ORGANIC LETTERS

2005
Vol. 7, No. 6
1039−1042

Synthesis of [1,2,4]Triazolo[4,3-α]piperazines via Highly Reactive Chloromethyloxadiazoles

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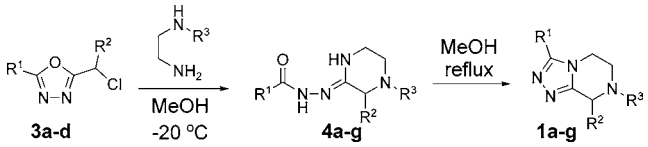
Received December 13, 2004

ABSTRACT



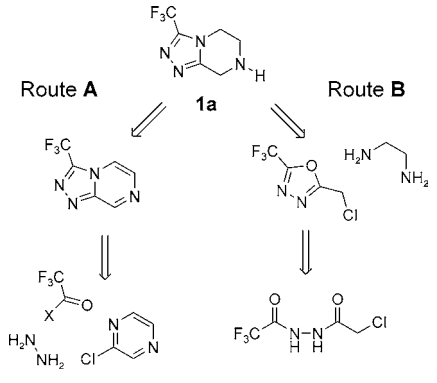
A concise, modular approach for the synthesis of [1,2,4]triazolo[4,3-α]piperazines via condensation of highly reactive chloromethyloxadiazoles with ethylenediamines is described. NMR studies of this reaction provide evidence that suggests a novel activation mechanism for electron-deficient chloromethyloxadiazoles.

[1,2,4]Triazolo[4,3-α]piperazines are interesting heterocyclic building blocks for the synthesis of bioactive molecules.[1] We recently required a method for the preparation of heterocycle **1a**, an intermediate in the synthesis of drug candidates for the pharmaceutical industry.

Most synthetic efforts toward the preparation of these heterocyclic systems have focused on benzene-fused piperazine analogues and involve condensation of an appropriate pyrazinone with hydrazine, followed by acylation of the terminal nitrogen and dehydration to form the triazole ring system.[2] The only preparation of triazolopiperazines such as **1** reported involved the addition of acetylhydrazide to a piperazinoimidate as the key step, followed by cyclodehydration to form the triazole ring.[3]

The method of Potts[4] was initially used for the preparation of triazolo[4,3-α]pyrazines (route A in Scheme 1). Triazole **1a** was obtained by reduction of the pyrazine ring with H_2/Pd, which, in turn, was prepared by trifluoroacetylation of 2-hydrazidopyrazine, followed by cyclization. The formation

Scheme 1. 3-Trifluoromethyl-[1,2,4]triazolo[4,3-α]piperazine



(1) (a) Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A.; Koe, B. K. *J. Med. Chem.* **1990**, *33*, 2240−2254. (b) Trivedi, B. K.; Bruns, R. F. *J. Med. Chem.* **1988**, *31*, 1011−1014. (c) Makino, K.; Sakata, G.; Morimoto, K. *Heterocycles* **1985**, *23*, 2025−2034.

(2) (a) Krishan, V. S. H.; Chowdary, K. S. *Indian J. Chem. Sect. B* **2000**, *39B*, 329−333. (b) Rashed, N.; El Massry, A. M.; El Ashry, S. H.; Amer, A.; Zimmer, H. *J. Heterocycl. Chem.* **1990**, *27*, 691−694.

(3) McCort, G. A.; Pascal, J. C. *Tetrahedron Lett.* **1992**, *33*, 4443−4446.

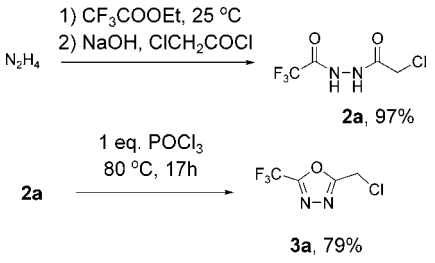
10.1021/ol0474406 CCC: $30.25
Published on Web 02/17/2005

of 2-hydrazidopyrazine by addition of hydrazine to 2-chloropyrazine involved the use of a large excess of hydrazine and a tedious extractive workup. Furthermore, 2-chloropyrazine is known to decompose under the reaction conditions. Thus, a different synthetic approach was desired for scale-up.

An alternative synthetic method[5] leading to benzo-fused cases (route B, Scheme 1) involved the condensation of a chloromethyloxadiazole with 1,2-phenylenediamine to afford the desired benzene-fused [1,2,4]triazolo[4,3-α]piperazines directly. The reaction conditions were rather harsh, and the yields reported were low, which can be attributed to the poor nucleophilicity of 1,2-phenylenediamine. The application of this approach to the synthesis of **1a** would result in milder reaction conditions due to the enhanced nucleophilicity of ethylenediamine and the electron-withdrawing nature of the trifluoromethyl[6] group.

