Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1077–1079

The first case of diastereoselective cycloadditions of enantiopure nitrilimines in aqueous media

Giorgio Molteni*

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Via Golgi 19, 20133 Milano, Italy

Received 28 January 2004; accepted 5 February 2004

Abstract—The diastereoselective cycloadditions of enantiopure nitrilimines **4** with ethyl acrylate were exploited in dry toluene and in aqueous sodium hydrogencarbonate as reaction media. Shorter reaction times and improved diastereoisomeric ratios of the resulting 5-ethoxycarbonyl-4,5-dihydropyrazoles **5** and **6** were observed in aqueous media.

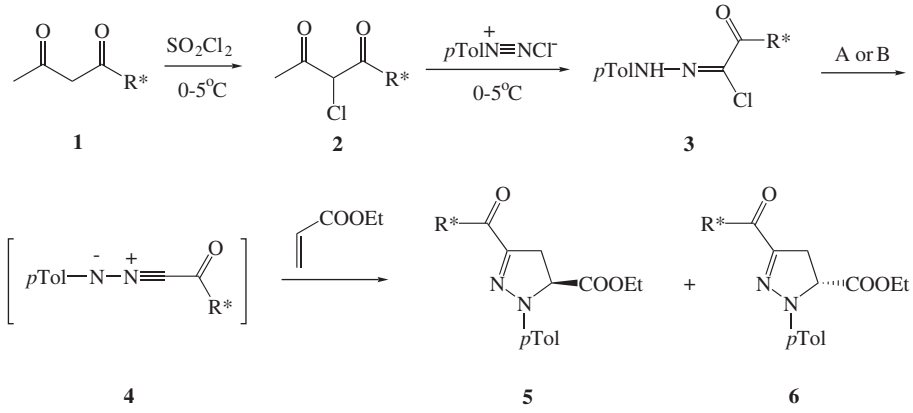
Nitrilimine cycloadditions to ethylenic dipolarophiles represent the choice method in the synthesis of variously substituted 4,5-dihydropyrazoles.[1] Due to the utility of these compounds in enantiopure forms,[2] diastereoselective nitrilimine cycloadditions have been developed in which the stereogenic centre(s) is placed on the dipolarophilic[3] or the 1,3-dipolar[4] reactants. In the latter case, however, the reported stereoselectivities are invariably low. To gain better insights about this methodology, it was felt advisable to investigate the behaviour of enantiopure nitrilimines **4** towards ethyl acrylate as a function of the reaction media. First, the enantiopure hydrazonoyl chlorides **3**[5] were synthesised through the reaction sequence outlined in the Scheme 1.[6] Second, base treatment of **3** in the presence of ethyl acrylate produced the diastereoisomeric cycloadducts **5** and **6**. Two different reaction conditions and media were exploited: (i) refluxing in dry toluene in the presence of a large excess (5 equiv) of triethylamine (homogeneous conditions, method A);[7] and (ii) aqueous 0.1 M sodium hydrogencarbonate at room temperature in the presence of tetrahexylammonium chloride (THAC) as a catalyst (heterogeneous conditions, method B).[8] Reaction times, product yields and diastereoisomeric ratio data are shown in Table 1. All reactions were completely regioselective giving only the 5-ethoxycarbonyl-4,5-dihydropyrazoles **5** and **6**, as expected from the electronic demands of nitrilimine cycloadditions onto electron-poor monosubstituted ethylenes.[9] Despite the separation of diastereoisomeric cycloadducts **5** and **6** not being feasible through standard chromatographic methods, enantiopure **5** was obtained by crystallisation from the reaction mixtures. Spectroscopic data of major **5**[10] are in full agreement with those of similar 5-substituted-4,5-dihydropyrazoles.[11]

