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Efficient highly diastereoselective synthesis of 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines

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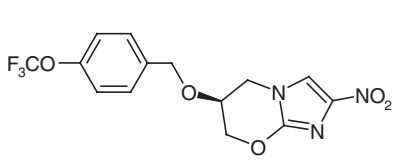
Abstract—1-Alkyl imidazoles react smoothly with dialkyl acetylenedicarboxylates in the presence of pyridine carboxaldehydes to diastereoselectively produce 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine derivatives in excellent yields.

1. Introduction

The development of simple synthetic routes to widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[2] The interest in fused bicyclic 5–6 systems with one ring junction nitrogen atom and two extra heteroatoms, one nitrogen in the five-membered ring and one oxygen in the six-membered ring, stems from the appearance of saturated and partially saturated imidazo[2,1-*b*][1,3]oxazine ring systems in biologically active compounds. Derivatives containing the imidazo[2,1-*b*][1,3]oxazine ring system have been shown to possess antimicrobial activity. For example, PA-824, PA-822, PA-653, PA-647, PA-601, and PA-602, are all members of bicyclic nitroimidazopyran family, drugs related to nitroimidazoles that have been studied as potent antituberculous compounds against a disease that kills one person every 15 s across the globe. The most promising compound in this series, PA-824, {4-[((3*S*)-6-nitro(2*H*,3*H*,4*H*-imidazolo[2,1-*b*]1,3-oxazaperhydroin-3-yloxy))methyl]phenoxy}trifluoromethane (**1**) which has a novel mechanism of action against mycobacterium tuberculosis and *Helobacter pylori* comparable with that of isoniazid.[3–7] However, only a few synthetic methods have been reported for the preparation of imidazo[2,1-*b*][1,3]oxazine ring systems.[8–11] As part of our current studies on the development of new routes in heterocyclic synthesis,[12–16] we have recently described a simple one-pot synthesis of 5*H*-imidazo[2,1-*b*][1,3]oxazines **2** from the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one.[17] In this paper, we wish to report an efficient diastereoselective synthesis of highly functionalized imidazo[2,1-*b*][1,3]oxazines.



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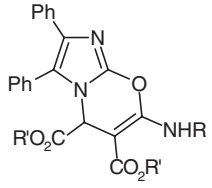

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2. Results and discussion

The reaction of 1-alkyl imidazoles **3** with dialkyl acetylenedicarboxylates **4** in the presence of pyridine carboxaldehydes **5** in dichloromethane at ambient temperature leads to 1-alkyl-7-pyridin-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylates **6** in 93–97% yields (Scheme 1).

Keywords: Diastereoselective synthesis; Pyridine carboxaldehydes; Acetylenic esters; 1-Alkyl imidazoles; 1,8a-Dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines.
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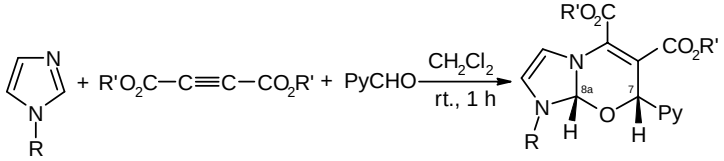


3 **4** **5** **6**

3	R
a	Me
b	^{n}Bu

4	R'
a	Me
b	Et

5	Py
a	2-C_5H_4N
b	4-C_5H_4N

6	R	R'	Py	Yield %
a	Me	Me	2-C_5H_4N	97
b	Me	Et	2-C_5H_4N	96
c	Me	Me	4-C_5H_4N	97
d	^{n}Bu	Me	2-C_5H_4N	94
e	^{n}Bu	Et	2-C_5H_4N	93
f	^{n}Bu	Me	4-C_5H_4N	95

Scheme 1.

The reactions were carried out by first mixing the 1-alkyl imidazole **3** and the pyridine carboxaldehyde **5** and then the acetylenic ester **4** was added slowly. The reactions proceeded spontaneously in CH_2Cl_2, and were complete within an hour. The ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine derivatives **6**. Any product other than **6** could not be detected by NMR spectroscopy. The reaction is stereoselective and leads to one diastereoisomer. Our attempts to detect the second diastereoisomer in the reaction mixture were not successful.