The key intermediate chloromethyloxadiazole **3a** was prepared in two steps from commercially available materials as shown in Scheme 2. Bishydrazide **2a** was prepared in a

Scheme 2. Preparation of Oxadiazole **3a**

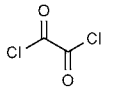
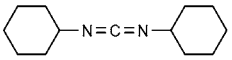
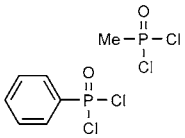


one-pot procedure by reaction of 35% aqueous hydrazine[7] with ethyl trifluoroacetate in acetonitrile and subsequent addition of an acyl chloride and base. This procedure affords the unsymmetrical bis(hydrazide) **2a**, which can be isolated by crystallization in higher than 95% yield.

Dehydration of **2a** to obtain the desired oxadiazole **3a**[8] can be accomplished using a variety of known reagents. The results for the preparation of oxadiazole **3a** are summarized in Table 1.

Although the best yield was obtained using phenylphosphonic dichloride (88%), the use of phosphorus oxychloride was overall more desirable because of the comparable yield, lower cost, and more benign waste streams.

Table 1. Use of Different Dehydrating Agents for the Formation of Oxadiazoles[a]

Dehydration reagent	Yield
$POCl_3$	79%
$(CH_3SO_2)_2O$/DMAP	Slow Reaction
CH_3SO_2Cl/DMAP	Slow Reaction
0.5 eq of $POCl_3$/DMAP	79%, slow react.
 /DMF	No Reaction
$SOCl_2$/DMAP	55%
4.1 eq of $SOCl_2$	56%
	Decomposition
	72%
	88%

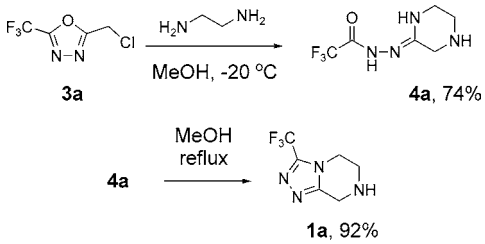
[a] All reactions were run under reflux in acetonitrile.

The dehydration reaction can be run with a substoichiometric amount of phosphorus oxychloride using a catalytic amount of DMAP. Comparable yields were obtained, albeit in much longer reaction times. Lower yields or more impurities were obtained when other dehydrating agents were used.

Under the optimized conditions, **3a** is obtained in 77−80% yield after aqueous workup. While **3a** can be isolated by distillation, it was used directly in the next step following removal of solvent.

When oxadiazole **3a** was added to a solution of 2 equiv of ethylenediamine in methanol at 0 °C, a new species formed that was found to crystallize from the reaction mixture at room temperature. This solid was isolated and identified as the amidine **4a**. Refluxing **4a** in methanol for 4 h afforded the desired triazole **1a** (Scheme 3).

Scheme 3. Preparation of Triazole **1a**



Further investigation of this reaction revealed that the amidine formed readily at −40 °C. At temperatures higher than 5 °C, the intermediate amidine **4a** slowly cyclizes to

(4) Nelson, P. J.; Potts, K. T. *J. Org. Chem.* **1962**, *27*, 3243−3248.
(5) Makino, T.; Kato, T. JP06128261(A), 1994.
(6) Perfluoroalkyl-substituted oxadiazoles are known to react readily with ammonia at room temperature to produce triazoles. (a) Brown, H. C.; Cheng, M. T. *J. Org. Chem.* **1962**, *27*, 3240−3243. (b) Brown, H. C.; Cheng, M. T.; Parcell, L. J. *J. Org. Chem.* **1961**, *26*, 4407−4409. (c) Reitz, D. B.; Finkes, M. J. *J. Heterocycl. Chem.* **1989**, *26*, 225−230. (d) Reitz, D. B.; Finkes, M. J. *J. Org. Chem.* **1989**, *54*, 1760−1762. (e) Barlow, M. C.; Bell, D.; O'Reilly, N. J.; Tipping, A. E. *J. Fluorine Chem.* **1983**, *23*, 293−299.
(7) A nonexplosive form of hydrazine is used as the limiting reagent. Hydrazine is completely consumed after the addition of trifluoroacetate. In this manner, no hazardous waste containing hydrazine is generated.
(8) (a) Perez, M. A.; Bermejo, J. M. *J. Org. Chem.* **1993**, *58*, 2628−2630. (b) Tashtoush, H.; Al-Talib, M.; Odeh, N. *Ann. Chem.* **1992**, *1992*, 291. (c) Al-Talib, M.; Tashtoush, H.; Odeh, N. *Synth. Commun.* **1990**, *20*, 1811−1817. (d) Shi, W.; Qian, X.; Song, G.; Zhang, R.; Li, R. *J. Fluorine Chem.* **2000**, *106*, 173−179. (e) Mogilaiah, K.; Chowdary, D. S.; Rao, R. B. *Indian J. Chem. Sect. B* **2001**, *40*, 43−48.