As can be inferred from Table 1, shorter reaction times and improved diastereoisomeric ratios were experienced in aqueous media in comparison to the classic[12] triethylamine–toluene cycloaddition protocol. The observed rate accelerations, which are abnormal for a typically concerted cycloaddition, can be accounted for by means of the high local concentration of the reactants promoted by hydrophobic effects.[13] Close association of organic reactants may also be responsible for the enhanced diastereoselectivity. To this point, chemical correlation experiments allowed us to assign the (5*S*)-absolute configuration to all the major cycloadducts **5** (Scheme 2). Basic hydrolysis of **5a–c** gave the known 3,5-dicarboxy-4,5-dihydropyrazole(*S*)-(+)-**7**, $[\alpha]_D^{25} = +5.8$ (*c* 0.40, DMSO) {lit.[3c] $[\alpha]_D^{25} = +5.5$ (*c* 0.40, DMSO)} while acidic hydrolysis of **5d** gave the 3-carboxy-5-ethoxycarbonyl-4,5-dihydropyrazole intermediate **8**. The subsequent basic hydrolysis of the latter also gave (*S*)-(+)-**7**.

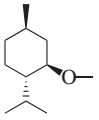
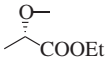
In conclusion, this first case of a diastereoselective nitrilimine cycloaddition in an aqueous media, displays some valuable features with respect to the usual homogeneous conditions: (i) rate acceleration and better diastereoselectivity were experienced; (ii) reaction work-up was greatly simplified by simple filtration of the crude mixture; and (iii) an environmentally friendly 1,3-dipolar cycloadditive protocol can be successfully elaborated upon.

* Tel.: +39-02-50314141; fax: +39-02-50314115; e-mail: giorgio.molteni@unimi.it

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.02.006



A; Et_3N, toluene,Δ; B: aq. $NaHCO_3$, THAC, rt

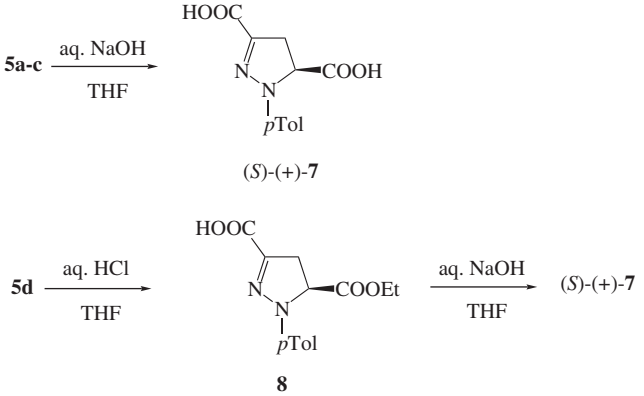
	a	b	c	d
R*				

Scheme 1.

Table 1. Cycloadditions between enantiopure nitrilimines **4** and ethyl acrylate

Nitrilimine	Method	Time (h)	**5** and **6**[a]	**5**:**6**[b]
4a	A	9	80	60:40
4a	B	2.5	73	68:32
4b	A	8	81	65:35
4b	B	3	74	68:32
4c	A	14	43[c]	57:43
4c	B	2	70	60:40
4d	A	8	40[c]	65:35
4d	B	1.5	75	72:28

[a] Isolated yields.
[b] Determined from ^1H NMR analysis of reaction crudes.
[c] Some amount of tarry material was formed.



Scheme 2.

Acknowledgements

Thanks are due to MURST and CNR for financial support.

References and notes

1. Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 3.
2. Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, 4265.
3. (a) Garanti, L.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1285; (b) Barluenga, J.; Fernàndez-Marì, F.; Aguilar, E.; Viado, A. L.; Olano, B. *Tetrahedron Lett.* **1998**, *39*, 4887; (c) Barluenga, J.; Fernàndez-Marì, F.; Gonzàles, R.; Aguilar, E.; Revelli, G. A.; Viado, A. L.; Fañanas, F. J.; Olano, B. *Eur. J. Org. Chem.* **2000**, 1773.
4. (a) Agocs, A.; Benyei, A.; Somogyi, L.; Herczegh, P. *Tetrahedron: Asymmetry* **1998**, *9*, 3359; (b) Grubert, L.; Galley, G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1137; (c) Tronchet, J. J. M.; Tronchet, J. F.; Barbalat-Rey, F. *Heterocycles* **1993**, *36*, 833.
5. Hydrazonoyl chlorides, **3a** and **3b**, were synthesised according to Ref. 4a.
6. Selected spectral data for hydrazonoyl chlorides **3c** and **d**. **3c**: IR (neat) 3270, 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, *J* 6.8), 1.58 (3H, d, *J* 6.4), 2.33 (3H, s), 4.25 (2H, q, *J* 6.8), 5.26 (1H, q, *J* 6.4), 7.1–7.3 (4H, m), 8.34 (1H, br s). **3d**: IR (Nujol) 3260, 3180, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (3H, d, *J* 6.5), 2.38 (3H, s), 5.18 (1H, q, *J* 6.5), 6.90 (1H, br s, *J* 7.2), 7.0–7.4 (9H, m), 8.18 (1H, br s).

