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A Synthesis of *N*-Bridged 5,6-Bicylic Pyridines via A Mild Cyclodehydration Using the Burgess Reagent and Discovery of A Novel Carbamylsulfonylation Reaction

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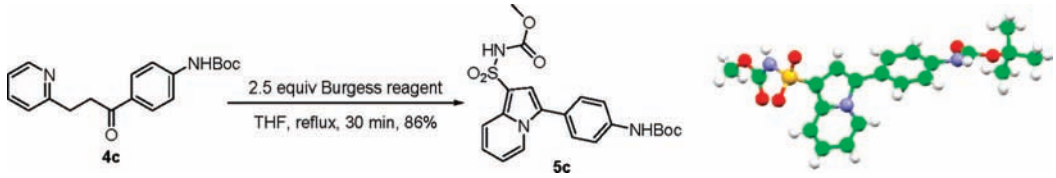
ABSTRACT



Cyclodehydration using the Burgess reagent provided a novel approach toward the synthesis of N-bridged 5,6-bicylic pyridines including pyrolo-, imidazo-, and triazolopyridines under mild and neutral conditions. The methodology tolerates acid-sensitive functional groups. A novel addition product was observed between the resulting pyrrolo- or imidazopyridine and an additional equivalent of the Burgess reagent, producing the corresponding sulfonylcarbamate adduct.

Pyrolo-, imidazo-, and triazolopyridines, belonging to a class of N-bridgehead 5,6-bicylic heterocycles, are important motifs in medicinal chemistry. For instance, pyrrolopyridine (indolizine) is the core structure of 5-HT_3 receptor antagonists such as **1**,[1a] calcium channel blockers,[1b] H_3 receptor antagonists,[1c] 15-lipoxygenase inhibitors,[1d] and phosphatase inhibitors.[1e] On the other hand, imidazopyridine is present in loprinone (Olprinone), a phosphodiesterase 3 (PDE-3) inhibitor,[2a] zolpidem (**2**, Ambien), and a γ-aminobutyric acid (GABA) modulator.[2b] Furthemore, triazolopyridines are found in MAP kinase inhibitors,[3a] growth hormone secretagogues,[3b] and CCR5 inhibitors such as [1,2,4]triazolo[4,3-*a*]pyridine **3**.[3c]

Conventional cyclodehydrations of substrate **4** to form bicyclic heterocycle **5** involve toxic, strong acidic, and/or corrosive reagents such as $POCl_3$,[4a] $SOCl_2$,[4b] Ph_3PCl_2,[4c] and

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(1) (a) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 1924–1929. (b) Gubin, J.; de Vogelaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425–1433. (c) Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767–1770. (d) Teklu, S.; Gundersen, L.-L.; Larsen, T.; Malterud, K. E.; Rise, F. *Bioorg. Med. Chem.* **2005**, *13*, 3127–3139. (e) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59–63.

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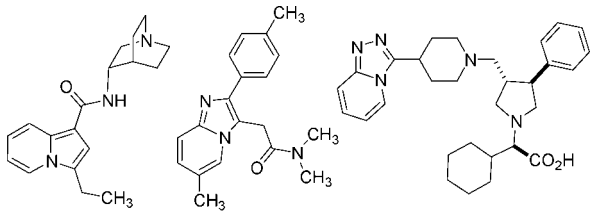
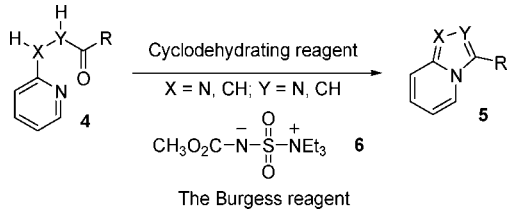


Figure 1. Examples of *N*-bridged 5,6-bicyclic pyridines in drugs.

