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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 842–845

Stereoselective intramolecular cycloadditions of homochiral nitrilimines as a source of enantiopure 2,3,3a,4,5,6-hexahydro-pyrrolo[3,4-*c*]pyrazoles

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Received 26 January 2006; accepted 16 February 2006

Abstract—Starting from the methyl esters of glycine, L-alanine, L-phenylalanine and (*S*)-2-phenylglycine, we developed a synthetic route to the title compounds in the enantiopure form by means of a stereoselective intramolecular 1,3-dipolar cycloaddition of homochiral nitrilimines **5a–d**. Fair to good overall product yields and high cycloaddition diastereoselectivity were obtained.

1. Introduction

Intramolecular 1,3-dipolar cycloadditions often constitute the key step of synthetic routes leading to complex cyclic as well as open-chain molecules.[1] The stereoselective version of these reactions allow the synthesis of enantiopure products, thus representing one of the most promising fields of contemporary organic chemistry.[2] Within this picture, stereoselective nitrone and nitrile oxide intramolecular cycloadditions play a major role in the construction of a number of enantiopure five-membered heterocycles.[3] Despite the utility of enantiopure 4,5-dihydropyrazole derivatives in organic synthesis,[4] the field of nitrilimine stereoselective cycloadditions occupy a less prominent position. In fact, this approach to fused bi- or tricyclic 4,5-dihydropyrazoles has received little attention, although it has been reviewed quite recently.[5]

The construction of pyrrolo[3,4-*c*]pyrazole skeleton is one of the first successes of the intramolecular nitrilimine cycloaddition methodology.[6] In a previous paper from our laboratory,[7] we first described the synthesis of the above skeleton in the enantiopure form by means of stereoselective cycloaddition of a homochiral nitrilimine bearing a pendant L-alanine benzylester as the chiral auxiliary. However, since the control of the absolute stereochemistry was modest, we reasoned that the large distance between the starting stereocentre and the new one was responsible for the disappointing outcome, which was observed. To circumvent this drawback, we planned the synthesis of novel nitrilimines **5b–d** in which the stereocentre is placed inside the tether joining the reactive groups. We herein report the behaviour of labile intermediates **5b–d** leading to enantiopure 2,3,3a,4,5,6-hexahydro-6-substituted-pyrrolo[3,4-*c*]-pyrazole derivatives **6** and **7**. Furthermore, with the synthesis of enantiopure molecules from simple starting materials being a valuable target,[8] we herein report the inexpensive, commercially available L-alanine, L-phenylalanine and (*S*)-2-phenylglycine methyl esters as suitable starting chiral units.

2. Results and discussion

N,*N*-bis-Allylamino acetates **1a–d**[9,10] were first submitted to basic hydrolysis followed by treatment with thionyl chloride. The corresponding *N*,*N*-bis-allylaminoacetyl chlorides **2a–d** were obtained as crude materials, which were used without isolation. Treatment of the latter with phenylhydrazine afforded acyl hydrazines **3a–d**, which were recovered as analytically pure compounds after chromatographic purification and subsequent crystallisation. Hydrazonoyl chlorides **4a–d** were obtained as crude oils by treating the appropriate acyl hydrazine precursor with triphenylphosphine and carbon tetrachloride, according to the original method by Wolkoff (Scheme 1).[11] The generation of nitrilimines **5a–d** was accomplished, in situ, by refluxing a

