

Research Article

Hantzsch Reaction Starting Directly from Alcohols through a Tandem Oxidation Process

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A Brønsted acidic ionic liquid, 3-(N,N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulphate ([DDPA][HSO₄]), has been successfully applied to catalyze sequential oxidation of aromatic alcohols with NaNO₃ followed by their condensation with dicarbonyl compound and ammonium acetate. The corresponding pyridine analogues of Hantzsch 1,4-dihydropyridines could be obtained as a major product with high yields by the multicomponent reaction. The present work utilizing alcohols instead of aldehyde in Hantzsch reaction is a valid and green alternative to the classical synthesis of the corresponding pyridine analogues of Hantzsch 1,4-dihydropyridines.

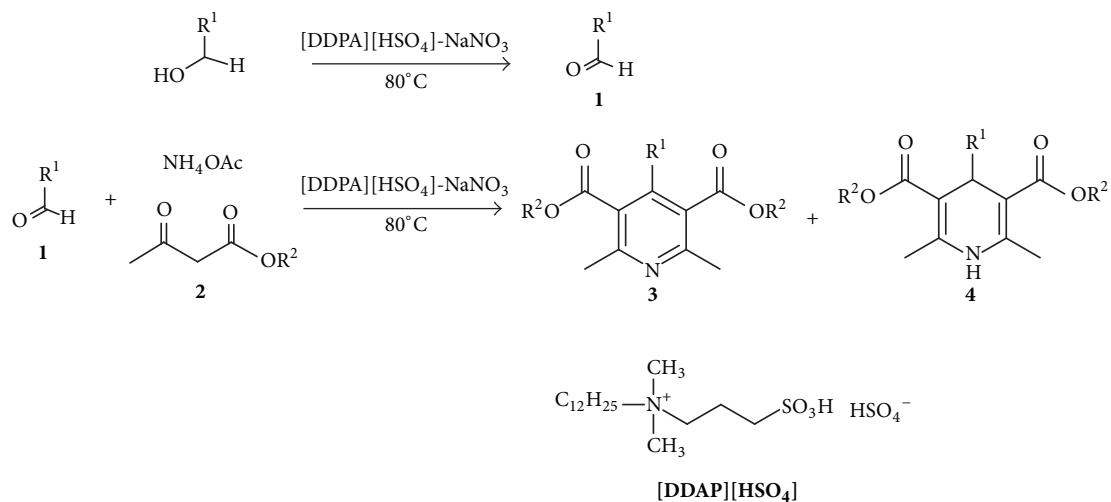
1. Introduction

1,4-Dihydropyridines and their derivatives are an important class of heterocycles in biologically active and naturally occurring molecules [1–3]. Many methods for the preparation of 1,4-dihydropyridines have been reported and most of them are mainly confined to the modification and optimization of the Hantzsch multicomponent synthesis between an aldehyde, a 1,3-dicarbonyl compound, and a source of ammonia [4–6]. At the same time, the oxidative aromatization of 1,4-dihydropyridines has also been extensively studied and numerous oxidizing reagents, namely, CuBr₂ [7], SiO₂/P₂O₅-SeO₂ [8], H₂O₂/Co(OAc)₂ [9], and Na₂S₂O₄/TBHP [10], have been used for the aromatization of 1,4-dihydropyridines. Some reports have observed that the direct oxidative procedure was very efficient for the preparation of Hantzsch pyridines under microwave-assisted condition or solvent-free condition [11–13]. However, the search for the new readily available and green methods is still being actively pursued.

The aldehydes in Hantzsch reaction are more volatile, toxic, or unstable than their corresponding alcohols. Recently, tandem oxidative processes (TOP) [14–16] in which the alcohol is oxidized to the aldehyde in situ have developed into an innovative addition to synthetic organic chemistry.

