

1,3-Dipolar Cycloaddition Between Ethyl Trifluoroacetoacetate and *N*-(Benzylidene)methylamine *N*-Oxide

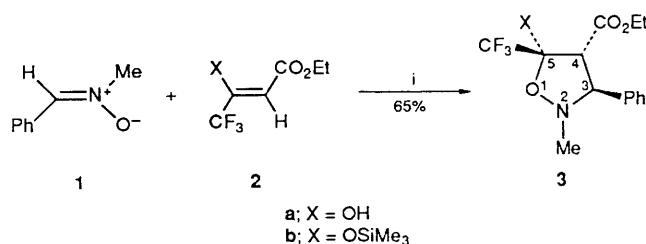
Jean-Pierre Bégué, Danièle Bonnet-Delpon* and Thierry Lequeux
CNRS-CERCOA, 2 Rue H. Dunant, 94320 Thiais, France

The 1,3-dipolar cycloaddition between ethyl trifluoroacetoacetate and *N*-(benzylidene)methylamine *N*-oxide, performed in boiling toluene, leads regio- and stereo-selectively to an isoxazolidine, while the corresponding ethyl acetoacetate is found to be unreactive under the same conditions. On the other hand, α -trifluoromethylstyrene behaves as α -methylstyrene and affords two diastereoisomeric trifluoromethyl-substituted cycloadducts.

Recent publications describe 1,3-dipolar cycloadditions between ethyl trifluoroacetoacetates and nitrones leading to a mixture of isoxazolidines.^{1,2} In the course of our studies on reactivity of ethyl trifluoroacetoacetate (ETFAA),^{3,4} we were tempted to know if its enol form could undergo such reactions.

Thus, cycloaddition between *N*-(benzylidene)methylamine *N*-oxide **1**⁵ and ETFAA (80% of enol form in its *Z* configuration, **2a**)⁶ afforded after 24 h the isoxazolidine **3a** in 65% yield (Scheme 1). The reaction is regio- and stereo-selective. The same results occurred with the corresponding silyl enol ether **2b** (*Z* isomer).⁷ The crude product **3b** was easily converted into **3a** by desilylation⁸ (55%).

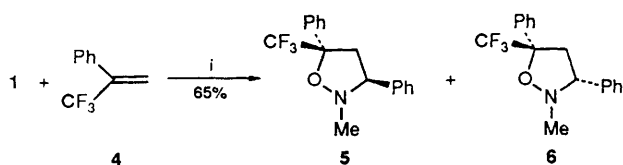
The structure of the isoxazolidine **3a** was determined from its NMR data: ¹³C NMR showed a hemiketal signal at δ 98.1 (q, ²*J*_{CF} 33 Hz), reflecting the C-5 position of the CF₃ group. The *trans* configuration of the 3-H and 4-H was deduced from their coupling constant (³*J*_{HH} 11 Hz) indicating a dihedral angle of about 170°. Molecular modelling confirms the value of this angle.⁹ In the *cis* isomer, the corresponding coupling constant



Scheme 1 Reagents and conditions: i, toluene, reflux, 24 h

would be expected to be of 2 Hz in view of the calculated dihedral angle (52°). The 4-H and CF₃ *cis* configuration was deduced from a heteronuclear NOE experiment: irradiation of CF₃ enhanced the integration of the 4-H NMR signal (about 10%).¹⁰

A priori, the observed regioselectivity in the cycloaddition **1** + **2** is surprising for at least two reasons: first, this result implicates that no cycloreversion occurred,^{1b} and secondly, in



Scheme 2 Reagents and conditions: i, toluene, reflux, 48 h

most cases, cycloaddition reactions between nitrones and olefins α,β -substituted by two electron-withdrawing groups (NO_2 and CO_2Et or CN) lead to two regioisomeric adducts.¹¹ In terms of the frontier-orbital model,^{12,13} two types of interaction can occur. In the case of the nitron HOMO control (as expected in the presence of two electron-withdrawing groups on the alkene), CO_2Et and OH effects on LUMO coefficients of the enol reinforce each other but are the opposite to that of CF_3 ; obtention of regioisomer **3** is expected. In the case of the nitron LUMO control, CO_2Et and CF_3 effects on HOMO coefficients reinforce each other but are the opposite to that of OH ; obtention of **3** thus implicates that OH effect dominates both CO_2Et and CF_3 effects.

The C(4)–C(5) configuration in **3a** and **3b** reflects the conservation of the geometry of the starting alkenes **2a** and **2b** thus confirming the well known *cis*-stereospecificity of 1,3-dipolar cycloaddition reactions.¹⁴

It is important to report that corresponding ethyl acetoacetate was found to be unreactive with nitron **1** under the same conditions. In order to evaluate the role of the CF_3 group we have performed the 1,3-dipolar reaction between **1** and the α -trifluoromethyl styrene **4** (Scheme 2) and compared our results to those of Huisgen concerning the same reaction with α -methylstyrene.¹⁵

The course of the reaction is quite similar to that of α -methylstyrene: in both cases, the reaction was incomplete even after a long reaction time. The styrene **4** afforded the two isoxazolidines **5** and **6** (65% yield) in the ratio 1:1. Evidence for this regiochemistry was deduced from NMR data: one ¹³C NMR signal (δ 82.6) and its multiplicity (quadruplet J_{CF} 30 Hz) indicate a carbon bearing both a heteroatom and a CF_3 group. The α -methylstyrene afforded the two corresponding isoxazolidines (55% yield) in the ratio 1:1.¹⁵ Concerning the regioselectivity, the phenyl group effect predominates: LUMO_{nitron}–HOMO_{olefin} interaction favours the formation of 5-disubstituted isoxazolidine,^{12,13} regardless of the opposite electronic effects of the CH_3 and CF_3 groups.

