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Aza-Michael Addition of Nosyloxycarbamates to 2-(Trifluoromethyl)acrylates[†]

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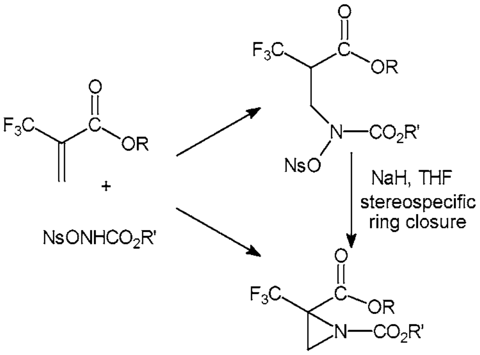
ABSTRACT



The amination of 2-(trifluoromethyl)acrylates, performed by nosyloxycarbamates, gives two different aminated products, the derivatives of α-trifluoromethyl *β*-amino esters or the aziridines, in high yields by changing the reaction conditions. The aza-Michael addition product was isolated for the first time in this kind of reaction. This finding confirms the aza-MIRC mechanism we previously proposed. Asymmetric induction was also pursued.

The presence of fluorine in organic compounds such as trifluoromethyl derivatives can influence their chemical, physical, and physiological properties.[1] Therefore these compounds have great interest in pharmaceutical and industrial fields.[2] Moreover, a high biological activity was found in fluorinated analogues of natural α- or *β*-amino acids, compounds with a wide range of potential applications either as is or as building blocks.

We have previously reported that olefins bearing two geminal EWG groups may be successfully aziridinated with ethyl nosyloxycarbamate ($NsONHCO_2Et$) in the presence of inorganic bases.[3]

Considering the synthetic relevance of CF_3-substituted compounds, we attempted direct amination reactions on 2-(trifluoromethyl)acrylates.

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(2) (a) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; John Wiley & Sons: New York, 1991. (b) Kitatsume, T.; Ito, K. Jpn. Kokai Tokkyo Koho JP02167252, 1990; *Chem. Abstr.* **1991**, *114*, 62757. (c) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagulpolskii, Y. L., Eds.; Elsevier: Amsterdam, The Netherlands, 1993. (d) *Organofluorine Chemistry*: *Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (e) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060−2063.

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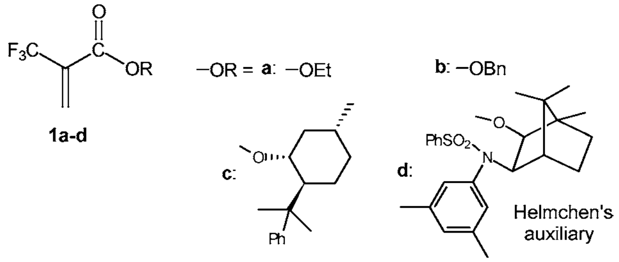
After transformation of commercially available 2-(trifluoromethyl)acrylic acid into the corresponding chloride,[4] the compounds **1a**−**d** (Scheme 1) were synthesized in high yields by using different alcohols in the presence of pyridine.

Scheme 1. 2-(Trifluoromethyl)acrylates



The direct amination reaction, involving the intermediate aza-anion ($NsON^{-}CO_2Et$) as the very likely reactive species, showed a new interesting outcome depending on reaction conditions.

Of special interest is the use of calcium oxide promoted aza-Michael 1,4-addition[5] giving *N*,*N*′-disubstituted α-trifluoromethyl *β*-amino esters in high yields (Table 1).

