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Enantiopure furo[3,4-*c*]pyrazole derivatives by intramolecular nitrilimine cycloaddition: a stereoselectivity rationale based upon MP2 calculations

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ABSTRACT

Silver carbonate treatment of hydrazonoyl chloride **4** promoted the in situ generation of the corresponding nitrilimine bearing a stereocentre at the α-position of the ethylenic dipolarophile. Intramolecular cycloaddition of the latter intermediate involves the formation of 4-(*S*)-methyl-6-oxo-3,3a,4,5-tetrahydro-furo[3,4-*c*]pyrazole derivatives with very good yield and diastereoselectivity. Full rationalization of the experimentally observed stereoselectivity has been pursued by means of MP2 calculations.

1. Introduction

The synthesis of annulated pyrazoles based on the intramolecular cycloadditions of C-substituted nitrilimines was pioneered by Garanti and Zecchi.[1] This route disclosed the opportunity to obtain annulated 4,5-dihydropyrazole derivatives of relevance in organic synthesis,[2] as well as some related products, which have received interesting biological applications.[3] In recent times, our main interest in intramolecular 1,3-dipolar cycloadditions of C-substituted nitrilimines focused on the behaviour of homochiral substrates towards stereoselection.[4] Thus, we were able to exploit this strategy as the key step of synthetic sequences leading to various kinds of annulated 4,5-dihydropyrazoles in enantiopure form, which are not easily accessible by other routes.[5] As far as stereoselectivity is concerned, we first described the synthesis of the pyrrolo[3,4-*c*]pyrazole skeleton in the enantiopure form by means of stereoselective cycloaddition of a homochiral nitrilimine bearing the L-alanine benzylester pendant as a chiral auxiliary at the γ-position with respect to the nitrilimine moiety.[6] However, since control of the absolute stereochemistry was really modest, we reasoned that the large distance between the starting stereocentre and the new one could be responsible for the observed and disappointing outcome. To circumvent this drawback, we planned another α-aminoester-based synthesis of C-substituted nitrilimines, in which the stereocentre was placed at the α-position with respect to the dipolar function. As a result, much better cycloaddition stereoselectivities were observed, which are superimposable to those obtained from analogous C-substituted nitrilimines synthesized from enantiopure α-hydroxyesters.[7] However, in all these cases, the observed diastereoselectivity found a very rough rationale since it was based upon the examination of stereomodels, which mimic the proposed transition structures. Thus, a validation of the stereochemical model, which works in the intramolecular cycloadditions of C-substituted nitrilimines, needs to be formulated. In order to achieve this goal, we herein report the behaviour of the novel C-substituted-nitrilimine intermediate **5**, which is derived from (*S*)-(+)-but-3-en-2-ol and hence bears the stereocentre in the α-position of the ethylenic dipolarophile, leading to enantiopure 4-(*S*)-methyl-6-oxo-3,3a,4,5-tetrahydro-furo[3,4-*c*]-pyrazole derivatives **6**. The cycloaddition stereoselectivity outcome was fully investigated through a computational study of the diastereoisomeric transition structures at the MP2 level.

2. Results and discussion

Our synthetic sequence starts from (*S*)-(+)-but-3-en-2-ol **1**, which was devised as a suitable starting chiral building block for our synthesis. Following literature procedures,[8] enantiopure (*S*)-**1** was prepared by yeast reduction of 3-chlorobutan-2-one ($[\alpha]_D^{25} = +25.9$, lit. +25.4). Hydrazonoyl chloride **4**, which constitutes as the precursor of nitrile imine **5**, was synthesized from (*S*)-**1** following a well-established procedure previously elaborated by Garanti and Zecchi[9] (Scheme 1). The in situ generation of the labile intermediate **5** was accomplished by treating the corresponding hydrazonoyl chloride **4** with a twofold molar excess of silver carbonate in dry dioxane at room temperature.[10] Diastereoisomeric 4-(*S*)-methyl-6-oxo-3,3a,4,5-tetrahydro-furo[3,4-*c*]pyrazoles **6** were formed after 96 h with 90% overall yield and 91:9 diastereoisomeric ratio. These cycloadducts were obtained as analytically (and enantiopure) solids after silica gel column chromatography followed by crystallization. Spectral data of products **6** were in good agreement with those reported for similar furo[3,4-*c*]pyrazoles.[6,11] The absolute configuration of the newly formed

