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AROMATIC Vs DIENE REACTIVITY OF 2(1H)-PYRIDINONE AND ITS DERIVATIVES

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Abstract: The reaction of 2(1H)-pyridinone and some of its derivatives with substituted propynenitriles was studied. The aromatic character of 1-methyl-2(1H)-pyridinone is reflected in its failure to give a 4+2 adduct. Instead, reaction occurs at lactam carbonyl function to give 1,2-dihydropyridine-2-methides. The O-methyl derivatives are dealkylated during reaction with propynenitriles to give N-substituted pyridones which are otherwise accessible in good yields from 2(1H)-pyridinone.

The interest in the chemistry of 2(1H)-pyridinone centres around the aromatic character exhibited by this molecule. Elvidge and Jackman[1] have estimated from NMR studies that 1-methyl-2(1H)-pyridinone has 36% of the aromaticity of benzene. The initial reports[2] on the failure to detect the formation of Diels-Alder adduct were attributed to the aromatic character of the pyridinone but subsequently several reports[3] describing the cycloaddition with both olefinic and acetylenic dienophiles have appeared. Judging from the yields and the experimental conditions employed, it may be concluded that the diene function in 2(1H)-pyridinone is a reluctant participant in the 4+2 cycloaddition reaction. The cycloaddition reaction of 2(1H)-pyridinone with acetylenic dienophiles[3,4] is of special interest in view of its utility in the preparation of 2-azabarrelenone. In a preliminary communication[5] we have described the reaction of 1-methyl-2(1H)-pyridinone with 4-ethoxyphenylpropynenitrile. The formation of a Diels-Alder adduct was not observed. Instead a cycloaddition reaction involving the lactam carbonyl function lead to the formation of 1,2-dihydro-2-(4-ethoxybenzoyl-cyano-methylidene)-1-methyl-pyridine (compound 6 where R=4-ethoxyphenyl) the structure of which was confirmed by X-ray analysis. In the present study the reaction of 1-methyl-2(1H)-pyridinone and its derivatives containing substituents on the diene function with different propynenitriles is reported.

Theoretical calculations[6] have predicted that the presence of electron donor substituents on the diene function enhance the reactivity in 4+2 cycloaddition. This finds support from the study by Gisby[3] et al. on the steric and electronic effects on cycloaddition with different substituted pyridinones using DMAD as dienophile. They have obtained under relatively mild conditions the Diels-Alder adducts in high yields in the case of some substituted pyridinones. In an attempt to study the substituent effect we have selected two compounds namely 1-methyl-4-phenyl- 3b and 1,6-dimethyl-4-phenyl-2(1H)-pyridinone 3c which have given highest yields of Diels-Alder adducts with DMAD. The pyridinone 3b and 3c were synthesised by the methylation of the corresponding secondary lactams[7,8] 1b,c. The use of methyl iodide and sodium ethoxide in DMF gave

