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Synthesis of 3-*tert*-Butylpyridine[1]

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3-*tert*-Butylpyridine (**11**) has been synthesized from neopentyl alcohol in 16% overall yield through a five-step sequence. Among the steps involved are the cycloaddition of α-*tert*-butylacrolein (**9**) to butyl vinyl ether and conversion of the resulting dihydropyran derivative (**10**) into the pyridine base (**11**).

Keywords——3-substituted pyridine; α,β-unsaturated aldehyde; vinyl ether; dihydropyran; bromination; Grignard reaction; Mannich reaction; Diels–Alder reaction

Our recent papers on the mercuric acetate–(ethylenedinitrilo)tetraacetic acid oxidation of 1,3-disubstituted piperidines[3,4] and on the ferricyanide oxidation of 3-substituted 1-ar-

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3) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 2695 (1973).

4) *a*) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **25**, 2336 (1977); *b*) T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, **25**, 3042 (1977); *c*) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731; *d*) S. Yoshifuji and T. Fujii, *ibid.*, **1975**, 1965.

alkylpyridinium ions[3,5] have described the effects of various 3-substituents on the orientation of oxidation in the nucleus. In order to extend the scope of the 3-substituent to include the *tert*-butyl group, we were compelled to prepare 3-*tert*-butylpyridine (**11**), the requisite starting material for such oxidation studies, at our hands in sufficient quantity. The only method known to date for synthesis of this base is that of Brown and Murphey,[6] who found that the interaction of 3-picoline, sodium amide, and methyl chloride in liquid ammonia solution gives 3-ethylpyridine, which may be further methylated to produce 3-isopropyl- and 3-*tert*-butylpyridine (**11**). Although we were able to obtain a certain quantity of **11** in a poor overall yield by following their procedure, the tedious repeated methylation procedure and careful fractional distillation of products using a highly rectifying device as required discouraged us from repeating these processes for further quantities of the pyridine base. Thus, we investigated a new stepwise synthesis of **11** (Chart 1), which involved a cycloaddition (of an α,β-unsaturated aldehyde to butyl vinyl ether) similar to that used by Botteghi *et al.*[7] for the preparation of (+)-(*S*)-3-*sec*-butylpyridine.

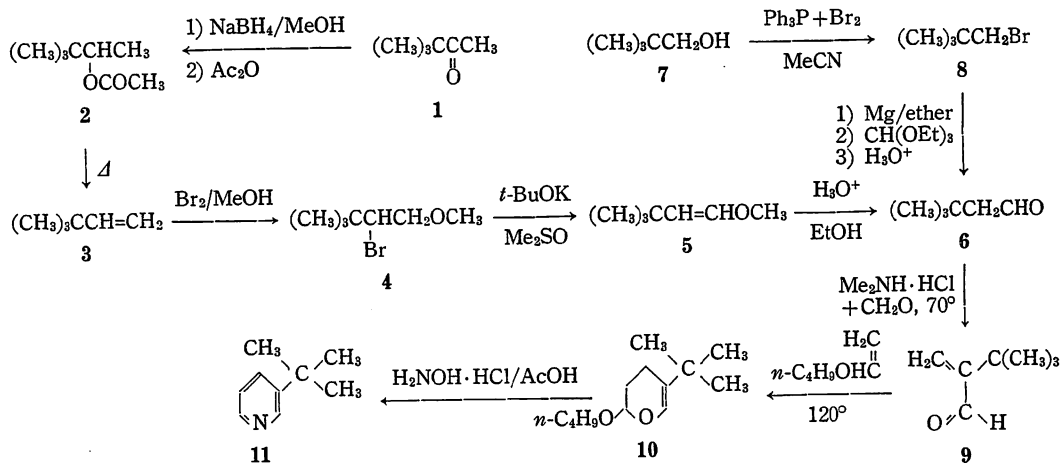

Chart 1

Aldehyde **6**, a key intermediate in the above scheme, was a known compound, and we first prepared it in 18% overall yield from pinacolone (**1**) through a five-step sequence (**1**→**2**→**3**→**4**→**5**→**6**) according to the procedure of Puterbaugh and Newman,[8] but with the following modification: $LiAlH_4$/ether for reduction of **1** was replaced by $NaBH_4$/MeOH;[9] $NaNH_2$/liquid NH_3 for dehydrobromination of **4**, by *tert*-BuOK/dimethyl sulfoxide. Since this route to **6** was too lengthy and inefficient, an alternative (**7**→**8**→**6**) was then examined. Bromination of neopentyl alcohol (**7**) with triphenylphosphine and bromine in N,N-dimethylformamide (DMF) was reported to give the corresponding bromide (**8**) in 79% yield.[10] We found that a similar bromination of **7** but in acetonitrile[11] instead of DMF improved the yield of **8** to 90%.

