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Two ammonium ionic liquids as efficient catalysts for the one-pot green synthesis of 3,4,5-substituted furan-2(5*H*)-ones

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An efficient and environmentally friendly method for one-pot preparation of 3,4,5-substituted furan-2(5*H*)-ones is described by condensation of aromatic aldehydes, aromatic amines and dialkyl acetylenedicarboxylates under solvent-free conditions using ammonium ionic liquids as catalysts. This synthetic approach benefits from cleaner reaction profiles, use of easily available, inexpensive, recyclable and environmentally benign catalyst, high yields, and simple experimental and work-up procedures.

Keywords: Ammonium ionic liquids ([Et_2NH_2][HSO_4], [Et_3NH][HSO_4]), Multi-component reaction, Green chemistry, Furan-2(5*H*)-ones.

INTRODUCTION

2(5*H*)-Furanones are attractive for organic chemists since they are key structural elements in many biologically active natural products [1]. They are abundant in nature and recently have been widely used as plant-growth regulators, antiulcer agents, and fish-growth promoters [2]. Attempts are ongoing to develop new synthetic approaches for the efficient preparation of natural products containing furanone ring units (Figure 1: freelingyne 1, tetrenoline 2, and sarcophine 3) because of their importance in biological activities such as antibacterial, antifungal, antimicrobial, antiviral, anticancer, anti-inflamatory, antipsoriasis, and anti–phospholipase A2 activities [3]. The wide range of application of compounds containing the butenolide ring results in considerable attention toward the synthesis of these compounds.

Recently, a multi-component reaction (MCR) of aromatic amines, aldehydes and dialkyl acetylenedicarboxylate has been used for the synthesis of furan-2(5*H*)-ones. Multi-component reactions offer an efficient and powerful mode of synthesis of complex structures, which is a convenient route for the synthesis of new drugs and chemical compounds by the combination of various starting materials [4].

Narayana *et al.* applied β-cyclodextrin for the synthesis of 2(5*H*)-furanone by condensation of anilines, aldehydes and diethyl acetylenedicarboxylate in a one pot three-component reaction [5]. Other synthetic methods have also been developed by employing nano-ZnO [6], $Al(HSO_4)_3$ [7], KOH [8] and $SnCl_2.2H_2O$ [9].

Ionic liquids (ILs) are considerably popular among chemists since they have some specific characteristics such as very low vapor pressure, non-explosiveness, thermal stability in a wide temperature range and environmental safety, which make them a green alternative to conventional organic solvents [10-13].

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 [14]. Because of their usefulness, preparation and application of various kinds of ionic liquids in chemical processes have been quickly developed. Of the many different kinds of ILs available, the Brönsted acidic ILs offer the greatest potential for the development of environmentally friendly acid catalysts for organic synthesis [15,16]. Combination of a Brönsted acid and a Brönsted base produces protic ionic liquids [17]. Protic ionic liquid such as [Et_3NH][HSO_4] has been used by Li as a catalyst and green solvent for the cracking reactions of dialkoxypropanes [18].

In continuation of our research [19-22], herein we present the ionic liquids ([Et_2NH_2][HSO_4] and [Et_3NH][HSO_4]) as catalysts in a simple and efficient method for the synthesis of 4,5-substituted furan-2(5*H*)-ones by one-pot condensation of aromatic aldehydes, aromatic amines and dialkyl acetylenedicarboxylates under solvent-free conditions.

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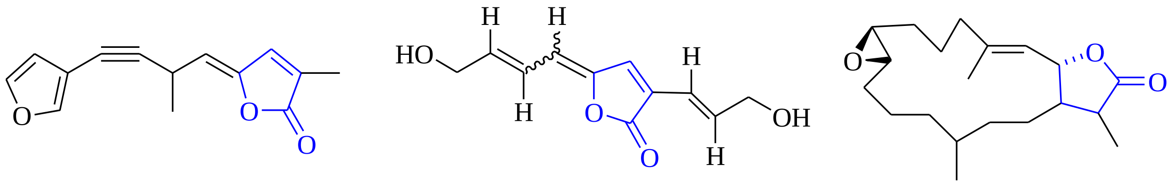


Freelingvne 1 Tetrenoline 2 Sarcophine 3

Fig. 1. Natural products containing a furanone ring fragment.

EXPERIMENTAL

General

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 Avance instrument with CDCl$_3$ as a solvent. All reagents and solvents were purchased from Fluka and Merck and were used without further purification.

