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N,N,N,N-Tetramethylguanidinium acetate as an efficient and reusable ionic liquid catalyst for the one-pot synthesis of dihydropyrrol-2-ones

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Abstract

An extremely facile and efficient procedure has been developed for the synthesis of dihydropyrrol-2-ones. One-pot four-component reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in the presence of N,N,N,N-tetramethylguanidinium acetate [TMG][Ac] in methanol at ambient temperature provides substituted dihydropyrrol-2-ones in good to high yields. The important aspects of this multi-component heteroannulation are simple operations under mild conditions, readily available starting material and catalyst. Furthermore, all products were obtained through a simple filtration and washed with ethanol, and there was no need for column chromatography. It is found that the catalyst is recyclable and can be used up to four times without significant loss of its activity.

Keywords: *N*-Heterocycle; dihydropyrrol-2-one; multi-component reaction; ionic liquid; [TMG][Ac]; reusable catalyst.

Introduction

Development of novel methodologies that reduce pollution in chemical synthesis has received considerable attention due to increasing environmental concerns. In this context, one active area is the utilization of eco-friendly reusable ionic liquid catalyst instead of conventional, toxic and polluting Brönsted acid catalyst. Ionic liquids have attracted considerable attention duo to their unique properties such as good solvating ability, a wide liquid range, tunable polarity, negligible vapor pressure, high thermal stability and non-flammability [1, 2]. They have been used in all areas of the chemical industries include solvents and catalysts in synthesis, matrices for mass spectroscopy, separation and extraction, lubricants, plasticizers, and electrolyte in batteries [3, 4].

Polyfunctionalized heterocyclic compounds are playing important roles in drug discovery processes, and in the analysis of drugs. In this context, the ubiquity of pyrrol-2-ones in pharmaceuticals and natural products makes them attractive targets for organic synthesis. Dihydropyrrol-2-one and its derivatives are key compounds for the synthesis of bioactive molecules such as Chaetoglobosin A and C [5], and Clausenamide [6]. Moreover, dihydropyrrol-2-ones have been successfully used as HIV integrase [7],

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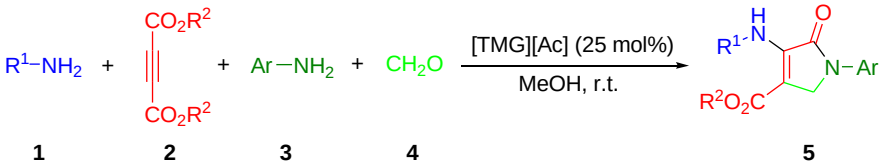
herbicidal [8], pesticides [9], anti-tumor and anticancer agents [10], mitomycin antibiotics [11], and also as inhibitors of DNA polymerase [12]. Recently, multi-component reactions have been used for one-pot synthesis of dihydropyrrol-2-ones using catalysts such as AcOH, I_2, benzoic acid, TiO_2 nanopowder and $Cu(OAc)_2 \cdot H_2O$ [13-18]. However, some of these methods displayed drawbacks, such as excess use amount of catalyst, long reaction times, and the use of chlorinated solvent under reflux conditions as well as environmental pollution. Owing to the importance of dihydropyrrol-2-ones from pharmaceutical and biological view points, there is still a need to develop efficient, mild and environmentally benign protocols for the synthesis of these heterocycles in the presence of recyclable catalyst. Therefore, in continuation of our work on heterocycles synthesis, especially synthesis of dihydropyrrol-2-ones [19-23], herein *N*,*N*,*N*,*N*-tetramethylguanidinium acetate [TMG][Ac] was employed as an efficient and recyclable ionic liquid catalyst for the one-pot four-component synthesis of dihydropyrrol-2-ones at ambient temperature (Scheme 1).



