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Catalyst-free synthesis of dihydropyridine from barbituric acid in water

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Abstract An operationally simple, atom-economical, and green procedure has been developed for the synthesis of dihydropyridine derivatives by a simple condensation of barbituric acid, aldehyde, and ammonium acetate in water under catalyst-free conditions. Excellent yields and purity were obtained with only filtration and washing with hot water and ethanol.

Keywords Aldehydes · Barbituric acid · Dihydropyridine · Novel hydrogen bonding · Water chemistry

Introduction

The development of multipoint hydrogen-bonding motifs that form complexes with high stability and selectivity is an important subject for the understanding of conformational analysis [1–3], protein structure [4–6], crystal packing [7], molecular recognition processes [8, 9], the stabilization of inclusion complexes [10], and the stability and possibly even in the activity of biological macromolecules [11, 12].

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With the increasing interest in developing environmentally benign reactions, the atom-economic processes, or reactions without using any catalyst, and organic solvent are one of the most exciting challenges in chemistry. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, which are widely used in large amounts for organic reactions, have posed a serious threat to the environment. Thus, the design of a green catalytic reaction under catalyst-free conditions in water has received tremendous attention in recent times in the area of green synthesis [13–16].

Experimental

Materials and methods

All chemicals were purchased from commercial sources and were used without further purification. Water and other solvents were distilled before being used. IR spectra were prepared on a Galaxy series FT-IR 5000 spectrophotometer using KBr discs. NMR spectra of DMSO-d_6 solutions of samples were recorded on Bruker spectrophotometer 500 MHz for ^{1}H NMR and 125 MHz for the ^{13}C NMR. Chemical shifts are reported in ppm units relative to TMS as internal standard. Most of these compounds have melting point higher than 300 °C.

General procedure

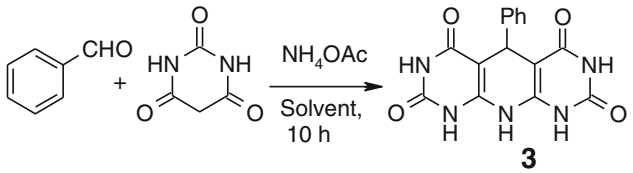
To a well-stirred mixture of an aldehyde (5 mmol), and barbituric acid (10 mmol) in water/ethanol (10 mL) was added ammonium acetate (8 mmol) and the reaction mixture was heated under reflux for 12–18 h. The reaction was allowed to cool and the resulting precipitate was filtered and then washed with hot water and ethanol to give pure dihydropyridines. All compounds were known and IR and ^{1}H NMR spectra were found to be identical to the ones described in literature.

Results and discussion

In continuation to our research work devoted to the development of green organic chemistry in water and deep eutectic solvent [17–22]. Herein, we described an efficient, novel, and green methodology for the direct synthesis of biologically active and hydrogen bond-forming dihydropyridine derivatives with a one-pot reaction of barbituric acid, aldehyde, and ammonium acetate performed at excellent yields without a catalyst in water (Table 1).

1,4-Dihydropyridines are generally synthesized by the classical Hantzsch reaction, which involves the condensation of aldehydes β-ketoester and ammonia or ammonium acetate in acetic acid [23]. However, this method cannot be applied for the synthesis of different substituted biologically active 1,4-dihydropyridines. Recently, several modifications for this classical method have been reported for the facile and efficient synthesis of important dihydropyridine derivatives [24–32].

Table 1 Optimization of reaction condition



Entry	Solvent (10 mL)	Temperature (°C)	Yields (%)
1	Toluene	110	30
2	CCl_4	80	20
3	THF	60	10
4	CH_3CN	80	50
5	CH_2Cl_2	50	30
6	CH_3OH	60	60
7	C_2H_5OH	80	70
8	Water	100	80
9	SFC	100	30
10	Water/ethanol (5:1)	100	85

Reaction condition: barbituric acid (10 mmol), benzaldehyde (5 mmol), ammonium acetate (8 mmol), solvent (10 mL)

In spite of the potential utility of these reagents, most of the existing methods for the synthesis of 1,4-dihydropyridines suffer from drawbacks such as low yields, long reaction times, occurrence of several side products, unsatisfactory yields, long reaction times, and pollution of the environment due to the use of organic solvent and/or acidic or basic promoters.

While searching for new acidic partners in the Hantzsch reaction, we thought that the suitable new active methylene compounds with additional acidic groups on the barbituric acid could trigger both the aldehyde activation and the conjugate addition in the key step of the reaction. Indeed, we were delighted to find for the first time that barbituric acid (10 mmol) reacts with benzaldehyde (5 mmol) and ammonium acetate (8 mmol) by a very efficient three-component reaction under catalyst-free conditions. This reaction proceeds smoothly at refluxing water within a few hours to provide the desired new dihydropyridine 3 in 80 % yield (Table 1).

