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Synthesis of 2-Aminobenzoxazoles Using Tetramethyl Orthocarbonate or 1,1-Dichlorodiphenoxymethane

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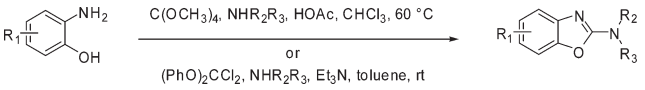

The synthesis of 2-aminobenzoxazoles can be readily achieved by two versatile, one-pot procedures utilizing commercially available tetramethyl orthocarbonate or 1,1-dichlorodiphenoxymethane, an amine, and an optionally substituted 2-aminophenol. The reactions were conducted under mild conditions and provided 2-aminobenzoxazoles in modest to excellent yields. A variety of amines and substituted 2-aminophenols were used to investigate the scope of the reactions.

2-Aminobenzoxazoles are ubiquitous scaffolds featured in a wide variety of therapeutic agents. Some examples of therapeutic indications treated by compounds containing this motif include CNS disorders,[1] cancer,[2] inflammation,[3] metabolic disorders,[4] irritable bowel syndrome (IBS),[5] viral infection,[6] thrombosis,[7] and insomnia.[8]

There are several approaches to this scaffold; however, each one has specific disadvantages (Scheme 1). The classical route involves nucleophilic displacement of a 2-substituted benzoxazole (2-substituents include Cl,[9] SH,[10] SCH_3,[11] or OPh[12]) with an amine. Drawbacks of these routes include penultimate intermediates that involve multiple steps to prepare, utilization of harsh reagents and conditions, or generation of undesirable byproducts. Cyclodesulfurization of an intermediary thiourea may involve a toxic heavy-metal oxide,[13] potentially explosive oxidant,[14] or transition metal[15] to facilitate cyclization. Previously reported methods to generate 2-aminobenzoxazoles directly from 2-aminophenols may require the preparation of either a thioisocyanate (**5**),[16] *N*-cyanodithioimidocarbonate (**6**),[17] or chloroformadinium salt (**7**)[18] prior to cyclization. 2-Aminobenzoxazoles have also been prepared directly from benzoxazoles using chloroamines[19] or formamides[20] as amine surrogates. However, these reactions either require initial chlorination of the amine prior to reaction with the benzoxazole or in the case of formamides Ag_2CO_3 and heating at 130 °C to furnish the desired products.

In our laboratories, we required a facile method for preparing a proprietary 2-aminobenzoxazole that was safe, efficient, and amenable to large-scale production. We sought easily handled, commercially available, and relatively inexpensive reagents that could facilitate formation of 2-aminobenzoxazoles from readily available amines and substituted 2-aminophenols in a single step. Herein we report two novel,

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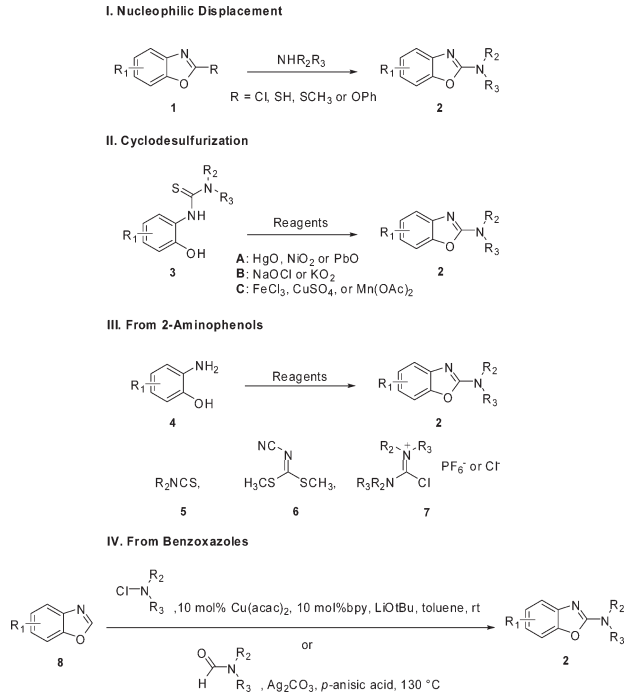
SCHEME 1. Examples of Common Methods for Generating 2-Aminobenzoxazoles



general, and one-pot processes for preparing this scaffold class[21] using either commercially available tetramethyl orthocarbonate (**9**) or 1,1-dichlorodiphenoxymethane (**10**).

