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## Note

# Aromatization of 1,4-dihydropyridines using tetraethylammonium bromate as an oxidizing agent

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Quaternary ammonium bromate have been prepared from the corresponding bromide and used as a mild and efficient oxidizing agent for the aromatization of Hantzsch esters and related compounds to pyridine derivatives

**Keywords**: Aromatization, dihydropyridines, quaternary ammonium bromate, oxidation, substituted pyridines

Dialkyl-1,4-dihydro-2,6-dimethyl-3,5-dicarboxylates and the diaryl analogs ( 1,4-DHP) are well known compounds having analgesic properties[1], antitumour, hypotensive[2] and coronary dilating activity[3]. Oxidative aromatization of 1,4-DHP has attracted attention because the metabolism of 1,4-DHP based drugs involved a cytochrome P-450 catalyzed oxidation in the liver[4]. Attempts to mimic the *in vivo* oxidation step leading to aromatization of 1,4-DHP has been the subject of elaborate studies.

Several methods are reported for the aromatization of 1,4-DHP and notable among them are the use of $HNO_3$ at 60°C[5], $NaNO_2$ in acidic media[6], $CrO_3$ in $Ac_2O$ (Ref 7), chloranil in benzene at reflux temperature[8], $K_2Cr_2O_7$ in $H_2SO_4$, $KMnO_4$ in acetic acid[9], clay supported metal nitrates[10], microwave irradiation[11] and by human liver chromosomes[4]. Herein is reported a simple, efficient and mild method for the aromatization of 1,4-DHPs by using tetraethyl ammonium bromate as the oxidizing agent. The oxidant was prepared from the easily available tetraethylammonium bromide and characterized by a procedure reported earlier[12]. Quaternary ammonium salts are versatile phase transfer catalysts and some of them have been used to assist oxidation using inexpensive primary oxidants such as $O_2$ (Ref 13), NaOCl (Ref 14), $H_2O_2$ (Ref 15), $KMnO_4$ (Ref 16) and others[17]. Research efforts are now directed towards modifying the usual quaternary ammonium salts and using them as reagents rather than as catalysts. The tetra-*n*-alkylammonium bromate prepared is one such oxidizing agent which is derived from the corresponding bromide. The tetra-*n*-alkyl-ammonium bromates were earlier used for the oxidative deoximation of oximes[12], conversion of the phenylhydrazones[18], and the semicarbazones[19] to the parent carbonyl compounds, oxidation of amines to nitro compounds[20] and the oxidation of alcohols to the corresponding carbonyl compounds[21]. In general, the tetra-*n*-alkylammonium bromates are versatile oxidizing agents which can also be used for the aromatization of several 1,4-DHPs and results are reported here. Further, synthesis of 1,4-dihydro-pyridines and their subsequent aromatization provides an elegant method for the synthesis of 4-substituted pyridines which are otherwise difficult to access *via* the Friedel Crafts alkylation.

Several 1,4-DHPs, from aliphatic as well as aromatic aldehydes were prepared by a classical three component reaction using procedures reported in the literature[22]. The 1,4-DHPs were then oxidized by using the tetraethylammonium bromate by simply refluxing a mixture of the 1,4-DHP and the bromate in suitable solvents for varying period of time as mentioned in **Table I**. The conversion is summarized in **Scheme I**.

## Experimental Section

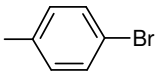
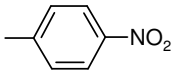
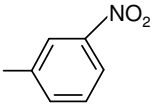
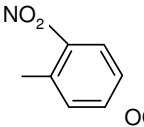
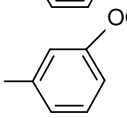
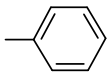
All reagents and solvents were purified before use by methods reported in literature[20]. The quaternary ammonium bromide was obtained from E. Merck Inc and the corresponding bromate was prepared. Melting points were determined in an apparatus from Scientific Devices, India, Type MP-D, in open capilliaries and are uncorrected. $^1$H NMR, CHN analysis and mass spectra were obtained from facilities available at the IIT Guwahati and SAIF NEHU, Shillong, India.