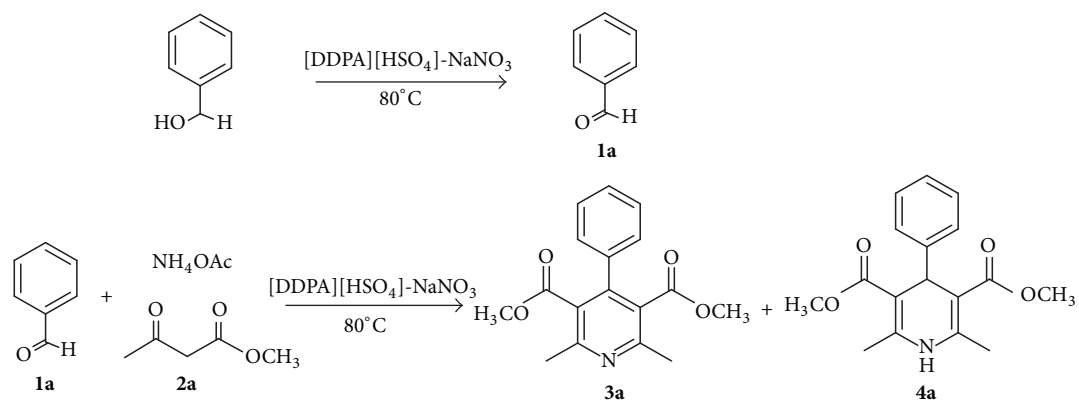
Garima et al. [17] reported an efficient oxidative access to 3,4-dihydropyrimidin-2-(1H)-ones directly from aromatic alcohols. In the literature, a Brønsted acidic ionic liquid has been successfully applied to catalyze sequential oxidation of aromatic alcohols with NaNO₃ followed by their condensation with urea and dicarbonyl compounds.

Ionic liquids have attracted extensive interest and played a dual solvent-catalyst role in organic synthesis due to their favourable properties [18]. Brønsted acidic ionic liquids combining the advantageous characteristics of solid acids and mineral acids are designed to replace traditional mineral liquid acids in catalytic action [19]. In continuation of our interest in exploring green catalysis of ionic liquids [20, 21], we herein report a Brønsted acidic ionic liquid 3-(N,N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulphate ([DDPA][HSO₄]) catalyzed sequential oxidation of aromatic alcohols with NaNO₃ followed by their condensation with dicarbonyl compound and ammonium acetate. We have found that the corresponding pyridine analogues of 1,4-dihydropyridines could be obtained as a major product by the multicomponent reaction, whereas only trace amounts of 1,4-dihydropyridines were detected (Scheme 1).



$\text{R}^1 = \text{aryl}$
 $\text{R}^2 = \text{CH}_3, \text{C}_2\text{H}_5$

SCHEME 1: Synthesis of the corresponding pyridine analogues of 1,4-dihydropyridines directly from aromatic alcohols.



SCHEME 2: Model Hantzsch reaction directly from benzyl alcohol in [DDPA][HSO₄].

2. Materials and Methods

2.1. General Reagents and Instrumentation. All starting chemicals (AR grade) were purchased from commercial suppliers and used without further purification. Melting points were determined on a Thomas-Hoover capillary apparatus and were uncorrected. The IR spectra were recorded with a Bomem Michelson model 102 FTIR. ¹H NMR spectra were recorded on Bruker DRX (500 MHz) spectrometer. Gas chromatography (GC) was recorded on a HP 6890 Plus GC instrument. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. The ionic liquid [DDPA][HSO₄] was synthesized according to the literature procedures [22].

2.2. Experimental Procedures. A mixture of an aromatic alcohol (3 mmol), sodium nitrate (6 mmol), and [DDPA][HSO₄] (1.2 mmol) was heated with stirring at 80°C for 5–30 min in a round-bottomed flask. After oxidation of the aromatic alcohol (monitored by TLC), dicarbonyl compound (3 mmol) and ammonium acetate (3 mmol) were added. The mixture

was heated with stirring at 80°C for 1–3 h. The reaction was monitored by TLC after an interval of 15 min. After completion, the reaction mixture was cooled to rt and extracted with ethyl acetate. The organic layer was separated and washed with brine solution and then dried over anhydrous Na₂SO₄. Solvent was removed in vacuo and the crude product was purified by chromatography over silica gel. The aqueous layer (containing the ionic liquid) could be reused directly in the next run without further purification.

3. Results and Discussion

In the initial experiments, the multicomponent reaction of benzyl alcohol, ethyl acetoacetate, and ammonium acetate was selected as a model reaction (Scheme 2). We studied the tandem oxidative cyclocondensation of benzyl alcohol, ethyl acetoacetate, and ammonium acetate in the presence of [DDPA][HSO₄] with NaNO₃ at 80°C, but no reaction took place even after stirring the reaction mixture for 12 h. However, we observed the formation of 1,4-dihydropyridine

