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Acidic ionic liquid *N*-methyl 2-pyrrolidonium hydrogen sulfate as an efficient catalyst for the one-pot multicomponent preparation of 3,4,5-substituted furan-2(5*H*)-ones

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Abstract We have developed an efficient method for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones via one-pot, three-component condensation reaction of aldehydes, amines, and dialkyl acetylenedicarboxylates using acidic ionic liquid catalyst (*N*-methyl 2-pyrrolidonium hydrogen sulfate ([H-NMP]HSO_4)). This reaction benefits from simple, inexpensive, and straightforward procedure, an environmental friendly method, and high yields.

Keywords *N*-methyl 2-Pyrrolidonium hydrogen sulfate ([H-NMP]HSO_4) · Ionic liquid · Dialkyl acetylenedicarboxylates · Aldehyde · Furan-2(5*H*)-ones

Introduction

Ionic liquids (ILs) have attracted great attention among organic chemists as appropriate green solvents and catalysts in organic synthesis [1]. ILs are categorized in a wide range such as acidic ILs, basic ILs, metal-containing ILs, guanidinium ILs, chiral-ILs, and ILs containing -OH groups [2]. In particular, Brønsted acidic ILs, which act similar to Brønsted acids, are simply formed via acid–base and nucleophilic reactions. Several researches have been done respect to this property [3–9].

Synthesis of furan-2(5*H*)-ones as a subunit in a large number of natural products [10–14] is a considerable target for organic and medicinal chemists. Since this unit is a key factor in synthetic structures with biological activities such as anticancer

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[15, 16], anti-inflammatory[17], antifungal [18, 19], antimicrobial [20, 21], and antiviral HIV-1 [22–24]. Butenolide which is referred to heterocycles containing furan-2(5*H*)-one moiety found in many bioactive natural products such as freelingyne, acetylmelodori, and sarcophin (Fig. 1).

Researchers have developed many synthetic methods to synthesize structures containing this fundamental core respect to their biological importance [25–32].

However, these methods have some drawbacks, such as low yields, time-consuming reactions, toxicity and expensive reagents. Therefore, efforts to overcome these flaws have been desirable for green chemists. Nageswar and coauthors [33] have reported synthesis of 3,4,5-substituted furan-2(5*H*)-one derivatives in one-pot, three-component reactions by using β-cyclodextrin as a reusable catalyst from reaction between anilines, aldehydes, and diethyl acetylenedicarboxylate. This reaction has been developed by employing nano-ZnO [34], $Al(HSO_4)_3$ [35], KOH [36], and $SnCl_2{\cdot}2H_2O$ [37].

In continuation of our research [38–41], herein we present an efficient method for the one-pot, multicomponent synthesis of 3,4,5-substituted furan-2(5*H*)-one derivatives in the presence of an acidic ionic liquid as a green solvent and catalyst. The three-component condensation of aldehydes, amines, and dialkyl acetylenedicarboxylates using 2-pyrrolidonium hydrogen sulfate ([H-NMP]HSO_4) as a catalyst lead to the formation of 3,4,5-substituted furan-2(5*H*)-one derivatives in high yields (Scheme 1). [H-NMP]HSO_4 can be easily synthesized from the readily available starting materials (Scheme 2) [3].

Results and discussion

As a primary model for optimizing the amount of catalyst loading and temperature, the reaction of benzaldehyde, aniline, and diethyl acetylenedicarboxylate was carried out under solvent-free conditions using different proportions of catalyst at different temperatures. The best result was obtained with 40 % mol of [H-NMP]HSO_4 at 45 °C under solvent-free conditions in 5 min with a 97 % yield (Table 1).

