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ORIGINAL PAPER

Carboxylic acid-catalyzed one-pot synthesis of cyanoacetylureas and their cyclization to 6-aminouracils in guanidine ionic liquid

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Abstract A novel, one-pot, carboxylic acid-catalyzed synthesis of cyanoacetylureas via in situ generated ureas and their cyclization to 6-aminouracils in the presence of the guanidine-based ionic liquid 1,1,3,3-tetramethylguanidine lactate [TMG][Lac] is described. The ureas were synthesized from amines and potassium cyanate, which on reaction with cyanoacetic acid in the presence of acetic anhydride in the same pot afforded cyanoacetylureas, which undergo cyclization in [TMG][Lac] as solvent as well as catalyst to afford 6-aminouracils. One-pot synthesis of cyanoacetylureas, efficient and rapid cyclization, better yield, shorter reaction time, easy workup procedure, and recyclability of the ionic liquid are some advantages of this procedure.

Keywords Cyanoacetylurea · Carboxylic acid · One-pot synthesis · 6-Aminouracil · Cyclization · Guanidine

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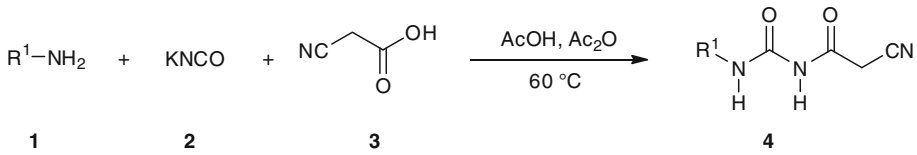
Introduction

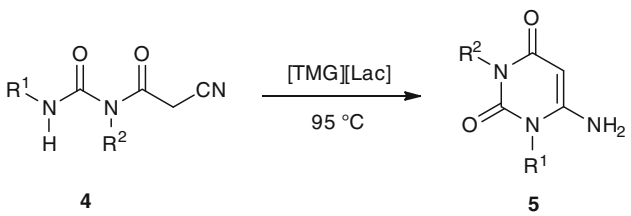
Cyanoacetylureas are key intermediates in the synthesis of 6-aminouracils, which possess a number of biological activities such as anticancer [1], antiviral [2], antihypertensive [3], insecticidal, herbicidal, and acaricidal [4] activities. 6-Aminouracils (6-aminopyrimidine-2,4(1*H*,3*H*)-diones) are key intermediates in the synthesis of xanthines [5], which constitute the scaffold of various drugs such as caffeine, 6-mercaptopurine, penciclovir, theophylline, theobromine, etc. 6-Aminouracils are also used as starting materials for the synthesis of various fused heterocycles of biological importance such as pyrido-, pyrazolo-, and pyrimidopyrimidines [6].

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

The first synthesis of 6-aminouracils was reported by Traube [10]. It involves the condensation of urea or *N*-mono- or *N*, *N*′-disubstituted ureas with cyanoacetic acid in the presence of phosphorus oxychloride to afford cyanoacetylureas, which on cyclization in the presence of strong base afford 6-aminouracils. In a modification, Speer and Raymond [11] used an excess of acetic anhydride instead of phosphorus oxychloride to afford intermediate cyanoacetylureas, which on cyclization in the presence of strong base afford 6-aminouracils. Another method described the ring closure of cyanoacetylureas to 6-aminouracils in the

Scheme 1





Scheme 2

presence of hexamethyldisilazane and chlorotrimethylsilane [12]. Similar reports [13–17] are available in the literature which lack simplicity in the experimental procedure. Some reactions are multi-step syntheses with isolation and purification of intermediates at each step, whereas some reactions are restricted to aliphatic ureas, some utilize an excess of base, expensive reagents for cyclization, require dry experimental conditions, and also have no recovery of catalysts. Therefore, developing a one-pot carboxylic acid-catalyzed synthetic method for cyanoacetylureas and their cyclization to 6-aminouracils in the presence of ionic liquid [TMG][Lac] as an environmentally friendly and recyclable solvent as well as catalyst is desirable.

This work reports the novel carboxylic acid-catalyzed, one-pot synthesis of cyanoacetylureas via in situ generated ureas (Scheme 1) and their cyclization to 6-aminouracils in the presence of the ionic liquid 1,1,3,3-tetramethylguanidine lactate [TMG][Lac] as recyclable solvent and catalyst (Scheme 2).

