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Original Research article

N^1,N^1,N^2,N^2-Tetramethylethylenediaminium-N^1,N^2-disulfonic Acid Trifluoroacetate as Highly Effectual and Dual-Functional Catalyst for the Reaction of β-Ketoesters with Aryl Aldehydes and Urea/Thiourea

Mostafa Karami, Bentolhoda Gholami, Tahereh Hekmat Zadeh, Abdolkarim Zare*

Department of Chemistry, Payame Noor University, PO Box 19395-3697 Tehran, Iran

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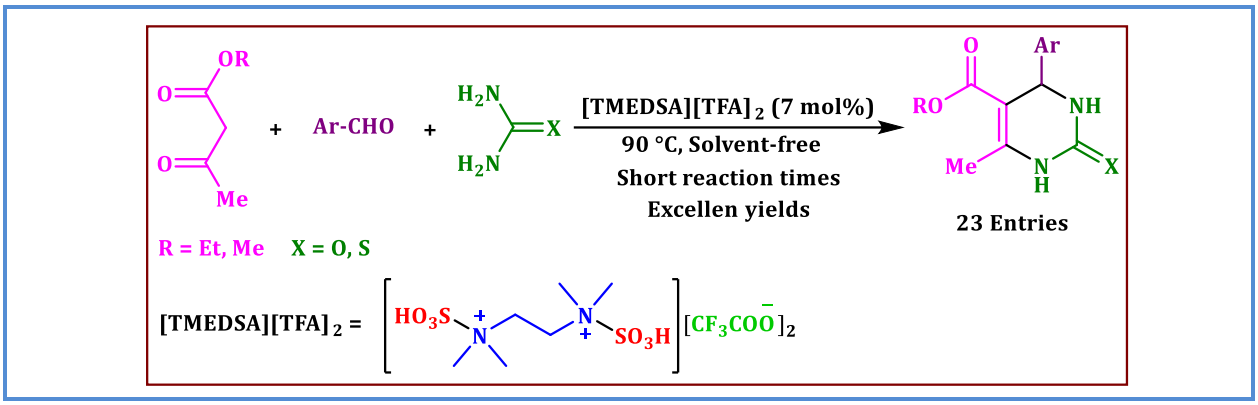
3,4-dihydropyrimidin-2-(1*H*)-thione
Ionic liquid
Dual-functional catalyst N^1,N^1,N^2,N^2-Tetramethylethylenediaminium-N^1,N^2-disulfonic acid trifluoroacetate ([TMEDSA][TFA]$_2$)

ABSTRACT

In this research, the one-pot multi-component reaction of β-ketoesters with aryl aldehydes and urea/thiourea has been performed using a dual-functional ionic liquid-catalyst namely N^1,N^1,N^2,N^2-tetramethylethylenediaminium-N^1,N^2-disulfonic acid trifluoroacetate ([TMEDSA][TFA]$_2$) in solvent-free conditions. By reason of dual-functionality of the catalyst (possessing acidic and basic sites), and also having two numbers of each site, it was highly effectual and general catalyst, and afforded the products {3,4-dihydropyrimidin-2-(1*H*)-ones and 3,4-dihydropyrimidin-2-(1*H*)-thiones} in short times with excellent yields. Moreover, a plausible mechanism based on dual-functionality of the catalyst has been proposed.

*Corresponding author: E-mail: (abdolkarimzare@pnu.ac.ir, abdolkarimzare@yahoo.com), Department of Chemistry, Payame Noor University, PO Box 19395-3697 Tehran, Iran, Tel: +982123320000,Fax: +982122455429

Graphical Abstract



Introduction

The multi-component reaction of *β*-ketoesters with aryl aldehydes and urea/thiourea is valuable, as it is a practical route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones (DHPs). These heterocyclic compounds are very considerable in medicinal and synthetic organic chemistry by reason of possessing a variety of therapeutic and biological properties, *e.g.* antiviral, anti-inflammatory, antibacterial and antitumor activities [1-3]. Moreover, DHP derivatives are essential units of several calcium channel blockers, and some of them are used as *α*-la-adrenergic receptor antagonists and antihypertensive agents [4, 5]. Several alkaloids bearing DHP backbone have potentially inhibitor activity against HIV gp-120-CD4 [6, 7]. Some catalysts have been reported to carry out this synthesis [8-17]. Nevertheless, many of the reported protocols are accompanied with one or more negative aspects, consisting of hazardous reaction medium, high reaction temperature, moderate yield, long reaction time, usage of large amount of catalyst, difficult procedure for catalyst preparation, need to microwave or ultra sound energies, and applicability of the method for the production of only 3,4-dihydropyrimidin-2-(1*H*)-ones (not 3,4-dihydropyrimidin-2-(1*H*)-thiones). Hence, introducing a catalyst for the above synthesis, without possessing the mentioned problems, would be favorable.

