applied in a series of examples, giving benzoxazol-2(3*H*)-ones **20** in good to excellent yields (Scheme 14).^[40] The reactions are carried out in refluxing tetrahydrofuran; thus, comparatively mild reaction conditions are sufficient.^[41]

Scheme 14 Benzoxazol-2(3H)-ones from 2-Aminophenols and 1,1'-Carbonyldiimidazole^[40]

R ¹	R ²	Yield (%)	mp (°C)	Ref
H	H	97	141.5	[40]
Me	H	75	145–146	[40]
OMe	H	73	154	[40]
OMe	OMe	95	180–180.5	[40]
NO ₂	H	97	145–146	[40]

5,6-Dimethylbenzoxazol-2(3H)-one (17, R¹ = R⁴ = H; R² = R³ = Me); Typical Procedure:^[30]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

A soln of phosgene (30 g, 0.3 mol) in EtOAc (400 mL) was added dropwise with vigorous stirring to a suspension of 2-amino-4,5-dimethylphenol (34.2 g, 0.25 mol) and dry KOAc (59 g, 0.6 mol) in EtOAc (600 mL). The soln was refluxed for a short period and then H₂O was added. The organic layer was separated and washed with H₂O and 5% aq HCl, and the solvent was evaporated. For purification, the residue was treated with 10% aq NaOH and cooled with ice, and the precipitated Na salt was isolated by filtration. The product was then suspended in H₂O and acidified. From the alkaline filtrate further product could be isolated; overall yield: 27.6 g (68%); mp 177–178 °C (EtOH).

Benzoxazol-2(3H)-one (18, R¹ = R² = R³ = H); Typical Procedure:^[38]

A mixture of 2-aminophenol (10.9 g, 0.1 mol), MeOH (50 mL), H₂O (50 mL), and NaHCO₃ (8.4 g, 0.1 mol) was treated at 25–30 °C with phenyl chloroformate (15.65 g, 0.1 mol), which was added over 10 min. The resulting slurry was stirred for 30 min and was treated dropwise, again at 25–30 °C, with a soln of NaOH (4 g, 0.1 mol) in H₂O (50 mL). The resulting product soln was acidified to about pH 5 with a soln of concd HCl (10 g) in H₂O (50 mL). The resulting tan precipitate was collected by filtration and washed with H₂O; yield: 11.2 g (83%); mp 139–140 °C.

Hydroxy-Substituted Benzoxazol-2(3H)-ones 19; General Procedure:^[33]

The hydroxyl-substituted 2-Aminophenol hydrochloride (3.23 g, 20 mmol) and urea (4.0 g, 67 mmol) were ground together and heated for 3 h to 145 °C. Upon cooling, the crude material crystallized and was then recrystallized (H₂O) in the presence of charcoal; yield: 34–65%.

Benzoxazol-2(3H)-ones 20; General Procedure:^[40]

1,1'-Carbonyldiimidazole (7.3 g, 45 mmol) was added to a soln of the 2-aminophenol (30 mmol) in dry THF (100 mL). The mixture was refluxed for 4 h, the solvent was removed under reduced pressure, and the residue was distributed between 2 M aq HCl and CHCl₃.

for references see p 50

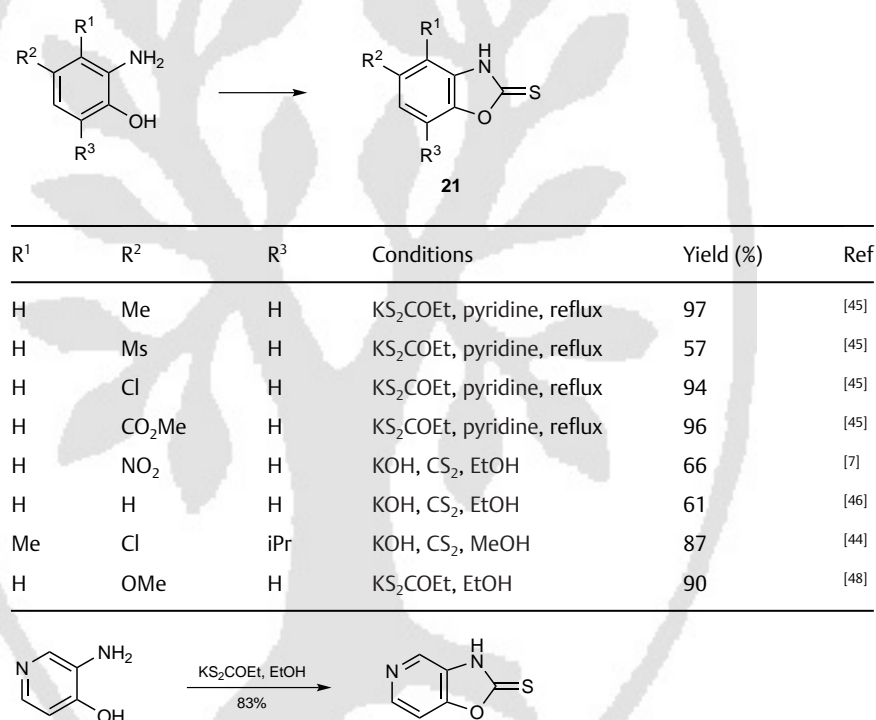
The organic layer was separated, treated with charcoal, dried (Na_2SO_4), and filtered, and the solvent was evaporated. The crude material was recrystallized (CH_2Cl_2).

11.13.1.1.1.2.2.2 Variation 2:

Synthesis of Benzoxazole-2(3H)-thiones

The synthetic routes to benzoxazole-2(3H)-thiones **21** from 2-aminophenols are similar to those for benzoxazol-2(3H)-ones (see Section 11.13.1.1.1.2.2.1). The most frequently applied reagents are thiophosgene^[7,42,43] or potassium *O*-alkyl carbonodithioates (KS_2COR^1 , $\text{R}^1 = \text{Me, Et}$) (Scheme 15).^[7,42–45] The *O*-alkyl carbonodithioate can be prepared in advance by reaction of carbon disulfide, potassium hydroxide, and an alcohol.^[44] Alternatively, it can be also formed in situ by heating carbon disulfide and potassium hydroxide with the 2-aminophenol in ethanol.^[7,34,46,47]

Scheme 15 Synthesis of Benzoxazole-2(3H)-thiones^[7,43–46,48]



5-Methylbenzoxazole-2(3H)-thione (21, $\text{R}^1 = \text{R}^3 = \text{H}$; $\text{R}^2 = \text{Me}$); Typical Procedure:^[45]

A mixture of 2-amino-4-methylphenol (12.3 g, 0.10 mol) and KS_2COEt (17.6 g, 0.11 mol) in pyridine (100 mL) was stirred and refluxed for 2 h. It was cooled to rt and poured into a mixture of ice water (400 mL) and concd HCl (40 mL). The solid was collected, washed with H_2O , and dried in the hood overnight and then in a vacuum oven at 45 °C for several hours to give a beige powder; yield: 16.0 g (97%); mp 220–223 °C.

Benzoxazole-2(3H)-thione (21, R¹ = R² = R³ = H); Typical Procedure:^[46]

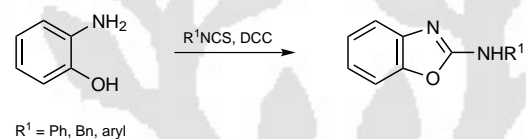
CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

2-Aminophenol (27.3 g, 0.25 mol), CS₂ (20 mL, 0.33 mol), and KOH (2.5 g, 45 mmol) were refluxed for 6 h in EtOH (10 mL). The solvent was removed and the residue was dissolved in H₂O. Subsequently, the product precipitated with 2 M aq HCl and was recrystallized (EtOH/H₂O 1:3); yield: 23 g (61%); mp 193 °C.

**11.13.1.1.1.2.2.3 Variation 3:
Synthesis of Benzoxazol-2-amines**

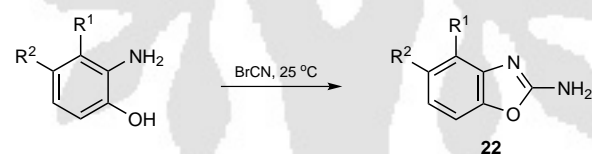
Upon reaction of 2-aminophenol with isothiocyanates in the presence of dicyclohexylcarbodiimide, N-substituted benzoxazol-2-amines are obtained (Scheme 16).^[49,50]

Scheme 16 Benzoxazol-2-amines from 2-Aminophenols and Isothiocyanates^[49,50]



Earlier, cyanogen bromide was applied in the synthesis of benzoxazol-2-amines **22** (Scheme 17).^[34,36,51,52]

Scheme 17 Benzoxazol-2-amines from 2-Aminophenols and Cyanogen Bromide^[34,36,51,52]



R ¹	R ²	Conditions	Yield (%)	Ref
H	Cl	EtOH, H ₂ O, 2 d	88	[34]
OH	H	H ₂ O, 2 d	50	[51]
H	NO ₂	EtOH, H ₂ O, 12 h	64	[52]

Benzoxazol-2-amines 22; General Procedure:^[36]

At rt, BrCN (116.6 g, 1.1 mol) was stirred in MeOH/H₂O (7:3; 200 mL). Then, a soln of the 2-aminophenol (1 mol) dissolved in a minimum amount of MeOH was added and the mixture was stirred for 40 min. The soln was subsequently neutralized with concd aq NaOH and most of the MeOH was removed by distillation. The residue was treated with H₂O and the crude material was collected by filtration. Recrystallization (H₂O) in the presence of charcoal led to pure products; yield: 50–70%.

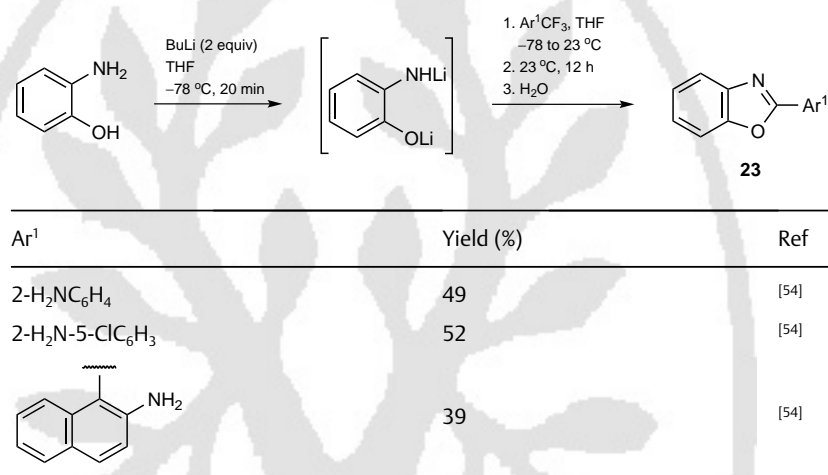
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11.13.1.1.1.2.3 Method 3:
Synthesis from 2-Aminophenols and Carboxylic Acid Derivatives

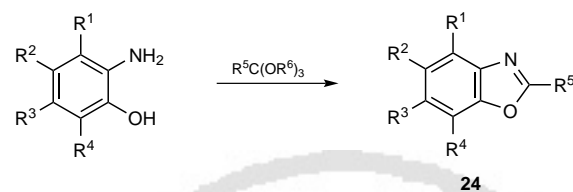
11.13.1.1.1.2.3.1 Variation 1:
Using (Trihalomethyl)arenes or Carboxylic Acid Ortho Esters

2-Arylbenzoxazoles are accessible via condensation of 2-aminophenols with (trifluoromethyl)- or (trichloromethyl)arenes in polyphosphoric acid as solvent (35–96% yield).^[53] Dilithiated 2-aminophenol also reacts with (trifluoromethyl)arenes to give benzoxazoles **23** (Scheme 18).^[54]

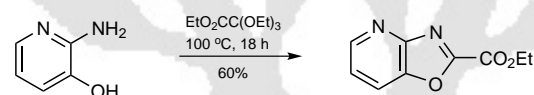
Scheme 18 Benzoxazoles from 2-Aminophenol and (Trifluoromethyl)arenes^[54]



2-Substituted benzoxazoles **24** are formed upon heating 2-aminophenols with trialkyl ortho esters, either neat^[55,56] or in the presence of an acid (e.g., concd H₂SO₄,^[57] pyridinium 4-toluenesulfonate/xylene,^[58] or glacial AcOH^[59]) (Scheme 19). The application of KSF clay (a commercial clay) as acid catalyst under thermal conditions and microwave irradiation has also been reported.^[60] Trialkyl orthoformates yield benzoxazoles unsubstituted at the 2-position, but 2-alkyl, 2-(chloromethyl)-, and 2-(alkoxycarbonyl)benzoxazoles can also be obtained via this method.^[56] Additionally, these acid-promoted methods have been applied in the synthesis of oxazolo[4,5-*b*]pyridines^[61,62] and oxazolo[4,5-*d*]pyrimidines.^[62]

Scheme 19 Benzoxazoles from 2-Aminophenols and Ortho Esters^[55,56,63]

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Conditions	Yield (%)	Ref
H	H	H	H	H	H	rt, 10 h, then distillation	67	[55]
H	F	H	F	CH ₂ Cl	Et	EtOH, 60 °C, 1–4 h	72	[63]
OMe	H	H	H	CO ₂ Me	Me	100 °C, 18 h	63	[56]
H	H	H	H	CO ₂ Me	Me	100 °C, 18 h	60	[56]
Cl	H	H	H	CO ₂ Me	Me	100 °C, 18 h	54	[56]
(CH=CH) ₂	H	H	H	CO ₂ Et	Et	100 °C, 18 h	48	[56]
H	(CH=CH) ₂	H	H	CH ₂ Cl	Et	EtOH, 60 °C, 1–4 h	86	[63]
H	Cl	CH=CHCH=N	H	CO ₂ Me	Me	100 °C, 18 h	51	[56]

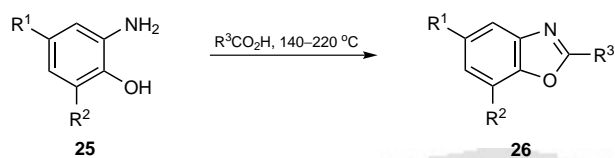
**Benzoxazole (24, R¹ = R² = R³ = R⁴ = R⁵ = H); Typical Procedure:**^[55]

2-Aminophenol (2.73 g, 25 mmol) was mixed with (EtO)₃CH (12 g, 80 mmol) and left to stand for 10 h. Then, the formed EtOH was distilled off at 130–135 °C (bath temperature) within 4 h. Subsequently, the temperature was raised and the excess (EtO)₃CH was distilled off before the product was collected at 200–230 °C (bath temperature); yield: 2.2 g (67%); bp 181 °C/760 Torr; mp 30 °C.

