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The first case of asymmetric induction in intramolecular nitrile imine cycloadditions: synthesis of enantiopure 3-substituted 6-oxo-2,3,3a,5-tetrahydro-4-carbomethoxy-furo[3,4-*c*]pyrazoles

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Abstract

Intramolecular cycloaddition of homochiral nitrile imines **5**, generated in situ from base treatment of the corresponding hydrazonoyl chlorides **4**, involves diastereoselective formation of the title compounds in the enantiomerically pure form.

1. Introduction

Stereoselective 1,3-dipolar cycloadditions have received much attention in the last two decades.[1] In this respect, the cycloadditive route has been successfully exploited in both inter-[2] and intramolecular[3] versions, and the number of available examples increases constantly. Many papers deal with stereoselective cycloadditions as key steps in the construction of complex targets such as natural products or their analogues,[4] while simpler systems have been studied to acquire an accurate rationale of the observed stereoselectivities.[5] Nitrile oxide and nitrone cycloadditions play a major role in this field,[1] due to the easy generation of the dipole and to the astonishing array of latent functionalities displayed by the corresponding cycloadducts.[6] Much less work has been done on other kinds of 1,3-dipoles. For example, a few reports on nitrile imines have recently appeared describing intermolecular nitrile imine cycloadditions onto a chiral dipolarophile,[7] but there is a complete lack of data regarding intramolecular versions.

We present here the first example of an intramolecular cycloaddition of homochiral nitrile imines **5** in which the stereogenic unit is placed inside the tether joining the reactive groups, in the allylic position with respect to the dipolarophile.

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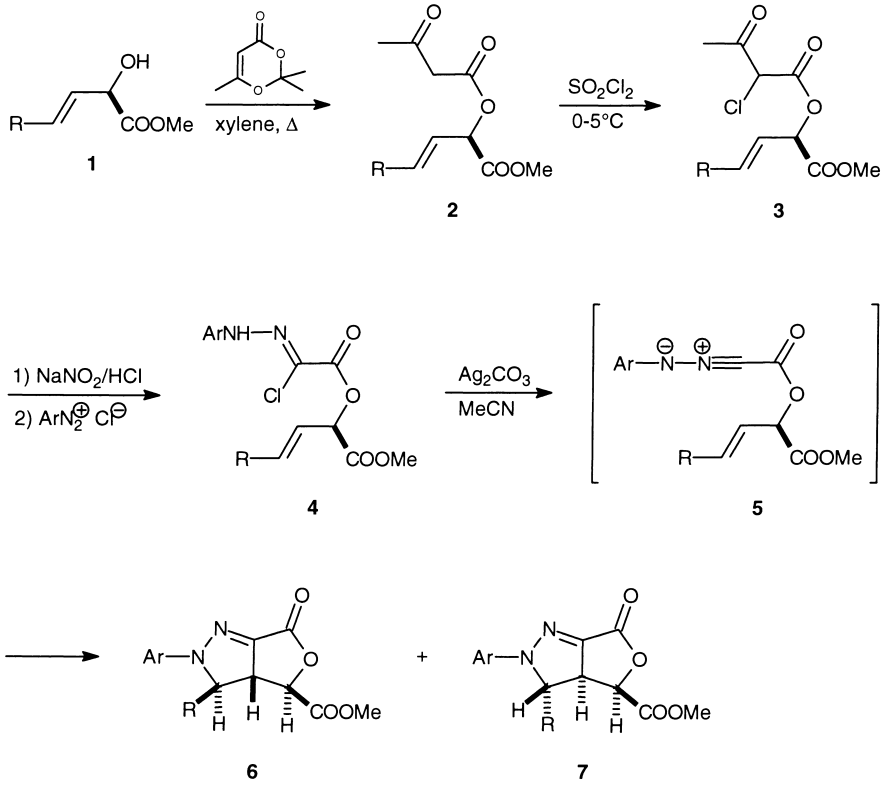
2. Results and discussion

Our synthetic sequence starts from the 4-substituted 2-(*R*)-hydroxy-3-(*E*)-butenoic acid methylesters **1** as chiral building blocks.[8] Hydrazonoyl chlorides **4**, which we devised as the suitable precursors of nitrile imines **5**, were synthesised from **1** following a well-established procedure elaborated by us[9] (Scheme 1). The in situ generation of the transient species **5** was accomplished by treating the appropriate hydrazonoyl chlorides **4** with a twofold molar excess of silver carbonate in dry acetonitrile at room temperature.[10]



entry	R	Ar
a	Me	Ph
b	Ph	4-Cl-C_6H_4

Scheme 1.

