

SYNTHESIS OF MILRINONE, A CARDIOTONIC AGENT

Min-Jen Shiao* and Li-Ming Shyu
 Institute of Chemistry, Academia Sinica
 Nankang, Taipei, Taiwan, Republic of China

Chieh-Fu Chen
 National Research Institute of Chinese Medicine
 Taipei Hsien, Taiwan, Republic of China

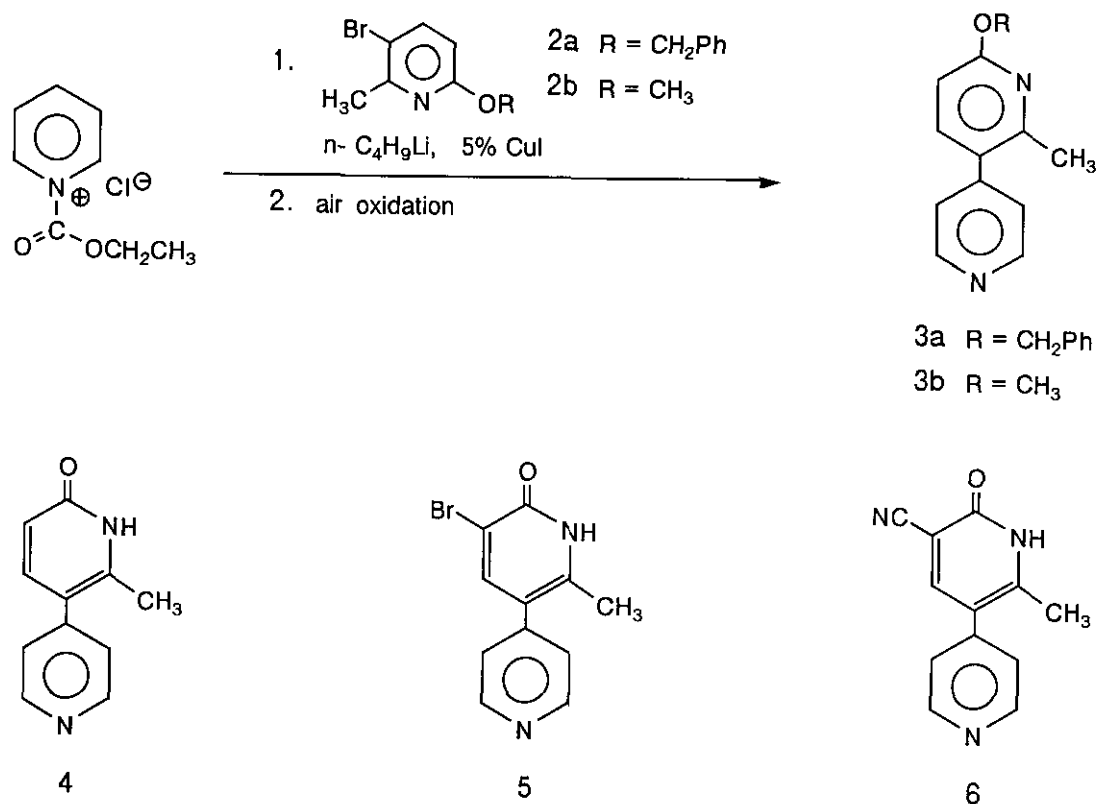
Abstract- A new synthesis of milrinone (6) from 6-methyl-5-(4-pyridinyl)-2(1H)-pyridone (4) is reported. A convenient synthesis of 3,4'-bipyridines (3a) and (3b) is achieved. 3a and 3b can be converted into pyridone 4 by hydrogenolysis and hydrolysis, respectively. Bromination at C-3 of the pyridone ring of 4 followed by cyanation affords milrinone (6).