5) *a*) T. Fujii, S. Yoshifuji, K. Yoshida, M. Ohba, S. Ikegami, and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 993 (1975); *b*) T. Fujii, K. Yoshida, M. Ohba, M. Mitsukuchi, I. Tanaka, S. Yoshifuji, and M. Kirisawa, *ibid.*, **25**, 2072 (1977); *c*) T. Fujii, M. Ohba, S. Yoshifuji, and M. Kirisawa, *ibid.*, **25**, 2887 (1977).
6) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).
7) D. Tatone, T. C. Dich, R. Nacco, and C. Botteghi, *J. Org. Chem.*, **40**, 2987 (1975).
8) W. H. Puterbaugh and M. S. Newman, *J. Am. Chem. Soc.*, **79**, 3469 (1957).
9) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
10) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
11) A study on the mechanism of the same reaction in this solvent has been reported by G. A. Wiley, B. M. Rein, and R. L. Hershkowitz (*Tetrahedron Lett.*, **1964**, 2509).

Conversion of **8** into aldehyde **6** was accomplished in 48% yield (43% overall yield from **7**) by Grignard reagent formation followed by the reaction with ethyl orthoformate and mild acid hydrolysis of the resulting acetal.[12]

For the preparation of the diene partner (**9**) for the cycloaddition to butyl vinyl ether to form the dihydropyran derivative (**10**), we adopted the method of Green and Hickinbottom.[13] Thus, aldehyde **6** was allowed to react with dimethylamine hydrochloride and formaldehyde, and the resulting Mannich base hydrochloride underwent elimination readily to give **9** in 71% yield. The Diels–Alder reaction between **9** and butyl vinyl ether was then effected at 120° for 24 hr, and treatment of the resulting dihydropyran derivative (**10**) (64% yield) with hydroxylamine hydrochloride in boiling acetic acid, according to a known procedure,[7] furnished the desired pyridine base (**11**) in 82% yield.

Although the overall yield (16%) of 3-*tert*-butylpyridine (**11**) from neopentyl alcohol (**7**) in the present five-step synthesis is not necessarily an acceptable one, samples of the base obtained by this method are of prime quality. It is hoped that the above synthesis of **11** will facilitate investigations which have been awaiting such an improvement.

Experimental

All melting points are corrected; boiling points, uncorrected. Gas–liquid chromatography (GLC) was performed on a Shimadzu GC-3AH gas chromatograph equipped with a 3 m × 3 mm column containing 1.5% SE-30 (methyl silicone) on Chromosorb W. For high performance liquid chromatography (HPLC) a Waters ALC/GPC 204 liquid chromatograph, equipped with a 30 cm × 4 mm i.d. stainless steel column packed with μPorasil, was employed. See also ref. 5*b* for details of instrumentation and measurement. The following abbreviations are used: d=doublet, m=multiplet, s=singlet, t=triplet.

1,2,2-Trimethylpropyl Acetate (2)——To an ice-cooled, stirred solution of pinacolone (**1**) (20.05 g, 200.2 mmol) in MeOH (20 ml) was added in small portions $NaBH_4$ (3.87 g, 102.2 mmol) over a period of 20 min. Stirring was continued at room temp. for additional 10 hr, and then AcOH (6.48 g) was added. The MeOH was removed from the mixture by evaporation, and Ac_2O (41.41 g, 405.6 mmol) was added to the residue. After having been heated at reflux for 4.5 hr, the mixture was poured on crashed ice (50 g). The resulting aqueous mixture was neutralized with $NaHCO_3$ and extracted with ether (4 × 30 ml). The ether extracts were washed with H_2O, dried over anhyd. Na_2SO_4, and subjected to fractional distillation to give acetate (**2**) (25.49 g, 88%) as a colorless oil, bp 138—140° [lit.[14] bp 138—138.5° (738 mmHg)]; IR ν_{max}^{film} cm^{-1}: 1735 (ester CO). Pyrolysis of this sample according to reported procedure[8] furnished 3,3-dimethyl-1-butene (**3**), bp 40—42°, in 77% yield.

(*E*)-3,3-Dimethyl-1-methoxy-1-butene (5)——To a stirred mixture of *tert*-BuOK (41.24 g, 367.5 mmol) and dimethyl sulfoxide (70 ml), which had been stirred at room temp. for 30 min, was added dropwise 2-bromo-3,3-dimethyl-1-methoxybutane (**4**)[8] (48.42 g, 248 mmol) over a period of 1 hr. After the mixture was stirred at room temp. for 5 hr, H_2O (700 ml) was added. The aqueous mixture was extracted with ether (6 × 200 ml), and the ether extracts were washed with H_2O, dried over anhyd. Na_2SO_4, and fractionally distilled to yield **5** (21.0 g, 74%) as a colorless oil, bp 102—109° (lit.[8] bp 103—106°); IR ν_{max}^{film} cm^{-1}: 1650 (C=C). NMR ($CDCl_3$) δ: 1.04 (9H, s, Me_3C), 3.50 (3H, s, OMe), 4.82 (1H, d, J=13.0 Hz, $Me_3CC\underline{H}$=CH), 6.25 (1H, d, J=13.0 Hz, CH=C$\underline{H}$OMe).

