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One-pot synthesis of tri- and tetra-substituted imidazoles using sodium dihydrogen phosphate under solvent-free conditions

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Abstract

Sodium dihydrogen phosphate (NaH_2PO_4) efficiently catalyzes the condensation reaction of benzil, aldehydes, amines and ammonium acetate in a four-component reaction under solvent-free conditions. The reaction proceeds rapidly and affords the corresponding tetra-substituted imidazoles in high yields. Also an efficient route was developed for the synthesis of tri-substituted imidazoles from condensation of benzil, aldehydes and ammonium acetate using NaH_2PO_4.

Keywords: Sodium dihydrogen phosphate; Imidazoles; Benzil; Solvent-free

The developing of new multi-component reactions, and improving known multi-component reactions are an area of considerable current interest [1,2]. One such reaction is the synthesis of imidazoles. The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles [3]. Substituted imidazoles have been identified as potent inhibitors of p38 MAP kinase [4], a core section in some biological systems such as Losartan and Olmesartan [5], modulators of P-glycoprotein (P-gp)-mediated multi-drug resistance (MDR) [6] and antibacterial agents [7].

There are several methods for the synthesis of highly substituted imidazoles [8]. Tetra-substituted imidazoles are generally synthesized in a four-component condensation of aldehydes, 1,2-diketones, amines, and ammonium acetate using a catalyst. In this context some methods and catalysts have been reported [9–16]. No doubt, these methods are good in terms of reactivity; however they suffer from the drawbacks of long reaction time, moderate yield, use of toxic organic solvents, the requirement of special apparatus, or harsh reaction conditions. Thus, there is a certain need for the development of an alternate route for the production of imidazole derivatives, which surpasses those limitations.

Following our systematic studies directed towards the development of practical, safe, and environmentally friendly procedures for several important organic transformations [17–19], in this paper we report a simple and environmentally benign methodology for the synthesis of tetra-substituted imidazoles *via* direct four-component condensation reaction between aldehydes, 1,2-diketones, amines, and ammonium acetate using catalytic amounts of NaH_2PO_4 under solvent-free conditions (Scheme 1).

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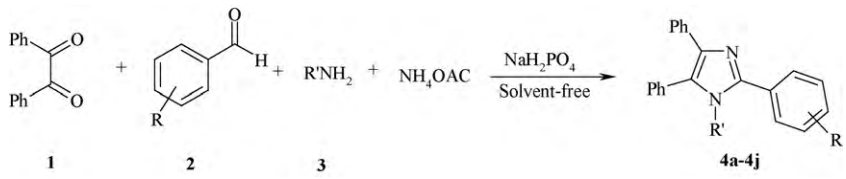


Scheme 1. Synthesis of tetra-substituted imidazoles.

Table 1
Synthesis of tetra-substituted imidazoles using NaH_2PO_4.

Entry	R	R′	Time (min)	Yield (%)	Product [Ref.]	m.p. (°C)
1	H	C_6H_5	35	90	**4a** [13]	215–217
2	H	$C_6H_5CH_2$	35	92	**4b** [11]	164–166
3	4-Cl	C_6H_5	40	89	**4c** [14]	150–152
4	4-CH_3	C_6H_5	35	90	**4d** [12]	183–185
5	4-CH_3	4-$CH_3C_6H_4$	25	92	**4e** [9]	186–189
6	4-CH_3	4-ClC_6H_4	35	88	**4f** [9]	165–167
7	H	CH_3	45	80	**4g** [12]	143–145
8	4-CH_3	CH_3	40	80	**4h** [9]	208–210
9	4-CH_3	CH_3CH_2	40	82	**4i** [9]	124–126
10	4-CH_3	*cyclo*-C_6H_{11}	40	80	**4j** [9]	164–165
11	2-Cl	$C_6H_5CH_2$	35	92	**4k** [14]	140–142

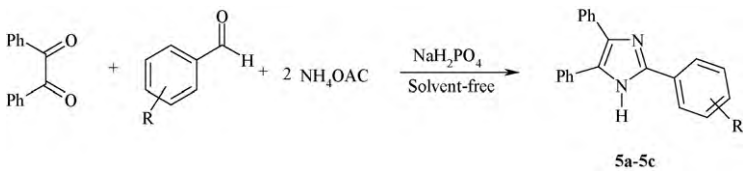
To optimize the reaction conditions, the synthesis of 1,2,4,5-tetraphenylimidazole by the reaction of benzil, benzaldehyde, aniline and ammonium acetate was used as a model reaction. Reactions at different temperatures and various molar ratios of substrates in the presence of H_2NaPO_4 revealed that the best conditions were solvent-free at 120 °C. To show the generality of this method the optimized system used for the synthesis of other imidazoles derivatives **4a–k** (Table 1).

This method offers some advantages in term of simplicity of performance, solvent-free condition, and low reaction time. Several examples illustrating this novel and general method for the synthesis of tetra-substituted imidazoles are summarized in Table 1. It should be noted that, this method is effective for the preparation of tetra-substituted imidazoles from both aliphatic as well as aromatic amines. All products are known compounds and structures of them were confirmed by comparison with their known physical and spectral (NMR and IR) data.

Under the same conditions, this approach can be repeated for synthesis of 2,4,5-tri-substituted imidazoles **5a–c** by condensation reaction between benzil, aldehydes and ammonium acetate (Scheme 2). The optimize molar ratio of benzil/aldehyde/ammonium acetate/NaH_2PO_4 was 1:1:2:0.33. Thus, ammonium acetate effectively participated in the condensation with aldehyde, and benzil to give the corresponding tri-substituted imidazoles **5a–c**. The results of the condensation of benzil, aldehydes and 2 equivalent of ammonium acetate are represented in Table 2.

