Highly efficient one-pot synthesis of trisubstituted imidazoles under catalyst-free conditions

Najmadin Azizi, Nairreh Dado, and Alireza Khajeh Amiri

Abstract: Operationally simple, atom economical, and scalable synthesis of 2,4,5-trisubstituted imidazoles from benzil, aldehydes, and ammonium acetate is shown to proceed readily in methanol with high yield. The scope of the reaction is quite broad; a variety of aromatic and aliphatic activated and unactivated aldehydes have all been shown to be viable substrates for this reaction. Excellent yields and purity were obtained by washing the products with hot ethanol.

Key words: aldehyde, benzil, imidazole, atom economic, solvent effect, catalyst free.

Résumé : On a montré qu'un procédé simple, économique d'un point de vue atomique et d'échelle variable peut être appliqué à la synthèse, avec un rendement élevé, dans le méthanol, d'imidazoles 2,4,5-trisubstitués à partir du benzile, d'aldéhydes et d'acétate d'ammonium. Le domaine d'application de la réaction est étendu; on a en effet montré qu'une variété d'aldéhydes aromatiques et aliphatiques, activés et non activés, peuvent être utilisés comme substrats pour la réaction. On a obtenu rendements élevés et une pureté excellente en lavant les produits avec de l'éthanol bouillant.

Mots-clés : aldéhyde, benzile, imidazole, économique d'un point de vue atomique, effet de solvant, sans catalyseur.

[Traduit par la Rédaction]

Introduction

Imidazole derivatives play an important role in chemical and biological systems.[1] Many of the substituted imidazoles are known as inhibitors of fungicides and herbicides, plant growth regulators, and therapeutic agents.[2] Recent advances in green chemistry have extended the boundary of imidazoles as ionic liquids that can be used as electrolytes or green solvents because of their low vapor pressure and wide chemical stability.[3] Furthermore, imidazolylidene carbenes have been used in coordination chemistry, as ligands in transition-metal and metal-free catalysts for organic synthesis.[4,5]

Owing to the wide applicability of imidazoles, preparative methodologies for this class of compounds have been intensively developed in the literature.[6] Conventional methods for imidazole core synthesis usually involve the reaction of α-diketones and α-haloketones with formamide (Bredereck synthesis),[7] the base-promoted reaction of tosylmethyl isocyanides and aldimines or imidoyl chlorides,[8] and catalytic multicomponent coupling reactions in the presence of a Lewis acid[9] and an organocatalyst.[10]

However, the use of high temperatures, expensive instruments such as microwaves, and corrosive reagents limit these methods, and there are few reports on practical methods for preparing them, and no method is catalyst-free. Thus, highly efficient and flexible protocols for the synthesis of imidazoles are still in need as there is a scope for further improvement towards milder reaction conditions, development of simple workup, inexpensive reagents, convenient procedures, and higher product yields. In this article, a simple, rapid, and catalyst-free imidazole formation with excellent yield has been developed.

Results and discussion

Recently, we were interested in performing organic reactions in water, and we have shown that the aqueous medium can strongly favor the reactivity and selectivity, even when they are carried out under heterogeneous conditions.[11] Herein, we wish to report the simple synthesis of new imidazole derivatives with the reaction of 1,2-diketones and variety of aldehydes performed in methanol with excellent yields and without using any catalyst.

First, we embarked upon a series of experiments to establish the optimum conditions. The one-pot three-component reaction of benzaldehyde **2**, benzil **1**, and ammonium salts were studied (Table 1). First findings indicated that the presence of ammonium acetate in methanol was an excellent solvent without using any catalyst or promoter and 2,4,6-triphenyimidazole **3** crystals were obtained in 97% yield by reacting equimolar amounts of **1** and **2** at 60 °C for 4 h. Other ammonium salts such as fluoride, chloride, nitrate, and hydrogen sulfate and ammonia solution (32%) give low yields of desired products for these reaction conditions. We also investigated the effects of common organic solvents and the influence of different solvents on the rate and the course of these reactions. In dichloromethane, cyclohexane, and THF the reaction did not take place and the starting materials were recovered and low yield of the product was observed in acetonitrile, water, ethanol, and solvent-free conditions (Table 1).