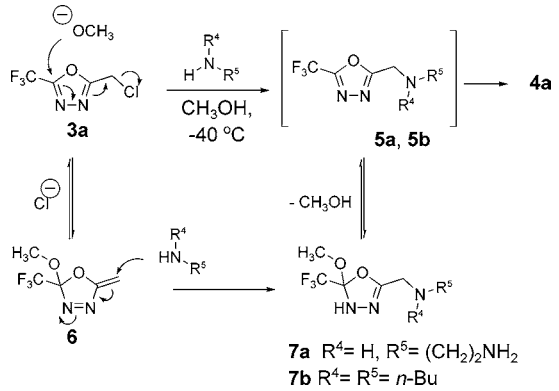
form triazole **1a**. An excess of ethylenediamine was necessary to neutralize the HCl generated and drive the reaction to completion. We found that complete reaction conversion can be achieved using 1.7 equiv of ethylenediamine. Under these conditions, a mixture of ethylenediamine hydrochloride and dihydrochloride is generated as a byproduct of the reaction. The ethylenediamine dihydrochloride, however, has low solubility in methanol and crystallizes contaminating the product. This can be avoided using a larger excess of ethylenediamine (2.8 equiv or more), which prevents the formation of ethylenediamine dihydrochloride by Schlenk equilibrium. Best yields were achieved at −20 °C, using 2.8 equiv of ethylenediamine. Under these reaction conditions, **4a** was isolated in 74% yield.

While the two-step transformation from **3a** to **1a** can be carried out in a one-pot procedure, the isolation of **1a** by crystallization from the reaction mixture containing excess ethylenediamine and its hydrochlorides proved to be troublesome. The amidine **4a** on the other hand can be isolated in high purity from the reaction mixture, and thus a two-step process was preferred.

The final cyclodehydration can be carried out thermally or by acid or base catalysis. Since **1a** was best isolated as its HCl salt, the reaction was run by addition of 1 equiv of concentrated HCl to a slurry of amidine **4a** at reflux in methanol. Under optimized conditions, triazole **1a** is isolated by filtration of the reaction slurry at 0 °C in 92% yield.

In an attempt to gain insight into the mechanism of this transformation, the reaction was examined by NMR at low temperature. At −40 °C in CD_3OD, oxadiazole **3a** was found to quickly disappear to form a new intermediate species that slowly converted to amidine **4a**. ^{13}C NMR data obtained for the intermediate species were consistent with an oxadiazole ring, where the chloride atom had been displaced by an amine nucleophile, and thus it was assigned to **5a** (Scheme 4).

Scheme 4. Proposed Mechanism for the Formation of **4a**



Neither of the two other possible intermediates resulting from nucleophilic attack on the heterocycle could be detected by NMR analysis of the reaction mixtures.[9]

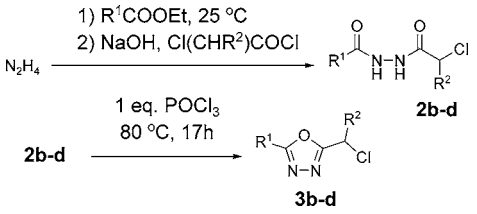
The observed fast nucleophilic displacement of the chloride of **3a** was unexpected even when considering the activation of this primary chloride by the inductive effect of the heterocycle. During experiments aimed at identifying byproducts generated during the reaction, two new species **6** and **7a** (Scheme 4) were detected in small amounts from the onset of the reaction and were almost completely consumed upon its completion. This suggests that **6** and **7a** are intermediates in the formation of **4a**, and a mechanism that explains their formation is proposed in Scheme **4**.

A molecule of solvent[10] acting as a nucleophile could attack on the more electrophilic C3, as expected from literature precedents.[6,11] Because of the presence of the leaving group, this would result in the elimination of chloride and formation of **6**. This species is likely to function as a Michael-type acceptor and react with ethylenediamine to generate **7a**. Elimination of methanol to regenerate the heterocycle would result in the formation of **5a**.

A simplified system was studied under the same reaction conditions, using 2 equiv of *N*,*N*-di-*n*-butylamine instead of ethylenediamine. As expected, **3a** cleanly underwent the chloride displacement to afford **5b**.

