A convenient Method for the Synthesis of 1,8-dioxodecahydroacridine derivatives using 1-methylimidazolium tricyanomethanide {[HMIM]C(CN)₃} as a nanostructured molten salt catalyst

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Abstract: A practical and convenient method for the synthesis of 1,8-dioxodecahydroacridine derivatives was achieved *via* the **one-pot condensation** reaction of cyclic 1,3-diketone, aldehydes and various anilines or ammonium acetate in the presence of 1-methylimidazolium tricyanomethanide {[HMIM]C(CN)₃} as a **nanostructured molten salt (NMS) catalyst** at room temperature. In the **present** work, more than thirty products **will be reported** for the first time.

Keywords: 1-Methylimidazolium tricyanomethanide; 1,8-Dioxodecahydroacridine; Nanostructure molten salt; Solvent-free conditions.

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1. Introduction

Nowadays, one-pot multi-component reactions (MCRs) are more demand due to the benefit of their convergence, efficiency, facile performance and high yield [1]. There has been an enormous development in multi-component reactions (MCRs), particularly the Ugi [2], Passerini [3], Bignelli [4] and Mannich [5] reactions. Great effort is needed to find new MCRs and/or to modify the previously known reported procedures. One such reaction is the synthesis of 1,8-dioxodecahydroacridines. Throughout the recent years, great attention has been paid to the synthesis of 1,8-dioxodecahydroacridines because of their highly complete physiological and biological activities for example antimicrobial [6], anti-multidrug-resistant [7], anti-tumor [8], cytotoxic [9], anti-cancer [10] and anti-fungal properties [11]. These compounds are commonly synthesized in a three-component reaction of 1,3-diketone, aldehydes and various anilines or ammonium acetate using several catalysts for example [2-MPyH]OTf [12], Cu(II) Schiff base [13], Fe₃O₄ nano particles [14], amberlyst-15 [15], silica-bonded *N*-propyl sulfamic acid (SBNPSA) [16], ceric ammonium nitrate (CAN) [17], 4-dodecylbenzenesulfonic acid (DBSA) [18] and proline [19].

Molten salts (MSs), ionic liquids (ILs) and room temperature ionic liquids (RTILs) are particularly combined of suitable cations and anions. Typically, ionic liquids (ILs) and molten salts (MSs), refer to organic onium salts which molten below and above 100 °C respectively [20]. MSs are an noteworthy class of liquids because of their unique ionic interactions and their broad number of scientific uses [21]. MSs have significant potentials for various purposes [22-24]. MSs and ILs can be engaged as a GC immobile phases for both packed and open-tubular columns [25-28].

Recently, the first nano ionic liquid (NILs) and nano molten salts (NMSs) have been reported by our research group and there have been also used as nano catalysts in a good range of organic reactions [29]. Therefore, as a part of our continuous study to the design, synthesis and application of homogeneous catalysts such as nano catalysts in organic synthetic procedures [30], herein, we wish to report an efficient method for synthesis of 1,8-dioxodecahydroacridine derivatives in the presence of 1-methylimidazolium tricyanomethanide {[HMIM]C(CN)₃} as a green, recycle and reusable nanostructured molten salt(NMS) catalyst under solvent-free conditions via condensation of 1,3-diketone, aldehydes and various anilines or ammonium acetate (Scheme 1).

>Scheme 1<

2. Experimental

General procedure for the preparation of nano structure molten salt catalyst: 1-methylimidazolium tricyanomethanide.

The nanostructured molten salt {[HMIM]C(CN)₃} as a catalyst was synthesized according to our previously reported procedure [29]. A pale pink solid was prepared in high purity which its physical data is as same as those reported data in the literature. M.p: >300 °C; Yield: 96% (0.498 g); Spectral data: IR (KBr): ν 3417, 2925, 2170, 2081, 1631, 1574, 1455 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.63 (s, 3H, —CH₃), 7.00 (s, 2H, —CH); 7.63 (s, 1H, —CH), 11.95 (brs, 1H, —NH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 46.4, 67.2, 74.8, 119.8, 134.9, 160.2; MS: *m/z* = 173 [M]⁺.

General procedure for the synthesis of 1,8-dioxodecahydroacridine derivatives.

{[HMIM]C(CN)₃} as a nanostructured molten salt catalyst (0.5 mol%; 0.0009 g) was added to a mixture of various aromatic aldehydes (1 mmol), 1,3-diketone (2 mmol) and ammonium acetate or several anilines (1 mmol) in a round bottom flask, and the produced mixture was stirred magnetically under solvent-free conditions at room temperature. After completion of the reaction, as monitored by TLC *n*-hexane/ethyl acetate (5:3), ethyl acetate (10 mL) was added to reaction mixture, stirred and refluxed for 3 min, and then was washed with water (10 mL) and decanted to separate catalyst from the other materials (the reaction mixture was soluble in hot ethyl acetate and described molten salt catalyst was soluble in water). The aqueous layer was decanted and the catalyst was separated after removing of water. The remained catalyst was used for alternative reaction. The solvent of organic layer was evaporated and the crude product was purified by recrystallization from ethanol/water (10:1). In this study, the described catalyst was recycled and reused for five times without important loss of its catalytic activity (spectral data for analysis compounds: refer to supplementary data).

