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A highly efficient and green approach for the synthesis of pyrimido[4,5-*b*]quinolines using *N,N*-diethyl-*N*-sulfoethanaminium chloride

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Abstract: A highly efficient and green protocol for the synthesis of pyrimido[4,5-*b*]quinolines has been described. The one-pot multicomponent reaction of dimedone with arylaldehydes and 6-amino-1,3-dimethyluracil in the presence of *N,N*-diethyl-*N*-sulfoethanaminium chloride ([Et_3N–SO_3H][Cl]) as an ionic liquid (IL) catalyst under solvent-free conditions afforded the mentioned compounds in high yields and short reaction times. Our protocol is superior to many of the reported protocols in terms of two or more of these factors: the reaction times, yields, conditions (solvent-free versus usage of organic solvents), temperature and catalyst amount.

Keywords: 6-amino-1,3-dimethyluracil; acidic ionic liquid; multi-component reaction; *N,N*-diethyl-*N*-sulfoethanaminium chloride ([Et_3N–SO_3H][Cl]); pyrimido[4,5-*b*]quinoline; solvent-free.

1 Introduction

Uracil, pyrimidine, quinoline, and pyrimido-quinoline are scaffolds of many pharmaceutical and bioactive compounds. Antimicrobial [1], antiviral [2], antioxidant [3], and gonadotropin-releasing hormone receptor antagonist [4] properties have been reported for the heterocycles in which uracil and pyrimidine building blocks are present. Quinoline-containing compounds have been utilized as antitumor [5], DNA intercalating carrier [6], antihistaminic [7], and antimalarial [8] agents. Pyrimido-quinoline moieties have been successfully integrated into heterocycles having various medicinal activities, such as antiallergic [9], antimicrobial [1], anti-inflammatory [1], antitumor [10], antifungal [11], antimalarial [12], and analgesic [13] properties. A significant class of heterocycles having uracil, pyrimidine, and pyrimido-quinoline moieties in its structure is pyrimido[4,5-*b*]quinolines. They could be prepared by the one-pot multi-component reaction of dimedone with arylaldehydes and 6-amino-1,3-dimethyluracil. Some catalysts have been reported for this transformation [14–22].

During the last decade, many research groups have focused on the synthesis and utilization of ionic liquids (ILs) in different scientific, pharmaceutical, and industrial fields, because these organic salts have many exclusive characteristics, consisting inter alia of good chemical and thermal stabilities, low vapor pressure, wide liquid range, ionic conductivity, and tunable chemical and physical properties through variation of cation and anion. Some applications of ILs include the use as electrolyte [23], simultaneous leaching and extraction of metallic ions [24], utilization as shale hydration inhibitors [25], preparation of homogeneous collagen and alginate hydrogels for skin dressing [26], usage in pharmaceutics and medicine [27], and use as solvent and catalyst in organic synthesis [28–36].

Multi-component reactions (MCRs) are reactions wherein at least three different reactants connect together to afford selectively a single product. They have several merits relative to conventional multi-step reactions, e.g., decreasing number of workups, simple operation, decreasing energy consumption, minimizing purification steps, and reduction of solvent consumption and waste production. Thereby they qualify as being eco-friendly in nature which contributes to their increasing significance in organic synthesis, medicine discovery and material science [37–40].

Solvent-free synthesis protocols have attracted special attention as being superior to traditional methods with regard to environmental and toxicity concerns, cost effectiveness, and simplicity. It has been claimed that the best solvent is no solvent [41–44].

In this work, we tried to combine the advantages of three green techniques, i.e., ionic-liquid catalysts, multi-component reactions and solvent-free conditions, and developed an effective ionic-liquid catalyst, namely *N,N*-diethyl-*N*-sulfoethanaminium chloride ([Et_3N–SO_3H][Cl]),

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for the preparation of pyrimido[4,5-*b*]quinolines *via* the one-pot multi-component reaction of dimedone with arylaldehydes and 6-amino-1,3-dimethyluracil under solvent-free conditions

2 Results and discussion

In order to attain the most appropriate quantity of the catalyst and the reaction temperature for the preparation of pyrimido[4,5-*b*]quinolines, the one-pot multicomponent condensation of dimedone (1 mmol) with 4-chlorobenzaldehyde (1 mmol) and 6-amino-1,3-dimethyl uracil (1 mmol) was chosen as model reaction (Scheme 1). It was evaluated without the catalyst and also in the presence of different quantities of $[Et_3N–SO_3H][Cl]$ at different temperatures under solvent-free conditions. The results are summarized in Table 1. Low yield of the product was obtained under catalyst-free conditions (Table 1, entry 1). The most appropriate conditions were found to be 15 mol% of the ionic-liquid catalyst at $T = 120$ °C (Table 1, entry 3). Increasing the reaction temperature to 125 °C did not improve the results (Table 1, entry 7). Increasing the catalyst quantity to 20 mol% slightly reduced the reaction time (Table 1, entry 4). Nonetheless 15 mol% was chosen as less quantity of the catalyst is more economic and more compliant with green chemistry principles.

