Pergamon

Tetrahedron 58 (2002) 8501–8504

TETRAHEDRON

N-Iodosuccinimide mediated regioselective heterocyclization of 3-cyclohex-2′-enyl-4-hydroxycoumarin

K. C. Majumdar* and S. Sarkar

Department of Chemistry, University of Kalyani, Kalyani 741 235, W. B., India

Received 29 May 2002; revised 24 July 2002; accepted 15 August 2002

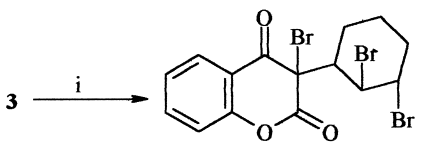
Abstract—A number of 3-cyclohex-2′-enyl-4-hydroxy[1]benzopyran-2-ones are regioselectively cyclized by treatment with *N*-iodosuccinimide in acetonitrile to afford 9′-iodo-2′-oxabicyclo[3,3,1]nonano[4′,3′-*c*][1]benzopyran-2-ones in excellent yield.

Coumarin[1] and its derivatives[2] are important due to their physiological activity. The biological activity[3,4] of 4-alkyl and 3-alkyl coumarins has made their synthesis[5] an attractive target. We have reported the regioselective synthesis of 3,4-fused pyrano- and furo coumarins.[6] In this context we attempted the cyclization of 3-(cyclohex-2′-enyl)-4-hydroxycoumarin with pyridine hydrotribromide[7] and failed to obtain any cyclized product. Our recent interest in the reagent *N*-iodosuccinimide prompted us to undertake a study on the use of this reagent for the regioselective cyclization of 3-(cyclohex-2′-enyl)-4-hydroxycoumarins. Here we report the results.

The starting materials, 3-(cyclohex-2′-enyl)-4-hydroxycoumarins (**3a–f**) for this study were prepared[8] in 65–70% yield by refluxing 4-hydroxycoumarins (**1a–f**) with 3-bromocyclohexene in acetone in the presence of anhydrous potassium carbonate for 20 h (Scheme 1).

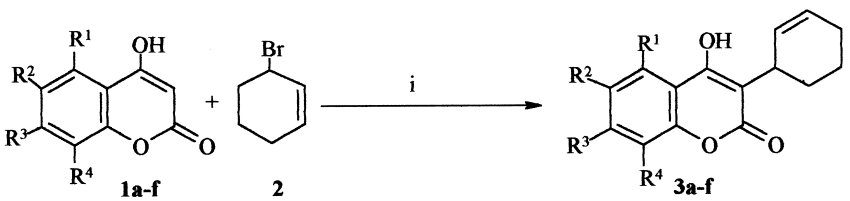
1. Results and discussion

We had earlier attempted the cyclization of 3-(cyclohex-2′-enyl)-4-hydroxycoumarin with pyridine hydrotribromide and observed exclusive formation of a tribromo derivative (**4**) with no indication of cyclization (Scheme 2). Therefore, we decided to treat substrates **3a–f** with this reagent. Substrate **3a** when treated with *N*-iodosuccinimide in acetonitrile at 0–5°C for 1 h gave a crystalline white



4

Scheme 2. *Reagents*: $PyHBr_3/CH_2Cl_2$, 0–5°c, 2 h (94%).



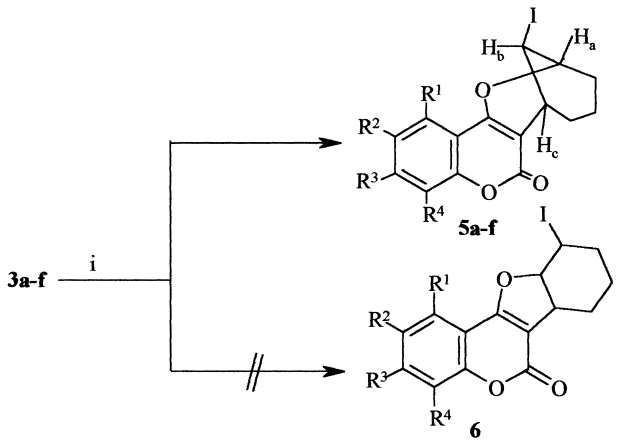
a. $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$
b. $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
c. $R^2 = R^3 = H$, $R^1 = R^4 = CH_3$
d. $R^1 = R^3 = H$, $R^2 = R^4 = CH_3$
e. $R^1 = R^3 = R^4 = H$, $R^2 = CMe_3$
f. $R^1 = R^2 = R^3 = R^4 = H$

Scheme 1. *Reagents*: (i) acetone, K_2CO_3, reflux, 20 h.

