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Synthesis of fluorinated α,β-diamino esters by ring opening of activated 3-trifluoromethyl-aziridine-2-carboxylates

Giuseppe Rinaudo,[a] Satoru Narizuka,[a,b] Néda Askari,[a] Benoît Crousse[a] and Danièle Bonnet-Delpon[a,*]

[a]*CNRS Biocis UMR 8076, Faculté de Pharmacie, Université Paris-Sud, 5, rue J.B. Clément, Châtenay-Malabry 92296, France*
[b]*Chemical Research Centre Central Glass Co. Ltd, 2805 Imafuku-Nakadai, Kawagoe, Saitama 350-1151, Japan*

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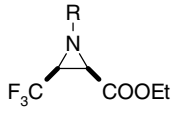
Abstract—The activation of trifluoromethyl aziridine-2-carboxylates resulted to be a suitable strategy for their ring opening under neutral conditions. Using amines as nucleophiles the reaction proceeded regio- and diastereoselectively, giving rise to α,β-diamino-β-trifluoromethyl esters in good yields.

The ring opening of aziridine-2-carboxylates represents a useful reaction to obtain α- and β-amino acids.[1] Its extension to fluorinated aziridines constitutes a promising route to fluorinated amino acids. The introduction of fluorine atoms in organic molecules often results in a deep modification of physical, chemical and thus, biological properties of the parent compounds.[2] This 'fluorine approach' has proved its viability and the synthesis of fluorinated amino acids and nitrogen-containing compounds finds increasing interest.[3]

A regio- and stereoselective synthesis of *anti*-α-functionalized-β-amino trifluoromethyl esters was described through the acid-catalyzed ring opening of non activated *trans*-ethyl 3-trifluoromethyl-aziridine-2-carboxylates.[4] More recently, our research group developed a stereoselective synthesis of non activated *cis*-ethyl 3-trifluoromethyl-aziridine-2-carboxylates as an access to *syn*-α-functionalized-β-amino trifluoromethyl esters.[5] These trifluoromethyl aziridine ring opening reactions require the in situ generation of an aziridinium ion under very harsh acidic conditions. They are consequently limited to only a few nucleophiles such as carboxylates, thiols and halides.

In order to better exploit this stereoselective route to new trifluoromethyl-α-substituted β-amino esters, we were interested in developing different reaction conditions. Our aim was in particular to have a good access to fluorinated diamino acids. If several methodologies have been developed for the preparation of fluorine-substituted amino acids,[3,6] only few examples of fluoroalkyl α,β-diamino acids are reported in the literature.[7] We report here our investigations on the ring opening of trifluoromethyl aziridine-2-carboxylates with amino-containing nucleophiles.

In this study it was anticipated that non activated *cis*-ethyl 3-trifluoromethyl-aziridine-2-carboxylates **1** and **2** (Fig. 1) would exhibit a low reactivity towards amines. Aziridine-2-carboxylates are reported to undergo ring opening with amines only when they are activated. Concerning non activated CF_3-substituted aziridines, there is only one example in the literature: *N*-benzyl-2-trifluoromethylaziridine is inert towards $BnNH_2$ even in Lewis acid-catalyzed ring opening.[7a] The presence of CF_3



cis-**1** R = Bn
cis-**2** R = PMP

Figure 1.

Keywords: Trifluoromethyl aziridine-2-carboxylates; Activated aziridine; Ring opening; Trifluoromethyl α,β-diamino esters.
* Corresponding author. Tel.: +33 146 835 738; fax: +33 146 835 740; e-mail: daniele.bonnet-delpon@cep.u-psud.fr

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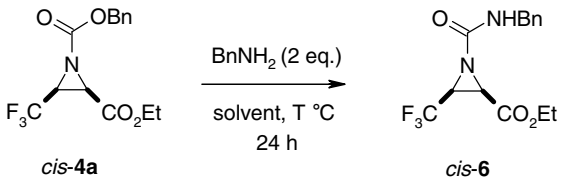
disfavors the coordination of the nitrogen atom with the Lewis acid. **1** and **2** combine the disadvantages of both substituents. Effectively, when *cis*-**1** and *cis*-**2** were submitted to reaction with amines, in the presence of Lewis acids ($Yb(OTf)_3$ and $Cu(OTf)_2$) at the reflux of dichloroethane for 36 h, no ring opening occurred.