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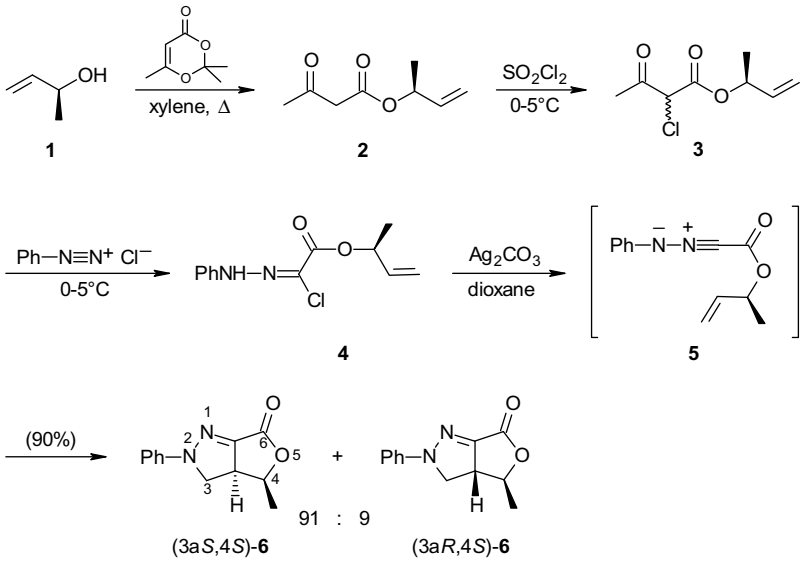

Scheme 1.

stereocentre of minor (3a*R*,4*S*)-**6** was determined by the mutual NOE enhancements between the methyl hydrogens and the hydrogen in the 3a- position of the furo[3,4-*c*]pyrazole skeleton (see Fig. 1d). It is apparent that the observed NOE effect can be operative only in the case of the stereochemical arrangement of minor (3a*R*,4*S*)-**6**. As far as the diastereoselection is concerned, the experimental ratio (3a*S*,4*S*)-**6**: (3a*R*,4*S*)-**6** = 91:9 was quite satisfactory in the light of the average stereoselectivities reported for the intramolecular cycloadditions of C-substituted nitrilimines.[4,12]

To gain deeper insights about this point, we undertook a computational study principally aimed at locating the relevant transition states. Despite the investigated molecules being medium-sized (28 atoms, 114 electrons), we were able to carry out correlated calculations (comprising full geometry optimization and harmonic analysis) using second-order Møller-Plesset (MP2) perturbation theory and Dunning's correlation consistent basis sets. Nitrilimine **5**, cycloadducts (3a*S*,4*S*)-**6** and (3a*R*,4*S*)-**6**, and the corresponding transition states **TS**[(3a*S*,4*S*)-**6**] and **TS**[(3a*R*,4*S*)-**6**] were fully optimized at the MP2/cc-pVDZ level. Harmonic analysis was performed to ensure that they actually were minimum energy and transition state structures, as appropriate. The results of second-order Møller-Plesset (MP2) calculations with three different basis sets are reported in Table 1, and the structure of the products and of the transition states are shown in Figure 1.

The conversion from **4** to **6** is exothermic and the most stable product is minor (3a*R*,4*S*)-**6**. Conversely, the activation energy is lower for the transition state leading to the major diastereoisomer (3a*S*,4*S*)-**6** by 1.2–1.4 kcal mol^{-1} depending on the basis set employed. The computed diastereoisomeric ratio is in excellent agreement with the experimental stereochemical outcome. The energy difference between the two transition states can be correlated to their structures. The distances between the atoms involved in the formation of the new bonds are as follows: C–C = 2.325 for (3a*S*,4*S*)-**6** and 2.234 for (3a*R*,4*S*)-**6**; C–N = 2.754 and (3a*S*,4*S*)-**6** and 2.938 for (3a*R*,4*S*)-**6**. Hence, the C–C bonds have an equal length in the two transition states whereas the C–N bond is significantly less developed in the higher-energy **TS**[(3a*R*,4*S*)-**6**]. The activation energy difference seems related to an unequal degree of formation of the C–N bond due to the structural constraints inherent to this intramolecular cycloaddition (see Fig. 1a and b).

