ORIGINAL PAPER



# 2-Hydroxyethylammonium acetate: an efficient and reusable homogeneous catalyst for the synthesis of Hantzsch 1, 4-dihydropyridines

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Abstract 2-Hydroxyethylammonium acetate ionic liquid was found to be an excellent catalyst for the one-pot synthesis of 1,4-dihydropyridine derivatives via Hantzsch reaction of ethyl acetoacetate or acetoacetanilide, ammonium acetate, and various aromatic aldehydes. The combinatorial syntheses were achieved for the first time using 2-hydroxyethylammonium acetate ionic liquid as a homogeneous catalyst. The catalyst was active for the Hantzsch reaction in alcohol at reflux. The products were isolated in good yields (78-93 %). The resulting substituted dihydropyridines were characterized and confirmed by<sup>1</sup>H NMR spectral data. The catalyst offers simple means for recovery and the isolated catalyst was reused for three rounds for the synthesis without significant loss of catalytic activity. For all the other reactions carried out with the recycled catalyst, results were similar to that with the fresh catalyst.

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Li-Qin Kang klq@sit.edu.cn Graphical abstract



Keywords Ionic liquid · Hantzsch dihydropyridines

## Introduction

1,4-Dihydropyridine (1,4-DHP) compounds are well known as calcium-channel modulators and important class of compounds in the field of drugs [1]. 1,4-DHPs are generally synthesized by classical Hantzsch method, which involves cyclocondensation of an aldehyde,  $\beta$ -ketoesters, and ammonia either in acetic acid or in refluxing ethanol for long reaction times which typically leads to low yields [2–4]. Recently, some new methods have been utilized to improve the yields for the synthesis of important dihydropyridine derivatives [5-8] using some catalysts such as  $RuCl_3$  [9], PEG [10],  $I_2$  [11], heteropolyacids catalyst [12], and solid supported synthesis under microwave [13]. These methods, however, suffer from some disadvantages that involve moisture sensitive, highly toxic in environment, and reagents which are expensive. In recent years, the direction of science and technology has been shifting more toward eco-friendly and reusable catalysts. Recently, ionic liquid has emerged as catalyst for the synthesis of 1,4dihydropyridines due to their relatively high stability

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Scheme 1



 $R' = OEt, NHC_6H_5$ 

toward air and moisture, lack of corrosion, and ease of handling [14, 15]. Our group has reported the use of ionic liquid 2-hydroxyethylammonium acetate (2-HEAA) as an efficient catalyst for organic synthesis [16]. Compared with other reported ionic liquids, 2-HEAA has the advantages such as low cost, simplicity of synthesis, and negligible toxicity. As a part of our program to explore the potential applications of functional ionic liquids, we now report ionic liquid 2-HEAA as catalyst for the synthesis of 1,4dihydropyridines via the three-component reaction of ethyl acetoacetate or acetoacetanilide, aromatic aldehydes, and ammonium acetate (Scheme 1). To the best of our knowledge, the use of 2-hydroxyethylammonium acetate ionic liquid as a catalyst for the synthesis of 1,4-dihydropyridines previously has not been reported.

### **Results and discussion**

We initially studied the three-component condensation reaction catalyzed by 2-HEAA using the model reaction of benzaldehyde, ethyl acetoacetate, and ammonium acetate. The desired yield was obtained at reflux in ethanol with 5 mol% of 2-HEAA using the molar ratio of 1:2:1 of benzaldehyde, ethyl acetoacetate, and ammonium acetate (Table 1). After the reaction, the mixture was poured into ice water and the resulted precipitate was filtered from the reaction mixture. The product was purified by recrystallization from ethanol–water to afford 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) in 92 % yield. The filtrate containing the 2-HEAA was recovered after removal of water under reduced pressure and was reused for subsequent reactions. It showed almost the same activity as that of the fresh catalyst. The ionic liquid was

 Table 1
 Effect of temperature and the amount of catalyst on model reaction

Entry <sup>a</sup>	2-HEAA <sup>b</sup> /%	Temp/°C	Time/h	Yield/% <sup>c</sup>	
1	1	40	5	10	
2	2	40	5	40	
3	2	60	5	78	
4	2	Reflux	5	85	
5	5	Reflux	3	92	
6	8	Reflux	3	90	
7	10	Reflux	3	91	

