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Note

A convenient method for the oxidation of Hantzsch 1,4-dihydropyridines with N-bromo succinimide

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A convenient and mild method for the conversion of Hantzsch 1,4-dihydropyridines to pyridines using N-bromo succinimide at room temperature in excellent yields has been described.

Keywords: Hantzsch 1,4-dihydropyridines, pyridines, N-bromo succinimide

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Dihydropyridines are of utmost importance in biological systems as a class of useful drugs particularly as anti-oxidants. 4-Substituted-1,4-dihydro-2,6-dimethyl 3,5-pyridine dicarboxylic acid esters have anti-hypotic and anti-ischemic activities. Some of the representative compounds of this class possess acaricidal, insecticidal, bactericidal and herbicidal activities[1]. Hantzsch 1,4-dihydropyridine derivatives are often regarded as the models of the natural reduced nicotinamine adenine dinucleotide (NADH) coenzyme which function as redox reagent for biological reactions by transferring an electron or a hydride ion to the surrounding substrate[2] and hence their oxidation behaviour under various conditions assumes greater significance.

Oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous issues in organic chemistry. In recent years several groups have reported various new oxidation methods which include oxidation with ferric nitrate on a solid support[3], ceric ammonium nitrate[4], clay-supported cupric nitrate (claycop)[5] under sonication conditions, pyridinium chlorochromate[6], bromo trichloro methane[7], nitric acid[8], nitric oxide and *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide[9,10]. Earlier we have reported a milder method for oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridine derivatives using urea nitrate and peroxydisulfate-cobalt (II) under microwave and refluxing conditions[11]. Recently Zhang *et al*. have reported the production of hydrogen in quantitative yield during the photocatalytic oxidation of Hantzsch dihydropyridine and its 4-alkyl and 4-aryl substituted derivatives using platinum catalysts[12].

However, most of the earlier reported methods require drastic reaction conditions, an extended period of time for the completion of oxidation and afford only modest yields of products. Even though various oxidants have been employed, application of N-bromosuccinimide has not been explored for the oxidation of dihydropyridines. N-Bromosuccinimide is a versatile reagent for the oxidation of primary and secondary alcohols[13,14], α-hydroxy carboxylic-acids[15,16], α-hydroxy carboxylic esters[17], α-amino carboxylic acids[14], mercaptans and thio-phenols[18], ketoximes[19], hydrazines and hydrazones[16]. In addition, NBS is a preferred reagent for allylic bromination. While hydroxy acids like malic acid, tartaric acid, citric acid etc. are converted to aldehydes and ketones, polyhydric alcohols (glycol, glycerol and hexitols) are quantitatively decomposed to carbon dioxide and water[18] with NBS. NBS also promotes reactions of sterically hindered cresols *via* *p*-benzoquinone methide[20]. Herein we describe a new, faster method for the oxidation of Hantzsch 1,4-dihydropyridines to the corresponding aromatic pyridine derivatives using commercially available N-bromosuccinimide in methanol at ambient temperature within five minutes. The reagent is mild and offers a convenient method for the aromatization in excellent yield in comparison to the earlier reported procedures. **(Scheme I, Table I)**

Oxidation of 4-substituted 1,4-dihydropyridines to the corresponding pyridines using NBS in methanol gives excellent yield. With phenyl and styryl groups as substituents at the *para* position of the 1,4-dihydropyridines, oxidation with NBS resulted in the formation of both alkylated and dealkylated products. However with other substituents only the alkylated pyridines were obtained.

Based on the results obtained it is proposed that the oxidation reaction could probably proceed through any

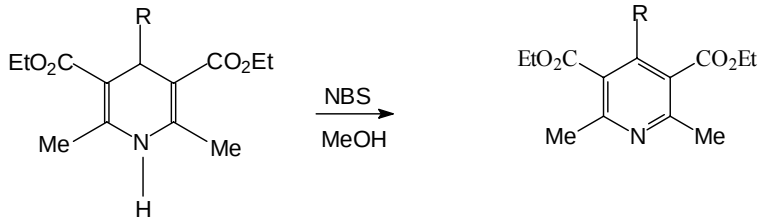
Table I — Oxidation of 1,4 dihydropyridines with N-bromosuccinimide

Substrate R=	Yield (%)	Dealkylated product (%)
H-	97	-
CH_3-	95	-
2-furyl-	78	-
C_6H_5-	70	16
4-CH_3-C_6H_4-	90	-
3-O_2N-C_6H_4-	87	-
4-CH_3O-C_6H_4-	94	-
Ph-CH=CH-	85	7

m.p, IR, Mass and NMR data are given in reference 11.