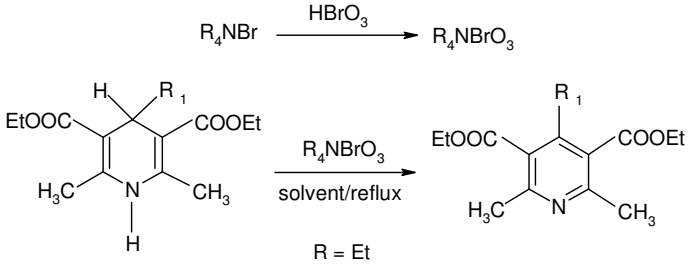
The quaternary ammonium bromate was prepared and characterized as reported earlier[21] and the 1,4-dihydropyridines (Hantzsch esters) were prepared by procedures reported in literature[22].

## General procedure for the preparation of the 1,4-dihydropyridines

Aldehyde ( 0.01 mol), ethylacetoacetate (20 mL) and conc aqueous ammonia (6 mL) in 100 mL of

**Table I** — Aromatization of 1,4-dihydropyridines to 4-substituted pyridines

| Entry | $R_1$ | 1,4-DHP m.p. ºC | | Reflux time | Pyr derivative m.p. ºC | | Yield (%) | Solvent |
|---|---|---|---|---|---|---|---|---|
| | | Obs | Lit | | Obs | Lit | | |
| 1 | H | 180 | 183-85(ref23) | 3 | 67 | 70-72(ref10) | 90 | $CH_3CN$ |
| 2 | Me | 130 | 130-31(ref6) | 3.5 | oil | | 66 | $CH_3CN$ |
| 3 | Et | 113 | 111-13(ref23) | 2 | oil | | 75 | dioxane |
| 4 | *i*-Pr | 96 | 97-98(ref23) | 4 | oil | | 67 | DCM |
| 5 | Pr | 125 | 125-26(ref23) | 3 | oil | | 87 | dioxane |
| 6 |  | 148 | 147(ref23) | 3.5 | 67 | 67-68(ref23) | 85 | dioxane |
| 7 |  | 167-70 | — | 3 | 112 | 111-13(ref10) | 72 | dioxane |
| 8 |  | 162 | 162-64(ref22) | 3.5 | 62 | 62(ref22) | 75 | dioxane |
| 9 |  | 201 | — | 3 | 73 | 75(ref10 | 65 | dioxane |
| 10 |  | 180 | 180(ref23) | 2 | 260 | 260(ref23) | 68 | $CH_3CN$ |
| 11 |  | 158 | 158(ref4) | 3 | 62 | 61-63(ref4) | 75 | DCM |




**Scheme I**

ethanol was taken in a 250 mL RBF and refluxed for 3 hr. To the reaction mixture was then added 50 mL of warm water and the solution was allowed to cool. In the case of solid products, the precipitated product was filtered off, washed with 10 mL 60% aqueous ethanol and purified by recrystallization from ethanol. In case where the products were found to be liquids, the workup involved pouring of the reaction mixture into a large excess of water and then extracting the resulting mixture with ether (3×100 mL). The ether

extract was dried (anhyd. $MgSO_4$) and the removal of ether gave the desired product which was chromatographed over silica gel column using petroleum ether and 5% ethyl acetate as the eluent for further purification.

**General procedure for aromatization of the 1,4-dihydropyridines**

1,4-DHP and the tetraethylammonium bromate (1:1 molar mixture) was dissolved in 150 mL of the appropriate solvent and the solution refluxed for 2.5-4 hr (**Table I**). The progress of the reaction was monitored by running TLC's on prepared silica gel plates. After completion of the reaction, the solvent was removed by evaporation, washed with water and the product extracted with ethyl acetate to remove the spent oxidant. The solvent was subsequently evaporated and the product purified by column chromatography over silica gel.

The 1,4-dihydropyridines and the aromatized products 4-substituted pyridine derivatives, were characterized by CHN analysis and by recording the mass spectra, 400 MHz $^1H$ NMR spectra in $CDCl_3$, UV-Vis spactra and IR spectra in KBr pellets and by comparing the melting points with those found in literature[4,6,23]. The yield of the 4-substituted pyridines were high and the work up was simple.

**Spectral data of some representative 4-substituted pyridine derivatives:**

**Pyr 1**: **Diethyl-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1720, 1591, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.65(s,1H), 4.34(q, *J*=7.2 Hz, 4H), 2.825(s,6H), 1.39(t, *J*=7.2 Hz, 6H). Anal. Calcd. for $C_{13}H_{17}NO_4$ (251): C, 62.1; H, 6; N, 5. Found C, 61.98; H, 5.8; N, 5%. EI-MS: *m/z* (%) 252 (M+1, 40).