Both electron-withdrawing and electron-donating groups lead to good results at the optimum conditions.Benzaldehydes bearing electron-withdrawing groups react with aniline better than electron-donating groups for preparing of furan-2(5*H*)-ones in good to high yields (Table 2). A proposed mechanism for this transformation is shown in scheme 3. First, nucleophilic Michael addition of amine **3** to acetylenic ester **2** generates the enaminone **A**. Next, nucleophilic attack of enaminone **A** to the aldehyde **1** would yield iminium–oxoanion intermediate **B**, which can be tautomerized to dialkyl 2-(hydroxy(phenyl)methyl)-3-(arylamino)-2-butenedioate **C**. γ-Lactonization of **C** would produce the alkyl-2,5-dihydro-5-oxo-2-aryl-4-(arylamino)furan-3-carboxylate derivatives **4** [42, 43].

To compare the applicability and efficiency of [H-NMP]HSO_4 with the reported catalysts in the literature for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones, we have tabulated the results of these catalysts in Table 3. As shown in Table 3, [H-

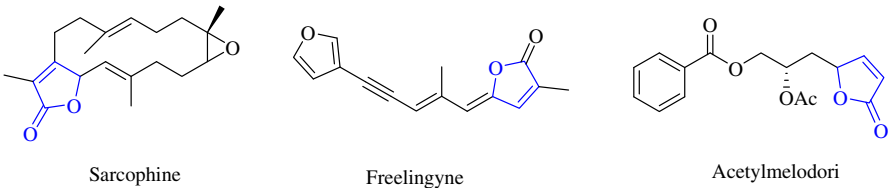
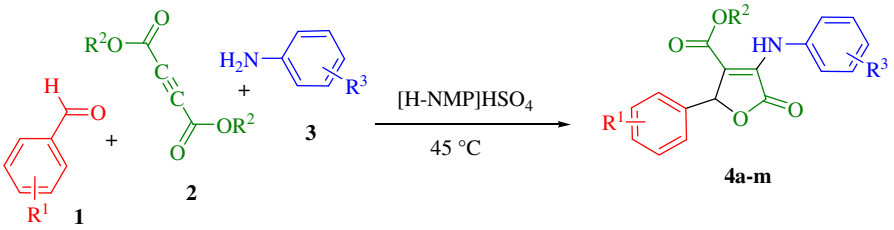
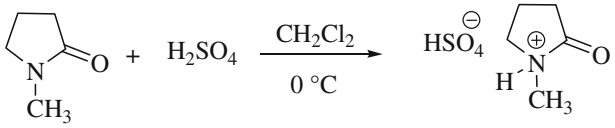


Fig. 1 Natural products containing butenolide fragment



Scheme 1 Synthesis of 3,4,5-substituted furan-2(5*H*)-ones derivative



Scheme 2 Preparation of ionic liquid *N*-methyl 2-pyrrolidonium hydrogen sulfate [H-NMP]HSO_4

NMP]HSO_4 can act as an efficient catalyst with respect to reaction time and yield of products.

Experimental

Melting points and IR spectra of all compounds were measured on an electrothermal 9,100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DRX-400 Avance instruments with $CDCl_3$ as a solvent. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. All reagents and solvents were purchased from Fluka and Merck, which were used without further purification.

Preparation of 2-pyrrolidonium hydrogen sulfate ([H-NMP]HSO_4)

2-Pyrrolidonium hydrogen sulfate ([H-NMP]HSO_4) was obtained by mixing 0.97 mL (10 mmol) of 1-methyl-2-pyrrolidon in dichloromethane (15 ml) in a 25-ml round-bottom flask. The mixture was cooled in an ice bath with continuous stirring. Then 0.53 ml of sulfuric acid 98 % (10 mmol) was added drop wise to the reaction mixture

Table 1 Optimization of reaction conditions[a]