Table 3 compares our results for the synthesis of 1-benzyl-2,4,5-triphenylimidazole **4b** with the results of different catalysts and reaction conditions obtained by other groups.

In conclusion a convenient and efficient protocol for the synthesis of tri- and tetra-substituted imidazoles in the presence of sodium dihydrogen phosphate under solvent-free conditions at 120 °C has been developed. The catalyst is readily available and inexpensive and can conveniently be handled and removed from the reaction mixture. The simple procedure combined with low reaction times, solvent-free condition and low cost make this method economic, benign, and a user-friendly process for the synthesis of substituted imidazoles of biological and medicinal importance.



Scheme 2. Synthesis of tri-substituted imidazoles.

Table 2
Synthesis of tri-substituted imidazoles using NaH_2PO_4.

Entry	R	Time (min)	Yield (%)
1	H	30	99
2	4-CH_3	25	99
3	4-Br	35	98

Table 3
Comparison of efficiency of various catalysts in the synthesis of 1-benzyl-2,4,5-triphenylimidazole **4b**.

Catalyst	Conditions	Time (min)	Yield (%)	Ref.
$NaHSO_4{\cdot}SiO_2$	140 °C/solvent-free	120	92	[9]
$K_5CoW_{12}O_{40}{\cdot}3H_2O$	140 °C/solvent-free	120	90	[11]
$HClO_4$–SiO_2	140 °C/solvent-free	6	96	[13]
$BF_3{\cdot}SiO_2$	140 °C/solvent-free	120	80	[14]
$InCl_3{\cdot}3H_2O$	Methanol/r.t.	440	79	[15]
$H_4[PMo_{11}VO_{40}]$	Ethanol/reflux	8	88	[12]
NaH_2PO_4	120 °C/solvent-free	35	92	This work

1. Experimental

*1.1. General procedure for the synthesis of 1,2,4,5-tetra-substituted imidazoles **4a–k***

A mixture of benzil (1 mmol), amine (1 mmol), aldehyde (1 mmol), ammonium acetate (1 mmol) and NaH_2PO_4 (0.33 mmol) was stirred at 120 °C for the appropriate time indicated in Table 1. The progress of reaction was monitored by TLC (ethyl acetate/n-hexane = 1/4). After completion of the reaction, the reaction mixture was cooled to room temperature. Acetone was added to the mixture which was filtered to remove the catalyst. After evaporation of the solvent under reduced pressure, the resulting solid residue was recrystalized from acetone–water (15:1) to obtain pure product **4**. Products were characterized by comparison of their physical and spectral data with those of authentic samples.

*1.2. General procedure for the synthesis of 2,4,5-tri-substituted imidazoles **5a–c***

A mixture of benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (2 mmol) and NaH_2PO_4 (0.33 mmol) was stirred at 120 °C for the appropriate time indicated in Table 2. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane = 1/4). After completion of the reaction, the reaction mixture was cooled to room temperature. Acetone was added to the mixture which was filtered to remove the catalyst. After separation of solid, the solvent was evaporated under reduced pressure. The resulting solid residue was purified by recrystallization from acetone–water (15:1). Products were characterized by comparison of their physical and spectral data with those of authentic samples.

References

[1] A. Domling, I. Ugi, Angew. Chem. Int. Ed. 39 (2000) 3168.
[2] P. Eilbracht, L. Barfacker, C. Buss, et al. Chem. Rev. 99 (1999) 3329.
[3] S.E. Wolkenberg, D.D. Wisnoski, W.H. Leister, et al. Org. Lett. 6 (2004) 1453.
[4] J. Sisko, J. Org. Chem. 63 (1998) 4529.
[5] J.C. Lee, J.T. Laydon, P.C. McDonnell, et al. Nature 739 (1994) 372.
[6] M.J. Newman, J.C. Rodarte, K.D. Benbatoul, et al. Cancer Res. 60 (2000) 2964.
[7] M. Antolini, A. Bozzoli, C. Ghiron, et al. Bioorg. Med. Chem. Lett. 9 (1999) 1023.
[8] A.R. Katritzky, A.J. Boulton (Eds.), Advances in Heterocyclic Chemistry, vol. 27, Academic, New York, 1980.
[9] A.R. Karimi, Z. Alimohammadi, J. Azizian, et al. Catal. Commun. 7 (2006) 728.
[10] M.R. Mohammadizadeh, A. Hasaninejad, M. Bahramzadeh, Synth. Commun. 39 (2009) 3232.
[11] L. Nagarapu, S. Apuri, S. Kantevari, J. Mol. Catal. A: Chem. 266 (2007) 104.
[12] M.M. Heravi, F. Derikvand, F.F. Bamoharram, J. Mol. Catal. A: Chem. 263 (2007) 112.

[13] S. Kantevari, S.V.N. Vuppalapati, D.O. Biradar, et al. J. Mol. Catal. A: Chem. 266 (2007) 109.
[14] B. Sadeghi, B.F. Mirjalili, M.M. Hashemi, Tetrahedron Lett. 49 (2008) 2575.
[15] S.D. Sharma, P. Hazarika, D. Konwar, Tetrahedron Lett. 49 (2008) 2216.
[16] R.A. Mekheimer, A.M. Abdel Hameed, S.A.A. Mansour, et al. Chin. Chem. Lett. 20 (2009) 812.
[17] Z. Karimi-Jaberi, M. Amiri, Heteroat. Chem. 21 (2010) 96.
[18] Z. Karimi-Jaberi, M. Keshavarzi, Chin. Chem. Lett. 21 (2010) 547.
[19] Z. Karimi-Jaberi, M.M. Hashemi, Monatsh. Chem. 139 (2008) 605.