**11.13.1.1.2.3.2 Variation 2:
Using Carboxylic Acids**

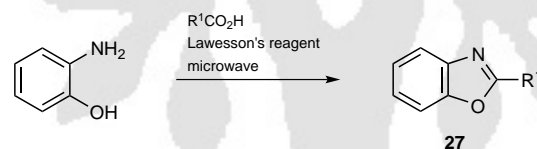
2-Aminophenols can cyclize to benzoxazoles in the presence of carboxylic acids upon heating to high temperatures, either neat or in a solvent, in the presence of a dehydrating agent (e.g., PPA, PPE, H₃BO₃). When equimolar amounts of 2-aminophenols **25** and aryl- or alkylcarboxylic acids are heated, temperatures of 140–220 °C are required^[34,64–68] for the formation of the corresponding 2-aryl- or 2-alkylbenzoxazoles **26** (Scheme 20). The above-mentioned methods can also be applied to the synthesis of oxazolo[5,4-*b*]pyridines [using PPA,^[69,70] polyphosphoric acid trimethylsilyl ester (PPSE),^[71,72] or H₃BO₃^[73]]. In some cases, solvents (xylene^[74]) can be used and the formed water can be removed by azeotropic distillation.

for references see p 50

Scheme 20 Benzoxazoles from 2-Aminophenols and Carboxylic Acids^[34,64–66,68]

R ¹	R ²	R ³	Conditions	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
Ph	H	Bn	200–220 °C, 3 h	49	52–54	[66]
H	H	<i>t</i> -Bu	<i>t</i> -BuCO ₂ H (excess), 220 °C, 10 h	60	124/17.25	[65]
H	H	(CH ₂) ₄ Me	1. reflux 2. distill	67	264–266	[68]
<i>t</i> -Bu	<i>t</i> -Bu	H	reflux, 2.5 h	83	53–55	[64]
CO ₂ H	H	H	1. reflux, 3 h 2. 170 °C, 3 h	94	249 (dec)	[34]

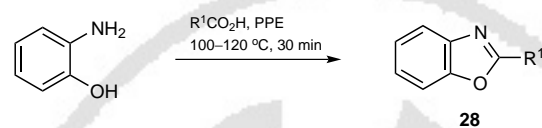
Since high temperatures are necessary for this process, microwave-assisted synthesis in ionic liquids has been used to accelerate this transformation.^[67] In the presence of substoichiometric amounts of Lawesson's reagent, a series of benzoxazoles **27** are formed within 2–4 minutes in 59–90% yield (Scheme 21).^[75]

Scheme 21 Microwave-Assisted Synthesis of Benzoxazoles^[75]

R ¹	Time (min)	Yield (%)	Ref
Ph	4	83	[75]
3,4-(MeO) ₂ C ₆ H ₃	4	79	[75]
2,4,5-(MeO) ₃ C ₆ H ₂	4	74	[75]
3-Tol	4	90	[75]
4-ClC ₆ H ₄	4	75	[75]
1-naphthyl	4	87	[75]
2-pyridyl	4	71	[75]
2-thienyl	4	80	[75]
CH=CHPh	4	59	[75]
Bn	2	90	[75]
3,4-(MeO) ₂ C ₆ H ₃ CH ₂	2	80	[75]
(CH ₂) ₅ Me	2	90	[75]
(CH ₂) ₁₆ Me	2	84	[75]

2-Aminophenols cyclize with carboxylic acids in polyphosphoric acid at 150–250 °C.^[76,77] When polyphosphate ester is used instead, milder reaction conditions (bath temperature 100–120 °C, 30 min) can be applied (Scheme 22). 2-Alkyl- and 2-arylbenzoxazoles **28** can be prepared via this method.^[78–80]

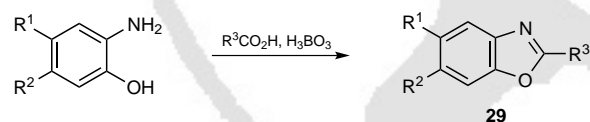
Scheme 22 Polyphosphate Ester Mediated Synthesis of Benzoxazoles from 2-Aminophenols and Carboxylic Acids^[78,81]



R ¹	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
Me	75	115/30	[78]
Ph	70	102–103	[78]
4-ClC ₆ H ₄	57	151–152	[78]
4-O ₂ NC ₆ H ₄	50	264–265	[78]
4-NCC ₆ H ₄ CH ₂	65	82–83.5	[79]
4-BrCH ₂ C ₆ H ₄	50	160–165	[81]
4-AcNHC ₆ H ₄	44	217	[78]

2-Aryl- and 2-hetarylbenzoxazoles **29** are obtained upon heating equimolar amounts of 2-aminophenols and carboxylic acids in high-boiling solvents in the presence of catalytic^[82,83] or stoichiometric amounts^[84] of boric acid (Scheme 23). The formed water has to be removed continuously. Since boric acid in xylene is a relatively weak acid compared to polyphosphoric acid, furancarboxylic acids and monomethyl terephthalates can also be reacted without major decomposition. Additionally, the workup procedure is less elaborate in the case of boric acid compared to polyphosphoric acid or polyphosphate ester.^[84]

Scheme 23 Boric Acid Mediated Synthesis of Benzoxazoles from 2-Aminophenols and Carboxylic Acids^[82–85]



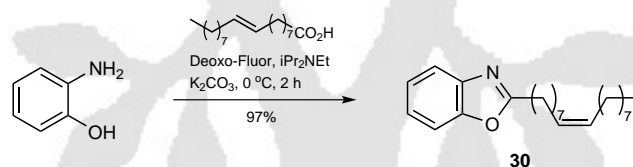
R ¹	R ²	R ³	Conditions	Yield (%)	mp (°C)	Ref
H	H	4-MeO ₂ CC ₆ H ₄	xylene, reflux, 24 h	60	197–198	[84]
H	H		ethylene glycol, reflux, 5 h	82	>360	[83]
H	H	4-Tol	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	53	114–115	[82]

for references see p 50

R ¹	R ²	R ³	Conditions	Yield (%)	mp (°C)	Ref
H	Me	4- <i>t</i> -BuC ₆ H ₄	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	95	69.5–70	[82]
H	Me	Ph	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	90	92.5–93	[82]
Me	Me	4-Tol	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	74	207–207.5	[82]
H	Ph	4-Tol	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	73	145.5–146	[82]
<i>t</i> -Bu	H	4-Tol	[EtO(CH ₂) ₂] ₂ O, [BuO(CH ₂) ₂] ₂ O, 240 °C, 3.5 h	53	113.5–114	[82]
Cy	H	4-Tol	pyridine, trichlorobenzene, 210–270 °C	85	136.5–137	[85]

A very efficient protocol uses Deoxo-Fluor {F₃SN[(CH₂)₂OMe]₂} for the synthesis of a series of 2-substituted benzoxazoles, e.g. **30**, from 2-aminophenols and carboxylic acids (Scheme 24).^[86] This protocol proves to be extremely high yielding, with yields of >95% for all the examples reported.

Scheme 24 Deoxo-Fluor Mediated Synthesis of (*E*)-2-(Heptadec-8-enyl)benzoxazole^[86]



Thionyl chloride/dimethylformamide has also been used in two examples in a high-yielding one-pot synthesis of 2-arylbenzoxazoles from 2-aminophenol and benzoic acids.^[87]

2-Benzyl-5-phenylbenzoxazole (26, R¹ = Ph; R² = H; R³ = Bn); Typical Procedure:^[66]

2-Amino-4-phenylphenol (89 g, 0.48 mol) and BnCO₂H (65 g, 0.48 mol) were heated together at 200–220 °C for 3 h. The product was treated with aq NaOH and the mixture was extracted with CHCl₃. Removal of the CHCl₃ gave an oil, which was crystallized [hexane (Norit carbon)] to give white needles; yield: 67 g (49%); mp 52–54 °C.

2-(3-Tolyl)benzoxazole (27, R¹ = 3-Tol); General Procedure:^[75]

A mixture of 3-TolCO₂H (136 mg, 1 mmol), 2-aminophenol (109 mg, 1 mmol), and Lawesson's reagent (141 mg, 0.35 mmol) was irradiated in an open vessel with microwaves in a monomode oven (Discover CEM, 300 W, temperature control set at 190 °C, measured with an IR sensor) for 4 min. The crude mixture was dissolved in CH₂Cl₂ (30 mL), and the soln was washed with 10% aq NaOH (2 × 20 mL), dried (Na₂SO₄), and concentrated to give pure (by NMR) 2-(3-tolyl)benzoxazole. Further purification by flash chromatography gave a white solid; yield: 188 mg (90%); mp 82–83 °C (EtOH).

2-Substituted Benzoxazoles 28; General Procedure:^[78]

To a mixture of 2-aminophenol (1.1 g, 10 mmol) and PPE (10 g) was added the carboxylic acid (15 mmol) at 100 °C (bath temperature) and the mixture was kept at that temperature for another 30 min. After cooling, ice water (50 mL) was added and the mixture was neu-

tralized with an excess of NaHCO_3 . The resulting precipitate was collected by filtration, washed, and dried. The crude product was purified either by extraction with hexane, benzene (**CAUTION: carcinogen**), or Et_2O , or by recrystallization.

2-(4-Tolyl)benzoxazole (29, $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^3 = 4\text{-Tol}$); Typical Procedure:^[82]

4-TolCO₂H (13.6 g, 0.1 mol), 2-aminophenol (11.0 g, 0.1 mol), and H_3BO_3 (0.5 g, 8 mmol) were heated to 240 °C in a mixture of bis[2-ethoxyethyl] ether (40 mL) and bis[2-butoxyethyl] ether (10 mL) under stirring and a N_2 atmosphere for 3 h. The H_2O that formed and the lower-boiling solvent were continuously removed by distillation. The mixture was kept at 240 °C for 30 min. Then, it was cooled and dioxane (40 mL) and then MeOH (60 mL) were added. The mixture was cooled to 0–5 °C and the precipitate was collected by filtration, washed with MeOH, and dried; yield: 11.1 g (53%); mp 114–115 °C (EtOH).

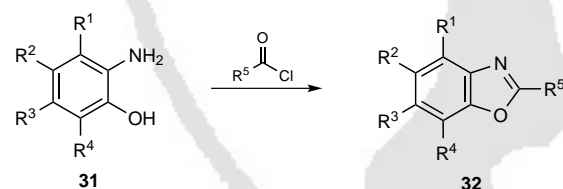
(E)-2-(Heptadec-8-enyl)benzoxazole (30); Typical Procedure:^[86]

(E)-Octadec-9-enoic acid (49.4 mg, 0.175 mmol), iPr_2NEt (80 μL , 0.46 mmol, 2.6 equiv), 2-aminophenol (42.10 mg, 0.385 mmol, 2.2 equiv), and K_2CO_3 (excess) were dissolved in CH_2Cl_2 (2 mL). The mixture was cooled to 0 °C, and Deoxo-Fluor (71 μL , 0.385 mmol, 2.2 equiv) was added dropwise. After 2 h, the reaction was quenched with sat. aq NaHCO_3 at 0 °C. After warming to rt, the biphasic mixture was extracted with CH_2Cl_2 . The combined organic extracts were dried (MgSO_4), filtered, and concentrated under reduced pressure. Flash column chromatography provided a light yellow solid; yield: 60.3 mg (97%).

**11.13.1.1.2.3.3 Variation 3:
Using Carboxylic Acid Chlorides**

Upon reaction of 2-aminophenols **31** with acyl chlorides and subsequent distillation^[4] at high temperatures (in high-boiling solvents such as xylene,^[88] *N,N*-dimethylaniline,^[89] or pyridine^[90]) the corresponding 2-alkyl- or 2-arylbenzoxazoles **32** are obtained (Scheme 25). In a two-step process, oxazolo[4,5-*b*]pyridines are prepared from 3-aminopyridin-2-one via acylation with acid chlorides and subsequent cyclization of the intermediate carboxamide with phosphoryl chloride.^[69]

Scheme 25 Benzoxazoles from 2-Aminophenols and Acid Chlorides^[88–90]



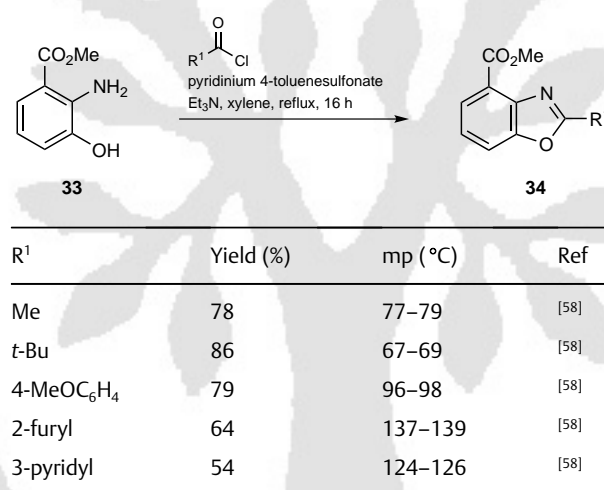
R^1	R^2	R^3	R^4	R^5	Conditions	Yield (%)	mp (°C)	Ref
H	H	H	H	1-adamantyl	PhNMe_2 , reflux, 45 min	90	100	[89]
F	F	F	F	Ph	xylene, 200 °C, 12 h	84	119.5–120.5	[88]
H	H	H	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	83	169–170	[90]
H	Cl	H	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	22	197–198	[90]

for references see p 50

R ¹	R ²	R ³	R ⁴	R ⁵	Conditions	Yield (%)	mp (°C)	Ref
H	NO ₂	H	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	38	174–175	[90]
H	Me	H	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	68	168–169	[90]
H	H	Me	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	50	187–188	[90]
H	H	OMe	H	2,5- <i>t</i> -Bu ₂ -4-HOC ₆ H ₂	1. pyridine, 120 °C 2. neat, 200 °C	42	169–170	[90]

If methyl 2-amino-3-hydroxybenzoate (**33**) is reacted with acyl chlorides in the presence of triethylamine in refluxing xylene, the corresponding amides are initially obtained; however, upon addition of pyridinium 4-toluenesulfonate cyclization to the corresponding 2-substituted methyl benzoxazole-4-carboxylates **34** occurs (Scheme 26).^[58]

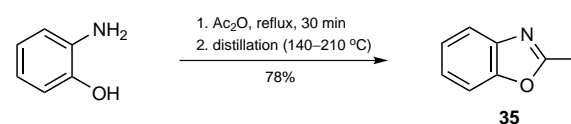
Scheme 26 Benzoxazoles from Methyl 2-Amino-3-hydroxybenzoate and Acid Chlorides^[58]



11.13.1.1.1.2.3.4 Variation 4: Using Carboxylic Acid Anhydrides or Imidates

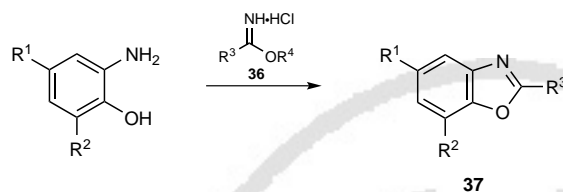
Upon heating of 2-aminophenol with acetic anhydride and subsequent distillation, 2-methylbenzoxazole **35** is obtained via *N,O*-diacetyl-2-aminophenol (Scheme 27).^[4,91,92] Other 2-methylbenzoxazoles,^[88] 2-(prop-1-enyl)benzoxazole,^[93] and oxazolo[5,4-*b*]pyridines^[94,95] have been prepared similarly.

