Synthesis and Use of 5-Vinyl-1,2,4-oxadiazoles as Michael Acceptors. A Rapid Synthesis of the Potent Muscarinic Agonist L-670,548

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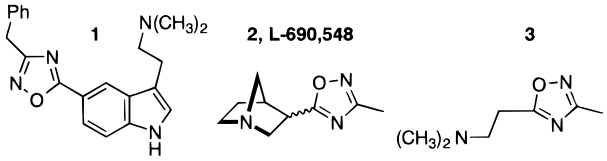
The 1,2,4-oxadiazole heterocycle has been identified and utilized as a metabolically stable analog of an ester or amide functionality in pharmacologically important molecules.[1] Recent examples of the use of 1,2,4-oxadiazoles as ester bioisosteres include the potent serotonin agonist (**1**)[2] for the treatment of migraine and the muscarinic receptor "super agonist" (**2**)[3] for the treatment of Alzheimer's disease. Oxadiazoles have been typically made as the last step in the synthesis of the biologically relevant molecule under study via the reaction of an ester or activated ester with an amide oxime. Convergent methods of synthesis of 1,2,4-oxadiazoles with other functional groups have not yet been exploited.



During the course of a general study of muscarinic agonists, we examined the efforts of Street and coworkers,[3] which had been focused on the discovery of the muscarinic "super agonists" (i.e., **2**). They reported that their efforts to synthesize the simplest, acyclic analog (**3**) of their azabicyclo[2.2.1]heptane (**2**)[3b] were unsuccessful. However, upon examination of the reaction between methyl 3-(dimethylamino)propionate and acetamide oxime (Scheme 1), we found that we were able to isolate consistently 30−45% yield of the desired 1,2,4-ozadiazole (**3**). Since our original interest in this compound was its muscarinic receptor activity, we converted the *N*,*N*-dimethylamine free base in **3** to its *N*,*N*,*N*-trimethyl quaternary ammonium salt (**4**). We believed that **4** would be the most analogous compound to acetylcholine, the natural substrate for muscarinic receptors which itself is a *N*,*N*,*N*-trimethyl quaternary ammonium salt. Accordingly, the reaction of **3** with methyl iodide in acetone afforded the quaternary salt **4** (95%) as a crystalline solid which was directly filtered from the reaction mixture (Scheme 1).

During the pharmacological examination of **4**, it was suspected that significant biological activity was masked by decomposition of the salt, likely to trimethylamine and the 5-vinyl-1,2,4-oxadiazole (**5**). Careful examination of a pH 7.4 aqueous solution of **4** revealed that the compound indeed rapidly decomposed to a single product, and the half-life ($t_{1/2}$) of **4** in pH 7.4 water was found to be only 45 min. Intrigued by this decomposition process, we purposefully subjected the salt (**4**) to decomposition conditions (Na_2CO_3 in water/CH_2Cl_2) and were able to isolate **5** in >90% yield (Scheme 1). This compound (**5**) was a low-boiling liquid making both isolation and characterization difficult.

The ease of elimination of trimethylamine from **4** was reminiscent of the ease of elimination of water and other leaving groups from β-substituted carbonyl compounds, and this premise led us to examine the Michael accepting character of the olefin found in **5**. Examination of the reaction of the 5-vinyl-1,2,4-oxadiazole (**5**) with nucleophiles under basic conditions is summarized in Scheme 1.[4] The olefin in **5** was found to be electrophilic in nature with a range of nucleophiles able to add into the electron-deficient olefin. Because of the volatility of **5**, its formation was carried out *in situ* with an appropriate base in methylene chloride/methanol (10:1). Methanol was needed to help solublize the quaternary salt. *As shown by TLC, formation of the 5-vinyl-1,2,4-oxadiazole (**5**) was rapid using any base.* Dimethylamine was both base and nucleophile in the formation of **6a**. Likewise, ammonia was both the base and nucleophile in the formation of **6f**. Only a catalytic amount of diisopropylethylamine (DIEA) was needed for the reaction of 3-hydroxypyrrolidine with the oxadiazole (example e), since trimethylamine was the elimination product. In cases where the nucleophile was formed by deprotonation of its conjugate acid, stronger bases were needed to, at least, partially deprotonate the acids. Accordingly, while DIEA was adequate for benzyl mercaptan (example b), a stronger base (DBU) was needed for deprotonation of malononitrile (example d). In the case of addition of methanol, we found that excess methoxide anion was required for reaction. The reaction of **5** with amines (dimethylamine, 3-hydroxypyrrolidine, and ammonia) was rapid at room temperature, and high yields of the desired products (**6a**, **6e**, and **6f**, respectively, Scheme 1) were isolated. Reaction of **5** with benzyl mercaptan was slower than the reaction with amines and required heating, but the thioether (**6b**) was also obtained in high yield. Use of NaH in MeOH with heating formed the methyl ether (**6c**), and the isolation of **6c** was complicated by its volatility. The reaction of **5** with malononitrile afforded the disubstituted malononitrile (**6d**) in which two molecules of the olefin (**5**) were added to the active methylene of malononitrile. In that example, 2 equiv of (**4**) was required.