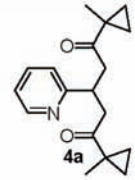
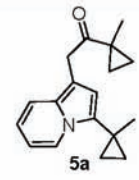
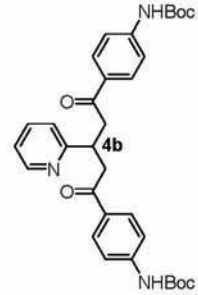
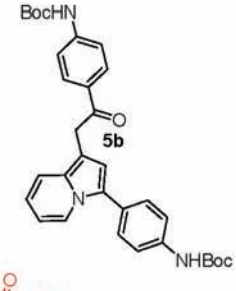
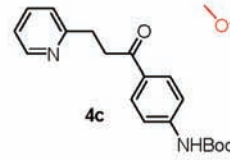
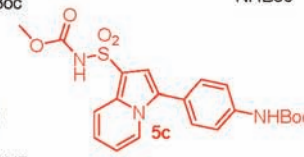
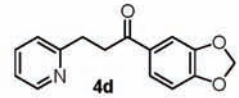
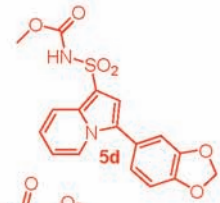
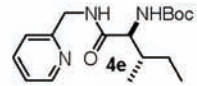
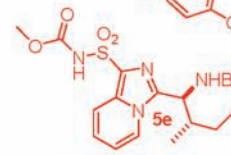
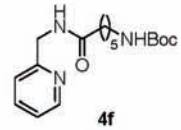
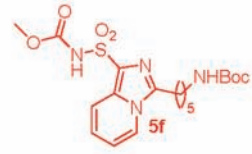
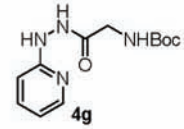
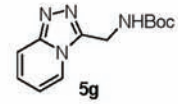
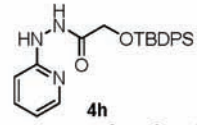
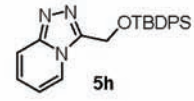
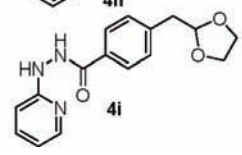
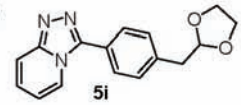
P_2O_5,[4d] etc. Cyclodehydration using Lawsson's reagent[5a] and a modified Mitsunobu reaction[5b] to prepare triazolopyridines and triazolopyrimidines have been reported recently. The Burgess reagent [**6**, (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt] is a neutral, white crystalline solid. Since Burgess invented the reagent (**6**) in 1968,[6] it had not received much attention from the organic chemistry community until Wipf used it to carry out cyclodehydrations of β-amino alcohols to make the corresponding oxazolines.[7] Recently, Nicolaou has incorporated the Burgess reagent into reaction sequences to make sulfamidates, glycosylamines, and sulfamides.[8] Several reviews have appeared during the past few years summarizing the utility of the Burgess reagent.[9] One potential drawback limiting the use of the Burgess reagent is the cost of the compound. However, the material can be conveniently prepared on a large scale,[10] and all the starting materials are readily available and inexpensive.

Scheme 1. Cyclodehydration



We investigated a unified approach of cyclodehydration using the Burgess reagent to prepare pyrolo-, imidazo-, and triazolopyridines (Scheme 1). Substrates **4a** and **4b** in Table 1 were prepared by aldol condensation of 2-pyridinecarboxaldehyde (**7**) with 2 equiv of methyl ketone **8** as shown in Scheme 2.[11] Also formed was the Claisen−Schmidt adduct

Table 1. Cyclodehydration Using the Burgess Reagent

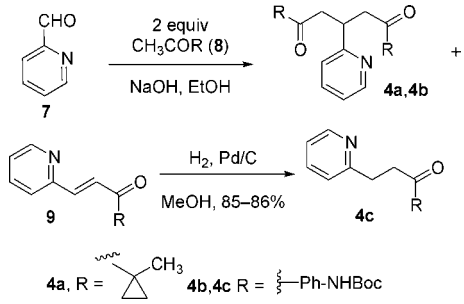
entry	substrate	product	yield (%)
1			75[a]
2			80[a]
3			86[a]
4			67
5			64
6			56
7			57
8			63
9			54

[a] Indolizidines **5a**, **5b**, and **5c** are unstable under light, and coloration (blue for **5a**, yellow for **5b**, and pink for **5c**, respectively) readily takes place if not stored in amber containers.

(2) (a) Endoh, M. *Cardiovasc. Drug Rev.* **1993**, *11*, 432–450. (b) Guzzo, P. R. *GABAA Receptor Agonists for Insomnia: Zolpidem (Ambien®), Zaleplon (Sonata®), Eszopiclone (Estorra®, Lunesta®), and Indiplon in The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; Wiley & Sons: Hoboken, NJ, 2007.