Scheme 27 2-Methylbenzoxazole from 2-Aminophenol and Acetic Anhydride^[91]



Alkyl imidates **36** cyclize easily with 2-aminophenols in various solvents at different temperatures to give 2-substituted benzoxazoles **37** (Scheme 28).^[79,96,97]

Scheme 28 Benzoxazoles from 2-Aminophenols and Alkyl Imidates^[79,96–101]



R ¹	R ²	R ³	R ⁴	Conditions	Yield (%)	mp (°C)	Ref
H	H	Me	Me	MeOH, reflux, 30 min	78	– ^a	[96,98]
H	H	CH ₂ CO ₂ Et	Et	EtOH, 20 °C, 24 h	73	56–57	[97]
H	H	CCl ₃	Me	EtOH, 20 °C, 96 h	60	60	[99]
H	Cl	CCl ₃	Me	EtOH, 80 °C, 2 h	50	58	[99]
Br	Br	CCl ₃	Me	EtOH, 80 °C, 2 h	60	120	[99]
I	I	CCl ₃	Me	EtOH, 80 °C, 2 h	70	105	[99]
H	H	4-BrC ₆ H ₄ CH ₂	Me	CHCl ₃ , N ₂ , 25 °C, 6 h	72	92–95	[79]
H	H	1,2,4-oxadiazol-3-yl	Me	MeOH, reflux, 1.5 h	62	158–159	[100]
CH ₂ CO ₂ H	H	4-pyridyl	Et	AcOH, MeOH, reflux, 6 h	54	310–320 (dec)	[101]

^a bp 203–208 °C.

Alternatively, *S*-methyl alkanimidothioate hydriodides in the presence of silica gel under microwave irradiation to give 2-substituted benzoxazoles in good yields in 2–2.5 minutes.^[102]

2-Methylbenzoxazole (35); Typical Procedure:^[91]

2-Aminophenol (20 g, 0.18 mol) was slowly added to cooled Ac₂O (50 g, 0.49 mol), and the mixture was then refluxed for 30 min. Subsequent distillation gave a fraction at 140–210 °C, which was extracted with aq K₂CO₃ until a basic pH was detected. The crude material was extracted with Et₂O and the ethereal layer was dried (K₂CO₃), filtered, and concentrated. The residue was distilled and the product was collected at 203–204 °C/760 Torr; yield: 19 g (78%).

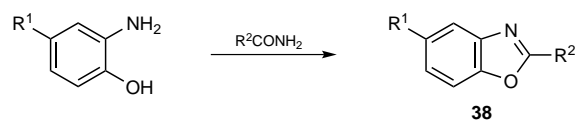
2-Methylbenzoxazole (37, R¹ = R² = H; R³ = Me); Typical Procedure:^[96]

2-Aminophenol (2.5 g, 22.9 mmol) and methyl acetimidate hydrochloride (2.5 g, 22.8 mmol) in dry MeOH (10 mL) were heated on a steam bath for 30 min. After the addition of H₂O containing a small amount of Na₂CO₃ to the semisolid sludge, the product was extracted with Et₂O and distilled to give a colorless oil; yield: 2.38 g (78%); bp 203–208 °C.

**11.13.1.1.1.2.3.5 Variation 5:
Using Carboxamides**

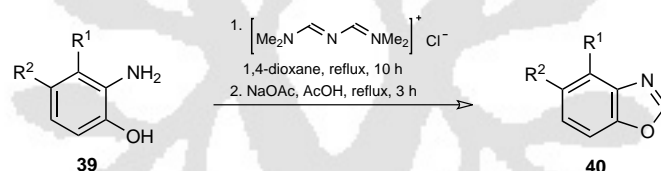
Benzoxazoles **38** are formed upon heating of 2-aminophenols and carboxamides, with loss of water and ammonia (Scheme 29).

for references see p 50

Scheme 29 Benzoxazoles from 2-Aminophenols and Carboxamides^[36,68,103]

R ¹	R ²	Conditions	Yield (%)	mp (°C)	bp (°C/Torr)	Ref
H	(CH ₂) ₅ Me	–	71	19	281–283	[68,103]
H	4-ClC ₆ H ₄	1.5 h	76	150	–	[103]
H	iBu	7 h	50	–	240/740	[103]
H	4-MeOC ₆ H ₄	1 h	96	101	–	[103]
Cl	H	170–180°C, 2 h	43	37–37.5	112–114/30	[36]

By reacting 2-aminophenols **39** with Gold's reagent {dimethyl[3-(dimethylamino)-2-azaprop-2-enylidene]ammonium chloride}, 2-unsubstituted benzoxazoles **40** are obtained (Scheme 30).^[104,105]

Scheme 30 Benzoxazoles from 2-Aminophenols and Gold's Reagent^[104,105]

R ¹	R ²	Yield (%)	Ref
H	H	58	[105]
Me	H	53	[105]
H	Me	89	[105]

Benzoxazoles 38; General Procedure:^[68]

Technical grade 2-aminophenol (1 equiv) and the amide (1 equiv) were refluxed for several hours in a Claisen flask. The temperature was slowly increased, as H₂O or NH₃ distilled from the flask, until the refluxing temperature remained constant. The black mixture was then distilled at atmospheric pressure. The crude product, if a liquid, was dissolved in petroleum ether and washed with 10% NaOH soln. This treatment destroyed the characteristic fluorescence noted in many of the crude benzoxazoles. The oil remaining after removal of the petroleum ether was purified by distillation. The liquids were usually straw colored. The solids were pulverized and washed with 10% aq NaOH and H₂O before recrystallization (dil alcohol or acetone).

Benzoxazoles 40; General Procedure:^[104]

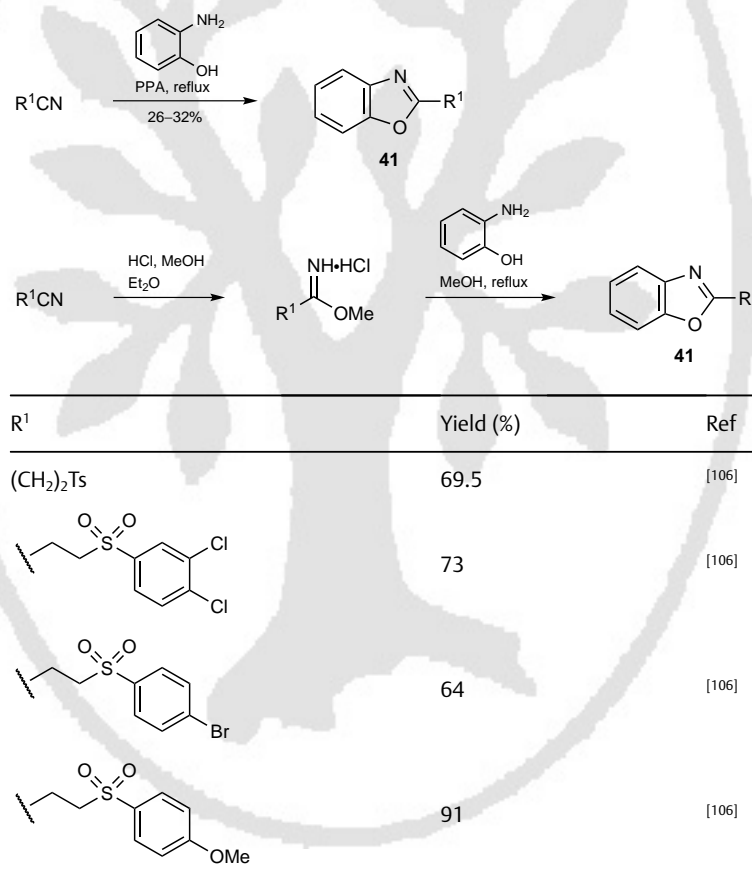
A mixture of 2-aminophenol **39** (50 mmol) and Gold's reagent (9.9 g, 61 mmol) was refluxed in dry dioxane (100 mL) for 17 h. The mixture was cooled to ambient temperature and dry NaOAc (4.1 g, 50 mmol) in AcOH (2 mL) was added. This mixture was refluxed for an additional 3 h. The solvent was removed under reduced pressure and the residue was

dissolved in CHCl_3 (100 mL). This organic layer was washed with sat. aq NaHCO_3 (3×50 mL), dried (MgSO_4), and filtered, and the solvent was evaporated. The crude material was purified by vacuum distillation.

11.13.1.1.2.3.6 Variation 6: Using Nitriles

Nitriles undergo reaction with 2-aminophenols to give benzoxazoles **41** at high temperatures, similar to the corresponding reaction using carboxamides (see Section 11.13.1.1.2.3.5).^[68] The reaction with nitriles is considerably slower since a significant decrease in the reaction rate is observed after $\sim 75\%$ conversion (Scheme 31).^[106] This reaction is carried out in analogy to the protocol reported for carboxamides. By first transforming the nitrile to the corresponding imidate hydrochloride, the outcome of the reaction can be significantly improved (see also Section 11.13.1.1.2.3.4).^[106]

Scheme 31 Benzoxazoles from 2-Aminophenols and Nitriles^[68,106]



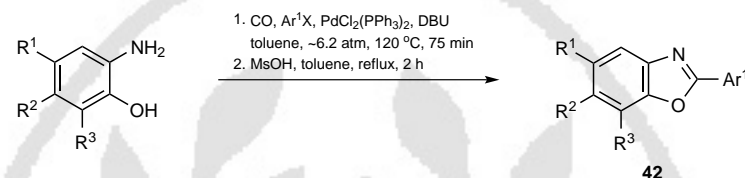
11.13.1.1.2.3.7 Variation 7: Using Carbon Monoxide and Aryl Halides

2-Arylbenzoxazoles **42** are obtained via the palladium-catalyzed reaction of 2-aminophenols^[107] or 2-fluoroanilines^[108] with carbon monoxide and aryl halides. As catalyst, dichlorobis(triphenylphosphine)palladium(II) is used. The reaction is carried out in the

for references see p 50

presence of 1,8-diazabicyclo[5.4.0]undec-7-ene as base in toluene at 120 °C and at a carbon monoxide pressure of 6.2 atm. Good yields are obtained when methanesulfonic acid or 4-toluenesulfonic acid are added (in toluene) to the in situ formed *N*-(2-hydroxyphenyl) carboxamide to drive the cyclization to completion (Scheme 32). Water formed in the course of the reaction is simultaneously removed by azeotropic distillation. Alternatively, diaryliodonium salts are used in a similar transformation.^[109]

Scheme 32 Palladium-Catalyzed Synthesis of Benzoxazoles^[107]

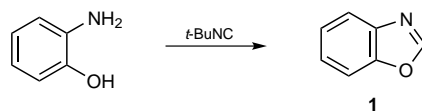


R ¹	R ²	R ³	Ar ¹	X	Yield (%)	Ref
H	H	H	4-PhC ₆ H ₄	I	97	[107]
H	H	H	4-AcC ₆ H ₄	Br	86	[107]
H	H	H	2-pyridyl	Br	82	[107]
Me	H	Me	Ph	I	82	[107]
Cl	H	H	Ph	I	79	[107]
(CH=CH) ₂	H	H	Ph	I	91	[107]

Benzoxazol-2(3*H*)-one can be obtained in the reaction of 2-aminophenol and carbon monoxide in the presence of sulfur and potassium carbonate. It is believed that carbon disulfide is formed in situ, which then reacts with the amine functionality to give a thiocarbamate salt. Subsequent oxidation with molecular oxygen leads to the benzoxazol-2(3*H*)-one.^[110]

11.13.1.1.1.2.3.8 Variation 8: Using Isocyanides

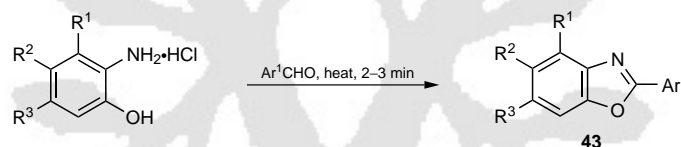
Equimolar amounts of 2-aminophenol and *tert*-butyl isocyanide react to give benzoxazole (**1**) (54% yield) and *tert*-butylamine in the presence of catalytic amounts of silver(I) cyanide at 90 °C.^[111] When palladium(II) chloride is used as catalyst and the reaction is performed in tetrahydrofuran at 66 °C the yield is improved to 75% (Scheme 33).^[112]

Scheme 33 Benzoxazole from 2-Aminophenol and an Isocyanide^[111,112]

Conditions	Yield (%)	Ref
AgCN, 90 °C	54	[111]
PdCl ₂ , THF, 66 °C, 1 h	75	[112]

11.13.1.1.2.4 **Method 4:** **Synthesis from 2-Aminophenols and Aldehydes**

Upon heating 2-aminophenols (or hydrochlorides thereof) with an excess of aromatic aldehydes (4 equivalents) without solvent over an open flame, 2-arylbenzoxazoles **43** are formed very quickly (2–3 min) (Scheme 34).^[113] Alternatively, the reaction mixture can be refluxed for an appropriate time.^[114]

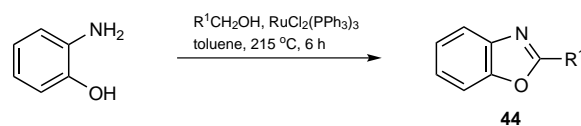
Scheme 34 Benzoxazoles from 2-Aminophenols and Aldehydes^[113,114]

R ¹	R ²	R ³	Ar ¹	Conditions	Yield (%)	mp (°C)	Ref
H	H	H	Ph	open flame, 2–3 min	80	102	[113]
H	H	H	4-MeOC ₆ H ₄	open flame, 2–3 min	83	99	[113]
Cl	H	Cl	Ph	reflux, 10 h	60	143–144.5	[114]
(CH=CH) ₂	CN	Ph	Ph	open flame, 2–3 min	90	191–193	[113]

11.13.1.1.2.5 **Method 5:** **Synthesis from 2-Aminophenols and Alcohols**

2-Aminophenol undergoes reaction with primary alcohols under catalysis by dichloro-tris(triphenylphosphine)ruthenium(II) to furnish 2-alkyl- and 2-arylbenzoxazoles **44** via the corresponding imines as intermediates (Scheme 35).^[115]

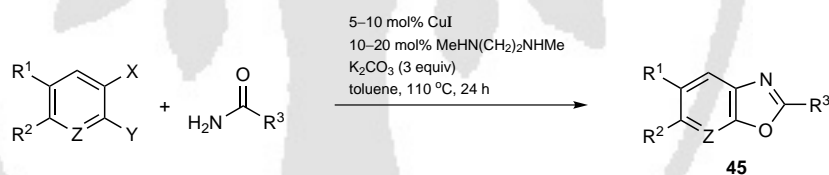
for references see p 50

Scheme 35 Benzoxazoles from 2-Aminophenol and Primary Alcohols^[115]

R ¹	Yield (%)	Ref
Pr	60	[115]
Bn	56	[115]
Ph	80	[115]
4-Tol	62	[115]

11.13.1.1.1.3 Fragments C–C and N–C–O**11.13.1.1.1.3.1 Method 1: Synthesis from 1,2-Dihaloarenes and Carboxamides**

Benzoxazoles **45** can be synthesized directly from 1,2-dihaloarenes and carboxamides (1.1 equivalents) under copper catalysis (Scheme 36). Under the optimized reaction conditions, 1,2-dibromo-, 1,2-diiodo-, or 1-bromo-2-chlorobenzene can be transformed to the corresponding 2-substituted benzoxazole; only 1,2-dichloroaryls do not react.^[116,13] Regarding the amide part, aryl, alkenyl, and alkyl amides are successfully applied in this transformation.