**Pyr 2**: **Diethyl-2,4,6-trimethyl-3,5-dicarboxylate**: IR (KBr): 1734, 1491, 1367 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 3.21(s,3H), 4.09(q, *J*=7.2 Hz, 4H), 2.86 (s,6H), 1.02(t, *J*=7.2 Hz, 6H). Anal. Calcd. for $C_{14}H_{19}NO_4$ (265): C, 63.39; H, 7.07; N, 5.21. Found C, 63.1; H, 6.98; N, 5.3%. EI-MS: *m/z* (%) 266 (M+1, 32).

**Pyr 3**: **Diethyl-4-ethyl-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1740, 1598, 1336 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.09 (q, *J*=7.2 Hz, 4H), 2.59(s,6H), 1.034(t, *J*=7.2 Hz, 6H), 3.2 (t,3H, *J*=6.4 Hz), 5.1( q, *J*=5.2, 2H). Anal. Calcd. for $C_{15}H_{21}NO_4$ (279): C, 64.44; H, 7.51; N, 5.01. Found C, 64.81; H, 7.12; N, 5.42%. EI-MS: *m/z* (%) 280(M+1, 51).

**Pyr 4**: **Diethyl-4-isopropyl-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1730, 1579, 1336 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.11(q, *J*=2 Hz, 4H), 4.28 (q, *J*=7.2 Hz, 4H), 1.28(t, *J*=7.2 Hz, 6H), 0.98(t, *J*=2 Hz, 3H). Anal. Calcd. for $C_{16}H_{23}NO_4$ (293): C, 65.47; H, 7.87; N, 4.77. Found C, 65.1; H, 8.03; N, 5.02%. EI-MS: *m/z* (%) 294(M+1, 32).

**Pyr 7**: **Diethyl-4-(4′-nitrophenyl)-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1730, 1533, 1354 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.25 (t, *J*=7.2 Hz, 1H), 8.23 (t, *J*=2 Hz, 1H), 8.16 (t, *J*=2 Hz, 1H), 7.58 (m, 1H), 4.03 ( q, *J*=6.8 Hz, 4H), 2.61 (s, 6H), 0.971 (t, *J*=6.8 Hz, 6H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$ (372): C, 61.33; H, 5.38; N, 7.53. Found C, 61.45; H, 5.88; N, 7.67%. EI-MS: *m/z* (%) 373 (M+1, 30).

**Pyr 8**: **Diethyl-4-(3′-nitrophenyl)-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1726, 1203 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 4.65 (q, *J*=7.2 Hz, 4H), 2.27 (s,6H), 1.27 (t, *J*=7.2 Hz, 6H), 1.167 (s,3H), 7.6-7.9 (br, 4H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$ (372): C, 61.33; H, 5.38; N, 7.53. Found C, 62.5; H, 5.4; N, 7.2%. EI-MS: *m/z* (%) 373(M+1, 30).

**Pyr 9**: **Diethyl-4-(2′-nitrophenyl)-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1725, 1560, 1234 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.48 (d, *J*=4.4 Hz, 2H), 7.24 (d, *J*=4.4Hz, 2H), 4.29 (q, *J*=7.2 Hz, 4H), 2.32 (s, 6H) 1.31 (t, *J*=7.2 Hz, 6H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$ (372): C, 61.33; H, 5.38; N, 7.53. Found C, 62.3; H, 5.15; N, 7.8%. EI-MS: *m/z* (%) 373 (M+1, 40).

**Pyr 10**: **Diethyl-4-(3′-benzoyloxyphenyl)-2,6-dimethyl-3,5-dicarboxylate**: IR (KBr): 1735, 1570, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.32 (d, *J*=4 Hz, 1H), 6.76 (d, *J*=4 Hz, 1H), 4.35 (q, *J*=7 Hz, 4H), 2.63 (s, 6H) 1.29 (t, *J*=7 Hz, 6H). Anal. Calcd. for $C_{26}H_{25}NO_6$ (447): C, 69.88; H, 5.6; N, 3.14. Found C, 69.81; H, 5.75; N, 3.26%. EI-MS: *m/z* (%) 448 (M+1, 56).

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