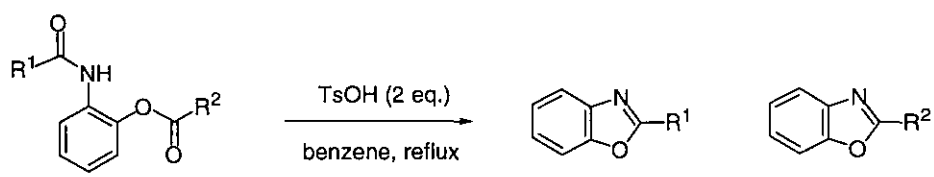
# THE CONVERSION OF MIXED *N,O*-DIACYLATED 2-AMINOPHENOLS TO 2-SUBSTITUTED BENZOXAZOLES

Mark R. DeLuca, Irach B. Taraporewala, and Sean M. Kerwin*

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

**Abstract**- When *N,O*-diacylated 2-aminophenols that have different acyl substituents on nitrogen and oxygen are treated with *p*-toluenesulfonic acid in refluxing xylenes, mixtures of benzoxazoles are produced. The major product is the benzoxazole in which the substituent at the 2-position is derived from the acyl group on nitrogen. This product may arise from an unusual case of acid-mediated neighboring amido-group assisted hydrolysis.

2-Aryl- and 2-alkyl-substituted benzoxazoles have received a considerable amount of attention in diverse areas of chemistry.[1] In our previous paper[2] we reported that the synthesis of 2-substituted benzoxazoles can be accomplished by treating *N,O*-diacylated 2-aminophenols with *p*-toluenesulfonic acid (TsOH) in refluxing xylenes or toluene. This procedure affords a variety of 2-aryl- and 2-alkyl-benzoxazoles in excellent yields, and is preferable to other methods for the preparation of benzoxazoles bearing electron withdrawing groups. In studying this transformation further, we were interested in examining the fate of *N,O*-diacylated 2-aminophenols in which the acyl groups on nitrogen and oxygen are not the same (**1**, $R^1 \neq R^2$). These mixed, *N,O*-diacylated 2-aminophenols are of interest because they are produced in a number of synthetically useful reactions,[3] and undergo a facile base-catalyzed acyl exchange reaction.[4] This paper reports the conversion of these mixed *N,O*-diacylated 2-aminophenols into benzoxazoles under the influence of TsOH. In addition to providing information concerning the potential synthetic utility of this conversion, this study has provided some mechanistic rationale for the conversion of *N,O*-diacylated 2-aminophenols to benzoxazoles under acidic reaction conditions.




**1** **2** **3**

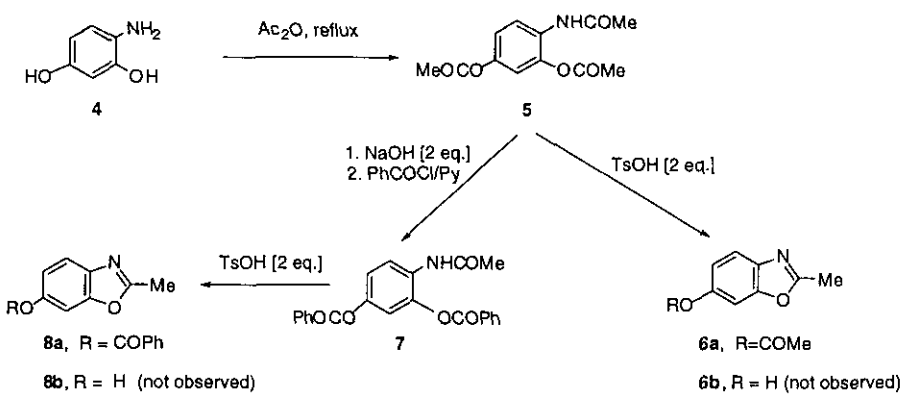
| Entry | $R^1$ = | $R^2$ = | Reaction Time (h) | Yield **2** + **3** (%) | Ratio **2**/**3** |
|---|---|---|---|---|---|
| **a** | Me | Et | 2 | 80 | 95:5 |
| **b** | Et | Me | 2 | 89 | 87:13 |
| **c** | Me | Ph | 7[a] | 96 | 65:35 |
| **d** | *p*-$C_6H_4OMe$ | Me | 24 | 88 | 77:23 |

[a] Reaction run in xylenes under reflux; when run in benzene under reflux, the reaction requires > 48 h for completion.

