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An efficient and mild procedure for the synthesis of β-aminoketones catalyzed by 2,3-dibromosuccinic acid: a new and homogenous catalyst for the Mannich reaction

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Abstract: An efficient and general one-pot protocol to generate β-aminoketone derivatives by three component Mannich reaction from acetophenone, aromatic aldehydes, and various anilines using 2,3-dibromosuccinic acid catalyst in ethanol as environmentally benign solvent at ambient conditions has been developed. It is noteworthy that, for the first time, we applied 2,3-dibromosuccinic acid as a catalyst for the synthesis of organic compound such as β-aminoketones. The main feature of the current method comprise mild reaction conditions, easy work-up, the use of green solvent, short times, no need to column chromatography and the products were isolated with high yields.

Keywords: 2,3-Dibromosuccinic acid, Homogeneous catalyst, Mannich reaction, Three component, β-Aminoketone.

Introduction

The significance of nature's molecules embracing amino acids, nucleic acids and most active compounds from biological point of view, contain nitrogen. Hence, developing new and simple synthetic methods for the construction of nitrogenous molecules [1] has defined the frontiers of organic synthesis since its very beginning. One of the synthetic methods is Mannich reaction that produces including nitrogen molecules [2]. Also, the Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis [3-6] and very useful compounds as building blocks in the synthesis of pharmaceuticals and natural products [7,8]. Multicomponent reactions (MCRs) [9-11] have gained eminence as a synthetic tool for producing structurally complex molecular entities with attractive biological features through the establishment and cleavage of numerous carbon–carbon and carbon–heteroatom bonds in one pot [12]. It is becoming increasingly important both in academia and in industry to design less toxic and more environmentally friendly MCRs [13-15]. As one of the mostly studied MCRs, discovered in 1912, Mannich reaction [5] that, it is an important basic reaction in organic synthesis [3] for the preparation of β-amino carbonyl compounds which are vital intermediates in pharmaceuticals and natural products [16]. Attempts have been made in the past to improve methodologies based on two-component reactions, where the imine as electrophile is preformed and then reacted with nucleophiles such as enolates, enol ethers, and enamines [17]. However, in most cases these protocols use hazardous organic solvents [18], and suffer from long reaction time with low yields and poor selectivity. Therefore, the development of modern versions [19] of the reaction that work under mild conditions is of great importance. The most preferable route is one-pot three-component strategy that allowed a wide range of

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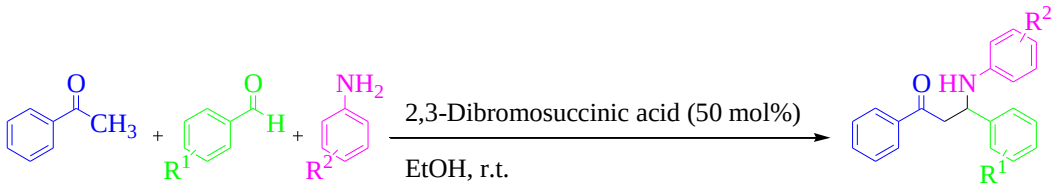
structural variations in the reactants-aldehydes, anilines, and ketones to give Mannich products using an appropriate catalyst in a single step. Recently, direct Mannich reactions for the synthesis of β-amino ketones have been realized via Lewis acids, lanthanides, transition metal salts and organic catalysts such as cerium (IV) ammonium nitrate (CAN) [20], $CeCl_3.7H_2O$ [21], SalenZn complex [22], Brönsted acidic ionic liquid [23], Tröger's base derivatives [24], Rare earth perfluorooctanoate ($RE(PFO)_3$) [25], Triton X10 (TX10) aqueous micelles [26], Cbz-protected [27], $HClO_4$-SiO_2 [28], $NbCl_5$ [29] and $Fe(Cp)_2PF_6$ etc [30-43]. Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts, expensive reagents or catalysts, use of expensive and air-sensitive catalyst**,** high temperature, tedious work-up procedures, toxic solvents, sometimes long reaction times and low yield.