The diastereoisomeric cycloadducts **6** and **7** were obtained chemically and enantiomerically pure by simple column chromatography. Their isolated yields were fair, since some amount of tarry material was formed. Structural assignments rely upon analytical and spectral data, and are unambiguous in the light of the ^{1}H NMR chemical shifts and scalar coupling values, compared with literature data.[11] The absolute configurations of the newly formed stereocentres were determined, taking into account the (*R*) configuration of the starting centre, by NOE measurements reported in Fig. 1. In order to gain deeper insight into the spatial relationships between H_A and H_C, full geometry optimisation of the major

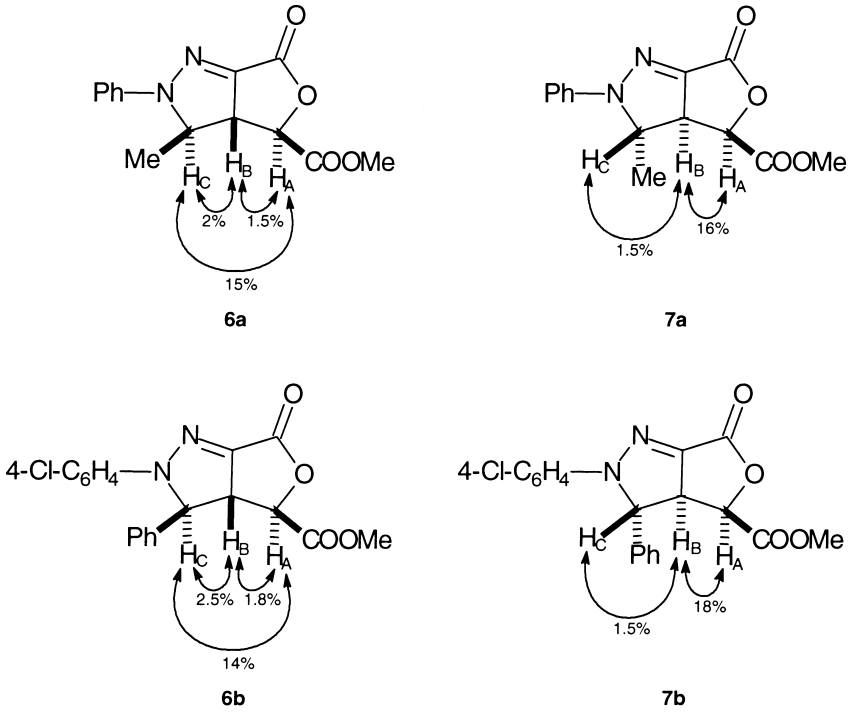


Figure 1. NOE enhancements for cycloadducts **6** and **7**

cycloadducts **6** was carried out[12] at the AM1 level of theory.[13] The calculated distances H_A–H_C were 2.43 Å for **6a** and 2.41 Å for **6b**; so justifying the observed mutual NOE enhancements.

Some particular features characterise the cycloaddition reactions described above: (i) they take place with good overall yields; (ii) the relative configuration of the two new stereocentres is exclusively *anti* as a consequence of the stereoconservative nature of the concerted mechanism; and (iii) a fair degree of stereoselectivity is operating due to the effect of the pre-existing stereocentre. The latter stereoselective result may be rationalised by means of the proposed transition states **A** and **B** (Fig. 2). The former of these is plausibly the more accessible because of the lack of steric encumbrance due to the carbomethoxy group. Hence, the preferred formation of **6** finds rationalisation.

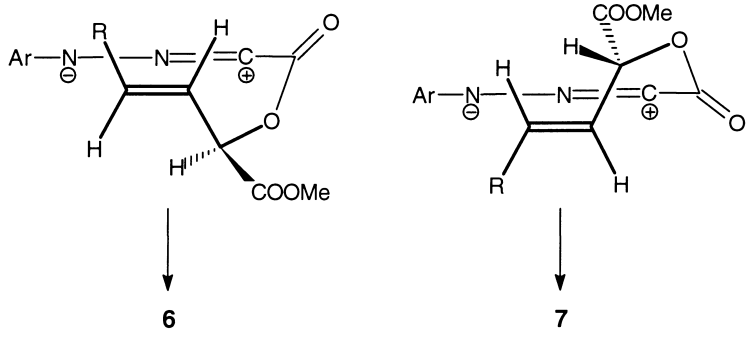


Figure 2. Proposed transition states for the formation of **6** and **7**

In conclusion, the present work has made accessible the enantiopure targets **6** and **7** by way of an unprecedented stereoselective intramolecular cycloaddition of homochiral nitrile imines.

3. Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR spectra were taken with a Bruker AC 300 instrument (in $CDCl_3$ solutions). Chemical shifts are given as ppm from tetramethylsilane and coupling constants are given in hertz. Optical rotations, $[\alpha]_D^{25}$, were recorded on a Perkin–Elmer Model 241 polarimeter at the sodium D line.

*3.1. General procedure for the preparation of alkenyl acetoacetates **2***

A solution of **1** (25 mmol) in xylene (8 mL) was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (3.55 g, 25 mmol). The mixture was refluxed for 1.5 h. Evaporation of the solvent under reduced pressure and subsequent in vacuo distillation of the residue gave the acetoacetates **2** as analytically pure samples.

2a (5.08 g, 95% yield) bp 56°C (1 mmHg); $[\alpha]_D^{25}$=−56 ($CHCl_3$, c=0.36); IR (neat): 1750, 1720, 1700 (cm^{-1}); ^{1}H NMR δ: 1.76 (3H, d, *J*=6.0), 2.32 (3H, s), 3.54 (2H, s), 3.78 (3H, s), 5.46 (1H, d, *J*=7.0), 5.50–5.60 (1H, m), 5.90–6.05 (1H, m); MS: *m/z* 214 (M^+). Anal. calcd for $C_{10}H_{14}O_5$: C, 56.05; H, 6.59. Found: C, 56.11, H, 6.64.

2b (4.35 g, 63% yield) bp 106°C (0.5 mmHg); $[\alpha]_D^{25}$=−74 ($CHCl_3$, c=0.23); IR (neat): 1745, 1720, 1700 (cm^{-1}); ^{1}H NMR δ: 2.27 (3H, s), 3.55 (2H, s), 3.75 (3H, s), 5.66 (1H, d, *J*=6.3), 6.20 (1H, dd, *J*=15.4, 6.3), 6.80 (1H, d, *J*=15.4), 7.20–7.40 (5H, m); MS: *m/z* 276 (M^+). Anal. calcd for $C_{15}H_{16}O_5$: C, 65.19; H, 5.84. Found: C, 65.23, H, 5.90.

*3.2. General procedure for the preparation of alkenyl chloroacetoacetates **3***

A solution of sulfuryl chloride (2.51 g, 18.6 mmol) in dry chloroform (30 mL) was slowly added (1 h) to a solution of **2** (15 mmol) in dry chloroform (15 mL), on keeping the temperature in the range 0–5°C. After 2 h at room temperature, chloroform (30 mL) was added and the organic solution was washed with 5% aqueous sodium hydrogencarbonate (25 mL). The organic layer was then washed with water (50 mL) and dried over sodium sulfate. The solvent was removed to give chloroacetacetates **3** as undistillable oils which were not analytically pure.

3a (3.53 g, 95% yield); $[\alpha]_D^{25}$=−27 ($CHCl_3$, c=0.28); IR (neat): 1760, 1730, 1700 (cm^{-1}); ^{1}H NMR: δ 1.76 (3H, d, *J*=6.0), 2.42 (3H, s), 3.76 (3H, s), 4.86 (1H, s), 5.49 (1H, d, *J*=6.9), 5.50–5.60 (1H, m), 5.85–6.00 (1H, m); MS: *m/z* 248 (M^+).

3b (1.86 g, 40% yield); $[\alpha]_D^{25}$=−39 ($CHCl_3$, c=0.48); IR (neat): 1760, 1730, 1690 (cm^{-1}); ^{1}H NMR: δ 2.42 (3H, s), 3.78 (3H, s), 4.89 (1H, s), 5.69 (1H, d, *J*=6.3), 6.20 (1H, dd, *J*=15.4, 6.3), 6.82 (1H, d, *J*=15.4), 7.30–7.40 (5H, m); MS: *m/z* 310 (M^+).

*3.3. General procedure for the preparation of hydrazonyl chlorides **4***

A cold aqueous solution of 4-chlorobenzenediazonium chloride (6.0 mmol) was added dropwise to a solution of **3** (6.0 mmol) in 80% aqueous methanol (25 mL) under vigorous stirring and ice-cooling. During the addition, the pH was adjusted to **5** by adding sodium acetate. The mixture was allowed to stand overnight under stirring at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethyl ether (75 mL). The organic layer was washed firstly with 5% sodium hydrogencarbonate (25 mL), then with water (75 mL), and dried over sodium sulfate.

Evaporation of the solvent gave a solid and subsequent recrystallisation with diisopropylether gave the hydrazonyl chlorides **4** in the pure state.

