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Efficient Phosphonium-Mediated Synthesis of 2-Amino-1,3,4-oxadiazoles

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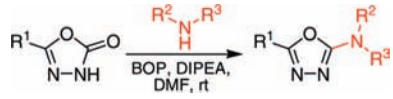
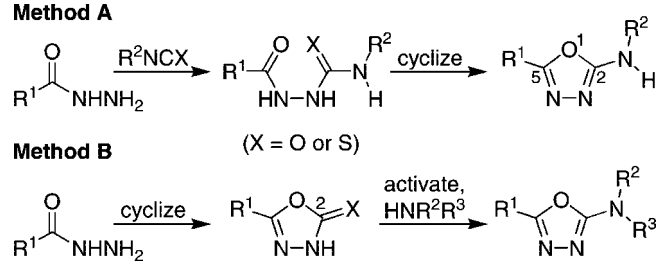
ABSTRACT



We present an efficient, room temperature procedure for the preparation of 2-amino-1,3,4-oxadiazoles. Oxadiazol-2-ones can be activated for S_NAr substitution using phosphonium reagents (e.g., BOP). This approach provides convenient access to N,N-disubstituted 2-amino-1,3,4-oxadiazoles, which are difficult to prepare using existing synthetic strategies.

The development of efficient methods for the synthesis of 1,3,4-oxadiazoles has attracted considerable interest. This heterocycle is a popular bioisostere for improving the pharmacological profile of biologically active amides, esters, and ureas.[1] Molecules containing 2-amino-1,3,4-oxadiazoles, in particular, exhibit a broad spectrum of biological activity.[2] In addition, 2-amino-1,3,4-oxadiazoles are functional tools for chemical synthesis; for example, Boger has exploited them as azadienes in [4 + 2] cycloaddition reactions for the synthesis of vinca alkaloids.[3] Certain oxadiazole derivatives also have interesting photochemical properties.[4]

Scheme 1. Literature Synthesis of 2-Amino-1,3,4-oxadiazoles



Two strategies for 2-amino-1,3,4-oxadiazole synthesis are illustrated in Scheme 1. Numerous procedures analogous to method A have been described both in solution and on solid-phase; these involve formation of the oxadiazole O1−C2 bond by cyclodehydration of semicarbazides or thiosemicarbazides. Semicarbazides can be cyclized using harsh reagents ($POCl_3$, $SOCl_2$); the Burgess reagent,[5] tosyl chloride,[3] and modified Appel conditions[6] have also been used.

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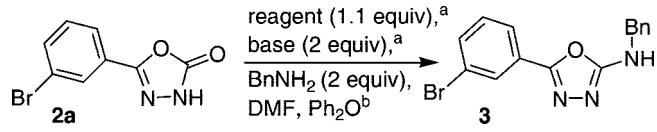
A variety of reagents have been employed for thiosemicarbazide cyclization, including I_2/NaOH,[2g] carbodiimides,[7] tosyl chloride,[8] and stoichiometric mercury salts.[2c,i,9] Although these procedures are often effective, they are usually performed above room temperature, and they do not provide ready access to N,N-disubstituted 2-amino-1,3,4-oxadiazoles.

By comparison, there are relatively few strategies analogous to method B (Scheme 1). The key steps are: (1) activation of an oxadiazol-2-one (X = O) or 2-thione (X = S) at C2; (2) addition of a nitrogen nucleophile to generate the C2−N bond. A typical procedure for oxadiazole-2-thione activation requires two steps: sulfur alkylation, then oxidation to the sulfone.[4,10,11] Oxadiazole-2-one chlorination using PCl_5/$POCl_3$ has been reported, though yields were poor (ca. 8−10%).[10]