<sup>a</sup> Reaction conditions: benzaldehyde (2 mmol), ethyl acetoacetate (4 mmol), NH<sub>4</sub>OAc (2 mmol), 2-HEAA, monitored by TLC

<sup>b</sup> mol equal to benzaldehyde

<sup>c</sup> Isolated yields

Table 2 Studies on the reuse of 2-HEAA ionic liquid

Round	Yield/%	Ionic liquid recovered/%		
Fresh	92	99		
1	91	98		
2	91	98		
3	90	97		
3	90	97		

recycled and reused in the same reaction for at least three times without apparent loss of activity in terms of yield (90–92 %; Table 2). To study the generality of this process, several examples illustrating this method for the synthesis 1,4-dihydropyridine derivatives were studied. The results are summarized in Table 3. Aromatic aldehydes containing electron-withdrawing groups (such as fluorine groups, nitro group) or electron-donating groups (such as alkoxyl groups, hydroxy) were employed and were

Entry	Prod.	R	R′	t/h	Yield <sup>b</sup> /%	M.p./°C	
						Found	Reported
1	4a	C <sub>6</sub> H <sub>5</sub>	OEt	3	92	153.3–153.9	158–160 [17]
2	4b	$2-HO-C_6H_4$	OEt	4	86	120.7-121.0	121–122 [18]
3	4c	$3-NO_2-C_6H_4$	OEt	4	90	167.5-167.7	169–171 [ <mark>19</mark> ]
4	4d	3-CH <sub>3</sub> O-4-HO-C <sub>6</sub> H <sub>3</sub>	OEt	3	91	162.2-162.5	158–162 [20]
5	4e	3,4-(OCH <sub>2</sub> O)-C <sub>6</sub> H <sub>3</sub>	OEt	3	93	132.8-133.8	132–133 [21]
6	4f	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	OEt	3	90	157.7-157.9	157–159 [22]
7	4g	$4-CH_3-C_6H_4$	OEt	3	89	132.8-133.5	135–138 [22]
8	4h	4-F-C <sub>6</sub> H <sub>4</sub>	OEt	3	92	145.7-146.6	147–149 [23]
9	<b>4i</b>	2-Furanyl	OEt	3	87	164.5-164.8	166–168 [ <mark>24</mark> ]
10	4j	$C_6H_5$	NHC <sub>6</sub> H <sub>5</sub>	5	80	>300	>300 [25]
11	4k	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	NHC <sub>6</sub> H <sub>5</sub>	5	78	206.1-207.6	205–207 [25]

Table 3 Preparation of 1,4-dihydropyridines catalyzed by 2-HEAA (Scheme 1)

<sup>a</sup> Products were characterized by<sup>1</sup>H NMR, and by comparison of their melting points with those reported in the literature

<sup>b</sup> Yield of isolated product

Scheme 2



found to react well to give the corresponding 1,4-dihydropyridines in good to excellent yields. The mechanism for the Hantzsch reaction catalyzed by ionic liquid 2-HEAA was hypothesized on the basis of previous reports with this type of catalyst in synthesis [16]. The ionic catalyst 2-HEAA applied is based on the effect of its special structure, functional group  $-NH_3^+$  and -OH. The group  $-NH_3^+$  makes the IL capable of bonding with the carbonyl oxygen of aldehydes increasing the reactivity of the parent carbonyl compounds. The group –OH prompts the active methylene H of ethyl acetoacetate to leave. Many current studies have established that hydrogen bonding can occur between the reactant and the cationic or anionic components of ILs [26, 27]. Based on this, the following mechanism for the condensation reaction catalyzed by ionic liquid 2-HEAA was postulated (Scheme 2).

In conclusion, we have developed an efficient and clean approach to the synthesis of 1,4-dihydropyridines using 2-HEAA ionic liquid as catalyst. The catalyst offers several advantages including non-toxic, non-corrosive, high yield of the products, simple experimental and isolation procedures. And it follows along the line of green chemistry. Also, the catalyst was able to be reused easily for three times without apparent loss of activity.