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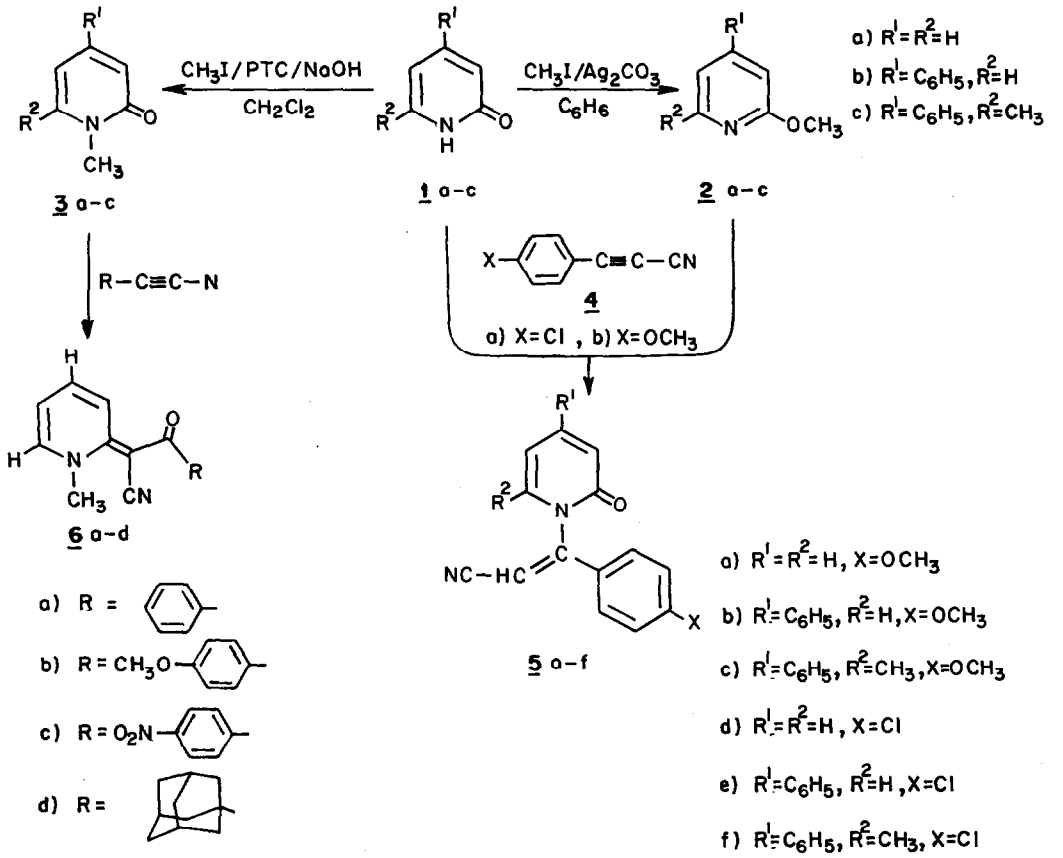

SCHEME

a mixture of N- and O-methyl derivatives. More authentic methods were then employed to prepare N- and O-methyl derivatives. The alkylation of lactams 1b,c with methyl iodide using in one case sodium hydroxide under phase transfer catalysis[9] and in the other silver carbonate[10] in dry benzene gave exclusively the N- and O-methyl derivatives respectively. During the course of this study we observed an interesting reaction between O-methyl derivatives and substituted propynenitriles and these results are also described here.

The reaction of 1-methyl- 3a, 1-methyl-4-phenyl- 3b and 1,6-dimethyl-4-phenyl-2(1H)-pyridinone 3c with different substituted propynenitriles was carried out under identical conditions used in the case of DMAD. However, no reaction was observed under these conditions. The reactions were then carried out in neat phase in a sealed tube at 110°. 1-Methyl-4-phenyl- 3b and 1,6-dimethyl-4-phenyl-2(1H)-pyridinone 3c did not undergo any reaction. However, 1-methyl-2(1H)-pyridinone 3a reacted with phenyl-, 4-nitrophenyl-, 4-methoxyphenyl- and adamantane-1-yl-propynenitrile to give the corresponding 1,2-dihdyro-pyridine-2-methide derivatives 6a-d (see Scheme) which were isolated in trace yields and characterised. It appears that the case of substituted propynenitrile is different

from that of DMAD and the failure to detect the Diels-Alder reaction may be attributed to the aromatic character of 1-methyl-2(1H)-pyridinone and also to the large energy gap[11] between the HOMO (diene) and LUMO (dienophile).

The reaction of the O-methyl derivatives 2a-c with substituted propynenitrile gave a product in very low yield. Spectral analysis showed that it contains a tertiary amide function and the methyl group is lost. A detailed study using 4-chlorophenyl- 4a and 4-methoxyphenyl-propynenitrile 4b revealed that 2-methoxypyridines 2a-c add to the former resulting in the transformation of the imidate function into a N-substituted 2(1H)-pyridinone of type 5. The structures of 5a-f were confirmed by an independent synthesis involving the reaction between the corresponding secondary lactam 1 and propynenitrile 4.

