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Enhancement of Alkene Reactivity by a Trifluoromethyl group : Synthesis of Pyrrolidines via 1,3-Dipolar Cycloaddition

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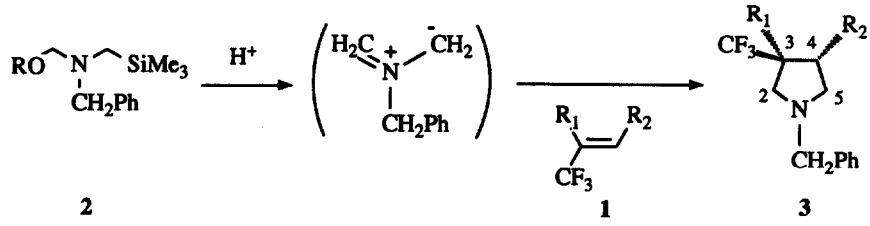
***Abstract** : Ethylenic compounds activated by a trifluoromethyl group undergo 1,3-dipolar cycloadditions with non-stabilized azomethine ylides to provide polysubstituted 3-trifluoromethyl-pyrrolidines in good yields, while non-fluorinated parent alkenes are in most cases unreactive in these reactions.*

Trifluoromethylated ethylenic compounds are valuable synthons and in our general interest on their particular reactivity we have studied some cycloaddition reactions.[1,2] In Diels-Alder reaction, as predicted by Frontier Molecular Orbital (FMO) theory, the LUMO of the olefin is involved in the transition state and the activating role of the CF_3 group has been proved to be weak but effective comparing to a CH_3 group.[1] In contrast, 1,3-dipolar cycloadditions with nitrones involve either the LUMO or the HOMO of the alkene.[3] Consequently the role of the CF_3 group could not be unambiguously assessed in these reactions.[2]

The 1,3-dipolar cycloaddition of non-stabilized azomethine ylides with an olefin represents one of the most convergent approaches for the construction of the pyrrolidine ring.[4] However its synthetic potential is restricted to the use of a class of electron-deficient alkenes.[5] Typical examples of dipolarophiles include α,β-unsaturated mono- or di- esters, ketones and nitriles. To date there has been no report on cycloadditions of non-stabilized azomethine ylides, generated by desylilation procedure, with trifluoromethylated olefins. We have checked that the σ-electron-withdrawing character of the CF_3 group would be sufficient to promote such a reaction and to provide a new access to trifluoromethylated pyrrolidines (scheme 1).

The study was run with olefins **1a-d** (table I). Ethyl 4, 4, 4-trifluoro-2-butenoate **1a** is commercially available. α-Trifluoromethylstyrene **1b** and ethyl 4, 4, 4-trifluoro-3-phenyl-2-butenoate **1c**, were prepared from 2, 2, 2-trifluoroacetophenone respectively *via* an addition of methyl lithium followed by a dehydration[6] and *via* a Wittig-Horner with triethyl phosphonoacetate.[7] Ethyl 4, 4, 4-trifluoro-3-propyloxy-2-butenoate **1d** was prepared from ethyl trifluoroacetoacetate by O-alkylation with propyl iodide.[8]



SCHEME 1

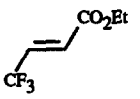
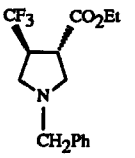
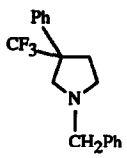
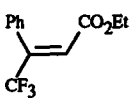
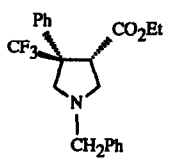
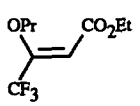
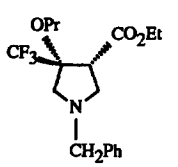
Cycloaddition reactions were performed between the azomethine ylide generated from the precursor **2** (R = C_5H_{11})[9] and the olefins **1** according to the procedure described by Achiwa (1% CF_3COOH in CH_2Cl_2).[10] The consumption of the olefin was controlled by GC analysis. The cycloaddition reactions proceeded easily at room temperature to give the corresponding pyrrolidines **3a-d**[11] (table I) which were purified, after usual work-up, by column chromatography (pentane/ethyl acetate : 9/1). Pyrrolidines were obtained in high yield (70-80%) from the olefins **1a-c**, but in low yield (30%) from the enol ether **1d**.[12] The configuration of C-3 and C-4 in **3** reflects the conservation of geometry of the starting alkenes **1**.

To determine the influence of the CF_3 substituent upon the reactivity of the olefinic double bond, we have performed the cycloaddition with methyl substituted ethylenic parent compounds. Non-fluorinated disubstituted olefins activated by a carbonyl group have been described to provide pyrrolidines in good yields.[5,13] Our attempts to obtain cycloadducts from α-methylstyrene, ethyl 3-ethoxy-crotonate and ethyl β-methyl-cinnamate [14] failed even after a long reaction time and at higher temperature. This lack of reactivity shows that azomethine ylides generated from **2**, cannot promote cycloaddition with non-fluorinated olefins if these latter are not activated by an ester group and if they are trisubstituted.

