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COMMUNICATION

Ionic liquid mediated one-pot synthesis of 6-aminouracils†

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A novel, one-pot synthesis of 6-aminouracils *via in situ* generated ureas and cyanoacetylureas in the presence of an ionic liquid catalyst, 1,1,3,3-tetramethylguanidine acetate, is described. The catalyst can be recycled for five consecutive runs without loss of activity. The mechanism for the ring closure of cyanoacetylurea to 6-aminouracil is also discussed.

Uracil has been found to be a common structural moiety of several bioactive compounds known for anticancer,[1] antiviral,[2] antihypertensive,[3] insecticidal, herbicidal, acaricidal[4] activity *etc*. 6-Aminouracils (6-aminopyrimidine-2,4(1*H*,3*H*)-diones) are key intermediates in the synthesis of xanthines[5] which constitute the basic nucleus of various drugs such as caffeine, 6-mercapto purine, penciclovir, theophylline, theobromine *etc* (Fig. 1). 6-Aminouracils are also used as starting materials for the synthesis of various fused heterocycles with biological importance, such as pyrido-, pyrazolo- and pyrimido-pyrimidines.[6]

Ureas have been traditionally synthesized using methodologies mainly based on the use of phosgene and isocyanates.[7] They are also synthesized by reacting primary amines or ammonia with carbon monoxide in presence of transition metal catalysts[8] or by reacting primary amines with sodium cyanate in presence of acid catalysts.[9] These classical methods are not environmentally safe as it involves the use of corrosive acid catalysts, hazardous reagents, volatile organic solvents and also there is often no recovery of the catalysts.

The first synthesis of 6-aminouracils was reported by Traube.[10] It involves the condensation of either urea, N-mono- or N,N′-disubstituted ureas with cyanoacetic acid (CAA) in the presence of phosphorous oxychloride to afford cyanoacetylureas, which on cyclization in the presence of a strong base affords 6-aminouracils. In a modification of this method, Speer and Raymond[11] used acetic anhydride in acetic acid instead of phosphorous oxychloride to afford intermediate cyanoacetylureas which on cyclization in the presence of a strong base also afford 6-aminouracils. Similar reports[12–16] are available in the literature which lack simplicity in their experimental procedure. Some reactions are multi-step syntheses with isolation and purification of intermediates at each step, some reactions are restricted to aliphatic ureas and have no recovery of catalysts. Therefore, developing a synthetic method for a one-pot synthesis of 6-aminouracils using an ionic liquid as an environmentally friendly and recyclable solvent as well as catalyst is desirable.

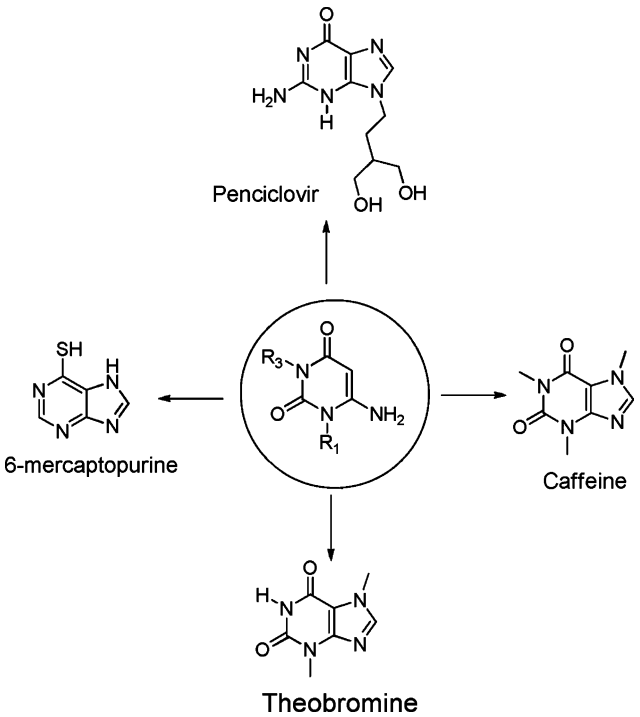

Fig. 1 Xanthine drugs obtained from 6-aminouracils.

