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Original Research Article

N,N,N′,N′-tetramethylethylene-diaminium-*N,N*'-disulfonic acid chloride as a highly effective catalyst for the synthesis of 4*H*-pyrano[2, 3-*c*]pyrazoles, *α*-carbamatoalkyl-*β*-naphthols and *α*-amidoalkyl-*β*-naphthols

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KEYWORDS

N,N,N′,N′-Tetramethylethylene-diaminium-*N,N*'-disulfonic acid chloride {[TMEDSA][Cl]$_2$}
Sulfonic acid-functionalized ionic liquid
4*H*-Pyrano[2, 3-*c*]pyrazole
α-Carbamatoalkyl-*β*-naphthol
α-Amidoalkyl-*β*-naphthol

ABSTRACT

In this work, *N,N,N′,N′*-tetramethylethylene-diaminium-*N,N*'-disulfonic acid chloride {[TMEDSA][Cl]$_2$} has been utilized as a highly effective catalyst in order to promote the following organic transformations under green, solvent-free and mild conditions: (i) the synthesis of 4*H*-pyrano[2, 3-*c*]pyrazoles from aromatic aldehydes, 3-methyl-1-phenyl-2-pyrazolin-5-one and malononitrile, (ii) the preparation of *α*-carbamatoalkyl-*β*-naphthols from arylaldehydes, *β*-naphthol and alkyl carbamates, and (iii) the production of *α*-amidoalkyl-*β*-naphthols from arylaldehydes, *β*-naphthol and amides.

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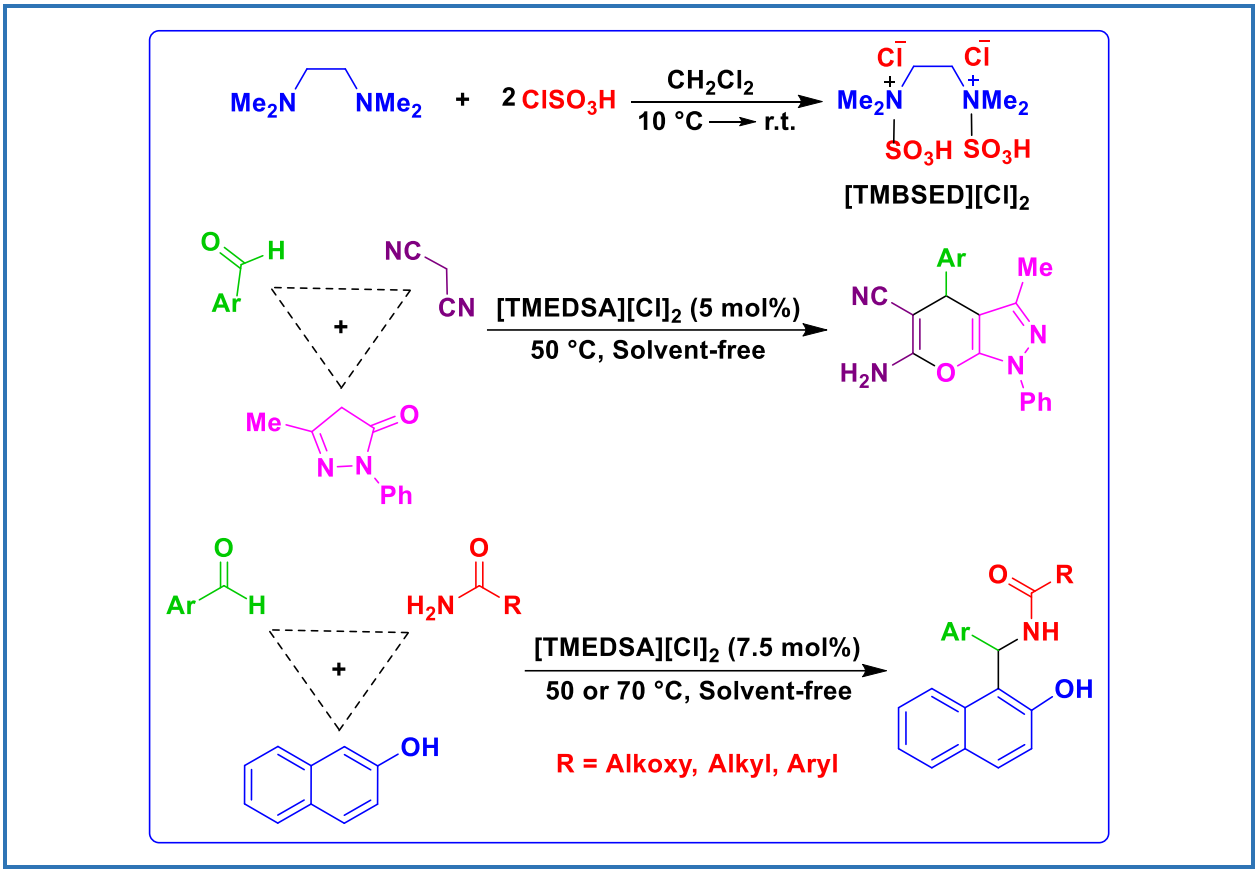
Graphical Abstract