The scope and effectiveness of the present protocol were studied through the synthesis of different derivatives of pyrimido[4,5-*b*]quinolines. For this purpose, dimedone was reacted with miscellaneous arylaldehydes and 6-amino-1,3-dimethyl uracil using 15 mol% of $[Et_3N–SO_3H][Cl]$ at 120 °C in the absence of solvent. The results are presented in Table 2. As it can be seen, benzaldehyde and arylaldehydes bearing electron-attracting, electron-donating and halogen substituents on *ortho*-, *meta*-, or *para*-positions afforded the relevant products in high yields and short times. These results confirmed the generality and high efficacy of the protocol for the synthesis of pyrimido[4,5-*b*]quinolines.

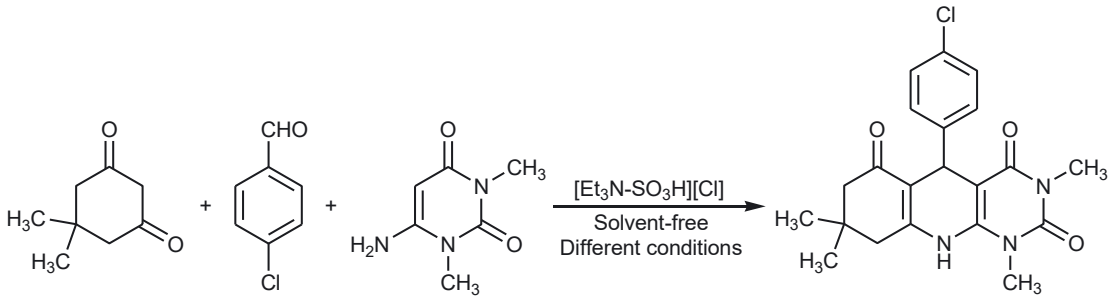
Table 1: Effect of the catalyst quantity and temperature on the model reaction.

Entry	Catalyst quantity (mol%)	Temp. (°C)	Time (min)	Yield (%)
1	–	120	60	27
2	12	120	35	92
3	15	120	30	96[a]
4	20	120	20	96[a]
5	15	100	60	78
6	15	115	30	89
7	15	125	30	96[a]

[a]The reaction was almost completed.

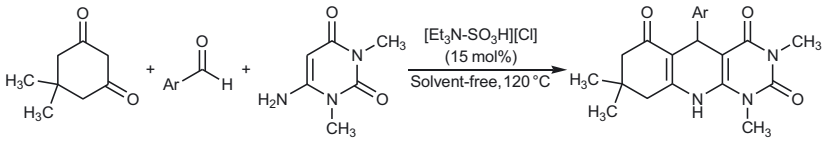
A plausible [14, 20 22] mechanism is proposed for the preparation of pyrimido[4,5-*b*]quinolines using the acidic IL ($[Et_3N–SO_3H][Cl]$) (Scheme 2). The tasks of the catalyst are obvious from the mechanism, and consist of (i) accelerating nucleophilic reactions in steps 1, 3, and 4 through activation of the electrophiles by its acidic hydrogen, (ii) accelerating the removal of H_2O in steps 2 and 5 *via* conversion of OH to a good leaving group by the acidic hydrogen, and (iii) accelerating the tautomerization of dimedone to the enol form.

To further confirm the merit of our protocol, the reaction conditions and results with $[Et_3N–SO_3H][Cl]$ for the synthesis of compounds **1**, **6**, and **10** were compared with those of other reported methods (Table 3). Our protocol is superior than the protocols in entries 2–9 of Table 3 in terms of two or more of these factors: reaction times, yields, conditions (solvent-free vs. usage of organic solvent), and temperature. The reaction times of our recently published method summarized in entry 10 are less than those of our new protocol, while the reaction temperature, the yields, and conditions of the two protocols are similar. Nevertheless, the procedure for the preparation of the catalyst in our new protocol is easier and the amount of catalyst used in the present protocol is less than in our previous one (0.033 vs. 0.080 g) while the workup procedure is also easier.