Keywords: *N*-iodosuccinimide; regioselective cyclization; 4-hydroxycoumarin; bridged tricyclic heterocycle; 6-*endo* cyclization.

* Corresponding author. Tel.: +91-33-582-7521; fax: +91-33-582-8282; e-mail: kcm@klyuniv.ernet.in

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01024-4



Scheme 3. *Reagents*: (i) NIS, CH_3CN, 0–5°C, 1 h.

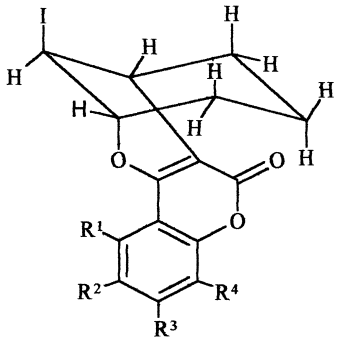


Figure 1.

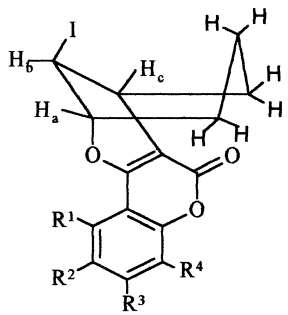


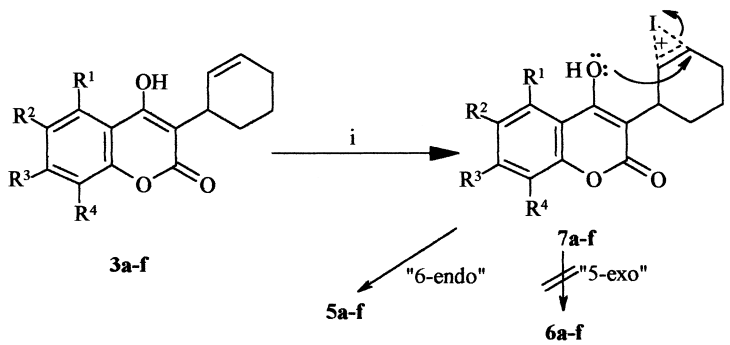
Figure 2.

solid, mp 140°C in 85% yield. IR showed the absence of the –OH absorption peak at 3300 cm^{-1}. Elemental analysis and spectral data indicated this to be the bridged product **5a**. The high-field ^1H NMR spectrum of the product showed three lone protons: at δ 4.44 assignable to proton H_a, at δ 5.24 assignable to proton H_b, and at δ 3.63 assignable to proton H_c. The signal at δ 4.44 due to H_a appeared as a ddd, J=7.3, 4.9 and 10.0 Hz. The signal at δ 5.24 due to H_b appeared as a dd with coupling constants J=6.9 and 7.3 Hz. The signal at δ 3.63 on careful expansion was found to be a dt with coupling constants J=6.9 and 7.1 Hz. From the splitting pattern and the coupling constant values it is clear that H_b and H_c are vicinal protons coupled to each other. This clearly shows that the product has the bridged tricyclic structure **5** instead of linearly fused structure **6** where H_b and H_c would not be on adjacent carbons. Other substrates **3b–f** were treated similarly to give products **5b–f** in 85–90% yield (Scheme 3).

A Dreiding model of compound **5a** can be constructed by 1,3 fusion of the pyran ring in the half-chair conformation with the cyclohexane ring in the chair conformation (distorted) as shown in Fig. 1. However, the coupling constant 10.0 Hz of H_a cannot be explained if the molecule **5a** attains this conformation. The alternative model that can be constructed, again by 1,3 fusion of the pyran ring in the half-chair form with the cyclohexane ring in the boat (distorted) form, is shown in Fig. 2. The coupling constant J=10.0 Hz can be explained if the molecule **5a** attains this conformation. It may be noted that [3.3.1] bicyclononane is known to exist in the chair–boat conformation.[9]

It is worths of note that the substrate 3-cyclohex-2′-enyl-4-hydroxycoumarin **3** did not react at all with *N*-bromosuccinimide in acetonitrile at 0–5°C and even at elevated temperature no characterizable product was obtained.