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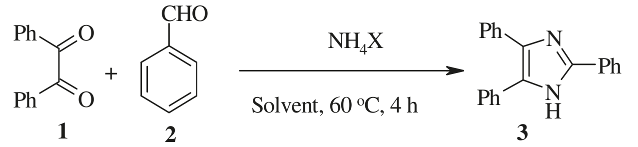
Table 1. Optimization of reaction conditions.



	Yield (%)
Solvent	
CH_2Cl_2	0
C_6H_{12}	0
CH_3CN	35
THF	5
SFC	60
H_2O	10
EtOH	70
MeOH	97
Amine/ammonium	
NH_3	20
NH_4F	40
NH_4Cl	0
NH_4NO_3	0
NH_4SO_4	15
NH_4OAc	97

Note: Reaction conditions: benzil (1 mmol), benzaldehyde (1 mmol), ammonium salts (3 mmol), and solvent (1 mL), 4 h.

With optimal conditions in hand, the reaction of benzil with different aldehydes was examined to explore the scope of the reaction. First, ammonium actate and benzil were used as model substrates (Table 2), and the results indicated that all commercially available aldehydes were good substrates for this system. Aromatic aldehydes bearing such functional groups as fluoro, chloro, bromo, methyl, or methoxy were able to effect the imidazole synthesis. We also observed that electronic effect on the aldehydes had little influence on the yield and the reaction conditions; that is, aryl aldehydes with electron-withdrawing groups reacted rapidly, whereas the substitution of electron-rich groups on the benzene ring did not decreased the reactivity. Moreover, a good yield for 3,5-dimethoxy benzaldehyde (Table 2, entry 24), the substrate with a strong electron-donating group, was observed. In addition, the 2-furaldehyde, (Table 2, entry 29), thiophenaldehyde (Table 2, entry 30), 2-naphthaldehyde (Table 2, entry 25), and 1-naphthaldehyde (Table 2, entry 26) also gave good yields of products. On the other hand, for the first time we have shown that fluorene-9-carbaldehyde (Table 2, entry 27), indole-3-carboxaldehyde (Table 2, entry 28), terephthaldehyde (Table 2, entry 31), isophthaldehyde (Table 2, entry 32), ferrocene carbaldehyde, (Table 2, entry 33), and aliphatic aldehydes still displayed high reactivity and clean reactions under these standard conditions.

It is noteworthy that the present method is very simple and that the process became even more attractive for large-scale applications when we found that it could be run at large scales without decreased yields and with the use of ethanol as the organic solvent in the workup without tedious column chromatography.

In summary, we have described a simple, highly efficient, and facile procedure for one-pot three-component synthesis of imidazole derivatives from readily available starting materials. To the best of our knowledge, this is the first report of the catalyst-free synthesis of imidazoles under very mild conditions. The procedure offers a simple experimental procedure and a short reaction time, is catalyst-free, is low cost, and provides efficient yields, which makes this method a useful and attractive strategy in view of economic and environmental advantages.

Experimental section

Instrumentation, analyses, and starting material

NMR spectra were recorded on a Bruker ACF 500 (^1H NMR at 500 MHz and ^{13}C NMR at 125 MHz) spectrometer in pure deuterated solvents with tetramethylsilane (Supplementary data). Melting points were determined in open capillary tubes in a Buchi-535 melting-point apparatus. All reagents, unless otherwise stated, were used as received from suppliers. Solvents were distilled before use.

General procedure for the synthesis of imidazole derivatives in methanol

To a well-stirred mixture of benzaldehyde (0.1 cm^3, 1 mmol) and benzil (0.21 g, 1 mmol) in methanol (1 cm^3) ammonium acetate was added (0.23 g, 3 mmol) and the reaction mixture was heated at 60 °C for 4–8 h. The reaction was allowed to cool and the resulting precipitates were recrystallized from ethanol to give pure imidazole derivatives.

Selected data for the new compounds

Table 1, entry 27

^1H NMR (500 MHz, DMSO-d_6) δ: 3.98 (s, 2H), 7.19–7.58 (m, 13H), 7.89 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 8.29 (s, 1H), 12.66 (brs, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 121.0, 122.7, 124.9, 126.0, 127.3, 127.7, 127.8, 127.9, 128.6, 129.0, 129.2, 129.5, 129.7, 131.9, 136.1, 138.0, 141.6, 142.0, 144.2, 144.3, 146.7. Anal. calcd for $C_{28}H_{20}N_2$: C 87.47, H 5.24, N 7.29; found: C 86.55, H 5.10, N 6.30.