Scheme 1: The model reaction.

Table 2: The synthesis of pyrimido[4,5-*b*]quinolines using [Et_3N–SO_3H][Cl].



Product No.	Ar	Time (min)	Yield[a] (%)	M.p. (°C) found (reported) [ref.]
1	C_6H_5	30	95[b]	270–272 (268–270) [16]
2	3-$O_2NC_6H_4$	30	89	287–289 (290–292) [18]
3	2-$O_2NC_6H_4$	30	94	285–287 (281–285) [15]
4	2,5-$(CH_3O)_2C_6H_3$	50	90	209–211 (208–210) [18]
5	3,4-$(CH_3O)_2C_6H_3$	30	84	297–299 (294–296) [19]
6	4-$CH_3OC_6H_4$	30	95[b]	305–307 (304–306) [22]
7	4-HOC_6H_4	35	89	323–325 (321–323) [22]
8	4-$CH_3C_6H_4$	30	95[b]	308–310 (305–308) [22]
9	2,4-$Cl_2C_6H_3$	30	96[b]	>300 (>300) [19]
10	4-ClC_6H_4	30	96[b]	286–288 (284–288) [15]
11	2-ClC_6H_4	30	95[b]	>300 (>300) [15]

[a]Isolated yields. [b]The reaction was almost completed.

3 Conclusion

In summary, we have developed a new method for the synthesis of pyrimido[4,5-*b*]quinolines having several advantages such as the use of an IL as catalyst, simple reaction procedure under solvent-free conditions, easy purification of the products by recrystallization, superiority relative to many of the previously reported methods, and good agreement with green chemistry principles.

4 Experimental section

4.1 Materials and instruments

Chemicals used were purchased from Fluka or Merck Chemical Companies. *N*,*N*-Diethyl-*N*-sulfoethanaminium chloride ([Et_3N–SO_3H][Cl]) was synthesized according to our published method [34]. For identifying the products, their melting points/spectral data were compared with those reported in the literature. Thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates was utilized for observing the respective reaction progress. ^{1}H NMR (300, 400 or 500 MHz) and ^{13}C NMR (75, 100, or 125 MHz) were obtained on Bruker Avance DPX, FT-NMR spectrometers. Melting points were measured using a Thermo Scientific 9200 instrument in open capillary tubes.

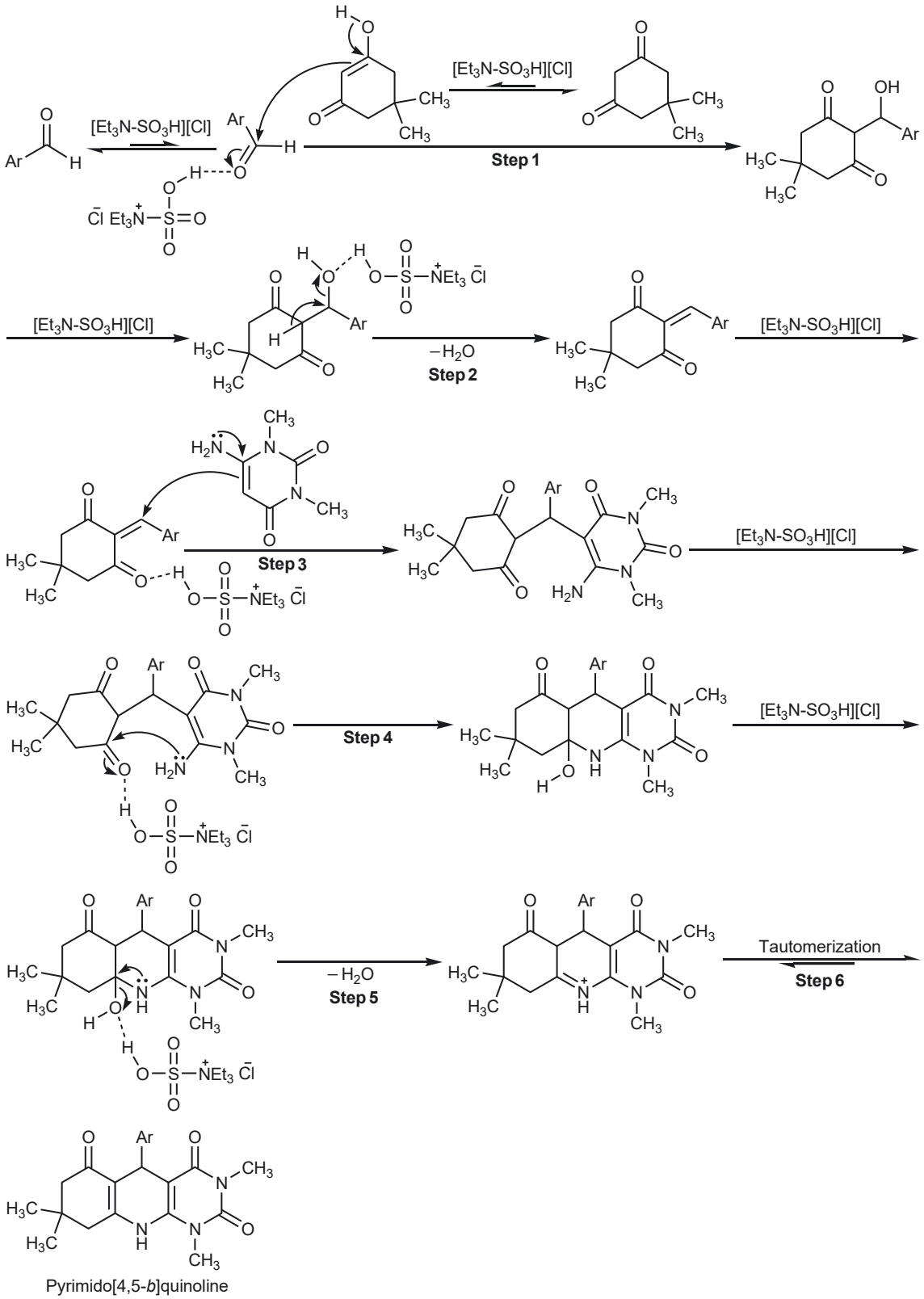
4.2 General procedure for the synthesis of pyrimido[4,5-*b*]quinolines

