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The *para*-Toluenesulfonic Acid-Promoted Synthesis of 2-Substituted Benzoxazoles and Benzimidazoles from Diacylated Precursors.

Mark R. DeLuca and Sean M. Kerwin*

Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712-1074 USA

Dedicated to Professor Clayton H. Heathcock on the occasion of his 60th birthday

Abstract: The synthesis of benzoxazoles and benzimidazoles is accomplished by treating *N,O*-diacylated 2-aminophenols or *N,N'*-diacylated 1,2-phenylenediamines with *p*-toluenesulfonic acid under reflux in xylenes or toluene. These reactions are operationally simple and proceed in excellent yield.
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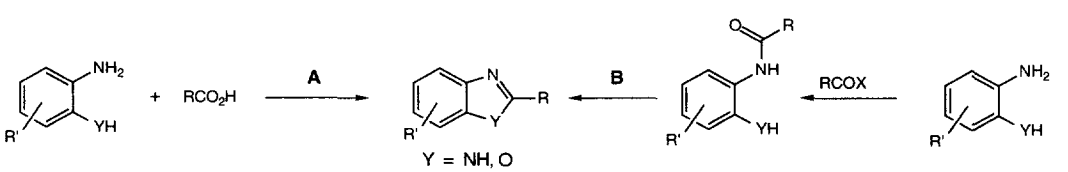
2-Aryl- and 2-alkyl-substituted benzoxazoles and benzimidazoles have received a considerable amount of attention in diverse areas of chemistry.[1-5] Synthetic routes that are common to the 2-substituted benzimidazoles and benzoxazoles typically involve direct coupling of a carboxylic acid or carboxylic acid derivative with an appropriate 1,2-phenylenediamine or 2-aminophenol under the influence of a strong acid at high temperature to afford 2-substituted benzimidazoles[6] or benzoxazoles,[7] respectively (Scheme 1, path A). Alternatively, a two-step procedure is used in which an appropriate 1,2-phenylenediamine or 2-aminophenol is treated with one equivalent of an acid chloride, and the resulting mono-acylated 1,2-phenylenediamine[8] or 2-aminophenol[9] derivative is then treated under a variety of conditions to effect cyclodehydration (Scheme 1, path B).



Scheme 1.

Much less common are routes to 2-substituted benzimidazoles and benzoxazoles that involve diacylated 1,2-phenylenediamine or 2-aminophenol precursors (equation 1). These diacylated materials are often more easily obtained than the mono-acylated counterparts, particularly in the case of electron rich 1,2-phenylenediamines.[10,11] Additionally, when the acylation reaction is forced to completion by the addition of a large excess of acid chloride or activated carboxylic acid reagent, as is often the case in solid-phase synthesis,[12] formation of the diacylated compounds is usually unavoidable.

Conversion of diacylated 1,2-phenylenediamines into the corresponding benzimidazoles has previously been accomplished by heating in aqueous acid (Phillips method),[13] or by pyrolysis at 200-350 °C.[14,15]

Although these methods suffice for the preparation of many benzimidazoles, the yields are sometimes quite poor,[10] and in some cases these methods fail,[16] presumably due to the rather harsh conditions involved.

(equation 1)

A few reports of pyrolytic methods for the direct conversion of diacylated 2-aminophenols to 2-substituted benzoxazoles (equation 1, Y = O) have appeared in the literature.[15,17] These pyrolytic conditions can also result in the formation of side products arising from Fries rearrangement of the starting material.[17] Conditions typically used for the direct synthesis (Scheme 1, path A, Y = O) have been found ineffective in converting diacylated 2-aminophenols to 2-substituted benzoxazoles, either due to very low yields[18] or the production of mixtures of products arising from Friedel-Crafts acylation as well as cyclodehydration reactions.[19]

In this paper, we report the conversion of diacylated 1,2-phenylenediamines and 2-aminophenols to benzimidazoles and benzoxazoles by the action of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing xylene. We have found that this procedure is operationally simple and produces benzimidazoles and benzoxazoles in yields comparable to, or better than, other methods.