Entry	Catalyst (mol %)	Temperature (°C)	Isolated yield (%)
1	[H-NMP]HSO_4 (5)	45	23
2	[H-NMP]HSO_4 (10)	45	46
3	[H-NMP]HSO_4 (20)	45	59
4	[H-NMP]HSO_4 (30)	45	71
5	[H-NMP]HSO_4 (40)	**45**	**97**[b]
6	[H-NMP]HSO_4 (40)	RT	83
7	[H-NMP]HSO_4 (40)	40	82
8	[H-NMP]HSO_4 (40)	50	79
9	[H-NMP]HSO_4 (40)	55	80
10	[H-NMP]HSO_4 (40)	65	76
11	[H-NMP]HSO_4 (40)	75	77
12	[H-NMP]HSO_4 (40)	85	72
13	[H-NMP]HSO_4 (50)	45	82
14	[H-NMP]HSO_4 (60)	45	83

[a] Reaction conditions: Benzaldehyde (1.0 mmol), aniline (1.0 mmol), diethyl acetylenedicarboxylate (1.0 mmol) and [H-NMP]HSO_4 as a catalyst in 5 min

[b] Optimized conditions

Table 2 Synthesis of furan-2(5*H*)-one derivatives

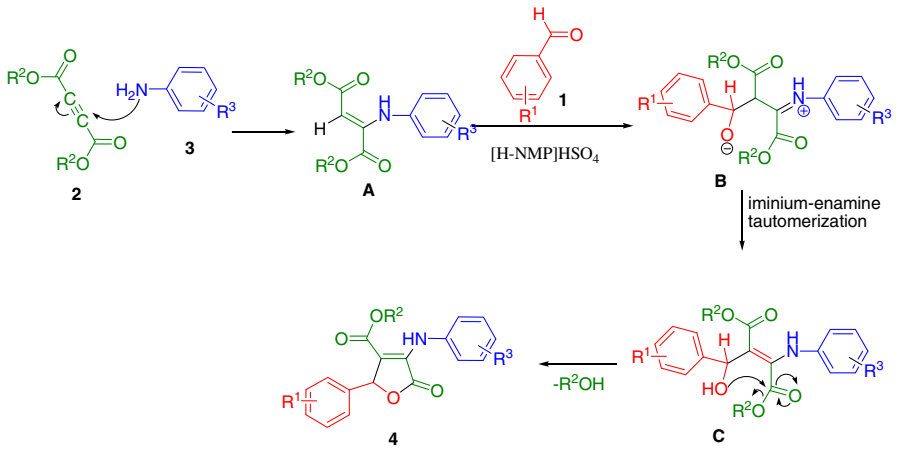
Entry	R^1	R^2	R^3	Products	Yield (%)[a]	Ref.
1	Ph	CH_3	Ph	**4a**	97	[40]
2	4-Me–C_6H_4	CH_3	Ph	**4b**	87	[40]
3	3-NO_2–C_6H_4	CH_3	Ph	**4c**	91	[40]
4	Ph	CH_3	4-F–C_6H_4	**4d**	76	[41]
5	Ph	CH_3	4-Cl–C_6H_4	**4e**	78	[41]
6	Ph	CH_3	3-NO_2–C_6H_4	**4f**	*85*	[41]
7	Ph	CH_3CH_2	Ph	**4g**	98	[40]
8	Ph	CH_3CH_2	4-Me–C_6H_4	**4h**	90	[40]
9	4-Me–C_6H_4	CH_3CH_2	Ph	**4i**	83	[40]
10	4-Cl–C_6H_4	CH_3CH_2	Ph	**4j**	87	[40]
11	4-OMe–C_6H_4	CH_3CH_2	Ph	**4k**	75	[41]
12	Ph	*tert*-butyl[c]	Ph	**4l**	95	b
13	3-NO_2–C_6H_4	*tert*-butyl	Ph	**4m**	93	b

[a] Isolated yield

[b] The new compounds synthesized in this work. All known products reported previously in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples

[c] Tertiary butyl

within 10 min and was stirred for 4 h at room temperature. The dichloromethane was removed under reduced pressure using a rotary evaporator then product was dried at 70 °C under vacuum for 30 min in a vacuum oven (Scheme 2) [3].