The regioselective formation of the products may be easily explained by the initial formation of an intermediate iodonium ion **7a–f** which may undergo a 6-*endo* cyclization to give products **5a–f**. The alternative pathway, a 5-*exo* cyclization to give products **6a–f** does not occur. In conclusion all six substrates studied so far gave only the bridged cyclic products by a 6-*endo* mode and the other mode of cyclization was found to be totally absent. This is therefore a regioselective method for the synthesis of bridged 3,4-fused pyranocoumarin derivatives in excellent yield (Scheme 4).



Scheme 4. *Reagents*: (i) NIS, CH_3CN, 0–5°C, 1 h.

2. Experimental

Melting points were determined in a sulphuric acid bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 spectrophotometer (λ_{max} in nm) and IR spectra as KBr discs on a Perkin–Elmer 1330 apparatus (ν_{max} in cm^{-1}). ^1H NMR spectra were run in $CDCl_3$ with $SiMe_4$ as internal standard on a Bruker 300 MHz instrument at the Indian Institute of Chemical Biology, Kolkata (chemical shifts in δ ppm). Elemental analysis and mass spectra were recorded by RSIC (CDRI), Lucknow. Silica gel (60–120 mesh) was used for chromatographic separation. Extracts were dried over anhydrous sodium sulphate.

2.1. Preparation of 3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3a–f)

A mixture of 4-hydroxycoumarin (0.02 mol), 3-bromocyclohexene (0.03 mol) and anhydrous potassium carbonate (3 g) was refluxed in acetone (150 mL) on a water bath for 20 h, cooled and filtered. The solvent was removed and the residue was extracted with chloroform (3×50 mL). The chloroform extract was washed with $NaHCO_3$ solution (10%, 2×50 mL) to remove the unreacted 4-hydroxycoumarin, water (50 mL), dried (Na_2SO_4) and solvent was removed to give a highly viscous liquid. This was purified by column chromatography over silica gel using pet-ether (60–80°C)/benzene (1:1) as eluent to give compound **3a–f**.

2.1.1. 6-Methyl-3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3a). Yield: 65%, mp 118°C; [Found C 75.15; H 6.33. $C_{16}H_{16}O_3$ requires C 75.00; H 6.25%]; ν_{max} (KBr) 3350, 2920, 1700, 1490, 1280, 1105, 830 cm^{-1}; λ_{max} 218, 313 nm; δ_H (300 MHz, $CDCl_3$) 1.61–2.01 (m, 6H), 2.47 (s, 3H), 3.87–3.90 (m, 1H, –C*H*–), 6.03–6.06 (m, 1H, =C*H*), 6.28–6.33 (m, 1H, =C*H*), 7.17 (s, 1H),7.37 (d, *J*= 9 Hz, 1H), 7.71 (d, *J*=9 Hz, 1H); *m*/*z* 256 (M^+).

2.1.2. 8-Methyl-3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3b). Yield: 67%, mp 126°C; [Found C 75.15; H 6.33. $C_{16}H_{16}O_3$ requires C 75.00; H 6.25%]; ν_{max} (KBr) 3350, 2930, 1700, 1490, 1280, 1105, 830 cm^{-1}; λ_{max} 210, 314 nm; δ_H (300 MHz, $CDCl_3$) 1.65–1.98 (m, 6H), 2.55 (s, 3H), 3.85–3.89 (m, 1H, –C*H*–), 6.04–6.07 (m, 1H, =C*H*), 6.29–6.33 (m, 1H, =C*H*), 7.13–7.18 (dd≅t, *J*=7.4, 8.1 Hz, 1H), 7.35 (d, *J*=7.4 Hz, 1H), 7.61 (d, *J*=8.1 Hz, 1H); *m*/*z* 256 (M^+).

2.1.3. 5,8-Dimethyl-3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3c). Yield: 70%, mp 148°C; [Found C 75.47; H 6.79. $C_{17}H_{18}O_3$ requires C 75.56; H 6.67%]; ν_{max} (KBr) 3300, 2920, 1705, 1490, 1280, 1100, 830 cm^{-1}; λ_{max} 217, 310 nm; δ_H (300 MHz, $CDCl_3$) 1.56–1.87 (m, 6H), 2.09 (s, 3H), 2.21 (s, 3H), 3.84–3.87 (m, 1H, –C*H*–), 6.03–6.07 (m, 1H, =C*H*), 6.29–6.33 (m, 1H, =C*H*), 7.22 (d, *J*=9 Hz, 1H), 7.55 (d, *J*=9 Hz, 1H); *m*/*z* 270 (M^+).