Synthesis of Benzoxazoles from *N,O*-Diacylated 2-Aminophenols

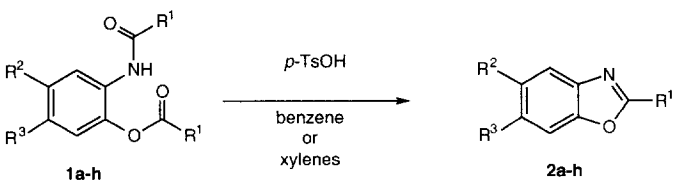
Although the synthesis of benzoxazoles from diacylated 2-aminophenols under acidic aqueous conditions is precluded by the lability of the benzoxazole nucleus to hydrolysis, we reasoned that non-aqueous acidic conditions might be employed to effect this conversion. We examined the conversion of diacylated aminophenols to benzoxazoles under the influence of a number of acids in aromatic hydrocarbon solvents. We found that *p*-TsOH in refluxing benzene,[20] toluene, or xylenes can be used to cleanly produce a variety of benzoxazoles in excellent yields. We studied the effect of various reaction condition parameters on the rate of conversion of *N*-(2-benzoyloxyphenyl)benzamide (**1a**) to 2-phenylbenzoxazole (**2a**), using HPLC to follow the course of the reactions. The reaction is first order in both **1a** and *p*-TsOH. The amount of water initially present in the reaction mixture has no significant effect on the rate of the reaction; reactions run in water-saturated xylenes proceed at the same rate as similar reactions run with dry xylenes with azeotropic removal of any water formed during the reaction.

A number of benzoxazoles were synthesized using a general procedure that involved heating under reflux a mixture consisting of the appropriate *N,O*-diacylated 2-aminophenol derivative **1**, *p*-TsOH (0.2 M), and xylenes or benzene[20] (Table 1). The conversion to benzoxazole was typically complete in 2 to 24 hours, as evidenced by tlc. After the reaction was complete, the acid by-products were removed by washing the

reaction mixture with a sodium bicarbonate solution, and the benzoxazole was isolated as pure material by evaporation of the solvent.

The reaction appears to be general. Various 2-arylbenzoxazoles can be prepared in high yields, although the nature of the substituents on the benzoyl groups of the starting *N,O*-dibenzoylated 2-aminophenols has an effect on the rate of the reaction. A number of 2-alkyl benzoxazoles can likewise be prepared in high yield. An example of the utility of this methodology is shown by the formation of 2-(4-methoxyphenyl)-5-nitrobenzoxazole (**2d**). Compound **2d** was synthesized in poor to moderate yields by thermal fusion (44% yield) or oxidation of the appropriate Schiff base.[27] This compound is easily synthesized by the use of *p*-TsOH in 87% yield.

Table 1. Synthesis of Benzoxazoles.



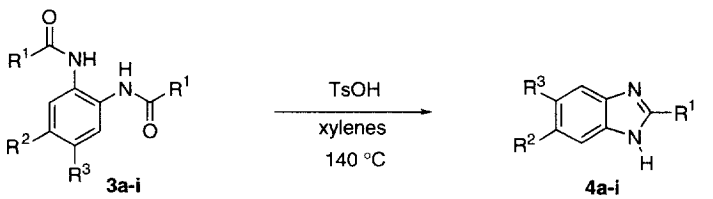
	Diacylated 2-aminophenol **1**			Time[a] (hours)	Yield of Benzoxazole **2** (%)[b]
	R^1	R^2	R^3		
a	Ph	H	H	7	88
b	*p*-C_6H_4OMe	H	H	3	96
c	*p*-$C_6H_4NO_2$	H	H	72(24)[c]	85
d	*p*-C_6H_4OMe	NO_2	H	3	87
e	*p*-C_6H_4OMe	H	NO_2	3	98
f	Me	H	H	2[d]	80
g	Et	H	H	2[d]	89
h	^{t}Bu	H	H	3[e]	74

[a] Time required for complete consumption of **1** for reactions run under standard conditions: 2 equivalents of *p*-TsOH, initial [**1**] = 0.1 M, refluxing xylenes. [b] All yields are for pure isolated material. [c] Reaction completed in 24 hours using 5 equivalents of *p*-TsOH. [d] Reaction run in benzene instead of xylenes. [e] Reaction requires 24 hours for completion in benzene; compare to **1f,g**.

Synthesis of Benzimidazoles

The facility of the *p*-TsOH-mediated conversion of *N,O*-diacylated aminophenols to benzoxazoles led us to explore the applicability of these reaction conditions for the conversion of *N,N'*-diacylated-1,2-phenylenediamines to benzimidazoles. The required *N,N'*-diacylated-1,2-phenylenediamines (**3a-i**, Table 2) were easily prepared from 1,2-phenylenediamine and 2.5 equivalents of the appropriate acid chloride in benzene or toluene as solvent with pyridine or triethylamine as base.

Table 2. Synthesis of Benzimidazoles.