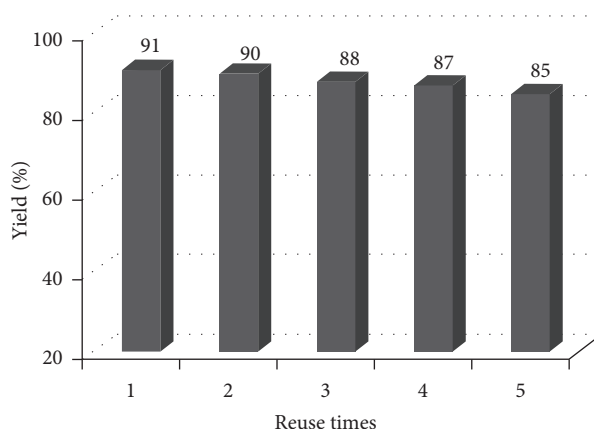


FIGURE 1: Reusability of the ionic liquid [DDPA][HSO₄].

TABLE 1: Model of Hantzsch reaction directly from benzyl alcohol in different ionic liquids^a.

Entry	Ionic liquid	Ratio ^b	Yield (%) ^c
1	[DDPA][HSO ₄]	3a : 4a = 93 : 7	91
2	[Hmim][H ₂ PO ₄]	3a : 4a = 86 : 14	37
3	[Hmim]NO ₃	—	—
4	[bmin]BF ₄	—	—

^aBenzyl alcohol (3 mmol), ethyl acetoacetate (3 mmol), ammonium acetate (3 mmol), ionic liquid (1.2 mmol), and NaNO₃ (6 mmol), 1 h. ^bYields and ratios were based on GC analysis. ^cYields referred to the desired product **3a**.

and its corresponding pyridine when ethyl acetoacetate and ammonium acetate were added to the reaction after the oxidation of the alcohol to the aldehyde was complete.

Subsequently, different ionic liquids were screened for the same model reaction. The results are summarized in Table 1. It was shown that the reaction was unsuccessful in [Hmim]NO₃ and [bmin]BF₄ because an acidic hydrogen is absent in the two ionic liquids. The reaction could proceed effectively in [DDPA][HSO₄] but relatively low yields of product in [Hmim][H₂PO₄]. This is probably due to the lower Brønsted acidity associated with [H₂PO₄]. Thus, [DDPA][HSO₄] plays a dual role as an acid catalyst and as a solvent for both the oxidation of alcohol and the subsequent condensation. The product **4a** could be converted to product **3a** in the exposure of air and the NaNO₃-[DDPA][HSO₄] system could speed up the process.

To explore the stability of the ionic liquid after reaction, the recycling performance of [DDPA][HSO₄] in the same model reaction was investigated. After the reaction, the products were separated from the catalytic system by extraction with ethyl acetate. The aqueous layer (containing the catalyst) was reused in the next run without further purification. As shown in Figure 1, the catalyst could be reused at least five times without significant decrease in catalytic activity.

With these results in hand, we decided to explore the scope of this method. A variety of substituted aromatic alcohols was extended in the procedure in the presence of

[DDPA][HSO₄] and the obtained results are summarized in Table 2. It can be seen that the tandem oxidation of aromatic alcohols followed by their condensation with dicarbonyl compound and ammonium acetate in the presence of [DDPA][HSO₄] proceeded smoothly to give the corresponding products in good yields. Aromatic alcohols with a strong electron-withdrawing group required a longer time for the reaction (Table 2, entries 8 and 9), whereas aromatic alcohols with electron-donating substituents gave excellent yields (Table 1, entries 2, 4, 5, and 6) in a shorter reaction time. An important feature of the present protocol is the ability to tolerate variation in all components simultaneously.

A plausible mechanism for the sequential oxidation of aromatic alcohols with NaNO₃ followed by their condensation with dicarbonyl compound and ammonium acetate is depicted in Scheme 3. In acidic ionic liquid [DDPA][HSO₄], aromatic alcohols were oxidized to aromatic aldehydes with NaNO₃. After the oxidation completion, a multicomponent reaction of the aromatic aldehydes, dicarbonyl compound, and ammonium acetate was conducted in [DDPA][HSO₄] and then the Hantzsch 1,4-dihydropyridines were formed. Subsequently, the Hantzsch 1,4-dihydropyridines could be further oxidized to the desired corresponding pyridine analogues with NaNO₃-[DDPA][HSO₄] in air.