Nevertheless, few reports have successfully used organic molecules as catalysts under aqueous medium [44] or in other green solvents. Organocatalysis has long existed as part of organic chemistry, for example, amine catalyzed Michael-additions, aldol condensation or Knoevenagel reactions. An early and systematical investigation in this field is reported by Langenbeck [45]. But the extremely high interest on organocatalysis since the pioneering publication of List and Barbas [46] in 2000 is based on the possibility to create stereogenic centers during an organocatalyzed execution of organic reactions. This opportunity to influence the configurative outcome during the construction of a C–C bond was the domain of metal catalysis or biocatalysis until that time. During the past decade an extremely high output of results of different organocatalyzed reactions and transformations was noticed. The subject matter of this work is organocatalyzed C–C bond formation processes, because these transformations provide an extremely mild and operationally simple access to required defined configured building blocks or natural products. In particular these include aldol additions, Mannich reactions, conjugate additions, cycloadditions, Bay-lis–Hillman reactions and cascade processes. Encouraged by the remarkable results obtained from above conditions, and also, in continuation of our ongoing green chemistry program that utilize homogeneous systems [47-49] in various organic transformations, we reveal herein for the first time a 2,3-dibromosuccinic acid catalyzed three-component Mannich reaction of acetophenone, aromatic aldehydes and aromatic amines. Therefore, we report a simple, mild and convenient procedure for effecting one-pot, three-component reaction of aldehyde, amine and ketone for preparation of β-aminocarbonyl compounds using homogeneous catalyst under mild reaction conditions at ambient temperature (Scheme **1**).



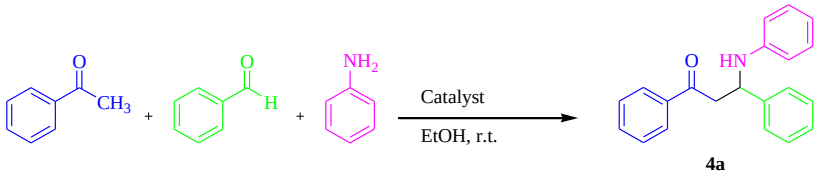
Scheme 1: Synthetic route for the three-component Mannich reaction.

Results and discussion

In order to optimize the reaction conditions, we have performed a set of preliminary experiments on acetophenone, aniline and benzaldehyde in ethanol at room temperature as a model reaction. In the initial investigation, different catalysts were screened in the model reaction (Table **1**). As could be seen in Table **1**, several common Lewis acids and Brønsted acids were used as catalysts, the admissible result was obtained from using 10 mol% of 2,3-dibromosuccinic acid in ethanol (Table **1**, entry 8). Also, it is noteworthy that, the reaction didnot progress even after 48 h in the absence of catalyst (Table **1**, entry 1).

Subsequently, in order to determine the best solvent for this work, different solvents such as ethanol, methanol, acetonitrile, water and water/ethanol were explored. The results are summarized in Table **2**. Among the screened solvent systems, ethanol was the solvent of choice, since the reaction proceeded smoothly and afforded the desired products in acceptable yields. Meanwhile, it was found that the room temperature was an appropriate condition for Mannich reaction. In the neat condition, the product was obtained in low yields after 48 h (22%), probably due to the lack of effective interaction of reactants with the catalyst (Table **2**, entry 6).