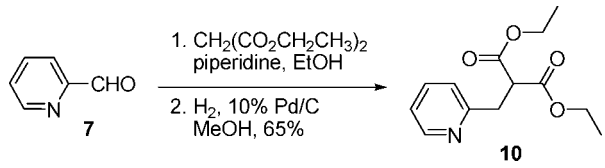
(3) (a) Dembroski, M. A.; Letvic, M. A.; McClure, K. F. USP Appl. 2004077682. (b) Yu, G.; Li, J.; Ewing, W. R.; Sulsky, R. B.; Li, J. J.; Tino, J. A. PCT Int. Appl. 2004021984. (c) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129–2134.

Scheme 2. Synthesis of Substrates **4a**−**c**



9 (where R = Ph-NHBoc), which was hydrogenated to produce substrate **4c**. Substrate **V**, as a bis-ester, was obtained by reaction of **7** with ethyl acetoacetate catalyzed by piperidine followed by hydrogenation (Scheme 3).[12] Substrate **4d** was prepared using a method similar to that of **4c**. Substrates **4e** and **4f** were prepared using the DCC-mediated

Scheme 3. Synthesis of Substrates **10**



coupling reactions between pyridin-2-ylmethaneamine and the corresponding carboxylic acids. Similarly, **4g**−**i** were readily assembled by the treatment of 2-hydrazinopyridine with the pivaloyl mixed anhydrides of the corresponding 2-substituted acetic acids.

With the substrates **4a**−**i** in hand, cyclodehydration was carried out by simply adding the Burgess reagent to a THF solution of the substrate. The resulting solution was heated to reflux. For different substrates, we observed stark differences in their reactivities toward cyclization. In the case of ketone **I** (see Figure 2) dehydrative cyclization proceeded

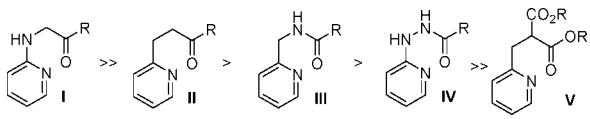


Figure 2. Substrates reactivities for cyclodehydration.

so readily that only the products **5** (Scheme 1 where X = N, Y = CH) were observed even during substrate preparation. In this situation, the Chichibabin indolizine synthesis,[13] involving quaternization of 2-substituted pyridine with α-halocarbonyl compounds followed by cyclization of the quaternary salt, is assumed to have occurred.[14] For substrate **II** (entries 1−4 in Table 1), spontaneous cyclization did not occur, and cyclodehydration with the Burgess reagent was effected within 0.5 h in refluxing THF. When R = $-C(OCH_3)_2CH_3$ for substrate **II**, no reaction took place possibly due to steric hindrance. While cyclodehydration of amide **III** was complete within 8 h, cyclodehydration of hydrazide **IV** was much more sluggish, taking over 18 h to finish. For substrate **10**, no cyclodehydration product was observed after 2 days of reflux. Presumably, the inactivity of **10** stems from the electronic effect of the ester. Furthermore, this method is sensitive to steric hindrance as well. Noteworthy is the observation that sensitive functionalities present in many of these substrates (e.g., NH-Boc, dimethyl ketal, OTBDPS) are stable under these conditions. Though limited in examples, the conditions are also mild enough to avoid racemization of epimerizable substrates (e.g., entry 5, Table 1).

Interestingly, as shown in entries 3−6 in Table 1, the initial cyclodehydration products were reactive enough to undergo an electrophilic substitution with an additional 1 equiv of the Burgess reagent, giving rise to adducts **5c**−**f**, respectively. The structures of **5c** (shown in Figure 3) and **5e** were

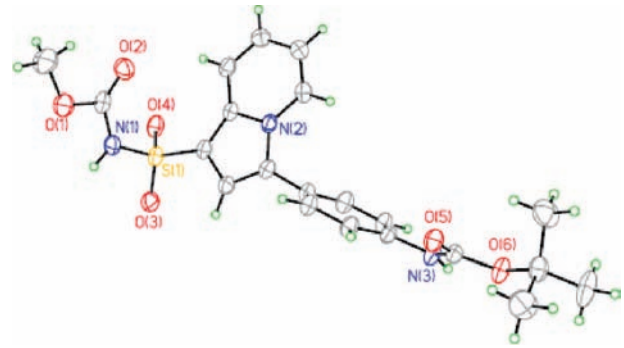


Figure 3. ORTEP of **5c** from X-ray crystallography.