A series of mixed *N,O*-diacylated 2-aminophenols (**1a-d**)[5,6] were treated with TsOH in benzene under reflux. After aqueous work-up, the benzoxazole products were isolated and the ratio of products was determined by GC analysis. For **1a** ($R^1$= Me, $R^2$= Et) the major product is 2-methylbenzoxazole, which is formed in a 95:5 ratio with 2-ethylbenzoxazole. When the nature of the *N*- and *O*-acyl groups is reversed, as in **1b** ($R^1$= Et, $R^2$= Me), the opposite result is obtained; 2-ethylbenzoxazole is formed predominantly. We also analyzed the reaction products from reactions of mixed diacylated 2-aminophenols in which $R^1$ or $R^2$ is an aromatic substituent. In the case of **1c** ($R^1$= Me, $R^2$= Ph), the product mixture consists mainly of 2-methylbenzoxazole, although a substantial amount of 2-phenylbenzoxazole is also formed (2:1 ratio). Similarly, the reaction of **1d** ($R^1$= *p*-$C_6H_4OMe$, $R^2$= Me) gives mainly the 2-(4-methoxyphenyl)benzoxazole as the major product, along with some 2-methylbenzoxazole (4:1 ratio).

The rates of the reactions vary significantly depending on the acyl substituents. The reactions of the mixed diacylated aminophenols in which the acyl groups are acetyl or propanoyl (**1a** or **1b**) proceed rapidly in refluxing benzene; whereas, the reaction of compound **1c** ($R^1$= Me, $R^2$= Ph) proceeds much more slowly, requiring that the reaction be carried out in refluxing xylenes rather than benzene. The reaction of **1d** ($R^1$= *p*-$C_6H_4OMe$, $R^2$= Me) can be accomplished in refluxing benzene, although the time for completion of this reaction is significantly longer than the reactions of either **1a** or **1b**.

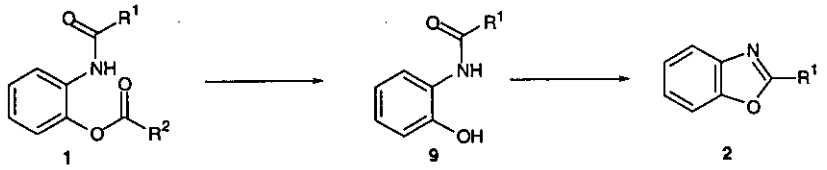
When *N,O,O'*-triacyl-4-aminoresorcinol (**5**, Scheme 1) was treated with two equivalents of TsOH in refluxing toluene for 16 h, 6-acetoxy-2-methylbenzoxazole (**6a**)[7] was isolated as the sole product in 86% yield. None of the phenol (**6b**) was observed in the product mixture. Similarly, when the *N*-acetyl-*O,O'*-dibenzoate ester (**7**), prepared from **5** using the procedure of LeRosen,[5] was subjected to the standard cyclization conditions above, 2-methyl-6-benzoyloxybenzoxazole (**8a**)[8] was obtained in 78% yield, along with a small amount of 2-phenyl-6-benzoyloxybenzoxazole (12% yield). Again, none of the phenol (**8b**) was observed in the product mixture.




