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Stereoselective nitrilimine cycloadditions to the C=N bond of enantiopure *N*-(1-phenylethyl)-1-arylmethanimines

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Abstract—Diastereoselective 1,3-dipolar cycloadditions between *C*-methoxycarbonyl-*N*-arylnitrilimines **2** and the C=N bond of enantiopure *N*-(1-phenylethyl)-1-arylmethanimines **3** gave diastereoisomeric 5-aryl-4,5-dihydro-1,2,4-triazolines **4** and **5**. A computational description of the *E*→*Z* isomerisation of the C=N bond of unsubstituted **3a** is given.

1. Introduction

A number of functional groups contain a C=N bond, which is capable of 1,3-dipolar cycloaddition with nitrilimines giving rise to a huge variety of 1,2,4-triazoles.[1] The behaviour of the imine C=N bond as a heterodipolarophile towards nitrilimines was described first by Huisgen et al. in 1964,[2] but there is a lack of data concerning the stereochemical output of these cycloadditions involving enantiopure imines.

2. Results and discussion

To gain further insight, we investigated the reaction between *C*-methoxycarbonyl-*N*-arylnitrilimines **2** and enantiopure *N*-(1-phenylethyl)-1-arylmethanimines **3** (Fig. 1).[3] Generation of labile intermediates 2 was accomplished in situ by refluxing the corresponding hydrazonyl chlorides **1**[4] in dry toluene in the presence of a large excess of triethylamine (5 equiv) and equimolecular amounts of **3**.[5] Although some amount of tarry material was always formed, diastereoisomeric 5-aryl-4,5-dihydro-1,2,4-triazoles **4** and **5** were obtained regioselectively as depicted in the Scheme 1. Reaction times, product yields and diastereoisomeric ratio data are shown in Table 1. The separation of diastereoisomeric cycloadducts **4** and **5** was not feasible through standard chromatographic methods and was obtained by crystallisation from a fraction containing the mixture of **4** and **5**;[5] it should be noted that both cycloadducts were obtained as amorphous solids, which precluded any diffractometric analysis. Spectroscopic data of major product **4**[6] are in full agreement with those of similar 5-aryl-4,5-dihydro-1,2,4-triazoles.[7] In particular, the ^{1}H NMR spectrum showed a diagnostic signal due to the hydrogen at the 5-position of the 1,2,4-triazoline ring, which resonates as singlet at δ 5.97–6.17. As can be inferred from Table 1, the diastereoisomeric preference towards major product **4** is low to fair as encompasses the range between 56:44 and 76:24. Nevertheless, this result is worth noting in the light of the lack of stereoselectivity reported for dipolar cycloaddition between imines **3** and benzonitrile oxide.[3c] It is known that imines **3** have an *E*-configuration[8] as

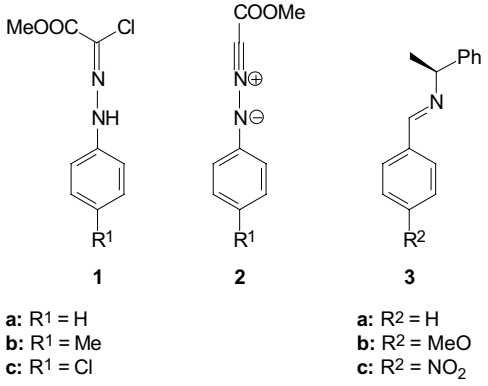

Figure 1.

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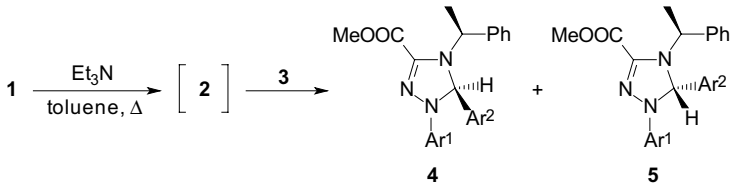
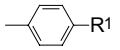
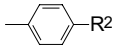


Ar1 =  R1

Ar2 =  R2

Entry	aa	ba	bb	bc	ca	cb	cc
R1	H	Me	Me	Me	Cl	Cl	Cl
R2	H	H	MeO	NO_2	H	MeO	NO_2

Scheme 1.

Table 1. Diastereoisomeric 1,2,4-triazoles **4** and **5**

Entry	R^1	R^2	Time[a] (h)	Product and yields[b] (%)		Product ratio[b] **4**:**5**
				4	**5**	
aa	H	H	25	24	16	60:40
ba	Me	H	20	39	27	59:41
bb	Me	MeO	36	19	15	56:44
bc	Me	NO_2	50	25	15	63:37
ca	Cl	H	18	46	24	66:34
cb	Cl	MeO	27	32	18	64:36
cc	Cl	NO_2	30	39	18	68:32

[a] In dry toluene at 100 °C.
[b] Deduced from ^{1}H NMR of reaction crudes.

depicted in Figure 1. Since the configurational stability of the C=N bond is crucial for determining the stereochemical output of cycloadditions, we undertook a computational study of imine **3a**.