3. Results and discussion

In our continued interest into the designing, synthesis, applications and knowledge-based development of task-specific nano ionic liquids (TSNILs) and nanostructured molten salts (NMSs), we decided to develop the scope and limitations of the described nanostructured salts in the organic synthetic methods [29]. Subsequent to the synthesis of {[HMIM]C(CN)₃} as nanostructured molten salt catalyst, to optimize the reaction conditions, we have confirmed the affection of the nano structure molten salt catalyst in the synthesis of 1,8-dioxodecahydroacridines (Scheme 1). For this purpose, as a model reaction, the condensation between dimedone, 4-biphenylcarbaldehyde and ammonium acetate were investigated in the presence of different amounts of the catalyst at range of 25–100 °C under solvent-free conditions (Table 1). As can be seen in the Table 1, the best results were obtained when the reaction was attained in the presence of 0.5 mol% of described catalyst at room temperature (Table 1, entry 3). Increasing the reaction temperature and catalyst loading did not improve the rate of the reaction (Table 1, entries 4-11). In the absence of catalyst a low yield of the products was achieved after 30 min (Table 1, entries 1 and 2).

>Table 1<

To compare the obtained results of solution with that of solvent-free conditions, a mixture of dimedone, 4-biphenylcarbaldehyde and ammonium acetate as a model reaction, using 0.5 mol% of nanostructured molten salt catalyst in various solvents for example H₂O, C₂H₅OH, CH₃CN, CH₃CO₂Et, CH₂Cl₂ and toluene was studied at room temperature. As it can be displayed in Table 2, solvent-free condition was the best condition in this reaction.

>Table 2<

With the intention of confirming this main procedure, we were encouraged to synthesize a good range of 1,8-dioxodecahydroacridine derivatives from Hantzsch three-component condensation reaction of several aromatic aldehyde, 1,3-diketone and several anilines or ammonium acetate under solvent-free conditions at room temperature using a catalytic amount of 1-methylimidazolium tricyanomethanide {[HMIM]C(CN)₃} as a nanostructured molten salt catalyst. The obtained results have been presented in Table 3. The effect of substituents on the aromatic ring displays estimated strong effects in terms of yields under these reaction conditions. All aromatic aldehydes bearing electron-withdrawing and electron-releasing substituents on their aromatic ring gave the linked products in high to excellent yields in short reaction time. The reaction time of aromatic aldehydes having electron-withdrawing groups was rather faster than that of electron donating groups. Moreover, in this reaction condition ammonium acetate reacted faster than aniline derivatives and 4-bromoaniline reacted faster than 4-chloroaniline. Furthermore, in this reaction condition dimedone reacted faster than 1,3-cyclohexanedione. Also, In the presence of terephthalaldehyde as an aldehyde derivative, bisacridine products were successfully synthesized (Table 3, entries 6, 12, 17, 22, 27 and 32).

>Table 3<

We suggest the probable following mechanism to explain the reaction (Scheme 2). The molten salt catalyst activates the carbonyl functional group of aldehyde into an active electrophile via protonation of the described carbonyl group and then one molecule of 1,3-dione condenses with the aromatic aldehyde to produce intermediate **10** (Aldol condensation). Then the active methylene group of the second molecule of 1,3-dione reacts with **10** to provide intermediate **11** (Michael addition). Nucleophilic attack of nitrogen of ammonium acetate or aniline derivatives to carbonyl group makes intermediate **12**. In the next step, cyclization will be occurred through the nucleophilic attack of amine group to carbonyl group to attain intermediate **13**. Lastly, through the removal of one water molecule, due to the driving force of full conjugation of double bonds with carbonyl groups, the acridine derivatives **4** will be produced [12].

>Scheme 2<

Furthermore, recycle and reusability of the {[HMIM]C(CN)₃} as a nanostructured molten salt (NMS) catalyst was confirmed from the condensation between dimedone, 4-biphenylcarbaldehyde and ammonium acetate. At the completion of the reaction, ethyl acetate was added to the reaction mixture and heated to extract the product. This solution was washed with water to separate catalyst from other materials (the product is soluble in hot ethyl acetate and NMS catalyst is soluble in water). The aqueous layer was decanted, separated and applied for subsequent reaction after removing of water. It has been shown that the catalytic activity of the catalyst was reformed within the limits of the experimental errors for five continuous runs. The deactivation of the NMS catalyst is low. The reaction was scaled up to 10 mmol of 4-biphenylcarbaldehyde and ammonium acetate and 20 mmol of dimedone in the presence of 5 mol% of NMS catalyst at room temperature. The yield of the reaction was 98% after 3 min and 91% after the fifth run. The results are summarized in Fig. 1.