The two isomers 1-methyl-2(1H)-pyridinone and 2-methoxypyridine exhibit contrasting reactivity towards substituted propynenitrile. In the former the reaction appears to take a course in which the first step can be formulated as a nucleophilic attack by the oxygen of the lactam carbonyl on the propynenitrile. The dipolar resonance contributing structure of 1-methyl-2(1H)-pyridinone (which accounts for the high dipole moment[12]) lends support to this assumption. Whether or not this leads to the formation of an oxete[5] intermediate, it results ultimately in the transfer of oxygen to give a pyridonemethide. The methyl group on the ring nitrogen remains intact. The reaction pathway is likely to involve energetically unfavourable intermediates, but it seems relatively favoured over a Diels-Alder reaction. 2-Methoxypyridine is aromatic and examples of its participation in 4+2 cycloaddition are not known so far. But the formation of N-substituted 2(1H)-pyridinones in the reaction between the respective pyridines 2a-c and propynenitrile 4a,b was not anticipated, as this amounts to the transformation of an aromatic pyridine ring into a pyridinone. However, chemical reactivity is not a measure of aromaticity[13]. The basic nature of the pyridine nitrogen and the electrophilic character of propynenitrile complement each other to bring about a reaction to form a zwitterionic intermediate which would then suffer the loss of methyl group present on oxygen. The vinyl carbanion centre then picks up a proton probably from the medium. The cleavage of methyl group in 2-methoxypyridine finds a parallel in its thermal rearrangement[14] to 1-methyl-2(1H)-pyridinone.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian FX-80A FT instrument in chloroform-d using TMS as internal standard. The IR and mass spectra were recorded on a Beckmann IR and a VG micromass 70-70H spectrometers respectively. Melting points reported are not corrected.

I. **Preparation of acetylenic nitriles:** The acetylenic nitriles were prepared via the intramolecular Wittig reaction of the oxo-substituted phosphoranes[15,16].

II. **Preparation of 2(1H)-pyridinones 1a-c:** The parent compound 1a and its 4-phenyl derivative 1b were prepared as described in literature[7,17]. The preparation of 6-methyl-4-phenyl derivative 1c from benzoylacetonitrile and acetone using polyphosphoric acid was reported in the literature[8]. We followed the same procedure but restricting the quantity of polyphosphoric acid (85%) to 50 g per 0.025 mole of the reactants.

III. **Preparation of 1-methyl-2(1H)-pyridinones 3a-c:** 1-methyl-2(1H)-pyridinone 3a was prepared from pyridine as described in literature[18]. 4-Phenyl- 1b and 6-methyl-4-phenyl-2(1H)-pyridinone 1c were N-methylated under phase transfer conditions using methyl iodide, sodium hydroxide and tetra-n-butyl-ammonium hydrogensulfate following a reported procedure[9].

IV. **Preparation of 2-methoxypyridines 2a-c:** Compound 2a was prepared from 2-chloropyridine as described in literature[19]. The methylation of lactams 1b-c using methyl iodide and silver carbonate in benzene as per procedure reported in the literature[10] gave the corresponding 2-methoxypyridines. The products were isolated by column chromatography over silica gel using first hexanes as eluent and progressively increasing the polarity by addition of ethyl acetate upto 10%.

a) 2-Methoxy-4-phenyl-pyridine 2b: Colourless liquid; yield: 68%; HRMS: found M^+ at m/e 185.0839 (calcd. for $C_{12}H_{11}NO$ 185.0841); IR ($CHCl_3$) ν_{max}: 3060, 3030, 2980, 2950, 2860, 1615 and 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 4.02(s,3H), 6.93(dd, 1H), 7.05(dd, 1H), 7.25-7.68(m, 5H), 8.18(dd, 1H).

b) 2-Methoxy-6-methyl-4-phenyl-pyridine 2c: Colourless liquid; yield: 65%; HRMS: found M^+ at m/e 199.0999 (calcd. for $C_{13}H_{13}NO$ 199.0998); IR ($CHCl_3$) ν_{max}: 3060, 3032, 2982, 2950, 2860, 1615 and 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 2.35(s, 3H), 4.0(s, 3H), 6.74(s, 1H), 6.94(s, 1H), 7.30-7.60(m, 5H).