Introduction

Ionic liquids (ILs) have attracted lots of attention as green reaction media, catalysts and reagents due to the fact that they perform organic transformations under different conditions. This extensive application in organic chemistry is attributed to the unique properties of ILs; including, non-flammability, reasonable thermal and chemical stability, negligible vapor pressures, excellent ionic conductivities, tunable hydrophobicity, green nature, and capability to catalyze a wide range of organic transformations [1–10]. In this sense, sulfonic acid-functionalized ILs can replace solid acids and traditional mineral liquid acids (such as sulfuric acid and hydrochloric acid) to catalyze different kinds of organic reactions [4–10].

4*H*-pyrano[2, 3-*c*]pyrazoles derivatives are very significant in medicinal chemistry, since they are used as precursors to potential drugs, and indicate different pharmaceutical activities, such as anti-inflammatory [11], antibacterial [12], anticonvulsant [13], analgesic [14], antimicrobial [15], antifungal [16] and anticancer [17] properties. One of the best synthetic route towards 4*H*-pyrano[2,

3-*c*]pyrazoles is the condensation reaction between arylaldehyde, 3-methyl-1-phenyl-2-pyrazolin-5-one and malononitrile; some catalysts have been used to promote this synthesis [18–26].

α-Carbamatoalkyl-*β*-naphthols and *α*-amidoalkyl-*β*-naphthols are utilized as precursors for the production of a variety of biologically significant natural products and potent drugs such as nucleoside antibiotics and HIV protease inhibitors (*e.g.* lipinavir and ritonavir) [27]. These compounds can also be hydrolyzed to important 'drug like' *α*-aminoalkyl-*β*-naphthols, besides, bradycardiac and hypotensive activities for *α*-aminoalkyl-*β*-naphtholshave been verified [28, 29]. Moreover, the intramolecular cyclization of *α*-amidoalkyl-*β*-naphthols produces 1,3-oxazines [30]. It is worth mentioning that the oxygen-containing heterocycles have a variety of biological activities [31–33]. The condensation reaction of arylaldehydes with *β*-naphthol and alkyl carbamates/amides is the practical route for the production of *α*-carbamatoalkyl-*β*-naphthols and *α*-amidoalkyl-*β*-naphthols; in this sense, several catalysts have been applied to achieve this reaction [34–45].

Herein, we report our results on the usage of *N*,*N*,*N*′,*N*′-tetramethylethylene-diaminium-*N*,*N*'-disulfonic acid chloride {[TMEDSA][Cl]$_2$} as a highly efficient ionic liquid-catalyst for the green preparation of three important classes of organic compounds, including 4*H*-pyrano[2, 3-*c*]pyrazoles, *α*-carbamatoalkyl-*β*-naphthols and *α*-amidoalkyl-*β*-naphthols.