Table 1: The effect of different catalysts on the synthesis of Mannich reaction **4a**.[a]

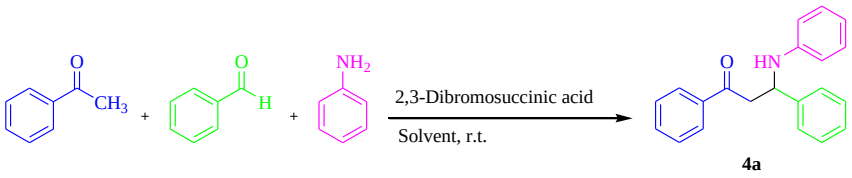


4a

Entry	Catalyst mol %	Solvent	Time/ h	Yield %[b]
1	-	EtOH	48	-
2	Chloroacetic acid (10)	EtOH	48	28
3	Formic acid (10)	EtOH	48	22
4	$NiCl_2$ (10)	EtOH	48	-
5	ZnO (10)	EtOH	48	-
6	$FeCl_3.6H_2O$ (10)	EtOH	48	-
7	H_3BO_3 (10)	EtOH	48	-
8	**2,3-Dibromosuccinic acid (10)**	**EtOH**	**19**	**48**

[a] Experimental conditions: benzaldehyde (1 mmol), aniline (1 mmol), and acetophenone (1 mmol), r.t.
[b] Isolated yield.

Table 2: 2,3-Dibromosuccinic acid catalyzed Mannich reaction in various solvents.[a]



4a

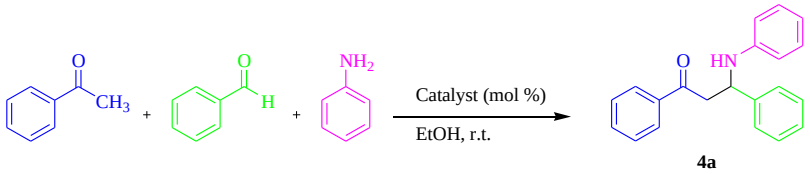
Entry	Catalyst mol %	Solvent	Time/ h	Yield %[b]
1	**2,3-Dibromosuccinic acid (10)**	**EtOH**	**19**	**48**
2	2,3-Dibromosuccinic acid (10)	MeOH	20	42
3	2,3-Dibromosuccinic acid (10)	CH_3CN	48	-
4	2,3-Dibromosuccinic acid (10)	$EtOH/H_2O$	48	25
5	2,3-Dibromosuccinic acid (10)	H_2O	48	-
6	2,3-Dibromosuccinic acid (10)	Neat	48	22

[a] Experimental conditions: benzaldehyde (1 mmol), aniline (1 mmol), and acetophenone (1 mmol), r.t.
[b] Isolated yield.

Next, to determine the catalytic amount of 2,3-dibromosuccinic acid, different ratios of the catalyst were examined. We found out that the product **4a** could be obtained in good yields ranging from 40 to 80% in different mole ratios of 2,3-dibromosuccinic acid (5, 10, 15, 20, 30, 40, 50 and 60 mol%) and the results are summarized in Table **3**. Better yields were obtained up to 80% by carrying out the reaction using

50 mol% of 2,3-dibromosuccinic acid in EtOH as solvent. Notably, no significant improvement in the yield of the product was observed on increasing the catalyst amount (Table **3**, entry 8). Therefore, 50 mol% of 2,3-dibromosuccinic acid should be the most suitable catalyst loading with the conditions employed in this work.

Table 3: Effect of mole percentage of catalyst on the Mannich reaction for the synthesis of β-aminoketones.[a]



4a

Entry	Catalyst mol%	Solvent	Time/ h	Yield %[b]
1	2,3-Dibromosuccinic acid (5)	EtOH	24	40
2	2,3-Dibromosuccinic acid (10)	EtOH	19	48
3	2,3-Dibromosuccinic acid (15)	EtOH	16	55
4	2,3-Dibromosuccinic acid (20)	EtOH	12	60
5	2,3-Dibromosuccinic acid (30)	EtOH	9	65
6	2,3-Dibromosuccinic acid (40)	EtOH	7	72
7	**2,3-Dibromosuccinic acid (50)**	**EtOH**	**6**	**80**
8	2,3-Dibromosuccinic acid (60)	EtOH	6	78

[a] Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), and acetophenone (1 mmol), r.t.
[b] Isolated yield.