Milrinone, 1,6-dihydro-2-methyl-6-oxo-(3,4'-bipyridine)-5-carbonitrile (6), a potent novel cardiotonic agent, is undergoing clinical investigation.^{1,2} It has been synthesized by the condensation of cyanoacetamide with 4-(dimethylamino)-3-(4-pyridyl)-3-buten-2-one in the presence of a base³ or the reaction of 1-(4-pyridyl)-2-propanone with ethoxymethylenemalononitrile.⁴ Recently in our laboratory, we have developed a method to prepare 3,4'-bipyridine derivatives by the addition of the lithium salt derived from 2-alkoxy-5-bromopyridine to N-ethoxycarbonylpyridinium chloride(1)^{5,6} and we have also applied it to the synthesis of amrinone, a cardiotonic agent.⁷ Here we report an application of this synthetic method to the synthesis of milrinone (6).

2-Benzyloxy-5-bromo-6-methylpyridine⁸ (2a) was treated with n-butyllithium (1.2 eq.) and a catalytic amount of 5% CuI in THF at -78 °C for 1 h. Addition of this solution to a preformed solution of N-ethoxycarbonylpyridinium chloride⁹ (1) (1 eq.) in THF gave the corresponding unstable 1,4-dihydropyridine which was oxidized in oxygen for overnight to give the 3,4'-bipyridine derivative 3a in 54% yield. Similarly, treatment of the lithium salt derived from 5-bromo-2-methoxy-6-methylpyridine⁸ (2b) with compound 1 followed by oxidation of the resulting 1,4-dihydropyridine gave rise to 3,4'-bipyridine (3b) in 51% yield.

Hydrogenolysis of the 3,4'-bipyridine (3a) in MeOH in the presence of 10% palladium on charcoal gave directly the pyridone compound 4 in 91% yield.³ Its spectrum showed a carbonyl band at 1643 cm⁻¹. Subsequently, we carried out

bromination of compound 4 using N-bromosuccinimide in MeOH and obtained the 3-bromopyridone compound 5, in 82% yield. Compound 5 showed a carbonyl absorption at 1656 cm^{-1} . The ms spectrum gave the molecular ion peaks at m/z 264 and 266 with a relative intensity of 100:96, which provide proof of the presence of a bromo-substituent. Treatment of compound 5 with "Naked" cyanide reagent¹⁰ in acetonitrile in the presence of catalytic amount of 18-Crown-6 gave 6 in 62% yield. Ir spectrum indicated the absorptions of a nitrile group at 2221 cm^{-1} and a carbonyl group at 1662 cm^{-1} , respectively. The ^1H nmr and mass spectra are in full agreement with milrinone. 2-Methoxy-3,4'-bipyridine (3b) was also converted to 4 in 82% yield by heating with 48% HBr in MeOH for 50 h. Thus, we achieved the synthesis of milrinone (6) via 6-methyl-5(4-pyridyl)-2(1H)-pyridone (4) from 6-alkoxy-2-methyl-3,4'-bipyridines (3a) or (3b) by a three-steps process.



ACKNOWLEDGEMENT

We thank the National Science Council of the Republic of China for financial support.

EXPERIMENTAL

Melting points are uncorrected. The ^1H -nmr spectra were recorded on a Bruker AW 80 and MSL 200 spectrometers. The ms spectra were measured with a Hewlett-Packard 5995 GC/MS system at 70 ev. The ir spectra were measured with a Perkin-Elmer 882 spectrophotometer. The elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer.

6-Benzoyloxy-2-methyl-3,1'-bipyridine (3a).