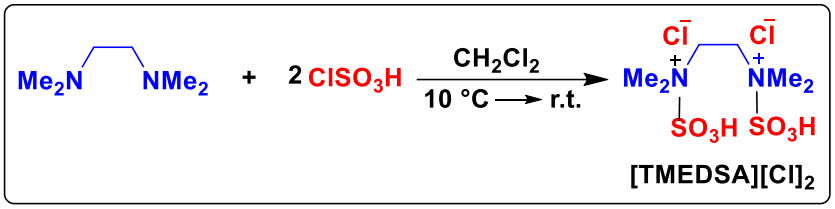
Experimental

Materials and methods

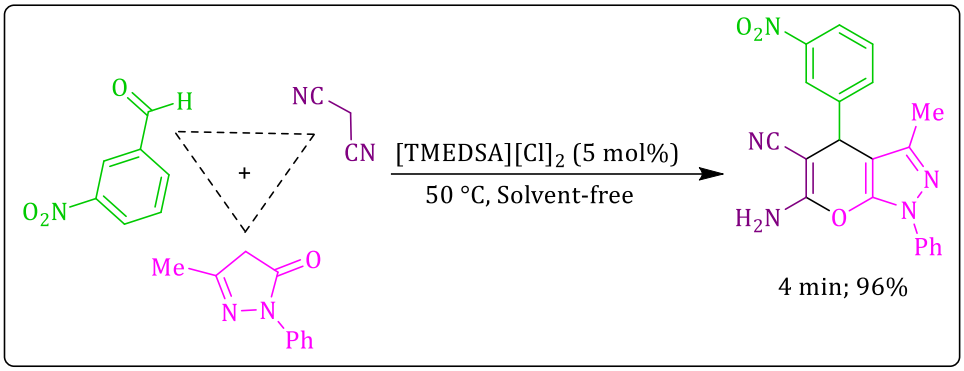
All chemicals were purchased from Fluka, Merck and Iranian Chemical Companies. All the known products were identified by comparing their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. The ^{1}H NMR (250, 300 or 400 MHz) and ^{13}C NMR (62.5, 75 or 100 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometers.

Procedure for the production of [TMEDSA][Cl]$_2$

A solution of *N*,*N*,*N*′,*N*′-tetramethylethylene-diamine (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. Then, the reaction mixture was allowed to heat to room temperature (accompanied with stirring), and stirred for another 4 h. 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]$_2$ as a viscous pale yellow oil in 97% yield (Scheme 1) [8].



Scheme 1. The synthesis of $[TMEDSA][Cl]_2$



Scheme 2. The model reaction for 4*H*-pyrano[2, 3-*c*]pyrazoles synthesis

General method for the production of 4H-pyrano[2, 3-c]pyrazoles

A mixture of arylaldehyde (1 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 mmol, 0.175 g), malononitrile (1 mmol, 0.066 g) and $[TMEDSA][Cl]_2$ (0.05 mmol, 0.017 g) was stirred magnetically at 50 °C, and after solidification of the reaction mixture, it was stirred by a small rod at the same temperature. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and the resulting solid was recrystallized from EtOH (96%) to give pure 4*H*-pyrano[2, 3-*c*]pyrazole.

General method for the synthesis of α-carbamatoalkyl-β-naphthols and α-amidoalkyl-β-naphthols

A mixture of compounds consisting of arylaldehyde (1 mmol), *β*-naphthol (1 mmol, 0.144 g), alkyl carbamate or amide (1.2 mmol) and $[TMEDSA][Cl]_2$ (0.075 mmol, 0.026 g) was magnetically stirred at 50 °C, and then, after the solidification of the reaction mixture, it was stirred by a small rod at the same temperature. After completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature, and the resulting solid was recrystallized from EtOH (96%) to give the pure product.

