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A SINGLE-STEP SYNTHESIS OF XYRIDINS A AND B, METABOLITES FROM *Xyris indica*

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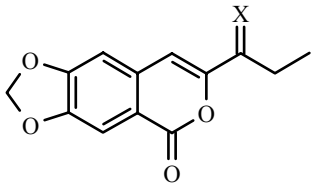
A facile single-step synthesis of the title isocoumarins isolated from Xyris indica has been elaborated. Condensation of butanoyl chloride and 2-oxobutanoyl chloride with 3,4-methylenedioxyhomophthalic acid afforded xyridin A and xyridin B, respectively. Xyridin A was saponified to the corresponding keto acid, which on reduction gave the (±)-3,4-dihydro-6,7-methylenedioxy-3-propylisocoumarin in which diastereotopy of the methylenic protons around the stereogenic center was observed. A mass fragmentation mechanism for xyridins has also been suggested.

Keywords: isocoumarins, xyridin A, xyridin B, *Xyris indica*, diastereotopy, mass fragmentation.

In 1995, Ruangrungsi et al. isolated from the nonpolar fraction of the chloroform extract of the flowering heads of the weed *Xyris indica* two new isocoumarins, which they named xyridins A and B [1]. *Xyris indica* L. (tall yellow-eyed grass) is one of the five species of the genus *Xyris* found throughout Thailand and is known locally as "Kra thin thung". In Bengal the plant has been used in folk medicine as a cure for ring worm, itch, and leprosy. The structures of xyridin A and B were established by modern spectroscopic techniques as 6,7-methylenedioxy-3-propylisocoumarin (**1a**) and 6,7-methylenedioxy-3-(1-oxopropyl)isocoumarin (**1b**), respectively.



1a,b

1 a X = H_2, **b** X = O

Although xyridins A and B, like the majority of other naturally occurring isocoumarins derived biogenetically from acetate *via* the acetate-polymalonate pathway, possess a C(8) or C(6) and C(8) oxygenation, xyridins A and B are unique in being 3-alkyl/acyl-substituted 6,7-methylenedioxyisocoumarins. In the literature unsubstituted 4,5-, 6,7-methylenedioxyisocoumarins and 4,5-, 5,6-, 6,7-methylenedioxy-3,4-dihydro-isocoumarins are known along with 3-methyl-6,7-methylenedioxy-3,4-dihydroisocoumarin as the only example of a 3-alkyl-substituted 6,7-methylenedioxyisocoumarin [2-4]. Some important examples of other natural products bearing a 6,7-methylenedioxydihydroisocoumarin moiety are hippeastrine [5], tetrabenzylcorricidin [6], lycoricidin [7], pancratistatin [8, 9], and tazettine [10]. Peshawarine contains an 3-aryl-7,8-methylenedioxy-3,4-dihydroisocoumarin skeleton [11].

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The synthesis of xyridins A and B was undertaken as a continuation of our efforts towards synthesis of naturally occurring isocoumarins and dihydroisocoumarins [12-16] which exhibit a wide variety of biological activities despite their relatively simple structure. The limited quantities available from natural sources together with the possibility of preparing analogues with improved biological activities show the imperative need for the total synthesis. The condensation of acid chlorides with homophthalic acid has recently emerged as a standard and authentic route for the preparation of the 3-substituted isocoumarin skeleton [17-19]. Herein a short and efficient synthesis of xyridins A and B achieved employing this method and the conversion of the former into corresponding the (±)-3,4-dihydroisocoumarin will be described.