Previously, we developed[12] an efficient procedure for direct amination of cyclic amides and ureas using BOP,[13] a well-known peptide coupling reagent.[14] We envisioned that activation of cyclic carbamates, like 1,3,4-oxadiazol-2-ones, could be achieved by a similar approach. 1,3,4-Oxadiazol-2-ones, readily prepared from acid hydrazides using phosgene or milder phosgene equivalents,[15] are vulnerable to ring opening by nitrogen nucleophiles, particularly at high temperature.[15b,d,16] We discovered that phosphonium reagents (e.g., BOP) promote a different reaction path: S_NAr substitution at C2 by primary and secondary amine nucleophiles, allowing synthesis of 2-amino-1,3,4-oxadiazoles in good to excellent yields. This provides a convenient method for preparing 2-amino-1,3,4-oxadiazoles through C2−N bond formation. The procedure avoids the use of iso[thio]cyanates and toxic metal salts. Furthermore, secondary amine nucleophiles generate products difficult to access through cyclodehydration (i.e., in Scheme 1, when R^2, $R^3 \neq H$). In this report, we discuss the results of our preliminary investigation.

Scheme 2. Model System for Reaction Optimization



[a] See Table 1 for list of bases and coupling reagents. [b] Internal standard for HPLC analysis.

We began by optimizing the reaction conditions. 1,3,4-Oxadiazol-2-one **2a** (from 3-bromobenzoic acid hydrazide, **1a**) was selected for screening (Scheme 2). $BnNH_2$ was coupled to **2a** in DMF at room temperature with BOP and one of seven bases; conversion to product **3** was determined by HPLC−MS analysis of each reaction mixture (Table 1, entries 1−7).[17] Proton sponge, DMAP, and diisopropylethylamine (DIPEA) all performed well under these conditions. Nearly quantitative conversion to **3** was achieved using DIPEA with BOP (entry 7).

Table 1. Results of Reaction Condition Screening

entry	base	reagent	hours	yield, **3**[a]
1	TMG[b]	BOP	18.5	30%
2	DBU	BOP	18.5	72%
3	Barton's base[c]	BOP	18.5	76%
4	2,6-lutidine	BOP	18.5	82%
5	proton sponge	BOP	18.5	94%
6	DMAP	BOP	18.5	95%
7	DIPEA	BOP	18.5	>99%
8	DIPEA	BOP	1	96%
9	DIPEA	BrOP[d]	1	92%
10	DIPEA	PyBOP[e]	1	76%
11	DIPEA	PyAOP[f]	1	74%
12	DIPEA	HATU[g]	16	0%
13	DIPEA	EDCI[h]	16	0%

[a] Chromatographic yield of **3** relative to Ph_2O internal standard. [b] Tetramethylguanidine. [c] *N*-*t*-butyl-*N*′,*N*′,*N*″,*N*″-tetramethylguanidine. [d] Bromotris(dimethylamino) phosphonium•PF_6.[18a] [e] (Benzotriazol-1-yloxy) tripyrrolidinophosphonium•PF_6.[18b] [f] (7-Azabenzotriazol-1-yloxy) tripyrrolidinophosphonium•PF_6.[18c,g] *O*-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium•PF_6. [h] *N*-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide•HCl.

A selection of coupling reagents were screened with the same model system using DIPEA as base (Table 1, entries 8−13). There was >90% conversion to product **3** within 1 h with phosphonium reagents BOP and BrOP. Neither PyBOP

(17) A sample containing a known concentration of **3** and Ph_2O was used to calibrate LCMS analysis.

(5) Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275–3278.

(6) (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811. (b) Košmrlj, J.; Kočevar, M.; Polanc, S. *Synlett* **1996**, 652–654. (c) Mazurkiewicz, R.; Grymel, M. *Pol. J. Chem.* **1997**, *71*, 77–82. (d) Dumčiūtė, J.; Martynaitis, V.; Holzer, W.; Mangelinckx, S.; De Kimpe, N.; Šačkus, A. *Tetrahedron* **2006**, *62*, 3309–3319.