7. For a typical run: a solution of **3** (2.0 mmol) and ethyl acrylate (0.60 g, 6.0 mmol) in dry toluene (10 mL) was treated with triethylamine (1.01 g, 10.0 mmol) and refluxed for the time indicated in the Table 1. The undissolved material was filtered off and the solvent evaporated under reduced pressure. The residue was taken up with chloroform (20 mL) and the solution slowly concentrated affording as the major product **5** as an amorphous powder, while the remaining solution contained diastereoisomeric **6**.
8. For a typical run: a mixture of **3** (5.0 mmol), ethyl acrylate (1.50 g, 15.0 mmol), THAC (0.19 g, 0.5 mmol) and aqueous 5% sodium hydrogencarbonate (20 mL), was stirred at room temperature for the time indicated in Table 1. Filtration gave a residue, which was taken up with chloroform (20 mL) and the solution slowly concentrated affording pure **5** as an amorphous powder, while the remaining solution contained diastereoisomeric **6**.
9. (a) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287; (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301; (c) Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 6397.
10. Selected spectral data for 5-ethoxycarbonyl-4,5-dihydropyrazoles **5a**–**d**. **5a**: IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (3H, d, *J* 7.2), 0.93 (6H, d, *J* 7.0), 1.22 (3H, t, *J* 6.8), 1.5–2.1 (9H, m), 2.32 (3H, s), 3.28 (1H, dd, *J* 17.7, 7.6), 3.52 (1H, dd, *J* 17.7, 11.9), 4.20 (2H, q, *J* 6.8), 4.80–4.94 (2H, m), 7.0–7.3 (4H, m). **5b**: IR (Nujol) 1735, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, *J* 6.8), 0.98 (3H, d, *J* 7.1), 1.18 (3H, t, *J* 7.4), 1.30–1.85 (5H, m), 2.30 (3H, s), 3.30 (1H, dd, *J* 17.9, 7.6), 3.51 (1H, dd, *J* 17.9, 12.0), 4.18 (2H, q, *J* 6.8), 4.87 (1H, dd, *J* 12.0, 7.6), 6.9–7.2 (4H, m). **5c**: IR (Nujol) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, t, *J* 6.8), 1.38 (3H, t, *J* 6.7), 1.56 (3H, d, *J* 6.8), 2.28 (3H, s), 3.31 (1H, dd, *J* 17.8, 7.3), 3.57 (1H, dd, *J* 17.8, 12.2), 4.22 (2H, q, *J* 6.7), 4.28 (2H, q, *J* 6.8), 4.93 (1H, dd, *J* 12.2, 7.3), 5.21 (1H, q, *J* 6.8), 6.9–7.2 (4H, m). **5d**: IR (Nujol) 3180, 1740, 1730, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3H, t, *J* 6.9), 1.62 (3H, d, *J* 7.4), 2.28 (3H, s), 3.40 (1H, dd, *J* 18.1, 8.4), 3.51 (1H, dd, *J* 18.1, 12.1), 4.23 (2H, q, *J* 6.9), 4.84 (1H, dd, *J* 12.1, 8.4), 5.22 (1H, q, *J* 7.4), 6.88 (1H, br d, *J* 7.0), 7.0–7.4 (9H, m).
11. Shimizu, T.; Hayashi, Y.; Nishio, T.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 787.
12. Huisgen, R.; Seidel, M.; Wallbillich, G.; Knupfer, H. *Tetrahedron* **1962**, *17*, 3.
13. (a) Molteni, G.; Ponti, A.; Orlandi, M. *New J. Chem.* **2002**, *26*, 1340; (b) Molteni, G.; Ponti, A. *New J. Chem.* **2002**, *26*, 1346.