Scheme 36 Benzoxazoles from 1,2-Dihaloarenes and Carboxamides^[116]

R ¹	R ²	X	Y	Z	R ³	Yield (%)	Ref
H	H	Br	Br	CH	Ph	90	[116]
	OCH ₂ O	Br	Br	CH	Ph	88	[116]
H	H	I	I	CH	Ph	65	[116]
H	H	Br	Cl	CH	Ph	95	[116]
H	H	Br	Cl	N	Ph	77	[116]
H	H	Cl	Br	CCl	Ph	75	[116]
H	CF ₃	Cl	Br	CH	Ph	59	[116]
H	Cl	Cl	Br	CH	Ph	72	[116]
H	H	Br	Br	CH	2-FC ₆ H ₄	86	[116]
H	H	Br	Br	CH	4-H ₂ NC ₆ H ₄	67	[116]
H	H	Br	Br	CH	4-MeOC ₆ H ₄	72	[116]

R ¹	R ²	X	Y	Z	R ³	Yield (%)	Ref
H	H	Br	Br	CH	3-pyridyl	78	[116]
H	H	Br	Br	CH	CH=CHPh	77	[116]
H	H	Br	Br	CH	<i>t</i> -Bu	92	[116]
H	H	Br	Br	CH	<i>i</i> Pr	68	[116]
H	H	Br	Br	CH	Pr	68	[116]

2-Phenylbenzoxazole (45, R¹ = R² = H; Z = CH; R³ = Ph); Typical Procedure:^[116]

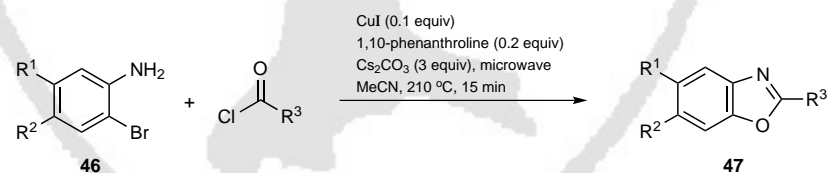
1,2-Dibromobenzene (120 μ L, 1.0 mmol), BzNH₂ (133 mg, 1.1 mmol), K₂CO₃ (414 mg, 3.0 mmol), and CuI (10 mg, 0.05 mmol) were weighed into a vial. The vial was evacuated and filled with argon, followed by the addition of *N,N'*-dimethylethylenediamine (11 μ L, 0.1 mmol) and toluene (3 mL). The vial was closed and the mixture was stirred at 110 °C for 24 h. After cooling to rt, the mixture was poured into 25% aq NH₄OH, the resultant mixture was extracted with EtOAc, and the extracts were dried (Na₂SO₄), filtered, and concentrated. Chromatography (silica gel, EtOAc/hexane 1:10) gave a white powder; yield: 176 mg (90%).

11.13.1.1.1.4 Fragments C—C—N and C—O

**11.13.1.1.1.4.1 Method 1:
Synthesis from 2-Bromoanilines and Carboxylic Acid Chlorides**

An interesting alternative to the copper-catalyzed formation of benzoxazoles from 1,2-dihaloarenes and carboxamides (see Section 11.13.1.1.3.1) is the copper-catalyzed reaction of 2-bromoanilines **46** and acid chlorides (1.2 equivalents). In this case, benzoxazoles **47** are also formed in a one-pot process and the reaction is quite general (Scheme 37).^[13] The transformations are carried out within 15 minutes under microwave heating to 210 °C with 10 mol% of copper(I) iodide as the catalyst.

Scheme 37 Benzoxazoles from 2-Bromoanilines and Carboxylic Acid Chlorides^[13]



R ¹	R ²	R ³	Yield (%)	Ref
H	Me	2-MeOC ₆ H ₄	97	[13]
H	Me	(CH ₂) ₁₀ Me	96	[13]
H	Me	2-thienyl	91	[13]
H	Me	2-ClC ₆ H ₄	33	[13]
H	F	2-MeOC ₆ H ₄	95	[13]
H	F	CH=CHPh	62	[13]
H	F	2-furyl	61	[13]

for references see p 50

R ¹	R ²	R ³	Yield (%)	Ref
CF ₃	H	2-MeOC ₆ H ₄	85	[13]
CF ₃	H	2-thienyl	31	[13]
CF ₃	H	2-ClC ₆ H ₄	71	[13]
	OCH ₂ O	CH=CHPh	66	[13]
	OCH ₂ O	2-furyl	70	[13]
	OCH ₂ O	2-ClC ₆ H ₄	59	[13]

2-Substituted Benzoxazoles 47; General Procedure:^[13]

A reaction vial with a stirrer bar was charged with CuI (5 mg, 0.025 mmol) and Cs₂CO₃ (245 mg, 0.75 mmol). Under a stream of N₂, a dry stock soln of 0.10 M bromoaniline **46** and 0.02 M 1,10-phenanthroline in MeCN (2.5 mL) was added, followed by a 0.12 M soln of the acyl chloride (2.5 mL, 0.3 mmol). The vial was crimped and heated by microwave irradiation to 210 °C for 15 min. After cooling to rt, the mixture was diluted with MeCN (25 mL) and filtered through a short pad of silica gel, rinsing with additional MeCN (15 mL). A small amount of silica gel was added to the filtrate, and the mixture was concentrated under reduced pressure. The product was isolated by semiautomated flash chromatography (Biotage SP-1, 12 mm × 25 cm silica gel columns, EtOAc/hexanes 1:9).

11.13.1.1.2 With Formation of One C—O Bond

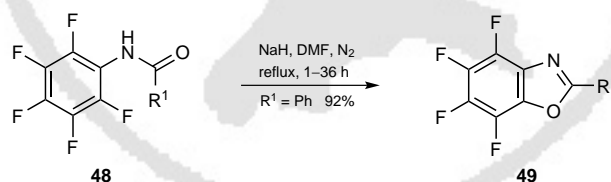
11.13.1.1.2.1 Fragment C—C—N—C—O

11.13.1.1.2.1.1 Method 1:

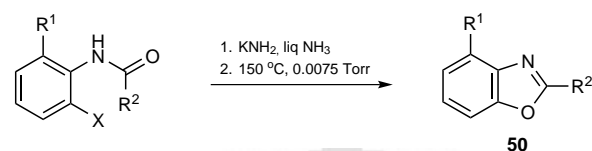
Synthesis from *N*-(2-Haloaryl)carboxamides

N-(Pentafluorophenyl)benzamide (**48**, R¹ = Ph) can cyclize to 4,5,6,7-tetrafluoro-2-phenylbenzoxazole (**49**, R¹ = Ph) in the presence of sodium hydride in boiling dimethylformamide (Scheme 38).^[117,118]

Scheme 38 Benzoxazoles from *N*-(2-Fluoroaryl)carboxamides^[117,118]

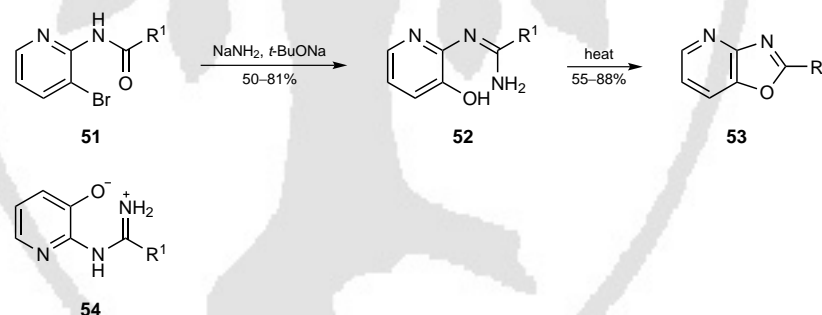


From *N*-(2-chlorophenyl)- or *N*-(2-bromophenyl)carboxamides, 2-substituted benzoxazoles **50** can be formed. The reaction is promoted by potassium amide in liquid ammonia, with subsequent sublimation of the reaction residue (Scheme 39).^[119–121] When *N*-(2-chlorophenyl)benzamide was used as starting material, initially only low amounts of 2-phenylbenzoxazole (10%) were obtained. The main product, identified as *N*-(2-hydroxyphenyl)benzencarboximidamide (90% yield), generated by ring opening of the benzoxazole, can be recycled via sublimation or under acidic conditions to the desired 2-phenylbenzoxazole.^[121]

Scheme 39 Benzoxazoles from *N*-(2-Haloaryl)carboxamides^[120,121]

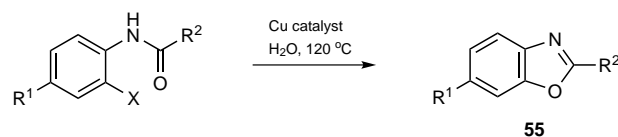
R ¹	R ²	X	Yield (%)	mp (°C)	Ref
H	H	Cl	85	28–30	[121]
H	Ph	Cl	85	102–103	[121]
H	Ph	Br	72	99–101	[120]
Me	Ph	Cl	85	92–93	[121]
H	4-MeOC ₆ H ₄	Cl	75	100–103	[121]
H	4-Tol	Cl	65	113–115	[121]
H	3-Tol	Cl	80	81–82	[121]
H	Me	Cl	67	117–118	[121]

For the synthesis of oxazolo[4,5-*b*]pyridines **53**, *N*-(3-bromo-2-pyridyl)carboxamides **51** are first treated with sodium amide/sodium *tert*-butoxide to give the isolable intermediate **52**. (In some cases, depending on the nature of the amide group, the intermediate is isolated in the zwitterionic form **54**.) These intermediates are cyclized by heating for 5–15 hours in dimethylacetamide at 170 °C or within minutes under microwave irradiation (Scheme 40).^[122]

Scheme 40 Oxazolo[4,5-*b*]pyridines from *N*-(3-Bromo-2-pyridyl)carboxamides^[122]

In more recent contributions it has been demonstrated that the use of strong bases can be avoided. Instead, cyclization to benzoxazoles can be mediated via copper catalysis (Scheme 41).^[123,124] By this method, a series of 2-arylbenzoxazoles **55** can be prepared in reasonably good yield.

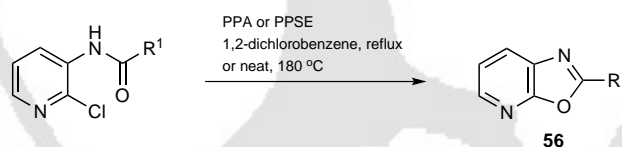
for references see p 50

Scheme 41 Copper-Catalyzed Cyclization of *N*-(3-Halo-2-pyridyl)carboxamides^[123]

X	R ¹	R ²	Cu Catalyst	Yield (%)	Ref
Cl	H	Ph	CuCl	73	[123]
Br	Me	Ph	Cu(OTf) ₂	73	[123]
Br	OCF ₃	Ph	CuCl/Cu(OTf) ₂	49	[123]
Cl	H	4-FC ₆ H ₄	CuCl	75	[123]
Br	Me	4-FC ₆ H ₄	Cu(OTf) ₂	61	[123]
Br	H	2-naphthyl	CuCl	72	[123]
Br	OCF ₃	2-naphthyl	Cu(OTf) ₂	57	[123]
Cl	Me	2-thienyl	CuCl	59	[123]
Br	H	2-thienyl	Cu(OTf) ₂	59	[123]
Cl	Me	3-furyl	Cu(OTf) ₂	60	[123]
Cl	H	4-pyridyl	Cu(OTf) ₂	38	[123]

Alternatively, the combination of iron(III) chloride and 2,2,6,6-tetramethylheptane-3,5-dione has also been reported as a catalyst system with dimethylformamide as solvent. Also in this case, comparatively mild bases (e.g., Cs₂CO₃) can be applied.^[125]

2-Substituted oxazolo[5,4-*b*]pyridines **56** can be obtained via cyclization of *N*-(2-chloro-3-pyridyl)carboxamides via treatment with polyphosphoric acid^[126] or polyphosphoric acid trimethylsilyl ester (PPSE) (Scheme 42).^[72,127]

Scheme 42 Oxazolo[5,4-*b*]pyridines from *N*-(2-Chloro-3-pyridyl)carboxamides^[72,126,127]

R ¹	Conditions	Yield (%)	mp (°C)	Ref
Ph	PPSE (excess), 1,2-dichlorobenzene, reflux	96	100–101	[127]
2-FC ₆ H ₄	PPSE (excess), 1,2-dichlorobenzene, reflux	98	122–123	[127]
4-MeOC ₆ H ₄	PPSE (excess), 1,2-dichlorobenzene, reflux	99	144–145	[127]

4,5,6,7-Tetrafluoro-2-phenylbenzoxazole (**49**, R¹ = Ph); Typical Procedure:^[117]

A soln of *N*-(pentafluorophenyl)benzamide (**48**, R¹ = Ph; 0.50 g, 1.75 mmol) in dry DMF (15 mL) was added to a mixture of NaH (60 mg, 2.5 mmol) and dry DMF (15 mL) over 30 min under N₂. The mixture was refluxed for 2 h and then extracted with Et₂O. The ethereal layer was washed with dil HCl and H₂O, dried (MgSO₄), and filtered, and the solvent

was evaporated. The crude material was purified by column chromatography [alumina, benzene (**CAUTION: carcinogen**)]; yield: 0.43 g (92%); mp 125.2–125.7 °C (MeOH).

2-Substituted Benzoxazoles 50; General Procedure:^[121]

CAUTION: Metallic potassium on prolonged exposure to air forms a coating of potassium superoxide, which is explosive under certain conditions.

A few small crystals of Fe(NO₃)₃ were added to liq NH₃ (250 mL). Then, K (4.7 g, 0.12 mol) was added in portions within 10 min. To the resulting gray soln was added the *N*-(2-halophenyl)carboxamide (21.7 mmol) in small portions as fast as possible. The mixture was stirred for 1 h and then quenched by careful addition of NH₄Cl (6.95 g, 0.13 mol). NH₃ was removed and the solid residue was extracted with MeCN (200 mL). After filtration, MeCN was evaporated and the residue was sublimed at 150 °C/0.008 Torr.