It is also interesting to analyze the dependence of the activation energy on the basis set. First, it should be noted that the variation

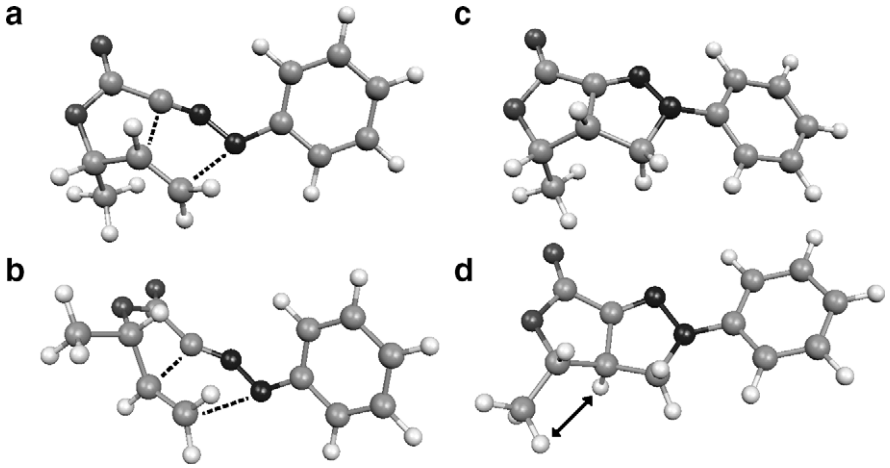

Figure 1. Structures of the transition states **TS**[(3a*S*,4*S*)-**6**] (a) and **TS**[(3a*R*,4*S*)-**6**] (b) leading to the major (3a*S*,4*S*)-**6** (c) and minor (3a*R*,4*S*)-**6** (d) diastereomeric products, respectively, optimized at the MP2/cc-pVDZ level. The double arrow marks the hydrogens giving rise to the NOE effect used to assign the absolute configuration (see text).

Table 1
Reaction energy ΔE_r, activation energy $\Delta E^{\ddagger}$ and diastereoisomeric ratio of the intramolecular 1,3-dipolar cycloaddition of **4** to (3a*S*,4*S*)-**6** and (3a*R*,4*S*)-**6** calculated at the MP2 level with three basis sets using the MP2/cc-pVDZ optimized geometry

Basis set	ΔE_r (kcal mol^{-1})		$\Delta E^{\ddagger}$ (kcal mol^{-1})		Diastereoisomeric ratio[a]
	(3a*S*,4*S*)-**6**	(3a*R*,4*S*)-**6**	(3a*S*,4*S*)-**6**	(3a*R*,4*S*)-**6**	(3a*S*,4*S*)-**6**:(3a*R*,4*S*)-**6**
cc-pVDZ	−50.9	−51.5	4.6	5.9	89:11
aug-cc-pVDZ	−51.9	−52.3	2.7	3.9	88:12
cc-pVTZ	−50.5	−51.0	4.0	5.4	91:9

[a] The predicted diastereoisomeric ratio has been computed assuming that the reaction occurs under purely kinetic control and with an exponential activation law.

in *molecular energy*, when different basis sets are used, amounts to ~400 kcal mol^{-1} (data not shown), the variation in *activation energy* to 2 kcal mol^{-1}, and the variation in the *activation energy difference* between the two transition states amounts to just 0.2 kcal mol^{-1}. This shows that the computed stereochemical outcome is very robust with respect to the choice of the basis set. Second, the augmentation of the cc-pVDZ set with diffuse functions, leading to the aug-cc-PVDZ set, improves the description of the long, incipient C–C and C–N bonds (as shown by the lower activation energy) but not the computed stereochemistry. The latter is improved when the double-ζ cc-pVDZ set is replaced by the triple-ζ cc-pVTZ set.

Finally, as further proof of the above assignment of the absolute configuration, the average distance between the methyl hydrogens and the hydrogen in the 3a-position of the furo[3,4-*c*]pyrazole skeleton is 3.06 Å for minor (3a*R*,4*S*)-**6** and 3.98 Å for major (3a*S*,4*S*)-**6**, which translate into average NOE distances (i.e., average of the inverse sixth power of the distance) of 2.3×10^{-3} Å^{-6} for minor (3a*R*,4*S*)-**6** and 0.3×10^{-3} Å^{-6} for major (3a*S*,4*S*)-**6**. These values substantiate the observed mutual NOE enhancement.

3. Conclusions

The dipolarophilic behaviour of the intramolecular cycloaddition between the ethylenic double bond bearing a stereocentre at the allylic position and the nitrilimine moiety occurred with good yield and stereoselectivity. This latter aspect of the intramolecular cycloaddition has found a full rationale on the basis of MP2 calculations. It is worth noting that the preferential formation of enantiopure furo[3,4-*c*] pyrazole (3a*S*,4*S*)-**6** can be predicted quantitatively when using the cc-pVTZ basis set.

4. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. NOE experiments were performed by setting the following parameters: relaxation delay (d1) 2 s, irradiation power (dl2) 74 dB, and total irradiation time (for each signal) 1.8 s. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line at 25 °C. (*S*)-(+)-But-3-en-2-ol **1** was prepared as described in the literature.[8]

4.1. Synthesis of (*S*)-but-3-en-2-yl acetoacetate 2

A solution of **1** (12.5 mmol) in xylene (5.0 mL) was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.78 g, 12.5 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 analytically pure **2** (1.81 g, 93% yield). Colourless oil; bp 71 °C (0.8 mmHg); $[\alpha]_D^{25} = +37.3$ (*c* 0.88, $CHCl_3$); IR (neat): 1740, 1720 cm^{-1}; ^{1}H NMR δ 1.31 (3H, d, *J* = 7.6, C*H*$_3$–CH<), 2.25 (3H, s, C*H*$_3$–), 3.42 (2H, s, –C*H*$_2$–), 4.89 (1H, dd, *J* = 7.6, 5.8, CH$_3$–CH<), 5.15–5.30 (2H, m, C*H*$_2$=), 5.75–5.90 (1H, m, –C*H*=). MS: *m*/*z* 156 (M$^+$). Anal. Calcd for $C_8H_{12}O_3$: C, 61.51; H, 7.75. Found: C, 61.43, H, 7.71.

4.2. Synthesis of (*S*)-but-3-en-2-yl 2-chloroacetoacetate 3

A solution of sulfuryl chloride (1.68 g, 12.5 mmol) in dry chloroform (15 mL) was added over 1 h to a solution of **2** (10 mmol) in dry chloroform (8 mL), on keeping the temperature in the range 0–5 °C. After 2 h at room temperature, chloroform (25 mL) was added and the organic solution was washed with 5% aqueous sodium hydrogencarbonate (20 mL). Then, the organic layer was washed with water (2 × 30 mL) and dried over sodium sulfate. The solvent was removed to give chloroacetoacetate **3** as an undistillable oil that was not analytically pure (2.19 g, 92% yield). Pale yellow oil; IR (neat): 1740, 1730 cm^{-1}; ^{1}H NMR δ 1.30 (3H, d, *J* = 7.1, C*H*$_3$–CH<), 2.25 (3H, s, C*H*$_3$–), 4.70 (1H, s, –C*H*Cl–), 5.11 (1H, dd, *J* = 7.1, 5.7, CH$_3$–C*H*<), 5.20–5.40 (2H, m, C*H*$_2$=), 5.75–5.90 (1H, m, –C*H*=). MS: *m*/*z* 190 (M$^+$).

4.3. Synthesis of hydrazonoyl chloride 4

A cold aqueous solution of benzenediazonium chloride (5.0 mmol) was slowly added to a solution of **3** (5.0 mmol) in 80% aqueous methanol (20 mL) under vigorous stirring and ice-cooling. During the addition, the pH was adjusted to 5 by adding sodium acetate. After 6 h at room temperature, the solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethylether (2 × 30 mL). The organic layer was washed with 5% sodium hydrogencarbonate (25 mL), then with water (50 mL), and dried over sodium sulfate. Evaporation of the solvent gave a solid and subsequent recrystallization from diisopropylether gave the hydrazonoyl chloride **4** in a pure state (0.71 g, 56% yield). Pale yellow powder; mp 90 °C; $[\alpha]_D^{25} = +59.7$ (*c* 0.52, $CHCl_3$); IR (Nujol): 3270, 1710 cm^{-1}; ^{1}H NMR δ 1.40 (3H, d, *J* = 7.0, C*H*$_3$–CH<), 4.92 (1H, dd, *J* = 7.0, 5.1, CH$_3$–C*H*<), 5.20–5.40 (2H, m, C*H*$_2$=), 5.75–5.90 (1H, m, –C*H*=), 7.05–7.20 (5H, m, –Ph), 8.30 (1H, br s, –N*H*–). MS: *m*/*z* 252 (M$^+$). Anal. Calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.02; H, 5.19; N, 11.09. Found: C, 56.97, H, 5.22; N, 11.12.

