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Research Paper

Citric Acid: An Efficient and Biodegradable Catalyst for the Convenient Synthesis of 1,5-Benzodiazepines in Water

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Abstract: In the present protocol, efficient synthesis of 1,5-benzodiazepines under milder reaction conditions in aqueous medium is described. Successful utilization of citric acid in water as a novel catalytic system is demonstrated.

Introduction

Development of novel synthetic methodologies to facilitate the preparation of desired molecule is an intense area of research. In this regard, efforts have been made constantly to introduce new methodologies that are efficient and more compatible with the environment. One of the most desirable approaches to address this challenge constitutes a search of surrogates for traditionally employed organic solvents, which suffer from various health and environmental concerns [1]. From the view point of green chemistry, water would be the perfect solvent to carry out chemical operations due to its safe, non-toxic, inexpensive and environmentally friendly nature [2]. In this way, aqueous media is acting as a stepping stone in the greener synthesis of bioactive heterocyclic compounds.

Benzodiazepines constitute an important class of biodynamic heterocycles and synthesis of these compounds has been receiving great attention in the field of medicinal and pharmaceutical chemistry owing to their broad spectrum of biological/pharmacological activities [3] and their often use as analgesic, sedative, hypnotic, *anti*-consultant, *anti*-anxiety, *anti*-depressive, and *anti*-inflammatory agents [4]. In addition, 1,5-Benzodiazepines are valuable synthetic intermediates for the preparation of other heterocyclic compounds such as triazolo-, oxadiazolo-, oxazino-, furano-, and quinazolino-benzodiazepines [5].

Cyclocondensation of *o*-phenylenediamines with carbonyl compounds is one of the well established synthetic methods for the construction of 1,5-benzodiazepine derivatives [6]. A wide range of catalysts,

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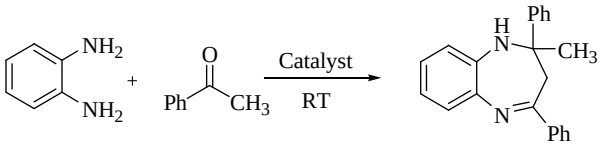
such as $BF_3.OEt_2$ [7], polyphosphoric acid [8], $CeCl_3$-NaI/SiO_2 [9], I_2 [10], $ZnCl_2$ [11], SmI_2 [12], $YbCl_3$ [13], MgO/$POCl_3$ [14], Amberlyst-15 [15], $Yb(OTf)_3$ [16], $Ga(OTf)_3$ [17], Al_2O_3/P_2O_5 [18], AcOH/MW [19], sulfated zirconia [20], NBS [21], cerium ammonium nitrate (CAN) [22], montmorillonite K10 [23], $Ag_3PW_{12}O_{40}$ [24], $InBr_3/InCl_3$ [25] and ionic liquids [26] have been utilized for this transformation, alongwith their own merits and demerits. Since, 1,5-Benzodiazepine derivatives keeps enormous significance in pharmaceutical and medicinal fields and hence, development of simple, eco-friendly and efficient routes for their synthesis is still desirable.

Utilization of naturally as well as easily available and biodegradable catalyst for organic transformation is achieving enormous significance in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of these reactions meet the standards of established organic reactions. In this regard, Citric acid keeps the potential of performing the role of ideal catalyst. It is a relatively strong organic acid. Citric acid and its salts are widely used because they are nontoxic, relatively non-corrosive, safe to handle, and easily biodegraded. Additionally, there is a single report on the use of citric acid as a catalyst in organic synthesis [27]. Therefore, in continuation our interest towards the development of novel synthetic methodologies [28], attempt has been made to carry out the synthesis of 1,5-benzodiazepines using citric acid as a catalyst.

Results and Discussion

For our initial study, reaction of *o*-phenylenediamine with acetophenone using water as a solvent was considered as a standard model reaction (Scheme 1). Model reaction in the absence of catalyst did not led to desired product formation. It means intervention of catalyst was must for initiation of the reaction.



1a **2a** **3a**

Scheme 1. Standard model reaction

To obtain best reaction conditions, different water-soluble acid catalysts were screened for the model reaction *viz*. boric acid, oxalic acid, *p*-TSA, EDTA.2Na salt and citric acid. With the use of EDTA.2Na salt the product was formed in poor yields, 39% (Table 1, entry 4). In contrast, boric acid, oxalic acid, and *p*-TSA afforded the product good yields (Table 1, entries 1-3). In comparison with these, citric acid proved to be most efficient catalyst which delivered the desired product in higher yield (84%) within 60 min (Table 1, entry 5).

