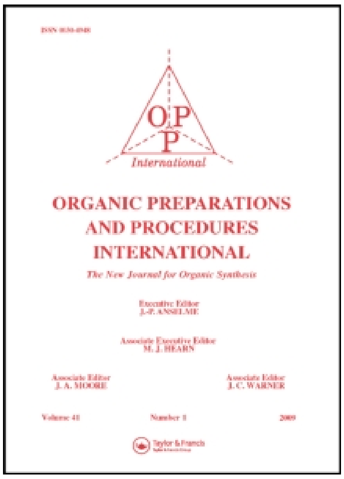

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Joe Murphy[a]; John W. Bunting[a]
[a] Department of Chemistry, University of Toronto, Toronto, Ontario, Canada

To cite this Article Murphy, Joe and Bunting, John W.(1971) 'DI-2-PYRIDYLMETHANOL AND 1,1-DI-2-PYRIDYLETHANOL', Organic Preparations and Procedures International, 3: 5, 255 — 260
To link to this Article: DOI: 10.1080/00304947109356785
URL: http://dx.doi.org/10.1080/00304947109356785

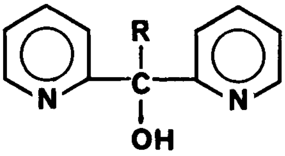
ORGANIC PREPARATIONS AND PROCEDURES INT. 3(5), 255-260 (1971)

DI-2-PYRIDYLMETHANOL AND 1,1-DI-2-PYRIDYLETHANOL

Joe Murphy and John W. Bunting

Department of Chemistry, University of Toronto
Toronto 181, Ontario, Canada

We wish to report improved routes to di-2-pyridylmethanol (I,R=H) and 1,1-di-2-pyridylethanol (I,R = CH_3) in overall yields of 65% and 90% respectively from readily available starting materials. Convenient routes to these compounds are desirable in view of the interest in bis-(pyridyl) compounds as chelating ligands with metal ions.



I

Di-2-pyridylmethanol (I: R = H) has been synthesized previously from 2-pyridinecarboxaldehyde and 2-pyridyllithium and also by decarboxylation of 2,2'-pyridilic acid formed by benzilic acid rearrangement of 2,2'-pyridil.[2] Our method is based on the latter route from 2,2'-pyridil which is readily available commercially and quite inexpensive. We have found that the decarboxylation step may be advantageously carried out in aqueous hydrochloric acid. The use of this mineral acid facilitates the work-up, and has consistently produced the alcohol in virtually quantitative yield from the sodium salt of 2,2'-pyridilic acid, compared with 58% yield obtained from decarboxylation in acetic acid solutions as suggested by Klosa.[2] We have been unable to reproduce Klosa's 86% yield for rearrangement of 2,2'-pyridil to the sodium salt of 2,2'-pyridilic acid.[2,3] Our best yield for this step is 67% under the most favourable conditions, and coupled with the almost quantitative decarboxylation, this leads to di-2-pyridylmethanol in an overall yield of 65% from 2,2'-pyridil.

We have also converted di-2-pyridyl ketone to di-2-pyridylmethanol in 95-100% yields, by reduction with sodium borohydride. Although di-2-pyridyl ketone is commercially available, this is not the method of choice since di-2-pyridyl ketone is much more expensive than 2,2'-pyridil from which it is most readily prepared.[4]

The di-2-pyridylmethanol synthesized by either route, is a pale yellow oil which we have been unable to crystallize. It is readily converted to the dihydrochloride salt or the zinc chloride complex, either of which is easily purified by recrystallization. Regeneration of the alcohol from these derivatives yielded the same non-crystallizable oil. The free alcohol is quite susceptible to air oxidation to di-2-pyridyl ketone. We recommend storage under nitrogen as the dihydrochloride or zinc chloride complex, with regeneration of the free alcohol immediately prior to use. Other workers have reported obtaining di-2-pyridylmethanol as a low-melting solid (Klosa[2] reports mp. 39-41° from benzene-petroleum ether; Beyerman and Bontekoe[1] report mp. 48° from ether-petroleum ether). Our attempts to recrystallize the free alcohol have resulted in oils having substantial carbonyl absorption at 5.90 μ in the infrared spectrum, which is identical to that present in the spectrum or an authentic sample of di-2-pyridyl ketone. We suspect that the low-melting solids of Klosa[2] and Beyerman and Bontekoe[1] may in fact be impure samples of di-2-pyridyl ketone (lit[4] mp. 54°).

1,1-Di-2-pyridylethanol ($I:R=CH_3$) has previously been synthesized in low yields (<20%) by two different routes[5,6]. We have obtained this tertiary alcohol in 90% yield by reaction of 2-acetylpyridine with 2-pyridyllithium. The product is readily separated from unreacted 2-acetylpyridine by distillation. The tertiary alcohol is quite stable to air oxidation and may be stored as such or as the dihydrochloride via which it is readily recrystallized.