The catalyst [TMG][Lac] is safe, easy to handle, environmentally benign, and stable in the reaction medium.

Results and discussion

The condensation of equimolar amounts of butylamine (**1b**) and potassium cyanate (**2**) in the presence of acetic acid at 60 °C resulted in the formation of butylurea, which on reaction with 1 M equiv. of cyanoacetic acid and 2 M equiv. of acetic anhydride at 60 °C afforded *N*-butylcyanoacetylurea (**4b**) in the same pot. Ring closure of *N*-butylcyanoacetylurea (**4b**) in the presence of [TMG][Lac] at 95 °C gave 1-butyl-6-aminouracil (**5b**). The scope and generality of the reaction as well as the influence of reaction parameters such as amount of [TMG][Lac], reaction time, and reaction temperature were next investigated.

Initially, *N*-butylcyanoacetylurea (**4b**) was prepared via in situ generated *N*-butylurea from butylamine and potassium cyanate in the presence of cyanoacetic acid, acetic anhydride, and acetic acid as solvent using a modification of the reported method [13]. In this reaction, the catalyst could be acetic acid or cyanoacetic acid. *N*-Butylurea was obtained in optimum yield at 60 °C in a short reaction time of 30 min in the presence of 2 molar equivalents of acetic acid. The synthesized *N*-butylurea was acylated with cyanoacetic acid in the presence of excess acetic anhydride in the same pot at 60 °C. The best results were obtained with 1 molar equivalent of cyanoacetic acid and 2 molar equivalents of acetic anhydride at 60 °C with a reaction time of 45 min.

With these optimized parameters, reactions of various aliphatic and aromatic amines with potassium cyanate, cyanoacetic acid, and acetic anhydride in the presence of acetic acid were carried out. The results of acid-catalyzed, one-pot synthesis of cyanoacetylureas are presented in Table 1. Aliphatic amines reacted faster than aromatic amines and yields obtained using aliphatic amines were slightly higher.

Table 1 Acetic acid-catalyzed, one-pot synthesis of cyanoacetylureas from amine (1 mmol), potassium cyanate (1 mmol), cyanoacetic acid (1 mmol), and acetic anhydride (2 mmol) at 60 °C (Scheme 1)

Entry	R^1	Product	Time/min	Yield[a]/%	M.p./°C	Lit. m.p./°C
1	*n*-C_3H_7	**4a**	75	90	168–169	169–170 [13]
2	*n*-C_4H_9	**4b**	75	91	151–153	152–154 [13]
3	*i*-C_3H_7	**4c**	75	91	144–147	145–146 [13]
4	$C_6H_5CH_2$	**4d**	90	88	208–210	209–211 [19]
5	4-$CH_3OC_6H_4CH_2$	**4e**	90	90	184–185	185 [19]
6	C_6H_5	**4f**	120	83	208–210	209–211 [20]
7	4-$CH_3C_6H_4$	**4g**	120	85	181–183	182–184 [10]
8	4-$NO_2C_6H_4$	**4h**	120	76	220–224	224–225 [10]
9	Cyclohexyl	**4i**	120	78	162–164	164 [13]

[a] Yield of isolated products

Table 2 Effect of different amounts of [TMG][Lac] on the cyclization of cyanoacetylurea **4b** (2.72 mmol) to 6-aminouracil **5b** in the presence of [TMG][Lac] at 95 °C

Entry	[TMG][Lac]/g	Time/h	Yield[a] of **5b**/%
1	–	12	NR
2	0.2	0.5	63
3	0.4	0.5	78
4	0.6	0.5	91
5	0.8	0.5	91
6	0.6	1	91
7	0.6	2	92
8	0.8	2	92
9	1.0	2	93

NR no reaction

[a] Isolated yield

In order to optimize the cyclization of cyanoacetylureas (**4a**–**4k**) to 6-aminouracils (**5a**–**5k**) in the presence of [TMG][Lac], cyclization of *N*-butylcyanoacetylurea (**4b**) to 1-butyl-6-aminouracil (**5b**) was selected as a model reaction. To optimize the amount of [TMG][Lac] required for the ring closure of cyanoacetylurea (**4b**) to 6-aminouracil (**5b**), several experiments were carried out and results are summarized in Table 2.

