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N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate as an efficacious and dual-functional catalyst for the solvent-free preparation of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines

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KEYWORDS

Pyrido[2,3-*d*:6,5-*d*′]dipyrimidine
Ionic liquid
N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$)
Multi-component reaction
Solvent-free

ABSTRACT

Ionic liquid N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) was utilized as an efficacious and dual-functional catalyst for the one-pot multi-component reaction of arylaldehydes, 2-thiobarbituric acid and ammonium acetate under the solvent-free conditions to afford pyrido[2,3-*d*:6,5-*d*′]dipyrimidine derivatives. Dual-functionality of [TMBSED][TFA]$_2$ (having acidic and basic groups) caused that the products were obtained in high yields and short reaction times. Moreover, a logical mechanism based on dual-functionality of the catalyst was proposed.

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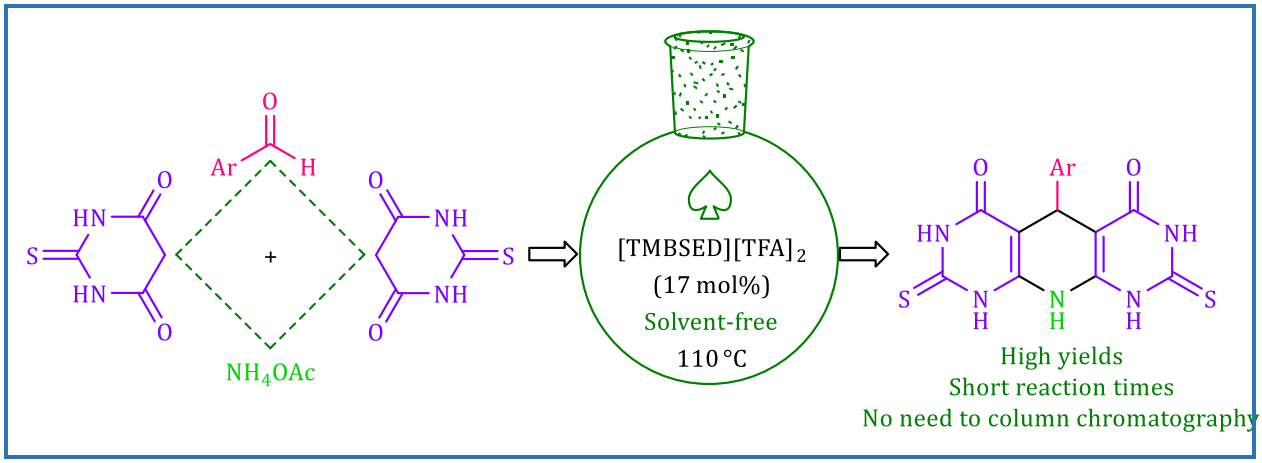
Graphical Abstract



Introduction

The pyrido-pyrimidine framework is of importance in pharmaceutical researches. The heterocycles containing this structure has shown a wide range of medicinal and biological activities including, anti-inflammatory [1], analgesic [1], antimicrobial [2], antibacterial [3], antitumor [4], anticonvulsant [5], anti-HIV [6], antihypertensive [7], tuberculostatic [8], calcium channel antagonists [9], tyrosine kinase inhibitory [10], and fibroblast growth factor receptor 3 inhibitory [11] properties. Pyrido[2,3-*d*:6,5-*d*′]dipyrimidines, as an pyrido-pyrimidine containing compounds, could be synthesized *via* the one-pot multi-component reaction of arylaldehydes (1 equivalent), 2-thiobarbituric acid (2 equivalents) and ammonium acetate (1 equivalent) in the presence of a catalyst [12–17]. Despite of high importance of this organic transformation, it has been scarcely studied in the literature; thus, studying this reaction can be valuable and interesting.

The inimitable features of ionic liquids (ILs) which caused their wide applications in all fields of chemistry include: (i) they are non-flammable and non-volatile, (ii) chemical and physical properties of them can modify by altering structures of their cation and anion, (iii) they have suitable stability (thermal, electrochemical and chemical), and (iv) they are liquid in extensive range of temperatures [18–31]. The especial use of ILs in organic chemistry is their utilization as solvent, reagent, and catalyst [19–31].

Multi-component reactions (MCRs) have been broadly utilized as highly efficient technique for synthesis of pharmaceutical, chemical, and industrial substances. MCRs are defined as reactions in which at least three starting materials react in one-pot to provide target product, and all or most of the reactants atoms are present in the product. This technique not only agrees with green chemistry principles, but also has many benefits in comparison with the multi-steps reactions, which include:

(i) it produces target substance in higher yield and shorter time, with consumption of fewer energy, (ii) workup and purification of product are easier, (iii) it minimizes utilization of volatile organic solvents, and (iv) it prevents or reduces production of waste and by-products [32–38].