Ionic liquids (ILs) have attracted much attention as an environmentally friendly alternative to conventional organic solvents in chemical processes, due to their physicochemical properties, such as negligible vapor pressure, excellent chemical and thermal stability, good solvating ability, ease of recyclability, non-flammability and their potential to enhance reaction rates.[17,18] Over the past few years, a number of reactions have been successfully conducted using ionic liquids as solvents or catalysts. As new generation ionic liquids, a wide range of guanidine ionic liquids (GILs) have been synthesized and used in many organic reactions such as the Henry reaction, aldol

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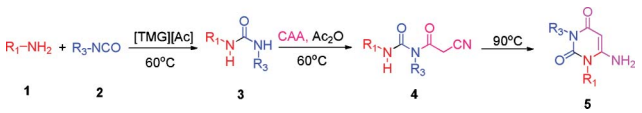
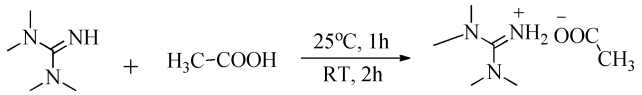
reaction and Heck reaction.[19–22] In the quest of developing simple, mild and environmentally friendly synthetic protocols, we have previously reported a hetero-Michael reaction,[23] a Knoevenagel condensation,[24] a Biginelli reaction[25] and a Heck reaction[26] using cost-effective ionic liquids as the recyclable solvent as well as the catalyst.

In the present work, for the first time, a one-pot synthesis of 6-aminouracils *via in situ* generated ureas and cyanoacetylureas (Scheme 1) using ionic liquid, 1,1,3,3-tetramethylguanidine acetate [TMG] [Ac] as the recyclable solvent and catalyst has been developed. The ionic liquid [TMG] [Ac] was prepared by the previously reported method (Scheme 2) without any modifications.[27]

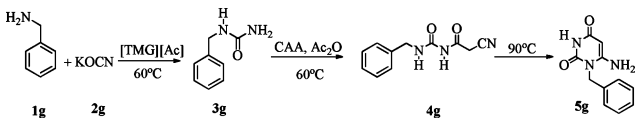


Scheme 1 One-pot synthesis of 6-aminouracils in the ionic liquid [TMG] [Ac].



Scheme 2 Synthesis of the ionic liquid [TMG] [Ac].

A one-pot reaction of equi-molar amounts of amine **1g** and cyanate **2g** in the presence of [TMG] [Ac] at 60 °C resulted in the formation of urea **3g**, which on reaction with 1 molar equivalent of cyanoacetic acid and 2 molar equivalents of acetic anhydride at 60 °C afforded cyanoacetylurea **4g**. Ring closure of cyanoacetylurea **4g** at 90 °C gave 6-aminouracil **5g** in the same pot (Scheme 3). The scope and generality of the reaction as well as the influence of reaction parameters such as amount of [TMG] [Ac], reaction time and reaction temperature were next investigated. Also, the mechanism of [TMG] [Ac] mediated ring closure of cyanoacetylurea to 6-aminouracil was discussed.



Scheme 3 One-pot reaction of amine **1g** and cyanate **2g**.

To optimize the amount of [TMG] [Ac] required for the one-pot synthesis of 6-aminouracil **5g**, several experiments were carried out using amine **1g**, cyanate **2g**, cyanoacetic acid and acetic anhydride as the substrates , the results are summarized in Table 1.

Initially, urea **3g** was prepared by the reaction of amine **1g** and cyanate **2g** in the presence of 0.2 g [TMG] [Ac] at room temperature. The reaction resulted in urea formation with a moderate yield. This could be due to the low solubility of cyanate. Use of water as the co-solvent in the reaction resulted in an increase in the yield of urea, probably due to the increase in solubility of the cyanate. Best results were obtained at 60 °C with a short reaction time of 30 min. Synthesized urea **3g** was acylated with 1 molar equivalent of cyanoacetic acid and 2 molar equivalents of acetic anhydride at 60 °C in 60 min to afford cyanoacetylurea **4g**. In order to cyclize cyanoacetylurea **4g** to 6-aminouracil **5g**, a range of reaction temperatures, from 60 °C to 120 °C, were tested. Results determined that an optimum temperature of 90 °C was required for the cyclization. Thus, when the reaction was performed with 0.2 g [TMG] [Ac], 6-aminouracil **5g** was obtained with a yield of 26% (entry 2, Table 1). The yield improved from 26% to 84% with increasing the amount of [TMG] [Ac] and reached a maximum with 1.0 g of [TMG] [Ac] (entry 6, Table 1) in a fixed reaction time of 2 h. However, further increase in the amount of [TMG] [Ac] did not affect the yields to a great extent (entries 7 and 8, Table 1). Thereafter, the reaction was evaluated by varying the reaction time (2 to 5 h.) while keeping the ionic liquid quantity (1.0 g) constant. An improved yield was obtained when the reaction was carried out for 2.5 h (entry 9, Table 1). Further increases in the reaction times and amounts of [TMG] [Ac] did not improve the result to a great extent (entries 10 and 11, Table 1). These experiments revealed that 1.0 g of [TMG] [Ac] and a reaction time of 2.5 h were the optimum parameters for the one-pot synthesis of 6-aminouracil **5g** with yield of 88%.