V. **Reaction of 1-methyl-2(1H)-pyridinone with acetylenic nitriles:** Equimolar amounts (0.01 mole) of pyridone and the acetylenic nitrile 4 were taken in a thick walled pyrex tube, degassed with nitrogen and sealed. The sealed tube was heated at 110° for 110 hrs, cooled and the reaction mixture was dissolved in chloroform and chromatographed over silica. The elution was carried out first with 200 ml of mixture containing petroleum ether (60-80°) and ethyl acetate in 2:1 ratio, then with 200 ml ethyl acetate and finally with a mixture containing ethyl acetate and methanol in 2:1 ratio. Unreacted acetylenic nitrile eluted first. This is followed by unreacted pyridone. The subsequent greenish yellow coloured fractions contain the reaction product and this is further purified by repeated chromatography over silica gel using acetonitrile as eluent and isolated as yellow microcrystalline powder in 4-10% yield. The data on the individual compounds are given below.

a) 1,2-Dihydro-2-benzoyl-cyanomethylidene-1-methyl-pyridine 6a: m.p.: 163°; HRMS: found M^+ at m/e 236.0939 (calcd. for $C_{15}H_{12}N_2O$ 236.0949); IR ($CHCl_3$) ν_{max}: 2170, 1630, 1588 and 1565 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ ppm: 186(s, -C=O), 124.2(s, -CN), 73(s, methide C), 46.5(q, N-CH_3), the signals for the pyridine ring appear at 157.6(s, C_2), 141.8(d, C_6), 138.9(d, C_4), 127.5(d, C_3), 118.1(d, C_5), the phenyl ring carbons gave signals at 140.3(s, for tertiary C), 130.2 (d, for para C) and 127.7(d, for carbons at ortho and meta position).

b) 1,2-Dihydro-2-(4-methoxybenzoyl-cyanomethylidene)-1-methyl-pyridine 6b: m.p.: 149°; HRMS: found M^+ at m/e 266.1055 (calcd. for $C_{16}H_{14}N_2O_2$ 266.1055); IR ($CHCl_3$) ν_{max}: 2177, 1630, 1606, 1587 and 1563 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ ppm: 185.6(s, -C=O), 124.8(s, -CN), 73.2(s, methide C), 46.8(q, N-CH_3), the signals for the pyridine ring appear at 158.3(s, C_2), 141.9(d, C_6), 138.7(d, C_4), 127.6(d, C_3), 117.8(d, C_5), the signals for paramethoxyphenyl group appear at 161.6(s), 132.8(s), 130.2(d), 113.2(d), 55.3(q).

c) 1,2-Dihydro-2-(4-nitrobenzoyl-cyanomethylidene)-1-methyl-pyridine 6c: m.p.: 198-199°; HRMS: found M^+ at m/e 218.0800 (calcd. for $C_{15}H_{11}N_3O_3$ 281.0801); IR ($CHCl_3$) ν_{max}: 2178, 1630, 1605

and 1580 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ ppm: 184(s, -C=O), 124.3(s, -CN), 73.9(s, methide C), 47.2(q, N-CH_3), the signals for the pyridine ring appear at 157.9(s, C_2), 141.8(d, C_6), 139.6(d, C_4), 128.7 (d, C_3), 119.1(d, C_5), the signals for paranitrophenyl group appear at 148.7(s), 146.2(s), 129.2(d), 123.3(d).

d) 1,2-Dihyro-2-(adamantane-1-carbonyl-cyanomethylidene)-1-methyl-pyridine 6d: m.p.: 167°; HRMS: found M^+ at m/e 294.1725 (calcd. for $C_{19}H_{22}N_2O_2$ 294.1733); IR ($CHCl_3$) ν_{max}: 2167, 1630 and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.76(s, 6H), 2.16(s, 9H), 3.80(s, 3H), 6.98(t, 1H), 7.58-8.02(m,3H); ^{13}C NMR ($CDCl_3$) δ ppm: 196.9(s, -C=O), 71.4(s, methide C), 46.9(q, N-CH_3), the signals for the pyridine ring appear at 160.5(s, C_2), 141.2(d, C_6), 137.9(d, C_4), 129(d, C_3), 117.4(d, C_5), the signals for adamantane group appear at 45.4(s), 38.9(t), 36.8(t), 28.8(d), the signal for the nitrile merges with the noise.