# **Experimental**

Melting points were measured on a WRS-IB digital melting point instrument.<sup>1</sup>H NMR were recorded on AVANG 500 MHz spectrometer with TMS as an internal standard. The ionic liquid 2-HEAA is synthesized and purified according to [28].

#### General procedure for the synthesis of 4a-4k

Aldehyde (2 mmol), ethyl acetoacetate (4 mmol) or acetoacetanilide (4 mmol), NH<sub>4</sub>OAc (2 mmol), 2-HEAA ionic liquid (0.1 mmol), and ethanol (5 cm<sup>3</sup>) were mixed and stirred at reflux for a certain period of time to complete the reaction (monitored by TLC). After completion of the reaction, the mixture was poured into ice cold water. The resulting solid crude product was filtered and then recrystallized from ethanol–water to obtain pure product 1,4-DHPs. All compounds were characterized by<sup>1</sup>H NMR. Melting points are found to be almost identical with those that reported in literature elsewhere.

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## References

- 1. Nakayama H, Kanaoka Y (1996) Heterocycles 42:901
- 2. Dondoni A, Massi A, Minghini E, Bertolasi V (2004) Tetrahedron 60:2311
- 3. Hantzsch A (1883) J Chem Soc Abstr 44:82
- 4. Love B, Sander KM (1965) J Org Chem 30:1914
- 5. Sharma GVM, Reddy KL, Lakshmi PS, Krishna PR (2006) Synthesis 55
- 6. Ruppert R, Jeandon C, Sgambati A, Callot H (1999) Chem Commun 2123
- 7. Kumar A, Maurya RA (2008) Synlett 883
- 8. Debache A, Boulcina R, Belfaitah A, Rhouati S, Carboni B (2008) Synlett 509
- 9. Suresh KD, Sandhu JS (2009) Synth Commun 39:1957
- 10. Siddaiah V, Basha GM, Rao GP, Prasad UV, Rao RS (2012) Synth Commun 42:627
- 11. Mohammad AZ, Peyman SAG, Morteza S (2007) J Chin Chem Soc 54:267
- 12. Gharib A, Jahangir M, Roshani M, Scheeren JW (2012) Synth Commun 42:3311
- 13. Agarwal A, Chauhan PMS (2005) Tetrahedron Lett 46:1345
- Heravi MM, Saeedi M, Karimi N, Zakeri M, Beheshtiha YS, Davoodnia A (2010) Synth Commun 40:523
- Reddy PB, Rajesh K, Vijayakumar V (2011) J Chin Chem Soc 58:384
- 16. Kang LQ, Cai YQ, Wang H, Li LH (2014) Monatsh Chem 145:337
- 17. Reddy BP, Rajesh KV, Vijayakumar (2011) Indian J Heterocycl Chem 20:281
- Subudhi BB, Panda PK, Swain SP, Sarangi P (2009) Acta Pol Pharm 66:147
- 19. Zonouz AM, Hosseini SB (2008) Synth Commun 38:290
- 20. Paul S, Sharma S, Gupta M, Choudhary D, Gupta R (2007) Bull Korean Chem Soc 28:336
- 21. Kametani T, Ogasawara K, Kozuka A (1966) Yakugaku Zasshi 86:815
- 22. Shaabani A, Rezayan AH, Rahmati A, Sharifi M, Shaabani A (2006) Monatsh Chem 137:77
- 23. Pei W, Wang Q, Li XN, Sun Li (2010) Chin J Chem 28:483
- 24. Salehi H, Guo QX (2004) Synth Commun 34:4349
- Gein VL, Kazantseva MI, Kurbatova AA (2011) Russ J Org Chem 47:1123
- 26. Anderson JL, Ding J, Welton T, Armstrong DW (2002) J Am Chem Soc 124:14247
- 27. Liu QB, Janssen MHA, van Rantwijk F, Sheldon RA (2005) Green Chem 7:39
- Victor HA, Silvana M, Manuel MP, Martin A, Miguel I (2011) J Chem Thermodyn 43:997