Scheme 1. Synthesis of highly substituted dihydropyrrol-2-one 5

Experimental

Preparation of the catalyst [TMG][Ac]

[TMG][Ac] was synthesized simply by neutralization of *N*, *N*, *N*, *N*-tetramethylguanidin with corresponding acetic acid. In a typical reaction, 0.1 mol *N*, *N*, *N*, *N*-tetramethylguanidin which was dissolved in 10 mL methanol was put into a 100 mL flask, and 0.1 mol acetic acid was slowly added under stirring. The solution was stirred at room temperature for 24 h to complete the reaction, and then the methanol was removed at 50 °C under reduced pressure to give a colorless viscous liquid [24].

General procedure for synthesis of dihydropyrrol-2-one 5

A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in methanol (3 mL) was stirred for 30 min. Next, aromatic amine **3** (1 mmol), formaldehyde **4** (37% solution, 1.5 mmol) and [TMG][Ac] (25 mol%) were added successively. The reaction mixture was allowed to stir at ambient temperature for the appropriate time. The progress of the reaction was monitored by TLC. After completion, the solid precipitate was filtered off and washed with ethanol to afford the pure products **5**. In order to recover the catalyst, filtrated solution was evaporated under reduced pressure, and the resulting ionic liquid was washed with diethyl ether, and dried. The recovered catalyst was reused four times.

Physical and spectral data for selected products

Methyl 3-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5b)

White solid; mp: 164-166 °C; IR (KBr, cm^{-1}): ν = 3284 (NH), 1676, 1649; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2-N), 7.01-7.16 (m, 6H, ArH), 7.73-7.76 (m, 2H, ArH), 8.05 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.3, 51.4,

102.3, 115.1 (d, J_{CF} = 23.0 Hz), 115.9 (d, J_{CF} = 22.0 Hz), 121.0 (d, J_{CF} = 7.0 Hz), 125.1 (d, J_{CF} = 8.0 Hz), 134.4 (d, J_{CF} = 3.0 Hz), 134.7 (d, J_{CF} = 2.0 Hz), 143.4, 153.7 (d, J_{CF} = 33.0 Hz), 161.2 (d, J_{CF} = 32.0 Hz), 163.5, 164.8.

Ethyl 3-(benzylamino)-1-(4-chlorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5j)

White solid; mp: 125-127 °C; IR (KBr, cm^{-1}): ν = 3310 (NH), 1698, 1641; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 4.27 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.44 (s, 2H, CH_2-N), 5.12 (s, 2H, CH_2-NH), 6.85 (br s, 1H, NH), 7.29-7.38 (m, 7H, ArH), 7.75 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 46.6, 47.8, 51.1, 60.0, 97.8, 120.1, 127.4, 127.5, 128.7, 129.0, 129.9, 137.4, 139.5, 164.5, 165.1; MS (EI, 70 eV): *m/z*, (%) = 372 (M+2, 13), 370 (M^+, 38), 341 (50), 325 (20), 323 (42), 297 (23), 261 (19), 142 (10), 105 (17), 91 (100), 65 (20); Anal. Calcd for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55; Found: C, 65.13; H, 5.44; N, 7.91.

Ethyl 1-(4-bromophenyl)-3-(butylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5r)

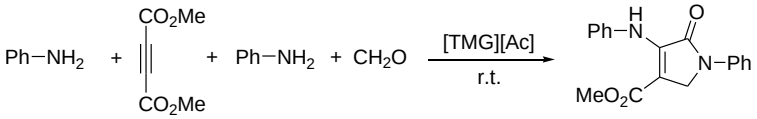
White solid; mp: 94-96 °C; IR (KBr, cm^{-1}): ν = 3323 (NH), 1698, 1647; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.2 Hz, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.43 (sextet, J = 7.6 Hz, 2H, CH_2), 1.61 (quintet, J = 7.6 Hz, 2H, CH_2), 3.87 (t, J = 7.2 Hz, 2H, CH_2-NH), 4.28 (t, J = 7.2 Hz, 2H, OCH_2CH_3), 4.40 (s, 2H, CH_2-N), 6.72 (br s, 1H, NH), 7.52 (d, J = 8.8 Hz, 2H, ArH), 7.71 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.5, 19.8, 33.4, 42.8, 47.8, 59.8, 98.1, 117.7, 120.6, 132.0, 137.9, 164.6, 165.5.

