

# The Reaction of Cyclic Carbinol Amides with Triflic Anhydride as a Method to Prepare $\alpha$ -Trifluoromethyl-Sulfonamido Furans

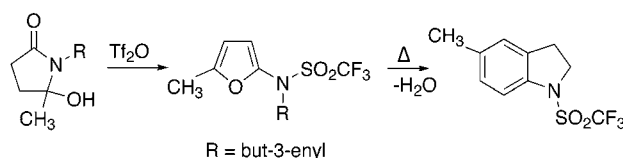
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## ABSTRACT



A novel synthesis of  $\alpha$ -trifluoromethyl-sulfonamido furans via the reaction of cyclic carbinol amides with triflic anhydride has been developed. The reaction proceeds under very mild conditions with a wide set of representative lactams to provide the  $\alpha$ -trifluoromethyl-sulfonamido-substituted furan in high yield. Rapid access to a 5-substituted indoline can be achieved by thermolysis of the *N*-but-3-enyl-substituted sulfonamido furan.

The  $\alpha$ -amidoalkylation/cyclization sequence involving *N*-acyliminium ions is widely regarded as a powerful method for the synthesis of nitrogenated heterocyclic compounds.<sup>1,2</sup> Cyclic  $\alpha$ -alkoxy amides are among the most popular precursors for *N*-acyliminium ions.<sup>3</sup> Typically, these versatile systems (e.g. **2a–c**) are prepared by electrochemical oxidation of amides<sup>4</sup> or by treating cyclic imides (i.e. **1**) with various organometallic reagents.<sup>5</sup> Subsequent *N*-acyliminium formation (**3**) by Lewis or protic acids followed by trapping with various tethered  $\pi$ -bonds returns the amido-alkylation

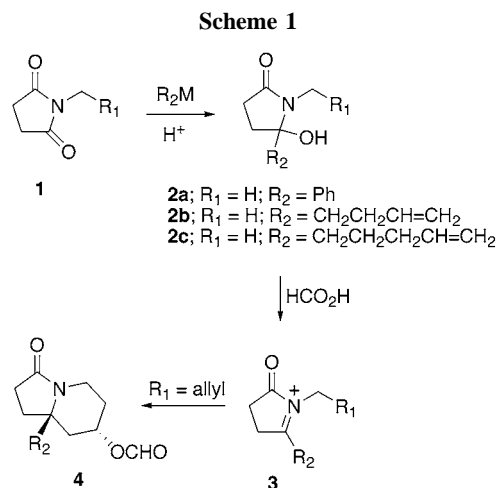
(1) For reviews see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 1047–1082.

(2) Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, p 227.

(3) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(4) (a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206.

(5) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 7115. De Koning, H.; Speckamp, W. N. In *Houben-Weyl, Methods in Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1995; Vol. E21b, pp 1953–2009.

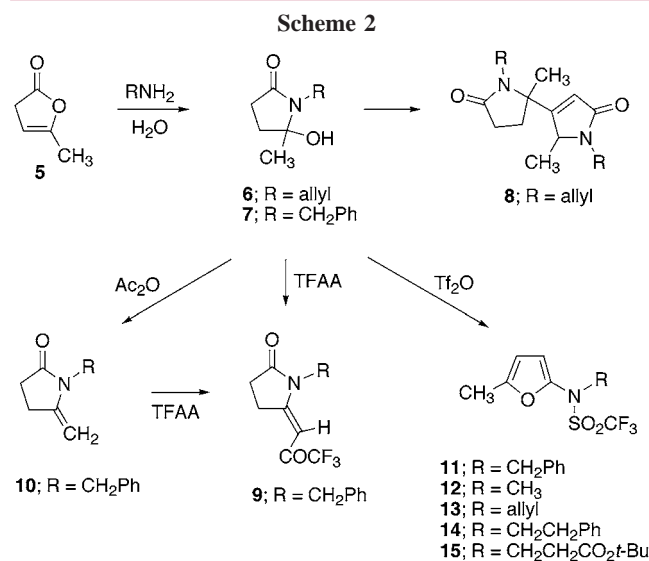


products (**4**) in good to excellent yields (Scheme 1).<sup>6</sup> Often the judicious choice of a Lewis acid can greatly influence

(6) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999. Pilli, R. A.; Zanotto, P. A.; Böckelmann, M. A. *Tetrahedron Lett.* **2001**, *42*, 7003.

the outcome of the cyclization reaction.<sup>7</sup> Herein, we report on the reaction of cyclic carbinol amides with triflic anhydride as a method to prepare various  $\alpha$ -trifluoromethyl-sulfonamido furans, some of which can be further utilized for cycloaddition chemistry.