In recent years, functionalized ionic liquids have been widely utilized as effectual catalysts and reagents in organic synthesis; this can be attributed to having abundant specific chemical and physical properties, consisting of very low vapor pressure, capacity to designing their structures to catalyze a variety of reactions, high chemical and thermal stability, controlled miscibility and tunable hydrophobicity [18-24].

Carrying out organic reactions by green techniques is of significance. Multi-component reactions (MCRs) are imperative instances of these techniques wherein at least three reactants are reacted in

one vessel to furnish a single product, without need to separate any intermediates. MCRs are accompanied with numerous merits, *e.g.* higher yield (in comparison to multi-step reactions), saving time and energy, having atom economic nature, reducing production of side-products, flexibility, and minimizing usage of volatile and toxic organic solvents [25-29].

A further environmentally friendly protocol, which has been widely used in organic synthesis, is solvent-free conditions. This protocol has various benefits in comparison to solution conditions in terms of yield, selectivity, operation simplicity and reaction time [30-34].

In view of the above issues, we introduce here an ionic liquid-catalyst namely N^1,N^1,N^2,N^2-tetramethylethylenediaminium-N^1,N^2-disulfonic acid trifluoroacetate ([TMEDSA][TFA]$_2$) for the reaction of *β*-ketoesters, aryl aldehydes and urea/thiourea to give 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones. Dual-functionality of [TMEDSA][TFA]$_2$ cause its highly effectuality and generality. This method is n't associated with the mentioned problems.

Material and Methods

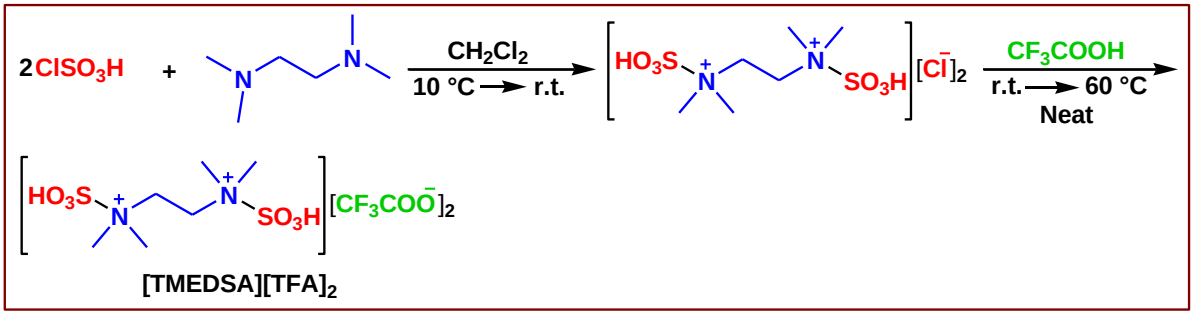
General

All starting materials and solvents were bought from Merck, Fluka or Acros Chemical Companies. The known compounds were identified by comparing their melting points/spectroscopic data with those reported in the previous papers. Monitoring progress of the reactions was achieved by thin layer chromatography (TLC). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Spectra were recorded on the following apparatus: ^{1}H NMR (250, 400 or 500 MHz), ^{13}C NMR (62.5, 100 or 125 MHz) and ^{19}F NMR (235 MHz) on Bruker Avance DPX, FT-NMR spectrometers, and mass spectra on spectrometer 5975C VL MSD model tripe-axis detector.