Table 1. Different Conditions for Amination Reactions

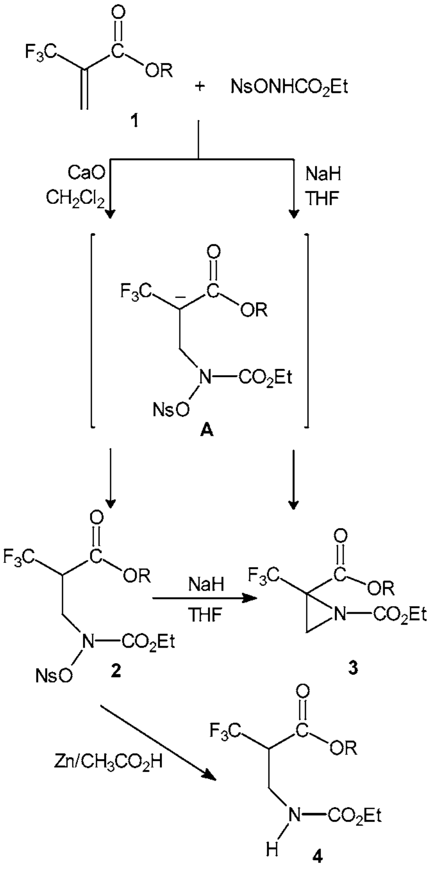
1	base	solvent	molar ratios[a]	time (h)	yield (%)[b] 2	yield (%)[b] 3
a	CaO	CH_2Cl_2	1:3:1.2	4	>95[c]	
a	LiOH	CH_2Cl_2	1:2:2	4	>95[c]	
a	CaO	THF	1:3:1.2	4	79	
b	CaO	CH_2Cl_2	1:4:2	7	90	
a	NaH	THF	1:4:1.2	4		86
b	NaH	THF	1:4:1.2	2		90

[a] Substrate:base:$NsONHCO_2Et$. [b] Isolated product by flash chromatography. [c] By ^1H NMR on the crude mixture.

Otherwise by using sodium hydride in THF at 0 °C an aza-MIRC (Michael-initiated ring closure) reaction[6] yielded directly aziridines **3a**,**b** (Scheme 2) in agreement with our previous findings.

The isolation of **2** for the first time in this kind of reaction supports the pathway proposed by us on the basis of first experimental evidence[7] for the aziridination of electron-poor alkenes. The presence of a CF_3- group probably affects the basicity/nucleophilicity of the intermediate carbanion **A**, leading to the *β*-amino esters by immediate protonation. The carbanion **A** did not undergo ring closure under these conditions.

Scheme 2. Direct Amination Reaction of **1a**−**d**



Accordingly, the use of a different inorganic base such as sodium hydride in THF on **2** promotes an α-deprotonation, followed by intramolecular ring closure to quantitatively give the corresponding aziridines **3** (Scheme 2). With NaH the absence of a protonated base might favor the ring closure reaction.

Moreover, the N−O bond reductive cleavage of **2** by Zn/CH_3COOH quantitatively gave the corresponding *N*-ethoxycarbonyl α-trifluoromethyl *β*-amino esters **4**. Thus, starting from **2** it is possible to obtain two different aminated precursors of a variety of important molecules.[8]

The synthesis of optically active trifluoromethyl amino derivatives is very important both in organic chemistry and in the biological and pharmacological fields.

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The diastereoselective substrate-controlled aminations were performed on the substrates **1c**,**d** (Table 2) derived from two different chiral auxiliaries.

Table 2. Amination of Chiral Substrates

1	base[a]	molar ratios[b]	time (h)	*t* (°C)	yield (%) 2	yield (%) 3	de (%)[c]
c	CaO	1:5:4	24	25	70		12
d	CaO	1:2:2	3	25	81		70
c	NaH	1:4:1.5	2	25		93	18
c	NaH	1:5:2	12	−78		90	19
d	NaH	1:4:1.2	2	25		85	68
d	NaH	1:4:1.2	10	−40		94	70
d	NaH	1:5:1.2	12	−78		96	72

[a] CH_2Cl_2 and THF were used as solvent with CaO and NaH, respectively. [b] Substrate:base:$NsONHCO_2Et$. [c] By ^1H and ^{19}F NMR on the crude mixture.

In both cases good yields of aziridines were observed. While the use of (−)-8-phenylmenthol[9,10] induced a low diastereoselectivity, more satisfactory results were obtained by using the bulkier Helmchen's auxiliary.[10,11] Lower temperatures did not allow any increase of the de values.

