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Aziridines versus Vinyl Carbamates from the Direct Amination of Electron-Withdrawing Group-Substituted Trifluoromethyl Enoates

Stefania Fioravanti,* Daniele Colantoni, Lucio Pellacani,* and Paolo A. Tardella*

Dipartimento di Chimica, Università degli Studi "La Sapienza", P. le Aldo Moro 2, I-00185 Roma, Italy

lucio.pellacani@uniroma1.it

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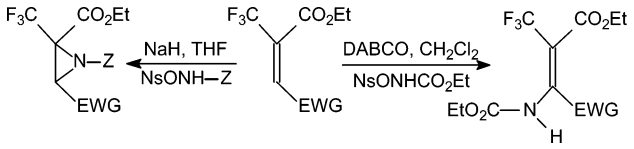
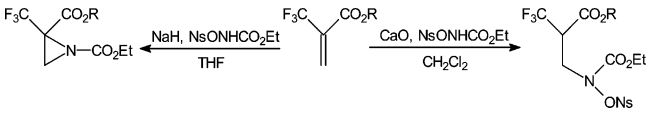


Aza-MIRC (Michael-initiated ring closure) and C−H insertion products were obtained in the reactions of trifluoromethylated olefins with different nosyloxycarbamates by changing base and solvent. Aza-Michael addition products were not isolated. The presence and the position of the trifluoromethyl group allow control of the outcome of the reactions.

Organofluorine compounds have received growing attention in the last years in synthetic organic chemistry as the replacement of hydrogen by fluorine can induce in these molecules particular chemical, physical, and biological properties.[1] For example, fluorine atom can increase stability and lipophilicity of fluorinated analogues of natural molecules, and their synthesis can give an important contribution for the development of new active drugs. Simple synthesis of fluorinated molecules containing nitrogen represents a promising goal to obtain readily available molecules of biological importance, like α- or β-amino acids, lactams, polypeptides, which usually present remarkable change in reactivity compared to the parent compounds.[2]

The introduction of a trifluoromethyl group into the α-carbon of amino acids to construct the trifluoromethylated quaternary carbon is a problem that remains to be solved.[3]

SCHEME 1. Amination of 2-(Trifluoromethyl)acrylates with Ethyl Nosyloxycarbamate



Starting from our previous results,[4] we recently considered the amination of 2-(trifluoromethyl)acrylates by a very simple procedure using nosyloxycarbamate (NsONHCO$_2$R, Ns = 4-nitrophenylsulfonyl) in the presence of inorganic bases.[5] We found an unusual outcome of this reaction (Scheme 1). In the presence of CaO, derivatives of α-trifluoromethyl β-amino esters were obtained, while using NaH as base an aza-MIRC (Michael-initiated ring closure)[6,7] reaction gave aziridines, useful molecules for a stereospecific construction of quaternary trifluoromethylated centers.[8] Such carbon atoms are the key chiral centers of inhibitory pharmaceuticals.[9]

Successively, our interest moved to investigate the effect of one more EWG group on this kind of reaction, aiming to synthesize CF$_3$-substituted 2,3-difunctionalized aziridines, useful building blocks for the construction of important molecules.[10]

In this paper, we report the results of amination reactions performed on EWG-substituted trifluoromethyl enoates **1**−**3** with different nosyloxycarbamates (NsONHZ)[11] in the presence of NaH in THF (method A) or CaO in CH_2Cl_2 (method B, Table 1).

Aziridines **4**−**6** were obtained in short times and high yields using NaH in THF (method A), with no significant differences in reactivity compared to 2-(trifluoromethyl)-

* To whom correspondence should be addressed. Fax: +39 06 490631. Phone: +39 06 49913673.

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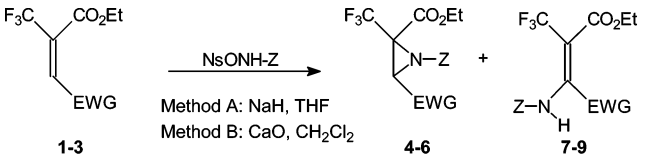
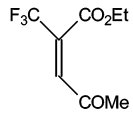
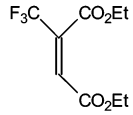
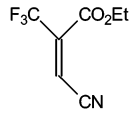
TABLE 1. Amination Reactions of EWG-Substituted Trifluoromethyl Enoates 1−3 with Nosyloxycarbamates