VI. **Reactions of 2(1H)-pyridinone with acetylenic nitriles:** 0.01 mole of 2(1H)-pyridinone and equimolar amount of the corresponding acetylenic nitrile were taken in 10 ml of freshly distilled dimethylformamide. The mixture was stirred and heated at 90-100° for 6 hrs in case of 2(1H)-pyridinone and 16 hrs in the case of substituted derivatives. The mixture was poured in water and extracted with dichloromethane. The dichloromethane was washed with water and dried over magnesium sulphate. The residue obtained after removal of the solvent was chromatographed over silica gel using first pure hexanes as eluent and progressively increasing polarity by addition of ethyl acetate. The final elution was done with 30% ethyl acetate in hexanes. The initial fractions gave the unreacted acetylenic nitrile followed by the addition products. The physical characteristics of the individual adducts are given below.

a) 1-[2-Cyano-1-(4-methoxyphenyl)-ethenyl]-2(1H)-pyridinone 5a: m.p.:116°; yield: 71%; HRMS: found M^+ at m/e 252.0894 (calcd. for $C_{15}H_{12}N_2O_2$ 252.0899); IR ($CHCl_3$) ν_{max}: 2215(-CN), 1660 (-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 3.9(s, 3H), 5.92(s, 1H), 6.33(m, 1H), 6.66(dd, 1H), 6.88(q, 2H), 7.06-7.43(m, 3H), 7.53(dd, 1H).

b) 1-[2-Cyano-1-(4-methoxyphenyl-ethenyl]-4-phenyl-2(1H)-pyridinone 5b: m.p.: 151°; Yield: 65%; HRMS: found M^+ at m/e 328.1214 (calcd. for $C_{21}H_{16}N_2O_2$ 328.1209); IR ($CHCl_3$) ν_{max}: 2215(-CN), 1660(-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 3.87(s, 3H), 5.98(s, 1H), 6.58(dd, 1H), 6.7-7.1(m, 3H), 7.16-7.85(m, 8H).

c) 1-[2-Cyano-1-(4-methoxyphenyl)-ethenyl]-6-methyl-4-phenyl-2(1H)-pyridinone 5c: m.p.: 144°; yield: 45%; HRMS: found M^+ at m/e 342.1369 (calcd. for $C_{22}H_{18}N_2O_2$ 342.1365); IR ($CHCl_3$) ν_{max}: 2215(-CN), 1660(-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 2.21(s, 3H), 3.86(s, 3H), 6.17(s, 1H), 6.45(br, 1H), 6.78(q, 2H), 6.96(br, 1H), 7.12-7.89(m, 7H).

d) 1-[2-Cyano-1-(4-chlorophenyl)-ethenyl]-2(1H)-pyridinone 5d: m.p.: 98.6°; yield: 64%; HRMS: found M^+ at m/e 256.0411 (calcd. for $C_{14}H_9{}^{35}ClN_2O$ 256.0404); IR ($CHCl_3$) ν_{max}: 2215(-CN), 1660(-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 6.08(s, 1H), 6.32(m, 1H), 6.65(dd, 1H), 7.06-7.46(m, 5H), 7.53(dd, 1H).

e) 1-[2-Cyano-1-(4-chlorophenyl)-ethenyl]-4-phenyl-2(1H)-pyridinone 5e: m.p.: 89.4°; yield: 67%; HRMS: found M^+ at m/e 332.0717 (calcd. for $C_{20}H_{13}{}^{35}ClN_2O$ 332.0713); IR ($CHCl_3$) ν_{max}: 2215 (-CN), 1660(-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 6.02(s, 1H), 6.58(dd, 1H), 6.81(d, 1H), 7.28-7.79 (m, 10H).

f) 1-[2-Cyano-1-(4-chlorophenyl)-ethenyl]-6-methyl-4-phenyl-2(1H)-pyridinone 5f: m.p.: 112°;

yield: 48%; HRMS: found M^+ at m/e 346.0879 (calcd. for $C_{21}H_{15}{}^{35}ClN_2O$ 346.0874); IR ($CHCl_3$) ν_{max} : 2215 (-CN), 1660 (-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm : 2.2(s, 3H), 6.25(s, 1H), 6.43(br, 1H), 6.72(br., 1H), 7.12-7.75(m, 9H).