The model reaction was further investigated using different solvent systems in a view, whether, the reaction rate could be accelerated and, the product yield could be enhanced. During this study solvent system like ethanol, aqueous ethanol, methanol and water were tested but, use of water proved to be suitable. Reaction under neat conditions afforded the product in 75% yield.

To evaluate the temperature effect on reaction rate model reaction was performed at different temperatures such as room temperature, 50 °C, 60 °C, 80 °C and reflux temperature. Temperature of 50 °C found to carry out the reaction efficiently in 91% yield (Table 1, entry 6). Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 50 °C did slow down the reaction rate.

Success of Citric acid as a catalyst in the presence of water as a solvent could be

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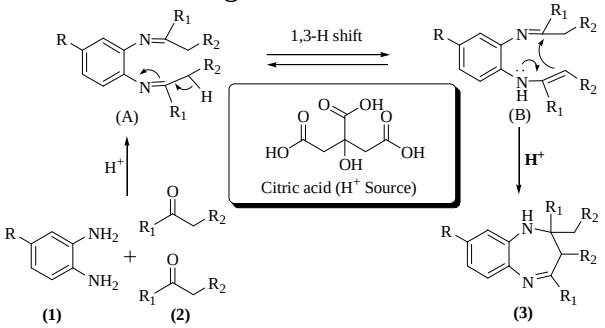
attributed to the following points - (i) Citric acid is a slightly stronger acid than typical carboxylic acids because the anion can be stabilized by intramolecular hydrogen-bonding from other protic groups on citric acid. (ii) One more aspect that could be helpful for bringing the reaction in favor of water is hydrophobic interactions which induce favorable aggregation of organic substrates in water.

To determine the exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of citric acid such as 2.5, 5, 10 and 15 mol%. During this study, formation of the product was observed in 41, 62, 91 and 90% yield respectively (Table 1, entry 7). This indicated that 10 mol% of citric acid was sufficient to carry out the reaction smoothly.

A plausible mechanism involved in citric acid catalyzed cyclocondensation reaction for the synthesis of 1,5-benzodiazepines can be outlined as follows: *o*-phenylenediamine (**1**) reacts with two molecules of ketone (**2**) in the presence of citric acid as a catalyst to form schiff base (**A**), which undergoes 1,3-H shift and get converted into intermediate (**B**). Thus formed intermediate (**B**) *via* subsequent cyclization affords the final product (**3**), i.e. 1,5-benzodiazepine. Diagrammatic representation of the mechanism is rationalized in Figure 1.



Scheme 2. A plausible mechanism involved in the synthesis of 1,5-benzodiazepines.

In further set of experiments, different *o*-phenylenediamines with respect to variety of ketones were examined. All of these substrates were found to be compatible under the optimized reaction condition delivering the product in good yields. All the results are summarized in Table 2. Structures of the products were confirmed on the basis of IR, ^{1}H NMR, and mass spectroscopic data.

Conclusion

In summary, we have developed an efficient, mild and clean synthetic protocol for 1,5-benzodiazepines. In this method, attempt has been made for exploitation of the catalytic activity of citric acid in organic transformation. Water is not only inexpensive and environmentally benign solvent but also plays a distinguished role in reactivity and selectivity. Citric acid catalyzed the reaction efficiently without using any harmful organic reagents/solvents.

Experimental Section

All chemicals were purchased and used without any further purification. Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^{1}H NMR spectra were recorded on NMR spectrometer Varian AS 400 MHz spectrometer in DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS. Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES).

Typical experimental procedure for the synthesis of compound (3a)

A mixture of *o*-phenylenediamine **1a** (110 mg, 1 mmol), acetophenone **2a** (240 mg, 2 mmol), citric acid (21 mg, 10 mol%) and

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water (10 mL) in a closed round bottomed flask of capacity 25 mL was allowed to stir vigorously at 50 °C. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane, 2:8). After completion of the reaction, reaction mixture was poured on ice-cold water and stirred well. Thus obtained yellow coloured solid product was collected by simple filtration, washed with water and dried. This crude product (**3a**) was then recrystallized from aqueous ethanol to get pure product.