RESULTS AND DISCUSSION

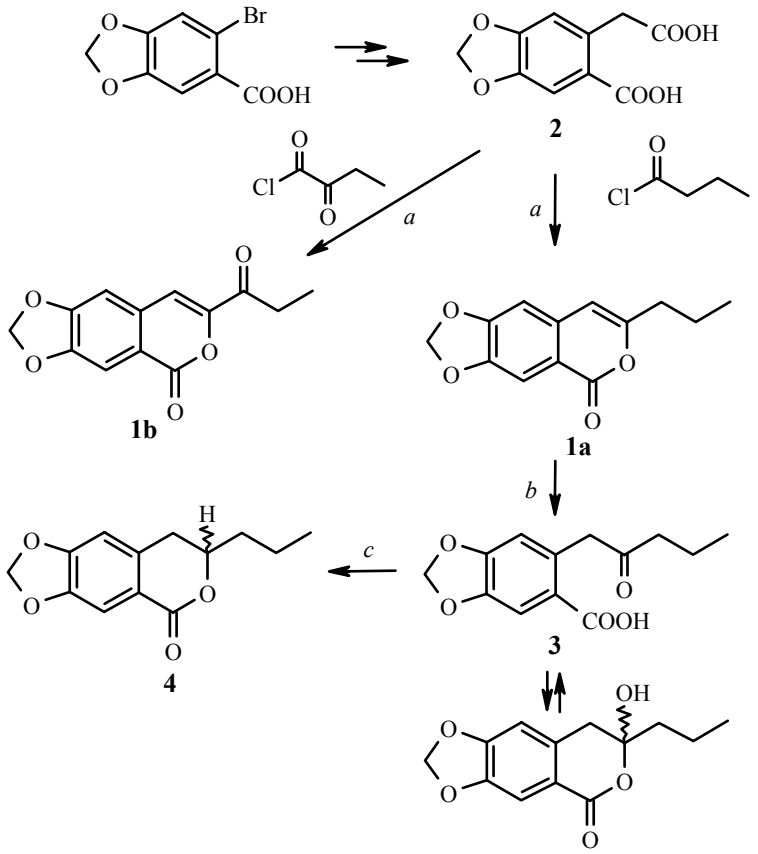
4,5-Methylenedioxyhomophthalic acid was prepared in two steps from 2-bromo-4,5-methylenedioxybenzoic acid according to the literature procedure [2]. Commercially available 2-oxobutanoic acid was converted into acid chloride by treatment with oxalyl chloride in dry benzene at room temperature; butanoyl chloride was the commercial product. Initial efforts to condense 4,5-methylenedioxyhomophthalic acid with acid chlorides led to opening of the methylenedioxy bridge due to its sensitivity towards acids. Eventually the condensation was successfully achieved in the presence of a few drops of pyridine. Normally, a yield of 60-85% is obtained in these condensations, which are carried out at 200°C, but in the case of xyridin A, due to the relatively lower boiling point of 1-butanoyl chloride (102°C) and the sensitivity of the methylenedioxy bridge to acids, only a moderate yield of 45% could be obtained despite a longer reflux time. In the case of xyridin B the limiting factor was the susceptibility to decomposition of 2-oxobutanoyl chloride, resulting in 58% yield. However, the relatively lower yields are more than compensated by the remarkable simplicity of one-pot synthesis (Scheme 1).

Thus, direct condensation of 4,5-methylenedioxyhomophthalic acid with butanoyl chloride at elevated temperatures afforded the xyridin A (**1a**). It has the characteristic 1H singlet of the isocoumarin moiety at δ 6.15 ppm for H(4), and a 2H singlet at 6.09 ppm for the methylenedioxy group in the ^{1}H NMR and signals at δ 103.20 (C(4)), 157.41 (C(3)), and 102.2 ppm (OCH_2O) in the ^{13}C NMR spectrum. The IR spectrum showed the lactonic carbonyl absorption at 1722 cm^{-1}. In the case of xyridin B, due to extension of conjugation, the characteristic H(4) singlet was found further downfield in the aromatic region at δ 7.30 H(4) and that of the methylenedioxy group at δ 6.20 ppm in the ^{1}H NMR, and at δ 109.1 (C(4)), 149.41 (C(3)), and 195.3 ppm (C=O) in the ^{13}C NMR spectrum. DEPT 90° and DEPT 135° experiments confirmed these assignments. The IR spectrum showed the lactonic and ketonic carbonyl absorptions at 1728 and 1685 cm^{-1}, respectively.

Alkaline hydrolysis of xyridin A (**1a**) furnished 4,5-methylenedioxy-2-(2-oxopentyl)benzoic acid (**3**) in good yield. The keto acid existed partially in its cyclic tautomeric lactol form (3-hydroxy-6,7-methylenedioxy-3-propyl-3,4-dihydroisocoumarin) as evidenced by the ^{1}H NMR. Thus, in addition to the 2H singlet at δ 3.94 ppm (H(4), open chain form) each proton of $ArCH_2$ showed a broad signal at δ 2.91 and 3.10 ppm (lactol form). In the ^{13}C NMR spectrum C(4) resonated at δ 51.80 ppm. The IR spectrum showed the carbonyl absorptions at 1680 and 1705 cm^{-1}.