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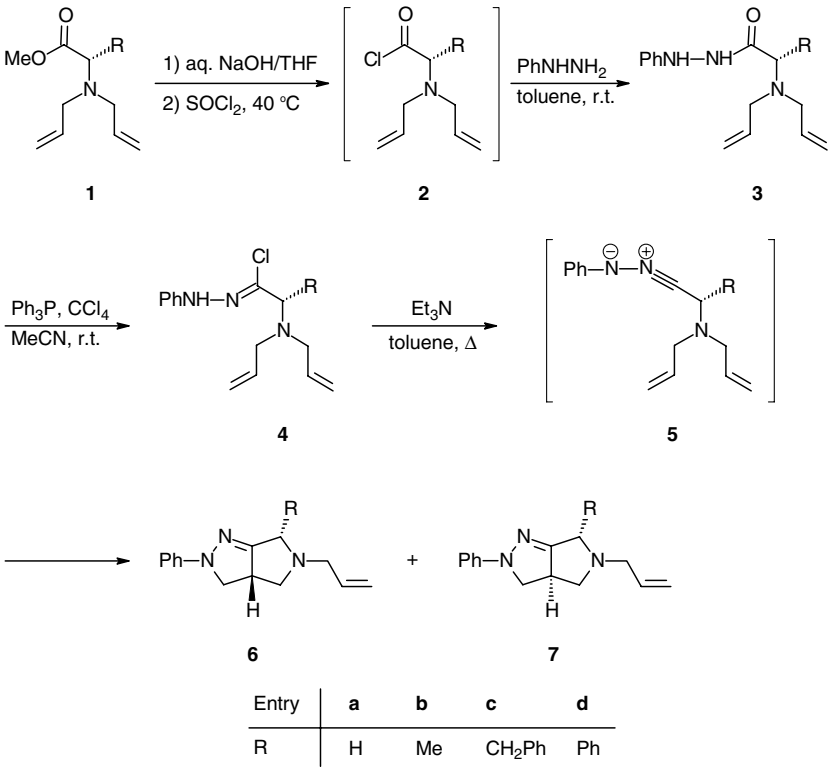
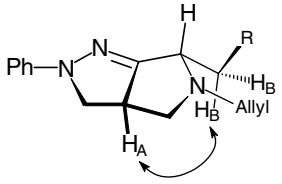
doi:10.1016/j.tetasy.2006.02.018



Scheme 1.

solution of the corresponding crude hydrazonoyl chlorides in the presence of a large excess of triethylamine (5 equiv) in dry toluene. Cycloaddition products, reaction times, product yields and diastereoisomeric ratios are shown in Table 1. It can be seen that unsubstituted **5a** gave a racemic mixture of cycloadducts **6a** and **7a** with 89% overall yield (Table 1, entry a). Spectral data of the latter cycloadducts agrees perfectly with that reported for similar pyrrolo[3,4-*c*]-pyrazoles.[7] The diastereoisomeric cycloadducts **6b–d** and **7b** were obtained as analytically and enantiomerically pure solids through silica gel column chromatography followed by crystallisation, while in the case of minor **7c**, a very small amount of isolated product precluded its full characterisation. As can be inferred from Table 1, cycloaddition yields ranged from fair to good, since some tarry material was always formed. The absolute configurations of the newly formed stereocentre of minor **7b**,**c** were determined, unambiguously, by the mutual NOE enhancements reported in Figure 1. It is apparent that the observed NOE effects can arise only for the stereochemical arrangement depicted. In order to further substantiate these NOE effects, the distances between H_A and the average position of H_B were calculated within the AM 1[12] semi-empirical method. Values of 2.86 Å for **7b** and 2.78 Å for **7c**[13] were found, which match the observed mutual NOE enhancements. As far as diastereoselection is concerned, we were pleased to find that the ratio **6**/**7** encompasses the range between 85:15 and 100:0, depending upon the size and shape of R. This high cycloaddition stereoselectivity can be rationalised on the basis of the proposed transition states **A** and **B** (Fig. 2). Due to the inner disposition of R, transition state **B** should be the more energetic one giving minor compounds **7b**,**c**; the intervention of such a transition state is made impervious in the case of the bulky phenyl pendant (Table 1, entry d). Hence, the preferred formation of major compounds **6b–d** finds rationalisation.



7b: R = H, 6.6%; **7c**: R = Ph, 7.2%

Figure 1. NOE enhancement for cycloadducts **7b** and **c**.

Table 1. Intramolecular cycloadditions of nitrilimines **5**[a]

Entry	R	Time (h)	**6** + **7** (%)[b]	**6**:**7**[c]
a	H	3	89	—
b	Me	4	50	85:15
c	CH_2Ph	3	59	>95:5
d	Ph	6	35	100:0

[a] In refluxing toluene.
[b] Overall yields from acyl hydrazines **3**.
[c] Determined from ^1H NMR analysis of reaction crudes.

3. Conclusions

The ready availability of α-amino acid methyl esters as valuable starting chiral building blocks allow the highly stereoselective synthesis of a variety of enantiopure

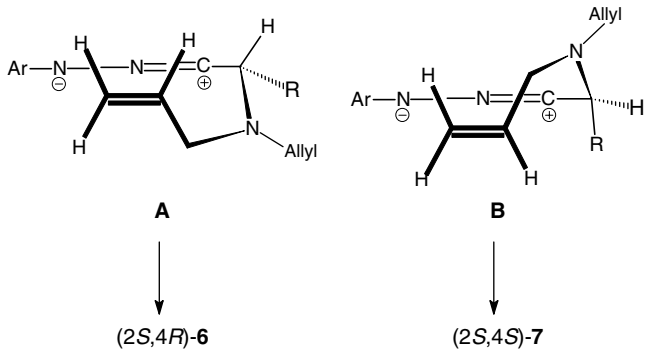


Figure 2. Proposed transition states for the formation of cycloadducts **6b–d** and **7b,c**.