Spectral data for representative compounds

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3a**): Yellow solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.63 (s, 3H), 2.85 (d, 1H, *J* = 14 Hz), 3.27 (d, 1H, *J* = 14 Hz), 5.66 (brs, 1H, -NH), 6.81-6.86 (m, 1H, Ar-H), 7.01 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.10 (dd, 2H, *J* = 1.6 and 2.8 Hz, Ar-H), 7.18 (t, 2H, *J* = 8.0 Hz, Ar-H), 7.23-7.31 (m, 3H, Ar-H), 7.52 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.66 (d, 2H, *J* = 7.6 Hz, Ar-H); IR (KBr, cm^{-1}): *v* 3352, 1648, 1597; ES-MS: m/z 313.2 (M^+).

2,4,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3b**): Pale yellow solid; ^{1}H NMR (DMSO- d_6, 400 MHz): δ 1.22 (s, 6H), 2.14 (s, 2H), 2.20 (s, 3H), 4.69 (brs, 1H, -NH), 6.45-6.91 (m, 4H, Ar-H); IR (KBr, cm^{-1}): *v* 3334, 1645, 1594; ES-MS: m/z 189.1 (M^+).

10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine (**3f**): Pale yellow solid; ^{1}H NMR (DMSO- d_6, 400 MHz): δ 1.21-1.98 (m, 16H), 2.42-2.66 (m, 3H), 4.69 (brs, 1H, -NH), 6.33-3.37 (m, 2H, Ar-H), 6.45-6.49 (m, 2H, Ar-H); IR (KBr, cm^{-1}): *v* 3308, 1638, 1601; ES-MS: m/z 269.2 (M^+).

Table 1. Screening of reaction medium[a]

Entry	Catalyst	Catalyst Conc. (mol%)	Time (min)	Yield[b] (%)
1	Boric acid	10	60	76
2	Oxalic acid	10	90	71
3	*p*-TSA	10	90	79
4	EDTA.2Na	10	120	39
5	Citric acid	10	60	84
6	Citric acid[c]	10	60	91
7	Citric acid[d]	2.5, 5, 10, 15	60	41, 62, 91, 90

[a]*Reaction conditions:* **1a** (1 mmol) and **2a** (2 mmol) in water (10 mL) at RT; [b]Isolated yields; [c]at 50 °C; [d]Consider respective yields.

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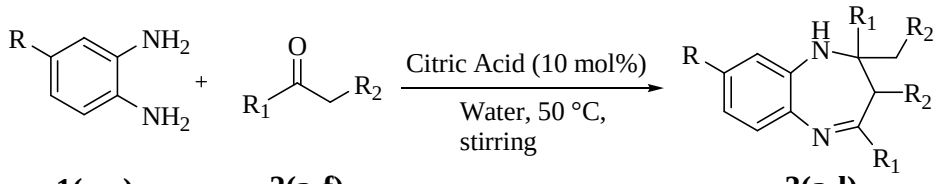
Table 2. Synthesis of 1,5-Benzodiazepine derivatives[a]



1(a-c) **2(a-f)** **3(a-l)**

Comp.	R	R_1	R_2	Time (min)	Yield[b] (%)	M.P.[c] (°C)
3a	H	Ph	H	60	91	151-153 [24]
3b	H	CH_3	H	120	89	135-136 [24]
3c	H	CH_3	CH_3	90	86	140-141 [24]
3d	H	C_2H_5	CH_3	150	89	144-146 [25]
3e	H	*i*-C_4H_9	H	120	85	117-119 [24]
3f	H	Cyclohexanone		120	88	136-138 [24]
3g	CH_3	Ph	H	60	85	93-94 [24]
3h	CH_3	CH_3	H	60	91	126-127 [24]
3i	CH_3	CH_3	CH_3	120	87	115-117 [24]
3j	CH_3	*i*-C_4H_9	H	120	86	124-126 [24]
3k	NO_2	Ph	H	90	83	137-139 [24]
3l	NO_2	CH_3	H	90	87	112-113 [24]

[a]*Reaction conditions:* **1** (1 mmol), **2** (2 mmol),citric acid (10 mol%) in water (10 mL) at 50 °C; [b]Isolated yields. [c]Melting points matches with literature reports.[24-25]

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