We conducted a reaction using 1 equiv of 2-aminophenol, 2 equiv of *N*-Boc-piperazine, 2 equiv of tetramethyl orthocarbonate, and 4 equiv of HOAc heated at 60 °C in $CHCl_3$. Gratifyingly, we observed clean formation of the desired product and a 97% isolated yield after SiO_2 gel column chromatography (Table 1, entry 1, Method A). In addition, we obtained a similar result when conducting an experiment using 1 equiv of 2-aminophenol, 2 equiv of *N*-Boc-piperazine, 1 equiv of 1,1-dichlorodiphenoxymethane, with 2 equiv of Et_3N in toluene at room temperature (Table 1, entry 1, Method B). Using these sets of conditions, we examined the versatility of both reactions using 2-aminophenol and various amines (Table 1).[21]

The desired product was obtained for primary and secondary amines with yields ranging from modest to excellent for both methods. Lower yields were obtained with hindered (Table 1, entries 7 and 12) and volatile amines (Table 1, entries 4, 11, 13, 16, and 17) when using Method A. However, yields for volatile amines were generally improved when the reaction was carried out in a sealed vessel. Volatile pyrrolidine performed well when using Method B (Table 1, entry 4), presumably due to the fact that the reaction was conducted at room temperature. Nearly all of the amines reacted smoothly for both methods with the exception of aniline, which produced unidentified byproducts in addition to the desired product as observed by TLC. Nonetheless, compound **20** was isolated in moderate to good yield for both methods after SiO_2 column chromatography (Table 1, entry 12).

On the basis of LC-MS analysis, both reactions appear to proceed via initial formation of intermediates **33** or **35**, which

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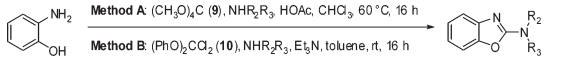
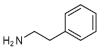
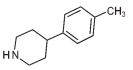
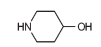
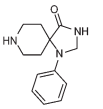
TABLE 1. Reactions with 2-Aminophenol and Various Amines



Entry	NHR_2R_3	Method	% Yield[a]	Entry	NHR_2R_3	Method	% Yield[a]
1	 11	A	97	12	 22	A	73
		B	92			B	40
2	 12	A	69	13	 23	A	11, 64[b]
		B	71				
3	 13	A	88	14	 24	A	36
		B	85				
4	 14	A	32, 90[b]	15	 25	A	69
		B	89			B	51
5	 15	A	72	16	 26	A	69
		B	58				
6	 16	A	65	17	 27	A	47
		B	75			B	69
7	 17	A	32	18	NH_3 (0.5 M/dioxane)[b,c] 28	A	38[b]
		B	42				
8	 18	A	63	19	 29	A	37
9	 19	A	50	20	 30	A	43
		B	67				
10	 20	B	91	21	 31	A	60
11	 21	A	25	22	 32	A	23

[a]Isolated yield after SiO_2 gel column chromatography. [b]Reaction conducted in a sealed vessel. [c]0.5 M NH_3 solution in 1,4-dioxane used as solvent.

were independently isolated and characterized by ^1H NMR and MS (Scheme 2). We postulate that formation of **33** could have occurred by direct condensation of **9** with 2-aminophenol,[22] which was followed by conversion to **34** via a S_NAr-type displacement by the amine, liberating CH_3OH as the sole byproduct (Scheme 2, eq 1). Our proposed pathway was further substantiated when we observed clean formation of **11** when reacting **33** directly with *N*-Boc-piperazine in the presence of 4 equiv of HOAc heated at 60 °C in $CHCl_3$ (data not shown). HOAc appears to enhance the reaction by either facilitating condensation of 2-aminophenol and **9** to **33** possibly by forming a reactive cationic species from **9** and/or

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SCHEME 2. Proposed Reaction Pathways

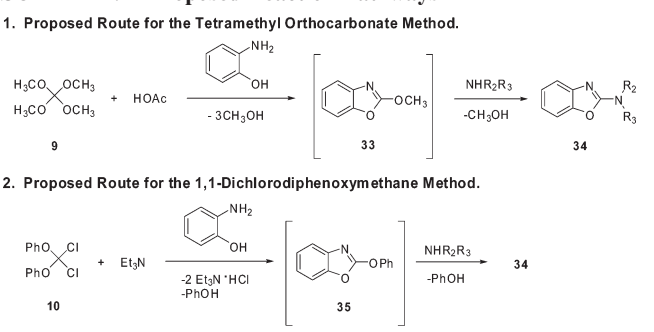
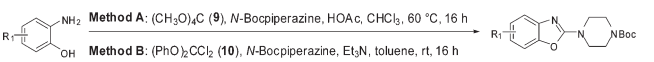