These unsuccessful experiments prompted us to activate the aziridines by introducing an electron withdrawing group on the nitrogen atom. Numerous ring opening reactions of activated aziridines are described in the literature,[8] but, to the best of our knowledge, only one example is known for fluorinated aziridines.[7b]

cis-*N*-Benzyl-trifluoromethylaziridine **1** was first reduced into the aziridine *cis*-**3**, which was further easily converted into *cis*-**4a** and *cis*-**4b**, in the presence of carbobenzyloxy chloride (CbzCl) or tosyl chloride (TsCl) (Scheme 1 and Table 1).

When reacted with *ortho*-nosyl chloride (NsCl) in the presence of pyridine, aziridine *cis*-**3** provided amino ester **5c**, resulting from the ring opening of the *N*-nosyl aziridine by the chloride present in the reaction mixture (entry 3).[9] This result clearly shows the more activating effect of the nosyl group as compared to that of the tosyl group. Several attempts were performed to selectively obtain aziridine *cis*-**4c** by varying solvents, bases, temperatures. The only successful result was obtained with Na_2CO_3 as base, but the reaction time was very long, even at reflux of dichloroethane (entry 4).

The reactivity of activated aziridines **4a–c** was first investigated towards benzylamine, in the presence or not of a Lewis acid as catalyst. The reaction of aziridine *cis*-**4a** with $BnNH_2$ required reflux of dichloroethane and was incomplete after 24 h (~ 60% conversion). Furthermore, the major reaction was the attack at the benzyloxycarbonyl group of Cbz instead of the ring opening[10a,b] (Scheme 2 and Table 2). The use of



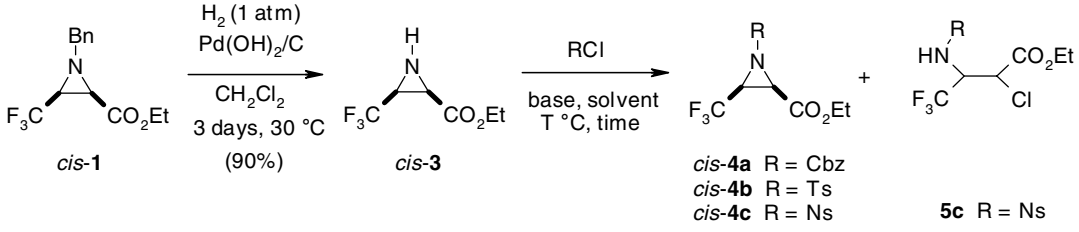
Scheme 2.

$Yb(OTf)_3$[11] or $BF_3{\cdot}Et_2O$ also failed to direct the reaction towards the ring opening.

Nevertheless, the preparation of α,β-diamino-β-trifluoromethyl esters could be achieved from the *N*-tosyl and *N*-nosyl trifluoromethyl aziridines **4b** and **4c**, under rather mild reaction conditions, using amines or NaN_3 as nucleophiles, without Lewis acid catalysis (Scheme 3). Optimized conditions and yields are reported in Table 3.[12]

It is noteworthy that the ring opening always occurred at the C-2 carbon with a complete regioselectivity. This is most often observed in nucleophilic reactions with CF_3-substituted rings (epoxides and cyclic sulfates),[13] and can be easily explained by the steric hindrance and electrostatic repulsion offered by trifluoromethyl group towards the attacking nucleophiles.[7a] Furthermore, in our case, the CF_3 substituent is less able than COOEt to stabilize a p orbital on the C_α carbon in a pure S_N2 process, and/or to accommodate the development of a positive charge in the dissociation of the C_α–N bond.[14] Concerning the stereoselectivity of these reactions, we always observed the sole formation of one diastereoisomer. The *syn* configuration for **7b** was determined by X-ray diffraction.[15]

This highly stereoselective ring opening prompted us to prepare the *trans*-*N*-tosyl trifluoromethyl aziridine in order to obtain the *anti*-stereoisomers. The aziridine *trans*-**1**,[4] was reduced into the aziridine *trans*-**3**, which was then used without purification. When tosylation was



Scheme 1.

Table 1. Preparation of activated trifluoromethyl aziridine-2-carboxylates

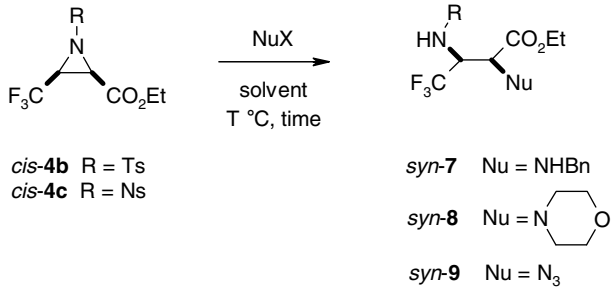
Entry	RCl (equiv)	Base (equiv)	Solvent	*T* (°C)	Time	Yield (%)[a]
1	CbzCl (1.2)	$NaHCO_3$ (1.5)	CH_2Cl_2	0	3 h	*cis*-**4a** (92)
2	TsCl (2)	Pyridine (3)	CH_2Cl_2	0	1 h	*cis*-**4b** (80)
3	NsCl (2)	Pyridine (3)	CH_2Cl_2	0–4	24 h	**5c** (65)[b,c]
4	NsCl (4)	Na_2CO_3 (9)	$ClCH_2CH_2Cl$	Reflux	8 days	*cis*-**4c** (60)