Scheme 3 Proposed mechanism for the synthesis of furan-2(5*H*)-ones

Table 3 Comparison result of [H-NMP]HSO_4 with the reported catalysts in literature for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones **4a** and **4g**

Entry	Product	Catalyst	Time	Yield (%)	Ref.
1	**4a**	β-Cyclodextrin	–	–	[35]
2		Nano-ZnO	2.5 h	94	[36]
3		$Al(HSO_4)_3$	8 h	84	[37]
4		$SnCl_2{\cdot}2H_2O$	6.5 h	90	[39]
5		AcOH	–	–	[40]
6		$[Bu_4N][HSO_4]$	5 h	92	[42]
7		PPA/SiO_2	1 h	90	[41]
8		Sucrose	9 h	97	[43]
9		[H-NMP]HSO_4	7 min	97	This work
10	**4g**	β-Cyclodextrin	12 h	85	[35]
11		Nano-ZnO	–	–	[36]
12		$Al(HSO_4)_3$	9 h	77	[37]
13		$SnCl_2{\cdot}2H_2O$	–	–	[39]
14		AcOH	1 h	95	[40]
15		$[Bu_4N][HSO_4]$	2 h	90	[42]
16		PPA/SiO_2	1 h	91	[41]
17		Sucrose	4.5 h	85	[43]
18		[H-NMP]HSO_4	7 min	98	This work

General procedure for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones derivatives

The mixture of aldehyde (1.0 mmol), amine (1.0 mmol), dialkylacetylenedicarboxylate (1.0 mmol) and [H-NMP]HSO_4 (40 mol %) were stirred for 4–7 min at 45 °C.

After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was washed with water/ethanol (3 × 3 mL) and then filtrated to separate the catalyst and obtain a pure product.

*Compound **4l***

Tert-butyl 2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)furan-3-carboxylate colorless solid: 0.333 g (95%); m.p. 167–169 °C; IR (KBr): 3,260, 3,030, 1,690, 1,451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H, $3CH_3$), 5.68 (s, 1H, $H_{benzylic}$), 7.08–7.49 (m, 10H, H_{Ar}), 9.35 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 and 162.9 (C=O), 156.9, 136.3, 135.92, 129.0, 128.9, 128.4, 127.6, 125.7, 122.4, 114.5 (C_{Ar} and C_{vinyl}), 83.3 (C–O), 61.67 ($C_{benzylic}$), 28.0 ($3CH_3$); MS *m/z* (%): 57 (63), 77 (57), 102 (40), 130 (100), 158 (61), 175 (46), 250 (43), 277 (24), 295 (87), 351 (M+, 29).

*Compound **4m***

Tert-butyl 2,5-dihydro-2-(3-nitrophenyl)-5-oxo-4-(phenylamino)furan-3-carboxylate colorless solid; 0.368 g (93 %); m.p. 175–178 °C; IR (KBr): 3,330, 3,090, 2,975, 1,710, 1,676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H, $3CH_3$), 5.83 (s, 1H, $H_{benzylic}$), 7.11–8.19 (m, 9H, H_{Ar}), 9.37 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 and 162.6 (C=O), 157.2, 148. 1, 138.0, 135.6, 132.9, 129.8, 129.3, 126.2, 123.6, 123.3, 122.2 and 113.6 (12 C_{Ar} and C_{vinyl}), 84.0(C–O), 60.0 ($C_{benzylic}$), 28.0 ($3CH_3$). MS *m/z* (%): 57(100), 119 (30), 175 (58), 203 (60), 322 (28), 340 (86), 370 (9), 354 (M+, 28).

Conclusions

In conclusion, we have developed an efficient method for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones through a one-pot, three-component reaction, between aldehydes, amines, and dialkyl acetylenedicarboxylates. This method has advantages such as simple and inexpensive starting materials, a straightforward procedure, an environmental friendly method, and high yields.

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