Journal of Molecular Liquids xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Acidic ionic liquids catalyzed one-pot, pseudo five-component, and diastereoselective synthesis of highly functionalized piperidine derivatives

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ARTICLE INFO

Article history:
Received 8 April 2012
Received in revised form 27 January 2013
Accepted 29 January 2013
Available online xxxx

Keywords:
Piperidine
Anilines
Aldehydes
β-Ketoester
Ionic liquid
Catalyst

ABSTRACT

An efficient and one-pot quantitative procedure for the preparation of functionalized piperidine derivatives from pseudo five-component reactions of aromatic aldehydes, substituted anilines, and ethyl/methyl acetoacetate (molar ratio: 2/2/1) in the presence of acidic ionic liquids such as 1-methylimidazolium hydrogen sulfate ([Hmim]HSO_4), 1,1,3,3-tetramethylguanidinium perchlorate ([TMG]ClO_4), and 1,1,3,3-tetramethylguanidinium trifluoroacetate ([TMG]TFA) as the catalysts has been developed. The ionic liquids were stable during the reaction process and could also be reused several times without significant loss of their activities.

1. Introduction

Ionic liquids (ILs) have been revealed as green reaction media owing to their negligible volatility, excellent thermal stability, and the variety of structures available [1–3]. This new chemical group can reduce the use of hazardous and polluting organic solvents due to their unique characteristic as well as taking part in various new syntheses [1–5]. The interesting features of the ionic liquids are high conversions, cleaner reaction profiles, operational simplicity and reaction time, which make ILs as useful and attractive strategy for the preparation of industrial, pharmacological, and therapeutic important compounds [1–7].

Piperidines and their analogs have received attention owing to their biological activities such as antimalarial [8], antihypertensive [9], antibacterial [10], anticonvulsant, and anti-inflammatory agents [11].

As part of our continuing interest in the development of new synthetic methods in heterocyclic compounds [12] and multi-component reactions [13], in this paper, we would like to report applications of some acidic ionic liquids such as 1-methylimidazolium hydrogen sulfate ([Hmim]HSO_4), 1,1,3,3-tetramethylguanidinium perchlorate ([TMG]ClO_4), and 1,1,3,3-tetramethylguanidinium trifluoroacetate ([TMG]TFA) (Fig. 1) as catalysts in a pseudo five-component reaction for the synthesis of piperidines (Scheme 1).

2. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. The acidic ionic liquids such as 1-methylimidazolium hydrogen sulfate ([Hmim]HSO_4) [14], 1,1,3,3-tetramethylguanidinium perchlorate ([TMG]ClO_4) [15], and 1,1,3,3-tetramethylguanidinium trifluoroacetate ([TMG]TFA) [16] were prepared according to literature. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. TLC was performed on silica-gel Poly Gram SIL G/UV 254 plates.

2.1. Synthesis of functionalized piperidine derivatives under solvent-free conditions

The mixture of the anilines (2 mmol), ethyl/methyl acetoacetate (1 mmol), and ionic liquids containing ([Hmim]HSO_4) (10 mol%), ([TMG]ClO_4) (20 mol%) and ([TMG]TFA) (20 mol%) as acidic catalysts was stirred at 100 °C for 10 min. Then, aromatic aldehydes (2 mmol) were added to the reaction mixture and stirred at 100 °C for the specific time. After completion of the reaction, it was cooled to room temperature and then, 5 mL of water was added to the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The solid product was recrystallized with ethanol to give the pure product. All of the desired product(s) were characterized by comparison of their

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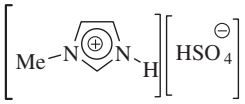
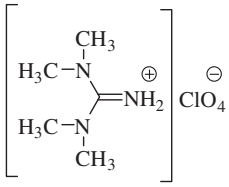
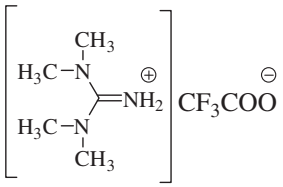
0167-7322/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.molliq.2013.01.020



