$Tl(NO_3)_3$. $3H_2O$: a convenient oxidising agent for aromatisation of Hantzsch 1,4-dihydropyridines

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An efficient oxidative aromatisation of Hantzsch 1,4-dihydropyridines to the corresponding pyridines by using $Tl(NO_3)_3$. $3H_2O$ at ambient temperature is reported. The reactions were fast and the products were isolated in high yields.

Keywords: Hantzsch, 1,4-dihydropyridines, aromatisation, $Tl(NO_3)_3$. $3H_2O$

A number of Hantzsch 1,4-dihydropyridines (1,4-DHPs) have been introduced as potential drug candidates for the treatment of congestive heart failure.[1] In addition, the DHP nucleus is common to numerous bioactive compounds which include various vasodilator, antihypertensive, antitumor, and antidiabetic agents.[2] Aromatisation of Hantzsch 1,4-dihydropyridines has attracted considerable attention due to the fact that 1,4-DHPs-based calcium channel blockers are oxidatively converted to pyridine derivatives by the reaction of cytochrome P-450 in the liver.[3] Furthermore, the oxidation of 1,4-DHPs provides an easy access to pyridine derivatives.

Significant research has been carried out and many approaches have appeared for the aromatisation of Hantzsch 1,4-dihydropyridine.[4-18] Despite these intensive efforts, the development of a more effective method still remains interesting since many of the known methods require long reaction times, the need of an excess of the reagent, the requirement of severe reaction conditions and afford only poor to moderate yields of the products.

In the course of our study on the chemistry of 1,4-dihydropyridines, oxidation with $BaMnO_4$[19] and photooxidation[20] of these compounds was reported. We were interested in developing a convenient method for the oxidation of these compounds. Here, we report on a simple and efficient procedure for the preparation of pyridines by oxidative aromatisation of Hantzsch 1,4-dihydropyridines, using $Tl(NO_3)_3$. $3H_2O$ in acetonitrile at ambient temperature (Scheme 1). $Tl(NO_3)_3$. $3H_2O$ has been used for oxidation of phenols,[21] sulfides[22] and alkenes.[23]

As shown in Table 1, the oxidation of 1,4-dihydropyridines containing alkyl groups, such as methyl and propyl substituents, produced exclusively 4-substituted pyridines (**14,15**). Contrary to this, the oxidation of 1,4-dihydropyridines with a secondary alkyl group (**4**) and a benzyl group (**5**) at the 4-position gave only dealkylated pyridine derivative (**16,17**). This is in agreement with the observation made by others employing different oxidative conditions.[10,14,17-19] However, aryl substituted 1,4-dihydropyridines (**6–12**) furnished corresponding pyridine derivatives (Table 1).

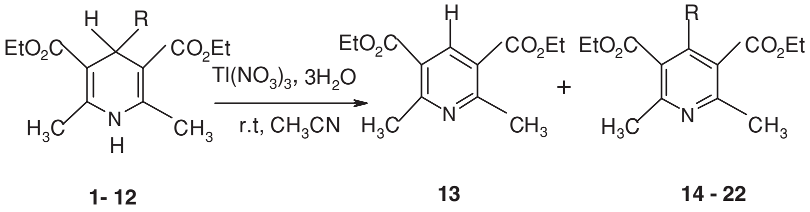
The influence of the various solvents on the yield and time of the reaction was investigated. The results obtained show that acetonitrile is a better choice for the oxidation reaction in comparison with chloroform, dichloromethane and carbon tetrachloride.

In summary, we have found that $Tl(NO_3)_3$. $3H_2O$ can serve as a mild, fast and efficient oxidant for the aromatisation of Hantzsch 1,4-dihydropyridines to pyridines.

Table 1 Oxidation of 1,4-dihydropyridines with $Tl(NO_3)_3$, $3H_2O$ in acetonitrile at r.t

Substrate	R	Product	Time/min	Yield/%[a]	M.p./°C	Lit. m.p./°C
1	H	13	5	92	71–72	70–71[12]
2	CH_3	14	15	85	Oil	Oil[12]
3	$CH_3CH_2CH_2$	15	20	96	Oil	Oil[24]
4	$(CH_3)_2CH$	13	20	93	71–72	70–71[12]
5	$C_6H_5CHCH_3$	13	30	90	71–72	70–71[12]
6	C_6H_5	16	5	90	60–61	62–64[12]
7	$3\text{-}NO_2C_6H_4$	17	180	90	62–63	62–63[13]
8	$4\text{-}NO_2C_6H_4$	18	150	96	112–114	113–115[12]
9	$4\text{-}ClC_6H_4$	19	10	93	65–67	65–66[14]
10	$3\text{-}BrC_6H_4$	20	20	89	68–70	70–72[16]
11	$2\text{-}CH_3OC_6H_4$	21	25	92	59–60	57–58[25]
12	2-Pyridyl	22	5	88	90–91	88[20]

[a]Isolated yields.



Scheme 1

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Experimental

1,4-dihydropyridines were synthesised by the reported procedures.[20,26] The oxidation products were characterised by comparison of their physical and spectral data with the authentic samples. Chemicals were purchased from Merk, Fluka and Aldrich chemicals companies.

Oxidation of Hantzsch 1,4-Dihydropyridines with thallium(III) nitrate trihydrate; General procedure: 1,4-dihydropyridines (0.2 mmol) and thallium(III) nitrate trihydrate (0.2 mmol) in acetonitrile (10 ml) was stirred at r.t for the time given in Table 1. The progress of the reaction was monitored by TLC. The mixture was filtered and then washed with acetonitrile. The filtrate was evaporated and, the product obtained was recrystalised with ethanol. Selected physical and spectroscopy data: Compound **13**, m.p. 71–72 °C [Lit.[12] 70–71 °C]; IR (KBr): 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 80 MHz): δ 1.4 (t, J = 7 Hz, 6H), 2.8 (s, 6H, 2- and 6-CH_3), 4.4 (q, J = 7 Hz, 4H), 8.6 ppm (s, 1H, 4-H). Compound **14**, m.p. oil [Lit.[12] oil]; IR (film): 1730 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 80 MHz): δ 1.4 (t, J = 7 Hz, 6H), 2.2 (s, 3H, 4-CH_3), 2.5 (s, 6H, 2- and 6-CH_3), 4.4 (q, J = 7 Hz, 4H). compound **22**, m.p. 90–91°C [Lit.[20] 88 °C]; IR (KBr): 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 80 MHz): δ 0.9 (t, J = 7 Hz, 6H), 2.6 (s, 6H, 2- and 6-CH_3), 4.0 (q, J = 7 Hz, 4H), 7.2–7.8 (m, 3H, pyridinyl), 8.6 ppm (s, 1H, pyridinyl 6-H).

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