Results and discussion

First, to find the optimal conditions the reaction of aniline, dimethyl acetylendicarboxylate (DMAD) and formaldehyde was performed using different quantities of [TMG][Ac] in different solvents at ambient temperature (Table 1). The use of 25 mol% of catalyst in methanol resulted in the highest yield in 5 h (Table 1, Entry 8). Note that a control experiment showed that product **5a** was obtained only in trace yield when the reaction was examined in the absence of catalyst (Table 1, Entry 10).

Under the optimized reaction conditions, various anilines and dimethyl and/or diethyl acetylenedicarboxylates were used to test the versatility of this reaction, and the results have been summarized in Table 2. This protocol efficiently coupled anilines with electron donating groups such as Me and OMe, as well as electron withdrawing groups including F, Cl and Br to produce the expected products **5a-h** in good to high yields (Table 2, Entries 1-8). Additionally, two different amines were used for the one-pot four-component synthesis of different highly functionalized dihydropyrrol-2-ones **5i-r** (Table 2, Entries 9-18). Aliphatic amines such as benzyl amine, 1-(pyridin-2-yl)methanamine, cyclohexyl amine, *n*-propyl amine and *n*-buthyl amine reacted smoothly with dialkyl acetylenedicarboxylates, aromatic amines and formaldehyde to generate the desired products in high yields.

Table 1. Optimization of the reaction conditions for the synthesis **5a**



Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	EtOH	5	8	51
2	MeOH	5	7	58
3	EtOAc	5	12	27
4	MeCN	5	12	50
5	MeOH	10	7	67
6	MeOH	15	6	73
7	MeOH	20	5	77
8	MeOH	25	5	81
9	MeOH	30	5	79
10	MeOH	No catalyst	24	Trace

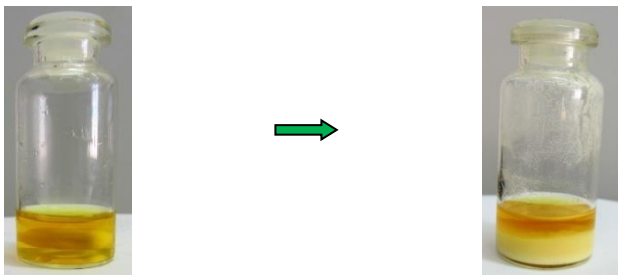
[a] Yield of isolated product

Table 2. Synthesis of dihydropyrrol-2-ones **5a-r**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	Mp (°C)	Lit. mp [Ref.][b]
1	Ph	Me	Ph	**5a**	5	81	153-155	155-156 [14]
2	4-F-C_6H_4	Me	4-F-C_6H_4	**5b**	4.5	83	164-166	163-165 [19]
3	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5c**	5	80	170-172	173-174 [14]
4	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5d**	4.5	84	168-170	168-170 [14]
5	Ph	Et	Ph	**5e**	4	80	133-135	138-140 [13]
6	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5f**	5	82	168-170	168-170 [21]
7	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5g**	5.5	78	164-166	169-171 [13]
8	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5h**	7	76	153-155	152-154 [20]
9	$PhCH_2$	Me	Ph	**5i**	5	82	138-140	140-141 [13]
10	$PhCH_2$	Et	4-Cl-C_6H_4	**5j**	5.5	85	125-127	This work
11	$PhCH_2$	Me	4-Me-C_6H_3	**5k**	5	81	144-146	144-146 [22]
12	C_5H_4N-2-CH_2	Me	4-Br-C_6H_4	**5l**	9	66	159-161	159-161 [23]
13	C_5H_4N-2-CH_2	Me	4-Me-C_6H_3	**5m**	8	69	106-108	106-108 [21]
14	Cyclohexyl	Et	Ph	**5n**	5	85	103-105	107-108 [13]
15	*n*-C_3H_7	Et	Ph	**5o**	5.5	83	76-78	78-79 [13]
16	*n*-C_4H_9	Me	4-F-C_6H_4	**5p**	5	80	81-83	81-83 [22]
17	*n*-C_4H_9	Me	4-Cl-C_6H_4	**5q**	4.5	84	91-93	92-94 [23]
18	*n*-C_4H_9	Et	4-Br-C_6H_4	**5r**	5	85	94-96	94-96 [19]