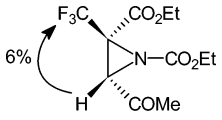


Z = **a**: CO_2Et; **b**: Boc; **c**: Cbz, **d**: Fmoc

Olefin	Method A Yield (%)	Method B Yield (%)	
	**4a** (81)	**4a** (74)	**7a** (16)
	4b (70)	**4b** (85)	–
	4c (87)	**4c** (83)	**7c** (7)
1	**4d** (74)	**4d** (69)	**7d** (4)
	**5a** (81)	**5a** (77)	**8a** (14)
	5b (40)	**5b** (25)[a]	–
	5c (72)	**5c** (75)	**8c** (traces)
2	**5d** (83)	**5d** (67)	**8d** (4)
	**6a** (78)	**6a** (44)	**9a** (traces)
	6b (85)	**6b** (traces)	–
	6c (79)	**6c** (33)	**9c** (traces)
3	**6d** (52)	**6d** (30)	**9d** (traces)

[a] Unreacted **2** was recovered.

acrylates (Scheme 1). The stereochemistry of the product was unambiguously assigned for **4a** by $^{19}F\{^1H\}$ NOE experiments (Figure 1).



4a

FIGURE 1. Observed $^{19}F\{^1H\}$ NOE enhancement in the aziridine **4a**.

Contrary to simple 2-trifluoromethyl acrylates, when CaO in CH_2Cl_2 (method B) was used there are no evidences of aza-Michael addition products (Scheme 1). Unexpectedly, in many cases vinyl carbamates **7**−**9** were observed in addition to aziridines **4**−**6**. Vinyl carbamates are interesting targets for industrial applications,[12] β-trifluoromethyl vinyl carbamates are known as neoplasm inhibitors,[13] and trifluoromethyl enaminones are recently used as synthons.[14] The presence of products **7**−**9** could possibly be explained by a ring-opening reaction of the aziridine, but all our attempts to obtain vinyl carbamates **7**−**9** from the corresponding aziridines failed.[11a,15] Vinyl carbamates **7**−**9** could also be considered as C−H insertion products of the corresponding nitrene, which can be formed by base-induced α-elimination from nosyloxycarbamates.[11a] In its singlet state the nitrene intermediate could be stabilized by the neighboring fluorine atoms.[16]

TABLE 2. Reaction of 1 with $NsONHCO_2Et$

entry	base	solvent	*T* (°C)	**4a/7a**
1	CaO	CH_2Cl_2	rt	82:18
2	CaO	CH_2Cl_2	−40	80:20
3	CaO	CH_2Cl_2	−70	81:19
4	CaO	CH_3CN[a]	rt	84:16
5	CaO	CH_3NO_2	rt	89:11
6	CaO	THF	rt	92:8
7	DABCO[b]	THF	rt	15:85
8	Et_3N[b]	CH_2Cl_2	rt	34:66
9	DABCO[b]	CH_2Cl_2	rt	7:93

[a] Small amounts of H_2O brought to only **4a**. [b] Molar ratios as those of method A, Experimental Section.

Two results seem to be in agreement with this hypothesis. In the reactions performed with NsONH-Boc, a carbamate that easily gives a Lossen transposition,[17] products **7b**−**9b** were not found. Moreover, low yields obtained with substrate **3** could be explained by the presence of a cyano group, which is known to react with nitrenes[18] giving unisolable byproducts.

To explore the influence of reaction conditions on the aziridines/vinyl carbamates ratio, the reaction of **1** with ethyl nosyloxycarbamate ($NsONHCO_2Et$) was performed with different bases, solvents, and temperature (Table 2).

While temperature seems to have no effect on the product distribution (entries 1−3), replacing CH_2Cl_2 with more polar solvents such as THF, CH_3CN, and CH_3NO_2, the relative amount of aziridine increases (entries 4−6), as expected for an aza-Michael addition giving **4a**. On the contrary, the **4a/7a** ratio can be changed in favor of **7a** changing CaO with Et_3N (entry 8) and, finally, the reaction performed in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO) leads to **7a** as the main product (entries 7 and 9).[19]

The small size and high electronegativity of fluorine can alter reactivities of fluorinated molecules compared to nonfluorinated analogues, and the reported data are a further example of this influence.[1c] In fact, other trifunctionalized electron-poor olefins led only to aziridines[20] showing no significant reactivity differences from *gem*-disubstituted olefins.