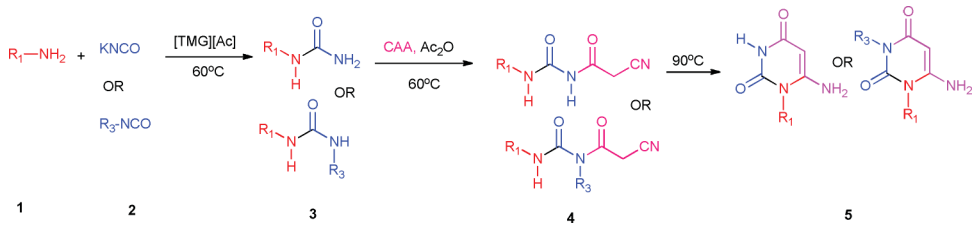
Table 1 Effect of the amount of [TMG] [Ac] on the yield of the products[a]

Sr. No.	Amount of [TMG] [Ac] (g)	Time (h)	Yield (%)[b]
1	—	12	NR
2	0.2	2.0	26
3	0.4	2.0	41
4	0.6	2.0	60
5	0.8	2.0	72
6	1.0	2.0	84
7	1.2	2.0	84
8	1.5	2.0	85
9	1.0	2.5	88
10	1.2	3.5	88
11	1.5	5.0	89

[a] Reaction conditions: amine **1g** (4.6 mmol), cyanate **2g** (4.6 mmol), [TMG] [Ac], water (0.3 ml) at 60 °C, for 30 min, cyanoacetic acid (4.6 mmol) and acetic anhydride (9.2 mmol) at 60 °C, for 60 min, and at 90 °C, for 60 min. [b] Isolated yield. NR: no reaction.

With these optimized reaction parameters, reactions of various aliphatic and aromatic amines **1a–1w** with cyanate **2a–2w**, cyanoacetic acid and acetic anhydride in [TMG] [Ac] were carried out. The results of the [TMG] [Ac] mediated one-pot synthesis of 6-aminouracils are presented in Table 2. Aliphatic amines reacted faster as compared to aromatic amines and also, the yields obtained were slightly higher. In the case of aromatic amines, amines with electron-donating groups on the benzene ring reacted smoothly under these reaction conditions (entries 10–13, 16, Table 2); whereas amines with electron-withdrawing groups on the aromatic ring did not undergo cyclization to give 6-aminouracils (entries 17–22, Table 2); only cyanoacetylureas were isolated, even after heating at 90 °C for 7–8 h. In the case of the perfluorinated alkylamine, only cyanoacetylurea was isolated (entry 23, Table 2). In addition, 1-phenyl-3-allyl-6-aminouracil and 1-benzyl-3-allyl-6-aminouracil were synthesized from allylamine and the corresponding isocyanates under the optimized reaction conditions (entries 14, 15, Table 2).

Table 2 Ionic liquid mediated one-pot synthesis of 6-aminouracils[a,e]



Sr. No.	Substrate	Amines (**1**) R_1	Cyanate (**2**) R_3	6-Aminouracil	Time (h)	Isolated yield (%)
1	**a**	CH_3	—	**5a**	2.0	87
2	**b**	*n*-C_3H_7	—	**5b**	2.0	85
3	**c**	*n*-C_4H_9	—	**5c**	2.0	86
4[b]	**d**	CH_3	CH_3	**5d**	2.0	91
5[b]	**e**	*n*-C_3H_7	*n*-C_3H_7	**5e**	2.0	83
6	**f**	C_6H_5	—	**5f**	5	89
7	**g**	$C_6H_5CH_2$	—	**5g**	2.5	88
8	**h**	4-(MeO)-$C_6H_4CH_2$	—	**5h**	4	90
9	**i**	$C_6H_5CH_2CH_2$	—	**5i**	2.5	84
10	**j**	4-(MeO)–C_6H_4	—	**5j**	3	86
11	**k**	4-(Me)–C_6H_4		**5k**	3	87
12	**l**	3-(Me)–C_6H_4	—	**5l**	3	86
13	**m**	2-(Me)–C_6H_4	—	**5m**	3	87
14[c]	**n**		C_6H_5	**5n**	2.5	80
15[d]	**o**		$C_6H_5CH_2$	**5o**	2.5	81
16	**p**	4-N(Me)$_2$–C_6H_4	—	**5p**	3.0	73
17	**q**	4-NO_2–C_6H_4	—	**5q**	7	NR
18	**r**	3-NO_2–C_6H_4	—	**5r**	8	NR
19	**s**	2-NO_2–C_6H_4		**5s**	8	NR
20	**t**	4-F–C_6H_4		**5t**	8	NR
21	**u**	3-F–C_6H_4		**5u**	8	NR
22	**v**	2-F–C_6H_4		**5v**	8	NR
23	**w**	CF_3CH_2		**5w**	7	NR