Preparation of diethylamine hydrogen sulfate [Et$_2$NH$_2$][HSO$_4$]

In an ice bath, 0.5 mol sulfuric acid was added dropwise to the solution of diethylamine (0.5 mol diethylamine in 150 mL chloroform) under vigorous stirring. After completion of the reaction, the chloroform was removed on a rotary evaporator. Finally, after cooling the ionic liquid a white solid was obtained. This white crystalline powder was dried in high vacuum at 50°C overnight (>99% yield) [23].

Preparation of triethylamine hydrogen sulfate [Et$_3$NH][HSO$_4$]

Solution of sulfuric acid 98% (19.6 g, 0.2 mol) in water was dropped into triethylamine (20.2 g, 0.2 mol) under stirring at 60 °C for 1 h. Afterwards, the reaction mixture was stirred for another 1 h at 70 °C to ensure completion of the reaction. Finally, in order to remove the traces of water, the residue was heated at 80°C in high vacuum until the weight of the residue remained constant [24].

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

The mixture of aldehyde (1.0 mmol), amine (1.0 mmol), dialkylacetylenedicarboxylate (1.0 mmol) and 40 mol % of the ionic liquids [Et$_2$NH$_2$][HSO$_4$] and [Et$_3$NH][HSO$_4$] was stirred for 10-15 minutes at 70-80°C. After completion of the reaction monitored by thin-layer chromatography (TLC), the reaction mixture was filtrated and washed with water/ethanol (3×3 mL) to purify the product and separate the catalyst. The analytical and spectral data for the unknown products (**4p** and **4q**) are represented below:

*t-Butyl-2,5-dihydro-5-oxo-2-(4-bromophenyl)-4-(phenylamino)furan-3-carboxylate (**4p**)*

White powder; m.p. 169-172 °C; IR (KBr): ν 3208, 1716, 1677, 1596, 1499 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ= 1.39 (s, 9H, 3×Me), 5.65 (s, 1H, H$_{benzylic}$), 7.09-7.14 (m, 3H, H$_{Ar}$), 7.27-7.31 (m, 2H, H$_{Ar}$), 7.38-7.41 (m, 2H, H$_{Ar}$), 7.34-7.45 (m, 2H, H$_{Ar}$), 9.32 (brs, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ=28.0 (3×Me), 61.0 (C$_{benzylic}$), 83.5 ($O\underline{C}Me_3$), 114.0, 122.3, 122.4, 125.9, 129.0, 129.3, 131.6, 134.5, 136.0 and 156.9 (C$_{Ar}$ and C=C), 162.7 and 164.8 (C=O).

*t-Butyl-2,5-dihydro-5-oxo-2-phenyl-4-(3-nitrophenylamino)furan-3-carboxylate (**4q**)*

White powder; m.p. 165-168 °C; IR (KBr): ν 3142, 1715, 1681, 1531, 1456 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ= 1.37 (s, 9H, 3×Me), 5.76 (s, 1H, H$_{benzylic}$), 7.24-7.32 (m, 5H, H$_{Ar}$), 7.64 (t, 1H, J=8.0 Hz, H$_{Ar}$), 7.93 (ddd, J=8.0 ,2.0, 0.8 Hz, 1H, H$_{Ar}$), 8.09 (ddd, J=8.4 ,2.4, 0.8 Hz, 1H, H$_{Ar}$), 8.32 (t, 1H, J=2.4 Hz, H$_{Ar}$), 9.40 (brs, 1H, NH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ= ^{13}C NMR (CDCl$_3$, 100 MHz): δ=27.9 (3×Me), 61.3 (C$_{benzylic}$), 83.8 ($O\underline{C}Me_3$), 115.1, 115.9, 119.9, 127.3, 127.5, 128.8, 128.9, 129.8, 134.4, 137.6, 148.3 and 156.9 (C$_{Ar}$ and C=C), 163.1 and 164.9 (C=O).

RESULTS AND DISCUSSION

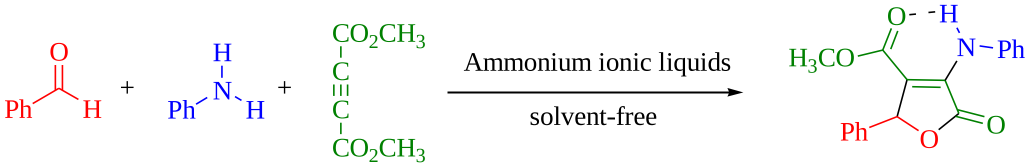
To examine the effect of catalyst loading and temperature on the three-component condensation reaction of 4,5-substituted furan-2(5*H*)-ones, the reaction of aromatic aldehydes, aromatic amines and dialkyl acetylenedicarboxylates was selected as a model in the presence of the ionic liquids, diethylamine hydrogen sulfate [Et$_2$NH$_2$][HSO$_4$] and triethylammonium hydrogensulfate ([Et$_3$NH][HSO$_4$]) as catalysts (Table 1). Different amounts of diethylamine hydrogensulfate and triethylammonium hydrogensulfate were applied as catalysts (15, 20, 30, 40, 50 and 55 mol %) at various temperatures (45, 50, 60, 70, 80, 90 and100