1-Methylimidazolium hydrogen sulfate

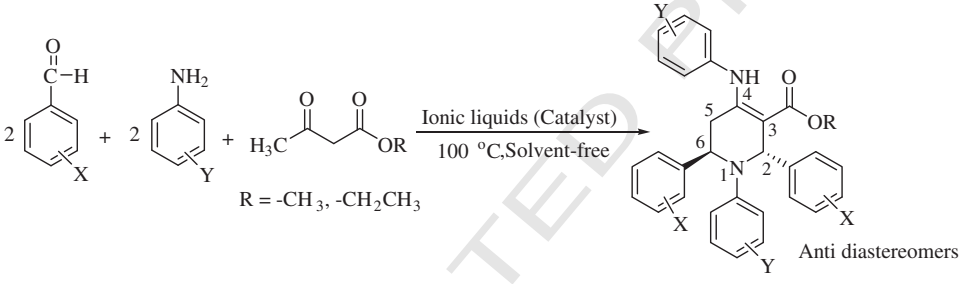


1,1,3,3- Tetramethylguanidinium perchlorate



1,1,3,3-Tetramethylguanidinium trifluoroacetate

Fig. 1. The structure of acidic Brønsted ionic liquids: 1-methylimidazolium hydrogen sulfate ([Hmim]HSO_4), 1,1,3,3-tetramethylguanidinium perchlorate ([TMG]ClO_4), and 1,1,3,3-tetramethylguanidinium trifluoroacetate ([TMG] TFA).



Ionic Liquids = ([Hmim]HSO_4) (10 mol%), ([TMG]ClO_4) (20 mol%), and ([TMG]TFA)(20 mol%)

Scheme 1. Synthesis of functionalized piperidine derivatives.

physical data with those of known compounds. For recycling the catalysts, after washing solid products with water completely, the water containing ionic liquid (IL is soluble in water) was evaporated under reduced pressure and ionic liquid was recovered and reused.

Selected spectra for two known pure anti diastereoisomers of the products are given below:

2,6-Bis-(4-chlorophenyl)-1-phenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (anti diastereoisomers)

Table 1
Pseudo five-component synthesis of functionalized piperidine derivatives from the reaction of aromatic aldehydes (2 mmol), anilines (2 mmol), and ethyl/methyl acetoacetate (1 mmol) in the presence of A: ([Hmim]HSO_4), B: ([TMG]ClO_4), and C: ([TMG]TFA) as catalysts.

Entry	Aldehydes	Y	R	Time (min)			Yield (%)[a]			Melting point m.p (°C)/(Lit. m.p (°C)) [Ref]
				A	B	C	A	B	C	
1	C_6H_5	H	Et	43	52	47	87	87	89	178/(176–177) [19]
2	4-ClC_6H_4	H	Et	45	55	60	91	91	89	230–231/(228–230) [24]
3	4-$CH_3C_2H_4$	H	Et	41	50	45	87	87	88	232/(228 − 231) [20]
4	4-BrC_6H_4	H	Et	51	42	45	89	88	89	235 − 237/(234 − 236) [24]
5	4-ClC_6H_4	4-Br	Et	50	41	45	89	90	90	203/(200 − 202) [24]
6	3-NO_2 C_6H_4	H	Et	54	43	46	86	86	87	187 − 188/(184 − 186) [24]
7	C_6H_5	4-Me	Et	51	42	47	88	89	89	181/(178 − 180) [24]
8	4-ClC_6H_4	4-Me	Et	50	41	45	90	90	90	239/(236–238) [24]
9	C_6H_5	H	Me	45	36	41	90	91	90	180–182/(178–180) [19]
10	C_6H_5	4-Cl	Me	44	35	40	89	90	90	204/(202–203) [19]
11	C_6H_5	4-Me	Me	46	35	40	90	89	89	223–224/(220–222) [19]
12	4-ClC_6H_4	H	Me	44	33	39	90	90	91	194–195/(193) [19]
13	3-$NO_2C_6H_4$	H	Me	47	35	41	87	87	88	182–184/(182) [19]
14	2-$NO_2C_6H_4$	H	Me	47	35	41	86	87	88	220/(218–219) [19]
15	4-BrC_6H_4	H	Me	46	34	40	89	89	90	231/(228–230) [24]
16	*n*-Heptanal	H	Et	24 h	–	–	–	–	Trace	–
17	C_6H_5	*n*-heptylamine	Et	24 h	–	–	–	–	Trace	–

[a] Yields refer to the isolated pure products. The desired known pure products were characterized by comparison of their physical data (melting points, IR, ^1H NMR) with those of known compounds.