3a-i **4a-i**

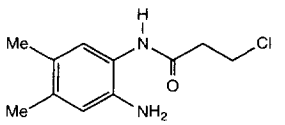
	Diacylated 1,2-phenylenediamine **3**			Time[a] (hours)	Yield of Benzimidazole **4** (%)[b]
	R^1	R^2	R^3		
a	Ph	H	H	1.5	87
b	*p*-C_6H_4OMe	H	H	1.5	85
c	*p*-$C_6H_4NO_2$	H	H	4	75
d	*m*-$C_6H_4NO_2$	H	H	5	72
e	*p*-$C_6H_4NO_2$	NO_2	H	4	76
f	Me	H	H	0.5	80
g	Et	H	H	0.5	89
h	^{t}Bu	H	H	12	74
i	CH_2CH_2Cl	Me	Me	32[c]	50

[a] Time required for complete disappearance of starting material as determined by tlc for reactions run under standard conditions: 2 equivalents of *p*-TsOH, initial [**3**] = 0.1 M, refluxing xylenes. [b] All yields are for pure isolated material. [c] Reaction run at 80 °C. When this reaction is run under reflux (0.75 h), an inseparable 1:1 mixture of **4i** and the corresponding 2-vinyl benzimidazole are isolated in 87% yield.

Treating *N,N'*-diacylated-1,2-phenylenediamines **3a-i** with 2.0 equivalents of *p*-TsOH in refluxing xylenes results in a rapid conversion to benzimidazoles **4a-i**. The benzimidazoles are obtained in high yield and purity after washing the reaction mixture with 1 N NaOH to remove the acid by-products and

crystallization of the product. For the synthesis of 2-aryl benzimidazoles **4a-e**, the nature of the substituents on the benzoyl groups has a modest effect on the reaction rate. There appears to be a strong dependence of the reaction rate on the steric bulk of the acyl substituents, in that the synthesis of 2-*tert*-butylbenzimidazole (**4h**) from **3h** proceeds significantly slower than the synthesis of 2-(primary-alkyl)benzimidazoles **4f,g,i**. Thus, the effect of substituents on the reaction rate for benzimidazole synthesis is similar to that observed for the synthesis of benzoxazoles under these reaction conditions.

The utility of this method is demonstrated by the transformation of **3i** to the labile 2-(2-chloroethyl)benzimidazole **4i**.[21] Alcade and co-workers reported that *N*-(2-amino-4,5-dimethylphenyl)3-chloropropanamide **5**, prepared with difficulty from the corresponding 1,2-phenylenediamine due to competing diacylation, does not react under standard Phillips conditions to afford benzimidazole products.[10]



5

Conclusions

We have found that diacylated 2-aminophenols and 1,2-phenylenediamines undergo clean conversion to benzoxazoles and benzimidazoles, respectively when treated with *p*-TsOH in refluxing benzene or xylenes. This reaction is operationally simple, can be used to prepare a wide variety of benzoxazoles and benzimidazoles, and may have particular utility in cases where diacylation of starting 2-aminophenols or 1,2-phenylenediamines is contemplated, such as in solid phase synthesis. Work is currently underway to explore the mechanistic details of these transformations.

EXPERIMENTAL SECTION

All melting points are uncorrected. 2-Aminophenol, 2-amino-4-nitrophenol, 2-amino-5-nitrophenol, 4-methoxybenzoyl chloride, and 4-nitrobenzoyl chloride were obtained from Aldrich Chemical Company and used without further purification. *p*-Toluenesulfonic acid monohydrate was obtained from Spectrum Chemical Corp. and used without further purification. The previously reported *N,O*-diacylated 2-aminophenols (**1a**, **1c**, **1f**) and *N,N'*-diacylated 1,2-phenylenediamines (**3a-d**, **3f-i**) were synthesized by literature procedures.[9,21-26,30] The previously unreported *N,O*-diacylated 2-aminophenols (**1b**, **1d-e**, **1g-h**) and *N,N'*-diacylated 1,2-phenylenediamine **3e** were prepared by standard procedures and provided satisfactory spectral and elemental analysis data. The identity of all known compounds was confirmed by ^{1}H NMR and comparison with literature spectral and m.p. values. HPLC was performed using a microsorb silica column, 4.5 x 250 mm, eluting with 25% EtOAc/hexanes at a flow rate of 2 mL/min. GC was performed with a Hewlett Packard 5890 using an HP-1 capillary column.