To a stirred solution of 2-benzoyloxy-5-bromo-6-methylpyridine⁸ (2a) (5.56 g, 20 mmol) in 80 ml of dry THF were added n-BuLi in hexane (15.5 ml, 24 mmol) and 0.19g of 5% CuI at -78°C under nitrogen for 1 h. The above solution was added to a preformed solution of pyridinium chloride (1) (from 2 ml of pyridine, 2.6 ml of ethyl chloroformate, 140 ml of THF at -25°C for 0.5 h) at -78°C over 3 h. The reaction mixture was warmed to room temperature and quenched by 5% NaHCO_3 solution (60 ml). After evaporation of THF the residue was stirred under an oxygen stream for overnight. The reaction mixture was extracted with ether, and the organic extracts were washed with water, and dried over anhydrous Na_2SO_4 . After evaporation under reduced pressure, the residue was purified by column chromatography on a silica gel (hexane- CH_2Cl_2 , 3:1) and then was recrystallized from hexane- CH_2Cl_2 to give 2.98 g (54%) of 3a, mp $83.5\text{--}84.5^\circ\text{C}$. Ir (KBr) : 3046, 2982, 1598, 1495 cm^{-1} ; ^1H -nmr (CDCl_3) : δ 2.45 (s, 3H, CH_3), 5.43 (s, 2H, benzylic H), 6.72 (d, $J = 8.4$ Hz, 1H, H-5), 7.41 (m, 7H, aromatic 5H and pyridine 2H), 7.49 (d, $J = 8.4$ Hz, 2H, H-4), 8.65 (AA'BB', $J=8.0, 2.0$ Hz, 2H, pyridine 2H); ms : m/z (relative intensity) 276 (M^+ , 14), 91 (100). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$: C, 78.23; H, 5.84; N, 10.14. Found : C, 78.24; H, 5.83; N, 10.10.

6-Methoxy-2-methyl-3,4'-bipyridine (3b).

5-Bromo-2-methoxy-6-methylpyridine⁸ (2b) (5.0 g) was reacted under the same condition as above to give 2.45 g (51%) of 3b, mp $64\text{--}66^\circ\text{C}$ (hexane- CH_2Cl_2). Ir

(KBr) : 3042, 1598, 1495 cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) : δ 2.45 (s, 3H), 3.97 (s, 3H, CH_3), 6.67 (d, $J = 8.4$ Hz, 1H, H-5), 7.43 (d, $J = 8.4$ Hz, 1H, H-4), 7.25 and 8.65 (AA'BB', $J=8.0$, 2.0 Hz, 4H, pyridine 4H); ms: m/z (relative intensity) 200 (M^+ , 85), 199 (100), 171 (32), 171 (25), 169 (37). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$: C, 71.98; H, 6.04; N, 13.99. Found : C, 72.14; H, 5.94; N, 13.88.

6-Methyl-5-(4-pyridinyl)-2(1H)-pyridone (4).

A mixture of compound **3a** (1 g, 3.6 mmol) and 10% Pd/C (0.10 g) in 30 ml of methanol was hydrogenated for 2 h, then filtered and concentrated in vacuum. The residue was purified by column chromatography on a silica gel (5% $\text{MeOH-CH}_2\text{Cl}_2$) and was recrystallized from methanol- CH_2Cl_2 to give 0.61 g (91%) of **4**, mp 288-289°C (lit.³ mp 287-288°C). Ir (Nujol) : 1643, 1597, 1455, 1376 cm^{-1} ; $^1\text{H-nmr}$ ($\text{CD}_3\text{OD} + \text{CDCl}_3$) : δ 2.36 (s, 3H, CH_3), 6.52 (d, $J = 9.2$ Hz, 1H, H-5), 7.51 (d, $J = 9.2$ Hz, 1H, H-4), 7.35 and 8.59 (AA'BB', $J=8.0$, 2.0 Hz, 4H, pyridine 4H), 12.87 (br s, 1H, NH); ms: m/z (relative intensity) 186 (M^+ , 21.9), 146 (53.4), 117 (47.4), 104 (22.4), 91 (100). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$: C, 70.95; H, 5.41; N, 15.05. Found : C, 70.89; H, 5.38; N, 15.01.

From (**3b**).

To a solution of compound **3b** (0.51 g, 2.5 mmol) in 10 ml of methanol, were added 17.5 ml of 48% HBr. The reaction mixture was refluxed for 50 h. 5% Sodium bicarbonate was added and the mixture was extracted with dichloromethane. The organic extracts were washed with water and dried over anhydrous Na_2SO_4 . After evaporation under reduced pressure, 0.38 g (82%) of **4** were obtained. Compound **4** was identified with that prepared from **3a** by its nmr and mp.

3-Bromo-6-methyl-5-(4-pyridinyl)-2(1H)-pyridone (5).