[a]Isolated yield
[b]Literature references for known compounds

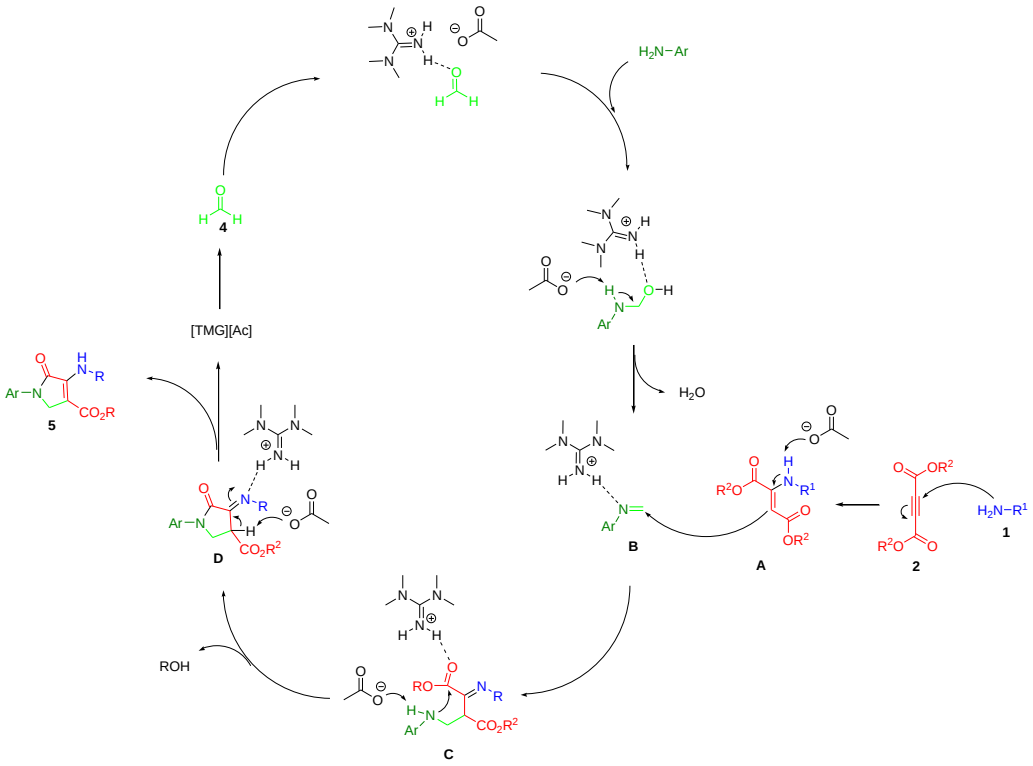
All known compounds have been reported previously in the literature and were characterized by comparison of melting points, IR and NMR spectra with authentic samples. The structure of new product **5j** was deduced on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **5j** displayed the molecular ion peak (M^{+}) at *m/z* = 370, and also peak M+2 at *m/z* = 372 due to the presence of chlorine atom within this compound, which is consistent with the proposed structure. The ^{1}H NMR spectrum of compound **5j** exhibit a triplet and a quartet at 1.34 (*J* = 7.2 Hz) and 4.27 (*J* = 7.2 Hz) ppm for ethoxy group. The methylene protons of dihydropyrrol-2-one ring were observed as a singlet at 4.44 ppm. A singlet at 5.12 ppm was appeared for methylene protons of benzyl amine moiety. The NH proton was exhibited as a broad singlet at δ 6.85 ppm. The aromatic protons were observed as multiplet and doublet at 7.29-7.38 and 7.75 (*J* = 8.8 Hz) ppm, respectively. The ^{13}C NMR spectrum of this compound showed 16 distinct resonances in agreement with the suggested structure, and partial assignment of these resonances is given in the experimental section. The IR spectrum of **5j** showed three absorption bands at 3310, 1698 and 1641 cm^{-1} due to the NH and carbonyl groups, respectively. In general, at the beginning of reactions, the reagents were completely soluble in reaction medium to form a homogeneous mixture. But, at the end of the reactions, the product **5** was precipitated and separated by simple filtration (Figure 1). No column chromatography technique was used for products purification. This avoids use of large amounts of volatile organic solvents, as the solvent is generally the main source of waste as well as environmental pollutions.