In all cases the diastereomeric aziridines were easily separated by HPLC and isolated as optically pure compounds.

It is interesting to note that the diastereoselective induction seems only to depend on the choice of the chiral auxiliary. Indeed de values do not vary to a significant extent when different reaction conditions are chosen to synthesize **3**. Starting from known mixtures of diastereomers **2c** or **2d** the intramolecular cyclization showed a highly stereospecific outcome, as demonstrated by ^{19}F NMR (Figure 1). Probably the stereochemistry was mostly controlled by the aza-anion addition step.

Diastereoselective reagent-controlled aminations were also attempted by using the chiral carbamate derived from the Helmchen's auxiliary ($NsONHCO_2R^*$).[12]

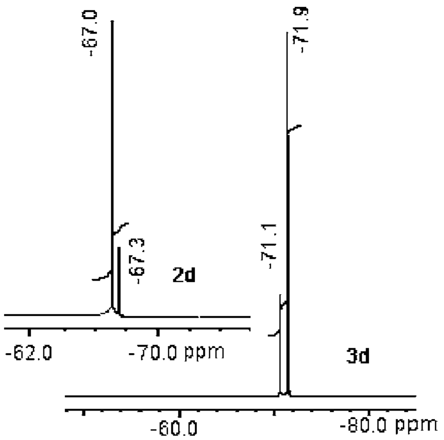
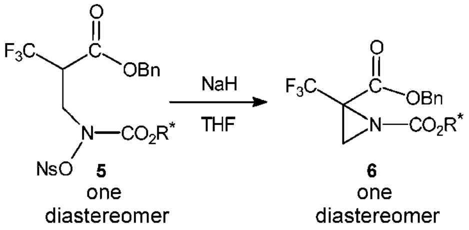


Figure 1. ^{19}F NMR spectra of diastereomeric mixtures of **2d** and **3d** (chemical shifts relative to $CFCl_3$).

The amination of **1b** with $NsONHCO_2R^*$, performed in THF with NaH at −40 °C, after 12 h gives the aza-Michael addition products **5** in high yields but in low diastereomeric excesses and only traces of the corresponding aziridines were formed. The different reactivity could be due to the steric hindrance on the nitrogen atom that likely disfavors the nucleophilic ring closure. However, by treating the separated major diastereomer **5** with NaH at room temperature only one aziridine (**6**) was obtained with complete stereoselectivity (Scheme 3), as shown by ^{19}F NMR spectra (Figure 2).

Scheme 3. Stereoselective Ring Closure As Determined by ^{19}F NMR Spectra



In summary, the aziridination reaction of 2-(trifluoromethyl)acrylates with nosyloxycarbamates proceeds in a stepwise manner, and simply by slightly changing the

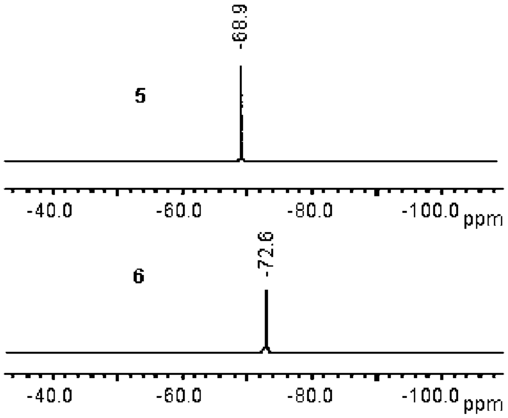


Figure 2. ^{19}F NMR spectra of **5** and **6** (chemical shifts relative to $CFCl_3$).

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reaction conditions we have been able to isolate for the first time the aza-Michael addition product, as well as the aziridination product, always in high yield. The stereochemical features of these reactions also have been studied and will be further investigated.

Given the mild conditions required, the reported reactions would provide valuable intermediates for synthetic applications.

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Supporting Information Available: General procedures and details of the spectroscopic characterization of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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