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Research Paper

Water Mediated Synthesis of Highly Functionalized Pyrazolone derivatives using Tetraethylammoniumbromide

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Abstract: *An efficient, cleaner and environment benign Knoevenagel condensation of aromatic aldehydes with 3-methyl-5-pyrazolone using TEAB in water media is described. The reaction is highly chemoselective with no side reactions. The procedure does not involve the use of any additional reagent/catalyst, produces no waste, and represents a green synthetic protocol.*

Keywords: Green synthetic protocol, Knoevenagel condensation, 3-methyl-5-pyrazolone, TEAB, Water mediated.

Introduction

There has been growing concern over the environmental impact of chemicals so that cleaner green reaction conditions in synthetic processes have been advocated. The tight legislation to maintain greenness requires us to prevent the generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagents) and minimize the energy requirement [1]. In this context, organic reactions under solvent-free[2,3] and aqueous[4-6] conditions have increasingly attracted chemists interests, particularly from the view point of green chemistry [7]. The use of water as the reaction medium offers several advantages as, (i) it is cheap, noninflammable, non-toxic and safe for use, (ii) it eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates the consumption of drying agents, energy and time, (iii) the unique physical and chemical properties of water often increase the reactivity or selectivity unattainable in organic solvents[8] and (iv) the product may be easily isolated by filtration. Thus, reactions in aqueous medium have gained considerable momentum [9-11].

We have focused our attention on the development of a green synthesis of pyrazolone derivatives due to their wide ranges of application. The derivatives of pyrazolone are important class of antipyretic and analgesic compounds [12]. 3-methyl-4-arylmethylene-5-pyrazolones are very useful intermediates in the synthesis of substituted pyrazolones, generally, which were prepared by the condensation of 3-methyl-5-pyrazolone with aromatic aldehydes [13,14]. Recently, some new methods such as microwave irradiation[15], supported solid catalyst[16], solid state reaction[17], etc. have been applied to facilitate this reaction. However, some of these methods are limited due to slow reaction rate, low yields, side products, tedious workup, and the use of toxic solvents or expensive catalysts. These necessitate the development of a more efficient/convenient and environmentally friendly methodology. Our efforts towards the synthesis of novel heterocycles using various green approaches[18,19] and catalyst[20] motivated us to synthesize some pyrazolone derivatives using greener approach. Herein, we wish to report a green synthesis for the pyrazolone derivatives using TEAB and water as a solvent.

Material and Methods

Melting points were determined on electro thermal apparatus using open capillaries and are uncorrected. Thin layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. All solvents and reagents were purchased from Aldrich and Merck with high-grade quality, and used without any purification. The products were known, their physical data were compared with those of authentic samples reported in literature and found to be identical [21-28].

Results and Discussion

In this paper, we wish to report an environment-friendly procedure for Knoevenagel condensation between aromatic aldehydes and 3-methyl-5-pyrazolone in the presence of tetra ethyl ammonium bromide (TEAB) using water as an energy transfer medium.

Our developed method involves the heating of a mixture of aromatic aldehyde with 3-methyl-5-pyrazolone using TEAB and water at 70°C temperature (Scheme 1). As soon as heating is stopped and after few minutes of cooling, 4-arylmethylene-3-methyl-5-pyrazolone are separated out. For instance, in case of 3a, Table 1, when a mixture of benzaldehyde 2a (5 mmol), 3-methyl-5-pyrazolone 1a (5 mmol), TEAB (2.5 mmol) and water (10 mL) was heated at 70°C, maximum Knoevenagel condensation took place within 6 hr and 4-benzyledine-3-methyl-5-pyrazolone was isolated in 83% yield. Furthermore, the reaction was carried out separately in distilled water and tap water. No significant difference was observed either in the reaction time or in the product yield.

Scheme 1: TEAB mediated synthesis in water

avoided. All the tested aromatic aldehydes bearing various substituents such as chloro, nitro, methyl, methoxy, hydroxyl, *N*,*N*′-dimethylamino, *etc.*, could successfully react with 3-methyl-5-pyrazolone within 6 to 6.5 hours with high yields (Table 1). The reactions were chemoselective and no substitution of the halogen atom (entries 4 and 5) or the nitro group (entries 7 and 8), dealkylation (entries 2 and 3), and reduction of the nitro group (entries 7 and 8) took place although NH is good nucleophile.

The dimethylamino (entry 9) and hydroxyl (entry 6) groups did not interfere. The examined tetraethylammoniumbromide as a catalyst and water as a solvent, were efficient and gave excellent results, which could truly be compared with other catalysts and classical molecular solvents with the advantage of rate acceleration and increase of yield. Interestingly, we have not obtained the side products 4, 4′-arylmethylene-bis-(3-methyl-5-pyrazolones), which were usually accompanied with the target compounds, when the reaction was carried out in classic molecular solvents [15,16].

When the supernatant water retained the product as a colloidal form, resulting in lower yields, the product was isolated by extraction of the reaction mixture with $CHCl_3$. In most cases, the isolated product was pure and did not require additional efforts at purification. Where required, the purification was achieved by crystallization with $CHCl_3$. When the residue obtained after decanting off the water was not free-flowing and stuck to the walls of the reaction flask, the product was isolated by dissolving the residue in Et_2O.

To demonstrate the generality, all the above chosen aromatic aldehydes were treated with 1-phenyl-3-methyl-5-pyrazolone as representatives of substituted 3-methyl-5-pyrazolone. All the aromatic aldehydes with various substituents could successfully react with 1-phenyl-3-methyl-5-pyrazolone with good yields (entries 10–18, Table 1).

The method is then extended for other aromatic aldehydes sub

To ensure the method as proficient on gram scale, the reaction of benzaldehyde (20 mmol) with 3-methyl-5-pyrazolone (20 mmol) was carried out and the corresponding 4-arylmethylene 3-methyl-5-pyrazolone was obtained in 85% yield.

Table 1
Knoevenagel condensation of aromatic aldehydes with 3-methyl-5-pyrazolone

Entry	Product	R	R_1	Yield(%)[a]	Mp °C
1	**3a**	H	H	83	171-172
2	**3b**	H	4-Me	76	164-166
3	**3c**	H	4-OMe	75	166-167
4	**3d**	H	2-Cl	65	156-158
5	**3e**	H	4-Cl	71	154-155
6	**3f**	H	2-OH	79	137-138
7	**3g**	H	2-NO_2	86	243-244
8	**3h**	H	4-NO_2	81	170-172
9	**3i**	H	4-$N(Me)_2$	80	158-160
10	**3j**	Ph	H	76	110-112
11	**3k**	Ph	4-Me	72	115-116
12	**3l**	Ph	4-OMe	68	125-127
13	**3m**	Ph	2-Cl	68	156-157
14	**3n**	Ph	4-Cl	74	160-162
15	**3o**	Ph	2-OH	79	144-145
16	**3p**	Ph	2-NO_2	65	159-160
17	**3q**	Ph	4-NO_2	71	186-188
18	**3r**	Ph	4-$N(Me)_2$	78	196-198

[a]Yields after purification.

General Procedure: The magnetically stirred mixture of 3-methyl-5-pyrazolone 1(a,b), aromatic aldehyde 2(a-i) (5 mmol), and TEAB (2.5 mmol) in water (10 mL) was heated at 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction (6 h), reaction mixture was cooled to room temperature, the water was decanted off, the residue was crystallized from chloroform to give pure 4-arylidine-3-methyl-5-pyrazolone 3(a-r) with good to excellent yields.

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