6-substituted-pyrrolo[3,4-*c*]pyrazoles via intramolecular nitrilimine cycloaddition. The resulting cycloadducts still possess an ethylenic double bond readily susceptible to further functionalisations, thus enhancing their potential as synthetic intermediates.

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) 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.

Compounds **1a**[10] and **1b,c**[9] were prepared according to the literature procedures.

4.1. Synthesis of *N,N*-bis-allyl-(*S*)-(−)-2-phenylglycine methyl ester 1d

A solution of (*S*)-(−)-2-phenylglycine methyl ester (2.01 g, 10.0 mmol), allyl bromide (3.03 g, 25.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in anhydrous toluene (25 mL) was warmed to 75 °C for 5 h. The mixture was then cooled and filtered over Celite. The organic layer was dried over sodium sulfate, the solvent evaporated and the residue distilled in vacuo to give **1d** (2.25 g, 92%); as a pale yellow oil; bp 146 °C (5 mmHg); $[\alpha]_D^{25} = -23.7$ (*c* 0.26, CH_2Cl_2); IR (neat) 1735 cm^{-1}; ^{1}H NMR δ: 3.20 (3H, d, *J* 10.7), 3.78 (3H, s), 4.67 (1H, s), 5.10–5.25 (4H, m), 5.80–5.94 (2H, m), 7.2–7.4 (5H, m). MS *m*/*z*: 245 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.50; H, 7.84; N, 5.76.

4.2. Synthesis of acyl hydrazines 3

A solution of the appropriate *N,N*-bis-allylaminoacetate **1** (6.5 mmol) in tetrahydrofuran (65 mL) was treated with 1 M aqueous sodium hydroxide (65 mL) and stirred at room temperature for 4 h. Aqueous 6 M hydrochloric acid was added to pH 1 and the mixture extracted twice with ethyl acetate (2 × 100 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. Thionyl chloride (0.77 g, 6.5 mmol) was added dropwise to the oily residue under vigorous stirring, and the mixture warmed to 40 °C for 2 h. The excess of thionyl chloride was removed by in vacuo distillation to give crude 2-allyloxyacetyl chlorides **2** as dark brown oils. Freshly distilled triethylamine (1.31 g, 13.0 mmol) and phenylhydrazine (0.70 g, 6.5 mmol) were added dropwise to a solution of **2** in dry toluene (20 mL) at room temperature and the mixture was stirred at room temperature for 4 h. Water (50 mL) was added to reaction mixture, the organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue was chromatographed on a silica gel column with ethyl acetate–hexane 4:1 giving acyl hydrazines **3**.

Compound **3a**: 0.64 g, 40%. Pale yellow powder; mp 63 °C (from diisopropyl ether); IR (nujol) 3300, 3240, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.28 (4H, d, *J* 12.8), 3.31 (2H, s), 5.28–5.31 (4H, m), 5.89–6.01 (2H, m), 6.08 (1H, br s), 6.9–7.3 (5H, m), 8.82 (1H, br s); MS *m*/*z* 245 (M^+). Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.51; H, 7.78; N, 17.19.

Compound **3b**: 0.57 g, 34%. Pale yellow powder; mp 57 °C (from diisopropyl ether); $[\alpha]_D^{25} = -16.4$ (*c* 0.24, CH_2Cl_2); IR (nujol) 3310, 3250, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52 (3H, d, *J* 7.3), 3.03 (2H, dd, *J* 13.4, 7.1), 3.13 (2H, dd, *J* 13.4, 5.0), 3.70 (1H, q, *J* 7.3), 5.08–5.12 (4H, m), 5.80–5.90 (2H, m), 6.03 (1H, br d, *J* 9.0), 6.9–7.1 (5H, m), 8.90 (1H, br s); MS *m*/*z* 259 (M^+). Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.51; H, 8.19; N, 16.26.

Compound **3c**: 0.61 g, 28%. Yellow powder; mp 59 °C (from diisopropyl ether); $[\alpha]_D^{25} = -9.4$ (*c* 0.15, CH_2Cl_2); IR (nujol) 3310, 3260, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.96 (2H, dd, *J* 13.4, 4.8), 3.16 (2H, dd, *J* 13.4, 7.2), 3.44 (1H, dd, *J* 15.6, 2.7), 3.48 (1H, dd, *J* 15.6, 9.8), 3.80 (1H, dd, *J* 9.8, 2.7), 5.25–5.28 (4H, m), 5.82–5.94 (2H, m), 6.08 (1H, br d, *J* 8.4), 6.9–7.2 (10H, m), 8.84 (1H, br s); MS *m*/*z* 335 (M^+). Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.23; H, 7.47; N, 12.58.

