ORGANIC LETTERS

2012
Vol. 14, No. 7
1900–1901

Preparation of Trifluoromethyl-Substituted Aziridines with in Situ Generated CF_3CHN_2

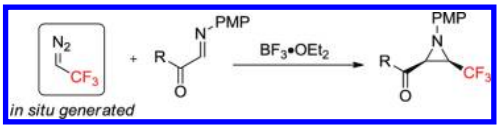
Stefan A. Künzi, Bill Morandi, and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

Received March 2, 2012

ABSTRACT

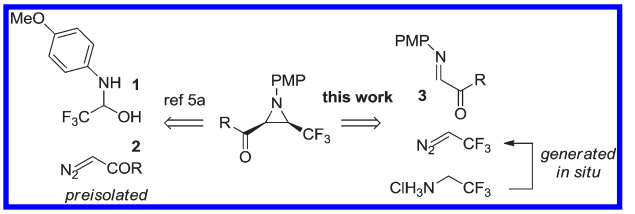


Direct access to trifluoromethyl-substituted aziridines through the use of a protocol in which trifluoromethyl diazomethane is generated in situ and subsequently undergoes addition to activated imines is reported.

Fluorinated units are important for drug discovery because of their ability to influence physical properties of drug candidates.[1] Consequently, there is a need for the discovery of efficient methods to prepare fluorinated building blocks. In line with previous work from our group dealing with the preparation of trifluoromethyl-substituted fragments using in situ generated trifluoromethyl diazomethane,[2] we report herein the development of an aza-Darzens reaction involving activated imines and trifluoromethyl diazomethane generated in situ that affords valuable functionalized trifluoromethylated aziridines.

The aza-Darzens is one of the most direct routes for the preparation of aziridines.[3] In this respect, the use of diazo alkanes as nucleophiles in combination with a variety of Brønsted or Lewis acids as catalysts or reagents have found widespread use.[4] Despite the rich literature on aziridine preparation, few examples of trifluoromethyl-substituted aziridines syntheses can be found, and these display limited substrate scope or involve the implementation of multistep synthesis sequences.[5]

Scheme 1. Strategies for Trifluoromethyl Aziridine Preparation



Two distinct strategies are possible as a means of accessing trifluoromethyl-substituted aziridines from imines and diazocompounds employing the aza-Darzens reaction (Scheme 1). The first one, reported by Akiyama and coworkers in 2003, involves the use of trifluoroacetaldehyde N,O-acetal **1** and a collection of diazoketones or ester

(1) (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (b) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (b) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (e) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (f) Morandi, B.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5984. (g) Morandi, B; Carreira, E. M. *Science* **2012**, *335*, 1471.

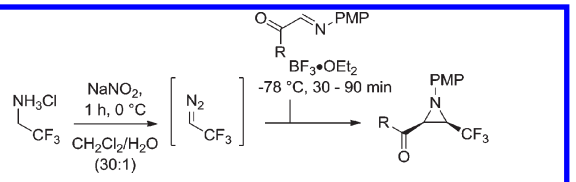
(3) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911.

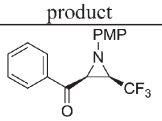
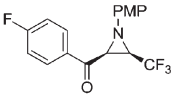
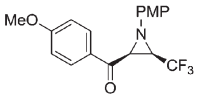
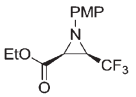
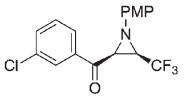
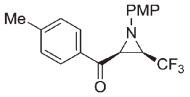
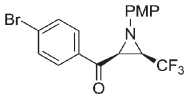
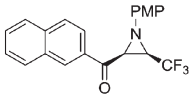
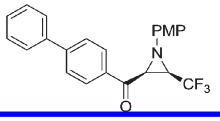
(4) For Lewis acid promoted reactions, see: (a) Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358. For Brønstedt acid promoted reactions, see: (b) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612. (c) Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643. (d) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445.

(5) (a) Akiyama, T.; Ogi, S.; Fuchibe, K. *Tetrahedron Lett.* **2003**, *44*, 4011. (b) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197. (c) Maeda, R.; Ooyama, K.; Anno, R.; Shiosaki, M.; Azema, T.; Hanamoto, T. *Org. Lett.* **2010**, *12*, 2548. (d) Khomutov, O. G.; Filyakova, V. I.; Pashkevich, K. I. *Russ. Chem. Bull.* **1994**, *43*, 261. (e) Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Synlett* **2001**, 679. (f) Spanneda, M. V.; Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1359.