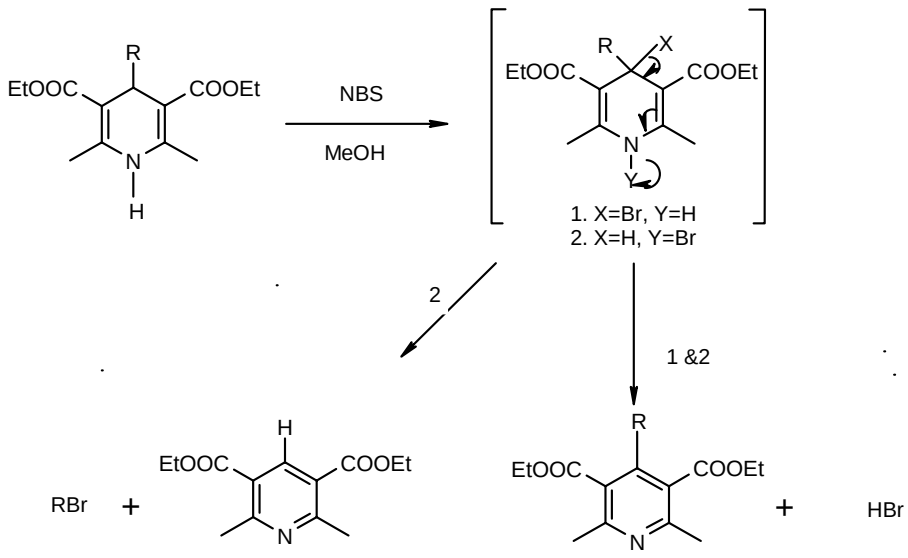
by the NBS replaces the hydrogen atom attached to the nitrogen atom of the Hantzsch pyridine. In the second step, elimination of either hydrogen bromide or allyl bromide takes place due to aromatization. The first mechanism does not explain the formation of dealkylated product but the second mechanism explains both de-alkylated and alkylated products. This methodology is specific for oxidation of dihydropyridines but resulted in a mixture of products when applied to analogous dihydropyrimidines.

In conclusion, we claim that oxidation of Hantzsch 1,4-dihydropyridines to corresponding pyridines with N-bromosuccinimide reported by us offers a simple



R= H, CH_3, 2-Furyl, CH_3-C_6H_4, NO_2-C_6H_4, CH_3O-C_6H_4

Scheme I



Scheme II

of the two types of mechanisms as suggested in **Scheme II**. In the first step the bromine radical produced by the NBS replaces the H atom in the fourth position of Hantzsch pyridine (as hydrogen radical and an intermediate is obtained) followed by elimination of hydrogen bromide from the above allylic bromide which occurs more readily because of aromatization. In the second mechanism the bromine radical produced

method using readily available reagent with excellent yield in short reaction time at room temperature.

Experimental Section

General procedure for the aromatization of 4-substituted Hantzsch 1,4-dihydropyridines: To a solution (or slurry) of 2,6-dimethyl-3,5-dicarbethoxy-4(methyl)-1,4-dihydro pyridine (0.5 g, 1.87 mmoles)

in 10 mL of methanol, N-bromosuccinimide (0.33 g, 1.87 mmoles) was added and the reaction mixture was stirred at room temperature. The colour of the solution changes immediately and the reaction proceeds instantaneously within five min. After completion of the reaction, as monitored by TLC, water (50 mL) was added and the mixture was extracted with chloroform (3 × 20 mL). The organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue obtained was column chromatographed over silica gel (60-120 mesh) and eluted with 20% ethylacetate and pet.ether mixture. Spectral data of diethyl 2,6-dimethyl-4-methylpyridine-3,5-dicarboxylate is given below: yield 95%, IR (Neat): 2981, 2937, 1725, 1567, 1239, 1107, 1041, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, 6H, J = 7.1 Hz), 2.28 (s, 3H), 2.53 (s, 6H), 4.42 (q, 4H, J = 7.2 Hz); ^{13}C NMR(75 MHz, $CDCl_3$): δ 14.2, 17.0, 22.8, 61.6, 127.7, 142.3, 154.9, 168.3; MS *m/z*: 265(M^+); Found: C, 63.55; H, 7.30; N, 5.21. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%. The analytical data for other products has been reported earlier[11].

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