Sodium borohydride reduction of the keto acid–lactol tautomeric mixture **3** afforded the corresponding racemic hydroxy acid which underwent spontaneous cyclodehydration on standing for a few minutes (as monitored by TLC) to (±)-6,7-methylenedioxy-3-propyl-3,4-dihydroisocoumarin (**4**) [20] without any dehydrating agent. The protons of methylene groups on either side of the newly created stereogenic center are nonequivalent, exhibiting a phenomenon called the diastereotopic effect [21, 22]. The motion of methylene at C(4) is restricted owing to its incorporation into the heterocyclic ring, whereas methylene at C(1') may undergo free rotation, thus corresponding to ABX and ABMNX systems, respectively. Thus, typical ABX splitting (dddd) of prochiral benzylic protons H(4) (AB) and H(3) (X) protons in ^{1}H NMR spectrum was observed. The AB part at δ 2.85-2.96 ppm showed that the hydrogen atom *trans* to the side chain is located slightly upfield and

Scheme 1



a 200 °C, 4–20 h, 45–58%; *b* 5% KOH/EtOH, 4 h reflux, 70%;
c $NaBH_4$, EtOH, 4 h, r. t., 85%

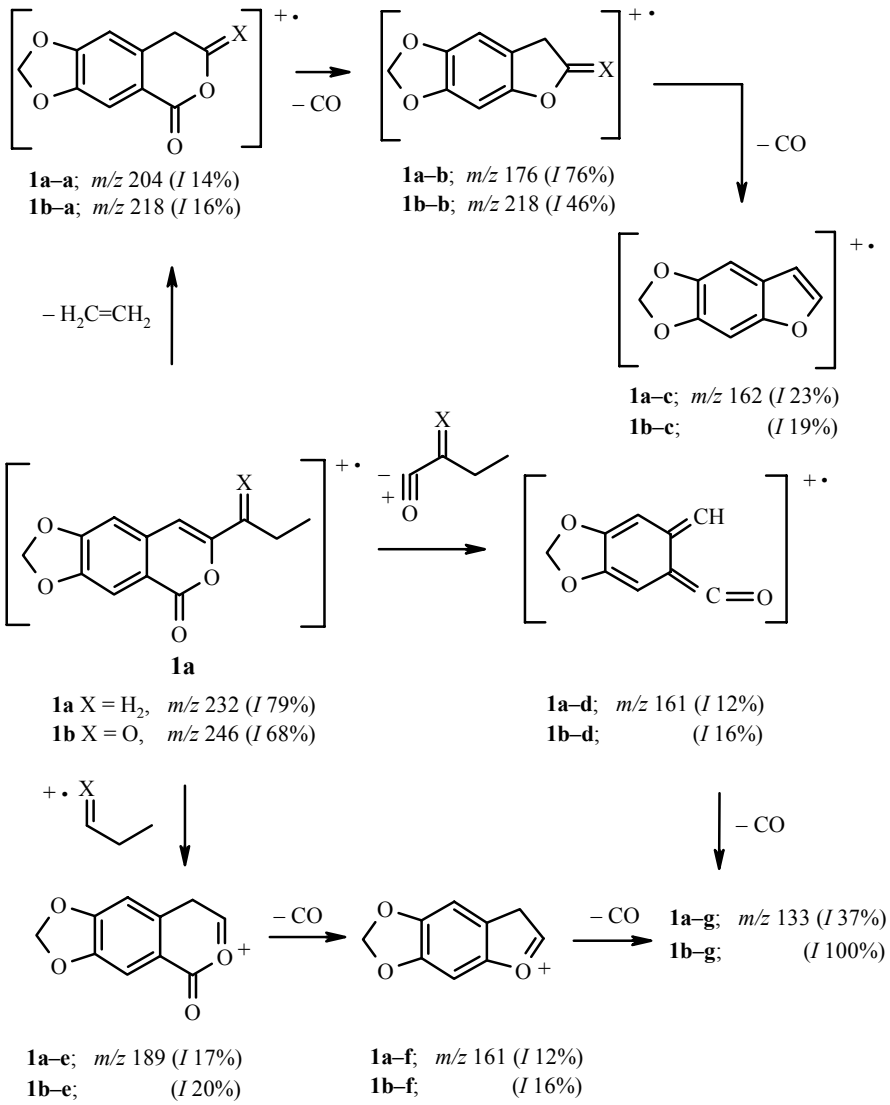
appeared as a doublet of doublets at δ 2.85 ppm (J_{gem} = 12.4, J_{trans} = 3.52 Hz), while the *cis* hydrogen resonated slightly downfield at 2.96 ppm (J_{gem} = 17.08, J_{cis} = 13.04 Hz) with a chemical shift difference ($\Delta\nu = H_{4A}–H_{4B}$) of about 0.1 ppm, which is a measure of the diastereotopy extent. The methine proton H(3) (X) showed a dddd pattern at δ 4.25 ppm, which is evidence of the presence of diastereotopic methylenes on both C(4) and C(1').