°C) (Table 1). As the Table shows, the addition of 40 mol % of acidic ionic liquid catalyst at 80 and 70 °C results in a corresponding product within 15 min with 85 % yield. Afterwards, the three-component condensation reaction of aromatic aldehydes, aromatic amines and dialkyl acetylenedicarboxylates was investigated under optimized conditions for preparation of 4,5-substituted furan-2(5*H*)-one derivatives (Table 2).

To better understanding the effect of the substituent, diverse substituted aldehydes were used to synthesize the desired products in high to excellent yields using the ammonium ionic liquids ($[Et_2NH_2][HSO_4]$, $[Et_3NH][HSO_4]$) as catalysts (Table 2).

The proposed speculative mechanism for the formation **4** is shown in Scheme 2. The mechanism can proceed through Michael addition, iminium-enamine tautomerization and γ-lactonization [25,26].

Table 1. Optimization of reaction conditions in the presence of different amounts of ionic liquids, A: diethylamine sulfate $[Et_2NH_2][HSO_4]$ B: triethylamine sulfate $[Et_3NH][HSO_4]$ as catalysts at different temperatures [a]



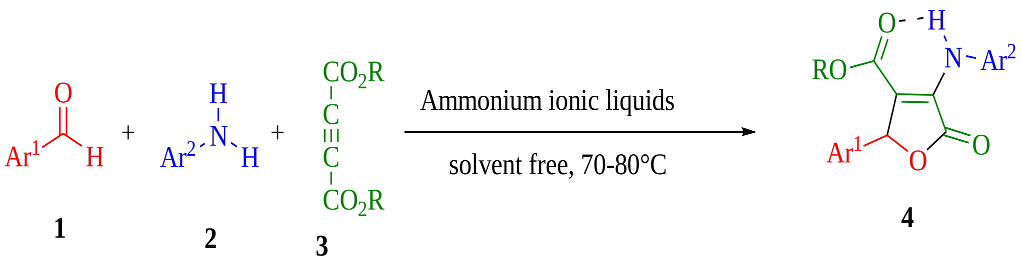
Entry	Catalyst/mol %		Temperature/ °C		Time/min		Isolated Yield/ %	
	A	B	A	B	A	B	A	B
1	15	15	80	70	15	15	36	49
2	15	15	80	70	20	20	57	55
3	20	20	80	70	15	15	65	67
4	30	30	80	70	15	15	83	81
5	**40**	**40**	**80**	**70**	**15**	**15**	**85**	**85**
6	50	50	80	70	15	15	87	83
7	55	55	80	70	15	15	88	83
8	30	40	45	45	20	20	56	46
9	30	40	50	50	20	20	57	50
10	30	40	60	60	15	15	61	73
11	30	40	70	70	15	15	74	81
12	30	40	80	80	15	15	83	77
13	30	40	90	90	15	15	66	72
14	30	40	100	100	15	15	70	70
15	30	40	80	70	5	5	66	61
16	30	40	80	70	10	10	78	79
17	30	40	80	70	15	15	83	81
18	30	40	80	70	20	20	80	77

[a] Reaction conditions: benzaldehyde (1.0 mmol), aniline (1.0 mmol), diethyl acetylenedicarboxylate (1.0 mmol)

Table 2. Synthesis of furan-2(5*H*)-one derivatives in the presence of ammonium ionic liquids, A: diethylammonium hydrogensulfate $[Et_2NH_2][HSO_4]$ B: triethylammonium hydrogensulfate $[Et_3NH][HSO_4]$ as catalysts.