unambigeously demonstrated by single-crystal X-ray crystallography (the X-ray coordinates for **5c** and **5e** may be found in the Supporting Information). *To the best of our knowledge, this is the first report of these sulfonylcarbamate adducts to pyrrolo- and imidazopyridines*. Although their utility is not immediately evident, it provides a means for making these unique heterocyclic sulfonylcarbamates. The scope and limitations of this novel reaction will be reported in due course. Attempts were made to stop the electrophilic substitution by using less than 1 equiv of the Burgess reagent.

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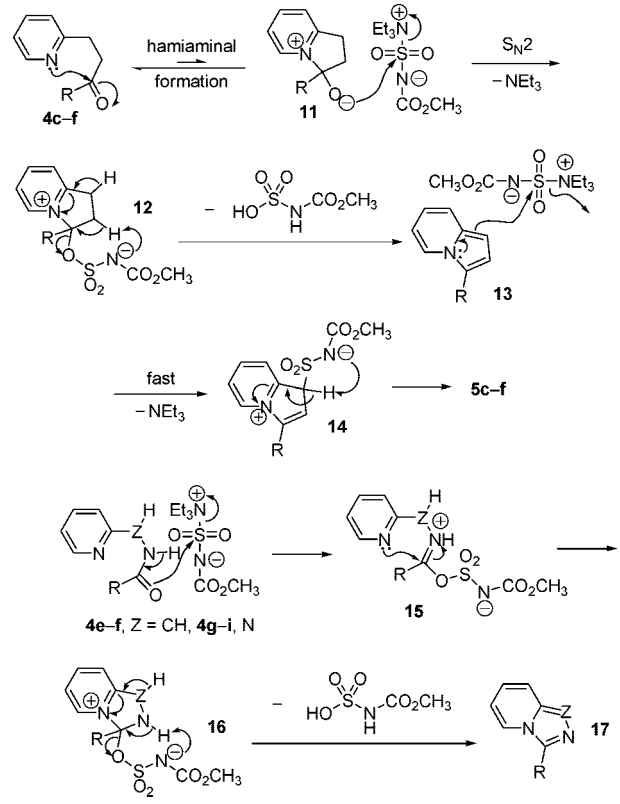
However, the sulfonylcarbamate adduct formation seems to be much faster than the cyclodehydration reaction, and no pyrrolo- and imidazopyridines were isolated.

The proposed mechanism for the cyclodehydration using the Burgess reagent is shown in Scheme 4.[15] For ketone substrates **4c**,**d**, a tiny percentage of the molecule might present in the form of hemiaminal **11**. However, addition of the Burgess reagent to **11** drives the equilibrium to the right where hemiaminal **11** forms adduct **12**. Intramolecular proton abstraction of **12** takes place to provide aromatized intermediate **13** while losing one molecule of methylcarbonylsulfamic acid. Pyrolopyridines **13** are reactive[16] toward the Burgess reagent. Thus, nucleophilic substitution between **13** and the additional equivalent of the Burgess reagent affords intermediate **14**, which undergoes rapid intramolecular proton abstraction followed by isomerization to afford sulfonylcarbamates **5c**,**d**. Similarly, amide substrates **4e**,**f** and hydrazide substrates **4g**−**i** may undergo mechanistic pathway invovling a Vilsmeier-type mechanism with iminium salts **15** as the key intermediates.

Scheme 4. Proposed Mechanism for the Cyclodehydration and Further Addition of the Second Equivalent of the Burgess Reagent



Supporting Information Available: Typical and detailed experimental procedures, ^1H and ^{13}C NMR spectra, and data of all substrates **4a**−**i** and as cyclodehydration products **5a**−**i**. X-ray crystallographic details and coordinates of **5c** and **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We are grateful to Prof. Phil Baran's insight into the mechanism.

(16) Imidazo[1,5-*a*]pyridine undergoes a regiospecific acylation through a similar mechanism; see: (a) Hlasta, D. *Tetrahedron Lett.* **1990**, *31*, 5833–58344.