Preparation of [TMEDSA][TFA]$_2$

"A solution of N^1,N^1,N^2,N^2-tetramethylethylenediamine (5 mmol, 0.581 g) in dry CH_2Cl_2 (30 mL) was added dropwise to a stirring solution of chlorosulfonic acid (10 mmol, 1.165 g) in dry CH_2Cl_2 (30 mL) over a period of 10 min, at 10 °C. After that, the reaction mixture was allowed to heat to room temperature (accompanied with stirring), and stirred for another 4 hours. The solvent was evaporated under reduced pressure, and the liquid residue was triturated with dry petroleum ether (3×2 mL), and dried under powerful vacuum at 90 °C to give [TMEDSA][Cl]$_2$ [23]. Then, trifluoroacetic acid (10 mmol, 1.140 g) was added dropwise to [TMEDSA][Cl]$_2$ (5 mmol, 1.746 g) over a period of 3 min at room temperature under pressure of nitrogen gas (to remove HCl produced during the reaction). The resulting mixture was stirred for 10 h at room temperature, and

2 hours at 60 °C under a continuous flow of nitrogen gas to give [TMEDSA][TFA]$_2$ as a viscous pale yellow liquid" (Scheme 3) [24].



Scheme 3. The preparation of [TMEDSA][TFA]$_2$

General procedure for the production of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones

A mixture of *β*-ketoester (1 mmol), aldehyde (1 mmol), urea/thiourea (1.3 mmol) and [TMEDSA][TFA]$_2$ (0.07 mmol, 0.035 g) was vigorously stirred with a small rod at 90 °C. Completion of the reaction was monitored by TLC. After completing the reaction, the mixture was cooled to room temperature, and the resulted precipitate was recrystallized from ethanol (95%) to afford the pure product.

Selected spectra data of the synthesized products

Compound 1a

^{1}H NMR (500 MHz, DMSO-d$_6$): *δ* (ppm), 1.0 (t, *J* = 7.2 Hz, 3H, CH_3-CH_2), 2.17 (s, 3H, CH_3-heterocycle), 3.89 (q, *J* = 7.2 Hz, 2H, CH_2-CH_3), 5.06 (s, 1H, methine CH), 7.15-7.25 (m, 5H, Ar), 7.67 (br., 1H, NH), 9.13 (br., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d$_6$): *δ* (ppm) 14.7, 18.4, 54.6, 59.8, 99.9, 126.9, 127.9, 129.0, 145.5, 148.9, 152.8, 165.9.

Compound 1d

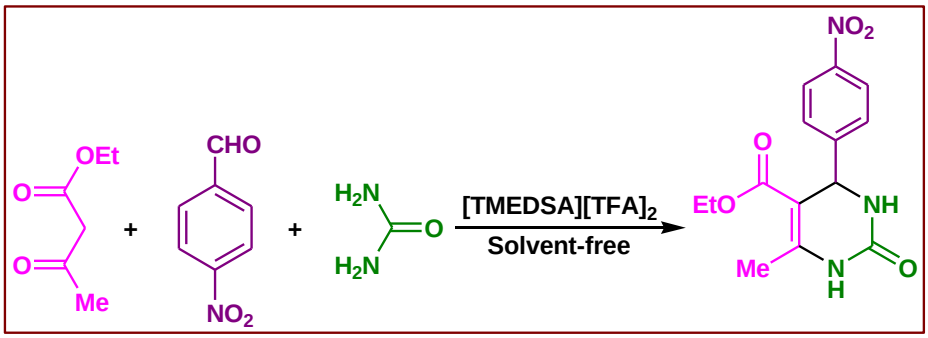
^{1}H NMR (250 MHz, DMSO-d$_6$): *δ* (ppm), 1.17 (t, *J* = 7.1 Hz, 3H, CH_3-CH_2), 2.27 (s, 3H, CH_3-heterocycle), 3.68 (s, 3H, CH_3O), 4.04 (q, *J* = 7.1 Hz, 2H, CH_2-CH_3), 5.16 (s, 1H, methine CH), 6.82 (d, *J* = 8.6 Hz, 2H, Ar), 7.09 (d, *J* = 8.6 Hz, 2H, Ar), 7.76 (br., 1H, NH), 9.06 (br., 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d$_6$): *δ* (ppm) 14.2, 17.7, 53.6, 56.0, 60.4, 101.2, 114.3, 127.6, 136.9, 148.4, 152.6, 158.5, 164.9.

Compound 1w

^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.19 (t, J = 7.3 Hz, 3H, CH_3-CH_2), 2.37 (s, 3H, CH_3-heterocycle), 4.08 (q, J = 7.3 Hz, 2H, CH_2-CH_3), 5.25 (s, 1H, methine CH), 7.27-7.41 (m, 2H, Ar), 7.45 (s, 1H, Ar), 7.53 (d, J = 7.5 Hz, 1H, Ar), 9.76 (br., 1H, NH), 10.48 (br., 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ (ppm) 14.0, 17.2, 53.6, 59.7, 100.2, 121.7, 125.4, 129.3, 130.6, 131.0, 145.6, 146.1, 165.0, 174.4.