2.1.4. 6,8-Dimethyl-3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3d). Yield: 70%, mp 154°C; [Found C 75.72; H 6.53. $C_{17}H_{18}O_3$ requires C 75.56; H 6.67%]; ν_{max} (KBr) 3300, 2920, 1700, 1490, 1280, 1100, 830 cm^{-1}; λ_{max} 218, 317 nm; δ_H (300 MHz, $CDCl_3$) 1.55–1.90 (m, 6H), 2.06 (s, 3H), 2.18 (s, 3H), 3.85–3.89 (m, 1H, –C*H*–), 6.03–6.06 (m, 1H, =C*H*), 6.27–6.32 (m, 1H, =C*H*), 7.19 (s, 1H), 7.58 (s, 1H); *m*/*z* 270 (M^+).

2.1.5. 6-Tertiarybutyl-dimethyl-3-[2′-cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3e). Yield: 65%, mp 160°C; [Found C 76.63; H 7.25. $C_{19}H_{22}O_3$ requires C 76.51; H 7.38%]; ν_{max} 3300, 2920, 1710, 1470, 1280, 1105, 820 cm^{-1}; λ_{max} 217, 310 nm; δ_H (300 MHz, $CDCl_3$) 1.43 (s, 9H), 1.51–1.85 (m, 6H), 3.91–3.96 (m, 1H, –C*H*–), 5.90–6.01 (m, 1H, =C*H*), 6.29–6.32 (m, 1H, =C*H*), 7.09 (d, *J*=9 Hz, 1H), 7.18 (d, *J*=9 Hz, 1H), 7.33 (s, 1H); *m*/*z* 298 (M^+).

2.1.6. 3-[2′-Cyclohexenyl]-4-hydroxy-1-benzopyran-2(*H*)-one (3f). Yield: 66%, mp 108°C Lit.[8] mp 110°C.

2.2. Attempted procedure for the cyclization of 3a by *N*-bromosuccinimide

N-bromosuccinimide (0.178 g, 1 mmol) was added to a dry and distilled acetonitrile solution of the compound **3a** (1 mmol) at 0–5°C. The reaction mixture was stirred for several hours at 0–5°C but no change was observed. Decomposition was observed when the reaction mixture was allowed to boil. No characterizable product was obtained.

2.3. General procedure for the cyclization of compounds 3a–f by *N*-iodosuccinimide

N-Iodosuccinimide (0.225 g, 1 mmol) was added to a dry and distilled acetonitrile solution of the compounds **3a–f** (1 mmol) at 0–5°C. The reaction mixture was then stirred for 1 h at 0–5°C. Stirring was continued for an additional period of 30–45 min at rt. On completion of the reaction (monitored by TLC) acetonitrile was removed from the reaction mixture under reduced pressure. The residual mass was then extracted with chloroform and the extract was washed with 5% $NaHSO_3$ solution (3×50 mL) and water (3×50 mL) and dried (Na_2SO_4). The residual mass after removal of the solvent was subjected to column chromatography over silica gel using petroleum ether (60–80°C)/benzene (3:1) as eluent to give cyclization product **5a–f**.

2.3.1. 6-Methyl-9′-iodo-2′-oxabicyclo[3,3,1]nonano[4′,3′-*c*]-[1]benzopyran-2-one (5a). Yield 90%; mp 140°C; [Found C 50.38; H 3.89 $C_{16}H_{15}IO_3$ requires C 50.26; H 3.92%]; ν_{max} (KBr) 2900, 1705, 1390, 1250, 1090, 800 cm^{-1}; λ_{max} 222, 293 nm; δ_H (300 MHz, $CDCl_3$) 1.33–1.39 (m, 1H), 1.57–1.66 (m, 1H), 1.83–1.96 (m, 3H), 2.07–2.17 (m, 1H), 2.42 (s, 3H), 3.63 (dt≅q, *J*=6.9, 7.1 Hz, H_c), 4.44 (ddd, *J*=10.0, 7.3, 4.9 Hz, H_a), 5.24 (dd, *J*=6.9, 7.3 Hz, H_b), 7.24 (d, *J*=8.5 Hz, 1H), 7.35–7.39 (dd, *J*=8.5, 1 Hz, 1H); 7.48 (d, *J*=1 Hz, 1H); *m*/*z* 382 (M^+).