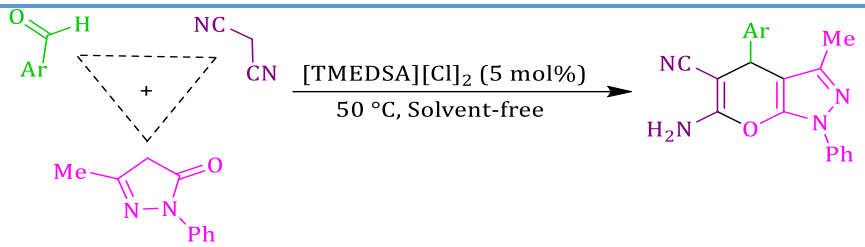
Note: Selected spectral data of 4*H*-pyrano[2, 3-*c*]pyrazoles, *α*-carbamatoalkyl-*β*-naphthols and *α*-amidoalkyl-*β*-naphthols have been given in supplementary material.

Results and Discussion

Initially, catalytic performance of *N*,*N*,*N*′,*N*′-tetramethylethylene-diaminium-*N*,*N*'-disulfonic acid chloride {[TMEDSA][Cl]$_2$} was examined for the production of 4*H*-pyrano[2, 3-*c*]pyrazoles. In this regard, the condensation of 3-nitrobenzaldehyde with 3-methyl-1-phenyl-2-pyrazolin-5-one and malononitrile (Scheme 2) was studied in the presence of different molar ratios of the ionic liquid (0-7 mol%) at the range of 25-60 °C in solvent-free conditions. The best results were observed when the reaction was carried out using 5 mol% of [TMEDSA][Cl]$_2$ at 50 °C (time=4 min; yield=96%). The use of the excess amount of the catalyst (up to 7 mol percent) or increment of the temperature (up to 60 °C) did not lead to increase the yield or decrease the reaction time.

Afterwards, different arylaldehydes were reacted with 3-methyl-1-phenyl-2-pyrazolin-5-one and malononitrile using 5% of [TMEDSA][Cl]$_2$ at 50 °C; the relevant results are summarized in Table 1. As the data show, the catalyst was highly efficient for the synthesis. Benzaldehyde and also arylaldehydes bearing electron-attracting, electron-donating and halogen substituents gave the desired 4*H*-pyrano[2, 3-*c*]pyrazoles in high yields and in short reaction times. Moreover, the ionic liquid catalyzed the reaction in mild conditions.

Table 1. The preparation of 4*H*-pyrano[2, 3-*c*]pyrazoles (**1a–k)** using [TMEDSA][Cl]$_2$