4.4. Intramolecular cycloaddition of hydrazonoyl chloride 4

A solution of the hydrazonoyl chloride **4** (3.0 mmol) in dry dioxane (150 mL) was treated with silver carbonate (1.66 g, 6.0 mmol), and stirred in the dark at room temperature for 96 h. The undissolved material was filtered off, the solvent evaporated and then the residue was chromatographed on a silica gel column with diethylether. Products and isolation yields are depicted in the Scheme 1. Both major (3a*S*,4*S*)-**6** and minor (3a*R*,4*S*)-**6** were

obtained as analytically pure samples by recrystallization from diisopropylether.

(3a*S*,4*S*)-**6**: 0.53 g, 82%. White powder, mp 154 °C; $[\alpha]_D^{25} = +66.1$ (*c* 0.77, $CHCl_3$); IR (Nujol): 1750 cm^{-1}; ^1H NMR δ 1.60 (3H, d, *J* = 6.5, C*H*$_3$–CH≺), 3.58–3.80 (2H, m, –C*H*$_2$–), 4.38–4.59 (2H, m, CH_3–C*H*≺ and –C*H*≺), 7.00–7.20 (5H, m, –Ph). After irradiation at 4.50 δ: 3.64 (1H, d, *J* = 11.4, –HC*H*–), 3.71 (1H, d, *J* = 11.4, –*H*CH–). After irradiation at 1.60 δ: 4.42 (1H, ddd, *J* = 10.0, 8.1, 6.5, –C*H*≺), 4.51 (1H, d, *J* = 8.1, CH_3–C*H*≺). ^{13}C NMR δ 23.8 (q, CH_3–), 40.2 (d, –C*H*≺), 47.4 (t, –CH_2N≺), 58.8 (d, ≻C*H*–O–), 112.0–119.0 (aromatics), 120.8 (s, aromatic ≻*C*–N), 141.2 (s, ≻*C*═N–), 170.8 (s, –*C*═O). MS: *m*/*z* 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.60; N, 12.96. Found: C, 66.70, H, 5.57; N, 13.01.

(3a*R*,4*S*)-**6**: 52 mg, 8%. White powder, mp 137 °C; $[\alpha]_D^{25} = -21.4$ (*c* 0.59, $CHCl_3$); IR (Nujol): 1750 cm^{-1}; ^1H NMR δ 1.55 (3H, d, *J* = 6.6, C*H*$_3$–CH≺), 3.60–3.90 (2H, m, –C*H*$_2$–), 4.40–4.60 (2H, m, CH_3–C*H*≺ and –C*H*≺), 7.00–7.20 (5H, m, –Ph). After irradiation at 4.50 δ: 3.68 (1H, d, *J* = 11.0, –HC*H*–), 3.76 (1H, d, *J* = 11.0, –*H*CH–). After irradiation at 1.55 δ: 4.47 (1H, ddd, *J* = 10.8, 8.0, 6.6, –C*H*≺), 4.56 (1H, d, *J* = 8.0, CH_3–C*H*≺). ^{13}C NMR δ 21.3 (q, CH_3–), 40.9 (d, –C*H*≺), 45.1 (t, –CH_2N≺), 58.8 (d, ≻C*H*–O–), 110–120 (aromatics), 122.3 (s, aromatic ≻*C*–N), 140.8 (s, ≻*C*═N–), 187.6 (s, –*C*═O). MS: *m*/*z* 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.60; N, 12.96. Found: C, 66.73, H, 5.66; N, 13.06.

4.5. Computational details

The structure of nitrilimine **5**, diastereomeric cycloadducts (3a*S*,4*S*)-**6** and (3a*R*,4*S*)-**6**, and the corresponding transition states **TS**[(3a*S*,4*S*)-**6**] and **TS**[(3a*R*,4*S*)-**6**] were fully optimized at the MP2//cc-pVDZ level in the frozen-core approximation. Harmonic analysis confirmed that reactant and product structures were minimum energy structures and that **TS**[(3a*S*,4*S*)-**6**] and **TS**[(3a*R*,4*S*)-**6**] structures were transition states with a single imaginary frequency. To check the reliability of the computed energy differences, calculations were also performed with an augmented double-ζ basis set (aug-cc-pVDZ) and with a triple-ζ basis set (cc-pVTZ). The latter calculation, involving 114 electrons (98 active) and 648 basis functions, is the largest calculation affordable with our present computing facilities. The stereochemical outcome was estimated by assuming that the reaction is first order in the reactant and that the reaction rates are given by an activation law, so that the diastereomeric excess is proportional to $\exp(-\delta\Delta E^{\ddagger}/kT)$, where $\delta\Delta E^{\ddagger}$ is the activation energy difference. All computations were carried out by the GAUSSIAN03 suite.[13]

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