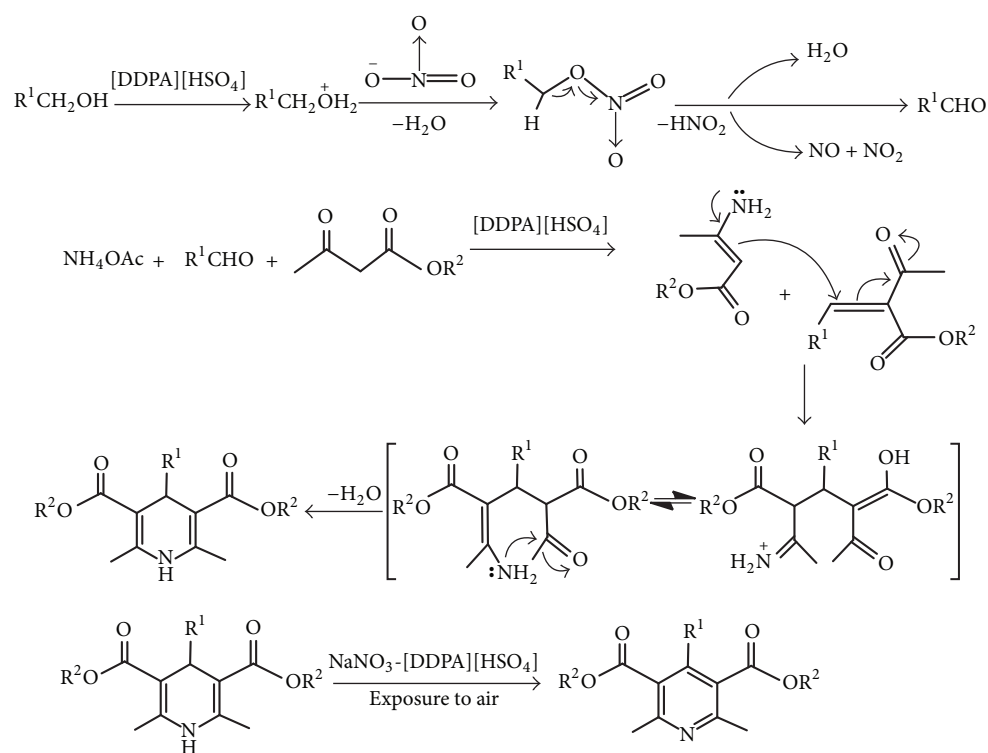
4. Conclusions

In conclusion, we have described an efficient protocol for Hantzsch reaction starting from alcohols using NaNO₃-[DDPA][HSO₄] system. The protocol involves [DDPA][HSO₄] catalyzed sequential oxidation of aromatic alcohols with NaNO₃ followed by their condensation with dicarbonyl compound and ammonium acetate. The corresponding pyridine analogues of Hantzsch 1,4-dihydropyridines could be obtained as a major product with high yields by the multicomponent reaction. The present work utilizing alcohols instead of aldehyde in Hantzsch reaction is a valid and green alternative to the classical synthesis of the corresponding pyridine analogues of Hantzsch 1,4-dihydropyridines.

TABLE 2: Hantzsch reaction of different substrates catalyzed by [DDPA][HSO₄]^a.

Entry	R ¹	R ²	Time (h)	Yield (%) ^b	Mp °C (lit. Mp °C) ^c
1	C ₆ H ₅	CH ₃	1	91	118 (118) [7]
2	4-MeO-C ₆ H ₄	CH ₃	1	93	91 (92) [7]
3	4-Cl-C ₆ H ₄	CH ₃	2	85	118 (120) [7]
4	C ₆ H ₅	CH ₃ CH ₂	1	90	60-61 (63-64) [23]
5	2-MeO-C ₆ H ₄	CH ₃ CH ₂	1	93	58 (55-57) [24]
6	4-MeO-C ₆ H ₄	CH ₃ CH ₂	1	91	52 (51-52) [7]
7	4-Cl-C ₆ H ₄	CH ₃ CH ₂	2	83	66 (65-67) [23]
8	3-NO ₂ -C ₆ H ₄	CH ₃ CH ₂	3	76	60 (60) [7]
9	4-NO ₂ -C ₆ H ₄	CH ₃ CH ₂	3	72	115 (114-115) [23]

^a Benzyl alcohol (3 mmol), ethyl acetoacetate (3 mmol), ammonium acetate (3 mmol), ionic liquid (1.2 mmol), and NaNO₃ (6 mmol). ^b Yields were based on GC analysis and referred to the desired product 3. ^c Mp of product 3.

SCHEME 3: Plausible mechanism for Hantzsch reaction directly from alcohol in [DDPA][HSO₄].

Conflicts of Interest

All authors declare no conflicts of interest.

Acknowledgments

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