1-Bromo-2,2-dimethylpropane (8)——The following procedure was patterned after that used by Schaefer *et al.*[15] for the bromination of cinnamyl alcohol. To a stirred, ice-cooled solution of triphenylphosphine (288 g, 1.10 mol) in dry MeCN (960 ml) was added dropwise Br_2 (173 g, 1.08 mol) over a period of 20 min. Stirring was continued at room temp. for 30 min, and a solution of neopentyl alcohol (**7**) (91.0 g, 1.03 mol) in dry MeCN (130 ml) was then added dropwise over a period of 15 min. After the resulting mixture was stirred at room temp. for 3 hr, the MeCN and product were evaporated at ordinary pressure. The distillate was poured into cold H_2O (3 l) and extracted with pentane (4 × 600 ml). The extracts were combined, washed with H_2O, dried over anhyd. $CaCl_2$, and subjected to fractional distillation to produce **8** (140 g, 90%) as a

12) This conversion is essentially the same as that reported by T. H. Fife and T. Rikihisa [*Biochemistry*, **9**, 4064 (1970)] without any experimental details. However, they used neopentyl chloride instead of the bromide (**8**) for the preparation of the Grignard reagent.
13) M. B. Green and W. J. Hickinbottom, *J. Chem. Soc.*, **1957**, 3262.
14) S. Sarel and M. S. Newman, *J. Am. Chem. Soc.*, **78**, 5416 (1956).
15) J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, "Organic Syntheses," Coll. Vol. V, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 249.

colorless oil, bp 106—108° [lit.[10] bp 104.8° (732 mmHg)]; NMR ($CDCl_3$) δ: 1.05 (9H, s, Me_3C), 3.28 (2H, s, CH_2).

3,3-Dimethylbutanal (6)——i) From Bromide **8**: The following procedure was patterned after that [16] employed for the synthesis of hexaldehyde from amyl bromide. To a stirred mixture of Mg turnings (29.0 g, 1.19 g.-atoms), a small crystal of I_2, and dry ether (50 ml) was added dropwise **8** (8.0 g). As soon as the reaction had started, dry ether (300 ml) was added and then, with external cooling, a solution of **8** (161.0 g) (total, 169.0 g; 1.12 mol) in dry ether (140 ml) within 30 min. The resulting mixture was refluxed with stirring for 1 hr, cooled to room temp., and ethyl orthoformate (166.0 g, 1.12 mol) was added over a period of 15 min. After the mixture had been refluxed for 6 hr, the ether was distilled away. The residual solid was cooled in an ice bath and treated with chilled 6% aq. HCl (760 ml). The aqueous mixture was extracted with ether (5×200 ml), and the ether was distilled away from the extracts to leave the acetal of **6** as an oil The oil was then distilled with a solution of conc. H_2SO_4 (98 g) in H_2O (680 ml). The distillate was added to a suspension of $NaHSO_3$ (120 g) in H_2O (330 ml), and the mixture was kept stirring at room temp. overnight. The colorless crystals that resulted were filtered off, washed with ether (10×50 ml), and combined with the aqueous filtrate, which had been washed with ether (3×200 ml). After addition of $NaHCO_3$ (95 g), the mixture was steam-distilled, and the distillate was extracted with ether (3×150 ml). The ether extracts were washed with a little H_2O, dried over anhyd. Na_2SO_4, and fractionally distilled to furnish **6** (53.9 g, 48%) as a colorless oil, bp 102—107° (lit.[17] bp 104—105°); IR ν_{max}^{film} cm^{-1}: 1720 (CHO); NMR ($CDCl_3$) δ: 1.08 (9H, s, Me_3C), 2.25 (2H, d, J=3.0 Hz, CH_2), 9.78 (1H, t, J=3.0 Hz, CHO). The infrared (IR) spectrum of this sample was superimposable on that of a sample of **6** prepared by method-(ii). A portion of the above oil was converted in the usual manner into the 2,4-dinitrophenylhydrazone to give yellow needles (recrystallized from EtOH), mp 148—149°, identical [by IR spectrum, thin-layer chromatography (TLC), and mixed melting-point test] with an authentic sample derived from method-(ii).

ii) Hydrolysis of Enol Ether **5**: A mixture of (**5**) (15.6 g, 137 mmol), H_2O (12 ml), EtOH (20 ml), and conc. aq. HCl (4 ml) was refluxed for 10 min. After cooling, the mixture was diluted with H_2O (200 ml), salted out with K_2CO_3, and extracted with ether (8×50 ml). The ether extracts were dried over anhyd. Na_2SO_4 and submitted to fractional distillation, affording **6** (11.6 g, 85%) as a colorless oil, bp 102—104°. The 2,4-dinitrophenylhydrazone, prepared in 79% yield in the usual manner, melted at 148—149° (lit.[8] mp 147.5—148°).