VII. **Reactions of 2-methoxypyridine with acetylenic nitriles:** Equimolar amount of 2-methoxypyridine and the acetylenic nitrile were taken in a long tube fitted with a vacuum stop cock. Vacuum (1-2 Torr) was applied and the tube under vacuum was heated at 130-140° for 120 hrs. After cooling the reaction mixture was dissolved in minimum amount of methanol and the product isolated by column chromatography as described in VI. From each of the methoxypyridine the corresponding N-substituted 2(1H)-pyridinone was isolated. The yield did not exceed 10%.

NOTES & REFERENCES

1. Elvidge, J.A.; Jackman, M.L. **J.Chem.Soc. 1961**, 859-866.
2. Thyagarajan, B.S.; Rajagopal, R. **Tetrahedron. 1963**, 19, 1483-1484.
3. Gisby, G.P.; Royall, S.E.; Sammes, P.G. **J.Chem.Soc.Perkin I. 1982**, 169-173 and references cited therein.
4. a) Acheson, R.M.; Tasker, P.A. **J.Chem.Soc.(C) 1967**, 1542-1543; b) Sheinin, E.B.; Wright, G.E.; Bell, C.L.; Bauer, L. **J.Heterocyclic Chem. 1968**, 5, 859-862; c) Gompper, R.; Schmidt, A. **Angew.Chem.Int.Ed.Engl. 1980**, 19, 463-464; d) Matsumato, K.; Ikemi, V.; Nakamura, S.; Uchida, T.; Acheson, R.M. **Heterocycles 1982**, 19, 499-502.
5. Yadla, R.; Rao, J.M.; Acharya, K.R.; Tavale, S.S.; Guru Row, T.N. **Ind.J.Chem. 1984**, 23B, 1-2.
6. Sustmann, R. **Tetrahedron Lett. 1971**, 2721-2724.
7. Albrecht, O.; Frei, J.; Sallmann, R. **Helv.Chim.Acta. 1941**, 24, 233E-247E.
8. Hauser, C.R.; Eby, C.J. **J.Am.Chem.Soc. 1957**, 79, 728-731.
9. Barco, A.; Benetti, S.; Pollini, G.P. **Synthesis 1976**, 124-125.
10. Hopkins, G.C.; Jonak, J.P.; Minnemeyer, H.J.; Tieckelmann, H. **J.Org.Chem. 1967**, 32, 4040-4044.
11. Jemmis, E.D. Personal Communication. Extended Huckel Calculations have shown that the difference between the HOMO(1-methyl-2(1H)-pyridinone) LUMO (but-2-ynenitrile) is 2.98 eV.
12. Albert, A. **Heterocyclic Chemistry**, Athlone Press, London, **1959**, page 355.
13. Craig, D.P. In **Non-Benzenoid Aromatic Compounds**, Ginsberg, D.Ed.; Interscience Publishers Inc., New York, **1959**, Chapter I.
14. Boulton, A.J.; McKillop, A. In **Comprehensive Heterocyclic Chemistry**, Katritzky, A.R.; Rees, C.W.; Ed. , Pergamon Press, Oxford, **1984**, Vol.2, page 57.
15. Claisse, J.A.; Foxton, M.W.; Gregory, G.I.; Sheppard, A.H.; Tiley, E.P.; Warbarton, W.K.; Wilson, M.J. **J.Chem.Soc.Perkin I. 1973**, 2241-2249.
16. a) Yadla, R.; Rao, V.S.; Rao, J.M. **Ind.J.Chem. 1982**, 21B, 1046-1048; b) Yadla, R.; Rao, J.M. **Ind.J.Chem. 1988**, 27B, 1125-1127.
17. Cava, M.P.; Bhattacharya, N.K. **J.Org.Chem. 1958**, 23, 1287-1289.
18. Prill, E.A.; McElvain, S.M. **Org.Synthesis**, Coll.Vol.II **1943**, pp. 419-421.
19. Grave, T.B. **J.Am.Chem.Soc. 1924**, 46, 1460-1470.