Variation of temperature from 70 to 110 °C resulted in the optimum temperature of 95 °C for the cyclization. When this reaction was carried out at temperatures below 95 °C, the reaction time was longer and the yield of **5b** was low and when at temperatures above 95 °C, no improvement in the yield of **5b** was observed. The yield improved with increasing the amount of [TMG][Lac] and reached a maximum of 91 % with 0.6 g of [TMG][Lac] (Table 2, entry 4) in a fixed reaction time of 0.5 h. However, further increase in the amount of [TMG][Lac] did not improve the yield significantly (Table 2, entries 5, 8, and 9). Thereafter, the reaction was evaluated by varying the reaction time (0.5–2 h) keeping the ionic liquid quantity of 0.6 g constant. Better yield was obtained when the reaction was carried out for 0.5 h (Table 2, entry 4). Further increase in reaction time and amount of [TMG][Lac] did not improve the result much (Table 2, entries 8 and 9). These experiments revealed that 0.6 g of [TMG][Lac] and a reaction time of 0.5 h were optimum for the cyclization of cyanoacetylurea (**4b**) to 6-aminouracil (**5b**) with a yield of 91 %.

With these optimized reaction parameters, ring closures of various aliphatic and aromatic cyanoacetylureas (**4a**–**4k**) to 6-aminouracils (**5a**–**5k**) in the presence of [TMG][Lac] were carried out. The results of [TMG][Lac]-mediated cyclization of cyanoacetylureas are presented in Table 3. Aliphatic cyanoacetylureas undergo ring closure faster than that of aromatic cyanoacetylureas (Table 3, entries 1–3, 8, 9) and also the yields obtained were slightly higher. In the case of aromatic cyanoacetylureas, cyanoacetylureas with electron-donating groups on the benzene ring reacted smoothly under these reaction conditions (Table 3, entry 7), whereas cyanoacetylureas with electron-withdrawing groups on the aromatic ring (Table 3, entry 10) and cyclohexyl cyanoacetyl urea did not undergo ring closure (Table 3, entry 11) even after heating at 95 °C for 7 h.

The recycling efficiency of catalyst [TMG][Lac] in the same model reaction was also explored (Table 4). After completion of the reaction, cold water was added to the reaction mixture and products were isolated by filtration. The catalyst [TMG][Lac] was recovered by removing water under reduced pressure and could be reused at least five times without appreciable decrease in yield.

A tentative reaction mechanism for [TMG][Lac]-catalyzed ring closure of cyanoacetylureas to 6-aminouracils is proposed in Scheme 3. Formation of hydrogen bonding

Table 3 Cyclization of cyanoacetylureas (1 mmol) to 6-aminouracils in the presence of 0.6 g [TMG][Lac] at 95 °C (Scheme 2)

Entry	R^1	R^2	Product	Time/h	Yield[a]/%	M.p./°C	Lit. m.p./°C
1	*n*-C_3H_7	H	**5a**	0.5	92	273–274	274–275 [13]
2	*n*-C_4H_9	H	**5b**	0.5	91	265–267	266–267 [13]
3	CH_3	CH_3	**5c**	0.5	91	289–291	290–292 [13]
4	$C_6H_5CH_2$	H	**5d**	1	93	284–286	285–286 [21]
5	4-$CH_3OC_6H_4CH_2$	H	**5e**	1	90	276–278	276–278 [14, 15]
6	C_6H_5	H	**5f**	2	84	285–286	285–287 [11]
7	4-$CH_3C_6H_4$	H	**5g**	2	90	292–294	292–294 [22]
8	CH_3	H	**5h**	0.5	90	304–305	305–306 [21]
9	*n*-C_3H_7	*n*-C_3H_7	**5i**	1	89	134–136	135–137 [21]
10	4-$NO_2C_6H_4$	H	**5j**	7	NR		
11	Cyclohexyl	H	**5k**	7	NR		

NR no reaction

[a] Isolated yield

Table 4 Recyclability of catalyst [TMG][Lac]

Entry	Cycle number	Yield of **5b**/%
1	Fresh	91
2	1	91
3	2	90
4	3	90
5	4	89
6	5	88

between [TMG][Lac] and cyanoacetylureas might facilitate the nucleophilic attack of the urea nitrogen atom on the electrophilic carbon of the cyano group to give an intermediate, which tautomerizes to the 6-aminouracils.