3,3-Dimethyl-2-methylenebutanal (9)——The procedure described below was based on that of Green and Hickinbottom.[13] A stirred mixture of **6** (30.0 g, 300 mmol), $Me_2NH \cdot HCl$ (31.0 g, 380 mmol), and 37% formalin (32.0 g, 394 mmol) was heated at 70° for 24 hr. The mixture was steam-distilled, and the distillate was extracted with ether (4×70 ml). The ether extracts were washed with a little H_2O, dried over anhyd. Na_2SO_4, and fractionally distilled to provide **9** (23.7 g, 71%) as a colorless oil, bp 121—125° (lit.[13] bp 125—126°); IR ν_{max}^{film} cm^{-1}: 1700 (CHO), 1610 (C=C); NMR ($CDCl_3$) δ: 1.20 (9H, s, Me_3C), 5.91 (1H, s, C=CH *trans* to CHO), 6.32 (1H, s, C=CH *cis* to CHO), 9.56 (1H, s, CHO).

The 2,4-dinitrophenylhydrazone of **9**: orange needles, mp 157—158° (from EtOH). *Anal.* Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.28; H, 5.61; N, 19.46.

2-Butoxy-3,4-dihydro-5-(1,1-dimethylethyl)-2*H*-pyran (10)——A mixture of **9** (26.0 g, 232 mmol), butyl vinyl ether (46.5 g, 464 mmol), and hydroquinone (0.7 g) was agitated at 120° for 24 hr in a stainless steel autoclave charged with 2 atm of N_2. After cooling, the reaction mixture was distilled to give **10** (31.7 g, 64%) as a colorless oil, bp 120—123° (18 mmHg); IR ν_{max}^{film} cm^{-1}: 1657 (C=C); NMR ($CDCl_3$) δ: 1.03 (s, Me_3C), 1.78—2.08 (4H, m, $H_{(3)}$'s and $H_{(4)}$'s), 4.90 (1H, t, J=3.0 Hz, $H_{(2)}$), 6.08—6.16 (1H, m, $H_{(6)}$).

3-(1,1-Dimethylethyl)pyridine (11)——A mixture of **10** (56.1 g, 264 mmol) and AcOH (600 ml) was heated at reflux under N_2 for 2 hr. After cooling, the resulting solution was added to a boiling mixture of $H_2NOH \cdot HCl$ (65.0 g, 935 mmol) and AcOH (300 ml). Heating was continued for additional 4 hr and the AcOH was distilled away *in vacuo*. The residue was dissolved in a cold mixture of H_2O (300 ml) and 10% aq. HCl (50 ml), and the aqueous solution, after having been washed with benzene (3×200 ml), was basified, salted out with K_2CO_3, and extracted with ether (4×200 ml). The ether extracts were dried over anhyd. K_2CO_3, and the ether was distilled away. Distillation of the residual oil furnished **11** (29.4 g, 82%) as a colorless oil, bp 82—83° (15 mmHg) [lit.[6] bp 194.3° (742 mmHg)]; shown to be homogeneous by a single spot or peak on TLC, GLC, or HPLC analysis; n_D^{20} 1.4963 (lit.[6] n_D^{20} 1.4965); MS *m/e*: 135 (M^+); NMR ($CDCl_3$) δ: 1.36 (9H, s, Me_3C), 7.24 (1H, $H_{(5)}$), 7.70 (1H, $H_{(4)}$), 8.44 (1H, $H_{(6)}$), 8.70 (1H, $H_{(2)}$) ($J_{2,4}$=2.5 Hz, $J_{2,5}$=1.0 Hz, $J_{4,5}$=8.0 Hz, $J_{4,6}$=1.7 Hz, $J_{5,6}$=4.7 Hz).

The picrate was prepared from a small portion (108 mg) of the above sample by dissolving it in ether (2 ml) and adding a sat. solution (17 ml) of picric acid in ether. The resulting precipitate (271 mg, 93% yield) was filtered off, washed with ether, and recrystallized from H_2O, giving yellow needles, mp 154—155°

16) G. B. Bachman, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 323.

17) L. Schmerling, *J. Am. Chem. Soc.*, **68**, 1650 (1946).

(lit.[6] mp 153.9—154.4°). *Anal.* Calcd. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.65; H, 4.29; N, 15.23.

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