Results and Discussion

Initially, the condensation of ethyl acetoacetate (1 mmol) with 4-nitrobenzaldehyde (1 mmol) and urea (1.3 mmol) was selected as a model reaction (Scheme 1). To obtain the suitable reaction conditions, the condensation was examined in the presence of various amounts of N^1,N^1,N^2,N^2-tetramethylethylenediaminium-N^1,N^2-disulfonic acid trifluoroacetate ([TMEDSA][TFA]$_2$) (3, 5, 7 and 9 mol%) at range of 70-95 °C in solvent-free conditions. The suitable results were obtained when the reaction was performed using 7 mol% of the catalyst at 90 °C (time: 15 min; yield: 98%).

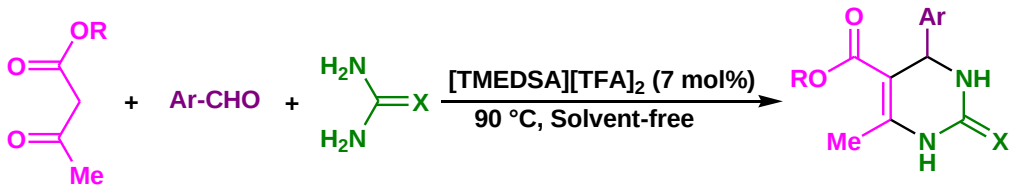


Scheme 1. The model reaction for the production of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones

After the reaction was optimized, *β*-ketoesters (ethyl and methyl acetoacetate) were reacted with numerous aryl aldeydes and urea (or thiourea); the results are depicted in Table 1. As it is clear from Table 1, all reactions proceeded efficiently, and the desired 3,4-dihydropyrimidin-2-(1*H*)-ones and 3,4-dihydropyrimidin-2-(1*H*)-thiones were produced with excellent yields in short times. Influence of electron-releasing and electron-withdrawing substituents on the aromatic ring of aldehydes upon the reaction results was investigated. The results showed that both electron-donating and electron-withdrawing substituents had no significant effect on the reaction yields; the yields using both substituents were excellent, and in all cases, the reaction times were short. Thiourea and methyl acetoacetate were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2-(1*H*)-thiones and 3,4-dihydropyrimidin-2(1*H*)-ones. In all

cases, 3,4-dihydropyrimidin-2(1*H*)-ones/thiones were the sole products, and no by-products were observed.

Table 1. The synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones using $[TMEDSA][TFA]_2$



Product	Ar	X	R	Time (min)	Yield[a] (%)	M.p. (ºC) [Lit.]
1a	C_6H_5	O	Et	10	97	205-207 (203-205) [8]
1b	3,4,5-$(MeO)_3C_6H_2$	O	Et	10	95	183-185 (180-182) [13]
1c	2,5-$(MeO)_2C_6H_3$	O	Et	15	93	215-216 (212-214) [13]
1d	4-$MeOC_6H_4$	O	Et	35	96	204-206 (200-202) [8]
1e	4-MeC_6H_4	O	Et	40	97	216-218 (218-220) [12]
1f	4-HOC_6H_4	O	Et	15	95	232-234 (231-233) [11]
1g	4-$O_2NC_6H_4$	O	Et	15	98	209-211 (207-209) [8]
1h	3-$O_2NC_6H_4$	O	Et	25	98	229-231 (225-227) [12]
1i	2,4-$Cl_2C_6H_3$	O	Et	30	97	246-248 (246-248) [11]
1j	4-ClC_6H_4	O	Et	20	98	210-212 (210-212) [8]
1k	2-ClC_6H_4	O	Et	20	95	221-223 (222-224) [13]
1l	3-BrC_6H_4	O	Et	40	96	191-193 (190-192) [11]
1m	C_6H_5	O	Me	30	95	209-211 (212-214) [11]
1n	4-$O_2NC_6H_4$	O	Me	15	98	235-237 (233-236) [8]
1o	2,4-$Cl_2C_6H_3$	O	Me	25	96	254-256 (256-258) [11]
1p	4-ClC_6H_4	O	Me	15	97	205-208 (204-207) [8]
1q	C_6H_5	S	Et	30	96	209-211 (207-209) [11]
1r	3,4,5-$(MeO)_3C_6H_2$	S	Et	25	92	203-205 (202-204) [13]
1s	4-$MeOC_6H_4$	S	Et	75	94	153-155 (150-151) [13]
1t	4-MeC_6H_4	S	Et	40	96	189-191 (189-191) [12]
1u	3-$O_2NC_6H_4$	S	Et	50	97	204-206 (207-209) [12]
1v	4-ClC_6H_4	S	Et	70	97	191-193 (193-195) [12]
1w	3-BrC_6H_4	S	Et	80	95	183-185 (182-184) [11]

