Enantioselective Intramolecular Nitrone Cycloaddition Route to 3-(Trifluoromethyl)-isoxazolidino[4,3-*c*]-chroman-4-ones and -quinolin-4-ones†

J. Chem. Research (S), 1998, 188–189†

Alberto Arnone,[a] Gianluigi Broggini,[b] Luca Bruché,*[c] Giorgio Molteni[b] and Gaetano Zecchi[b]

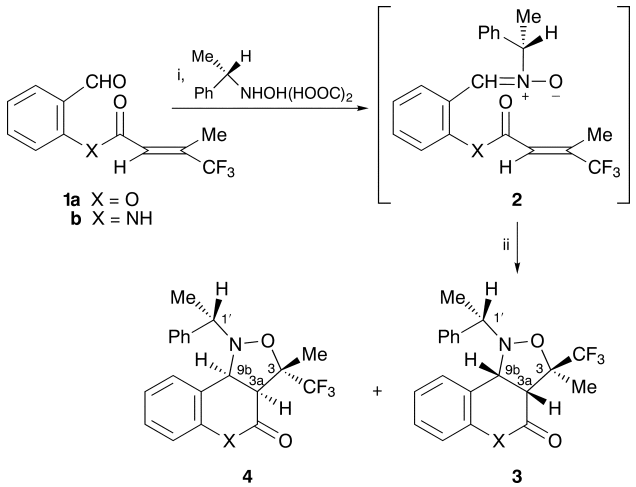
[a]*C.N.R.-Centro di Studio sulle Sostanze Organiche Naturali, via Mancinelli 7, 20131 Milano, Italy*
[b]*Dipartimento di Chimica Organica e Industriale, Università, via Golgi 19, 20131 Milano, Italy*
[c]*Dipartimento di Chimica, Politecnico, via Mancinelli 7, 20131 Milano, Italy*

Optically active 3-(trifluoromethyl)isoxazolidino[4,3-*c*]-chroman-4-ones and -quinolin-4-ones are synthesised by the stereoselective intramolecular cycloaddition of homochiral nitrones.

In light of the peculiar biological activity shown by many fluorinated heterocycles[1] we aimed to synthesise such compounds *via* 1,3-dipolar cycloadditions.[2] In this context, we have recently described an intramolecular nitrone cycloaddition route to 3-(trifluoromethyl)isoxazolidino[4,3-*c*]-chroman-4-ones and -quinolin-4-ones.[3] The present report is concerned with a version of the same synthetic approach leading to enantiopure molecules. The asymmetric cycloaddition reactions of nitrones to alkenes are the object of a great interest, as shown by recent reviews.[4,5]

The fluorinated substrates **1**, containing an alkene moiety as a potential dipolarophile, were reacted with (*S*)-(α-phenylethyl)hydroxylamine oxalate in order to originate the desired homochiral nitrones **2**, Scheme 1. The latter were not isolated, but directly submitted to heating. The reaction gave, in addition to trivial side-products due to degradative processes, a mixture of the intramolecular cycloadducts **3** and **4** with an overall yield of *ca.* 50%. The diastereoisomeric ratio was 9:1 for **3a**–**4a** and 5:1 for **3b**–**4b**. Compounds (3a*R*,9b*R*,1′*S*)-**3a**, (3a*R*,9b*R*,1′*S*)-**3b** and (3a*S*,9b*S*,1′*S*)-**4b** were obtained chemically and enantiomerically pure after chromatographic treatment, whilst compound **4a** was only available as an enriched mixture.

The structure of compounds **3a,b** and **4b** was elucidated on the basis of the ^{1}H, ^{13}C and ^{19}F NMR analyses reported



Scheme 1 *Reagents and conditions*: i, $MgSO_4$–$NaHCO_3$, benzene, r.t.; ii, benzene, reflux

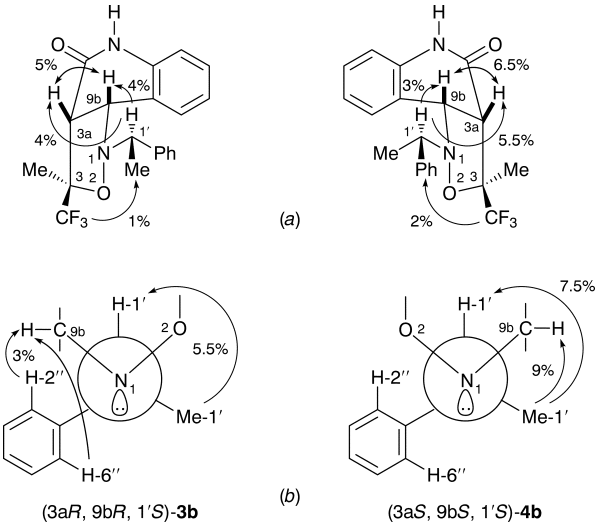


Fig. 1 Selected spatial connectivities from {^{1}H}- and {^{19}F}-^{1}H NOE measurements in the diastereoisomeric products **3b** and **4b**