[a] Isolated yield.
[b] *cis*-**4c** was present as 12% of the crude mixture after work-up (calculated by ^{19}F NMR).
[c] Only one diastereoisomer of **5c** was present in the crude mixture (determined by ^{19}F NMR).

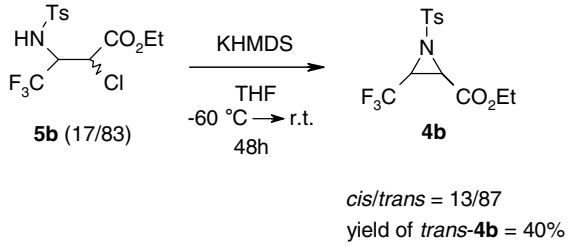
Table 2. Attack of benzyl amine at benzyloxycarbonyl of *N*-Cbz activated aziridine

Entry	Lewis acid (equiv)	Solvent	*T* (°C)	Product	Yield (%)[a]
1	—	$ClCH_2CH_2Cl$	Reflux	*cis*-**6**	25
2	$Yb(OTf)_3$ (0.2)	THF	Reflux	*cis*-**6**	52
3	$BF_3{\cdot}Et_2O$ (1 equiv)	Et_2O	Reflux	*cis*-**6**	67

[a] Isolated yield.



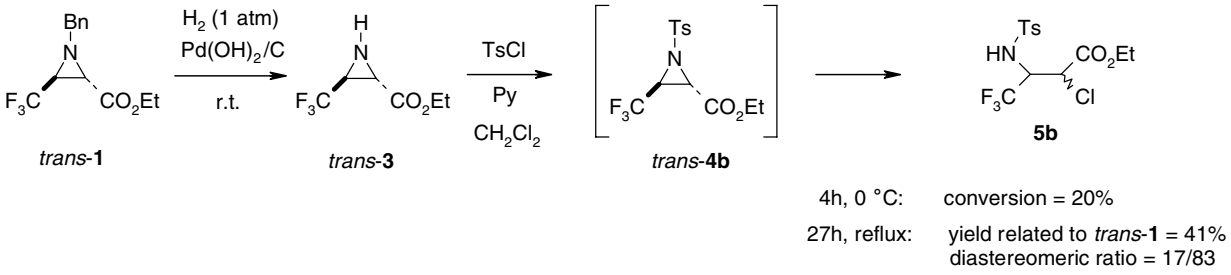
Scheme 3.



Scheme 5.

performed at 0 °C in CH_2Cl_2, only 20% conversion occurred after 4 h, giving rise to the ring opening product **5b**, as already observed from the *cis*-*N*-nosyl aziridine **4c** (Scheme 4).

The diastereoselective formation of *syn* and *anti* diamino esters, from respectively, *cis* and *trans* aziridines, confirms the supposed S_N2 mechanism for this reaction. No isomerization of products in the reaction medium was observed.



Scheme 4.

For a complete conversion of *trans*-**3** into **5b** a 1 day reaction at reflux was required, but a partial isomerization occurred, producing a 17/83 mixture of both diastereoisomers (ratio determined by ^{19}F NMR) (Scheme 4). This mixture was used for preparing the *trans*-*N*-tosyl trifluoromethyl aziridine by ring closure using NaHMDS.[9] After purification and separation, the aziridine *trans*-**4b** could be obtained in 40% yield (Scheme 5).

The ring opening of *trans*-**4b** with benzyl amine proceeded under the same reaction conditions as for *cis*-**4b** to provide the *anti*-isomer **7b** as the only product (74% yield) (Scheme 6).

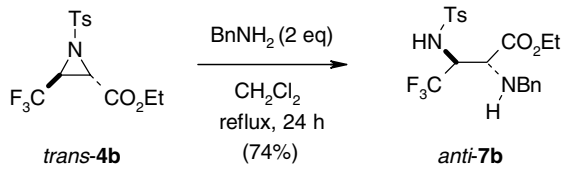
Preliminary experiments were performed to evaluate the usefulness of these new ring opening conditions. The reaction of aziridine *cis*-**4b** with potassium ethyl xanthate was thus investigated. The reaction proceeded at room temperature in CH_3CN/H_2O as solvent, producing a 66% yield of **10** as a (58/42) mixture of both diastereoisomers (Scheme 7).