These results demonstrate that 5-(2-(*N*,*N*-dimethylamino)ethyl)-1,2,4-oxadiazoles (i.e., **3**) can be easily used as synthons for NUC-CH_2CH_2-1,2,4-oxadiazoles, where NUC is an appropriate nucleophile which contains other functional groups. The utility of this concept can be demonstrated by the retrosynthetic analysis shown in Scheme 2. Disconnection of the muscarinic agonist L-670,548 (**2**) at the carbon−carbon bond between the azabicyclic bridgehead carbon and the carbon α to C5 of

(1) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282−2291.

(2) Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. *J. Med. Chem.* **1993**, *36*, 1529−1538.

(3) (a) Saunders, J. and Freedman, S. B. *Trends Pharmacol. Sci.* **1989**, Dec Suppl., 70−75. (b) Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. *J. Med. Chem.* **1990**, *33*, 2690−2697.

(4) A typical procedure is as follows: To a stirred mixture of **4** (2.00 mmol) in methylene chloride/methanol (10:1, 11 mL) was added the appropriate base (DIEA and DBU were used catalytically (10 mol %), NaH was used in excess) as shown in Scheme 1, followed by the appropriate nucleophile (amines were used in 3-fold excess, methanol was used as solvent, and only 0.5 equiv of malononitrile was used). The resulting reaction solution was stirred for the time and temperature shown in Scheme 1. The resulting reaction solution was then evaporated under reduced pressure. Purification of the residue could be accomplished via removal of insoluble solids through trituration using diethyl ether (or methylene chloride)/hexanes followed by evaporation of the filtrate or via chromatography using silica gel and an appropriate solvent system.

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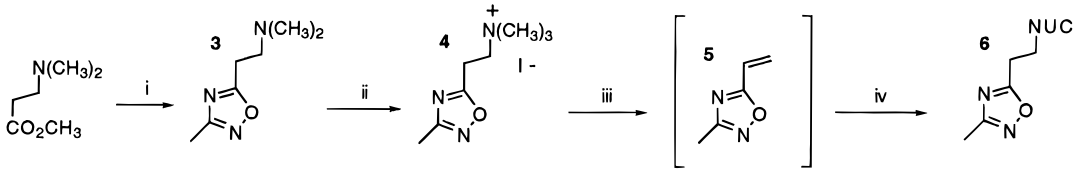
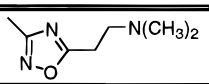
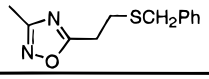
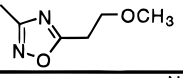
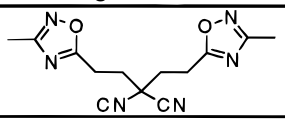
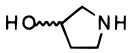
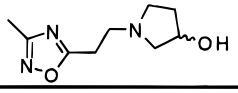
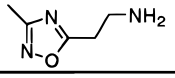
Scheme 1