To gain insights on the importance of CF_3 position, we synthesized **10**,[21] an isomer of substrate **2**. Also in this

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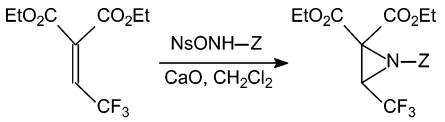
SCHEME 2. Amination of 10 with Different Nosyloxycarbamates



10

11a 88%
11b 68%
11c 80%
11d 85%

case, reactions performed with different carbamates led only to aziridines **11a**−**d** even by using CaO, in very short times and very good yields, showing once again the importance of both presence and position of the CF_3 group on the molecule reactivity (Scheme 2).

In conclusion, different trifluoromethylated amino compounds can be obtained by the same amination procedure, depending on reaction conditions and on the backbone of CF_3 functionalized olefins. These results confirm unusual chemical properties of fluorine-containing molecules and encourage us to continue our investigations on the amination of such kind of compounds.

Experimental Section

Synthesis of Substrates 1−**3**. According to a reported procedure,[22] commercial ethyl 3,3,3-trifluoropyruvate (1.70 g, 10 mmol) was added dropwise to a stirred solution of corresponding commercial ylides (10 mmol) in 20 mL of toluene at 0 °C. After 2 h, the mixture was quickly filtered through a 3 in. plug of silica gel to remove triphenylphosphine oxide. Solvents were evaporated under reduced pressure, affording products **1**−**3** as a mixture of *E*/*Z* isomers (from 85/15 up to 92/8). The *E* isomer was purified by HPLC.

1:[23] pale yellow liquid; IR 1737, 1715 cm^{-1}; ^1H NMR δ 1.31 (t, J = 7.2 Hz, 3 H), 2.38 (s, 3 H), 4.30 (q, J = 7.2 Hz, 2 H), 6.95 (q, J = 1.2 Hz, 1 H); ^{13}C NMR δ 13.6, 29.8, 62.6, 120.8 (q, J = 273.0 Hz), 127.8 (q, J = 32.6 Hz), 140.9 (q, J = 4.3 Hz), 160.8, 197.6; ^{19}F NMR δ −67.22; GC MS *m/z* 210 (M^+, 0.2), 195 (44), 167 (100), 165 (62), 147 (19), 137 (18), 103 (14), 75 (15), 53 (10), 43 (55); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_8H_9F_3O_3$ 233.0401, found 233.0400.

Typical Experimental Procedure of Amination (Method A). To a stirred solution of the substrate (1.0 mmol) in 2 mL of anhydrous THF at room temperature were added NaH (3 mmol) and $NsONHCO_2R$ (2 mmol) portionwise. The reaction was monitored by TLC until completion (1−3 h), and then the crude mixture was quenched with saturated $NaHCO_3$ solution and extracted twice with diethyl ether. The collected organic phases were dried over Na_2SO_4 and after solvent evaporation under reduced pressure, the residue was purified by fast filtration through a 3 in. plug of silica gel (90:10 hexane/ethyl acetate).

Typical Experimental Procedure of Amination (Method B). To a stirred solution of the substrate (1.0 mmol) in 2 mL of CH_2Cl_2 at room temperature were added CaO (4 mmol) and $NsONHCO_2R$ (3 mmol) portionwise. The reaction was monitored by TLC until completion (3−6 h), and then the crude mixture was diluted with 10 mL of diethyl ether and filtered. After solvent evaporation under reduced pressure, the residue was purified by fast filtration through a 3 in. plug of silica gel (90:10 hexane/ethyl acetate).

4a: pale yellow oil; R_f 0.44; IR 1748 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7.2 Hz, 6 H), 2.32 (s, 3 H), 3.51 (s, 1 H), 4.16−4.30 (m, 4 H); ^{13}C NMR δ 13.7, 13.9, 28.3, 46.0, 48.7 (q, J = 35.5 Hz), 63.5, 64.0, 121.1 (q, J = 279.9 Hz), 156.2, 160.9, 198.2; ^{19}F NMR δ −69.46; GC MS *m/z* 297 (M^+, 9), 152 (100), 43 (10); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{11}H_{14}F_3NO_5$ 320.0722, found 320.0728.