2.3.2. 8-Methyl-9′-iodo-2′-oxabicyclo[3,3,1]nonano[4′,3′-*c*]-[1]benzopyran-2-one (5b). Yield 85%, mp 136°C; [Found C 50.43; H 4.11. $C_{16}H_{15}IO_3$ requires C 50.26; H 3.92%]; ν_{max} (KBr) 2900, 1705, 1390, 1250, 1090, 800 cm^{-1}; λ_{max} 222, 293 nm; δ_H (300 MHz, $CDCl_3$) 1.32–1.39 (m, 1H), 1.58–1.66 (m, 1H), 1.81–1.95 (m, 3H), 2.01–2.08 (m, 1H),

2.47 (s, 3H), 3.63 (dt≅q, J=6.9, 7.1 Hz, H_c), 4.47 (ddd, J=10.04, 7.3, 4.9 Hz, H_a), 5.24 (dd, J=6.9, 7.3 Hz, H_b), 7.16–7.21 (dd≅t, J=7.1, 7.7 Hz, 1H), 7.40 (d, J=7.1 Hz, 1H), 7.53 (d, J=7.7 Hz, 1H); m/z 382 (M^+).

2.3.3. 5,8-Dimethyl-9′-iodo-2′-oxabicyclo[3,3,1]nonano-[4′,3′-*c*][1]benzopyran-2-one (5c). Yield 88%, mp 148°C; (Found C 51.79; H 4.44; $C_{17}H_{17}IO_3$ requires C 51.51; H 4.29%); ν_{max} (KBr) 2900, 1700, 1420, 1230, 1090, 820 cm^{-1}; λ_{max} 219, 292 nm; δ_H (300 MHz, $CDCl_3$) 1.25–1.33 (m, 1H), 1.58–1.65 (m, 1H), 1.79–1.91 (m, 3H), 2.04–2.11 (m, 1H), 2.44 (s, 3H), 2.47 (s, 3H), 3.61 (dt≅q, J=6.9, 7.1 Hz, H_c), 4.36 (ddd, J=10.0, 7.3, 4.9 Hz, H_a), 5.21 (dd, J=6.9, 7.3 Hz, H_b), 6.94 (d, J=7.5 Hz, 1H), 7.25 (d, J=7.5 Hz, 1H); m/z 396 (M^+).

2.3.4. 6,8-Dimethyl-9′-iodo-2′-oxabicyclo[3,3,1]nonano-[4′,3′-*c*][1]benzopyran-2-one (5d). Yield 86%, mp 153°C; [Found C 51.63; H 4.38. $C_{17}H_{17}IO_3$ requires C 51.51; H 4.29%]; ν_{max} (KBr) 2900, 1700, 1420, 1230, 1090, 820 cm^{-1}; λ_{max} 220, 292 nm; δ_H (300 MHz, $CDCl_3$) 1.26–1.33 (m, 1H), 1.56–1.63 (m, 1H), 1.79–1.92 (m, 3H), 2.01–2.19 (m, 1H), 2.41 (s, 3H), 2.43 (s, 3H), 3.63 (dt≅q, J=6.9, 7.1 Hz, H_c), 4.38 (ddd, J=10.0, 7.3, 4.9 Hz, H_a), 5.24 (dd, J=6.9, 7.3 Hz, H_b), 6.99 (s, 1H), 7.39 (s, 1H); m/z 396 (M^+).

2.3.5. 6-Tertiarybutyl-9′-iodo-2′-oxabicyclo[3,3,1]-nonano[4′,3′-*c*][1]benzopyran-2-one (5e). Yield 85%, mp 130°C; [Found C 53.65; H 4.87. $C_{19}H_{21}O_3$ requires C 53.77; H 4.95%]; ν_{max} (KBr) 2905, 1705, 1390, 1250, 1080, 800 cm^{-1}; λ_{max} 222, 295 nm; δ_H (300 MHz, $CDCl_3$) 1.25–1.36 (m, 1H), 1.59–1.63 (m, 1H), 1.70–1.92 (m, 3H), 2.01–2.13 (m, 1H), 1.44 (s, 9H), 3.61 (dt≅q, J=6.9, 7.1 Hz, H_c), 4.54 (ddd, J=10.0, 7.3, 4.9 Hz, H_a), 5.24 (dd, J=6.9, 7.3 Hz, H_b), 7.27 (d, J=10.0 Hz, 1H), 7.35 (d, J=10.0 Hz, 1H), 7.63 (s, 1H); m/z 424 (M^+).