TABLE 2. Reactions with Substituted 2-Aminophenols



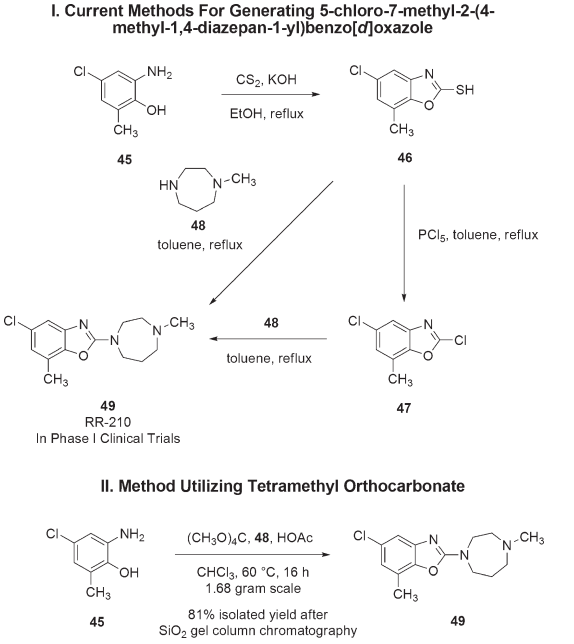
Entry	Aminophenol	Method	% Yield[a]	Entry	Aminophenol	Method	% Yield[a]
1	 36	A B	83 80	6	 41	A B	63 43
2	 37	A B	>99 96	7	 42	A B	18 75
3	 38	A B	50 40	8	 43	A	32
4	 39	A B	50 >99	9	 44	A	23
5	 40	A	88				

[a]Isolated yield after SiO_2 gel column chromatography.

displacement of **33** to **34**. The reaction involving components of entry 1 in Table 1 does proceed in the absence of HOAc, but at a slower rate (incomplete at 48 h), lower isolated yield (54%), and with unidentified byproducts. We propose a similar pathway for the reaction involving **10** in that 2-phenoxybenzoxazole **35** could be formed by direct condensation of **10** with 2-aminophenol[23] followed by displacement of phenol by the amine (Scheme 2, eq 2). The ability of the 1,1-dichlorodiphenoxymethane facilitated reaction to proceed at room temperature is presumably due to the higher reactivity of the reagent and/or intermediate **35**. Room temperature displacement of 2-phenoxybenzoxazles such as **35** by amines has been previously reported.[12] We also observed clean formation of **11** when reacting **35** directly with *N*-Boc-piperazine in the presence of 2 equiv of Et_3N in toluene at room temperature (data not shown).

We further examined the scope of both reactions using various substituted 2-aminophenols and *N*-Boc piperazine (Table 2). Both electron-donating and -withdrawing groups were well tolerated, again providing yields ranging from modest to excellent. Entry 7 in Table 2 demonstrates the complementarity of both reactions as ester **42** underwent competitive amide formation using the tetramethyl orthocarbonate method, which was circumvented by using 1,1-dichlorodiphenoxymethane at room temperature (Table 2, entry 7).

SCHEME 3. Synthesis of the 5-HT_3 Receptor Partial Agonist RR-210 (43)



A screening of common organic solvents (CH_3OH, EtOH, EtOAc, toluene, CH_3CN, and THF) for the tetramethyl orthocarbonate method using the same conditions for entry 1 in Table 1 was conducted and all of them performed as well as chloroform (data not shown). Heating at or above 60 °C was required for the reaction to proceed; product formation was not observed when run at room temperature regardless of the solvent used. In addition, it was discovered that the less expensive tetraethyl orthocarbonate could also be used in place of tetramethyl orthocarbonate without compromising isolated yields (data not shown).

A similar solvent screen was conducted for the 1,1-dichlorodiphenoxymethane method ($CHCl_3$, CH_3CN, and THF) using the same conditions for entry 1 in Table 1 and it was observed that the others were inferior to toluene for clean product formation by LC-MS. Of the bases surveyed (*i*-Pr_2NEt, DBU, DABCO, and pyridine), *i*-Pr_2NEt and Et_3N led to smoothest product formation by LC-MS (data not shown).