(a) (b)

Figure 1. (a) Homogeneous mixture at the beginning of the reaction, and (b) at the end of the reactions; the products has precipitated

A reasonable mechanism for the synthesis of dihydropyrrol-2-one **5** was proposed in Scheme 2. The reaction between amine **1** and dialkyl acetylenedicarboxylate **2** give intermediate **A**. Next, the reaction of amine **3** whit formaldehyde **4** produce imine **B**. Attack of **A** on **B** leads to intermediate **C**, which converts to intermediate **D** by intamolecular cyclization. In the final step, tautomerization of intermediate **D** produces the corresponding dihydropyrrol-2-one **5**.



Scheme 2. Suggested mechanism for the synthesis of dihydropyrrol-2-one **5**

Table 3. Reusability of [TMG][Ac] in the synthesis of compounds **5a**[a]

Run No.	Time (h)	Yield (%)[b]
1	5	82
2	5	80
3	5	77
4	6.5	76

[a]Reaction conditions: Aninline (as amines 1 and 3, 20 mmol), benzaldehyde 1 (10 mmol), formaldehyde 4 (37% solution, 15 mmol), [TMG][Ac] (25 mol%) and methanol (5 mL)
[b]Isolated yields

To show the efficiency and the applicability of present work for the synthesis of dihydropyrrol-2-ones, we compared results of [TMG][Ac] with previously reported catalysts in the synthesis of compound **5a** (Table 4). The results clearly show that [TMG][Ac] can act as an effective and efficient catalyst with respect to yields and reaction times.

Table 4. Comparation of [TMG][Ac] with reported catalysts for the synthesis of dihydropyrrol-2-ones

Entry	Compound	Conditions	Time (h)	Yield (%)	Ref.
1	**5a**	I_2 (10 mol%), MeOH, r.t.	1	82	[14]
		$Cu(OAc)_2 \cdot H_2O$ (0.4 mmol), benzaldehyde (2 mmol, as additive), MeOH, r.t.	6	91	[17]
		$Al(H_2PO_4)_3$ (0.1 g), MeOH, r.t.	5	81	[20]
		p-TsOH·H_2O (15 mol%), MeOH, r.t.	3	84	[23]
		[TMG][Ac] (25 mol%), MeOH, r.t.	5	81	—[a]

[a]This work

Conclusion

In conclusion, we have developed simple and efficient method for the one-pot multi-component synthesis of dihydropyrrol-2-ones using [TMG][Ac] as an ionic liquid catalyst under mild reaction conditions. The noteworthy aspects of this procedure are high atom economy, good to high yields, readily available starting material, recyclable catalyst and operational simplicity. Moreover, all products were obtained through simple filtration and no need to column chromatography, which reduces the waste as well as environmental pollutions.

Acknowledgments

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