

Oxidation of Hantzsch 1,4- Dihydropyridines to Pyridines with Thallium Triacetate

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ABSTRACT: Hantzsch 1, 4-dihydropyridines (1,4-DHPs) can be oxidized to the corresponding pyridine derivatives by thallium triacetate in high yields.

KEY WORDS: Oxidation, Thallium triacetate, Hantzsch dihydropyridines, Pyridine.

INTRODUCTION

Aromatization of Hantzsch 1,4-dihydropyridines (1,4-DHPs) has attracted considerable attention because these calcium channel blocker are oxidized to the corresponding pyridines by the action of cytochrome P-450 in the liver [1]. Also, some of these compounds act as NADH mimics, which reduce carbonyl groups [2]. In this reaction, 1,4-DHPs are oxidized to pyridines. In addition, the oxidation of Hantzsch 1,4-dihydropyridines is a way to achieve pyridine derivatives.

Many methods have been developed for the oxidation of 1,4-DHPs [3], but some of them suffer from low chemical yields [3f,j], strong oxidative conditions [3e,f,k], side product formation or dealkylation at 4-position [3f,i].

Because of the limitation mentioned, we decided to find a mild oxidant, thallium triacetate, which has been utilized in the dehydrogenation of α,β -unsaturated carbonyl compounds[4], oxidation of olefins [5], oxidation of enamines [6], and electrophilic aromatic bromination [7]. We hereby use it for oxidation of 1,4-dihydropyridines to their corresponding pyridines. Acetic

acid is the solvents of the reactions, other solvents such as dichloromethane and methanol were also experienced, but the yields were unsatisfactory. The oxidation was accomplished at reflux temperature, except for 1a which was performed at room temperature.

Compared to other methods, this aromatization was very clean as indicated by the absence of any side products in TLC. The outstanding features of this reaction are, excellent yields and the stability of the substituents at 4-position, i.e. dealkylation was not occurred by this oxidant.

EXPERIMENTAL

Thallium triacetate was purchased from Merck Co. and the 1,4-dihydropyridines were prepared according to the literature procedure [1a].

Typical procedure

To a solution of thallium triacetate (0.409 g, 1 mmol) in acetic acid (10 ml) was added Hantzsch 1,4-DHP (1e, 0.329 g, 1 mmol) as a representative substance. Then,

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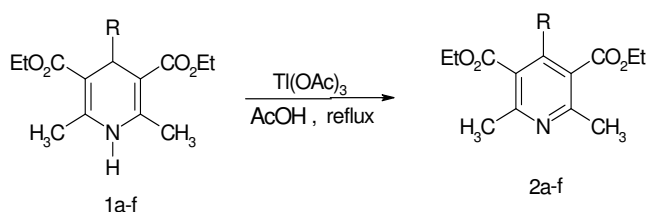
Table: Oxidation of Hantzsch 1,4-DHPs with thallium triacetate

1,4-DHPs ^b	Pyridines ^b	R	Time (min) ^a	Yield (%) ^c	m.p. (oC) ^a	Lit. m.p. (oC)
1a	2a	H	20	91	70	70-71
1b	2b	CH ₃	60	90	oil	oil
1c	2c	CH ₃ CH ₂	60	88	oil	oil
1d	2d	CH ₃ CH ₂ CH ₂	60	87	oil	oil
1e	2e	C ₆ H ₅	180	90	61-62	61-62
1f	2f	4-CH ₃ C ₆ H ₄	180	86	72-73	72-73

a: all the reaction are performed at reflux temperature except for 1a which was treated at room temperature.

b: all 1,4-DHPs and corresponding pyridines are fully characterized by their mps, IR and ¹H-NMR spectra.

c: yields refer to pure isolated products.



reaction mixture was stirred at reflux temperature. Then progress of the reaction was followed by TLC. After 3 h, the reaction was completed and the mixture was poured into water. The content was diluted with ether (45 ml) and wash with water (3 x 10 ml) and then neutralized by Na₂CO₃ solution, extracted with ether (3 x 15 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and resulting crude product was crystallized from ethanol to give pure product in 90 % yield (3.012 g) as a pale yellow solid, m.p. 60-61 oC (lit. m.p. 61-62 oC).

In summery, we have found a, mild and clean oxidant for oxidation of 1,4-DHPs to the corresponding pyridines in excellent yields and the substituents at 4-position are stable.

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