Encouraged by this result, it seemed appropriate to explore the influence of the other solvents. After substantial solvent screening in the model reaction, it was found that the use of water/ethanol (5:1) resulted in a slightly improved yields. The nonpolar solvents, such as toluene, CCl_4 did not give desired products under similar reaction conditions (Table 1, entries 1, 2). The polar aprotic solvents (CH_2Cl_2, THF, and CH_3CN) also afforded comparatively lower yields (Table 1, entries 3–5). The polar protic solvents (C_2H_5OH and CH_3OH) still gave comparatively lower conversions (Table 1, entries 6, 7).

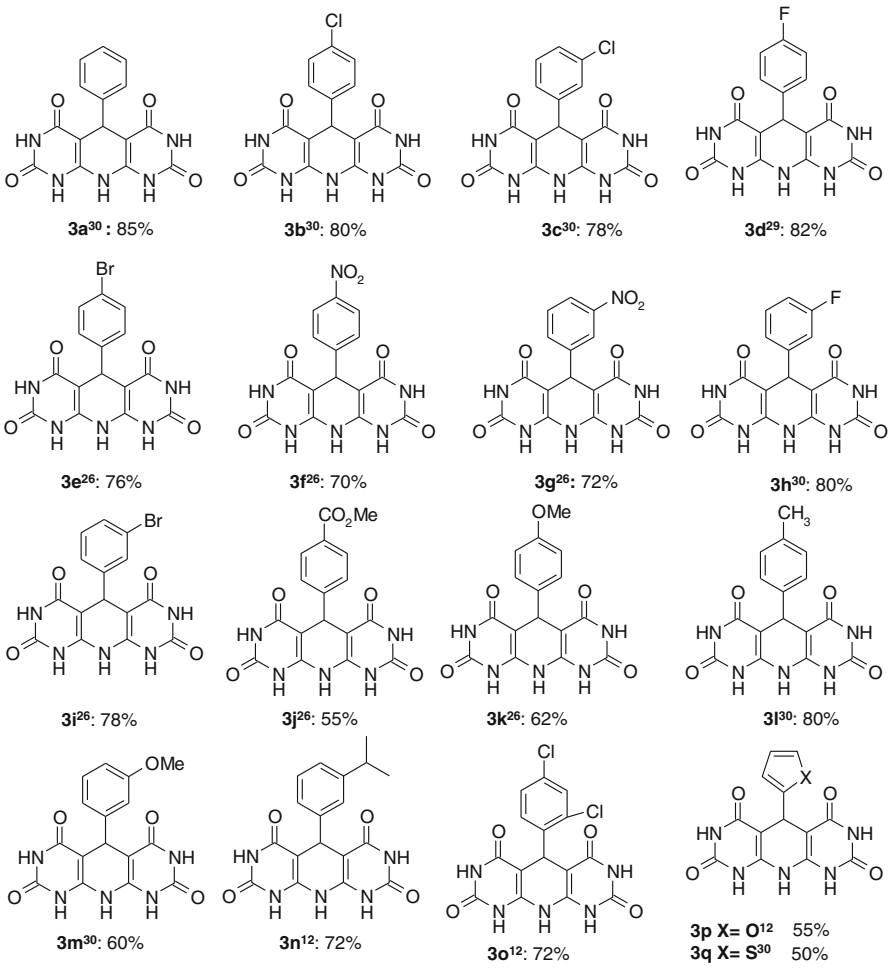


Fig. 1 Synthesis of dihydropyridines in water

The high-yield, simple reaction protocol, and originality of this green process prompted us to explore the reaction more widely. The reaction between various aromatic aldehydes with different substituents, barbituric acid, and ammonium acetate were carried out under optimum conditions and the selected data are summarized in Fig. 1. From these results, we could see that all reactions proceeded smoothly to afford the corresponding products in moderate to good yields. We also found that all aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently to give improved yields compared to the classical Hantzsch reaction. When aliphatic aldehydes were used in this protocol under the above-optimized conditions, unfortunately, the expected products could not be obtained.

Conclusions

In summary, a simple and entirely green protocol has been devised for the first practical synthesis of novel dihydropyridine via a one-pot three-component reaction of aromatic aldehydes, barbituric acid, and ammonium acetate in water. The yields are excellent and the product isolation is very straightforward. Because of the organic and catalyst-free reaction condition, pure products were obtained with simple filtration and washing with hot water.

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