Thus, H(1'A) and H(1'B) and each of the protons of methylene at C(1') also showed a dddd at δ 1.61 and 1.80 with a chemical shift difference of 0.19 ppm, almost double the extent of diastereotopy compared to that between H(4A) and H(4B). It is quite interesting to note that the diastereotopic effect extends up to the C(2') methylenic protons, corresponding to an $ABMNX_2$ system with two sets of multiplets at δ 1.45 and 1.54, respectively; in this case Δν is reduced to ≈ 0.1 ppm due to the higher separation from the chiral center. The ^{13}C NMR spectrum showed signals at δ 77.63 and 35.01 ppm for C(3) and C(4), respectively. The lactonic carbonyl absorption appeared at 1720 cm^{-1} in the IR spectrum.

Scheme 2 delineates the mass fragmentation pattern of the EIMS spectra of xyridins A and B, which is consistent with the general mass fragmentation mechanism for isocoumarins. The major peaks correspond to α-cleavage, γ-H rearrangement, and retro-Diels–Alder cleavage products.

Thus, a facile single-step synthesis of the medicinally important isocoumarins xyridins A and B has been elaborated and their structures were unambiguously confirmed, which makes the substances available for biological evaluation.

Scheme 2



EXPERIMENTAL

General: 2-Oxobutanoic acid and 1-butanoyl chloride were commercial products from Aldrich. 2-Bromo-4,5-methylenedioxybenzoic acid was prepared from piperonal according to the reported procedure [23]. ^{1}H and ^{13}C NMR spectra (δ) were recorded in $CDCl_3$ at 400 and 100 MHz, respectively (Bruker AM-100). IR spectra were recorded on a Bruker Vector 22, mass spectra (EI, 70eV) on a MAT 312 instrument, and elemental analyses with a CHN-Rapid Heräus. Flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh).

6,7-Methylenedioxy-3-propylisocoumarin (1a, Xyridin A). A stirred mixture of 4,5-methylenedioxyhomophthalic acid **2** (0.25 g, 1.11 mmol) and butanoyl chloride (0.46 ml, 4.46 mmol) containing a few drops of dry pyridine was heated on an oil bath at 200°C for 20 h. Flash column chromatography of the residue (petroleum ether–ethyl acetate, 8:1) afforded **1a** (0.11 g, 45%) as yellow scales; mp 64-65°C (lit. [1] 67-88°C).

IR spectrum (KBr), ν, cm^{-1}: 3072, 2913, 2849, 1722, 1685, 1645, 1575, 1260, 1120, 935, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (3H, t, *J* = 7.2, H(3')); 1.67 (2H, tq, *J* = 7.2, *J* = 7.24, H(2')); 2.44 (2H, t, *J* = 7.0, H(1')); 6.09 (2H, s, OCH_2O); 6.15 (1H, s, H(4)); 6.70 (1H, s, H(5)); 7.59 (1H, s, H(8)). ^{13}C NMR spectrum, δ, ppm: 163.03 (C(1)), 157.41 (C(3)), 153.7 (C(7)), 148.3 (C(6)), 135.8 (C(8a)), 114.65 (C(4a)), 104.01 (C(5)), 103.20 (C(4)), 102.2 (OCH_2O); 35.71 (C(1')), 20.86 (C(2')), 13.51 (C(3')). EIMS, *m/z* (*I*, %): 232 $[M]^+$ (79), 204 (14), 203 (77), 189 (17), 176 (76), 162 (23), 161 (12), 133 (37), 75 (24). Found, %: C 67.26; H 5.19. $C_{13}H_{12}O_4$. Calculated, %: C 67.23; H 5.21.