Compound **3d**: 0.65 g, 31%. Pale yellow powder; mp 67 °C (from diisopropyl ether); $[\alpha]_D^{25} = -12.2$ (*c* 0.21, CH_2Cl_2); IR (nujol) 3300, 3240, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.02 (2H, dd, *J* 13.6, 7.3), 3.44 (2H, dd, *J* 13.6, 5.9), 4.64 (1H, s), 5.18–5.21 (4H, m), 5.80–5.93 (2H, m), 6.08 (1H, br s), 6.9–7.3 (10H, m), 8.89 (1H, br s); MS *m*/*z* 321 (M^+). Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.73; H, 7.21; N, 13.07. Found: C, 74.70; H, 7.18; N, 13.14.

4.3. Intramolecular cycloaddition of nitrilimines 5

A solution of the appropriate acyl hydrazine **3** (4.0 mmol) in dry acetonitrile (40 mL) and carbon tetrachloride

(3.08 g, 20.0 mmol) was treated with triphenylphosphine (4.72 g, 60 mmol) and stirred at room temperature for 12 h. Brine (20 mL) was then added to reaction mixture. The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure. The dark red residue contained crude hydrazonoyl chlorides **4** whose IR spectra exhibited the typical N–H stretch band at 3230–3250 cm^{-1}. A solution of crude hydrazonoyl chloride **4** (4.0 mmol) in dry toluene (200 mL) was treated with triethylamine (2.02 g, 20.0 mmol) and refluxed for the time indicated in Table 1. The crude was evaporated under reduced pressure, and then the residue was chromatographed on a silica gel column with ethyl acetate–hexane 2:1. The first fractions contained major cycloadduct **6**, further elution gave minor cycloadduct **7**.

Racemic cycloadducts **6a** and **7a**: 0.81 g, 89%. White powder; mp 74 °C (from diisopropyl ether–methanol); IR (nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (1H, dd, J 10.2, 8.6), 3.17 (2H, dd, J 12.3, 8.8), 3.20–3.90 (5H, m), 4.16 (1H, dd, J 9.1, 8.6), 5.10–5.25 (2H, m), 5.85–6.00 (1H, m), 6.9–7.2 (5H, m); ^{13}C NMR ($CDCl_3$) δ 38.3 (d), 44.1 (t), 46.7 (t), 47.1 (t), 48.5 (t), 113.6 (t), 119.1 (d), 129.2 (d), 129.8 (d), 131.4 (s), 133.7 (d), 145.3 (s); δ MS m/z 227 (M^+). Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.48. Found: C, 74.02; H, 7.51; N, 18.56.

Major cycloadduct **6b**: 0.40 g, 42%. Pale yellow powder; mp 68 °C (from diisopropyl ether); $[\alpha]_D^{25} = -106.0$ (c 0.43, $CHCl_3$); IR (nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3H, d, J 6.5), 2.24 (1H, dd, J 10.0, 8.6), 3.18 (2H, dd, J 12.2, 8.9), 3.37 (1H, q, J 6.5), 3.40–3.72 (3H, m), 4.13 (1H, dd, J 9.1, 8.6), 5.20–5.30 (2H, m), 5.85–5.96 (1H, m), 6.9–7.2 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.7 (q), 38.8 (d), 46.3 (t), 47.4 (t), 47.8 (t), 50.3 (t), 111.6 (t), 119.0 (d), 125.4 (d), 128.8 (d), 133.0 (d), 134.9 (s), 143.1 (s); MS m/z 241 (M^+). Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.70; H, 7.97; N, 17.49.

Major cycloadduct **6c**: 0.72 g, 57%. Pale yellow powder; mp 57 °C (from diisopropyl ether); $[\alpha]_D^{25} = -83.2$ (c 0.51, $CHCl_3$); IR (nujol) 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (1H, dd, J 16.8, 7.0), 2.26 (1H, dd, J 16.8, 5.6), 2.34 (1H, dd, J 10.5, 8.6), 3.21 (2H, dd, J 12.2, 8.6), 3.41 (1H, dd J 7.0, 5.6), 3.50–3.80 (3H, m), 4.13 (1H, dd, J 9.2, 8.6), 5.12–5.28 (2H, m), 5.83–5.96 (1H, m), 6.9–7.4 (10H, m); ^{13}C NMR ($CDCl_3$) δ 19.7 (q), 37.4 (d), 44.3 (t), 46.4 (t), 47.1 (t), 48.9 (t), 112.2 (t), 119.0–127.0, 130.3 (d), 131.6 (s), 140.7 (s); MS m/z 317 (M^+). Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.50; H, 7.32; N, 13.33.