As a demonstration of utility for the tetramethyl orthocarbonate approach, we sought to prepare the 5-HT_3 receptor partial agonist 5-chloro-7-methyl-2-(4-methyl-1,4-diazepan-1-yl)-benzo[*d*]oxazole (RR-210, **49**),[24] which was reported to be in phase I clinical trials for IBS-d (Scheme 3).[25] Previously reported methods to prepare **49** involve nucleophilic displacement of either the 2-mercaptobenzoxazole intermediate **46** or the 2-chlorobenzoxazole intermediate **47** with *N*-methylhomopiperazine (**48**).[23] Our method allowed for the preparation of **49**

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directly from 2-aminophenol **45** in good yield. We believe this method to be superior when considering the large-scale production of **49** in that it is more efficient (one less step), does not require using the toxic and harsh reagents CS_2 or PCl_5, and produces CH_3OH as a byproduct instead of H_2S (when **46** is used in the displacement). It is our expectation that the synthesis of other therapeutically relevant 2-aminobenzoxazoles can be improved in a similar way using this method.

In summary, we have discovered two novel, versatile, and facile methods for synthesizing 2-aminobenzoxazoles using readily available amines, substituted 2-aminophenols, and commercially available tetramethyl orthocarbonate or 1,1-dichlorodiphenoxymethane. The advantages to our procedures are as follows: (1) the reactions are single-pot and utilize accessible, easy-to-handle, and off-the-shelf reagents; (2) the reaction conditions are mild, thus various functional groups are well tolerated; (3) the reactions are clean, providing virtually spot-to-spot conversion from 2-aminophenol to 2-methoxybenzoxazole or 2-phenoxybenzoxazole to 2-aminobenzoxazole in most cases (as observed by TLC and LC-MS analysis); (4) the reactions are versatile for both amines and substituted 2-aminophenols; and (5) the tetramethyl orthocarbonate reaction performs well in a variety of solvents.

The reactions are also complementary. The 1,1-dichlorodiphenoxymethane reaction performs well at room temperature and is essentially pH neutral, which is desired in cases when volatile amines are used and/or acid-sensitive functionality is present. Although the tetramethyl orthocarbonate reaction requires mild heating, the byproduct generated is CH_3OH. Such conditions should be amenable to large-scale production and could present a "greener" and more environmentally friendly approach to this important heterocyclic motif. We are currently attempting to extend these methodologies to other heterocyclic systems, such as 2-aminobenzimidazoles and benzthiazoles.

Experimental Section

Representative Tetramethyl Orthocarbonate Procedure. To a mixture of 2-aminophenol (2.0 g, 18.3 mmol), *tert*-butyl piperazine-1-carboxylate (6.8 g, 36.6 mmol), and HOAc (4.2 mL, 73.3 mmol) in $CHCl_3$ (70 mL) was added tetramethyl orthocarbonate (4.8 mL, 36.6 mmol) at room temperature. A suspension typically formed, which became a clear solution once the mixture was heated at 60 °C. The reaction was heated at 60 °C for 16 h and cooled to room temperature. The mixture was washed with 1 N NaOH, 1 N HCl, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed over SiO_2 gel (10% to 30% EtOAc in hexanes) to give *tert*-butyl 4-(benzo[*d*]oxazol-2-yl)piperazine-1-carboxylate as a white solid (5.38 g, 97%); R_f 0.4 (hexanes/EtOAc, 3:1); mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.1 Hz, 1H), 7.28 (d, J = 7.1 Hz, 1H), 7.20 (t, J = 6.7 Hz, 1H), 7.06 (t, J = 6.7 Hz, 1H), 3.69 (m, 4H), 3.57 (m, 4H), 1.49 (s, 9H); ESI MS m/z 304 $[C_{16}H_{21}N_3O_3 + H]^+$.

Representative 1,1-Dichlorodiphenoxymethane Procedure. To a mixture of 2-aminophenol (1.0 g, 9.1 mmol), morpholine (0.80 g, 9.1 mmol), and Et_3N (2.5 mL, 18.3 mmol) in toluene (36 mL) was added 1,1-dichlorodiphenoxymethane (2.4 g, 9.1 mmol) at room temperature. The reaction continued to stir at room temperature for 16 h and was washed with 1 N NaOH, 1 N HCl, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed over SiO_2 gel (10% to 30% EtOAc in hexanes) to give 2-morpholinobenzo[*d*]oxazole as a white solid (1.32 g, 71%); R_f 0.3 (hexanes/EtOAc, 3:1); mp 90−92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 1H), 7.27 (d, J = 7.1 Hz, 1H), 7.19 (t, J = 6.7 Hz, 1H), 7.05 (t, J = 6.7 Hz, 1H), 3.82 (m, 4H), 3.69 (m, 4H); ESI MS m/z 205 $[C_{11}H_{12}N_2O_2 + H]^+$.

Acknowledgment. We thank Drs. Mark Wolf, David Manning, and Peter Guzzo (AMRI, Departments of Medicinal Chemistry and Discovery Research and Development) for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data including ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.