10.1021/ol300539e
Published on Web 03/28/2012

Table 1. Reaction Scope[a]



entry	product		yield[b]	cis/trans[c]
1		**4a**	64%	17:1
2		**4b**	78%	19:1
3		**4c**	50%	12:1
4		**4d**	60%[d]	11:1
5		**4e**	61%	16:1
6		**4f**	60%	16:1
7		**4g**	47%	13:1
8		**4h**	70%	15:1
9		**4i**	73%	15:1

[a] General procedure: 3 equiv of $F_3CCH_2NH_3Cl$ and 3.6 equiv of $NaNO_2$ were stirred at 0 °C for 1 h in CH_2Cl_2/H_2O (30:1), followed by addition of imine (0.5 mmol, 1 equiv) and $BF_3 \cdot OEt_2$ (1.8 equiv) at −78 °C. [b] Isolated yield of *cis* product. [c] Based on ^{19}F NMR spectroscopy of the crude reaction mixture. [d] Isolated yield of 72% (83% purity).

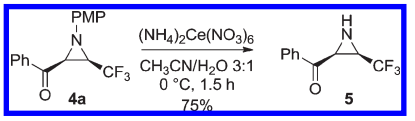
derivatives **2**.[5a] A limitation of this approach is the need to prepare and isolate the various diazoalkanes for each aziridine. The second strategy, reported herein, involves the use of a single diazocompound, trifluoromethyl diazomethane, and a variety of imine starting materials, such as **3**, easily prepared from the corresponding glyoxals.

We commenced our investigations with the reaction conditions reported previously for the preparation of trifluoromethyl-substituted dehydrobenzofuranols:[2f] $F_3CCH_2NH_3Cl$, $NaNO_2$ in H_2O/CH_2Cl_2, followed by $BF_3 \bullet OEt_2$ and substrate. Under these conditions, the test substrate (2-((4-methoxyphenyl)imino)-1-phenylethanone) gave full conversion to the product **4a** in 64% yield and 17:1 diastereoselectivity, as measured by analysis of the unpurified product by ^{19}F NMR spectroscopy (Table 1). The use of other Lewis or Brønsted acids led to no reaction, slow conversion ($Cu(OTf)_2$, $Ti(O^iPr)_4$, TfOH, $(RO)_2P(O)OH$), or decomposition of the reactant or product ($SnCl_4$, $SbCl_5$).

With a workable protocol in hand, we studied the scope of the reaction (Table 1). A wide range of aromatic glyoxyl imines and an ethyl glyoxal imine (entry 4), easily prepared from the corresponding glyoxals, afforded products in good yields and dr. The functionalized trifluoromethyl aziridines obtained are valuable fluorinated building blocks for further transformations. As an example, 3-trifluoromethyl-aziridine-2-carboxylates (e.g., **4d**) have been shown to undergo regio- and diastereoselective ring opening to give trifluoromethylated β-amino acids and β-lactams.[6]

To further establish the utility of the products generated, aziridine **4a** was subjected to deprotection using CAN ($(NH_4)_2Ce(NO_3)_6$) to give free aziridine **5** in an unoptimized 75% yield (Scheme 2).

Scheme 2. Deprotection of **4a** Giving Free Aziridine **5**



In conclusion, we have developed a facile one-pot preparation of trifluoromethyl-substituted aziridines in good yield and good diastereoselectivity starting from trifluoroethylamine hydrochloride and PMP-protected glyoxal imines. The *cis* substituted aziridine was obtained as the major product. Deprotection of the products is easily performed with CAN as shown on a test substrate.

The functionalized trifluoromethylated aziridines described in this work offer many opportunities for further elaboration in the preparation of nitrogen-containing trifluoromethylated compounds for drug discovery.

Acknowledgment. We are grateful to the SSCI for a fellowship to B.M. and the ETH-Zurich for generous support through Grant 0-20744-11.

Supporting Information Available. Full experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

(6) (a) See ref 5e. (b) Davoli, P.; Froni, A.; Franciosi, C.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2361. (c) Rinaudo, G.; Narizuka, S.; Askari, N.; Crousse, B.; Delpon, D. *Tetrahedron Lett.* **2006**, *47*, 2065.

The authors declare no competing financial interest.