A mixture of **4** (0.44 g, 2.38 mmol) and N-bromosuccinimide (0.63 g, 3.6 mmol) in 30 ml of methanol was stirred at room temperature for 5 h, then filtered and concentrated in vacuum. Purification of the residue by column chromatography on a silica gel (5% $\text{MeOH-CH}_2\text{Cl}_2$) and was recrystallized from MeOH to give 0.52 g (82%) of **5**, mp 253-255°C (lit.³ mp 252-254°C). Ir (Nujol) : 1656, 1600, 1458 cm^{-1} ; $^1\text{H-nmr}$ ($\text{CD}_3\text{OD} + \text{CDCl}_3$) : δ 3.32 (s, 3H, CH_3), 7.80 (s, 1H, H-4), 7.27 and 8.61 (AA'BB', $J=8.0$, 2.0 Hz, 4H, pyridine 4H), 12.09 (br s, 1H, NH); ms : m/z (relative intensity) 266 ($\text{M} + 2$, 95.5), 264 (M^+ , 100), 237 (43.6), 235 (35.5), 185 (35.5).

Anal. Calcd for $C_{11}H_9N_2OBr$: C, 49.83; H, 3.42; N, 10.57. Found : C, 49.78; H, 3.43; N, 10.50.

Milrinone (1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile) (6).

Into a 50 ml round bottom flask equipped with a magnetic stirring bar and a condenser drying tube system were placed 0.56 g (10 mmol) of dry KCN and 25 ml of acetonitrile containing 0.57 g (2.15 mmol) of bromo compound 5 and 48.3 mg of 18-Crown-6. The two-phase system was heated to reflux with vigorous stirring and the extent of reaction was followed by glc techniques. After 5 days, the reaction mixture was cooled, filtered, and evaporated to dryness. The residue was extracted with CH_2Cl_2 . The organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and recrystallized from ethanol to give 0.37 g (62%) of 6, mp $> 300^\circ C$ (lit.³ mp $> 300^\circ C$). Ir (KBr) : 2221, 1662, 1598, 1543 cm^{-1} ; 1H -nmr (d_6 -DMSO + $CDCl_3$) : δ 3.75 (s, 3H, CH_3), 8.46 (s, 1H, H-4), 7.72 and 8.91 (AA'BB', 4H, J=8.0, 2.0 Hz, pyridine 4H), 13.08 (br s, 1H, NH); ms : m/z (relative intensity) 211 (M^+), 182 (41.8), 156 (40.3). Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found : C, 68.19; H, 4.23; N, 19.81.

REFERENCES

- 1 A. A. Alousi, J. M. Canter, M. J. Montenegro, D. J. Fort, and R. A. Ferrari, J. Cardiovasc. Pharmacol., 1983, **5**, 792.
- 2 B. I. Ureid, T. Generalovich, P. S. Reddy, R. B. Spangenberg, and W. P. Follander, Circulation, 1983, **67**, 823.
- 3 G. Y. Leshner, and R. E. Philion, U. S. Patent, 4, 313, 951 (Chem. Abstr., 1982, **97**, 216005f).
- 4 B. Singh, Heterocycles, 1985, **23**, 1479.
- 5 W.-P. Fang, P. Shieh, and M.-J. Shiao, Heterocycles, 1986, **24**, 1585.
- 6 M.-J. Shiao, P. Shieh, and J.-S. Lai, Synth. Commun., 1988, **18**, 1397.
- 7 M.-J. Shiao, P. Shieh, and J.-S. Lai, J. Chinese Chem. Soc., 1986, **35**, 233.
- 8 M.-J. Shiao and K.-Y. Tarng, Heterocycles, accepted for publication, 1989.
- 9 K.-Y. Akiba, Y. Iseki, and M. Wada, Tetrahedron Lett., 1982, **23**, 429; D. L. Comins and A. H. Abdullah, J. Org. Chem., 1982, **47**, 4315.
- 10 F. L. Cook, C. W. Bowers, and C. L. Liotta, J. Org. Chem., 1974, **39**, 3416.

Received, 1st December, 1989