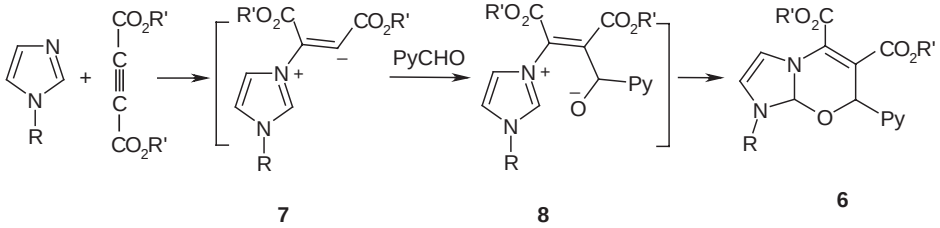
The structures of compounds **6a–f** were deduced from their elemental analyses, their IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of compound **6a** displayed molecular ion (M^+) peak at $m/z=331$, which is consistent with the 1:1:1 adduct of 1-methyl imidazole, dimethyl acetylenedicarboxylate, and pyridine-2-carboxaldehyde. The ^{1}H NMR spectrum of **6a** exhibited five sharp lines readily recognized as arising from N–CH_3 ($\delta=3.64$ ppm), methoxy ($\delta=3.67$ and 3.89 ppm), and methine ($\delta=5.46$ and 6.37 ppm) protons and two fairly broad singlets ($\delta=6.90$ and 7.00 ppm) for NCH=CHN moiety, along with characteristic multiplets for the aromatic protons. The proton decoupled ^{13}C NMR spectrum of **6a** showed 16 distinct resonances in agreement with the proposed structure.

The ^{1}H and ^{13}C NMR spectra of compounds **6b–f** are similar to those of **6a** except for the alkyl groups, the ester moieties, and the pyridine rings, which exhibit characteristic signals with appropriate chemical shifts and coupling constants. The signals of the two protons of the NCH=CHN moiety appeared as two doublets ($J=1.1$ Hz) only for **6d**.

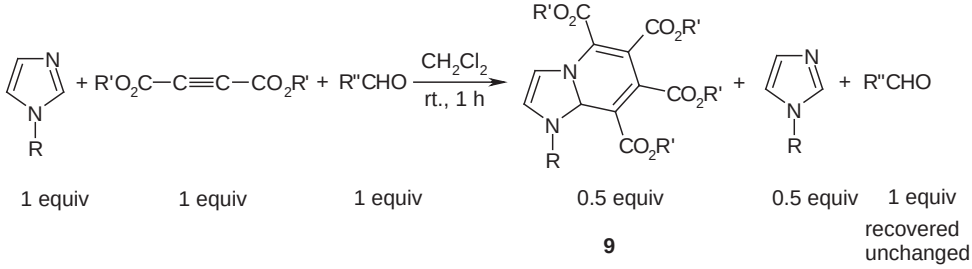
The stereochemistry of the products was established by nuclear Overhauser effect measurement.[18] Thus, when the resonance of C_7H proton of compound **6a** at $\delta=6.37$ ppm was saturated, the intensity of the signal of C_{8a}H proton at $\delta=5.46$ ppm increased by at least 10%. Thus the two protons are in a close *syn* relationship together.

Although we have not established the mechanism of the reaction between 1-alkyl imidazoles and acetylenic esters in the presence of pyridine carboxaldehydes in an experimental manner, a possible explanation is proposed in Scheme 2. The first step may involve addition of the 1-alkyl imidazole to the acetylenic ester and formation of the 1:1 adduct **7**. Subsequent nucleophilic attack of the adduct to the aldehyde would yield the 1:1:1 adduct **8**. The observed product is formed from the intramolecular addition of the oxygen anion to the imidazolium moiety.

Our attempts to carry out this reaction under the same reaction conditions with a wide range of aliphatic, aromatic, and heteroaromatic aldehydes, from highly electron-rich such as 4-(dimethylamino)benzaldehyde to highly electron-poor such as 4-nitrobenzaldehyde were not successful. For all of the aldehydes apart from 4-nitrobenzaldehyde the TLC and ^{1}H NMR spectrum of the reaction mixture clearly indicated the formation of 1,8a-dihydroimidazo[1,2-*a*]pyridine-5,6,7,8-tetracarboxylates **9** (Scheme 3), and the aldehyde recovered unchanged. Only with 4-nitrobenzaldehyde the TLC and ^{1}H NMR spectrum of the reaction mixture clearly indicated a complex mixture of at least five products together with some of the unreacted 1-alkyl imidazole and the aldehyde.



Scheme 2.



Scheme 3.

3. Conclusion

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides a simple one-pot method for the stereoselective preparation of polyfunctional 1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazines.