Performing reactions under solvent-free conditions has been applied as a green protocol in organic chemistry. The advantages of this protocol in comparison with carrying out reactions in solvents consist of: (i) it affords higher yield of product in shorter reaction time, and consumes fewer energy; thus, it is more economic, (ii) the reaction profile is safe, (iii) selectivity is often higher, (iv) the reaction workup and purifying product are easier, and (v) generation of by-products/waste is prevented or decreased [39–44].

Collecting the advantages of ILs, MCRs, and solvent-free conditions in a synthetic protocol can be valuable and attractive. In this work, we have achieved this, and introduced ionic liquid N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) as an efficacious and dual-functional catalyst for the preparation of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines *via* the one-pot multi-component reaction of arylaldehydes (1 equivalent), 2-thiobarbituric acid (2 equivalents) and ammonium acetate (1 equivalent) under solvent-free conditions.

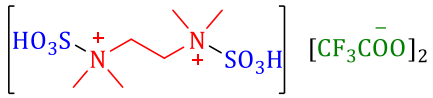
Experimental

Materials and methods

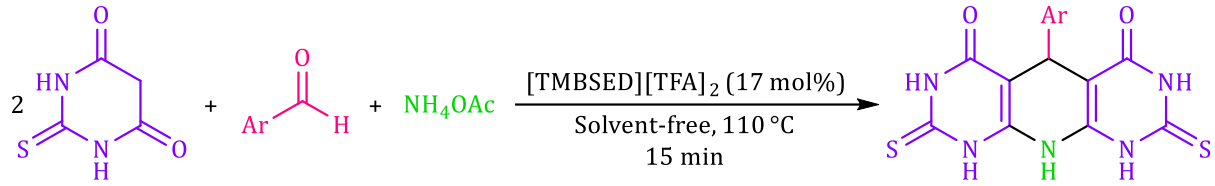
The reactants and solvents were purchased from Merck, Fluka or Iranian chemical companies. N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) (Scheme 1) was prepared according to our published procedure [24]. To identify the known compounds, their melting points/spectral data were compared with the reported data in the literature. Progress of the reactions was observed by thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates. Fourier-transform infrared spectroscopy (FT-IR) spectrums were run on a Shimadzu IR-60 instrument. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) were run on a Bruker avance DPX, FT-NMR spectrometers. Melting points were measured using a Buchi B-545 apparatus in open capillary tubes.

General procedure for the synthesis of pyrido[2,3-d:6,5-d′]dipyrimidines using [TMBSED][TFA]$_2$

A mixture of aldehyde (1 mmol), 2-thiobarbituric acid (2 mmol, 0.288 g) and NH_4OAc (1.4 mmol, 0.108 g) was added to [TMBSED][TFA] (0.17 mmol, 0.086 g), and stirred by a small rod for 1 min at room temperature, followed by stirring vigorously by a small rod at 110 °C for 15 min. Afterward, it was cooled down to room temperature, and purified by recrystallization in EtOH/H_2O (3/1).



Scheme 1. The structure of [TMBSED][TFA]$_2$



Scheme 2. The synthesis of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines

5-phenyl-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′]dipyrimidine-4,6(1H,5H)-dione (1a)

^{1}H NMR (500 MHz, DMSO-d$_6$): δ 5.97 (s, 1H, methine CH), 7.01 (d, J = 7.7 Hz, 2H, H$_{Ar}$), 7.06 (t, J = 7.1 Hz, 1H, H$_{Ar}$), 7.17 (t, J = 7.5 Hz, 2H, H$_{Ar}$), 7.57 (br., 1H, NH), 11.53 (br., 3H, NH), 17.16 (br., 1H, NH). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 30.8, 96.2, 125.3, 126.9, 128.1, 143.4, 163.0, 164.1, 173.2.

5-(3,4-dimethoxyphenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′]dipyrimidine-4,6(1H,5H)-dione (1d)

IR (KBr) (ν_{max}/ cm^{-1}): 3534, 3179, 3141, 3095, 2895, 1681, 1608, 1533, 1502, 1451, and 1429. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.63 (s, 3H), 3.69 (s, 3H), 5.92 (s, 1H), 6.54-6.58 (m, 2H), 6.77 (dd, J = 8.3, 2.3 Hz, 1H), 11.50-11.64 (br., 5H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 30.5, 55.9, 56.5, 96.5, 111.7, 112.1, 119.3, 136.1, 147.0, 148.6, 163.1, 164.0, 173.2.