Experimental

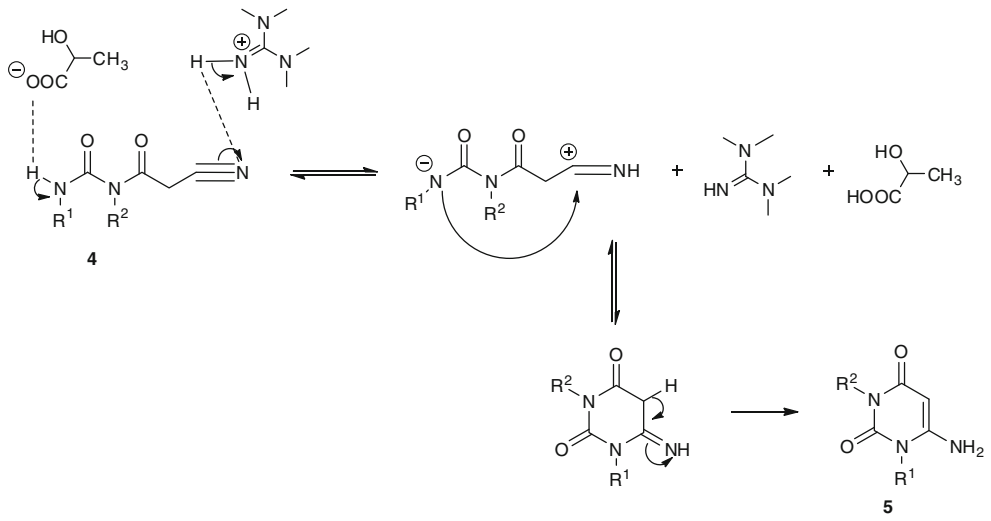
The ionic liquid was prepared by a previously reported method without any modifications and characterized by FTIR and ^{1}H NMR spectroscopy [18]. All chemicals and reagents were purchased from S. D. Fine and Spectrochem, India. FTIR spectra were obtained on a Perkin-Elmer infrared spectrometer with KBr discs ($\bar{\nu}$ in cm^{-1}). ^{1}H NMR spectra were recorded in DMSO-d_6 on a JEOL 300 MHz spectrometer with tetramethylsilane as internal standard (δ in ppm). Melting points were determined on a Kofler melting point apparatus. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) and visualization was with ultraviolet light (254 nm). The physical and spectroscopic data of products were compared with those reported in literature [10–17, 19–22].

*General procedure for the one-pot synthesis of cyanoacetylureas **4***

To a 50-cm^3 round-bottom flask containing acetic acid (27.3 mmol) was added amine (13.6 mmol) and potassium cyanate (13.6 mmol). The reaction mixture was heated at 60 °C for 0.5–2 h. To this, a solution of cyanoacetic acid (13.6 mmol) in acetic anhydride (27.3 mmol) was added and heated at 60 °C for 0.75 h to get a clear solution. The progress of the reaction was monitored by TLC. After the completion of reaction, the mixture was cooled to room temperature and product was precipitated. To this, 10 cm^3 diethyl ether was added and stirred for 5 min. The precipitated solid was filtered, washed with 5 cm^3 diethyl ether, and dried to obtain cyanoacetylurea.

*General procedure for the cyclization of cyanoacetylureas **4** to 6-aminouracils **5***

To a 10-cm^3 round-bottom flask containing cyanoacetylurea (5.46 mmol) was added 0.6 g [TMG][Lac] and the reaction mixture was stirred at 95 °C for 0.5–2 h (see Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, 5 cm^3 cold water was added and the reaction mixture was stirred for 5 min. The precipitated solid was filtered and washed with 3 cm^3 water to afford 6-aminouracil. The catalyst [TMG][Lac] was recovered by removing water under reduced pressure and reused in subsequent catalytic runs. The pure products



Scheme 3

were characterized by melting point determination, IR and ^{1}H NMR spectroscopy, according to literature.

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