in the experimental section, while the stereochemical assignment of the new stereogenic centres was deduced from the {^{1}H}- and {^{19}F}-^{1}H NOE results shown in Fig. 1, taking into account that the absolute configuration at C-1′ is *S*. Thus, the mutual NOE enhancements observed in compounds **3b** and **4b** between H-3a and H-9b (5 and 6.5%, respectively), assumed as β-disposed in Fig. 1*a*, established their *cis* relationship; these protons, in turn, underwent similar NOE enhancements by irradiation of H-1′. Such findings not only indicate that in both diastereoisomers **3b** and **4b** the *N*-pendant is β-pseudoaxially positioned, but also suggest that the main rotamer around the N(1)—C(1′) bond has H-1′ oriented towards the C(3a)—C(9b) bond. This supposition was confirmed by the spatial NOE connectivities shown in Fig. 1*b*. Specifically, H-9b showed in compound **3b** significative NOEs to H-2″ and -6″ (3%), but no sizeable effect (< 0.5%) to the C-1′ methyl protons, which implies that H-9b is spatially closer to the aromatic ring than to the methyl group; on the contrary, in compound **4b** H-9b is spatially much closer to the C-1′ methyl protons (7.5%), since no significative NOE was observed between H-9b and the aromatic protons. Finally, the presence of NOEs between the fluorine atoms and the C-1′ methyl protons in compound **3b**, but between the fluorine atoms and H-2″ and -6″ in compound **4b**, gave additional evidence in favour of the absolute configurations assigned to the two diastereoisomers.

The preferred formation of **3** (among the eight conceivable stereoisomeric cycloadducts) can be rationalised in

*To receive any correspondence.
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

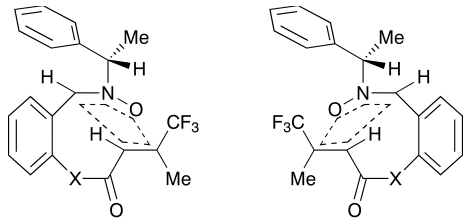


Fig. 2 Proposed transition states for the formation of **3** and **4**

terms of the transition state **A** depicted in Fig. 2. Within the very plausible assumption that the nitrone *Z*-configuration is the reactive one,[6] and that it approaches the dipolarophile face *syn* to the X moiety, the *N*-pendant remains external, with the smallest substituent (*i.e.* hydrogen) oriented towards the reaction centres and the phenyl in front of the vinylic hydrogen. The analogous transition state **B**, having the phenyl in front of the larger CF_3 group, would originate the minor product **4**.

In conclusion, the intramolecular nitrone cycloaddition studied, which involves the creation of three stereocentres, is fully stereoselective as far as their relative configuration and exhibits a good degree of asymmetric induction by the homochiral pendant. Hence, in spite of the modest yields of isolation, the present synthetic approach seems worthy of attention.

Experimental

Mps were obtained using a Büchi apparatus and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker CPX 300 or AC 250L instrument in $CDCl_3$ solutions using $SiMe_4$ or C_6F_6 as internal standards. In the ^{13}C NMR signal assignment capital letters refer to the pattern resulting from directly bonded (C, H) couplings and lower case letters to the one from (C, F) couplings. Mass spectra were taken on a VG 70 EQ spectrometer. Compounds **1** were prepared as described previously.[3]