5-(4-chlorophenyl)-2,8-dithioxo-2,3,7,8,9,10-hexahydropyrido[2,3-d:6,5-d′]dipyrimidine-4,6(1H,5H)-dione (1f)

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 5.97 (s, 1H), 7.02 (d, J = 7.9 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 9.60 (br., 1H), 11.60 (br., 4H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 30.6, 96.0, 128.1, 128.9, 137.6, 142.6, 163.1, 164.0, 173.3.

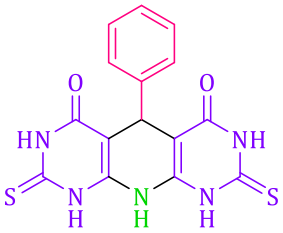
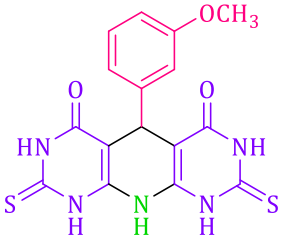
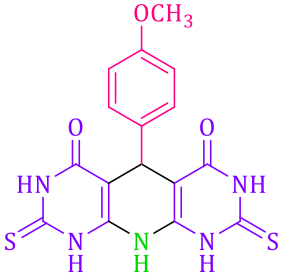
Results and Discussion

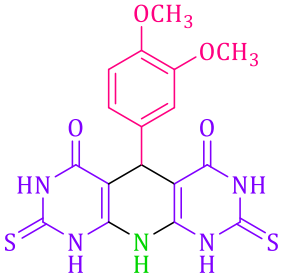
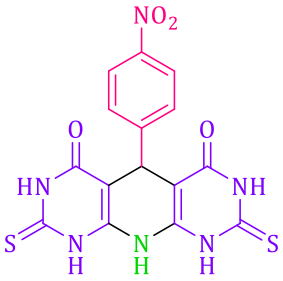
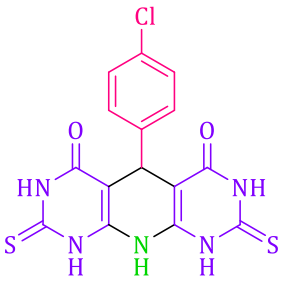
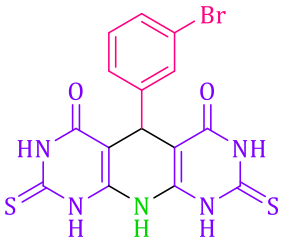
At first, the condensation of benzaldehyde (1 mmol), 2-thiobarbituric acid (2 mmol) and NH$_4$OAc (1.4 mmol), was investigated at the presence of various amounts of *N*¹,*N*¹,*N*²,*N*²-tetramethyl-*N*¹,*N*²-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][TFA]$_2$) (10-20 mol%) at the range of

100-120 °C under the solvent-free conditions to optimize the reaction conditions in terms of the catalyst amount and the reaction temperature (Scheme 2).

The reasonable reaction time and yield were acquired when 17 mol% of [TMBSED][TFA]$_2$ was utilized at 110 °C (time: 15 min, yield: 93%). After acquiring the optimal reaction conditions, effectiveness and scope of [TMBSED][TFA]$_2$ for the production of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines was assessed by examining the reaction of diverse arylaldehydes with 2-thiobarbituric acid and NH_4OAc; the results are represented in Table 1. The obtained results verified the effectiveness and generality of the ionic-liquid catalyst for the reaction, since benzaldehyde and the other arylaldehydes (bearing electron-reach and electron-deficient substituents) were reacted well with 2-thiobarbituric acid and NH_4OAc to provide the desired products in high yields and short reaction times.

Table 1. The solvent-free synthesis of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines using [TMBSED][TFA]$_2$

Entry	Product	Yield[a] (%)	M.p. (°C)	
			Found	Reported
1a		93	209-211	(211) [15]
1b		90[b]	244-246	(242) [15]
1c		92	275-277	(277-279) [14]

1d		88	279-281	-
1e		94	318-320	(321-323) [14]
1f		95	261-263	(257) [12]
1g		87	248-250	(246-248) [14]