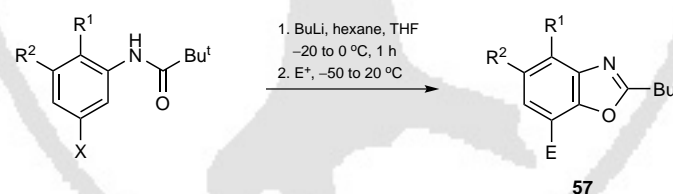
2-Phenylbenzoxazole (55, R¹ = H; R² = Ph); Typical Procedure:^[123]

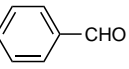
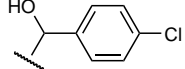
A flask was charged with *N*-(2-chlorophenyl)benzamide (81.2 mg, 0.35 mmol), CuCl (3.1 mg, 0.031 mmol), TMEDA (0.18 mL, 0.31 mmol), and H₂O (4.1 mL). The flask was sealed with a screw cap and the resulting soln was heated overnight at 120 °C. The product was extracted from the aqueous layer with CH₂Cl₂, dried, and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (EtOAc/hexane 1:9) to give a white solid; yield: 50.3 mg (73%).

11.13.1.1.2.1.2 Method 2: Synthesis from *N*-(3-Halophenyl)carboxamides

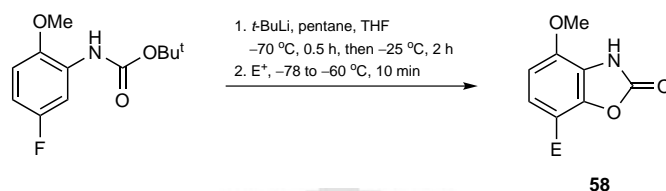
N-(3-Halophenyl)carboxamides^[128,129] and *N*-(3-halophenyl)carbamates^[130] cyclize in the presence of an excess of butyllithium or *tert*-butyllithium in tetrahydrofuran to 7-lithio-benzoxazoles via the corresponding aryne intermediates. Quenching with electrophiles leads to substituted benzoxazoles **57** and benzoxazol-2(3*H*)-ones **58**, respectively (Scheme 43). In the reaction of *N*-(3-fluorophenyl)benzamide (**59**), lithiation is observed not only in position 7 of the benzoxazole but also in the phenyl group.

Scheme 43 Benzoxazoles from *N*-(3-Halophenyl)carboxamides and -carbamates^[128–130]

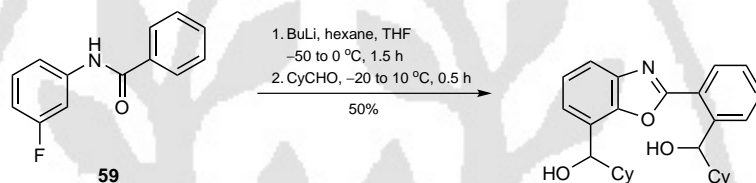


R ¹	R ²	X	E ⁺	E	Yield (%)	Ref
H	H	F	EtI	Et	89	[128]
H	H	F	(MeS) ₂	SMe	56	[128]
H	H	F	Cl-  -CHO		68	[128]
Me	H	Cl	CO ₂	CO ₂ H	55	[129]
H	Cl	Cl	CO ₂	CO ₂ H	53	[129]

for references see p 50



E ⁺	E	Yield (%)	Ref
TMSCl	TMS	71	[130]
(PhS) ₂	SPh	65	[130]
DMF	CHO	62	[130]



2-*tert*-Butyl-7-ethylbenzoxazole (57, R¹ = R² = H; E = Et); Typical Procedure:^[128]

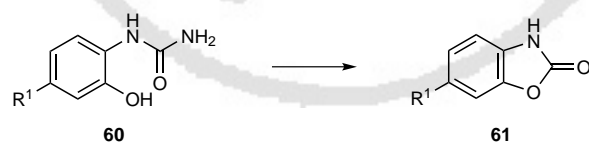
A 1.6 M soln of BuLi in hexane (15.6 mL, 25 mmol) was added dropwise at -20 °C to a soln of *N*-(3-fluorophenyl)-2,2-dimethylpropanamide (1.95 g, 10 mmol) in dry THF (50 mL). The mixture was then warmed to 0 °C within 1 h. After cooling again to -50 °C, EtI (1 mL, 12.5 mmol) was added. The mixture was warmed to rt, poured into H₂O, and subsequently extracted with Et₂O. The organic layer was washed with H₂O and brine, dried (Na₂SO₄), and filtered, and the solvent was removed by evaporation. The crude material was purified by column chromatography (silica gel, hexane/Et₂O 86:14) to give an oil; yield: 1.80 g (89%).

11.13.1.1.2.2 Fragment O—C—C—N—C

11.13.1.1.2.2.1 Method 1: Synthesis from *N*-(2-Hydroxyphenyl)ureas

When 1-(2-hydroxyphenyl)ureas **60** are heated above their melting point, benzoxazol-2(3*H*)-ones **61** are obtained (Scheme 44).^[131]

Scheme 44 Benzoxazol-2(3*H*)-ones from 1-(2-Hydroxyphenyl)ureas^[131]

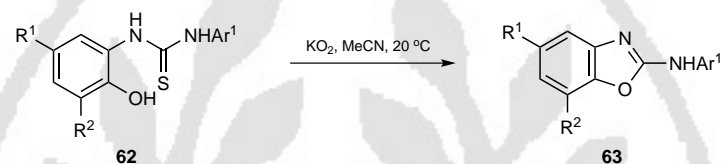


R ¹	Conditions	Yield (%)	Ref
OMe	165 °C, 0.5 h	55	[131]
H	160 °C, 15 min	81	[131]
NO ₂	180 °C, 1 h	78	[131]

11.13.1.1.2.2.2 **Method 2:**
Synthesis from *N*-(2-Hydroxyphenyl)thioureas

Good yields of benzoxazol-2-amines are obtained upon desulfurization of 1-(2-hydroxyphenyl)thioureas with various metal oxides such as potassium superoxide (superoxide radical anions),^[132] nickel peroxide,^[133] or lead(II) oxide.^[36] *N*-Arylbenzoxazol-2-amines **63** are synthesized by reaction of 1-aryl-3-(2-hydroxyphenyl)phenylthioureas **62** and potassium superoxide in acetonitrile at 20 °C (Scheme 45). The cleaved sulfur is oxidized to potassium sulfate.^[132]

Scheme 45 Benzoxazol-2-amines from *N*-(2-Hydroxyphenyl)thioureas^[132]



R ¹	R ²	Ar ¹	Time (h)	Yield (%)	Ref
H	H	4-O ₂ NC ₆ H ₄	1.5	98	[132]
Me	H	4-Tol	6	88	[132]
Me	Me	Ph	3	80	[132]
Cl	H	Ph	2.5	96	[132]
Me	H	Ph	2	92	[132]
Me	H	Ph	8	88 ^a	[132]
H	H	Ph	1	86	[132]
Me	H	4-O ₂ NC ₆ H ₄	3	91	[132]
Cl	H	4-O ₂ NC ₆ H ₄	2	94	[132]
Cl	H	4-Tol	3.5	85	[132]

^a The reaction temperature was -35 °C.

2-[(Methoxycarbonyl)amino]oxazolo[5,4-*d*]pyrimidines are prepared via dicyclohexylcarbodiimide assisted cyclization of 1-(methoxycarbonyl)-3-(4-oxo-1,4-dihydropyrimidin-5-yl)thioureas.^[134,135]

5-Methyl-*N*-phenylbenzoxazol-2-amine (63, R¹ = Me; R² = H; Ar¹ = Ph); Typical Procedure:^[132]

CAUTION: Potassium superoxide is explosive under certain conditions, and reacts violently with water.

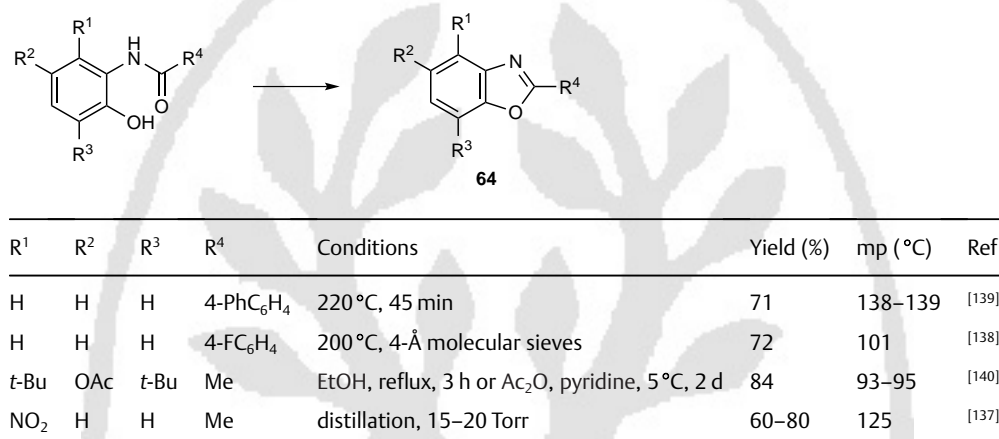
A soln of 1-(2-hydroxy-5-methylphenyl)-3-phenylthiourea (**62**, R¹ = Me; R² = H; Ar¹ = Ph; 258 mg, 1 mmol) in MeCN (2 mL) was added at 20 °C to a suspension of KO₂ (370 mg, 5 mmol) in MeCN (1 mL). The reaction soln was vigorously stirred for 2 h at 20 °C, and then poured into cold H₂O and extracted with CHCl₃. The organic layer was dried (MgSO₄) and filtered and the solvent was evaporated. If necessary, the crude product was purified by column chromatography; yield: 206 mg (92%); mp 204–207 °C.

for references see p 50

11.13.1.1.2.2.3 Method 3: Synthesis from *N*-(2-Hydroxyphenyl)carboxamides

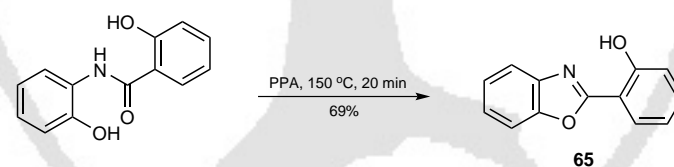
2-Substituted benzoxazoles **64** are obtained via cyclization of *N*-(2-hydroxyphenyl)carboxamides upon thermolysis or in the melt (Scheme 46). The starting materials are heated to 200–300 °C (neat, without a solvent) and the formed water is removed by distillation.^[136,137] Molecular sieves can be added to promote the elimination of water.^[138] The crude benzoxazole is then purified either by distillation or recrystallization.

Scheme 46 Benzoxazoles via Cyclization of *N*-(2-Hydroxyphenyl)carboxamides^[137–140]



As alternative dehydrating agents, polyphosphoric acid (Scheme 47),^[141,142] polyphosphate ester,^[143,80] or pyridinium 4-toluenesulfonate^[143] can be used to give benzoxazoles, such as **65**.

Scheme 47 Polyphosphoric Acid Promoted Synthesis of Benzoxazoles from *N*-(2-Hydroxyphenyl)carboxamides^[141]



Milder reaction conditions have been developed in a solid-supported approach toward 2-substituted benzoxazoles. Since the aforementioned protocols cannot be applied to solid-phase chemistry, the benzoxazole formation is carried out under Mitsunobu conditions with an excess of triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran at room temperature.^[144]

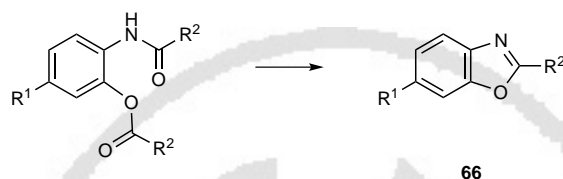
Various regioisomeric 2-substituted oxazolopyridines have been prepared by a similar method. The various *N*-(2-hydroxypyridyl)carboxamides are treated with triphenylphosphine, hexachloroethane, and triethylamine in dichloromethane at room temperature, which leads to the formation of oxazolopyridines in good yields (41–93%).^[145]

N-(2-Hydroxyphenyl)thiobenzamides can also cyclize in the presence of the oxidation reagent potassium superoxide to give 2-arylbenzoxazoles in high yields.^[146]

At high temperature, *N*-(2-acyloxyphenyl)carboxamides cyclize to benzoxazoles **66** under cleavage of the corresponding carboxylic acid.^[91] The temperature necessary for

the cyclization reaction can be reduced by the addition of dehydrating reagents. A very convenient method has been reported using 4-toluenesulfonic acid in refluxing benzene or xylenes (Scheme 48).^[147]

Scheme 48 Benzoxazoles from *N*-(2-Acyloxyphenyl)carboxamides^[91,147]



R ¹	R ²	Conditions	Yield (%)	Ref
H	Me	210 °C	84	[91]
H	Ph	TsOH, xylenes, reflux, 7 h	88	[147]
H	4-MeOC ₆ H ₄	TsOH, xylenes, reflux, 3 h	96	[147]
H	4-O ₂ NC ₆ H ₄	TsOH, xylenes, reflux, 72 h	85	[147]
NO ₂	4-MeOC ₆ H ₄	TsOH, xylenes, reflux, 3 h	98	[147]
H	Et	TsOH, benzene, reflux, 2 h	89	[147]
H	<i>t</i> -Bu	TsOH, xylenes, reflux, 3 h	74	[147]

The use of solid-supported 4-toluenesulfonic acid has been reported for this transformation under microwave irradiation.^[148]

2-(4-Fluorophenyl)benzoxazole (64, R¹ = R² = R³ = H; R⁴ = 4-FC₆H₄); Typical Procedure:^[138]
4-Fluorobenzoyl chloride (1.62 g, 10.3 mmol) was added dropwise to a soln of 2-aminophenol (1.12 g, 10.3 mmol) and Et₃N (1.04 g, 10.3 mmol) in dry THF (200 mL) at -42 °C (dry ice/MeCN bath) and then stirred for 6 h. The mixture was added to H₂O (500 mL), and the product was isolated by filtration and dried under vacuum to give the intermediate amide. The amide was heated in a sublimator at 200 °C together with 4-Å molecular sieves (4.6 g) under N₂ to give the title product as a light yellow crystalline solid; yield: 1.58 g (72%); mp 101 °C.

2-(2-Hydroxyphenyl)benzoxazole (65, R¹ = H; R² = 2-HOC₆H₄); Typical Procedure:^[141]
A mixture of 2-hydroxy-*N*-(2-hydroxyphenyl)benzamide (0.3 g, 1.3 mmol) and PPA (1 g) was heated to 150 °C for 20 min. The crude product was obtained from the resulting dark brown melt by addition of H₂O and concomitant scratching, and was purified by recrystallization (dil EtOH); yield: 0.2 g (69%); mp 125 °C.

