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Diastereoselective Cycloadditions of New Trifluoromethyl Azomethine Ylides Derived from Trifluorothioacetamides

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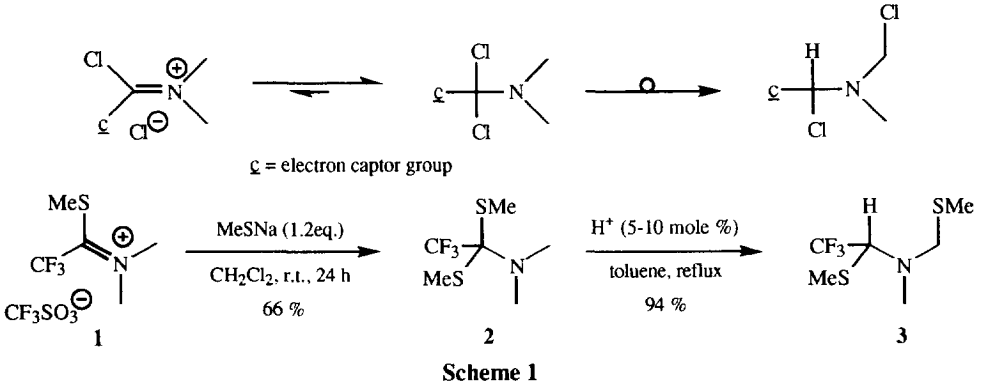
Abstract: *Two methods of generation of new trifluoromethyl azomethine ylides are described: by heating N,N-dimethyl-bis(methylthio)-orthotrifluoroacetamide 2 or by deprotonation of trifluoromethyl thioamidium salts. Trapping by dipolarophiles leads to 2-trifluoromethyl pyrrolidines and pyrrolizidines with high diastereoselectivity.*

Whereas most amide chlorides are generally rather stable on heating[1], amide chlorides with dichloromethylene in *capto-dative* position undergo thermal isomerisation to α,α'-dichlorosubstituted tertiary amines[2]. Most efficient are π-acceptors but CF_3 or CCl_3 substituents also permit this α,α'-rearrangement. We have found that analogous dithioethers such as the N,N-dimethyl-*bis*(methylthio)-orthotrifluoro-acetamide **2**, derived from trifluorothioamidium salt **1**, follow the same pattern of rearrangement producing **3**, but under acid catalysis (**Scheme 1**).

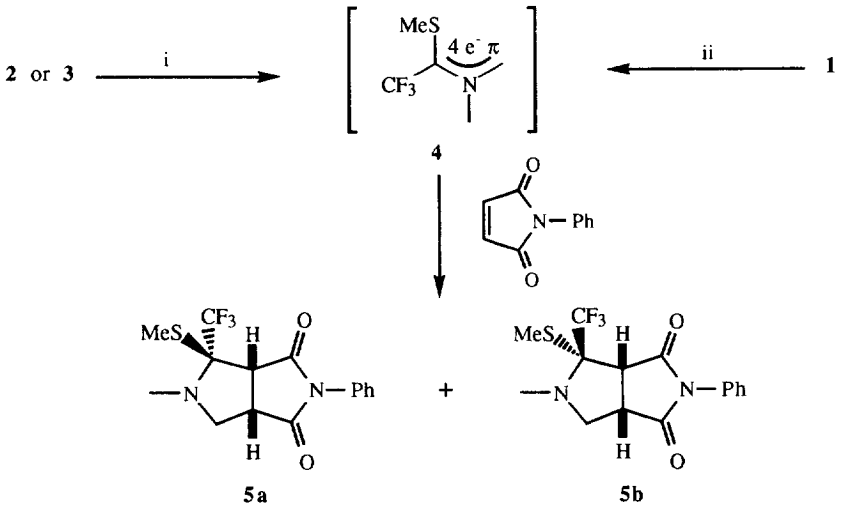


1 **2** **3**

Scheme 1

This rearrangement was obviously thought to proceed through a 1,3 dipolar pathway. Therefore, on heating **2** or **3** in the presence of N-phenylmaleimide, the intermediate azomethine ylide **4** was intercepted leading to 2-trifluoromethyl pyrrolidine diastereomers **5a** and **5b** in 81% yield. The direct formation of the

azomethine ylide **4** from trifluorothioamidium salt **1** by deprotonation was also successfully performed (**Scheme 2**). Thus, either the readily accessible thioamidium salt **1** or the derived dithioether amines **2** or **3** are starting materials for the intermediate dipole **4**. Our direct approach is particular for the trifluoromethyl substitution but complementary to the methods already described and reviewed recently[3].



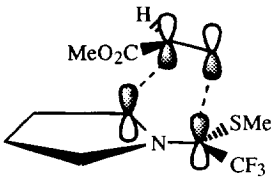
5a **5b**

i. toluene, reflux, 24 h (81 %) (**5a:5b**=1:1.5)

ii. DBU (1.2eq.), CH_2Cl_2, 0°C, 12 h (67 %) (**5a:5b**=1:1.7)

Scheme 2

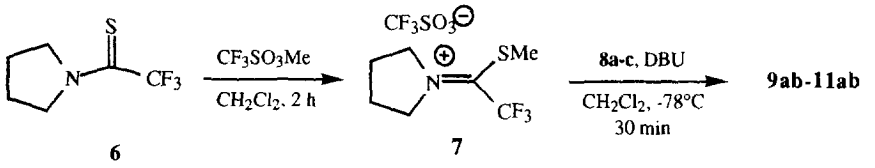
We describe here the deprotonation procedure[4] typically employed for the transformations outlined in **Scheme 4** and **Table 1**. These results show that the trifluoromethyl thioamidium salts derived from pyrrolidine can also be used[5]. The electron-withdrawing CF_3 group facilitates deprotonation of thioamidium salts. Cycloadditions performed at -78°C with 1.5 eq. of DBU produce, with electron deficient olefins **8a-c**, pyrrolizidine structures with high diastereoselectivity. This can be rationalised both by mainly *syn* CF_3 dipole formation and *endo* dipolarophile approach and by HOMOdipole-LUMOdipolarophile interaction leading to only one regioisomer (**Scheme 3**).