4. Experimental

Dimethyl- and diethyl acetylenedicarboxylates, 1-methyl- and 1-butyl imidazoles, and pyridine carbaldehydes were obtained from Merck (Germany) and were used without further purification. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.1. General procedure

To a magnetically stirred solution of the appropriate pyridine carbaldehyde (0.107 g, 1 mmol) and the appropriate 1-alkyl imidazole (1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise a solution of the appropriate dialkyl acetylenedicarboxylate (1 mmol) in CH_2Cl_2 (2 mL) at −5 °C for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h. The solvent was removed and the residue was purified by column chromatography using ethyl acetate as eluent. The solvent was removed under reduced pressure and the product was obtained.

4.1.1. Dimethyl 1-methyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6a). Viscous brown oil, yield: 0.32 g, 97%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1720 (C=O), 1631, 1439, 1215, 1148, 761. MS, *m*/*z* (%): 331 (M^+, 2), 272 (28), 240 (51), 212 (25), 190 (12), 184 (27), 172 (100), 158 (23), 131 (17), 117 (21), 101 (31), 78 (66), 59 (69). Anal. Calcd for $C_{16}H_{17}N_3O_5$ (331.33): C, 58.00; H, 5.17; N, 12.68. Found: C, 58.2; H, 5.6; N, 11.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.64 (3H, s, NCH_3), 3.67 and 3.89 (6H, 2s, $2OCH_3$), 5.46 (1H, s, N_2CHO), 6.37 (1H, s, Ar-CH), 6.90 and 7.00 (2H, 2s, NCH=CHN), 7.28 (1H, dd, J=6.9, 4.9 Hz, CH), 7.63 (1H, d, J=7.8 Hz, CH), 7.80 (1H, t, J=7.8 Hz, CH), 8.57 (1H, d, J=4.9 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 33.28 (NCH_3), 51.60 and 52.99 ($2OCH_3$), 77.88 (Ar-CH), 96.82 (N_2CHO), 121.96, 123.05, 123.66, 128.22, and 137.30 (5CH), 142.66 (C), 149.34 (CH), 154.96 and 159.49 (2C), 163.54 and 165.90 (2C=O).

4.1.2. Diethyl 1-methyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6b). Viscous brown oil, yield: 0.35 g, 96%. IR (KBr) (υ_{max}/cm^{-1}): 1740 and 1718 (C=O), 1630, 1375, 1196, 1144, 1043, 910, 733. MS, *m*/*z* (%): 360 (M^++1, 6), 286 (29), 258 (20), 240 (55), 212 (40), 186 (44), 172 (100), 158 (34), 104 (24), 93 (39), 78 (70). Anal. Calcd for $C_{18}H_{21}N_3O_5$ (359.38): C, 60.16; H, 5.89; N, 11.69. Found: C, 59.9; H, 5.8; N, 11.5%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.13 and 1.26 (6H, 2t, J=7.1 Hz, $2OCH_2CH_3$), 3.60 (3H, s, NCH_3), 4.01 and 4.26 (4H, 2q, J=7.1 Hz, $2OCH_2CH_3$), 5.39 (1H, s, N_2CHO), 6.36 (1H, s, Ar-CH), 6.85 and 6.91 (2H, 2s, NCH=CHN), 7.21 (1H, dd, J=6.9, 5.3 Hz, CH), 7.56 (1H, d, J=7.9 Hz, CH), 7.72 (1H, t, J=7.6 Hz, CH), 8.48 (1H, d, J=4.5 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.68 and 13.96 ($2OCH_2CH_3$), 33.30 (NCH_3), 60.39 and 62.19 ($2OCH_2CH_3$), 77.45 (Ar-CH), 97.03 (N_2CHO), 121.92, 123.08, 123.62, 127.71, and 137.30 (5CH), 142.65 (C), 149.21 (CH), 154.90 and 159.36 (2C), 163.03 and 165.29 (2C=O).