In contrast, in the case of trifluoromethylated alkenes, the lowering of the LUMO level of olefins by the presence of the CF_3 group[15] and the high HOMO level[16] of the azomethine ylide narrow sufficiently the gap between the two frontier orbitals to promote the cycloaddition, despite a lack of π-electron-withdrawing substituent. The strong activating effect of the CF_3 group is particularly notable in the case of α-trifluoromethylstyrene since cycloaddition failed with α-methylstyrene and provided only 20% of adduct with styrene.[17] Reactions are successful with hindered trifluoromethylated olefins (**1c**) even when an alkoxy donor substituent is present (**1d**). It is the first example of such 1,3-dipolar reactions with trisubstituted alkenes bearing only one conjugated electron-withdrawing group.[5c] The effect of the CF_3 group in these reactions seems to be comparable to that of an ester group.

Besides these mechanistic considerations, the cycloaddition reactions of trifluoromethylated alkenes to non-stabilized azomethine ylides constitute the first access to 3-trifluoromethyl-pyrrolidines in high yields.

Table I

Dipolarophile	Product[a]	Yield[b]
1a 	**3a** 	**80%**
1b 	**3b** 	**80%**
1c 	**3c** 	**70%**
1d 	**3d** 	**30%**

a. Satisfactory spectroscopic data have been obtained for all new compounds.[11]

b. Isolated yield after column chromatography

references and notes :

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11. ***General procedure:*** A 1M solution of trifluoroacetic acid (0.2 mL; 0.2 mmol) in CH_2Cl_2 was added at 0°C to a stirred solution of **2** (2.4 mmol) and dipolarophile **1** (2 mmol) in CH_2Cl_2 (10 mL). After 3 h of stirring at room temperature the solution was washed with a saturated solution of sodium bicarbonate and with brine, then dried over $MgSO_4$. After evaporation of solvent, the residual oil was chromatographied on silica gel with pentane-ethyl acetate (9:1), leading to pyrrolidine **3**.
3a: ^{19}F NMR ($CDCl_3$, ref $CFCl_3$) δ -70.9 (d, J_{HF} 9 Hz); ^1H NMR ($CDCl_3$) δ 1.2 (t, *J* 7 Hz, 3H, CH_3), 2.8 (m, 4H), 3.1 (qddd, J_{HF} 1 Hz, J_1 6 Hz, J_2 6 Hz, J_3 8 Hz, 1H, H-4), 3.4 (m, 1H, H-3), 3.6 (s, 2H, NCH_2), 4.3 (q, *J* 7 Hz, 2H, OCH_2), 7.3 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 43.4, 44.0 (q, *J* 28 Hz, C-3), 52.9, 56.6, 58.8, 61.1, 126.9 (q, *J* 277 Hz, CF_3), 127.0, 128.1, 128.2, 137.6 (Ph), 172.1 (CO).
3b: ^{19}F NMR ($CDCl_3$, ref $CFCl_3$) δ - 73.3; ^1H NMR ($CDCl_3$) δ 2.3-2.8 (m, 4H, H-4 and H-5), 3.1 (d, *J* 10 Hz, 1H, H-2), 3.25 (d, *J* 10 Hz, 1H, H-2'), 3.7 (s, 2H, CH_2Ph), 7.2 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 33.6 (C-4), 53.5 (C-5), 56.5 (q, *J* 32 Hz, C-3), 59.9 (CH_2N), 60.6 (CH_2N), 127.1, 127.7, 128.1, 128.4, 128.6, 128.7, 136.9, 138.9 (Ph), 127.2 (q, *J* 275 Hz, CF_3).
3c: ^{19}F NMR ($CDCl_3$, ref $CFCl_3$) δ - 71.3; ^1H NMR ($CDCl_3$) δ 0.80 (t, *J* 7 Hz, 3H, CH_3), 3.1-3.35 (m, 4H), 3.60 (m, 3H, CH_2O + CH), 3.75 (s, 2H, CH_2N), 7.20 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 49.8 (C-4), 56.1 (OCH_2), 57.9 (q, J_{CF} 24 Hz, C-3), 59.3, 60.5, 61.0 (C-2, C-5, NCH_2), 127.5 (q, J_{CF} 283 Hz, CF_3), 126.9, 127.5, 127.7, 127.9, 128.1, 128.2, 136.9, 138.7 (Ph), 171.3 (CO).
3d: ^{19}F NMR ($CDCl_3$, ref $CFCl_3$) δ - 76.9; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* 7 Hz, 3H, CH_3), 1.25 (t, *J* 7 Hz, 3H, CH_3), 1.5 (m, 2H, CH_2), 2.9 (m, 3H), 3.2 (m, 1H), 3.30 (m, 1H), 3.50 (m, *J* 7 Hz, 2H, OCH_2), 3.70 (s, 2H), 4.2 (q, *J* 7 Hz, 2H, OCH_2), ^{13}C NMR ($CDCl_3$) δ 10.2 (CH_3), 14.0 (CH_3), 23.3 (CH_2), 49.5 (C-4), 54.8, 56.7, 59.4, 60.7, 67.4, 84.4 (q, *J* 27 Hz, C-3), 126.8 (q, *J* 284 Hz, CF_3), 127.2, 128.4, 138.1 (Ph), 169.1 (CO).
12. **3d** was accompanied with starting alkene **1d**.
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