Recent work in our laboratory has shown that the reaction of  $\alpha$ -angelica lactone (**5**) with various alkylamines under aqueous conditions afforded 5-hydroxy-5-methylpyrrolidinones (**6**, **7**) in high yield (Scheme 2).<sup>8</sup> When **6** was treated



with *p*-TsOH in benzene at 100 °C, dimer **8** was formed as the major product. On the other hand, the reaction of **7** with trifluoroacetic anhydride (TFAA) furnished enamide **9** in 79% yield, presumably by an elimination/acylation process. The structure of **9** was unequivocally established by a single-crystal X-ray analysis. The pathway suggested for the formation of **9** was supported by the finding that the reaction of **7** with acetic anhydride gave enamide **10** which, in turn, was converted to **9** upon treatment with TFAA. Most interestingly, when a sample of **7** was allowed to stir with 2 equiv of triflic anhydride<sup>9</sup> and pyridine in  $\text{CH}_2\text{Cl}_2$ ,  $\alpha$ -trifluoromethyl-sulfonamido furan **11** was formed in 79% yield. This reaction was quite general affording related sulfonamido furans with a broad range of alkylamines (i.e., **12**–**15**). The same reaction occurred in good yield when cyclic carbinol amides **2a**–**c** were treated with triflic anhydride in  $\text{CH}_2\text{Cl}_2$ . Cyclization to the sulfonamido furan also came about with the isomeric  $\gamma$ -keto amide system **16**,<sup>10</sup> giving rise to furan **17** in excellent yield (Scheme 3). In fact, cyclization to the

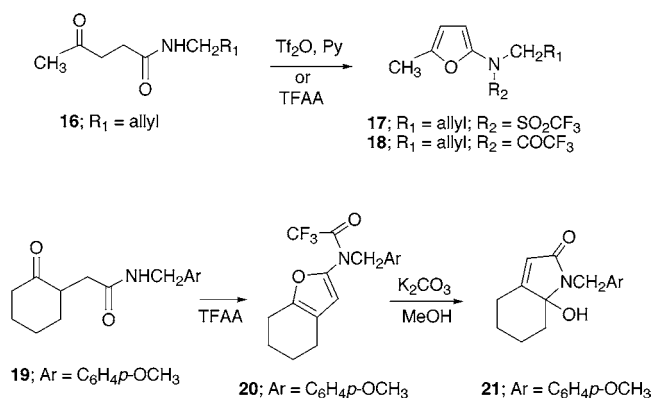
(7) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419. Keum, G.; Kim, G. *Bull. Korean Chem. Soc.* **1994**, *15*, 278. Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641.

(8) For some related work, see: Jones, J. B.; Young, J. M. *Can. J. Chem.* **1966**, *44*, 1059.

(9) For some reviews dealing with triflic anhydride, see: Ritter, K. *Synthesis* **1993**, 735. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077.

(10) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. J. *Org. Chem.* **1997**, *62*, 2080.

**Scheme 3**



furan also took place when trifluoroacetic anhydride was used as the acylating agent. Both **16** and the related cyclic keto amide **19** underwent smooth cyclization with TFAA to furnish furans **18** and **20** in high yield. Attempts to remove the trifluoroacetyl group of **20** under basic conditions with  $\text{K}_2\text{CO}_3/\text{MeOH}$  resulted in an oxidative rearrangement giving carbinol amide **21** in modest yield.

Recently, Charette and co-workers have demonstrated that secondary and tertiary amides can be activated with triflic anhydride to generate the corresponding iminium salts which can react further with various nucleophiles.<sup>11</sup> Iminium triflates were originally used by Ghosez as precursors of ketiminium cations which can function as electrophilic substrates in [2+2]-cycloadditions.<sup>12</sup> It would seem that when a hydroxy pyrrolidinone such as **7** is used as the tertiary amide, the resulting iminium ion (i.e., **22**) derived from the reaction of **7** with triflic anhydride undergoes a facile ring opening as a consequence of the adjacent hydroxyl group to produce imino triflate **23** (Scheme 4). Subsequent cyclization of this highly electrophilic imine<sup>13</sup> with the oxygen atom of the adjacent carbonyl group results in the formation of imino dihydrofuran **24**. This transient species reacts further with another equivalent of triflic anhydride to give the observed furan. By using only 1 equiv of triflic anhydride and then adding a second equivalent of acetyl chloride, acetylation of **24** occurred in modest yield leading to the related *N*-acetyl furan **25** (R =  $\text{CH}_2\text{Ph}$ ).