4.1.3. Dimethyl 1-methyl-7-pyridin-4-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6c). Viscous brown oil, yield: 0.32 g, 97%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1724 (C=O), 1634, 1560, 1443, 1373, 1148, 910, 735. MS, *m*/*z* (%): 331 (M^+, 3), 272 (34), 244 (22), 212 (19), 186 (26), 172 (100), 157 (29), 131 (14), 106 (26), 86 (58), 84 (98), 59 (47). Anal. Calcd for $C_{16}H_{17}N_3O_5$ (331.33): C, 58.00; H, 5.17; N, 12.68. Found: C, 58.0; H, 5.2; N, 12.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.31 (3H, s, NCH_3), 3.49 and 3.76 (6H, 2s, $2OCH_3$), 5.43 (1H, s, N_2CHO), 6.29 (1H, s, Ar-CH), 6.73 and 6.87 (2H, 2s, NCH=CHN), 7.10 (2H, d, J=5.9 Hz, 2CH), 8.47 (2H, d, J=5.9 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 32.15 (NCH_3), 51.32 and 52.75 ($2OCH_3$), 77.05 (Ar-CH), 95.69 (N_2CHO), 120.44, 121.34, and 128.31 (3CH), 141.59 and 144.78 (2C), 150.05 (CH), 158.75 (C), 163.19 and 165.58 (2C=O).

4.1.4. Dimethyl 1-butyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6d). Viscous brown oil, yield: 0.35 g, 94%. IR (KBr) (υ_{max}/cm^{-1}):

1747 and 1722 (C═O), 1630, 1437, 1373, 1209, 1146, 910, 732. MS, *m/z* (%): 373 (M^+, 5), 314 (18), 282 (39), 258 (17), 240 (20), 214 (55), 186 (58), 172 (46), 158 (48), 123 (47), 101 (59), 78 (99), 69 (62), 59 (100). Anal. Calcd for $C_{19}H_{23}N_3O_5$ (373.41): C, 61.12; H, 6.21; N, 11.25. Found: C, 61.2; H, 6.2; N, 11.1%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.86 (3H, t, J=7.0 Hz, CH_2CH_3), 1.24–1.89 (4H, m, $CH_2CH_2CH_3$), 3.58 (3H, s, OCH_3), 3.80 (2H, dt, ^2J=10.1 Hz, ^3J=7.1 Hz, NCH_2), 3.83 (3H, s, OCH_3), 5.41 (1H, s, N_2CHO), 6.32 (1H, s, Ar-CH), 6.91 and 6.98 (2H, 2d, J=1.1 Hz, NCH═CHN), 7.23 (1H, dd, J=6.8, 5.2 Hz, CH), 7.58 (1H, d, J=7.8 Hz, CH), 7.75 (1H, t, J=7.5 Hz, CH), 8.52 (1H, dd, J=4.9, 1.1 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.86 (CH_2CH_3), 19.15 and 32.19 ($CH_2CH_2CH_3$), 45.72 (NCH_2), 51.08 and 52.46 ($2OCH_3$), 77.14 (Ar-CH), 96.37 (N_2CHO), 121.16, 121.71, 123.48, 128.33, and 137.30 (5CH), 142.29 (C), 149.23 (CH), 155.22 and 159.67 (2C), 163.47 and 165.96 (2C═O).

4.1.5. Diethyl 1-butyl-7-pyridin-2-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6e). Viscous brown oil, yield: 0.37 g, 93%. IR (KBr) (υ_{max}/cm^{-1}): 1742 and 1721 (C═O), 1633, 1370, 1189, 1144, 915, 729. MS, *m/z* (%): 401 (M^+, 3), 330 (61), 303 (32), 284 (89), 256 (30), 231 (45), 217 (100), 201 (43), 188 (82), 174 (61), 160 (66), 135 (50), 124 (44), 119 (68), 106 (36), 96 (54), 80 (98), 58 (93). Anal. Calcd for $C_{21}H_{27}N_3O_5$ (401.46): C, 62.83; H, 6.78; N, 10.47. Found: C, 62.9; H, 6.9; N, 10.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.79 (3H, t, J=7.1 Hz, $CH_2CH_2CH_3$), 1.20 and 1.25 (6H, 2t, J=7.3 Hz, $2OCH_2CH_3$), 1.26–1.91 (4H, m, $CH_2CH_2CH_3$), 3.76 (2H, dt, ^2J=10.5 Hz, ^3J=7.4 Hz, NCH_2), 4.05 and 4.29 (4H, 2q, J=7.3 Hz, $2OCH_2CH_3$), 5.34 (1H, s, N_2CHO), 6.26 (1H, s, Ar-CH), 6.86 and 6.97 (2H, 2s, NCH═CHN), 7.25 (1H, dd, J=6.8, 5.0 Hz, CH), 7.69 (1H, d, J=7.5 Hz, CH), 7.83 (1H, t, J=7.8 Hz, CH), 8.44 (1H, d, J=4.6 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.77, 13.01, and 13.30 ($3CH_2CH_3$), 19.12 and 32.08 ($CH_2CH_2CH_2CH_3$), 45.61 (NCH_2), 59.93 and 61.70 ($2OCH_2CH_3$), 78.91 (Ar-CH), 96.54 (N_2CHO), 121.06, 121.56, 123.37, 128.31, and 137.16 (5CH), 142.38 (C), 149.11 (CH), 155.32 and 159.71 (2C), 163.04 and 165.38 (2C═O).