Major cycloadduct **6d**: 0.42 g, 35%. Pale yellow powder; mp 78 °C (from diisopropyl ether); $[\alpha]_D^{25} = -76.1$ (c 0.29 $CHCl_3$); IR (nujol) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (1H, dd, J 10.4, 8.7), 3.20 (2H, dd, J 12.0, 8.9), 3.43 (1H, s), 3.50–3.75 (3H, m), 4.15 (1H, dd, J 9.2, 8.7), 5.10–5.24 (2H, m), 5.80–5.93 (1H, m), 6.9–7.4 (10H, m); ^{13}C NMR ($CDCl_3$) δ 42.2 (t), 46.5 (t), 47.0 (t), 52.4 (t), 108.7 (t), 119.0–130.0, 134.6 (s), 137.2 (d), 141.4 (s); MS m/z 303 (M^+). Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.22; H, 7.02; N, 13.93.

Minor cycloadduct **7b**: 71 mg, 7.4%. Pale yellow powder; mp 59 °C (from diisopropyl ether); $[\alpha]_D^{25} = +112.7$ (c 0.58, $CHCl_3$); IR (nujol) 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, d, J 6.5), 2.84 (1H, dd, J 11.4, 8.5), 3.16 (2H, dd, J 12.2, 8.9), 3.29 (1H, q, J 6.5), 3.40–3.70 (3H, m), 4.17 (1H, dd, J 9.2, 8.5), 5.20–5.30 (2H, m), 5.90–6.04 (1H, m), 6.9–7.2 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.2 (q), 34.8 (d), 44.6 (t), 45.4 (t), 47.1 (t), 48.8 (t), 110.2 (t), 117.8 (d), 126.3 (d), 128.0 (d), 130.3 (d), 131.6 (s), 142.0 (s); MS m/z 241 (M^+). Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.72; H, 7.98; N, 17.50.

Major cycloadduct **7c**: 38 mg, 2%. Pale yellow oil; $[\alpha]_D^{25} = +16.7$ (c 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.11 (1H, dd, J 16.8, 7.0), 2.32 (1H, dd, J 16.8, 6.0), 2.40 (1H, dd, J 10.5, 8.5), 3.32 (2H, dd, J 12.5, 8.5), 3.50 (1H, dd J 7.0, 6.0), 3.70–3.90 (3H, m), 4.21 (1H, dd, J 9.0, 8.5), 5.10–5.30 (2H, m), 5.80–5.90 (1H, m), 6.9–7.4 (10H, m); ^{13}C NMR ($CDCl_3$) δ 20.4 (q), 38.1 (d), 44.0 (t), 46.7 (t), 47.0 (t), 50.2 (t), 110.9 (t), 118.0–127.0, 130.8 (s), 134.7 (d), 142.9 (s); MS m/z 317 (M^+).

Acknowledgements

Thanks are due to MURST for financial support.

References

1. (a) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: New York, 1992; pp 1111–1168; (b) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 277–406.
2. (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-WCH: Weinheim, 2002; (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002.
3. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev* **1998**, *98*, 863; (b) Karlsson, S.; Högberg, E.-H. *Org. Prep. Proc. Int.* **2001**, *33*, 105; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449.
4. Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4265.
5. Molteni, G. *Heterocycles* **2005**, *65*, 2513.
6. Garanti, L.; Sala, A.; Zecchi, G. *Synth. Commun.* **1976**, *6*, 269.
7. Broggini, G.; Molteni, G.; Pilati, T.; Zecchi, G. *Synth. Commun.* **2001**, *31*, 3799.
8. Gung, B. W.; Le Noble, B., Eds.; *Chem. Rev*. **1999**, *99*, 1069–1480.
9. Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871.
10. Murzina, L. T.; Baires, S. V.; Nekhoroshkov, V. M.; Ivanov, B. E. *Izv. Akad. Nauk SSSR* **1991**, *7*, 1705.
11. Wolkoff, P. *Can. J. Chem.* **1975**, *53*, 1333.
12. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
13. As implemented in the Hyperchem 7.04 Professional package of programs. Hypercube, 2002.