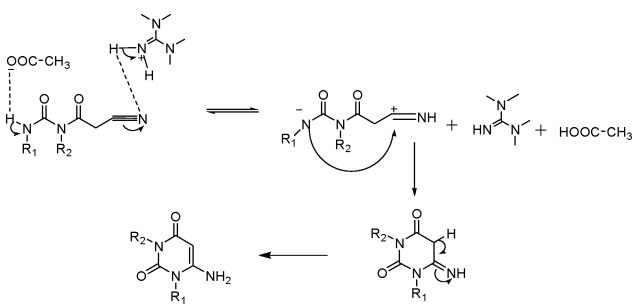
[a] Reaction conditions: amine **1** (1 mmol), cyanate **2** (1 mmol), [TMG] [Ac] (1 g), water (0.3 ml) at 60 °C, for 0.5 h, cyanoacetic acid (1 mmol) and acetic anhydride (2 mmol) at 60 °C, for 1 h, and at 90 °C, for 0.5–3.5 h. [b] Dimethylurea and dipropylurea were directly used for the synthesis of 6-aminouracils **5d** and **5e**, respectively. [c] Reaction conditions: amine **1** (1 mmol), cyanate **2** (1 mmol), [TMG] [Ac] (1 g), at RT, for 0.5 h, cyanoacetic acid (1 mmol) and acetic anhydride (2 mmol) at 60 °C, for 1 h, and at 90 °C, for 1 h. [d] Reaction conditions: amine **1** (1 mmol), cyanate **2** (1 mmol), [TMG] [Ac] (1 g), at RT, for 0.5 h, cyanoacetic acid (1 mmol) and acetic anhydride (2 mmol) at 60 °C, for 1 h, and at 90 °C, for 1 h. [e] All products were identified by their melting point, IR and ^{1}H-NMR spectra, according to the literature[10,12,14,15,16] and references cited therein. NR: no formation of 6-aminouracil; only cyanoacetylureas were isolated.

Table 3 Results for recyclability of the ionic liquid catalyst [TMG] [Ac] for the synthesis of 6-aminouracil **5g**

Sr. No.	Cycle number	Yield (%)
1	1	88
2	2	88
3	3	87
4	4	86
5	5	85
6	6	85

The recycling efficiency of [TMG] [Ac] in the same model reaction was also explored (Table 3). After the completion of the reaction, cold water was added to the reaction mixture and the products were isolated by filtration. The ionic liquid was recovered by removing the water under reduced pressure and could be reused at least five times without any appreciable decrease in yield.

The proposed reaction mechanism for the [TMG] [Ac] mediated cyclization of cyanoacetylureas to 6-aminouracils could be explained by the formation of hydrogen bonding between [TMG] [Ac] and the cyanoacetylureas (Scheme 4). This facilitates the nucleophilic attack of the nitrogen on the electrophilic carbon of the cyano group to give an intermediate, which on migration of a proton gives the corresponding 6-aminouracil.



Scheme 4 Proposed mechanism for cyclization of cynoacetylureas to 6-aminouracils.

Conclusions

In summary, for the first time, a facile and efficient [TMG] [Ac] mediated one-pot synthesis of 6-aminouracils from aromatic, as well as aliphatic, amines is described. In this procedure, three C–N bonds are formed in the one-pot process. Thus, the conventional multistep synthetic methodologies for 6-aminouracils were replaced by a one-pot catalytic system, which provides a means to improve the economical and environmental aspects of chemical process. The catalytic system is easy to prepare and very efficient in terms of work up and reusability, with additional advantages being that isolation and purification of the intermediates is not required. Moreover, the same catalyst can catalyze different consecutive steps in a single reaction vessel, which reduces the operating time and the amount of waste produced.

General procedure for Table 2 and Table 3

To a stirred mixture of [TMG] [Ac] (1 g) and water (0.3 ml) was added amine (1 mmol) followed by cyanate (1 mmol) and the mixture was heated to 60 °C for 30 min. To this, a solution of cyanoacetic acid (1 mmol) in acetic anhydride (2 mmol) was added and heated at 60 °C for 60 min to give a clear solution, then the reaction temperature was raised to 90 °C and stirred for a further 60 min. The progress of the reaction was monitored by TLC. After completion of the reaction, cold water (5 ml) was added and stirred for 5 min. The precipitated solid was collected by filtration, washed with water (5 ml) and dried to obtain the corresponding 6-aminouracil. The ionic liquid was recovered by removing the water under reduced pressure and could be reused at least five times without any appreciable decrease in yield.

Acknowledgements

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