2-(4-Methoxyphenyl)-6-nitrobenzoxazole (66, R¹ = NO₂; R² = 4-MeOC₆H₄);

Typical Procedure:^[147]

A suspension of 2-[(4-methoxybenzoyl)amino]-5-nitrophenyl 4-methoxybenzoate (133 mg, 0.31 mmol) and TsOH·H₂O (120 mg, 0.63 mmol) in xylenes (3.0 mL) was refluxed for 3 h. The mixture was allowed to cool, diluted with EtOAc, and washed with sat. aq NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated to give a tan solid; yield: 83.7 mg (98%); mp 208–210 °C.


for references see p 50

11.13.1.1.2.2.4 Method 4: Synthesis from 2-(Alkylidenamino)phenols

The oxidation of 2-(alkylidenamino)phenols **67** (obtained from 2-aminophenols and aldehydes) to give 2-substituted benzoxazoles **68** can be carried out with a wide range of different oxidation reagents such as 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (Scheme 49),^[149] dibenzoyl peroxide,^[150] *N*-bromosuccinimide,^[150] *N*-iodosuccinimide,^[151] (diacetoxyiodo)benzene,^[152,153] solid-supported (diacetoxyiodo)benzene,^[154] oxygen/Darco KB,^[155] manganese(III) acetate,^[156] nickel peroxide,^[157] dichlorobis(triphenylphosphine)ruthenium(II),^[115] silver(I) oxide,^[158] lead(IV) acetate,^[159,160] silica-supported pyridinium chlorochromate,^[161] and an iridium catalyst [$\text{Ir}(\text{Cp}^*)\text{I}_2$]₂.^[162]

A very mild method for the cyclization of 2-(alkylidenamino)phenols is the reaction with silver(I) oxide in dichloromethane. Via this method 2-aryl-, 2-(alk-1-enyl)-, and 2-alkylbenzoxazoles can be prepared (Scheme 49).^[158]

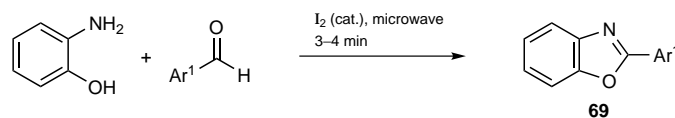
Scheme 49 Benzoxazoles by Oxidation of 2-(Arylidenamino)phenols Using 2,3-Dichloro-5,6-dicyanobenzo-1,4-quinone or Silver(I) Oxide^[149,158]



R ¹	R ²	R ³	Conditions	Yield (%)	Ref
H	H	Ph	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	93	[149]
H	H	3-pyridyl	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	74	[149]
H	H	4-MeOC ₆ H ₄	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	83	[149]
H	NO ₂	4-ClC ₆ H ₄	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	92	[149]
Me	H	2-thienyl	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	94	[149]
Cl	H	2-furyl	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	81	[149]
Cl	H	4-MeOC ₆ H ₄	DDQ, CH ₂ Cl ₂ , 25 °C, 0.5 h	82	[149]
H	H	Ph	Ag ₂ O, CH ₂ Cl ₂ , rt, 2–5 h	76	[158]
H	H	CH=CHPh	Ag ₂ O, CH ₂ Cl ₂ , rt, 2–5 h	87	[158]
H	H	<i>i</i> Pr	Ag ₂ O, CH ₂ Cl ₂ , rt, 2–5 h	54 ^a	[158]
H	H	<i>t</i> -Bu	Ag ₂ O, CH ₂ Cl ₂ , rt, overnight	57 ^a	[158]
H	H	CMe=CHEt	Ag ₂ O, CH ₂ Cl ₂ , rt, overnight	41 ^a	[158]

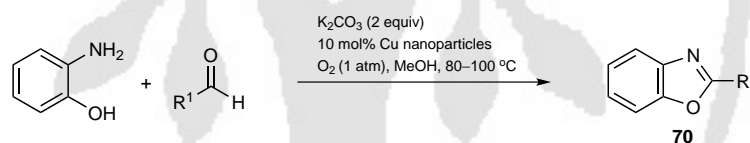
^a Yield over two steps, starting from 2-aminophenol.

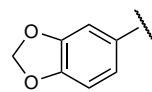
The reaction of 2-aminophenols and aldehydes in the presence of an oxidizing agent under microwave irradiation is very efficient. By using manganese(IV) oxide on silica^[163] or molecular iodine^[164] as catalyst, the corresponding benzoxazoles **69** can be formed within minutes in high yields (Scheme 50).

Scheme 50 Benzoxazoles from 2-Aminophenol and Aromatic Aldehydes under Microwave Conditions^[164]

Ar ¹	Time (min)	Yield (%)	mp (°C)	Ref
Ph	3	92	102–104	[164]
4-MeOC ₆ H ₄	4	65	103–105	[164]
2-HOC ₆ H ₄	3	82	119–121	[164]
4-BrC ₆ H ₄	3	93	156–157	[164]
2-ClC ₆ H ₄	3	85	128–129	[164]
4-ClC ₆ H ₄	3	95	147–149	[164]
4-Tol	3	71	115–116	[164]

Another method for the preparation of 2-arylbenzoxazoles uses copper nanoparticles and potassium carbonate in methanol as solvent (Scheme 51).^[165] The products **70** are formed at an oxygen pressure of 1 atm at 80–100 °C, usually in excellent yields.

Scheme 51 Benzoxazoles from 2-Aminophenol and Aromatic Aldehydes Using Copper Nanoparticles^[165]

R ¹	Time (h)	Yield (%)	Ref
Ph	3	90	[165]
4-ClC ₆ H ₄	4.7	87	[165]
4-MeOC ₆ H ₄	3.6	92	[165]
4-Tol	4.5	83	[165]
4-O ₂ NC ₆ H ₄	4.6	75	[165]
3,4,5-(MeO) ₃ C ₆ H ₂	1.5	95	[165]
(E)-CH=CHPh	3.2	86	[165]
	3.0	74	[165]
2-thienyl	4.8	69	[165]
2-furyl	5.0	71	[165]

for references see p 50

2-(4-Methoxyphenyl)benzoxazole (68, R¹ = R² = H; R³ = 4-MeOC₆H₄); Typical Procedure Using 2,3-Dichloro-5,6-dicyanobenzo-1,4-quinone:^[149]

To a soln of 2-aminophenol (0.109 g, 1.0 mmol) in MeOH (5 mL) was added 4-methoxybenzaldehyde (0.136 g, 1.0 mmol). The resulting mixture was heated at 45 °C for 12 h. After concentration under reduced pressure, the residue was dissolved in CH₂Cl₂ (10 mL) and DDQ (0.250 g, 1.1 mmol) was then added. After stirring at rt for 30 min, the resulting mixture was diluted with additional CH₂Cl₂ (10 mL) and washed sequentially with sat. Na₂CO₃ (2 × 10 mL) and brine (10 mL). The organic layer was dried (Na₂SO₄). After concentration, the residue was purified by flash column chromatography (EtOAc/hexane 1:9); yield: 0.187 g (83%).

2-Arylbenzoxazoles 69; General Procedure:^[164]

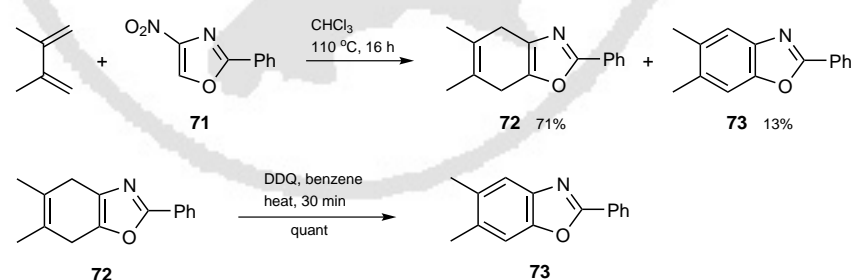
A mixture of 2-aminophenol (109 mg, 1 mmol), aromatic aldehyde (1 mmol), and a catalytic amount of I₂ (127 mg, 0.5 mmol) was placed in a 20-mL Teflon flask and subjected to microwave irradiation for 3–4 min. The mixture was chromatographed (silica gel, petroleum ether/EtOAc 4:1).

2-Arylbenzoxazoles 70; General Procedure:^[165]

A 50-mL round-bottomed flask was charged with 2-aminophenol (109 mg, 1 mmol), the aromatic or heteroaromatic aldehyde (1 mmol), K₂CO₃ (0.28 g, 2 mmol), and Cu nanoparticles (10 mol%; 16 ± 2 nm in size), followed by MeOH (10 mL). The resulting soln was refluxed at 100 °C for the appropriate time. The extent of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with distilled H₂O (2 × 10 mL) and the 2-arylbenzoxazole was extracted with EtOAc (2 × 15 mL). The organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure. The crude product was subjected to purification by column chromatography (silica gel, EtOAc/petroleum ether 1:4).

11.13.1.2 By Annulation to the Heterocyclic Ring

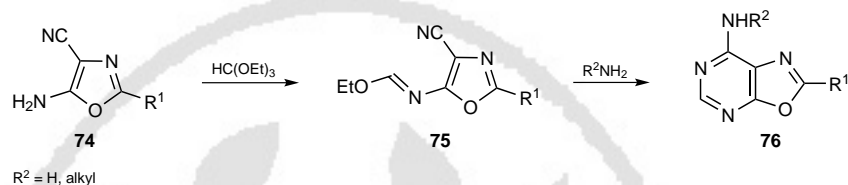
When 4-nitro-2-phenyloxazole (**71**) is reacted with an excess of 2,3-dimethylbuta-1,3-diene in chloroform at 110 °C a mixture of 5,6-dimethyl-2-phenylbenzoxazole (**72**) (13%) and 5,6-dimethyl-2-phenyl-4,7-dihydrobenzoxazole (**73**) (71%) is obtained (Scheme 52).^[166] The latter can be transformed quantitatively into the former by heating with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone in benzene.

Scheme 52 Cyclization of a 4-Nitroxazole and a Diene To Give a Benzoxazole^[166]

Besides formation of a carbocyclic 6-membered ring, oxazolopyrimidines and oxazolopyridines have also been prepared. Various methods have been applied for the synthesis of the 6-membered heterocycle. Starting from 5-aminoxazole-4-carbonitriles **74**, oxazo[5,4-*d*]pyrimidin-7-amines **76** are prepared via reaction with ortho esters (Scheme 53).^[95] An intermediate of the transformation is 5-[(ethoxymethylene)amino]oxazole-4-

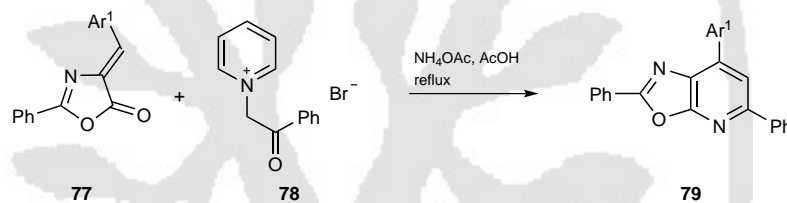
carbonitrile **75**, which can be isolated and then further reacted with ammonia or amines to give the corresponding oxazolo[5,4-*d*]pyrimidin-7-amines **76**.^[167,168] Instead of the nitriles, 5-aminoxazole-4-carboxamides can also be used as starting materials, and lead to oxazolo[5,4-*d*]pyrimidin-7-ols.^[169]

Scheme 53 Oxazolo[5,4-*d*]pyrimidines from 5-Aminooxazole-4-carbonitriles^[95,167,168]



2,5,7-Triaryloxazolo[5,4-*b*]pyridines **79** are synthesized from 4-benzylidene-2-phenyloxazol-5(4*H*)-ones **77** via reaction with pyridinium bromide **78** and ammonium acetate in glacial acetic acid (Scheme 54).^[170]

Scheme 54 2,5,7-Triaryloxazolo[5,4-*b*]pyridines from 4-Benzylidene-2-phenyloxazol-5(4*H*)-ones^[170]



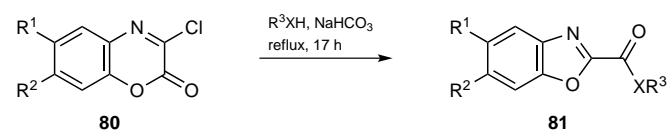
Ar ¹	Yield (%)	mp (°C)	Ref
Ph	50	262	[170]
2-O ₂ NC ₆ H ₄	65	230	[170]
4-ClC ₆ H ₄	70	158–159	[170]
4-MeOC ₆ H ₄	65	267	[170]

11.13.2 Synthesis by Ring Transformation

11.13.2.1 Ring Contraction of 1,4-Benzoxazines

3-Chloro-2*H*-1,4-benzoxazin-2-ones **80** are transformed into benzoxazole derivatives **81** by heating with alcohols, phenols, or thiols in the presence of sodium hydrogen carbonate. By this method, various alkyl or phenyl benzoxazole-2-carboxylates or -thiocarboxylates can be obtained (Scheme 55).^[171]

for references see p 50

Scheme 55 Benzoxazoles from 3-Chloro-2*H*-1,4-benzoxazin-2-ones^[171]

R ¹	R ²	XR ³	Yield (%)	mp (°C)	Ref
H	H	SBu	64 ^a	66–68	[171]
H	H	OCH ₂ C≡CH	70	73–75	[171]
H	H	OPh	60	145–148	[171]
H	H	OMe	87	99	[171]
Ph	H	OMe	61	131–133	[171]
H	H	OEt	60	101	[171]
Cl	H	OEt	74	81–82	[171]
Me	Me	OMe	41	175	[171]
Me	H	OMe	78	96–98	[171]

^a Conditions: THF, reflux, 10 h.

3-Aryl-2*H*-1,4-benzoxazin-2-ones can be transformed into 2-arylbenzoxazoles in the presence of potassium hydroxide in methanol.^[172]

Methyl Benzoxazole-2-carboxylate (81, R¹ = R² = H; XR³ = OMe); Typical Procedure:^[171]

A mixture of 3-chloro-2*H*-1,4-benzoxazin-2-one (**80**, R¹ = R² = H; 54.5 g, 0.3 mol), NaHCO₃ (25.2 g, 0.3 mol), and MeOH (500 mL) was stirred under reflux for 17 h. The mixture was filtered hot and the product that crystallized upon cooling was collected by suction filtration. The filtrate was concentrated to obtain a second product fraction; yield: 46.0 g (87%); mp 99°C (benzene).