6,7-Methylenedioxy-3-(1-oxopropyl)isocoumarin (1b, Xyridin B). A stirred mixture of compound **2** (0.25 g, 1.11 mmol) and 2-oxobutanoyl chloride (0.53 g, 4.46 mmol) containing a few drops of dry pyridine was heated on an oil bath at 200°C for 4 h. Flash chromatography of the residue (petroleum ether–ethyl acetate, 15:1) afforded **1b** (0.16 g, 58%) as scales; mp 188-190°C (lit. [1] 198-199°C). IR spectrum (KBr), ν, cm^{-1}: 3084, 2913, 2849, 1728, 1685, 1645, 1575, 1260, 1120, 935, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.2, H(3')); 3.01 (2H, q, *J* = 7.2, H(2')); 6.20 (2H, s, OCH_2O); 7.10 (1H, s, H(5)); 7.30 (1H, s, H(4)); 7.38 (1H, s, H(8)). ^{13}C NMR spectrum, δ, ppm: 195.3 (C(1'), C=O), 161.03 (C(1)), 149.41 (C(3)), 154.0 (C(7)), 151.0 (C(6)), 132.8 (C(8a)), 118.65 (C(4a)), 109.10 (C(4)), 106.41 (C(5)), 102.8 (OCH_2O), 31.86 (C(2')), 7.51 (C(3')). EIMS, *m/z* (*I*, %): 246 $[M]^+$ (68), 189 (20), 162 (19), 161 (16), 133 (100), 75 (24). Found, %: C 63.29; H 4.16. $C_{13}H_{10}O_5$. Calculated, %: C 63.42; H 4.09.

4,5-Methylenedioxy-2-(2-oxopentyl)benzoic Acid (3). A stirred solution of xyridin **A** (**1a**) (0.095 g, 0.40 mmol) in ethanol (10 ml) was treated with 5% KOH (20 ml) and the mixture refluxed for 4 h. After cooling the reaction mixture, cold water (10 ml) was added and the mixture acidified with diluted hydrochloric acid and immediately extracted with dichloromethane (2 × 30 ml). The organic phase was dried ($MgSO_4$) and the solvent evaporated under vacuum to leave **3** as a yellowish solid. Recrystallized from petroleum ether–ethyl acetate (0.066 g, 70%); mp 104-106°C. IR spectrum (KBr), ν, cm^{-1}: 3011, 2949, 1715, 1694, 1601, 1202, 1162. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 6.02, H(3')); 1.44 (2H, br. m, H(2')); 1.75 (2H, br. m, H(1')); 2.38 (2H, br. m, H(1') open chain); 2.91 (1H, br. m, H(4) lactol); 3.10 (1H, br. m, H(4) lactol); 3.94 (2H, br. m, H(4) open chain); 6.17 (2H, s, OCH_2O); 6.73 (1H, s, H(5)); 7.65 (1H, s, H(8)); 11.22 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 195.54 (C(3), C=O), 168.30 (COOH), 57.70 (C(4)), 153.9 (C(7)), 148.3 (C(6)), 104.43 (C(8a)), 112.90 (C(5)), 102.2 (OCH_2O), 42.99 (C(1')), 19.73 (C(2')), 13.80 (C(3')). EIMS, *m/z* (*I*, %): 250 $[M]^+$ (11.45), 232 (80.1), 203 (11.61), 179 (41.43), 134 (100). Found, %: C 62.23; H 5.67. $C_{13}H_{14}O_5$. Calculated, %: C 62.39; H 5.64. (In order to avoid confusion and for direct comparison C/H numbering is the same as in isocoumarins **1a**,**b**.)