General procedure for the synthesis of benzoxazoles:

2-(4-Methoxyphenyl)-6-nitrobenzoxazole (2e). A suspension of 4-methoxy-*N*-[2-(4-methoxybenzoyloxy)-4-nitrophenyl]benzamide (**1e**) (133 mg, 0.31 mmol) and *p*-TsOH (120 mg, 0.63 mmol) in xylenes (3.0 mL) was heated under reflux for 3 hours. The reaction mixture was allowed to cool, diluted with EtOAc, and washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic layer was dried (Na_2SO_4) and evaporated to give the pure product as a tan solid (83.7 mg, 98%): m.p. 208-210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J=2.0 Hz, 1H), 8.28 (dd, J=8.7, 2.0 Hz, 1H), 8.20 (d, J=8.9 Hz, 2H), 7.76 (d, J=8.7 Hz, 1H), 7.04 (d, J=8.9 Hz, 2H), 3.9 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 163.4, 149.8, 147.8, 144.7, 130.2, 120.8, 119.2, 118.3, 114.7, 107.0, 55.6; IR ($CHCl_3$) 1622, 1500 cm^{-1}; MS (CI) 271, 255; HRMS (CI) *m/e* found: 271.0715, $C_{14}H_{11}N_2O_4$ requires 271.0719.

2-Phenylbenzoxazole (2a). 96% yield: m.p. 103-104 °C (Lit.[28] 102-103 °C).

2-(4-Methoxyphenyl)benzoxazole (2b). 88% yield: m.p. 99-100 °C (Lit.[27] 100-101 °C).

2-(4-Nitrophenyl)benzoxazole (2c). 85% yield: m.p. 262-264 °C (Lit.[28] 268-269 °C).

2-(4-Methoxyphenyl)-5-nitrobenzoxazole (2d). 87% yield: m.p. 180-182 °C (Lit.[28] 184-186 °C).

2-Methylbenzoxazole (2f). 80% yield. Product identified by ^{1}H NMR and gc vs. authentic material.

2-Ethylbenzoxazole (2g). 89% yield. Product identified by ^{1}H NMR and gc vs. authentic material.

2-(1,1-Dimethylethyl)benzoxazole (2h). 74% yield. Product identified by ^{1}H NMR.[28]

General procedure for the synthesis of 2-substituted benzimidazoles:

A suspension of the *N,N'*-diacylated 1,2-phenylenediamine (0.75 mmol) and *p*-TsOH (1.2 mmol) in xylenes (6 mL) was heated under reflux for the time indicated in Table 2. After this time the mixture was cooled to room temperature and diluted with EtOAc (30 mL). The resulting solution was washed with 1 M NaOH (10 mL) and sat. aq. NaCl, dried (Na_2SO_4), and evaporated. The resulting solid was recrystallized from EtOH to give the desired 2-substituted benzimidazole.

2-Phenylbenzimidazole (4a). 87% yield: m.p. 293-295 °C (Lit.[30] 296 °C).

2-(4-Methoxyphenyl)benzimidazole (4b) 85% yield: m.p. 232-234 °C (Lit.[29] 235-236 °C).

2-(4-Nitrophenyl)benzimidazole (4c). 75% yield: m.p. 323-325 °C (Lit.[30] 327 °C).

2-(3-Nitrophenyl)benzimidazole (4d). 72% yield: m.p. 204-206 °C (Lit.[28] 207-208 °C).

5(6)-Nitro-2-(4-nitrophenyl)benzimidazole (4e). 76% yield: m.p. 355-357 °C (Lit.[30] 356-358 °C).

2-Methylbenzimidazole (4f). 98% yield: m.p. 173-174 °C (Lit.[30] 175 °C).

2-Ethylbenzimidazole (4g). 80% yield: m.p. 169-172 °C (Lit.[31] 166-168 °C).

2-(1,1-Dimethylethyl)benzimidazole (4h). 77% yield: m.p. 331-333 °C (Lit.[24] 334 °C).

5,6-Dimethyl-2-(2-chloroethyl)benzimidazole (4i). Reaction run at 80 °C for 32 hours. Phosphate buffer (pH 7.0) was used in place of 1 N NaOH for the work-up. The product was crystallized from CH_2Cl_2 to afford **4i** as a white solid (50% yield): mp 238-240 °C (dec); ^{1}H NMR (MeOH-d_4) δ 7.26 (s, 2H), 3.95 (t, J = 6.8 Hz, 2H), 3.28 (t, J=6.8 Hz, 2H), 2.33 (s, 6H); ^{13}C NMR (MeOH-d_4) δ 152.2, 138.0, 132.4, 115.6, 42.7, 33.3, 20.3; MS (CI) 209, 201, 173; HRMS (CI) *m/e* found: 209.0855, $C_{11}H_{14}ClN_2$ requires 209.0846.

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