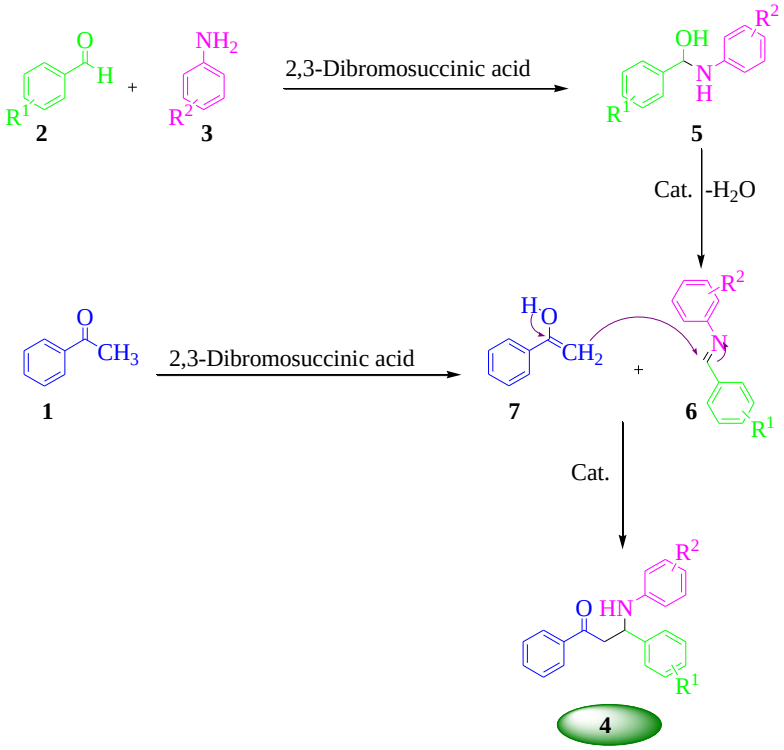
Encouraged by the remarkable results obtained for above conditions, to further illustrate the power of this reaction procedure, the various aldehydes and amines including electron-withdrawing and electron-donating groups such as NO_2, Cl and CH_3, were also employed to react with acetophenone under similar reaction conditions and the corresponding desired products **4a-4g** were isolated in good yields (55-84%) using catalytic amount of catalyst and the results are shown in Table **4**.

Table 4: Preparation of β-aminoketone derivatives **4**.

Entry	R^1	R^2	Product	Time/ h	Yield %[a]	m.p./ °C	Lit.[b] m.p./ °C
1	H	H	**4a**	6	80	169-170	169-171 [22]
2	H	4-Cl	**4b**	10	62	167-169	171-172 [49]
3	H	4-Br	**4c**	7	60	178-179	181-183 [26]
4	4-Me	H	**4d**	8	55	127-130	130-131 [21]
5	4-Cl	H	**4e**	7	70	114-116	115-117 [22]
6	4-O_2N	H	**4f**	12	84	105-107	105-106 [30]
7	4-Cl	4-Cl	**4g**	15	84	118-120	118-119 [44]

[a] Isolated yield.
[b] All known products have been reported previously in the literature.

The plausible reaction mechanism of this one-pot three-component reaction is described in Scheme **2**. The first reaction is the formation of imine **6** that obtained from the reaction aromatic aldehyde and amine in the presence of 2,3-dibromosuccinic acid. The second reaction is the formation of enol **7** form acetophenone in the presence of catalyst. The imine **6** obtained in the first reaction as an intermediate followed by the attack of in situ generated enol **7** to give the corresponding β-aminoketone derivatives **4.**



Scheme 2: Probable path for the product formation in three-component Mannich reaction.

Conclusion

In summary, we have successfully developed a one-pot three-component reaction of acetophenone, aromatic aldehydes and anilines with 2,3-dibromosuccinic acid as acidic catalyst. This reaction can proceed smoothly under mild conditions to afford the β-aminoketones in moderate to good yields. The advantages of this reaction included readily available starting materials, mild reaction conditions, operational simplicity, easy work-up, short times and the products were isolated with good yields in high purity without need to column chromatography. The potential uses of this reaction in synthetic and medicinal chemistry may be quite significant.