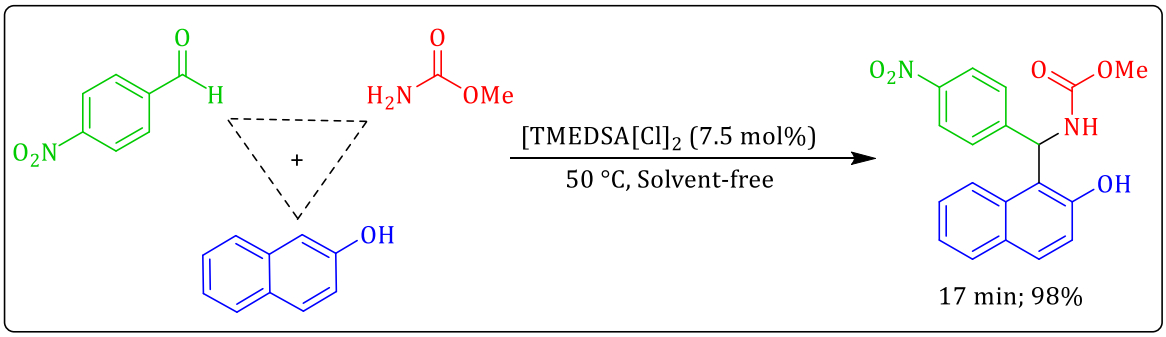


Ar	Product	Time (min)	Yield[a] (%)	M.p. °C (lit.)
C_6H_5	**1a**	10	93	167-169 (168-170) [18]
3-O_2N-C_6H_4	**1b**	4	96	192-194 (190-192) [19]
4-O_2N-C_6H_4	**1c**	15	95	196-198 (196-198) [18]
4-HO-C_6H_4	**1d**	10	94	207-209 (205-207) [18]
4-MeO-C_6H_4	**1e**	15	87	172-174 (174-175) [20]
4-Me-C_6H_4	**1f**	7	96	178-180 (176-177) [19]
4-$PhCH_2O$-C_6H_4	**1g**	6	95	160-162 (158-159) [20]
3,4,5-$(MeO)_3$-C_6H_2	**1h**	10	92	193-195 (194-196) [18]
2-Cl-C_6H_4	**1i**	4	93	147-149 (145-146) [19]
4-Cl-C_6H_4	**1j**	15	97	176-178 (174-176) [18]
4-Br-C_6H_4	**1k**	25	85	189-191 (187-189) [22]

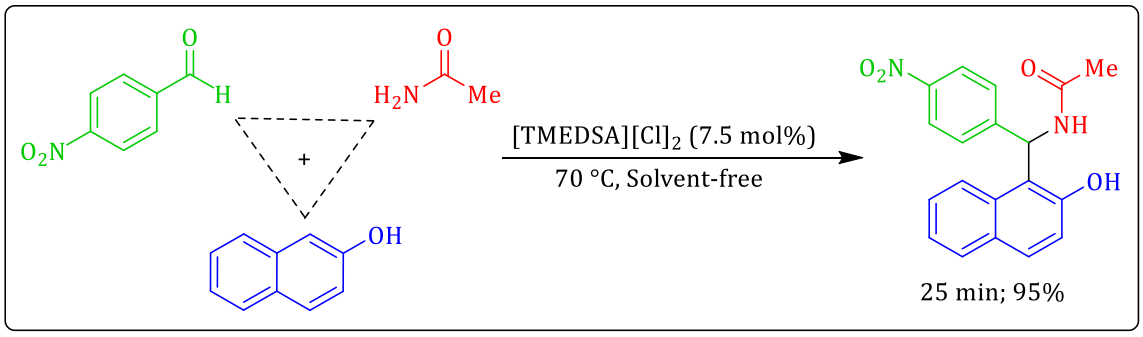
[a] Isolated yield

In another study, the catalytic activity of $[TMEDSA][Cl]_2$ was checked for the synthesis of *α*-carbomatoalkyl/amidoalkyl-*β*-naphtols. Thus, the condensation of *β*-naphthol with 4-nitrobenzaldehyde and methyl carbamate was selected as model reaction in order to provide the corresponding *α*-carbomatoalkyl-*β*-naphtol (Scheme 3). This reaction was studied in the presence of different amounts of $[TMEDSA][Cl]_2$ (5-10 mol%) at the range of 40-60 °C in the absence of solvent. The results were obtained when 7.5 mol% of the catalyst was used at 50 °C (time=17 min; yield=98%).

Moreover, the solvent's reaction of *β*-naphthol with 4-nitrobenzaldehyde and acetamide, for the synthesis of *α*-amidoalkyl-*β*-naphtols (Scheme 4), was tested in the presence of various mol percents of the ionic liquid (5-10 mol%) at the range of 50-75 °C in which the best catalyst amount and reaction temperature were 7.5 mol% and 70 °C, respectively (time=25 min; yield=95%).