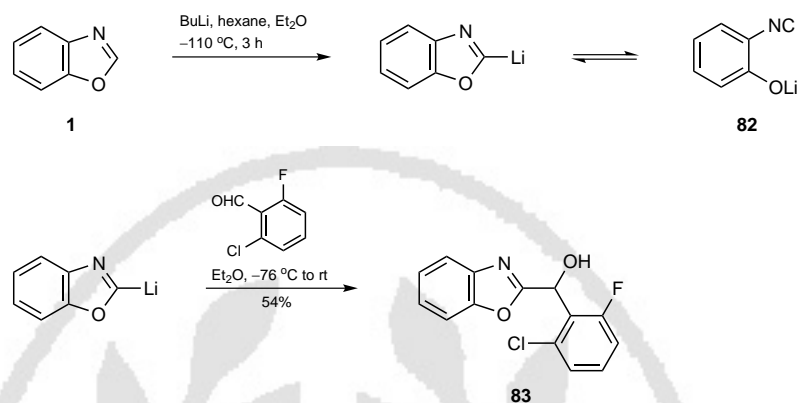
11.13.3 Synthesis by Substituent Modification

11.13.3.1 Substitution of Existing Substituents

11.13.3.1.1 Of Hydrogen

11.13.3.1.1.1 Method 1: Lithiation

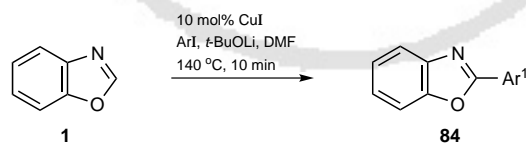
2-Lithiobenzoxazole is obtained from benzoxazole (**1**) via lithiation with butyllithium at -110°C in diethyl ether (Scheme 56). It is believed that it exists in an equilibrium with lithium 2-isocyanophenolate (**82**) since it gives 2-(trimethylstannyl)benzoxazole upon reaction with chlorotrimethylstannane, but (2-isocyanophenoxy)trimethylsilane with chlorotrimethylsilane.^[173] The lithiated intermediate can also be quenched with suitable electrophiles, such as benzaldehyde derivatives, e.g. to give benzoxazole **83**.^[74]

Scheme 56 Lithiation of Benzoxazole^[74,173]**Benzoxazol-2-yl(2-chloro-6-fluorophenyl)methanol (83); Typical Procedure:**^[74]

To benzoxazole (**1**; 10 g, 84 mmol) in dry Et₂O (200 mL) at -76 °C under N₂ was added 1.55 M BuLi (54 mL, 84 mmol, 1 equiv) in hexane, dropwise, over 15 min, and the soln was stirred for 30 min at -76 °C. 2-Chloro-6-fluorobenzaldehyde (14.6 g, 92 mmol, 1.1 equiv) in Et₂O (100 mL) was added dropwise over 30 min. The mixture was stirred for 2 h at -76 °C. The mixture was allowed to warm to rt and stirred over 15 h. A 7.5% aq soln of NH₄Cl (250 mL) was added. The soln was extracted with Et₂O (3 × 200 mL), and the ethereal extract was washed with brine, dried (Na₂SO₄), and concentrated to give a yellow solid. The solid was recrystallized (hexane/EtOAc); yield: 12.5 g (54%); mp 146–147 °C.

11.13.3.1.1.2 Method 2: Arylation

Benzoxazoles can be directly arylated at the 2-position via transition-metal-catalyzed C–H activation. Several protocols have been reported using different types of aryl donors such as aryl iodides,^[174–176] aryl bromides,^[174] aryl chlorides,^[174] aryl trifluoromethanesulfonates,^[177] and aryl 4-toluenesulfonates.^[178] Palladium^[174,177,178] and copper^[175,176] have proved to be the most efficient metals for this type of transformation. Oxazolo[4,5-*b*]pyridine can be arylated under very mild conditions [30 °C, Pd(OAc)₂, Ph₃P, aryl halide] and yields between 33 and 74% are obtained.^[174] A very high yielding method for the arylation of benzoxazole (**1**) uses simple copper(I) iodide as catalyst, lithium *tert*-butoxide as base, and aryl iodides as the aryl donor (Scheme 57).^[176] Usually, yields of substituted benzoxazoles **84** of >80% are obtained.

Scheme 57 Direct Arylation of Benzoxazoles at the 2-Position^[176]

Ar ¹	Yield (%)	Ref
4-F ₃ CC ₆ H ₄	91	[176]
4-FC ₆ H ₄	90	[176]
4-MeOC ₆ H ₄	80	[176]

for references see p 50

Ar ¹	Yield (%)	Ref
3,5-Me ₂ C ₆ H ₃	85	[176]
2-Tol	91	[176]
Mes	55	[176]
1-naphthyl	90	[176]
2-pyridyl	89	[176]

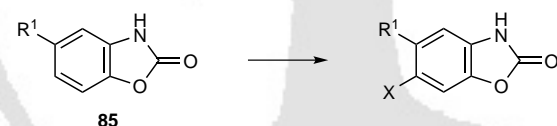
2-Arylbenzoxazoles 84; General Procedure:^[176]

A 1-dram vial equipped with a magnetic stirrer bar was charged with the benzoxazole (1.0 mmol), iodoarene (3.0 equiv), and DMF (1 mL). The vial was flushed with argon, capped, and placed inside a glovebox. To this mixture was added CuI (10 mol%) and *t*-BuOLi (2.0 equiv). The sealed vial was taken out of the glovebox, stirred at rt for 5 min, and placed in a preheated oil bath (140 °C) for 10 min. The mixture was allowed to cool to rt and diluted with EtOAc (50 mL). The resulting soln was washed with brine (3 × 15 mL), dried (MgSO₄), and concentrated under reduced pressure to a volume of about 2 mL. The mixture containing the product was subjected to flash chromatography (silica gel, hexanes followed by an appropriate solvent). After concentrating the fractions containing the product, the residue was dried under reduced pressure.

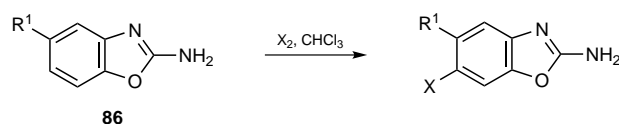
11.13.3.1.1.3 Method 3: Halogenation

The chlorination and bromination of benzoxazol-2(3*H*)-ones **85**,^[30,179] 2-(methylsulfonyl)benzoxazoles,^[32] and benzoxazol-2-amines **86**^[36] proceed at the 6-position. Halogenations are carried out with chlorine in chloroform,^[36] sulfuryl chloride in acetic acid,^[30,179] or bromine in chloroform (Scheme 58).^[32,36]

Scheme 58 Halogenation of Benzoxazol-2(3*H*)-ones and Benzoxazol-2-amines^[30,36,179]



R ¹	X	Conditions	Yield (%)	mp (°C)	Ref
H	Cl	Cl ₂ , CHCl ₃ , 10–15 °C, 1–2 h	60–80	195–196	[36]
H	Cl	SO ₂ Cl ₂ , AcOH, 20 °C, 12 h	81	194–195	[30]
Cl	Cl	SO ₂ Cl ₂ , AcOH, 20 °C, 12 h, then 90 °C, 1 h	quant	202–203	[179]
Cl	Br	Br ₂ , CHCl ₃ , 10–15 °C, 1–2 h	60–80	204–205	[36]

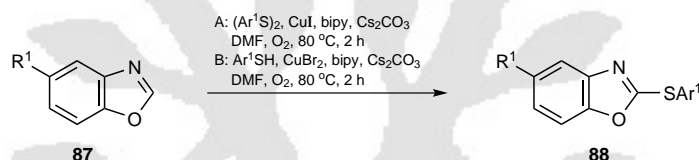


R ¹	X	Yield (%)	Ref
H	Cl	60–80	[36]
Cl	Br	60–80	[36]

11.13.3.1.1.4

**Method 4:
Sulfanylation**

The copper-catalyzed direct sulfanylation of benzoxazoles **87** at the 2-position using diaryl disulfides or arenethiols to give 2-(arylsulfanyl)benzoxazoles **88** has been reported (Scheme 59).^[180]

Scheme 59 Copper-Catalyzed Sulfanylation of Benzoxazoles^[180]

R ¹	Ar ¹	Method	Yield (%)	Ref
H	4-MeOC ₆ H ₄	A	71	[180]
H	2-MeOC ₆ H ₄	A	34	[180]
H	Ph	A	81	[180]
Me	Ph	A	49	[180]
H	4-Tol	A	64	[180]
H	Ph	B	72	[180]
H	4-Tol	B	62	[180]
H	4-ClC ₆ H ₄	B	38	[180]

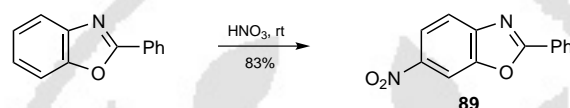
2-(Phenylsulfanyl)benzoxazole (88, R¹ = H; Ar¹ = Ph), Typical Procedure:^[180]

Under O₂ (balloon), (PhS)₂ (55 mg, 0.25 mmol), CuI (9.5 mg, 0.05 mmol), bipy (7.8 mg, 0.05 mmol), and Cs₂CO₃ (326 mg, 1.0 mmol) were placed in a Schlenk tube containing a stirrer bar, and a soln of benzoxazole **87** (R¹ = H; 71.5 mg, 0.6 mmol) in DMF (3.0 mL) was then added. The resulting mixture was heated at 80 °C for 2 h. H₂O (20 mL) was added, and the mixture was then extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (MgSO₄), and filtered. GC/MS analysis of the soln showed the presence of the title product; the yield was determined using biphenyl as an internal standard. Evaporation of the solvent left a residue, which was subjected to preparative TLC (silica gel, hexane/EtOAc 8:1); yield: 81%.

for references see p 50

**11.13.3.1.1.5 Method 5:
Nitration**

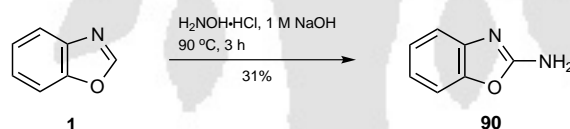
Nitration of various benzoxazole derivatives takes place preferentially at the 6-position,^[181] such as in the preparation of 6-nitro-2-phenylbenzoxazole (**89**) (Scheme 60).^[159] Hydrolysis was reported during the nitration of benzoxazole but the obtained nitroformanilides can be recycled.^[8]

Scheme 60 Nitration of 2-Phenylbenzoxazole^[159]**6-Nitro-2-phenylbenzoxazole (89); Typical Procedure:**^[159]

2-Phenylbenzoxazole (6.0 g, 30.7 mmol) was added slowly (10 min) to HNO₃ (45 mL, *d* 1.5) and the mixture was set aside for 30 min at rt. The nitration mixture was poured into H₂O (150 mL), and the pale yellow precipitate was collected by filtration. Crystallization (AcOH) gave yellow needles; yield: 6.1 g (83%); mp 178–180 °C.

**11.13.3.1.1.6 Method 6:
Amination**

Benzoxazol-2-amine (**90**) is obtained in low yield upon heating of benzoxazole (**1**) with hydroxylamine hydrochloride in sodium hydroxide solution (Scheme 61).^[103]

Scheme 61 Amination of Benzoxazole at the 2-Position^[103]**11.13.3.1.2 Of Metals****11.13.3.1.2.1 Method 1:
Cross-Coupling Reactions**

Benzoxazoles have only been rarely applied to transition-metal-catalyzed cross-coupling reactions. Examples for Negishi, Liebeskind–Srogl, and Stille cross couplings are shown in Scheme 62.

Scheme 62 Cross-Coupling Reactions of Benzoxazoles^[41,182–185]

R ¹	R ²	X	Ar ¹	Y	Conditions	Yield (%)	Ref
H	H	ZnCl	1-naphthyl	OTf	PdCl ₂ (PPh ₃) ₂ , THF, reflux, 2 h	78	[182]
H	H	ZnCl	3-MsC ₆ H ₄	Br	Pd(PPh ₃) ₄ , THF	67	[183]
H	H	SCH ₂ CONH ₂	2,5-(MeO) ₂ C ₆ H ₃	B(OH) ₂	Pd ₂ (dba) ₃ , TFP, CuTC, ^a THF, 50 °C, 18 h	74	[184]
H	H	SnBu ₃	Ph	Br	PdCl ₂ (PPh ₃) ₂ , xylene, 120 °C	75	[185]
CO ₂ Me	Me	SMe		SnMe ₃	Pd(PPh ₃) ₄ , CuBr, THF, reflux, 1.5 h	83	[41]

^a TFP = tri-2-furylphosphine; CuTC = copper(I) thiophene-2-carboxylate.

11.13.3.1.3 Of Halogen

11.13.3.1.3.1 Method 1: Cyanation of 2-Chlorobenzoxazoles

2-Chlorobenzoxazoles **91** react generally with nucleophiles to give 2-substituted benzoxazoles. With sodium cyanide in dimethyl sulfoxide^[186] or with potassium cyanide in dimethylformamide^[171] the corresponding benzoxazole-2-carbonitriles **92** are obtained in better yields at room temperature than at elevated temperatures (Scheme 63).^[187]

Scheme 63 Cyanation of 2-Chlorobenzoxazoles^[171,186]

R ¹	Conditions	Yield (%)	mp (°C)	Ref
H	NaCN, DMSO, iPrOH	58	102–104	[186]
Me	NaCN, DMSO, iPrOH	68	75–77	[186]
Cl	NaCN, DMSO, iPrOH	50	94–96	[186]
H	KCN, DMF, 10 °C, 4 h	63	– ^a	[171]

^a mp not reported.

for references see p 50

Benzoxazole-2-carbonitriles 92; General Procedure:^[186]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

To a suspension of powdered and dry NaCN (7.8 g, 0.16 mol) in DMSO (180 mL) and iPrOH (20 mL), 2-chlorobenzoxazoles (0.13 mol) were added dropwise while cooling (18–20 °C) and stirring (solids were dissolved in DMF). An intense blue-purple color was observed, which immediately became dark brown. After 3 h of stirring at 18–20 °C, the mixture was poured into ice water and extracted with benzene (**CAUTION: carcinogen**). The benzene layer was concentrated to about 50 mL and then chromatographed. The product was finally recrystallized (MeOH/H₂O).