2.3.6. 9′-Iodo-2′-oxabicyclo[3,3,1]nonano[4′,3′-*c*][1]benzopyran-2-one (5f). Yield 85%, mp 92°C; [Found C 49.11; H 3.73. $C_{15}H_{13}IO_3$ requires C 48.91; H 3.53%]; ν_{max} (KBr) 2900, 1700, 1420, 1250, 1090, 800 cm^{-1}; λ_{max} 219, 293 nm; δ_H (300 MHz, $CDCl_3$) 1.38–1.44 (m, 1H), 1.54–1.69 (m, 1H), 1.82–1.95 (m, 3H), 2.07–2.15 (m, 1H), 3.63 (dt≅q, J=6.9, 7.1 Hz, H_c), 4.28 (ddd, J=10.0, 7.3, 4.9 Hz, H_a), 5.25 (dd, J=6.9, 7.3 Hz, H_b), 7.30 (d, J=7.70 Hz, 1H), 7.54–7.60 (dd≅t, J=7.70, 8.2 Hz, 2H), 7.70 (d, J=8.2 Hz, 1H); m/z 368 (M^+).

Acknowledgements

We thank the CSIR (New Delhi) for financial assistance. One of us (S. S.) is thankful to CSIR (New Delhi) for a Junior Research Fellowship.

References

1. Audus, L. J.; Quastel, J. H. *Nature* **1947**, *159*, 320.
2. Feur, G. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; North-Holland: New York, 1974. (b) Dean, F. M. *Naturally Occuring Oxygen Ring Compounds*; Butterworths: London, 1963.
3. Deana, A. A.; Stokker, G. E.; Schultz, E. M.; Smith, R. L.; Cragoe, Jr. E. J.; Russo, H. F.; Walson, L. S. *J. Med. Chem.* **1983**, *26*(4), 580–585.
4. Gordon, M.; Grover, S. H.; Strothers, J. B. *Can. J. Chem.* **1973**, *51*, 2092–2097. (b) Wenkert, E.; Bruckwalter, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 4367–4369.
5. (a) Wawzoneck, S. *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1951; Vol. 2, pp 176–180. (b) Staunton, J. *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon: Oxford, 1979; Vol. 4, p 646.
6. Majumdar, K. C.; Khan, A. T.; De, R. N. *Synth. Commun.* **1988**, *18*, 1589–1595. (b) Majumdar, K. C.; Das, D. P.; Khan, A. T. *Synth. Commun.* **1988**, *18*, 2027–2036. (c) Majumdar, K. C.; Khan, A. T.; Das, D. P. *Synth. Commun.* **1989**, *19*, 917–930. (d) Majumdar, K. C.; De, R. N.; Khan, A. T.; Chattopadhyay, S. K.; Dey, K.; Patra, A. *J. Chem. Soc., Chem. Commun.* **1988**, 777–779. (e) Majumdar, K. C.; De, R. N. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1901–1905. (f) Majumdar, K. C.; Choudhury, P. K.; Khan, A. T. *Synth. Commun.* **1989**, *19*, 3249–3257.
7. Majumdar, K. C.; Kundu, A. K. *Indian J. Chem.* **1993**, *32B*, 605–606. (b) Majumdar, K. C.; Kundu, A. K. *Can. J. Chem.* **1995**, *73*, 1727–1732. (c) Majumdar, K. C.; Choudhury, P. K.; Nethaji, M. *Tetrahedron Lett.* **1994**, *35*, 5927–5930.
8. Majumdar, K. C.; Khan, A. T.; Gupta, A. K.; Kundu, A. K.; Choudhury, P. K. *Indian J. Chem.* **1992**, *31B*, 667–672.
9. Eliel, E. L. *Streochemistry of Carbon Compounds*; McGraw Hill: New York, 1962; p 296.