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(10) (a) Madhavan, R.; Srinivasan, V. R. *Ind. J. Chem.* **1969**, *7*, 760–765. (b) Alternate route to 2-chloro-1,3,4-oxadiazoles: Deshukh, M. B.; Shelar, M. A.; Mulik, A. R. *Ind. J. Heterocycl. Chem.* **2000**, *10*, 13–16.

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(12) (a) Wan, Z.-K.; Binnun, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877–5880. (b) Wan, Z.-K.; Wacharasindhu, S.; Binnun, E.; Mansour, T. *Org. Lett.* **2006**, *8*, 2425–2428. (c) Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194–10210.

(13) Benzotriazol-1-yloxytris(dimethylamino)-phosphonium•PF_6^-.

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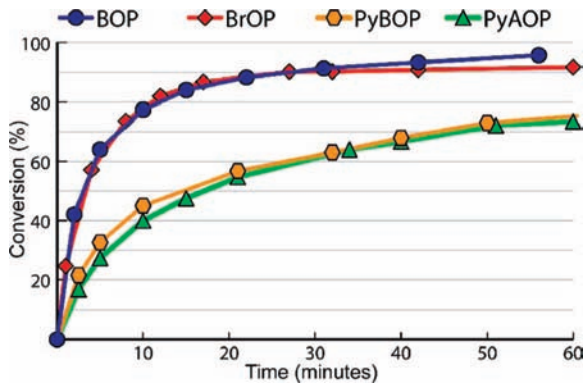
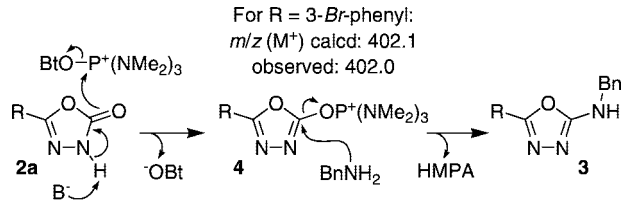


Figure 1. Percent conversion to **3** from **2a** (Scheme 2) plotted as a function of time for each phosphonium reagent.

nor PyAOP proved as effective; <80% conversion to **3** was achieved within 1 h using these reagents. With the carbodiimide EDCI and the uronium salt HATU,[18c] only starting material **2a** was detected by LCMS analysis of the reaction mixtures, even after 16 h.

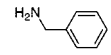
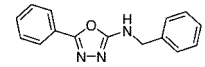
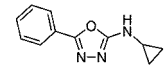
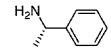
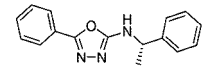
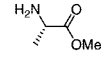
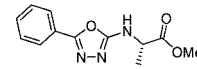
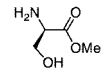
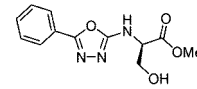
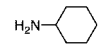
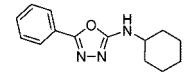
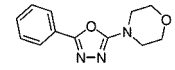
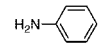
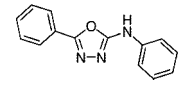
Scheme 3. Proposed Mechanism and Intermediate



Conversion from **2a** to **3** using pyrrolidine-substituted phosphonium reagents PyAOP and PyBOP was measurably slower than with BOP or BrOP (Figure 1). The anionic leaving group (OBt^-, OAt^-, Br^-) does not seem to influence the reaction significantly. These observations are consistent with the putative mechanism illustrated in Scheme 3. LCMS analysis revealed a compound with the *m*/*z* ratio of proposed intermediate **4**; there is no evidence that the OBt^- anion attacks this phosphonium salt. This is in contrast to the BOP mediated S_NAr substitution of six-membered heterocyclic amides and ureas we examined previously; in those cases, the "OBt adduct" does play a role in the reaction mechanism.