Scheme 3. The model reaction for the production of *α*-carbamatoalkyl-*β*-naphthols

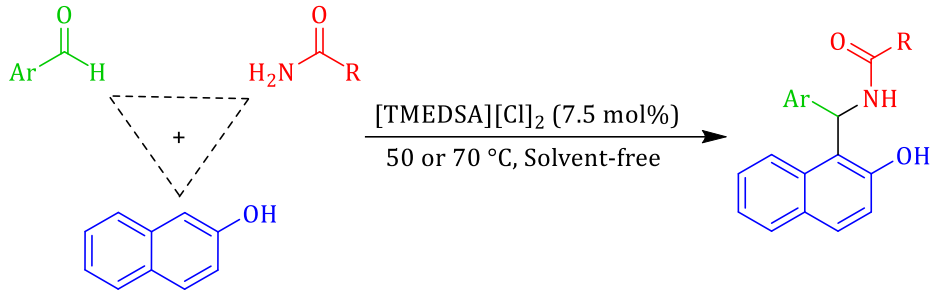


Scheme 4. The model reaction for the preparation of *α*-amidoalkyl-*β*-naphthols

To assess generality and efficacy of $[TMEDSA][Cl]_2$ for the synthesis of *α*-carbamatoalkyl/amidoalkyl-*β*-naphthols, various arylaldehydes were reacted with *β*-naphthol and alkyl carbamates (or amides) under the optimal conditions; the respective results are summarized in Table 2. As it can be seen, all arylaldehydes (benzaldehyde and arylaldehydes possessing electron-withdrawing, electron-releasing andhalogen substituents), and also all alkyl carbamates (or amides)

afforded the desired products in high to excellent yields within short reaction times. Thus, the catalyst was general and highly efficient for the reactions.

Table 2. The production of *α*-carbamatoalkyl-*β*-naphthols (**2a–h**) and *α*-amidoalkyl-*β*-naphthols (**3a–e**) catalyzed by $[TMEDSA][Cl]_2$



Ar	R	Product	Time (min)	Yield (%)[a]	M.p. °C (lit.)
C_6H_5	MeO	**2a**	7	98	219-221 (220-222) [34]
4-O_2N-C_6H_4	MeO	**2b**	17	98	202-204 (202-203) [34]
2-O_2N-C_6H_4	MeO	**2c**	17	90	238-240 (241-242) [40]
4-Me-C_6H_4	MeO	**2d**	12	98	185-187 (187-189) [45]
3-Br-C_6H_4	MeO	**2e**	12	95	192-194 (191-193) [40]
3-Cl-C_6H_4	MeO	**2f**	6	98	200-202 (199-201) [34]
C_6H_5	$PhCH_2O$	**2g**	10	97	179-181 (179-180) [38]
3-Br-C_6H_4	$PhCH_2O$	**2h**	15	92	181-183 (183-185) [40]
C_6H_5	CH_3	**3a**	25	95	243-245 (240-242) [34]
4-O_2N-C_6H_4	CH_3	**3b**	25	95	246-248 (245-247) [39]
4-Br-C_6H_4	CH_3	**3c**	20	92	230-232 (228-230) [35]
4-O_2N-C_6H_4	C_6H_5	**3d**	15	92	233-235 (233-235) [34]
4-MeO-C_6H_4	C_6H_5	**3e**	15	93	202-204 (202-204) [34]

[a] Isolated yield

Conclusions

In conclusion, we have introduced a new catalyst for the synthesis of 4*H*-pyrano[2, 3-*c*]pyrazole, *α*-carbamatoalkyl-*β*-naphthol and *α*-amidoalkyl-*β*-naphthol derivatives as biologically interesting compounds. The advantages of the presented work are generality and efficiency of the catalyst, availability and cheapness of the reactants for the preparation of the catalyst, simplicity of the catalyst synthesis, easy work-up and purification of the products, short reaction times, high products yields, mild reaction conditions, achieving the reactions without using volatile organic solvents, and good agreement with green chemistry protocols.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at DOI: 10.22034/AJGC/2020.2.5

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