(±)-6,7-Methylenedioxy-3-*n*-propyl-3,4-dihydroisocoumarin (4). Sodium borohydride (0.67 g, 18 mmol) was added portionwise to a stirred solution of compound **3** (0.05 g, 0.21 mmol) in ethanol (10 ml) and water (30 ml). The reaction mixture was stirred for 4 h at room temperature, diluted with water (50 ml), acidified with conc. HCl, and stirred for a further 2 h. It was then saturated with ammoniunm sulfate and extracted with EtOAc (3 × 30 ml). The layers were separated and the organic layer dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether–ethyl acetate, 7:1) afforded **4** as light yellow prisms (0.16 g, 85%); mp 54-57°C. IR spectrum (KBr), ν, cm^{-1}: 2960, 2853, 1720, 1604, 1583, 1464, 1198, 1085, 840. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 7.3, H(3')); 1.64 (1H, m, $H(2_A')$); 1.71 (1H, m, $H(2_B')$); 1.71 (1H, dddd, *J* = 13.5, *J* = 10.2, *J* = 7.4, *J* = 5.2, $H(1_A')$); 1.87 (1H, dddd, *J* = 13.5, *J* = 10.8, *J* = 5.0, *J* = 5.0, $H(1_B')$); 2.85 (1H, dd, J_{gem} = 16.3, J_{trans} = 4.0, H(4)); 2.96 (1H, dd, J_{gem} = 16.5, J_{cis} = 11.11, H(4)); 4.48 (dddd, *J* = 10.5, *J* = 7.6, *J* = 5.4, *J* = 4.6, H(3)); 6.14 (2H, s, OCH_2O); 6.74 (1H, s, H(5)); 7.59 (1H, s, H(8)). ^{13}C NMR spectrum, δ, ppm: 162.46 (C(1)), 76.71 (C(3)), 36.03 (C(4)), 114.92 (C(4a)), 106.05 (C(5)), 147.7 (C(6)), 154.2 (C(7)), 107.30 (C(8)), 134.90 (C(8a)), 32.71 (C(1')), 18.10 (C(2')), 13.80 (C(3')). EIMS, *m/z* (*I*, %): 234 $[M]^+$ (36), 232 (41), 163 (31), 162 (100), 191 (29), 134 (65). Found, %: C 66.59; H 6.09. $C_{13}H_{14}O_4$. Calculated, %: C 66.66; H 6.02.

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REFERENCES

1. N. Ruangrungsi, T. Sekine, T. Phadungcharoen, S. Suriyagan, and I. Murakoshi, *Phytochemistr*y, **38**, 481 (1995).
2. V. H. Belgaonkar and R. N. Usgaonkar, *J. Chem. Soc.*, *Perkin Trans. 1*, 702 (1977).
3. J. N. Srivasta and D. N. Chaudhury, *J. Org. Chem.*, **27**, 4337 (1962).
4. B. H. Bhide and K. K. Shah, *Indian J. Chem.*, **19B**, 9 (1980).
5. J. Katakawa, H. Meguri, and H. Irie, *Heterocycles*, **22**, 2213 (1984).
6. R. C. Thompson and J. Kallmerten, *J. Org. Chem.*, **55**, 6076 (1990).
7. H. Paulsen and M. Stubbe, *Liebigs Ann. Chem.*, 535 (1983).
8. T. K. Park and S. J. Danishefsky, *Tetrahedron Lett*., **36**, 195 (1995).
9. G. E. Keck, S. F. McHardy and J. A. Murry, *J. Am. Chem. Soc.*, **117**, 7289 (1995).
10. M. M. Abelman, L. E. Overman and V. D. Tran, *J. Am. Chem. Soc.*, **112**, 6959 (1990).
11. J. J. Fitzgerald, A. R. Pagano, V. M. Sakoda and R. A. Olofson, *J. Org. Chem.*, **59**, 4117 (1994).
12. N. H. Rama, A. Saeed and C. W. Bird, *Liebigs Ann. Chem*., 1331 (1993).
13. N. H. Rama, A. Saeed and C. W. Bird, *Liebigs Ann. Chem*., 711 (1995).
14. A. Saeed and N. H. Rama, *J. Chem. Soc. Pak.*, **16**, 220 (1994).
15. A. Saeed and N. H. Rama, *Arabian J. Sci. Eng.*, **21**, 403 (1996).
16. N. H. Rama, R. Iqbal, Kh. Zamani, A. Saeed**,** M. Z. Iqbal, and M. I. Chaudary, *Indian J. Chem.*, **37B**, 365 (1998).
17. K. Nozawa, M. Yamada, Y. Tsuda, K. I. Kawai, and S. Nakajima, *Chem. Pharm. Bull*., **29**, 2491 (1981).
18. K. Nozawa, M. Yamada, Y. Tsuda, K. I. Kawai, and S. Nakajima, *Chem. Pharm. Bull*., **29**, 3486 (1981).
19. H. Kaji, M. Yamada, K. Nozawa, K. I. Kawai, and S. Nakajima, *Org. Prep. Proced. Int.*, **18**, 253 (1986).
20. T. Kanda, S. Kato, T. Sugino, N. Kambe, A. Oganawa, and N. Sonoda, *Synthesis*, 1102 (1995).
21. J. K. Kendall, T. H. Fisher, H. P. Schultz, and T. P. Schultz, *J. Org. Chem.*, **54**, 6076 (1989).
22. D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, 4th Ed., McGraw-Hill, UK, 1987, p. 88.
23. D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc.*, *Perkin Trans. 1*, 1674 (1977).