Reaction of the Aldehydes **1** *with* (*S*)-(α-*Phenylethyl*)*hydroxylamine Oxalate and* 1,3-*Dipolar Cycloaddition of the Nitrone Intermediates* **2**.—A suspension of (*S*)-(α-phenylethyl)hydroxylamine oxalate (2.0 mmol), magnesium sulfate (2.0 mmol) and sodium hydrogencarbonate (4.0 mmol) in benzene (40 ml) was cooled at 0 °C and then a solution of aldehyde **1a,b** (1.9 mmol) in benzene (10 ml) was slowly added. After stirring at 0 °C for 30 min, the suspension was refluxed for 72 h. The undissolved material was filtered off, the solvent evaporated under reduced pressure, and the residue chromatographed on a silica gel column with CH_2Cl_2–Et_2O (3:1) as eluent. Cycloadducts **3a, 3b** and **4b** were isolated in the pure state. (3a*R*,9b*R*,1′*S*)-**3a**. Yield 45%. $[\alpha]_D$ +24.2 (*c* 0.30, $CHCl_3$); δ_H 1.24 (3 H, br s, Me-3), 1.57 (3 H, d, *J* 6.2 Hz, Me-1′), 4.10 (1 H, br q, *J* 6.2 Hz, H-1′), 4.22 (1 H, d, *J* 7.7 Hz, H-3a), 4.66 (1 H, br d, *J* 7.7 Hz, H-9b), 6.97, 7.20, 7.27 and 7.59 (4 H, m, H-6, -8, -7 and -9), 7.28, 7.37 and 7.46 (5 H, m, Ph-1′); δ_F −79.67 (3 F, br s, CF_3-3); *m*/*z* 377 (M+) (Found: C, 63.5; H, 4.9; N, 3.6%. $C_{20}H_{18}F_3NO_3$ requires: C, 63.66; H, 4.81; N, 3.71%). (3a*R*,9b*R*,1′*S*)-**3b**. Yield 39%. Mp 204 °C (from diisopropyl ether); $[\alpha]_D$ +36.6 (*c* 0.80, $CHCl_3$); δ_H 1.20 (3 H, br s, Me-3), 1.58 (3 H, d, *J* 6.2 Hz, Me-1′), 3.99 (1 H, d, *J* 8.1 Hz, H-3a), 4.10 (1 H, br q, *J* 6.2 Hz, H-1′), 4.62 (1 H, br d, *J* 8.1 Hz, H-9b), 6.68, 7.01, 7.07 and 7.56 (4 H, m, H-6, -8, -7 and -9), 7.28, 7.37 and 7.56 (5 H, m, Ph-1′), 9.59 (1 H, br s, H-5); δ_F -79.37 (3 F, br s, CF_3-3); δ_C 17.58 and 21.44 (Q, CH_3-3 and -1′), 49.43, 62.96 and 66.09 (D, C-3a, -9b and -1′), 87.03 (Sq, $J_{C,F}$ 29.9 Hz, C-3), 115.21 (D), 121.48 (S), 124.57 (D), 127.24 (D), 127.74 (D), 128.24 (D), 129.06 (D), 129.24 (D), 134.96 (S), and 142.54 (S) (ArC), 124.70 (Sq, $J_{C,F}$ 284.2 Hz, CF_3-3), 166.70 (S, C-4); 129.24 (D), 134.96 (S), and 142.54 (S) (ArC), 124.70 (Sq, $J_{C,F}$ 284.2 Hz, CF_3-3), 166.70 (S, C-4); *m*/*z* 376 (M^+) (Found: C, 63.9; H, 5.0; N, 7.6%. $C_{20}H_{19}F_3N_2O_2$ requires: C, 63.82; H, 5.09; N, 7.44%). (3a*S*,9b*S*,1′*S*)-**4b**. Yield 9%. Mp 186 °C (from diisopropyl ether); $[\alpha]_D$−75.7 (*c* 0.35, $CHCl_3$); δ_H 1.26 (3 H, br s, Me-3), 1.46 (3 H, d, *J* 6.5 Hz, Me-1′), 3.89 (1 H, d, *J* 8.1 Hz, H-3a), 4.16 (1 H, br q, *J* 6.5 Hz, H-1′), 4.83 (1 H, br d, *J* 8.1 Hz, H-9b), 6.83, 7.16, 7.28 and 7.70 (4 H, m, H-6, -8, -7 and -9), 7.28, 7.37 and 7.48 (5 H, m, Ph-1′), 8.93 (1 H, br s, H-5); δ_F -79.58 (3 F, br s, CF_3-3); δ_C 17.79 and 23.08 (Q, CH_3-3 and -1′), 50.44, 61.70 and 63.21 (D, C-3a, -9b and 1′), 84.96 (Sq, $J_{C,F}$ 29.6 Hz, C-3), 115.47 (D), 120.30 (S), 124.24 (D), 127.26 (D), 127.77 (D), 128.31 (D), 128.43 (D), 129.62 (D), 135.65 (S) and 142.18 (S) (ArC), 124.45 (Sq, $J_{C,F}$ 284.2 Hz, CF_3-3), 166.61 (S, C-4); *m*/*z* 376 (M^+) (Found: C, 63.7; H, 5.2; N, 7.3%. $C_{20}H_{19}F_3N_2O_2$ requires: C, 63.82; H, 5.09; N, 7.44%).

Received, 13th November 1997; Accepted, 3rd December 1997
Paper E/7/08184G

References

1 M. J. Silvester, *Aldrichim. Acta*, 1991, **24**, 31; *Biomedical Aspects of Fluorine Chemistry*, ed. R. Filler and Y. Kobayashi, Elsevier, New York, 1992; M. J. Silvester, *Adv. Heterocycl. Chem.*, 1994, **59**, 1; K. Burger, U. Wucherpfennig and E. Brunner, *Adv. Heterocycl. Chem.*, 1994, **60**, 1.
2 P. Bravo, L. Bruché, G. Fronza and G. Zecchi, *Tetrahedron*, 1992, **48**, 9775; P. Bravo, L. Bruché, A. Farina, G. Fronza, S. V. Meille and A. Merli, *Tetrahedron: Asymmetry*, 1993, **4**, 2131; A. Arnone, P. Bandiera, P. Bravo, L. Bruché and M. Zanda, *Gazz. Chim. Ital.*, 1996, **126**, 773; A. Arnone, P. Bravo, L. Bruché, P. Seresini and M. Zanda, *J. Heterocycl. Chem.*, 1997, **34**, 489.
3 A. Arnone, L. Bruché, L. Garanti and G. Zecchi, *J. Chem. Res.* (*S*), 1995, 282.
4 M. Cinquini and F. Cozzi, in *Houben-Weyl, Methods of Organic Chemistry: Stereoselective Synthesis*, ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1995, vol. E21c, ch. 1.6.1.2.
5 M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
6 K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH, New York, 1988, p. 85; P. M. Wovkulich and M. R. Uskokovic, *Tetrahedron*, 1985, **41**, 3455.