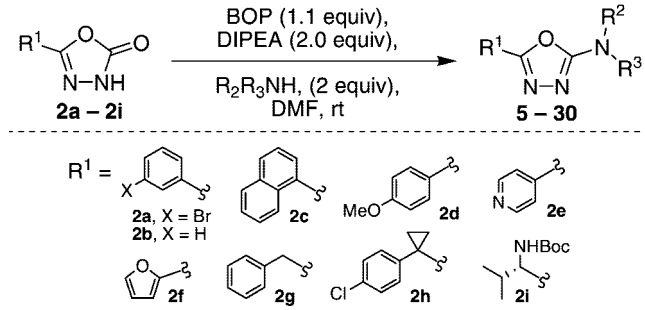
Amination using BOP and DIPEA was very clean. Accordingly, these reagents were selected to prepare an array of 2-amino-1,3,4-oxadiazoles to illustrate the scope of the method. We prepared a number of 1,3,4-oxadiazol-2-ones from commercially available hydrazides using triphosgene (Scheme 4, **2a**−**i**; for details, see Supporting Information). These substrates provided representative aryl (**2b**, **2c**), heteroaryl (**2e**, **2f**), alkyl (**2g**, **2h**, **2i**), electron donating (**2d**), and electron withdrawing (**2a**) substituents at C5. Nitrogen nucleophiles were coupled to these oxadiazol-2-ones using the optimized reaction conditions (Scheme 4, Tables 2 and 3).

Table 2. Products from BOP-Mediated Coupling of Amine Nucleophiles to **2b**

entry	amine	product		yield (%)[a]
1			**5**	94
2			**6**	89
3			**7**	94
4			**8**	71
5			**9**	50[b]
6			**10**	99+
7			**11**	92
8			**12**	67

[a] Isolated yield after column chromatography. [b] Unoptimized yield.

Scheme 4. Substrates for Reaction Screening



To gauge the scope of nucleophiles compatible with this method, we coupled an assortment of primary and secondary amines to **2b** (Table 2). The desired products were generally obtained in good yield. We were pleased to discover that the reaction with morpholine worked well; the desired product **11** was isolated in 92% yield. Serine methyl ester was coupled directly to **2b**, affording 50% isolated yield of product **9**. Notably, this did not require separate steps for

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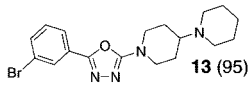
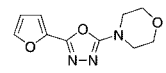
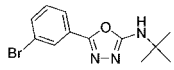
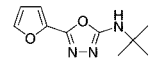
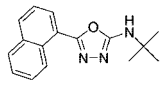
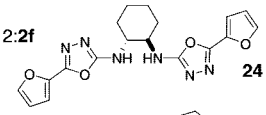
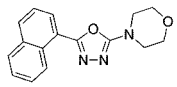
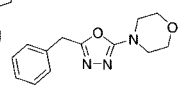
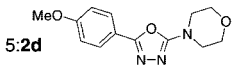
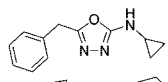
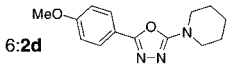
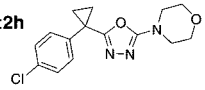
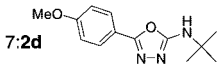
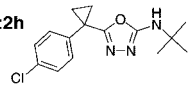
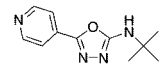
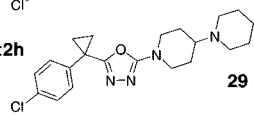
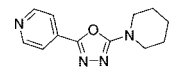
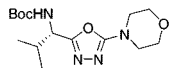
Table 3. Products from BOP-Mediated Coupling between Secondary and Hindered Amines with Various Substrates