The geometry of the *E* and *Z* isomers and of the C=N isomerisation transition state of imine **3a** (see Fig. 2) have been fully optimised and characterised by frequency analysis at the B3LYP/cc-pVDZ level by the GAUSSIAN 98 program suite.[9] The internal energy *U* (sum of the electronic, zero-point, vibrational, rotational and translational energy) and the Gibbs free energy *G* computed at 373 K are reported in Table 2. The activation energy for the *E*→*Z* isomerisation was found to be $\Delta G^{\ddagger} = 26.5$ kcal/mol, much larger than the thermal energy RT = 0.74 kcal/mol. It is clear from the former value that **3a** can hardly isomerise under the cycloaddition conditions.[10]

Having recognised the configurational stability of imines **3**,[11] the absolute configurations of the newly-formed stereocentres of diastereoisomeric triazolines **4** and **5** were assigned upon low temperature NOE enhancements[12] and conformational analysis calculations. Because a large number of constrained optimisations had to be carried out in order to evaluate the average distance between the protons subjected to the NOE measurement, we performed semiempirical AM1 calculations on a model of compounds **4aa** and **5aa** wherein the methoxycarbonyl group and the phenyl group linked to the triazole ring were replaced by hydrogens (Fig. 3). Such models will be referred to as **M4aa** and **M5aa**. For both compounds,

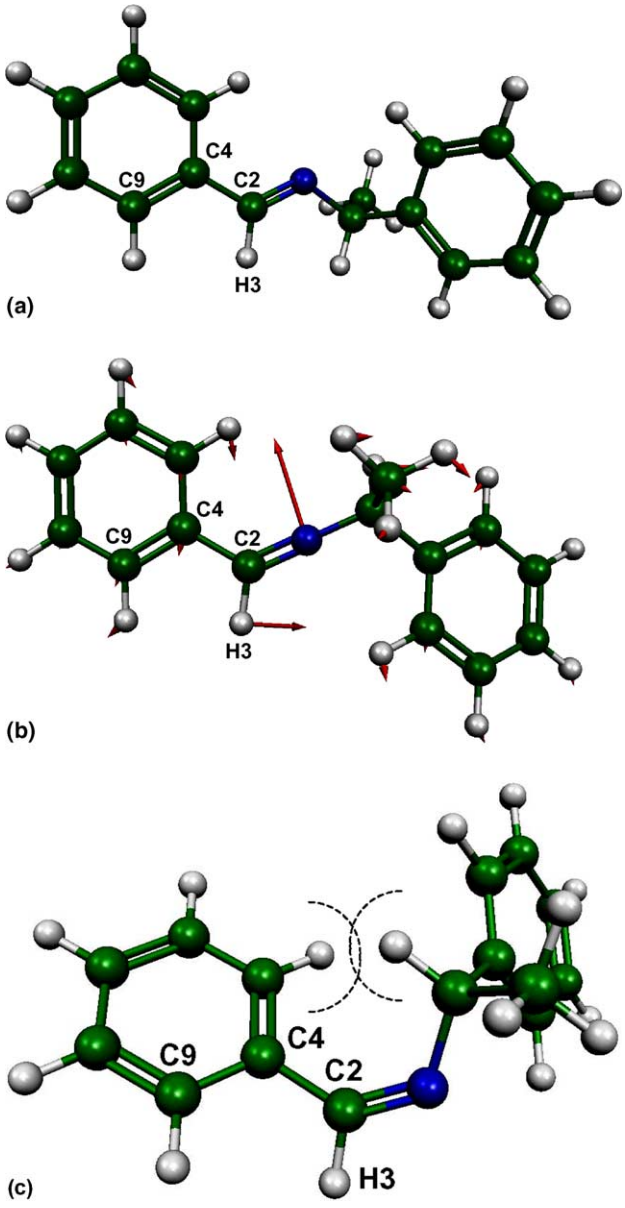


Figure 2. Geometry of the *E* and *Z* isomers and of the isomerisation transition state of imine **3a** fully optimised at the B3LYP/cc-pVDZ level. (a) *E* isomer; (b) transition state with arrows representing the normal mode with imaginary frequency; (c) *Z* isomer; the dotted arcs show the region of largest sterical overcrowding.