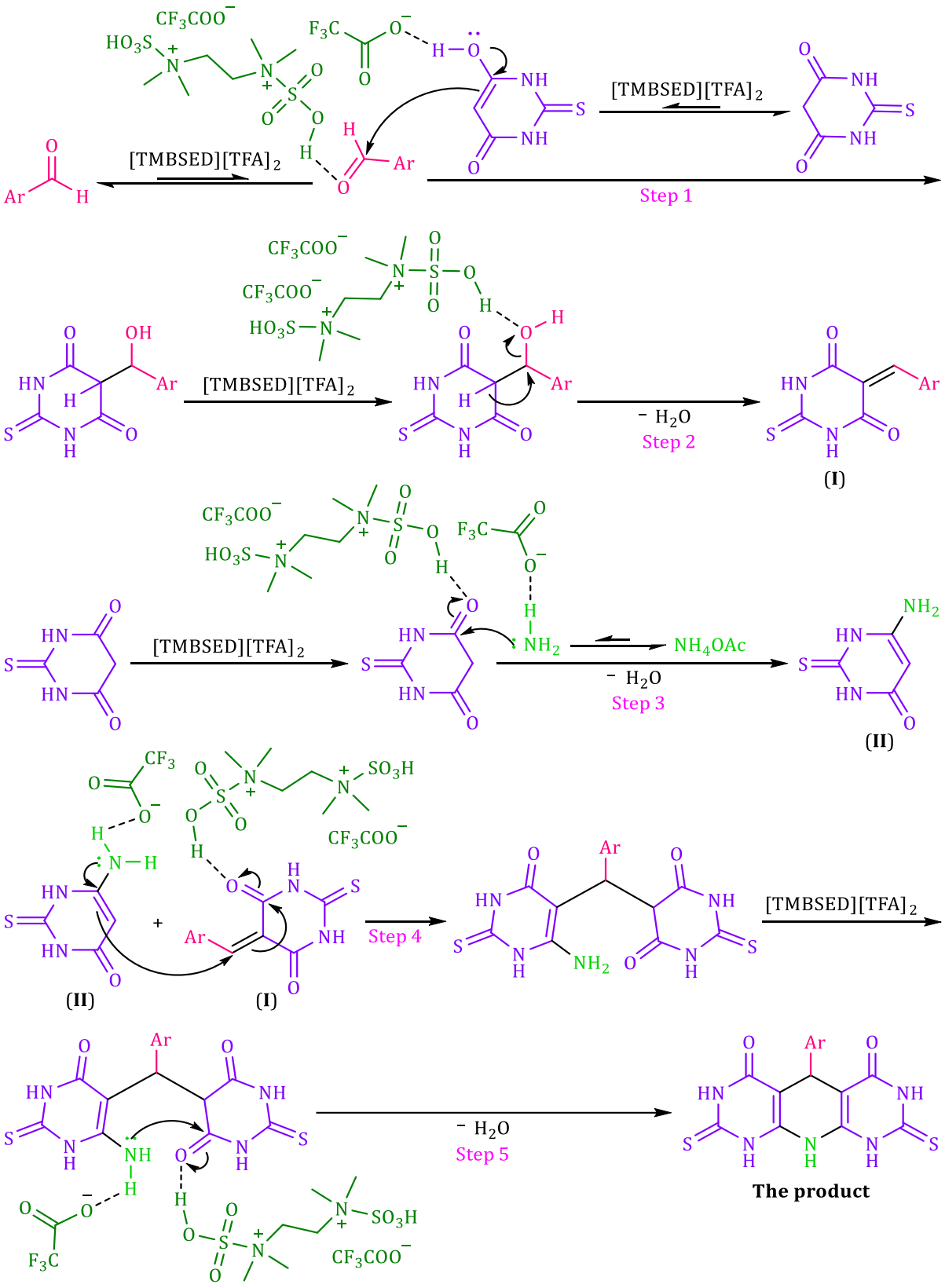
[a] Isolated yield

[b] The time of this reaction was 30 min

[TMBSED][TFA]$_2$ is a dual-functional catalyst (SO_3H group is acidic, and trifluoroacetate is a weak base). The acidic site of the catalyst activates the carbonyl groups to accept nucleophiles (steps 1, 3, 4, and 5); moreover, the SO_3H group accelerates conversion of 2-thiobarbituric acid to its tautomer, and can remove H_2O molecule from the intermediates (steps 2, 3, and 5). The basic anion can activate the nucleophiles (steps 1, 3, 4 and 5). The roles of cation and anion of the ionic liquid are illustrated in Scheme 3 [12–14].

Conclusions

In this work, a new protocol for the preparation of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines using an ionic-liquid catalyst was proposed and studied. The features of this method include effectuality, wide



Scheme 3. The proposed mechanism for the preparation of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines

scope, producing the compounds in high yields, and short times, no chromatography for purification of the products, simple workup, easy production of the catalyst, collecting the advantages of ionic-liquid catalysts, multi-component reactions and solvent-free conditions in the method, and good agreement with green chemistry principles.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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