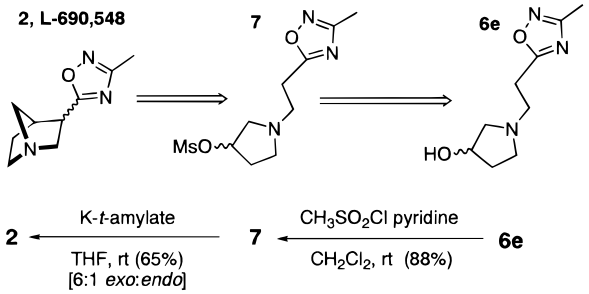


i) $CH_3(C{=}N\text{-}OH)NH_2$, NaH, THF, Δ (39%); ii) CH_3I (excess), acetone (95%);

iii) base/solvent (see below); iv) nucleophile (see below)

	Nucleophile	Base	Solvent	Time (h)	Temp (°C)	Product (6)	Yield (%)
a	$(CH_3)_2NH$	$(CH_3)_2NH$	CH_2Cl_2/MeOH	1	20		85
b	$PhCH_2SH$	DIEA	CH_2Cl_2/MeOH	48	reflux		84
c	CH_3OH	NaH	MeOH	3	reflux		80
d	$CH_2(CN)_2$	DBU	CH_2Cl_2/MeOH	4	reflux		77
e		DIEA	CH_2Cl_2/MeOH	3	20		97
f	NH_3	NH_3	CH_2Cl_2/MeOH	18	20		61

Scheme 2



the oxadiazole in **2** (Scheme 2) affords a NUC-CH_2CH_2-1,2,4-ozadiazole (**7**) that is directly available via the pyrrolidine (**6e**) synthesized as per Scheme 1. The conversion of **7** to **2** would take advantage of the acidity of the methylene α to C5 of the 1,2,4-oxadiazole ring as demonstrated by the facile conversion of the quaternary salt (**4**) to the olefin (**5**) under mildly basic conditions.

Accordingly, **6e** (36% from methyl 3-(dimethylamino)-proprionate, Scheme 1) was treated with methanesulfonyl chloride in methylene chloride with pyridine (6 equiv) as the acid scavenger (Scheme 2). Extraction with saturated sodium hydrogen carbonate, chromatography of the residue, and trituration with diethyl ether afforded the mesylate (**7**) in high yield (88%). Deprotonation of the oxadiazole methylene at C5 was accomplished with excess potassium *tert*-amylate, and the resulting carbanion effected a presumably S_N2 displacement of the mesylate at room temperature overnight affording a 6:1 *exo*:*endo* isolated ratio of the desired azabicyclo[2.2.1]-heptane (65% for both isomers). The previously reported synthesis of L-670,548 required six steps,[3b] synthesized the oxadiazole as the last step, and produced **2** (as a 6:1 *exo*:*endo* mixture) in an overall yield of 4%. Our convergent approach synthesized the oxadiazole as the first (and worst) step, and the overall yield of **2** (also as a 6:1 *exo*:*endo* mixture) was 21%. This result demonstrates the utility of our convergent approach to functionalized oxadiazoles. Clearly, the synthesis of the individual pairs of enantiomers of **2** should be straightforward given the commercial availability of both (*R*)- and (*S*)-3-hydroxypyrrolidine. We are presently pursuing such a chiral synthesis as well as examining the range of substituents which can be carried at C3 of the oxadiazole ring in the above described Michael-like reactions. We also are presently examining the potential use of compounds such as **5** in Diels–Alder reactions.

In conclusion, we have synthesized 5-vinyl-3-methyl-1,2,4-oxadiazole (**5**) via elimination of trimethylamine from (2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)trimethylammonium iodide (**4**). We have found that the vinyl group in **5** functions as a Michael acceptor with a diverse group of nucleophiles having been shown to add into the olefin in high yield. This approach suggests the use of (2-(1,2,4-oxadiazol-5-yl)ethyl)trimethylammonium iodides as synthons for the 2-(1,2,4-oxadiazol-5-yl)ethyl group in the formation of medicinally important targets. The concept is demonstrated in an efficient and convergent synthesis of the potent muscarinic agonist, L-670,548, from a high-yielding, two-step synthesis from **6e**.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR and FAB MS spectra for compounds **2**, **3**, **4**, **5**, **6a**–**f**, and **7** (32 pages).

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