

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

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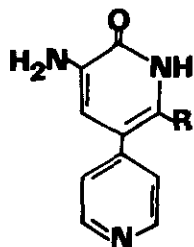
Nankang, Taipei, Taiwan, Republic of China 115

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 1¹ and mirinone 2^{2,3}. These cardiogenic agents of considerable interests are normally prepared via the modifications of 4-substituted pyridines, such as 4-picoline^{4,5}, α -pyridylmalonaldehyde⁶ and α -pyridylacrolein⁶. 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 Akiba⁷ and Comins⁸ 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 3a⁹ and 3b¹⁰ to *N*-ethoxycarbonylpyridinium chloride 4a⁷. 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 6b¹¹, mp 104-106°C (hexane-dichloromethane), in 59% yield. We have also attempted the addition reactions using *N*-phenoxycarbonylpyridinium chloride 4b¹³.

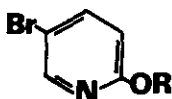
However, it was found that the yield of the desired product 6a and 6b were considerably lower than those obtained previously. In order to improve the aromatization of 5a→6a and 5b→6b, oxidants such as o-chloranil and sulfur were also used. These reagents were proved to be inferior to molecular oxygen.

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 h¹⁵. 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.



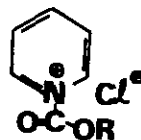
1 R=H

2 R=CH₃



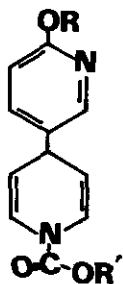
3a R=CH₃

3b R=CH₂C₆H₅



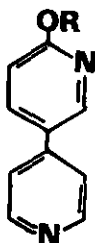
4a R=C₂H₅

4b R=C₆H₅



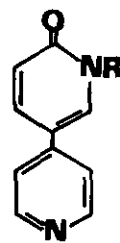
5a R'=C₂H₅ R=CH₃

5b R'=C₂H₅ R=CH₂C₆H₅



6a R=CH₃

6b R=CH₂C₆H₅



7a R=H

7b R=CH₃

7c R=CH₂C₆H₅

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. A. A. Alousi and J. Edelson, "Pharmacological and Biochemical Properties of Drug Substances", eds by M. E. Goldberg, American Pharmaceutical Association, Washington, D.C., 1982, Vol.3, P120.
2. A. A. Alousi, J. M. Canter, M. J. Montenegro, D. J. Fort and R. A. Aerrari, J. Cardiovasc. Pharmacol., 1983, 5, 792.
3. A. A. Alousi, J. P. Stankus, J. C. Stuart and I. H. Walton, J. Cardiovasc. Pharmacol., 1983, 5, 804.
4. S. M. Pedro, Span. E S 512, 599; Chem. Abstr., 1984, 100, 174671t.
5. B. Singh, Heterocycles, 1985, 23, 1479.
6. G. Y. Leshner and C. J. Opalka, U.S. Pat. 4,004,012; Chem. Abstr., 1977, 86, 189725e.
7. K. -Y. Akiba, Y. Iseki and M. Wada, Tetrahedron Lett., 1982, 23, 429.
8. L. Comins and H. Abdullah, J. Org. Chem., 1982, 47, 4315.
9. E. Spinner and J. C. B. White, J. Chem. Soc.(B), 1966, 991.
10. W. A. Lott and E. Shaw, J. Am. Chem. Soc., 1949, 71, 70.
11. 6a: ^1H nmr (CDCl_3) δ : 4.00(s, 3H, OCH_3), 6.86(d, 1H, H-5), 7.45 and 8.64(AA'BB', 4H, $J=6\text{Hz}$, pyridine), 7.86(dd, 1H, $J=3\text{Hz}$, 9Hz, H-6), and 8.46(d, 1H, $J=3\text{Hz}$, H-2).
6b: ^1H nmr (CDCl_3) δ : 5.44(s, 2H, CH_2Ph), 6.96(d, 1H, $J=9\text{Hz}$, H-5), 7.25-7.60 (m, 7H, pyridine 2H and aromatic 5H) and 7.82(dd, 1H, $J=3\text{Hz}$, 9Hz, H-6), 8.46(d, 1H, $J=3\text{Hz}$, H-2), and 8.58(d, 2H, $J=6\text{Hz}$, pyridine). 7a: ir(KBr) 1650cm^{-1} ; ^1H nmr($\text{DMSO}-d_6+\text{CDCl}_3$) δ : 7.44(d, 1H, $J=9\text{Hz}$, H-5), 8.51(dd, 1H, $J=3\text{Hz}$, H-6), 8.36, and 8.87(AA'BB', 4H, $J=6\text{Hz}$, pyridine), 8.61(d, 1H, $J=3\text{Hz}$, H-2). 7b: ir(KBr) 1650cm^{-1} ; ^1H nmr($\text{DMSO}-d_6+\text{CDCl}_3$) δ : 3.36(s, 3H, N-CH_3), 7.08(d, 1H, $J=9\text{Hz}$, H-5), 8.42(dd, 1H, $J=3\text{Hz}$, 9Hz, H-6), 8.55 and 9.04(AA'BB', 4H, $J=6\text{Hz}$, pyridine), and 8.96(d, 1H, $J=3\text{Hz}$, H-2). 7c: ir(KBr) 1645cm^{-1} ; ^1H nmr($\text{DMSO}-d_6+\text{CDCl}_3$) δ : 5.28(s, 2H, $\text{N-CH}_2\text{Ph}$), 6.92(d, 1H, $J=9\text{Hz}$, H-5), 7.20-7.60(m, 5H, aromatic), 8.16(dd, 1H, $J=3\text{Hz}$, 9Hz, H-6), 8.63(d, 1H, $J=3\text{Hz}$, H-2), 8.25 and 9.37(AA'BB', d, 4H, $J=6\text{Hz}$, pyridine).
12. All Compounds gave correct molecular ions in mass spectrometry. All crystalline

compounds gave accepted elemental analysis.

13. D. L. Comins, Tetrahedron Lett., 1983, 24, 2807.
14. G. Y. Leshner and C. J. Opalka, Jr., U.S. Pat. 4,072,746; Chem. Abstr., 1979, 90, 103844r.
15. M. -J. Shiao, T. Y. R. Tsai and K. Wiesner, Heterocycles, 1981, 16, 1879;
M. -J. Shiao, J. Org. Chem., 1982, 47, 5189.

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