Table 1, entry 28

^1H NMR (500 MHz, DMSO-d_6) δ: 7.12–7.60 (m, 13H), 7.96 (s, 1H), 8.45 (s, 1H), 11.33 (brs, NH, 1H)), 12.23 (brs, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 107.7, 112.6, 120.5, 122.3, 122.7, 124.6, 125.9, 126.6, 127.0, 127.7, 128.2, 129.0, 129.5, 132.5, 136.2, 136.8, 137.12, 144.5. HRMS: 334 (M$^+$), 335 (100). Anal. calcd for $C_{23}H_{17}N_3$: C 82.36, H 5.11, N 12.53; found: C 81.90, H 4.88, N 12.01.

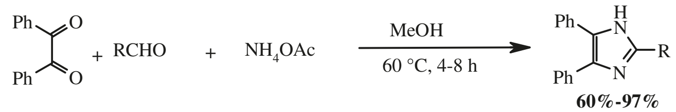
Table 1, entry 33

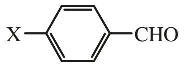
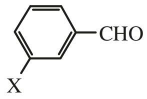
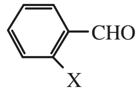
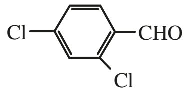
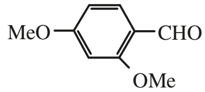
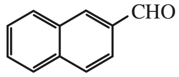
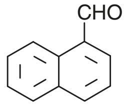
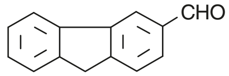
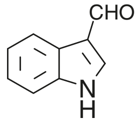
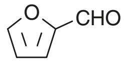
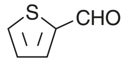
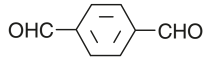
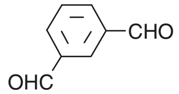
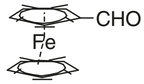
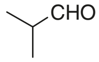
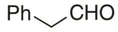
^1H NMR (500 MHz, DMSO-d_6) δ: 4.14 (s, 5H), 4.36 (t, J = 1.6 Hz, 3H), 4.96 (t, J = 1.9 Hz, 2H), 7.20–7.52 (m, 10H), 12.19 (brs, NH, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 67.1, 69.5, 70.0, 76.6, 127.1, 127.8, 128.3, 128.9, 129.1, 129.4, 136.2, 146.8. HRMS: 404 (100).

Supplementary data

Supplementary data (experimental details and spectroscopic characterization (^1H and ^{13}C NMR and mass) of the compounds) are available with the article through the journal

Table 2. Practical synthesis of new imidazoles under catalyst-free conditions.



Entry	Aldehyde	X	Yield (%)	mp (°C)		Ref.
				Found	Reported	
1		Cl	97	264	262–264	10c
2		F	95	242	188–190	10c
3		Br	90	260	265	9m
4		OH	80	235	232–233	10c
5		OCH_3	92	232	228–230	9n
6		CH_3	90	234	233–235	10c
7		C_2H_5	88	224	223–224	9o
8		C_3H_7	90	230	232–234	10c
9		CO_2CH_3	84	246	246–248	9o
10		NO_2	86	245	242	9m
11		H	97	275	276–278	9n
12		Cl	97	295–297	295	9m
13		Br	97	307–308	305–310	10c
14		OCH_3	97	263–265	267–268	9b
15		CH_3	95	298–299	300	9c
16		OH	92	258	259	9m
17		Cl	97	197–198	195–197	9n
18		F	97	256	254.5–255	9a
19		Br	97	206–207	206–208	9d
20		OCH_3	90	209–210	206–211	10c
21		CH_3	90	255	252.5–253.5	9a
22		NO_2	85	230–233	230–231	10c
23			80	176	178	9m
24			60	165–167	164–165	9e
25			72	279	277–278	9a
26			80	290	297	9m
27			75	281–283		
28			82	307		
29			80	245–247	242	9m
30			84	264–266	260–262	9m
31			70	>350	442	1d
32			74	288–290	294–296	1d
33			64	97–99		
34			62	248	246	9c
35			68	238	238–240	9p

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