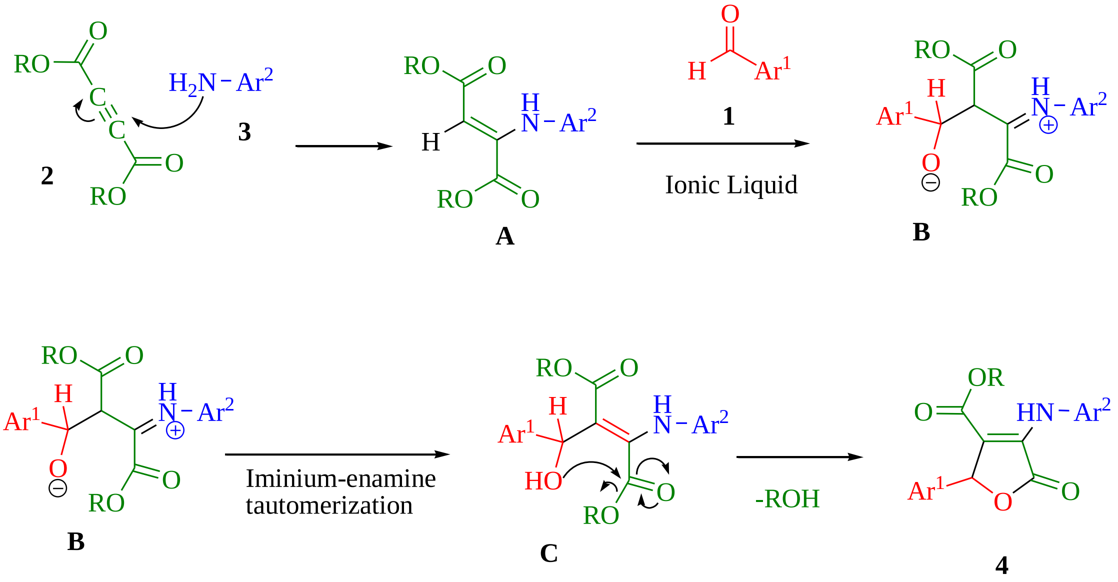
Entry	Ar^1	Ar^2	R	Products	Isolated Yield/ %		Ref.
					A	B	
1	Ph	Ph	CH_3	**4a**	88	85	7
2	4-Me- C_6H_4	Ph	CH_3	**4b**	80	76	7
3	3-NO_2- C_6H_4	Ph	CH_3	**4c**	81	78	7
4	4-NO_2-C_6H_4	Ph	CH_3	**4d**	89	85	19
5	4-OMe- C_6H_4	Ph	CH_3	**4e**	88	87	19
6	Ph	4-F-C_6H_4	CH_3	**4f**	71	67	19
7	Ph	4-Cl-C_6H_4	CH_3	**4g**	72	69	19
8	Ph	3-NO_2-C_6H_4	CH_3	**4h**	*79*	*78*	19
9	Ph	Ph	CH_3CH_2	**4i**	89	85	5
10	Ph	4-Me-C_6H_4	CH_3CH_2	**4j**	90	87	5
11	4-Me-C_6H_4	Ph	CH_3CH_2	**4k**	85	82	5
12	4-Cl-C_6H_4	Ph	CH_3CH_2	**4m**	91	89	5
13	4-OMe-C_6H_4	Ph	CH_3CH_2	**4n**	90	85	5
14	1- naphtyl	Ph	CH_3CH_2	**4o**	64	63	5
15	4-Br-C_6H_4	Ph	*t*-Bu	**4p**	86	81	*a*
	Ph-C_6H_4	3-NO_2-C_6H_4	*t*-Bu	**4q**	80	76	*a*

[a] New compounds synthesized in this work.



Ammonium ionic liquids: $[Et_2NH_2][HSO_4]$, $[Et_3NH][HSO_4]$

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



Scheme 2. Proposed mechanism for the formation of furan-2(5H)-one derivatives.

CONCLUSION

In summary, a simple method for the preparation of furan-2(5*H*)-one derivatives in solvent-free conditions *via* one-pot three-component reaction from commonly available starting materials was ben developed. The products can be easily collected by filtration.

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ДВЕ АМОНИЕВИ ЙОННИ ТЕЧНОСТИ КАТО ЕФЕКТИВНИ КАТАЛИЗАТОРИ ЗА ЕДНОСТАДИЙНА ЗЕЛЕНА СИНТЕЗА НА 3,4,5-ЗАМЕСТЕНИ ФУРАН-2(5*Н*)-ОНИ

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(Резюме)

Описана е едностадийна и екологично съвместима кондензация на ароматни алдехиди, ароматни амини и диалкил-ацетилен-дикарбоксилати за синтезата на 3,4,5-заместени фуран-2(5*H*)-они без разтворител с амониеви йонни течности като катализатори. Този подход има предимствата на чисти реакционни профили, използването на лесно достъпни, евтини, рециклируеми и екологично съвместими катализатори и проста процедура.