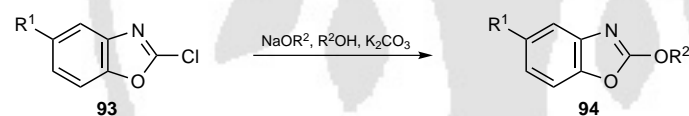
**11.13.3.1.3.2 Method 2:
Fluorination of 2-Chlorobenzoxazoles**

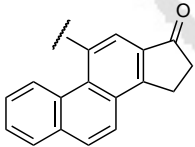
2-Fluorobenzoxazole is prepared from 2-chlorobenzoxazole via reaction with dry potassium fluoride in the presence of 18-crown-6 under dry conditions at 110–120 °C. Due to its high reactivity, the compound is best stored as a solution in petroleum ether at –10 °C.^[188]

**11.13.3.1.3.3 Method 3:
Alkoxy- or Aryloxylation of 2-Halobenzoxazoles**

2-Chlorobenzoxazoles **93** react with sodium alkoxides or phenolates to give the corresponding 2-alkoxy-^[36,189] or 2-(aryloxy)benzoxazoles **94** (Scheme 64).^[190,191] In the course of a total synthesis, a 2-(aryloxy)benzoxazole has been obtained by reaction with a phenol in the presence of potassium carbonate in acetone or acetonitrile.^[192] A series of 2-alkoxybenzoxazoles have been synthesized starting from 2-fluorobenzoxazole.^[188]

Scheme 64 Alkoxy- and Aryloxylation of 2-Chlorobenzoxazoles^[36,189,191]



R ¹	R ²	Conditions	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
H	CH ₂ CH=CH ₂	H ₂ C=CHCH ₂ ONa, H ₂ C=CHCH ₂ OH, 0–20 °C, 10 h Na, toluene, reflux, 70 h	80	71–72/0.5–0.6	[189]
H		Na, toluene, reflux, 70 h	31	237–238	[191]
Cl	Me	Na, MeOH, cold	96	80.5–81.5	[36]

**11.13.3.1.3.4 Method 4:
Amination of 2-Chlorobenzoxazoles**

2-Hydrazino- or 2-aminobenzoxazoles can be prepared from 2-chlorobenzoxazoles by reaction with hydrazine hydrate, ammonia, or amines.^[36] Benzoxazol-2-amine is either obtained via reaction with concentrated ammonia^[193] or with ammonia in methanol. *N*-Al-

aryl- and *N*-arylbenzoxazol-2-amines **95** can be formed in a solvent-free reaction of 2-chlorobenzoxazoles and amines.^[193,194] Alternatively, the reaction is carried out in aqueous solution,^[195,196] refluxing benzene or toluene,^[197,198] 1,1,2,2-tetrachloroethane,^[199] or acetonitrile/triethylamine (Scheme 65).^[45] Dimethylformamide is not suitable since *N,N*-dimethylbenzoxazol-2-amine is formed after prolonged heating.^[200]

Scheme 65 Amination of 2-Chlorobenzoxazoles^[45,193–195,197]



R ¹	R ²	R ³	R ⁴	Conditions	Yield (%)	Ref
Cl	H	H	CH ₂ C≡CH	Et ₃ N, MeCN, reflux, 4 h	63	[45]
<i>t</i> -Bu	Cl	H	H	NH ₄ OH, rt, 1 h	85	[193]
<i>t</i> -Bu	Cl	H	Bn	120 °C, 15 min	90	[193]
H	H	H	2-naphthyl	130–140 °C, 4 h	62	[194]
Cl	H	H	Me	H ₂ O, rt, 1 h	62	[195]
H	H	Et	Et	benzene, 24 h, reflux	83	[197]

11.13.3.1.4 Of Oxygen

11.13.3.1.4.1 Method 1: Thionation of Benzoxazol-2(3*H*)-ones

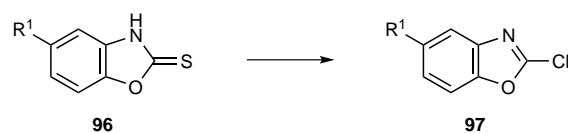
Benzoxazol-2(3*H*)-ones are transformed by Lawesson's reagent in refluxing xylene into benzoxazole-2(3*H*)-thiones (70–90% yield).^[201]

11.13.3.1.5 Of Sulfur

11.13.3.1.5.1 Method 1: Chlorination of Benzoxazole-2(3*H*)-thiones

2-Chlorobenzoxazoles **97** are often prepared via chlorination of benzoxazole-2(3*H*)-thiones **96**. Gaseous chlorine is bubbled through a chloroform solution of the substrate.^[187,195] Alternatively, the transformation can be carried out using phosphorus pentachloride at 130–170 °C^[193,202] or in refluxing benzene, with phosgene in chloroform/dimethylformamide,^[199] with phosphorus pentachloride/phosphoryl chloride,^[45] or thionyl chloride/dimethylformamide (Scheme 66).^[45]

for references see p 50

Scheme 66 2-Chlorobenzoxazoles from Benzoxazole-2(3H)-thiones^[45,195]

R ¹	Conditions	Yield (%)	Ref
Cl	Cl ₂ , CHCl ₃ , 10–20 °C	82	[195]
Ms	SOCl ₂ , DMF, 65–70 °C, 30 min	100	[45]
OMe	SOCl ₂ , DMF, 65–70 °C, 30 min	97	[45]
Me	PCl ₅ , POCl ₃	74	[45]

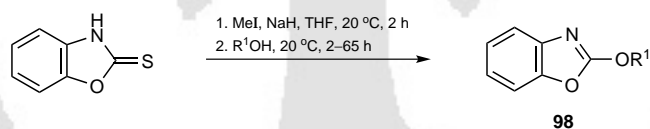
2,5-Dichlorobenzoxazole (97, R¹ = Cl); Typical Procedure:^[195]

A suspension of 5-chlorobenzoxazole-2(3H)-thione (**96**, R¹ = Cl; 100 g, 0.54 mol) in dry, EtOH-free CHCl₃ (800 mL) was saturated with dry Cl₂ (passed through concd H₂SO₄) at 10–20 °C. The soln was then poured into ice water (4 L). The organic phase was removed and washed with 2% NaOH soln and H₂O, dried (CaCl₂), and filtered, and the product was isolated by distillation; yield: 84.3 g (82%); bp 130–133 °C/25 Torr; mp 44–46 °C.

11.13.3.1.5.2

Method 2:**Alkoxylation of Benzoxazole-2(3H)-thiones**

For the synthesis of 2-alkoxybenzoxazoles **98**, alcohols are added slowly to a reaction mixture of benzoxazole-2(3H)-thione, sodium hydride, and iodomethane in tetrahydrofuran at room temperature (Scheme 67).^[203]

Scheme 67 2-Alkoxybenzoxazoles from Benzoxazole-2(3H)-thione via S-Alkylation^[203]

R ¹	Time (h)	Yield (%)	mp (°C) or bp (°C/Torr)	Ref
iPr	15	74	122–127/6.75	[203]
<i>t</i> -Bu	65	63	107–109/9.75	[203]
CHMePh	15	76	130–140/2.25	[203]
CHPh ₂	37	63	104–106 °C	[203]

2-Alkoxybenzoxazoles 98; General Procedure:^[203]

CAUTION: Inhalation, ingestion, or skin absorption of iodomethane can be fatal.

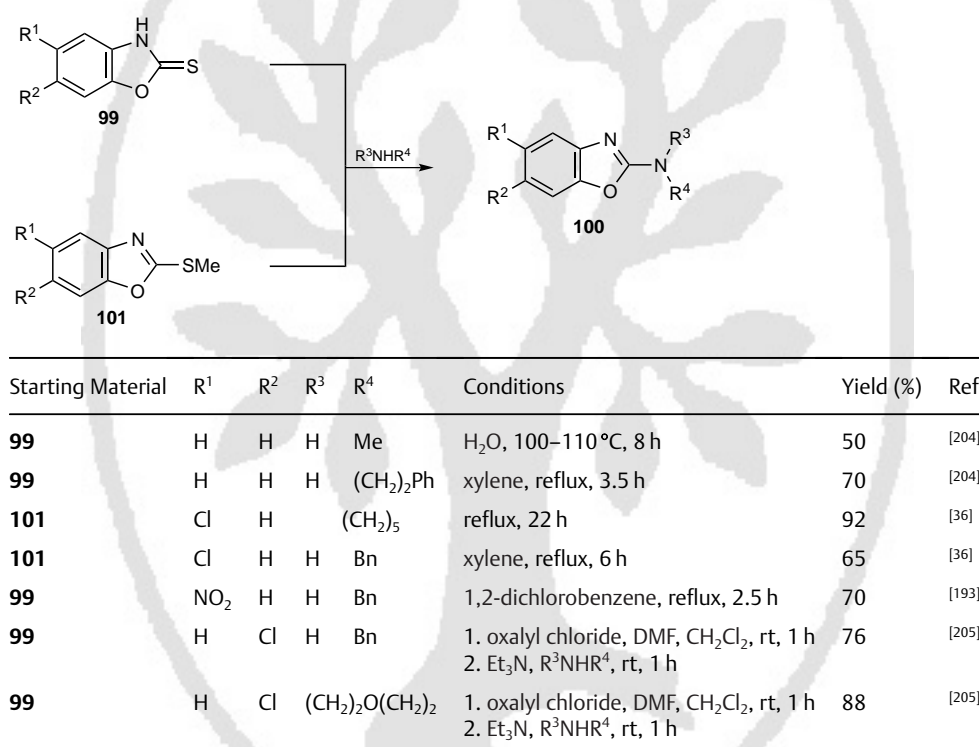
To a cooled soln of benzoxazole-2(3H)-thione (1.51 g, 10 mmol) and MeI (2.84 g, 20 mmol) in THF (100 mL), 50% NaH in mineral oil (0.96 g, 20 mmol) was added. The suspension was stirred for 2 h at 20 °C and then the alcohol (10 mmol) was added slowly; the mixture was stirred at 20 °C for 2–65 h. The mixture was then poured into ice water and extracted

with EtOAc, the organic layer was washed with H₂O and dried, and the solvent was evaporated. The crude product was purified either via distillation or recrystallization.

11.13.3.1.5.3 Method 3: Amination of Benzoxazole-2(3H)-thiones

Benzoxazol-2-amines **100** can be readily prepared from benzoxazole-2(3H)-thiones **99** by heating with amines either neat ($\leq 95\%$ yield),^[204] in xylene ($\leq 80\%$),^[36,204] or in 1,2-dichlorobenzene ($\leq 70\%$).^[193,199] In a modified procedure, benzoxazole-2(3H)-thiones **99** are reacted with oxalyl chloride in dimethylformamide and the obtained 2-chloro intermediates lead to N-substituted benzoxazol-2-amines **100** upon reaction with various amines.^[205] Similarly, the transformation can be achieved starting from the 2-(methylsulfanyl) product **101** (Scheme 68).^[36,193]

Scheme 68 Amination of Benzoxazole-2(3H)-thiones and 2-(Methylsulfanyl)benzoxazoles^[36,193,204,205]

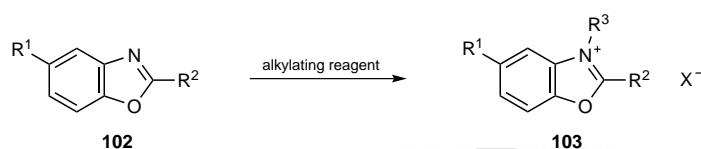


11.13.3.2 Addition Reactions

11.13.3.2.1 Method 1: Synthesis of 3-Alkylbenzoxazolium Salts

2-Alkylbenzoxazoles **102** are converted into the corresponding 2,3-dialkylbenzoxazolium salts **103** by alkylation reagents such as iodomethane,^[92] trialkyloxonium tetrafluoroborates,^[206,207] dialkyl sulfates,^[52] methyl 4-toluenesulfonate,^[65] or methyl vinyl ketone.^[66] 2-(Methylsulfanyl)benzoxazole can also be alkylated by this method (Scheme 69).^[206,208] 2-Pyridylbenzoxazoles on the other hand are alkylated at the pyridine nitrogen.^[209]

for references see p 50

Scheme 69 N-Alkylation of Benzoxazoles^[65,66,92,208]

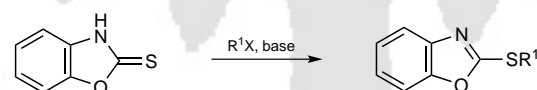
R ¹	R ²	R ³	X	Conditions	Yield (%)	mp (°C)	Ref
H	Me	Me	I	MeI, 100 °C, 8 h	89	196–198	[92]
H	(CH ₂) ₁₄ Me	Me	OTs	MeOTs, 130 °C, 1 h	90	112	[65]
H	SMe	Me	OTs	1. MeOTs, 140–150 °C, 30 min 2. H ₂ NNHCHO, EtOH, reflux	60 ^a	241–243	[208]
Ph	Bn•HBr	(CH ₂) ₂ Ac	Br	H ₂ C=CHAc, MeCN, 20 °C, 40 min	40	106–108	[66]

^a R² = NHNH₂ in product.

11.13.3.3 Modification of Substituents

11.13.3.3.1 Method 1: S-Alkylation of Benzoxazole-2(3H)-thiones

The alkylation or arylation of benzoxazole-2(3H)-thiones with alkyl or activated aryl halides, dimethyl sulfate,^[36,46,47] or diazomethane^[7,33,35] takes place preferentially at the S-atom (Scheme 70). In most cases, benzoxazole-2(3H)-thiones are reacted with alkyl halides^[41–43,48,94,210–213] or reactive aryl halides^[214,215] in the presence of a base. In contrast, acylations occur at the ring nitrogen.^[7,46]

Scheme 70 S-Alkylation of Benzoxazole-2(3H)-thione^[211–213]

R ¹	X	Base	Conditions	Yield (%)	Ref
		Et ₃ N (2 equiv)	CH ₂ Cl ₂ , 45 °C, 30 min		
	Br	Et ₃ N (2 equiv)	CH ₂ Cl ₂ , 45 °C, 30 min	96 ^a	[213]
Bn	Cl	Et ₃ N (2 equiv)	CH ₂ Cl ₂ , 45 °C, 2 h	70 ^a	[213]
(CH ₂) ₆ Me	Br	Et ₃ N (2 equiv)	CH ₂ Cl ₂ , 45 °C, 16 h	83	[213]
Cy	Br	Et ₃ N (0.66 equiv)	DMF, 80 °C, 22 h	45	[213]
CH ₂ Cl	Br	KOH	TEBAB (cat.) DMF, rt, 2 h	80	[211]
	Br	K ₂ CO ₃	DMF, rt, 2 h	44 ^b	[212]

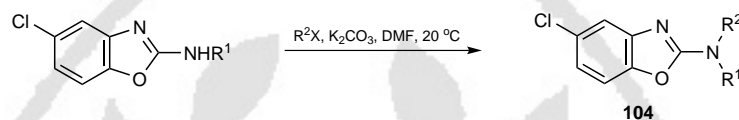
^a Yield of crude product.

^b Yield over two steps, starting from 2-(2-hydroxyethyl)benzyl alcohol.

11.13.3.3.2 **Method 2:**
N-Alkylation of Benzoxazol-2-amines

Alkylation reagents (e.g., MeI,^[32,195,216] Me₂SO₄,^[217] alkyl halides^[218]) react with benzoxazol-2-amines at the ring nitrogen when no base is added. In the presence of potassium carbonate in dimethylformamide at 20 °C, alkylation takes place at the exocyclic nitrogen, e.g. to give *N,N*-dialkyl-5-chlorobenzoxazol-2-amines **104** (yields ~90%) (Scheme 71).^[218]

Scheme 71 N-Alkylation of Benzoxazol-2-amines^[218]



for references see p 50

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