A CONVENIENT SYNTHESIS OF 5-(4-PYRIDINYL)-2(1H)-PYRIDONES

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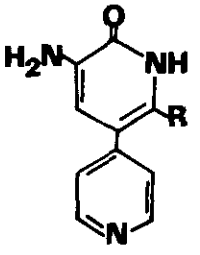
Abstract - A convenient synthesis of 3,4-bipyridine derivatives is reported. The addition of lithium salt derived from 2-alkoxy-5-bromopyridines 3a and 3b to N-ethoxycarbonylpyridinium chloride 4a gave the corresponding unstable 1,4-dihydropyridines which were readily oxidized by air to the 3,4′-bipyridines 6a and 6b. Compounds 6a and 6b can be converted into 5-(4-pyridinyl)-2(1H)-pyridones by hydrogenolysis and by alkylation in basic conditions.

The title compounds are potential synthetic precursors of amirinone 1[1] and mirinone 2[2,3]. These cardiotonic agents of considerable interests are normally prepared via the medifications of 4-substituted pyridines, such as 4-picoline[4,5], α-pyridylmalonaldehyde[6] and α-pyridylacrolein[6]. A convenient method for the preparation of pyridines with substituent at C-4 involves, as a key step, addition of lithium dialkylcuprates to pyridine in the presence of methyl chloroformate. This method has also been extensively studied by Akiba[7] and Comins[8] using similar conditions. We wish to report herein, a facile preparation of the title compounds by the addition of the lithium salt derived from 2-alkoxy-5-bromopyridines 3a[9] and 3b[10] to N-ethoxycarbonylpyridinium chloride 4a[7]. Bromopyridine 3a was treated with n-butyllithium (1.3 eq.) and a catalytic amount of 5% cuprous iodide in THF at -50°C for 1 h. Addition of this solution to a preformed solution of pyridinium salt 4 (1 eq.) in THF gave rise to the corresponding 1,4-dihydropyridine 5a which was found to be highly sensitive to air. On exposure to oxygen for 8 h, compound 5a was readily oxidized to give the crystalline 3,4′-bipyridine derivatives 6a[11,12], mp 60-61°C (hexane-dichloromethane), in an overall yield of 54%. Similarly, treatment of the lithium salt derived from bromopyridine 3b and compound 4a followed by oxidation of the resulting adduct 5b gave rise to 3,4′-bipyridine 6b[11], mp 104-106°C (hexane-dichloromethane), in 59% yield. We have also attempted the addition reactions using N-phenoxycarbonylpyridinium chloride 4b[13].

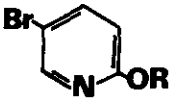
However, it was found that the yield of the desired product 6a and 6b were considerably lower than those obtained previously. In order to improve the aromatization of 5a→6a and 5b→6b, oxidants such as o-chloranil and sulfur were also used. These reagents were proved to be inferior to molecular oxygen.

Hydrogenolysis of benzyl derivative 6b in methanol using 5% palladium on charcoal gave directly the known pyridone 7a [mp 259-260°C(lit.,[14] 260-261°C)] in 64% yield along with partial recovery of 32% of the starting material. The conversion of compound 6a to the corresponding pyridone derivatives 7b and 7c was shown to be equally facile. The former compound 7b was readily produced in crystalline form [mp 216-218°C(methanol-dichloromethane)] in 58% yield. Compound 6a was subjected to treatment with potassium carbonate and methyl iodide in refluxing ethanol for 12 h[15]. Similarly, treatment of 6a with benzyl bromide and potassium carbonate resulted in the formation of the N-benzyl analog 7c, mp 262-264°C (hexane-ethyl acetate) in 84% yield.



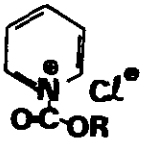
1 R=H

2 R=CH_3



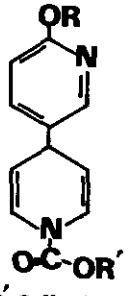
3a R=CH_3

3b R=$CH_2C_6H_5$



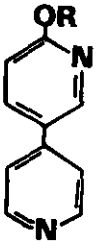
4a R=C_2H_5

4b R=C_6H_5



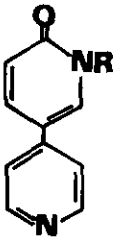
5a R'=C_2H_5 R =CH_3

5b R'=C_2H_5 R =$CH_2C_6H_5$



6a R=CH_3

6b R=$CH_2C_6H_5$



7a R=H

7b R=CH_3

7c R=$CH_2C_6H_5$

ACKNOWLEDGEMENT

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11. 6a:^{1}H nmr ($CDCl_3$) δ:4.00(S,3H,OCH_3), 6.86(d,1H,H-5), 7.45 and 8.64(AA'BB', 4H,J=6Hz,pyridine), 7.86(dd,1H,J=3Hz,9Hz,H-6), and 8.46(d,1H,J=3Hz,H-2). 6b:^{1}H nmr($CDCl_3$) δ:5.44(S,2H,CH_2ph),6.96(d,1H,J=9Hz,H-5), 7.25-7.60 (m,7H, pyridine 2H and aromatic 5H) and 7.82(dd,1H,J=3Hz,9Hz,H-6), 8.46(d,1H, J=3Hz,H-2), and 8.58(d,2H,J=6Hz, pyridine). 7a: ir(KBr) 1650cm^{-1}; ^{1}H nmr(DMSO-d_6+$CDCl_3$) δ:7.44(d,1H,J=9Hz,H-5), 8.51(dd,1H,J=3Hz,H-6). 8.36, and 8.87(AA'BB',4H,J=6Hz, pyridine),8.61(d,1H,J=3Hz,H-2). 7b:ir(KBr)1650cm^{-1}; ^{1}H nmr(DMSO-d_6+$CDCl_3$) δ:3.36(S,3H,N-CH_3), 7.08(d,1H,J=9Hz,H-5), 8.42(dd,1H, J=3Hz,9Hz,H-6), 8.55 and 9.04(AA'BB',4H,J=6Hz, pyridine), and 8.96(d,1H, J=3Hz, H-2). 7c:ir(KBr) 1645cm^{-1};^{1}H nmr(DMSO-d_6+$CDCl_3$) δ:5.28(S,2H,N-CH_2ph), 6.92(d,1H,J=9Hz,H-5), 7.20-7.60(m,5H, aromatic), 8.16(dd,1H,J=3Hz,9Hz,H-6), 8.63(d,1H, J=3Hz,H-2), 8.25 and 9.37(AA'BB',d,4H,J=6Hz, pyridine).
12. All Compounds gave correct molecular ions in mass spectrometry. All crystalline

compounds gave accepted elemental analysis.

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