The lack of diastereoselectivity is probably the result of an isomerization due to the higher acidity of H_α, vicinal to the carboxylate and xanthate functions. The use of this new synthon **10** for further radical reactions[16] is under investigation.

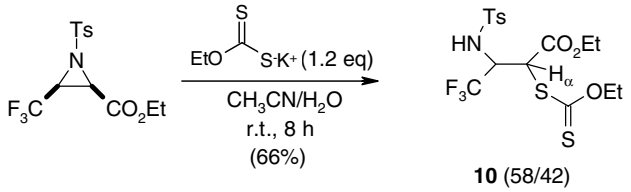
Table 3. Ring opening of *N*-sulfonyl activated aziridines with amino containing nucleophiles

Entry	Substrate	NuX (equiv)	Solvent	*T* (°C)	Time	Product	Yield (%)[a]
1	*cis*-**4b**	$BnNH_2$ (2.5)	CH_2Cl_2	Reflux	24 h	*syn*-**7b**	78
2	*cis*-**4c**	$BnNH_2$ (1.2)	$ClCH_2CH_2Cl$	Reflux	8 h	*syn*-**7c**	75
3	*cis*-**4b**	Morpholine (2.5)	$ClCH_2CH_2Cl$	Reflux	22 h	*syn*-**8b**	90
4	*cis*-**4c**	Morpholine (1.2)	$ClCH_2CH_2Cl$	Reflux	3 h	*syn*-**8c**	74
5	*cis*-**4c**	NaN_3 (3)	DMF	rt	1 h	*syn*-**9c**	90

[a] Isolated yield.



Scheme 6.



Scheme 7.

In this study of ring opening of trifluoromethyl aziridine carboxylates, we have found conditions to circumvent their low reactivity towards nucleophiles. We could demonstrate that after their activation by a sulfonyl *N*-substituent, trifluoromethyl aziridine carboxylates could undergo a nucleophilic ring opening without any Lewis acid catalysis. The ring opening reaction with amino-containing nucleophiles proceeded in good yield and with a total regio- and diastereoselectivity to provide the corresponding trifluoromethyl-containing diamino esters. This is a good alternative to the harsh conditions hitherto required, which could be suitable to a wider range of nucleophiles.

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12. Typical procedure for the synthesis of *syn*-ethyl 2-benzylamino-4,4,4-trifluoro-3-(4-methylphenyl)sulfonylaminobutanoate (*syn*-**7b**): To a stirred solution of the aziridine (167 mg, 0.5 mmol) in CH_2Cl_2 (2 mL), $BnNH_2$ (0.11 mL, 1.0 mmol) was added at rt. The reaction mixture was then stirred at reflux of CH_2Cl_2 for 24 h. After dilution with CH_2Cl_2 (100 mL), the mixture was washed with water (50 mL) and brine (50 mL) and then dried on $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (petroleum ether/AcOEt = 2/1) to give a colourless solid (78% yield): mp: 77 °C. IR (neat) 3330, 3263, 1739 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, $^3J = 7.2$ Hz), 2.4 (br s, 1H), 2.42 (s, 3H), 3.62 (d, 1H, $^3J = 2.1$ Hz), 3.77 (d, 1H, $^3J = 14.0$ Hz), 3.78 (d, 1H, $^3J = 14.0$ Hz), 4.16 (dq, 1H, $^2J = 10.7$ Hz, $^3J = 7.2$ Hz), 4.17 (dq, 1H, $^2J = 10.7$ Hz, $^3J = 7.2$ Hz), 4.37 (m, 1H), 5.8 (br s, 1H), 7.23–7.37 (m, 7H), 7.70–7.76 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.8, 21.3, 52.6, 55.8 (q, $^2J_{CF} = 31$ Hz), 58.0, 62.5, 123.3 (q, $^1J_{CF} = 275$ Hz), 126.9, 127.3, 128.1, 128.4, 129.4, 137.5, 138.6, 143.6, 170.4. ^{19}F NMR ($CDCl_3$) δ −73.6 (d, $^3J_{FH} = 7$ Hz). Anal. Calcd for $C_{20}H_{23}F_3N_2O_4S$: C, 54.05%; H, 5.22%; N, 6.30%. Found: C, 54.02%; H, 5.27%; N, 6.24%.
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15. Crystallographic data (excluding structure factors) for compound *syn*-**7b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 291307. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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