EXPERIMENTAL

Di-2-Pyridylmethanol.A. - 2,2'-Pyridil (10 gm). was added to a solution of sodium (1.7 gm) in 98% methanol (55 ml). After refluxing for 40 minutes, the precipitated sodium 2,2'-pyridilate was collected, washed with absolute ethanol and dried (7.9 gm, 67%). This salt was slowly added to aqueous hydrochloric acid (4N; 100 ml) and after effervescence had ceased, the solution was basified by the addition of solid potassium carbonate. The di-2-pyridylmethanol was extracted with chloroform, and after drying over magnesium sulfate, the chloroform was removed under reduced pressure to yield the alcohol as a pale yellow oil (5.7 gm; 65% from 2,2'-pyridil).

B. A solution of sodium borohydride (1.17 gm) in aqueous sodium hydroxide (0.1M; 50 ml.) was slowly added at 0° to a solution of di-2-pyridyl ketone (5.9 gm) in methanol (50 ml.).The pale red solution was stirred for 1 hour at 0°, and then at room temperature for 6 hours. Dilute hydrochloric acid was added to destroy excess sodium borohydride. The methanol was removed by rotary evaporator, and the resulting aqueous solution was basified with sodium hydroxide and extracted with chloroform. Removal of the chloroform and distillation of the resulting oil gave di-2-pyridylmethanol (5.7 gm; 96%), bp. 110-112°/1mm.(lit.[1] 143-4°/2mm. (see text)). p.m.r. (DMSO-d_6): δ 6.18(d,1H,$J_{\underline{CH}\underline{OH}}$=5 cps), δ 7.2 (m, 2H), δ 7.6 (m, 4H), δ 8.48 (d, 2H, J = 5 cps.), δ 5.80 (d, 1H, $J_{\underline{CH}\underline{OH}}$= 5 cps).

Di-2-pyridylmethanol Dihydrochloride and Zinc Chloride Complex

The base (4.8 gm) was dissolved in aqueous hydrochloric acid (1N; 100 ml) and the water removed under reduced pressure. A fresh portion of water was added and the evaporation repeated, and this process was continued until excess hydrogen chloride had been removed. The residual yellow syrup was taken up in absolute ethanol (20 ml), and upon addition of anhydrous ether (200 ml) the dihydrochloride salt precipitated as a white solid

(4.2 gm). Recrystallization from absolute ethanol gave white needles, mp. 195-198° (dec).

Anal. Calcd. for $(C_5H_4N)_2CHOH.2HCl$: C 50.98%; H 4.67%; N 10.81% Cl 27.36%. Found: C 51.11%; H 4.83%; N 10.77%; Cl 27.45%. Addition of excess anhydrous zinc chloride to di-2-pyridylmethanol in ether solution gave the zinc chloride complex, which was recrystallized from aqueous methanol, mp. 261-262° (dec.). Breakdown of this complex is readily achieved by the addition of excess aqueous ammonia. The free base may be extracted from the ammoniacal solution with dichloromethane.

1,1-Di-2-pyridylethanol. - A solution of n-butyl-lithium (2.25M) in a mixture of hexane (23 ml.) and tetrahydrofuran (50 ml.) was added over 15 minutes to 2-bromopyridine (5 ml.) in tetrahydrofuran (50 ml) at -76°, and stirring continued at -76° for 20 minutes. 2-Acetylpyridine (3.1 gm) in tetrahydrofuran (50 ml) was added to this dark red solution over 15 minutes. Stirring was continued at -76° for 8 hours and then at room temperature for 2 days. After addition of water (150 ml) and conc. hydrochloric acid (100 ml.), the tetrahydrofuran was removed by rotary evaporation. The aqueous solution was extracted with dichloromethane and then basified by addition of sodium carbonate. Further extraction with dichloromethane, drying these extracts over magnesium sulfate, and removal of the solvent gave a red oil which on distillation yielded 2-acetylpyridine (0.5 gm; bp. 49-50°/3mm.), and 1,1-di-2-pyridylethanol (4.0 gm; 91%) bp. 120-123°/3mm. (lit.[6] 109-112°/1mm.). p.m.r.

($CDCl_3$): δ 1.98 (s,3H), δ 6.33 (broad s,1H), δ 7.13 (m,2H), δ 7.67 (m,4H), δ 8.47 (d,2H,J=5cps).

Conversion to the dihydrochloride as described for di-2-pyridylmethanol, and recrystallization from absolute ethanol gave prisms, mp. 198-202° (dec.) (lit.[5] mp. 200-202°).

This research was supported by a research grant and post-graduate scholarship (to J.M.) from the National Research Council of Canada.

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(Received September 20, 1971)