4.1.6. Dimethyl 1-butyl-7-pyridin-4-yl-1,8a-dihydro-7*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (6f). Viscous brown oil, yield: 0.35 g, 95%. IR (KBr) (υ_{max}/cm^{-1}): 1747 and 1724 (C═O), 1633, 1599, 1442, 1373, 1209, 1147, 910, 735. MS, *m/z* (%): 373 (M^+, 2), 288 (18), 228 (46), 214 (21), 200 (24), 172 (33), 158 (29), 125 (100), 106 (25), 97 (77), 82 (73), 69 (30), 59 (47). Anal. Calcd for $C_{19}H_{23}N_3O_5$ (373.41): C, 61.12; H, 6.21; N, 11.25. Found: C, 61.1; H, 6.2; N, 11.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.80 (3H, t, J=7.3 Hz, CH_2CH_3), 1.22–1.86 (4H, m, $CH_2CH_2CH_3$), 3.51 and 3.78 (6H, 2s, $2OCH_3$), 3.81 (2H, dt, ^2J=10.1 Hz, ^3J=7.2 Hz, NCH_2), 5.52 (1H, s, N_2CHO), 6.38 (1H, s, Ar-CH), 6.81 and 6.92 (2H, 2s, NCH═CHN), 7.16 (2H, d, J=5.8 Hz, 2CH), 8.49 (2H, d, J=5.8 Hz, 2CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.28 (CH_2CH_3), 19.49 and 32.82 ($CH_2CH_2CH_2CH_3$), 46.63 (NCH_2), 51.56 and 52.50 ($2OCH_3$), 75.60 (Ar-CH), 97.39 (N_2CHO), 120.36, 121.72, and 128.48 (3CH), 141.82 and 144.98 (2C), 150.20 (CH), 158.98 (C), 163.31 and 165.66 (2C═O).

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References and notes

1. Laszlo, P. *Organic Reactions: Simplicity and Logic*; Wiley: New York, 1995.
2. Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. *Adv. Heterocycl. Chem.* **1987**, *23*, 103.
3. Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barry, C. E.; Baker, W. R. *Nature* **2000**, *405*, 962.
4. Mullan, Z. *Lancet* **2000**, *355*, 2223.
5. Duncan, K. *Tuberculosis* **2003**, *83*, 201.
6. Choi, K.-P.; Bair, T. B.; Bae, Y.-M.; Daniels, L. *J. Bacteriol.* **2001**, *183*, 7058.
7. Akira, K.; Tsuneo, K.; Kunio, H.; Fumiyoshi, I. *Chem. Pharm. Bull.* **1979**, *27*, 848.
8. Miyamoto, M.; Tomari, K.; Kimura, Y. *Macromol. Chem. Phys.* **1999**, *200*, 594.
9. Ferris, J. P.; Devadas, B. *Tetrahedron Lett.* **1986**, *27*, 323. Ferris, J. P.; Devadas, B. *J. Org. Chem.* **1987**, *52*, 2355.
10. Luknitskii, F. I.; Taube, D. O.; Vovsi, B. A. *Zh. Org. Khim.* **1969**, *5*, 1844.
11. Shikhaliev, K. S.; Leshcheva, E. V.; Medvedeva, S. M. *Chem. Heterocycl. Compd.* **2002**, *420*, 852.
12. Yavari, I.; Adib, M.; Jahani-Moghaddam, F.; Bijanzadeh, H. R. *Tetrahedron* **2002**, *58*, 6901.
13. Yavari, I.; Adib, M.; Sayahi, M. H. *Tetrahedron Lett.* **2002**, *43*, 2927.
14. Yavari, I.; Adib, M.; Hojabri, L. *Tetrahedron* **2002**, *58*, 6895.
15. Yavari, I.; Adib, M.; Sayahi, M. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, *13*, 1517.
16. Adib, M.; Mollahosseini, M.; Yavari, H.; Sayahi, M. H.; Bijanzadeh, H. R. *Synlett* **2004**, 1086.
17. Adib, M.; Ghanbary, K.; Mostofi, M.; Bijanzadeh, H. R. *Tetrahedron* **2005**, *61*, 2645.
18. Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.