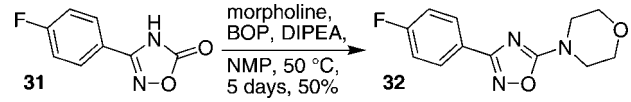
entry: substrate	product	no. (% yield)[a]	entry: substrate	product	no. (% yield)[a]
1:**2a**		**13** (95)	10:**2f**		**22** (98)
2:**2a**		**14** (88)	11:**2f**		**23** (77)
3:**2c**		**15** (89)	12:**2f**		**24** (86)
4:**2c**		**16** (89)	13:**2g**		**25** (77)
5:**2d**		**17** (94)	14:**2g**		**26** (84)
6:**2d**		**18** (88)	15:**2h**		**27** (81)
7:**2d**		**19** (65)	16:**2h**		**28** (82)
8:**2e**		**20** (63)	17:**2h**		**29** (74)
9:**2e**		**21** (76)	18:**2i**		**30** (74)

[a] Isolated yields after column chromatography.

protection and deprotection of the hydroxy side chain. The reaction with aryl amines was slow; product yields with these nucleophiles were modest at best (e.g., aniline; see Table 2, entry 8). Increasing reaction temperature to 50 °C and the use of stronger bases (DBU, TMG, Cs_2CO_3) did not improve product recovery. In these reactions, we observed unconverted starting material, product, and the phosphonium intemediate by LCMS. Attempts to couple azide (as NaN_3) or phenol to **2b** were unsuccessful as well; product was not observed, though a significant amount of phosphonium intermediate (see Scheme 3) was detected by LCMS. With thiophenol, we observed a complex mixture of products, as well as unconverted starting material.

Next, amine nucleophiles were coupled to 1,3,4-oxadiazol-2-ones **2a**−**i** to explore the effect of substitution at C5 (Table 3). We focused on secondary amine nucleophiles (e.g., morpholine) because of the lack of efficient methods for the synthesis of N,N-disubstituted 2-amino-1,3,4-oxadiazoles. We also explored the feasibility of hindered amines (i.e., *t*-$BuNH_2$) as nucleophiles. Coupling with secondary amines worked particularly well (e.g., products **13**, **17**, **22**). We were also pleased to find that the reaction also worked well with hindered amines (e.g., **15**, **28**); some reactions with *t*-$BuNH_2$ were nearly complete within a few hours. To emphasize the mildness of the reaction conditions, we prepared a substrate with an acid-sensitive functional group. 1,3,4-Oxadiazol-2-one **2i** was prepared in 84% yield from the acid hydrazide derived from Boc-valine (see Supporting Information). Morpholine was coupled to **2i** using the standard conditions; the desired product **30** was obtained in 74% yield after column chromatography.

Scheme 5. 1,2,4-Oxadiazol-2-one Amination



Finally, we examined whether isomeric 5-amino-1,2,4-oxadiazoles could be prepared under similar conditions. 1,2,4-Oxadiazol-3-one **31** (Scheme 5) was synthesized from 4-fluorobenzamidoxine using triphosgene. BOP mediated amination of this substrate was sluggish. For example, coupling morpholine to **31** gave product **32** in only 50% yield, despite stirring for 5 days at 50 °C in NMP[19] (Scheme 5).[20] LCMS analysis revealed no phosphonium intermediate in reactions using substrate **31**; possibly, the phosphonium intermediate from **31** is less stable than those from 1,3,4-oxadiazol-2-ones.[21]

In summary, an efficient and mild BOP-mediated formation of 2-amino-1,3,4-oxadiazoles is developed. The reactions are typically complete within a few hours at room temperature, and the desired products are obtained in good to excellent yields. The method provides convenient access to N,N-disubstituted 2-amino-1,3,4-oxadiazoles and is complementary to existing literature methodologies.[21]

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Amination with primary amines *n*-$BuNH_2$ or $BnNH_2$ produced only trace amounts of product. Reaction mixtures contained unconverted starting material **31** even when the reaction was performed at higher temperature or with DBU or Cs_2CO_3 as base.

(20) NMP was used to avoid problems with DMF decomposition.

(21) We are currently extending this method to other biologically interesting scaffolds and also exploring the use of these reagents for heterocycle synthesis through intramolecular cyclizations.