4a (1.41 g, 76% yield) mp 65°C; $[\alpha]_D^{25}=-80$ ($CHCl_3$, c=0.29); IR: 3180, 1730, 1710 (cm^{-1}); ^1H NMR δ: 1.78 (3H, d, *J*=6.6), 3.78 (3H, s), 5.58 (1H, d, *J*=7.0), 5.60–5.80 (1H, m), 6.00–6.17 (1H, m), 6.80–7.20 (5H, m), 8.58 (1H, br s); MS: *m/z* 310 (M^+). Anal. calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.18; H, 4.88; N, 9.03. Found: C, 54.24; H, 4.86; N, 8.95.

4b (1.02 g, 42% yield) mp 152°C; $[\alpha]_D^{25}=-59$ ($CHCl_3$, c=0.36); IR: 3180, 1750, 1715 (cm^{-1}); ^1H NMR: δ 3.80 (3H, s), 5.75 (1H, dd, *J*=6.3, 1.0), 6.32 (1H, dd, *J*=15.4, 6.3), 6.90 (1H, dd, *J*=15.4, 1.0), 7.20–7.50 (9H, m), 8.40 (1H, br s); MS: *m/z* 406 (M^+). Anal. calcd for $C_{19}H_{16}Cl_2N_2O_4$: C, 56.15; H, 3.97; N, 6.90. Found: C, 56.09; H, 4.02; N, 6.99.

*3.4. General procedure for the reaction of hydrazonyl chlorides **4** with silver carbonate*

A solution of the hydrazonyl chlorides **4** (2.5 mmol) in dry acetonitrile (125 mL) was treated with silver carbonate (1.38 g, 5.0 mmol), and stirred in the dark at room temperature for 20 h (entry **a**, Scheme 1) or 2 h (entry **b**, Scheme 1). The undissolved material was filtered off, the solvent evaporated, and then the residue was chromatographed on a silica gel column with ethyl acetate:hexane, 2:1. Products and isolation yields are collected in the Scheme 1. All compounds were obtained in analytically pure state by recrystallisation.

6a (0.30 g, 44% yield) mp 116°C (from hexane–benzene); $[\alpha]_D^{25}=-98$ ($CHCl_3$, c=0.31); IR: 1760, 1720 (cm^{-1}); ^1H NMR δ: 1.58 (3H, d, *J*=6.0), 3.70 (3H, s), 3.85 (1H, dd, *J*=11.1, 9.0), 4.45 (1H, dq, *J*=11.1, 6.0), 4.90 (1H, d, *J*=9.0), 7.00–7.10 (5H, m); MS: *m/z* 274 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 61.29; H, 5.15; N, 10.22. Found: C, 61.36; H, 5.20; N, 10.29.

7a (0.15 g, 22% yield) mp 89°C (from diisopropyl ether); $[\alpha]_D^{25}=+34$ ($CHCl_3$, c=0.33); IR: 1770, 1740 (cm^{-1}); ^1H NMR δ: 1.68 (3H, d, *J*=6.0), 3.76 (3H, s), 4.04 (1H, dd, *J*=12.1, 9.4), 4.30 (1H, dq, *J*=12.1, 6.0), 5.25 (1H, d, *J*=9.4), 7.00–7.15 (5H, m); MS: *m/z* 274 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 61.29; H, 5.15; N, 10.33. Found: C, 61.28; H, 5.22; N, 10.29.

6b (0.46 g, 50% yield) mp 187°C (from hexane–benzene); $[\alpha]_D^{25}=-128$ ($CHCl_3$, c=0.38); IR: 1770, 1730 (cm^{-1}); ^1H NMR δ: 3.70 (3H, s), 3.92 (1H, dd, *J*=11.5, 9.0), 4.96 (1H, d, *J*=11.5), 5.53 (1H, d, *J*=9.0), 6.90–7.40 (9H, m); MS: *m/z* 370 (M^+). Anal. calcd for $C_{19}H_{15}ClN_2O_4$: C, 61.61; H, 4.08; N, 7.57. Found: C, 61.57; H, 4.02; N, 7.62.

7b (0.15 g, 16% yield) mp 125°C (from diisopropyl ether); $[\alpha]_D^{25}=+19$ ($CHCl_3$, c=0.25); IR: 1760, 1730 (cm^{-1}); ^1H NMR δ: 3.88 (3H, s), 4.28 (1H, dd, *J*=12.4, 9.4), 5.15 (1H, d, *J*=12.4), 5.26 (1H, d, *J*=9.4), 6.90–7.40 (9H, m); MS: *m/z* 370 (M^+). Anal. calcd for $C_{19}H_{15}ClN_2O_4$: C, 61.61; H, 4.08; N, 7.57. Found: C, 61.66; H, 4.13; N, 7.66.

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