A mixture of compounds including dimedone (1 mmol, 0.140 g), aldehyde (1 mmol), 6-amino-1,3-dimethyl uracil (1 mmol, 0.155 g), and [Et_3N–SO_3H][Cl] (0.15 mmol, 0.033) was well mixed at room temperature, and then vigorously stirred at T = 120 °C by a small rod. After consuming the starting materials (as observed by TLC), the reaction mixture was cooled to room temperature, and the obtained precipitate was recrystallized from EtOH-H_2O (95:5) to afford the pure pyrimido[4,5-*b*]quinoline.

4.3 Selected spectral data of the synthesized pyrimido[4,5-*b*]quinolines

4.3.1 Product 3

M.p. 285–287 °C (lit. 281–285 °C [15]). —^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 0.87 (s, 3H, CH_3–C), 1.05 (s, 3H, CH_3–C), 1.97 (d, J = 16.0 Hz, 1H, CH–C=C), 2.21 (d, J = 16.1 Hz, 1H, CH–C=C), 2.52–2.59 (AB system, 2H, CH_2–C=O), 3.05 (s, 3H, CH_3–N), 3.47 (s, 3H, CH_3–N), 5.77 (s, 1H, CH–Ar), 7.31 (t, J = 7.6 Hz, 1H, Ar), 7.45 (dd, J = 8.4, 1.4 Hz, 1H, Ar), 7.54 (t, J = 7.1 Hz, 1H, Ar), 7.76 (d, J = 8.1 Hz, 1H, Ar), 8.99 (s, 1H, NH). —^{13}C NMR (75 MHz, DMSO-d_6, 25 °C, TMS): δ = 26.9, 28.0, 29.4, 30.5, 30.8, 32.2, 32.5, 50.4, 90.2, 111.6, 124.1,



Scheme 2: The proposed mechanism.

Table 3: Comparison of the reaction conditions and the results of our protocol with those of other reported ones with the syntheses of compounds **1**, **6**, and **10** as examples.