Scheme 3

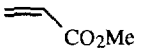
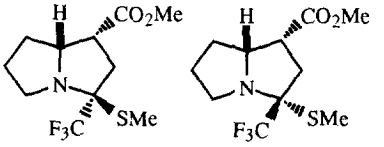
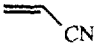
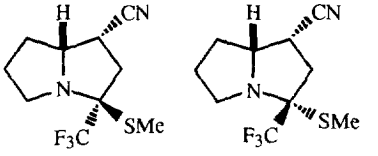
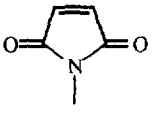
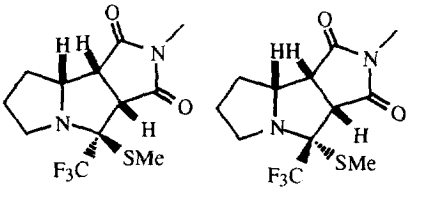
General Procedure: Methyl triflate (1.1 eq) was added to a solution of 1 g. of thioamide **6**[6] in 1 ml of dry dichloromethane. After 2 h of stirring at room temperature, 30 ml of dry dichloromethane followed by 1.5 eq. of dipolarophile were added to the solution. The mixture was cooled to -78°C and then 1.5 eq. of DBU was added *via* a syringe. After 30 min at -78°C, the solvent was evaporated and 10 ml of water was added. The mixture was extracted with ether and the organic phase was dried over Na_2SO_4. Evaporation of the solvent followed by chromatography on silica gel or alumina then furnished the pure cycloadducts. The configuration of the new compounds was assigned based on NMR data and *via* their correlation with the structure of the morpholino

analogue proven by X-ray analysis[7]. In the products **5a** and **5b**, coupling constants $^3J_{CF_3\text{-}H}$ are respectively 0 Hz and 4.5 Hz. These results are indicative of a *trans* (**5a**) and a *cis* (**5b**) relationship between trifluoromethyl group and the proton. Similar coupling constants are observed for **11a** and **11b**; respectively 0 Hz and 4 Hz.



6 **7**

Scheme 4

Dipolarophiles	**Products[a] (ratio a:b)[b]**	**Yields**
 **8a**	 **9a** (95 : 5) **9b**	57 %
 **8b**	 **10a** (96 : 4) **10b**	50 %
 **8c**	 **11a** (88 : 12) **11b**	66 %

a Satisfactory spectroscopic data have been obtained for all new compounds[8].
b Ratios have been determined from ^{19}F NMR spectra of the solution after reaction.

Table 1

In conclusion, we have described that trifluoromethyl thioamidium salts, derived from readily accessible trifluorothioacetamides, are easily deprotonated to give new azomethine ylides which undergo cycloaddition to olefins with high regio- and diastereoselectivity and allow access to new trifluoromethylated pyrrolidines or pyrrolizidines.

Acknowledgements

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References and notes

1. Depending on their substituents, dehydrochlorination or dehaloalkylation are well documented: a) Bonnett, R. in *The Chemistry of the Carbon-Nitrogen Double Bonds*, Patai Ed.; Interscience, New York 1970, Chapter 13; b) Ulrich, H. in *The Chemistry of Imidoyl Halides*, Plenum Press, New York 1968, Chapter 3; c) Kantlehner, W. in *Iminium salts in organic chemistry*, Part 2; Böhme H. and Viehe H.G. Eds.; Wiley Interscience, New York 1976, p. 118.
2. a) Huys, F.; Merényi, R.; Janousek, Z.; Stella, L.; Viehe, H. G. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 615-616; b) Viehe, H. G.; Merényi, R.; Janousek, Z. *Pure & Appl. Chem.* **1988**, *60*, 1635-1644; c) Viehe, H. G.; Janousek, Z.; Merényi, R. in *Free Radicals in Synthesis and Biology*; Minisci F. Ed.; Kluwer Academic Publishers 1989. pp. 1-26 and references cited therein.
3. a) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1996**, *37*, 711-714; b) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1995**, *36*, 9409-9412; c) Magedov, I.; Kornienko, A. V.; Zotova, T. O.; Drozd, V. N. *Tetrahedron Lett.* **1995**, *36*, 4619-4622; d) Katritzky, A. R.; Zhu, L.; Lang, H.; Denisko, O.; Wang, Z. *Tetrahedron* **1995**, *51*, 13271-13276 and references cited therein.
4. The formation of **4** *via* **2** or **3** and the related rearrangement studies will be published separately.
5. Other cyclic amino derivatives are currently being studied.
6. The starting thioamides were prepared from amides by thionation with P_4S_{10} in excellent yields.
7. Tinant, B.; Declercq, J. P.; Laduron, F.; Viehe, H. G.; to be published separately.
8. New structures have been characterized by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, IR, mass spectroscopy and micro analysis. ^{19}F NMR spectroscopic data of the cycloadducts are as follow ($CDCl_3$, ref. $CFCl_3$): **5a**: -66.8, **5b**: -68.2, **9a**: -70.4, **9b**: -76.5, **10a**: -71.5, **10b**: -75.7, **11a**: -68.1, **11b**: -71.8 ppm.

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