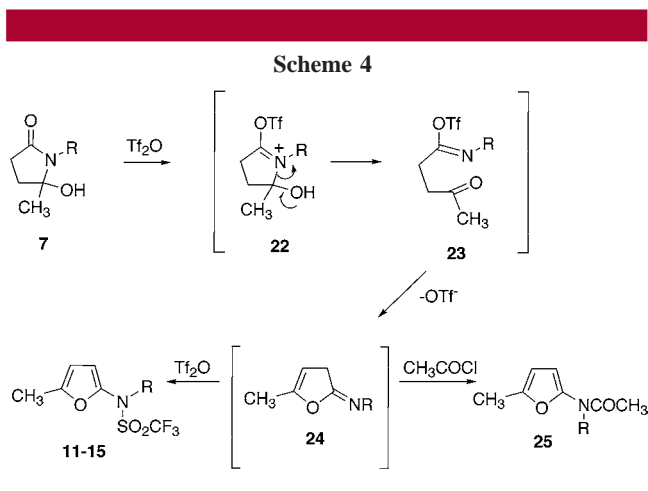
The indoline nucleus is a key structural feature found in a large number of alkaloids and related compounds, many of which exhibit potent pharmacological activity.<sup>14</sup> It is not surprising that numerous routes have been devised over the

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years to construct this important heterocyclic system.<sup>15</sup> New procedures that can selectively generate indolines with substituent groups in the aromatic ring would be of use to the medicinal community. During the course of our studies with these novel 2-sulfonamido furans, we found that rapid access to 5-substituted indolines could easily be achieved from thermolysis of the *N*-but-3-enyl furan **17** (or **18**).

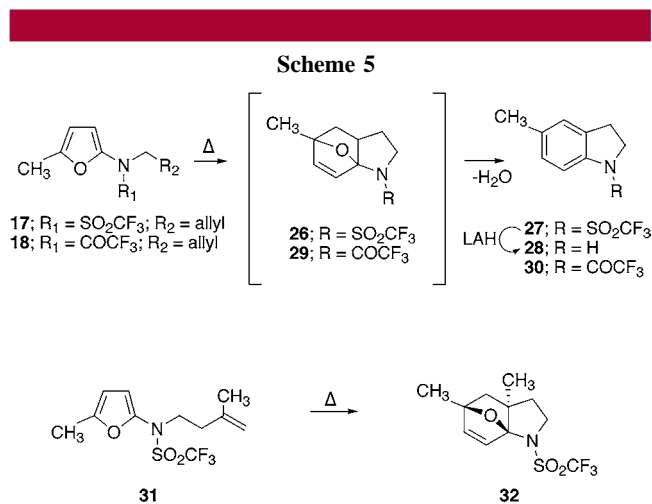
Previously we had prepared 2-amido furans from either the *N*-alkylation of carbamates or the copper-catalyzed amidations of 2-bromo furans<sup>16</sup> and have shown that these heteroaromatic systems are useful substrates for [4+2]-cycloaddition chemistry.<sup>17</sup> We have extended our earlier studies to include the IMDAF (intramolecular Diels–Alder of furans)<sup>18</sup> reaction of furans **17** and **18** which are easily prepared from  $\alpha$ -angelica lactone **5**. Thermolysis of furan **17** in toluene at 130 °C for 4 h furnished indoline **27** in 96% yield. More than likely the reaction proceeds through the [4+2]-cycloadduct **26**, which readily loses water to produce **27** (Scheme 5). Reduction of **27** with LiAlH<sub>4</sub> furnished indoline **28** in 90% yield. A related set of reactions also occurred with the *N*-trifluoroacetyl furan **18** leading to indoline **30** via cycloadduct **29**. The cycloaddition of furan **17** is about three times faster than that of **18** and is probably related to HOMO–LUMO considerations. It would seem as though the  $\pi$ -electron-withdrawing trifluoroacetyl group diminishes the ability of the electron pair on nitrogen to interact with the adjacent  $\pi$ -array of the heteroaromatic ring thereby decreasing the overall rate of the HOMO-controlled reaction.

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The [4+2]-cycloaddition was also carried out with tethered alkenes that possess a substituent on the 3-position of the  $\pi$ -bond and, in this case, cycloadduct **32** could be isolated in 85% yield. The formation of a single diastereomer where the oxygen bridge and methyl groups are anti to each other is perfectly consistent with other reports in the literature for related furanyl systems possessing short tethers.<sup>19</sup> The Diels–Alder prefers to occur where the sidearm of the tethered alkenyl group is oriented syn (*exo*) with respect to the oxygen bridge. This result is not so surprising since, in these mobile cycloaddition equilibria, the *exo*-adducts are expected to be thermodynamically more favored.

In summary, an efficient method for the conversion of cyclic carbinol amides into  $\alpha$ -trifluoromethyl-sulfonamido furans has been uncovered. The procedure takes place under very mild conditions with a wide set of representative hydroxy lactams. In certain cases the resulting sulfonamido furans have been utilized as substrates for the synthesis of indolines and related heterocyclic systems. We are further evaluating their cycloaddition behavior for alkaloid synthesis and results along these lines will be disclosed in due course.

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**Supporting Information Available:** Complete description of the synthesis and characterization of all compounds prepared in this study and an Ortep drawing for compound **9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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