The lack of stereoselectivity, in comparison with results from **2a** and **2b**, confirms the determining role of the steric hindrance in the transition states of the 1,3-dipolar cycloadditions.^{14,16}

In spite of its electron-withdrawing character, the trifluoromethyl group seems to have little influence on the course of 1,3-dipolar cycloaddition. We are thus tempted to explain the difference of reactivity between ETFAA and the corresponding ethyl acetoacetate by the predominant presence of the enol form in **2a**. Besides these mechanistic considerations, the substituted isoxazolidines can be precursors of β -amino trifluoromethyl alcohols. This class of compounds is especially important because of their potential biological applications.

Experimental

All reactions were performed in boiling toluene (15 cm³) using equimolar (10 mmol) amounts of the reactants. At the end of

reaction (followed by GC), evaporation of the solvent, column chromatography (SiO_2 , pentane/ CH_2Cl_2) and recrystallization afforded products **3** or **5** and **6**.

Compound 3a (Found: M^+ , 319.1033. $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_4$ requires M , 319.1031); white crystals, m.p. 94–96 °C; δ_{H} (200 MHz; CDCl_3) 7.35 (m, 5 H, Ph), 5.61 (m, 1 H, OH), 4.15 (m, 3 H, $\text{O}-\text{CH}_2$, 3-H), 3.72 (d, 3J 11, 1 H, 4-H), 2.70 (s, 3 H, CH_3-N) and 1.15 (t, 3J 7, 3 H, CH_3); δ_{C} (50 MHz; CDCl_3) 138.9, 134.5, 129.1, 128.9, 127.8, 120.1 (q, J_{CF} 274, CF_3), 98.1 (q, $^2J_{\text{CF}}$ 33, C-5), 75.1 (C-3), 62.1 ($\text{O}-\text{CH}_2$), 58.7 (C-4), 43.9 (CH_3-N) and 13.7 (CH_3); δ_{F} (CDCl_3 , CFCl_3) – 84.1.

Compounds 5 + 6 (mixture) (Found: M^+ , 307.1179. $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}$ requires M , 307.1184); m.p. 52–54 °C (colourless crystals); δ_{H} (200 MHz; CDCl_3) 7.2–7.4 (m, 10 H, 2 \times Ph), 3.4–3.8 (m, 1 H, 3-H), 2.7–3.3 (m, 2 H, 4-H) and 2.62 (s, 3 H, CH_3); δ_{C} (50 MHz; CDCl_3) 139.0, 138.1, 136.9, 127.0–129.1, 126.6 (q, J_{CF} 270, CF_3), 82.6 (q, $^2J_{\text{CF}}$ 30, C-5), 72.6 and 74.0 (C-3, **5** and **6**), 48.3 and 49.3 (CH_3-N , **5** and **6**), and 43.1 and 43.5 (C-4, **5** and **6**); δ_{F} (CDCl_3 ; CFCl_3) – 78.2 and – 78.9 (ratio 1:1 according to the integration of ¹⁹F NMR signals and confirmed by GC analysis).

Acknowledgements

We wish to thank Prof. Hans-Ulrich Reissig for helpful comments during the preparation of this article.

References and Notes

- (a) K. Tanaka, T. Mori and K. Mitsuhashi, *Chem. Lett.*, 1989, 1115; (b) In 1(a) authors show that cycloreversion leads to a mixture of two regioisomeric adducts even after 17 h of heating at 140 °C.
- P. Bravo, L. Bruché, A. Mele and G. Zecchi, *J. Chem. Res. (S)*, 1991, 81.
- J. P. Bégue, M. Charpentier-Morize and G. Née, *J. Chem. Soc., Chem. Comm.*, 1989, 83.
- C. Aubert, J. P. Bégue, M. Charpentier-Morize, G. Née and B. Langlois, *J. Fluor. Chem.*, 1989, **44**, 361 and 377.
- C. M. Dicken and P. DeShong, *J. Org. Chem.*, 1982, **47**, 2047.
- F. Camps, J. Coll, A. Messegueur and A. Roca, *Tetrahedron*, 1977, **33**, 1637.
- J. P. Bégue, D. Bonnet-Delpon, D. Mesureur and M. Ourevitch, *Magn. Reson. Chem.*, 1991, **29**, 675.
- For desilylation of silylated alcohols see: J. E. Nyström, T. D. McCanna, P. Helquist and R. S. Iyer, *Tetrahedron Lett.*, 1985, **26**, 5393.
- ALCHEMY II, Molecular modeling software, Tripos Associates, Inc., St. Louis (Missouri).
- J. K. M. Sanders and B. K. Hunter, *Modern NMR Spectroscopy*, Oxford University Press, Oxford, 1989, p. 168.
- A. Padwa, L. Fisera, K. F. Koehler, A. Rodriguez and G. S. K. Wong, *J. Org. Chem.*, 1984, **49**, 276.
- H. U. Reissig and R. Zschiesche, *Liebigs Ann. Chem.*, 1989, 551, and references therein.
- K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301.
- (a) R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.*, 1969, **102**, 736; (b) M. Joucla, D. Grée and J. Hamelin, *Tetrahedron*, 1973, **29**, 2315.
- (a) R. Huisgen, R. Grashey, H. Seidl and H. Hauck, *Chem. Ber.*, 1968, **101**, 2559; (b) J. J. Tufariello, S. Asrof Ali, *Tetrahedron Lett.*, 1978, **47**, 4647.
- P. Dalla Croce, C. La Rosa, R. Stardi and M. Ballabio, *J. Heterocycl. Chem.*, 1983, **20**, 519.

Paper 1/04281E

Received 15th August 1991

Accepted 15th August 1991