>Fig. 1<

4. Conclusion

In conclusion, a green, efficient and eco-friendly nanostructured molten salt catalyst namely 1-methylimidazolium tricyanomethanide {[HMIM]C(CN)₃} was used in the synthesis of 1,8-dioxodecahydroacridine derivatives through three-component Hantzsch condensation reaction of various aromatic aldehydes, 1,3-diketone and ammonium acetate or anilines under solvent-free conditions at room temperature. Further works offered that the nanostructured molten salt basicity and acidity shows a major role to play in the dual-catalyzed reactions. Significant advantages of this study are reasonably cleaner reaction profile, ease of product isolation, high yield, short reaction time, recycle and reusability of the nanostructured molten salt catalyst and accordance with the green chemistry disciplines.

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Scheme, Table and Figure section:

Scheme 1. The synthesis of 1,8-dioxodecahydroacridine derivatives in the presence of {[HMIM]C(CN)₃} as a nanostructured molten salt (NMS) catalyst.

Table 1. Effect of amount of the catalyst and temperature in the synthesis of 1,8-dioxodecahydroacridine under solvent-free conditions.^a

Entry	Catalyst loading (mol%)	Reaction temperature (°C)	Reaction time (min)	Yield ^b (%)
1	Catalyst-free	r.t.	30	21
2	Catalyst-free	100	30	30
3	0.5	r.t.	3	98
4	0.5	50	3	98
5	0.5	100	3	98
6	1	r.t.	3	98
7	1	100	3	98
8	2	r.t.	3	97
9	2	100	3	97
10	5	r.t.	5	95
11	5	100	5	95

Reaction conditions: ^aDimedone (2 mmol), 4-biphenylcarbaldehyde (1 mmol), ammonium acetate (1 mmol); ^bIsolate yield.

Table 2. The effect of various solvents in the synthesis of 1,8-dioxodecahydroacridine at room temperature.^a

Entry	Solvent	Reaction time (min)	Yield ^b (%)
1	Solvent-free	3	98
2	H ₂ O	10	97
3	C ₂ H ₅ OH	12	97
4	CH ₃ CN	15	95
5	CH ₃ CO ₂ Et	20	87
6	CH ₂ Cl ₂	30	80
7	Toluene	45	71

Reaction conditions: ^aDimedone (2 mmol), 4-biphenylcarbaldehyde (1 mmol), ammonium acetate (1 mmol); ^bIsolate yield.

Table 3. The three-component Hantzsch synthesis of 1,8-dioxodecahydroacridine derivatives using 0.5 mol% of {[HMIM]C(CN)₃} as a nanostructured molten salt (NMS) catalyst.^a

Entry	Aldehyde	NH ₄ OAc or aniline	1,3-Diketone	Time (min)	Yield ^b (%)	M.p (°C) [Lit.] ^{Ref.}
1		NH ₄ OAc		3	98	234-236
2		NH ₄ OAc		5	97	207-209
3		NH ₄ OAc		10	95	192-194
4		NH ₄ OAc		5	96	226-228
5		NH ₄ OAc		5	96	212-214
6		NH ₄ OAc		15	95	282-284

7		NH ₄ OAc		5	97	302-304
8		NH ₄ OAc		7	96	283-285
9		NH ₄ OAc		12	93	212-214
10		NH ₄ OAc		8	95	341-343
11		NH ₄ OAc		8	95	232-234
12		NH ₄ OAc		18	94	285-287
13				10	96	286-288
14				15	95	293-295
15				25	93	268-270
16				15	94	209-211
17				30	93	292-294 [282] ¹⁵

18				15	93	223-225
19				20	92	221-223
20				30	90	283-285
21				20	91	207-209
22				35	90	281-283
23				7	97	207-209
24				10	96	238-240
25				20	94	221-223
26				10	95	189-191
27				25	94	232-234 [210] ¹⁵
28				10	95	218-220

29				15	94	215-217
30				25	92	299-301
31				15	93	216-218
32				30	92	275-277

Reaction conditions: ^a1,3-Diketones (2 mmol), aldehydes (1 mmol), various anilines or ammonium acetate (1 mmol); ^bIsolate yield.

Scheme 2. The suggested mechanism for the synthesis of acridines in the presence of {[HMIM]C(CN)₃} as a nanostructured molten salt (NMS) catalyst.

Fig. 1. Recycle and reusability studies of the {[HMIM]C(CN)₃} nanostructured molten salt (NMS) catalyst in the synthesis of 9-(biphenyl-4-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione in 3 minutes.