Experimental

General:

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purifications. All products are known and were identified by the comparison of their spectral data and physical properties with those of the authentic samples. ^{1}H NMR spectra was determined on a Bruker 400-DRX Avance instrument with $CDCl_3$ as solvent at 400 MHz. Chemical shifts (δ) are reported in ppm, downfield from internal TMS standard. Melting points were recorded on an Electrothermal 9100 apparatus.

General procedure for the Preparation of β-aminoketones:

To mixture of acetophenone (1 mmol), aldehyde (1 mmol) and aniline (1 mmol) with 4 mL ethanol as solvent, 2,3-dibromosuccinic acid was added and the mixture was stirred at room temperature for the period of time listed in Table **4**. After the reaction completed as indicated by TLC, the solid precipitated was separated with a simple filtration, washed with ethanol and dried to afford the desired product. All the products were characterized by ^{1}H NMR and their melting points were identical to those of the known compounds reported in the literature.

*Physical and spectral data of the products (**4a**, **4b** and **4d**):*

1,3-diphenyl-3-(phenylamino)propan-1-one (**4a**):

White solid (80 %), m.p. 169-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ / ppm): 3.44 (dd, 1H, *J* = 16.0, 7.6 Hz), 3.54 (dd, 1H, *J* = 16.0, 5.2 Hz), 4.59 (br s, 1H, NH), 5.03 (dd, 1H, *J* = 7.6, 5.2 Hz), 6.59 (dd, 2H, *J* = 8.6, 1.0 Hz, ArH), 6.67-6.71 (m, 1H, ArH), 7.09-7.14 (m, 2H, ArH), 7.24-7.28 (m, 1H,ArH), 7.35 (dd, 2H, *J* = 10.4, 7.6 Hz, ArH), 7.45-7.49 (m, 4H, ArH), 7.57-7.61 (m, 1H, ArH), 7.93-7.95 (m, 2H, ArH).

3-(4-chlorophenylamino)-1,3-diphenylpropan-1-one (**4b**):

White solid (62 %), m.p. 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ / ppm): 3.43 (dd, 1H, *J* = 16.0, 7.6 Hz), 3.52 (dd, 1H, *J* = 16.0, 4.8 Hz), 4.64 (br s, 1H, NH), 4.96 (dd, 1H, *J* = 7.6, 4.8 Hz), 6.47-6.51 (m, 2H, ArH), 7.02-7.06 (m, 2H, ArH), 7.24-7.27 (m, 1H, ArH), 7.33-7.36 (m, 2H,ArH), 7.43 (d, 2H, *J* = 7.2 Hz, ArH), 7.44-7.49 (m, 2H, ArH), 7.57-7.61 (m, 1H, ArH), 7.91-7.93 (m, 2H, ArH).

1-phenyl-3-(phenylamino)-3-p-tolylpropan-1-one (**4d**):

White solid (55 %), m.p. 127-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ / ppm): 2.33 (s, 3H, CH_3), 3.42 (dd, 1H, *J* = 16.0, 7.8 Hz), 3.52 (dd, 1H, *J* = 16.0, 5.2 Hz), 4.99 (dd, 1H, *J* = 7.6, 5.2 Hz), 6.58 (dd, 2H, *J* = 8.6, 1.0 Hz, ArH), 6.66-6.69 (m, 1H, ArH), 7.08-7.12 (m, 2H, ArH), 7.15 (d, 2H, , *J* = 7.6 Hz, ArH), 7.34 (d, 2H, *J* = 8.0 Hz, ArH), 7.44-7.48 (m, 2H, ArH), 7.56-7.60 (m, 1H, ArH), 7.92-7.94 (m, 2H, ArH).

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