5a: pale yellow oil; R_f 0.42; IR 1747 cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H), 3.54 (s, 1 H), 4.17−4.31 (m, 6 H); ^{13}C NMR δ 13.8, 13.9, 40.8, 48.5 (q, J = 35.8 Hz), 62.6, 63.3, 63.9, 121.11 (q, J = 280.5 Hz), 155.9, 160.3, 163.4; ^{19}F NMR δ −69.52; GC MS *m/z* 327 (M^+, 0.2), 210 (15), 182 (100), 181 (14), 164 (23), 154 (72), 153 (56), 134 (14), 133 (13), 106 (10); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{12}H_{16}F_3NO_6$ 350.0827, found 350.0824.

6a: pale yellow oil; R_f 0.45; IR 2256 (vw), 1760, cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.2 Hz, 3 H), 1.36 (t, J = 7.2 Hz, 3 H), 3.56 (s, 1 H), 4.22−4.34 (m, 2 H), 4.35−4.46 (m, 2 H); ^{13}C NMR δ 13.4, 14.6, 29.2 (q, J = 2.5 Hz), 46.9 (q, J = 37.5 Hz), 64.5, 64.6, 110.3, 120.0 (J = 277.9 Hz), 153.7, 159.3; ^{19}F NMR δ −72.20; GC MS *m/z* 280 (M^+, 0.1), 235 (14), 208 (14), 207 (46), 181 (13), 180 (57), 163 (32), 162 (38), 153 (100), 152 (13), 143 (12), 136 (15), 135 (62), 134 (82), 133 (69), 115 (13), 108 (15), 77 (18), 69 (46), 67 (24), 56 (58), 45 (21), 43 (18); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{10}H_{11}F_3N_2O_4$ 303.0569, found 303.0563.

7a: pale yellow oil; R_f 0.52; IR 3206, 1753, 1738, 1686 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 2.49 (s, 3 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.30 (q, J = 7.2 Hz, 2 H), 11.11 (br, 1 H); ^{13}C NMR δ 13.9, 14.2, 30.1, 62.1, 63.4, 96.7 (q, J = 33.2 Hz), 122.8 (q, J = 270.8 Hz), 141.6, 155.7, 166.0, 194.4; ^{19}F NMR δ −55.82; GC MS *m/z* 297 (M^+, 39), 224 (25), 210 (37), 206 (24), 196 (11), 183 (11), 182 (67), 164 (15), 162 (36), 155 (20), 154 (33), 139 (13), 138 (29), 137 (11), 136 (24), 134 (100), 114 (12), 111 (17), 91 (19), 90 (12), 43 (66); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{11}H_{14}F_3NO_5$ 320.0722, found 320.0731.

8a: ^{19}F NMR δ −58.32; GC MS *m/z* 327 (M^+, 21), 282 (17), 281 (16), 262 (12), 254 (41), 233 (12), 210 (13), 207 (24), 206 (10), 205 (21), 182 (58), 181 (56), 161 (54), 154 (20), 153 (18), 152 (15), 138 (17), 136 (10), 135 (33), 133 (100), 115 (10), 113 (16), 110 (25), 91 (22), 90 (24), 89 (11), 44 (14), 43 (14), 42 (13).

11a: colorless oil; R_f 0.39; IR 1752, 1738 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 3.74 (q, J = 5.1 Hz, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.28−4.36 (m, 4 H); ^{13}C NMR δ 13.9, 14.2, 14.3, 44.5 (q, J = 41.5 Hz), 52.4, 62.2, 62.4, 64.0, 121.1 (q, J = 274.9 Hz), 156.6, 161.7, 163.1; ^{19}F NMR δ −71.89 (d, J = 4.8 Hz); GC MS *m/z* 327 (M^+, 0.05), 227 (9), 199 (55), 182 (26), 181 (62), 168 (9), 164 (12), 154 (19), 140 (12), 136 (12), 110 (20), 109 (100), 90 (38), 68 (20), 45 (15), 43 (14); HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{12}H_{16}F_3NO_6$ 350.0827, found 350.0833.

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Supporting Information Available: General experimental details; spectroscopic data for compounds **2**, **3**, **4b**−**d**, **5b**−**d**, **6b**−**d**, **7c**,**d**, **8d**, and **11b**−**d**; ^1H NMR and/or ^{13}C NMR spectra for compounds **1**−**3**, **4a**−**d**, **5a**−**d**, **6a**−**d**, **7a**, and **11a**−**d**; ^{19}F NMR spectra for **7c**,**d**, **8a**, and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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