**Scheme 1**

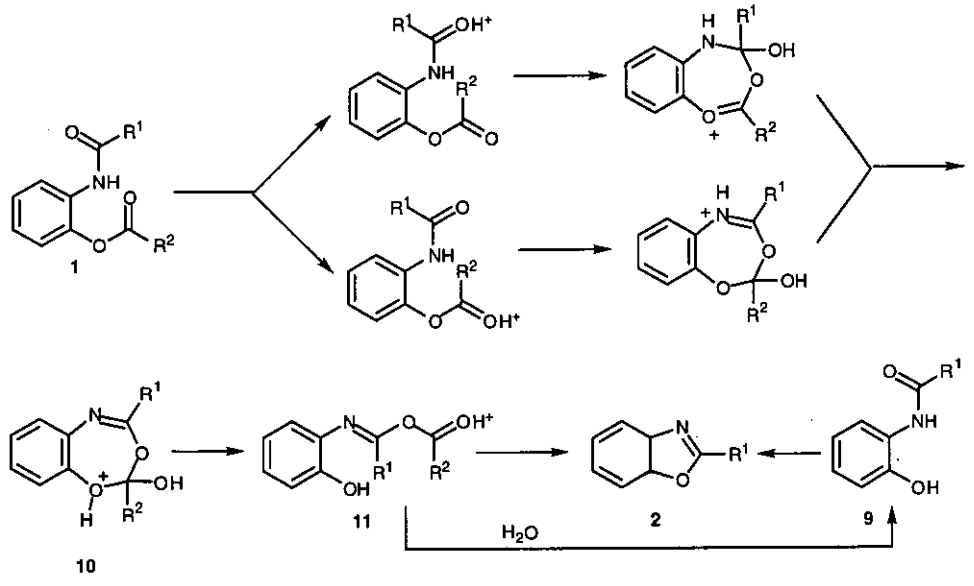
One potential mechanism for the formation of benzoxazoles (**2**) from *N,O*-diacylated 2-aminophenols (**1**) in the presence of TsOH involves the initial hydrolysis of the ester moiety in **1** to give the 2-amidophenol (**9**), Scheme 2. Subsequent acid-catalyzed cyclization[9] of this intermediate leads to the benzoxazole (**2**) with the 2-substituent being derived from the substituent on the amide group, in accordance with our results. Support for hydrolysis occurring during the reaction is provided by the isolation of the 2-amidophenol (**9d**) ($R^1$ = *p*-$C_6H_4OMe$) from the reaction of **1** ($R^1$,$R^2$ = *p*-$C_6H_4OMe$) when the reaction is stopped after 30 min. However, when simple phenol esters, such as phenyl benzoate are treated under these reaction conditions, no ester hydrolysis is observed. Also, the failure to detect the phenol products

(**6b**) or (**8b**) from the cyclization of the esters (**5**) and (**7**) indicates that if benzoxazole formation proceeds through initial ester hydrolysis, this hydrolysis must require the adjacent amido group.



**Scheme 2**

Amide-assisted hydrolysis is well-studied in the case of base-catalyzed ester hydrolysis,[10] but is less well studied in the case of acid-catalyzed hydrolysis. In the former case, assisted hydrolysis takes place through nucleophilic attack of the amide nitrogen on the ester carbonyl.[11] This type of assisted hydrolysis would lead to the same 2-imidophenol intermediate, and thus the same product mixtures, from both *N,O*-diacylated 2-aminophenols (**1a**) and (**1b**), in contrast to what is observed. A similar mechanism has been proposed for the facile base-catalyzed acyl-exchange reaction of mixed, *N,O*-diacylated 2-aminophenols.[12] However, the observation of different product mixtures from the reactions of **1a** and **1b** also argues against acyl exchange occurring during the reaction.



**Scheme 3**

In the case of acid-catalyzed amide-assisted phosphinic ester hydrolysis, the oxygen, rather than the nitrogen atom, of the amide serves as the nucleophilic center.[13] In the present case, amide-assisted hydrolysis of *N,O*-diacylated 2-aminophenols (**1**), intramolecular attack of the amide oxygen on the protonated ester (or conversely, attack of the ester carbonyl oxygen on the protonated amide) might afford a 3,5,1-benzodioxazepine intermediate (**10**), Scheme 3. This 3,5,1-benzodioxazepine intermediate may rearrange to the carboxyimidoyl anhydride (**11**). Under anhydrous conditions this anhydride (**11**) can be converted directly to the benzoxazole (**2**) by attack of the hydroxyl onto the carboxyimidoyl anhydride followed by the loss of carboxylic acid. A similar mechanism has been proposed by Mazurkiewicz[14] for the conversion *N,N'*-diacyl-2-phenylenediamines into benzimidazoles under the influence of the Lewis acid $Ph_3PBr_2$. In the presence of water in the reaction mixture or during workup of the reaction, the anhydride intermediate (**11**) would be hydrolyzed to form the amidophenol (**9**). The