Table 2. Thermodynamic parameters for the $E \rightarrow Z$ isomerisation of imine **3a** computed at the B3LYP/cc-pVDZ level

	$E \rightarrow Z$		$E \rightarrow [\ddagger]$	$Z \rightarrow [\ddagger]$
ΔU_0[a]	7.5	$\Delta U^{\ddagger}$	26.3	18.7
ΔG_0	7.9	$\Delta G^{\ddagger}$	26.5	18.6
K[b]	23×10^{-6}			

All energies are given in kcal/mol.

[a] The internal energy U is the sum of the electronic, zero-point, vibrational, rotational and translational energy; the zero-point energy has been scaled by 0.98 as usual.

[b] The equilibrium constant $K = a(Z)/a(E) \cong [Z]/[E]$.

a series of AM1 geometry optimisations has been carried out while stepping the dihedral angle H4–C10–N1–C2 (ϕ) defining the conformation of the (*S*)-1-phenylethyl group with respect to the ring. The results are shown as potential energy curves in Figure 4. Both **M4aa** and **M5aa** showed three well defined energy minima separated by barriers several kcal/mol high. The curves are similar for $240° < \phi < 360°$ but largely differ for $0° < \phi < 240°$. In particular, diastereomeric molecules **M4aa** and **M5aa** have different minimum energy conformations with $\phi = 174°$ and 63°, respectively. This corresponds to different distances between the protons subjected to the NOE measurement, put in evidence by the double arrows in Figure 3, since for $\phi = 174°$ the two protons are on opposite sides with respect to the N1–C2 bond. The distances of interest have been averaged over all conformations weighted by Boltzmann factors; they were calculated to be 2.66 Å for **M5aa** and 3.30 Å for **M4aa**. Low temperature NOE enhancement between the mentioned protons was observed in the case of minor product **5aa** (5.9%), while it was lacking for major product **4aa**. To this point, an (*S*)-configuration can be assigned to the stereocentre at the 5-position of the 1,2,4-triazoline ring of minor product **5**.

3. Conclusion

In conclusion, this first example of stereoselective nitrilimine cycloaddition to the imine C=N heterodipolarophile proceeds with full regioselectivity, while the (*S*)-1-phenylethyl chiral auxiliary promotes a moderate degree of asymmetric induction.

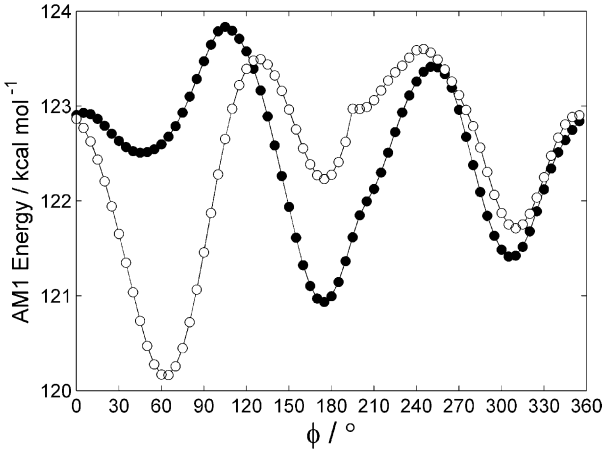


Figure 4. AM1 energy as a function of the dihedral angle ϕ between atoms C10–H4–N1–C2. Solid circles = **M5aa**; empty circles = **M4aa**.

Acknowledgements

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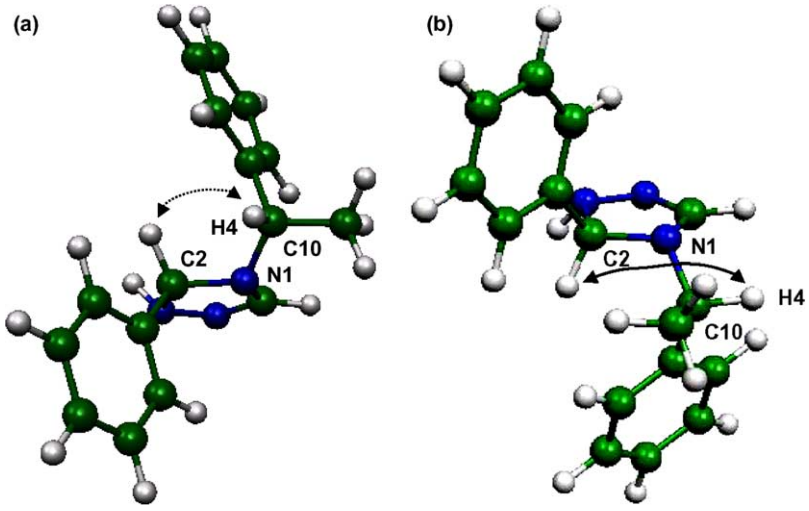

Figure 3. Geometry of the triazole model compounds **M5aa** and **M4aa** fully optimised at the AM1 level. (a) **M5aa**; (b) **M4aa**. The dotted double arrows show the protons involved in the NOE experiments. For the sake of clarity, multiple bonds are not explicitly shown.