[a]Isolated yield

To indicate superiority of our catalyst with respect to the reported ones, we have compared the results and the reaction conditions when the catalysts were used for the synthesis of compounds **1a** {3,4-dihydropyrimidin-2-(1*H*)-one} and **1q** {3,4-dihydropyrimidin-2-(1*H*)-thione}; this comparison is tabulated in Table 2. As this Table displays, our catalyst is superior in relation to the reported catalysts in terms of the reaction times, yields and conditions. Moreover, our catalyst was more

general in relation to most of the reported catalysts (we have utilized diverse aryl aldehydes for the synthesis of both 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidin-2(1*H*)-thiones).

Table 2. Comparing effectuality and conditions of our catalyst relative to the reported catalysts for the production of compounds **1a** and **1q**

Catalyst	Conditions	Time (min) (1a/1q)	Yield (%) (1a/1q)	Reference
$[TMEDSA][TFA]_2$	Solvent-free, 90 °C	10/30	97/97	Our work
$H_4SiMO_{12}O_{40}$	MeCN, Reflux	90/-[a]	65/-[a]	[8]
3D printed α-Al_2O_3	Solvent-free, 100 °C, Microwave	15/15	95/93	[9]
$[Et_3N\text{-}SO_3H][HSO_4]$	Solvent-free, 70 °C	40/100[b]	98/93[b]	[10]
$Cu(NH_2SO_3)_2$	AcOH, 100 °C	300/300	79/65	[11]
P_2O_5/SiO_2	Solvent-free, 85 °C	120/150	95/83	[12]
[cmmim][BF_4][c]	Solvent-free, Microwave (700 W)	1.5/2.5	97/92	[13]
$CuCl_2$	BMI.PF_6[d], 80 °C	120/120	95/60	[14]
Gallium nafionate	Solvent-free, 120 °C	60/60	84/74	[16]
Fe_3O_4@mesoporous SBA-15	EtOH, Reflux	360/-[a]	85/-[a]	[17]

[a] In this work, the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones hasn't been achieved
[b] Moreover, compound **1q** hasn't been synthesized; thus, we have tabulated the results of the preparation of compound **1u** (the time and yield of this compound in the presented work were 50 min and 98%, respectively)
[c] 1-Carboxymethyl-3-methylimidazolium tetrafluoroborate
[d] 1-Butyl-3-methylimidazolium hexafluorophosphate

Our ionic liquid is a dual-functional catalyst, because it has both acidic and basic sites (SO_3H group is acidic, and trifluoroacetate is basic); furthermore, there are two acidic sites, and two basic sites in the catalyst (Figure 1). As a result, $[TMEDSA][TFA]_2$ can especially act as a highly effectual and general catalyst for reactions which need both acidic and basic catalysts simultaneously; e.g. the production 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones. This issue has been shown in the reaction mechanism (Scheme 2). In a plausible mechanism which was supported by the literature [17], initially, *β*-ketoester is converted to its tautomer form in the presence of $[TMEDSA][TFA]_2$. Afterward, basic moiety of the catalyst (trifluoroacetate) assists the tautomer to react with the activated aldehyde (by the acidic site) to give **I**. Removing a water molecule from **I** and using the catalyst give **II**. Conjugate addition of urea to intermediate **II** affords **III** (both acidic and basic sites help this step). By intramolecular nucleophilic addition of NH_2 (activated by the anion) to the activated carbonyl (by the sulfonic acid moiety), intermediate **IV** is produced. Finally, elimination of

a H_2O molecule from **IV** in the presence of $[TMEDSA][TFA]_2$ furnishes the product. Two acidic and two basic sites of the ionic liquid can simultaneously catalyze the reaction.