amidophenol (**9**) can subsequently be converted to the benzoxazole (**2**) under the acidic reaction conditions.[9] The effect of the nature of the acyl groups on the rate of the reaction (*vide supra*) is also consistent with the route shown in Scheme 3.

In conclusion we have shown that the formation of benzoxazoles from *N,O*-diacylated 2-aminophenols in the presence of TsOH occurs readily to give benzoxazoles in which the substituent on position 2 is predominately derived from the acyl group on the nitrogen. The isolation of 2-amidophenols from the reaction mixtures, and the observed hydrolytic stability of simple esters to the reaction conditions indicate that the reaction may proceed through neighboring amido group-assisted ester hydrolysis. One possible mechanism, consistent with the data obtained to date, involves the 3,5,1-benzodioxazepine intermediate (**10**), Scheme 3. Future work will investigate this mechanism further.[15]

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3. See for example: D. L. Boger and H. Zarrinmayeh, *J. Org. Chem.*, 1990, **55**, 1379.
4. T. Sakurai, K. Kubo, and H. Inoue, *Rev. Het. Chem.*, 1997, **16**, 213, and references therein.
5. The known compounds (**1a**) and (**1c**) were synthesized from the appropriate 2-amidophenol according to the literature procedure: A. L. LeRosen and E. D. Smith, *J. Am. Chem. Soc.*, 1948, **70**, 2705. Compound (**1b**) was synthesized according to literature procedure. All compounds provided satisfactory spectral and elemental analysis data. All benzoxazoles (**2a-d**) are known compounds and their structures confirmed by comparison with literature values: H. Gershon, D. D. Clarke, and M. Gershon, *Montash. Chem.*, 1993, **124**, 367.
6. The synthesis of compound (**1d**) was based on the procedure of Gershon *et al.*[5] : mp 136-138 °C; $^1$H NMR (300 MHz, benzene- $d_6$) δ 8.65 (dd, J=8.2, 1.1 Hz, 1H), 7.86 (br s, 1H), 7.75 (d, J=8.8 Hz, 2H), 7.11 (dd, J=8.0, 1.4 Hz, 1H), 7.00 (dt, J=8.0, 1.3 Hz, 1H), 6.82 (dt, J=8.0, 1.5 Hz, 1H), 6.61 (d, J=8.8 Hz, 2H), 3.16 (s, 3H); 1.64 (s, 3H); $^{13}$C NMR (75 MHz, benzene- $d_6$) δ 167.94, 164.41, 162.74, 141.58, 130.88, 129.23, 128.66, 126.57, 124.50, 123.43, 122.21, 114.15, 54.83, 20.19; IR (KBr) 1747, 1669 cm$^{-1}$; MS (CI) 286, 244, 225; HRMS (CI) *m/z* calcd for $C_{16}H_{16}NO_4$: 286.1079, found 286.1074; Anal.Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.32; H, 5.43; N, 4.85.
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12. The small amount of benzoxazole product in which the 2-substituent is derived from the *O*-acyl group of the starting *N,O*-diacyl-2-aminophenol may arise from this type of process. Alternatively, this may arise from the well-established *N*- to *O*- rearrangement of mixed *N,O*-diacylated 2-aminophenols: E. D. Smith and L. Elrod, Jr., *J. Org. Chem.*, 1977, **42**, 652.
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15. We gratefully acknowledge research support from the US Public Health Service Grant GM-50892.

Received, 5th February, 1999