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4. (a) Compound **1a**: Fusco, R.; Romani, R. *Gazz. Chim. Ital.* **1946**, *76*, 419; (b) Compound **1b**: El-Abadelah, M. M.; Hussein, A. Q.; Kamal, M. R.; Al-Adhami, K. H. *Heterocycles* **1988**, *27*, 917; (c) Compound **3c**: Cocco, M. T.; Maccioni, A.; Plumitallo, A. *Il Farmaco, Ed. Sci.* **1985**, *40*, 272.
5. For a typical run: a solution of **1** (1.5 mmol) and **3** (2.0 mmol) in dry toluene (5 mL) was treated with triethylamine (0.76 g, 7.5 mmol) and refluxed for the time indicated in Table 1. The undissolved material was filtered off and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column with diethyl ether to afford a fraction containing the mixture **4** and **5**. The solid mixture was taken up with chloroform (5 mL) and the solution slowly concentrated to afford the major cycloadduct **4** as an amorphous powder.
6. Selected spectral data for 5-aryl-4,5-dihydro-1,2,4-triazoles **4**. Compound **4aa**: IR (Nujol) 1725 cm^{-1}; $[\alpha]_D^{25} = +28.5$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.26 (3H, d, *J* 6.9), 3.90 (3H, s), 5.78 (1H, q, *J* 6.9), 6.00 (1H, s), 6.9–7.2 (15H, m). Compound **4ba**: IR (Nujol) 1730 cm^{-1}; $[\alpha]_D^{25} = +12.8$ (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24 (3H, d, *J* 6.9), 2.27 (3H, s), 3.84 (3H, s), 5.76 (1H, q, *J* 6.9), 5.97 (1H, s), 6.9–7.2 (14H, m). Compound **4bb**: IR (Nujol) 1735 cm^{-1}; $[\alpha]_D^{25} = +11.2$ (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.20 (3H, d, *J* 7.0), 2.28 (3H, s), 3.76 (3H, s), 3.90 (3H, s), 5.78 (1H, q, *J* 7.0), 6.08 (1H, s), 6.7–7.3 (13H, m). Compound **4bc**: IR (Nujol) 1725 cm^{-1}; $[\alpha]_D^{25} = +34.1$ (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24 (3H, d, *J* 6.9), 2.22 (3H, s), 3.96 (3H, s), 5.80 (1H, q, *J* 6.9), 6.11 (1H, s), 6.9–8.2 (13H, m). Compound **4ca**: IR (Nujol) 1725 cm^{-1}; $[\alpha]_D^{25} = +8.8$ (*c* 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.22 (3H, d, *J* 7.0), 3.94 (3H, s), 5.81 (1H, q, *J* 7.0), 6.02 (1H, s), 6.8–7.7 (14H, m). Compound **4cb**: IR (Nujol) 1735 cm^{-1}; $[\alpha]_D^{25} = +49.3$ (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24 (3H, d, *J* 6.9), 3.82 (3H, s), 3.91 (3H, s), 5.80 (1H, q, *J* 6.9), 5.97 (1H, s), 6.7–7.2 (13H, m). Compound **4cc**: IR (Nujol) 1725 cm^{-1}; $[\alpha]_D^{25} = +13.9$ (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.23 (3H, d, *J* 7.0), 3.97 (3H, s), 5.83 (1H, q, *J* 7.0), 6.17 (1H, s), 6.7–8.4 (13H, m).
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10. The *E* isomer was about 8 kcal/mol more stable than the *Z* one. Therefore, even if an $E \rightarrow Z$ equilibrium is established, the concentration of the *Z* isomer is several orders of magnitude less than that of the *E* isomer. The stabilisation of the *E* isomer over the *Z* one is mostly due to the lack of coplanarity between the Ar^2 and C=N π systems induced by sterical overcrowding (see Fig. 2). The coplanarity is measured by the dihedral angle defined by atoms C9–C4–C2–H3, which is less than 1° in the *E* isomer (and in the transition state) and is 36° in the *Z* isomer.
11. High-temperature ^1H NMR of **3a** was recorded in DMSO-d_6 at 420 K and showed no differences with the spectrum taken at 298 K.
12. Low-temperature NOESY spectra of **4aa** and **5aa** were performed in $CDCl_3$ at 248 K.