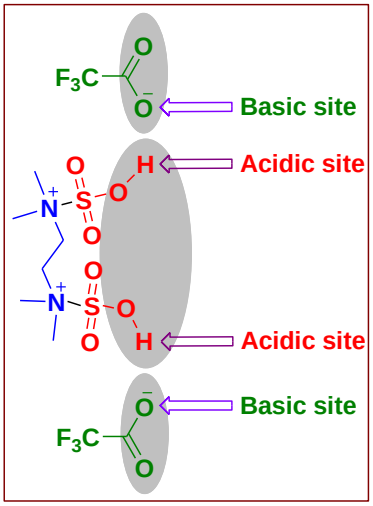
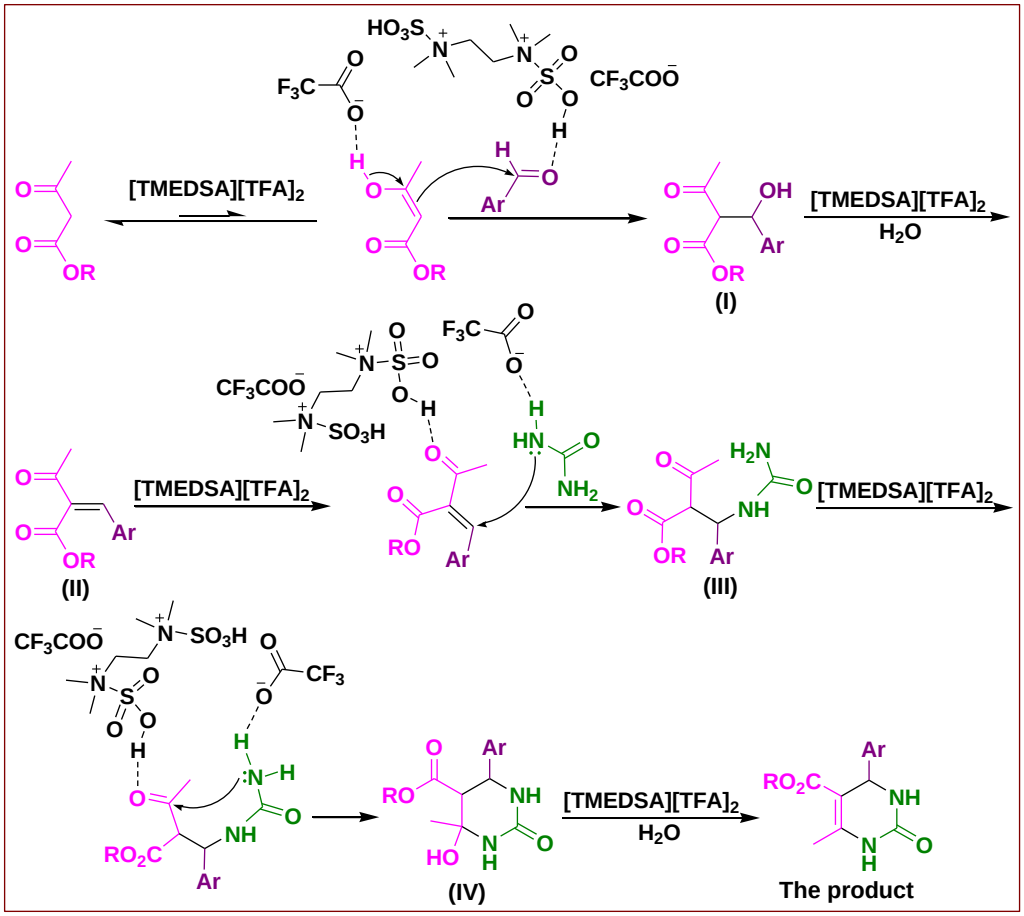


Figure 1. The acidic and basic sites of $[TMEDSA][TFA]_2$



Scheme 2. The proposed mechanism

Conclusions

In summary, we have introduced ionic liquid [TMEDSA][TFA]$_2$ as a homogeneous catalyst for the production of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones. The promising points for the presented protocol are efficiency, generality, excellent yields, short reaction times, cleaner reaction profile, simple experimental procedures, purification of compounds by non-chromatography method (crystallization only), wide range of substrate applicability, low cost, use of a few amount of the catalyst, easy preparation of the catalyst from available reactants, and good agreement with the green chemistry protocols.

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