After optimizing reaction conditions for the preparation of **4a** and **1a**, the use of other substrates in the synthesis was investigated. Three chloromethyloxadiazoles (**3b**−**d**) were prepared in two steps from commercially available materials as shown in Table 2. Bishydrazides **2b**,**c** were

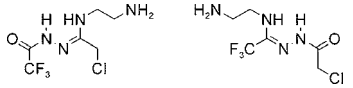
Table 2. Preparation of bishydrazides **2** and oxadiazoles **3**



entry	R^1	R^2	**2** (%)	**3** (%)
b	CF_3	Me	95	71
c	CF^3	Ph	95	65
d	Ph	H	70	80

prepared in a one-pot procedure by reaction of 35% aqueous hydrazine with ethyl trifluoroacetate in acetonitrile and subsequent addition of an acyl chloride and base. Bis(hydrazide) **2d** was prepared by treatment of the commercially available benzoylhydrazide with chloroacetyl chloride and base in acetonitrile. These procedures afforded the unsymmetrical bis(hydrazides) **2b**−**d**, which could be crystallized or, in most cases, carried through as an aceto-

(9) The other two possible structures resulting from nucleophilic attack on the heterocycle:



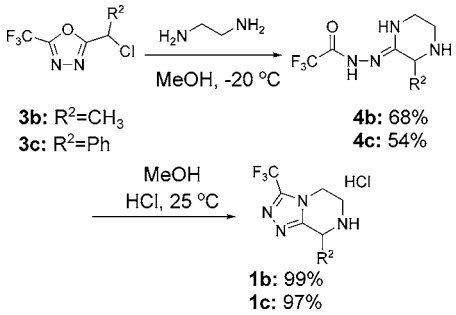
(10) When a nonnucleophilic solvent was used (acetonitrile), all the oxadiazole was consumed but only traces of amidine were observed.

(11) Similar reactivity has been reported on furans: (a) Divald, S.; Chun, M. C.; Joullie, M. M. *J. Org. Chem.* **1976**, *41*, 2835−2846. (b) Yamamoto, K.; Tanaka, A. *J. Heterocycl. Chem.* **1979**, *16*, 1293−1294.

nitrile solution and dehydrated using $POCl_3$, to obtain the desired oxadiazoles **3b**−**d** (Table 2).[8]

Oxadiazoles **3b** and **3c** having substitution on C7 and bearing the electron-withdrawing trifluoromethyl group reacted smoothly at low temperature with ethylenediamine to afford amidines **4b** and **4c** in 68 and 54% yields, respectively, after unoptimized crystallization from the reaction mixture.[12] The cyclodehydration reactions occurred in a few minutes at room temperature in the presence of HCl to afford the hydrochlorides of **1b**,**c** in quantitative yield (Scheme 5).

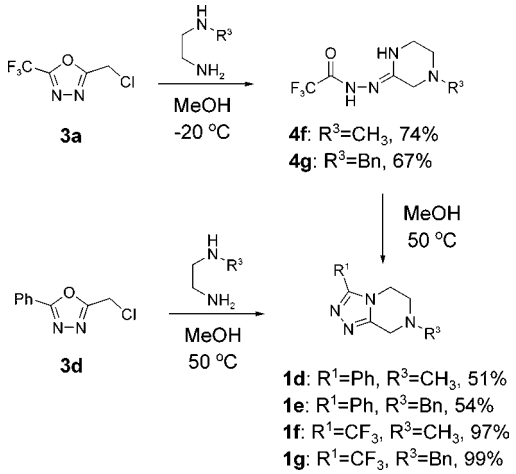
Scheme 5. Preparation of Substituted Triazoles **1b**,**c**



Not surprisingly, when we attempted the reaction using oxadiazole **3d**, which lacks the electron-withdrawing trifluoromethyl group, the reaction was not observed to occur at low temperatures. Warming the reaction mixtures to 50 °C for 8 h was required to facilitate the reaction. Under these conditions, however, other byproducts were generated that made purification of the desired compounds difficult. This problem can be overcome by using unsymmetrical diamines as nucleophiles in the reaction (Scheme 6), which leads to cleaner reactions and compounds than can be easily purified by chromatography. Both *N*-methyl and *N*-benzyl ethylenediamines reacted regioselectively with **3a** to afford amidines **4f**,**g** in good yields. Oxadiazole **3d** also reacted regioselectively with *N*-alkylethylenediamines at 50 °C. The resulting amidines spontaneously cyclized to afford triazoles **1d**,**e** in moderate yields.

(12) Chromatographic isolation is difficult due to the highly polar nature of these compounds.

Scheme 6. Preparation of Substituted Triazoles **1e**,**f**



In summary, we have developed an efficient synthesis for [1,2,4]triazolo[4,3-α]piperazines using a novel, modular approach that involves as a key step the reaction of a chloromethyloxadiazole with ethylenediamine. We also propose a mechanism that explains the high reactivity of electron-deficient chloromethyloxadiazoles in this reaction.

Acknowledgment. We thank Dr. Tom J. Novak for his help performing the high-resolution mass spectrometry analysis. We acknowledge Drs. Norihiro Ikemoto and Edward J. J. Grabowski for their help in editing this manuscript and helpful discussion.

Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0474406