Entry	Catalyst	Conditions	Time (min) of product 1/6/10	Yield (%) of product 1/6/10	Ref.
1	$[Et_3N–SO_3H][Cl]$	Solvent-free, 120 °C	30/30/30	95/95/96	–
2	SBA-15/$PrN(CH_2PO_3H_2)_2$	Solvent-free, 100 °C	20/–[a]/15	89/–[a]/85	[14]
3	$[H_2$-DABCO$][ClO_4]_2$	H_2O, 75 °C	30/45/25	90/93/95	[15]
4	Nano-Fe_3O_4@SiO_2-SO_3H	H_2O, 70 °C	30/40/25	92/86/92	[16]
5	*p*-Toluenesulfonic acid	H_2O, 90 °C	180/180/150	85/84/89	[17]
6	[TSSECM][b]	Solvent-free, 125 °C	40/30/40	93/95/92	[18]
7	Catalyst-free	[bmim]Br[c], 95 °C	–[a]/180/210	–[a]/95/90	[19]
8	$[H_2$-DABCO$][HSO_4]_2$	H_2O/EtOH, 75 °C	65/–[a]/70	90/–[a]/93	[20]
9	$InCl_3$	H_2O, reflux	–[a]/60/60	–[a]/89/91	[21]
10	Nano-[FSRN]$[H_2PO_4]$[d]	Solvent-free, 120 °C	10/10/10	96/95/96	[22]

[a]In the work, this product has not been synthesized. [b]*N*,*N*,*N*′,*N*′-Tetramethyl-*N*-(silica-*n*-propyl)-*N*′-sulfonic acid-ethylenediaminium chloride/mesylate. [c]1-*n*-Butyl-3-methylimidazolium bromide. [d]Nano-[Fe_3O_4@SiO_2@R-$NHMe_2$][H_2PO_4].

127.3, 131.1, 133.2, 141.6, 144.7, 148.8, 150.5, 150.9, 161.0, 194.9.

4.3.2 Product 6

M.p. 305–307 °C (lit. 304–306 °C [22]). —^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 0.89 (s, 3H, CH_3–C), 1.03 (s, 3H, CH_3–C), 2.04 (d, J = 16.1 Hz, 1H, CH–C=C), 2.20 (d, J = 16.0 Hz, 1H, CH–C=C), 2.52 (d, J = 17.9 Hz, 1H, CH–C=O), 2.60 (d, J = 17.4 Hz, 1H, CH–C=O), 3.09 (s, 3H, CH_3–N), 3.44 (s, 3H, CH_3–N), 3.66 (s, 3H, CH_3–O), 4.82 (s, 1H, CH–Ar), 6.73 (d, J = 7.1 Hz, 2H, Ar), 7.12 (d, J = 7.1 Hz, 2H, Ar), 8.96 (s, 1H, NH). —^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 27.1, 28.2, 29.7, 30.7, 32.7, 33.5, 40.4, 50.7, 55.5, 91.0, 112.5, 113.7, 129.2, 139.3, 144.2, 149.8, 151.2, 158.0, 161.3, 195.1.

4.3.3 Product 9

M.p. >300 °C (lit. >300 °C [19]). —^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ = 0.90 (s, 3H, CH_3–C), 1.05 (s, 3H, CH_3–C), 1.99 (d, J = 16.1 Hz, 1H, CH–C=C), 2.21 (d, J = 16.5 Hz, 1H, CH–C=C), 2.47 (d, J = 17.9 Hz, 1H, CH–C=O), 2.60 (d, J = 18.2 Hz, 1H, CH–C=O), 3.06 (s, 3H, CH_3–N), 3.46 (s, 3H, CH_3–N), 5.15 (s, 1H, CH-Ar), 7.26 (dd, J = 8.4, 2.0 Hz, 1H, Ar), 7.33–7.37 (m, 2H, Ar), 9.04 (s, 1H, NH). —^{13}C NMR (125 MHz, DMSO-d_6, 25 °C, TMS): δ = 26.8, 28.0, 29.1, 29.6, 30.7, 32.4, 34.0, 50.5, 89.6, 110.9, 127.0, 128.7, 131.3, 133.7, 134.0, 143.1, 144.7, 150.5, 150.9, 160.9, 194.8.

4.3.4 Product 11

M.p. >300 °C (lit. >300 °C [15]). —^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ = 0.89 (s, 3H, CH_3–C), 1.04 (s, 3H, CH_3–C), 1.99 (d, J = 16.2 Hz, 1H, CH–C=C), 2.21 (d, J = 16.2 Hz, 1H, CH–C=C), 2.49–2.61 (AB system, 2H, CH_2–C=O), 3.06 (s, 3H, CH_3–N), 3.47 (s, 3H, CH_3–N), 5.17 (s, 1H, CH–Ar), 7.09 (t, J = 7.7, 2.1 Hz, 1H, Ar), 7.17–7.23 (m, 2H, Ar), 7.35 (d, J = 7.6 Hz, 1H, Ar), 9.03 (s, 1H, NH).

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