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Formic acid as an efficient catalyst for the one-pot preparation of furan-2(5H)-ones under solvent-free condition

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Abstract: The three-component condensation reaction of aldehydes, amines, dialkyl acetylenedicarboxylates, leading to production of 3,4,5-substituted furan-2(5H)-ones. This reaction is performed in the presence of formic acid as a cheap and readily available catalyst under room temperature.

Keywords: Three-component reaction, Dialkyl acetylenedicarboxylates, 3,4,5-Substituted furan-2(5H)-ones, Formic acid.

Introduction

A key goal of modern organic chemistry is to both maximize the efficiency of using readily available materials and minimize the generation of waste, which also is one of the prime principles of green chemistry [1] and one of the most challenging tasks in organic synthesis is the efficient preparation of complex molecules starting from easily available raw materials. Multicomponent reactions (MCRs) have emerged as efficient and powerful tools in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate [2-4].

Heterocycles containing furan-2(5H)-one fragment generally named as butenolides are a key moiety of natural and synthetically bio-active molecules. For examples some natural products such as acetogenins, muconolactones, leptospharin and strigol have butenolide cores [5-8].

These skeletons show a wide range of biological activities such as antimicrobial [9], antifungal [10], anti-inflamatory [11], anticancer [12] and anti-viral HIV-1 [13].

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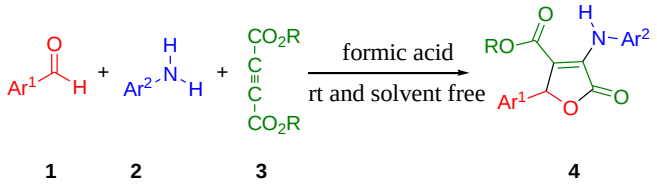
Thus efforts for the synthesis of butenolides scaffolds are in demand for organic chemists and a variety of synthetic approaches for the synthesis of butenolides is desirable [14-21]. Among the available methods for the construction of butenolides, the nucleophilic reaction between zwitterions of amine and dialkyl acetylenedicarboxylates with aldehyde is the most convenient [22-23]. The three-component condensation of aldehydes, amines and dialkyl acetylenedicarboxylates lead to the formation of 3,4,5-substituted furan-2(5H)-one derivatives.

The design of new environmentally safe synthetic methodologies for preparation of organic compounds is a major task for organic chemists. One strategy to achieve this goal involves the development of reactions in which reactants are combined, without any solvent.

However, the generality of the existing reports for the construction of 3,4,5-substituted furan-2(5H)-one is relatively good but development of simple and environmentally safe synthetic routes toward widely used organic compounds from readily available catalysts for the preparation of substituted 3,4,5-substituted furan-2(5H)-ones is highly desirable.

In continuation of our research work on the synthesis of furan, [24-33] herein we described a novel use of formic acid for the multi-component coupling of

aldehyde, dialkyl acetylenedicarboxylates and aniline derivatives to produce furan-2(5H)-one derivatives under mild conditions (Scheme **1**).



1 **2** **3** **4**

Scheme 1: Synthesis of furan-2(5H)-one derivatives.

Results and discussion

Initially the reaction of benzaldehyde, *p*-methylaniline and diethyl acetylenedicarboxylate was chosen as a model of the reaction and carried out in ethanol using different catalysts (Table **1**). Among of various catalysts tested, formic acid was found to be most effective in catalyzing the reaction under room temperature.

Table 1: Optimization of catalyst for the synthesis of furan-2(5*H*)-ones.

Entry	Catalyst	Time (h, min)	Yield(%)[a]
1	TiO_2	15h	25
2	$Zn(SO_4)_2.7H_2O$	15h	25
3	$Zr(NO_3)_4$	12h	30
4	$ZrCl_4$	12h	50
5	$HClO_4$-SiO_2	12h	20
6	formic acid	20min	98

[a] Isolated yield.

To optimize the catalyst loading, above model reaction was carried out under different amounts of formic acid (0.02, 0.05, 0.09, 0.15 g). It was observed that 0.09 g loading of formic acid provided the maximum yield. Higher percentage loading of the catalyst increased the reaction time. Data in Table **2** outline the optimization of the reaction conditions.

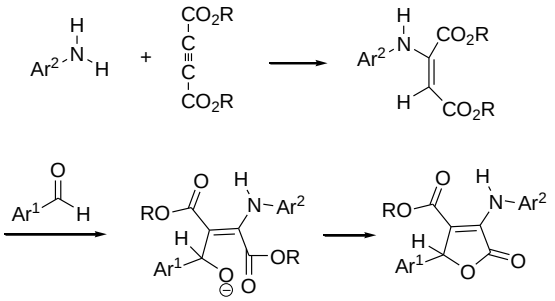
Under the optimized reaction conditions, the generality of the reaction was investigated by the using of various aldehydes, anilines and dialkyl acetylenedicarboxylate to produce furan-2(5H)-one derivatives. The results are summarized in Table **3**. These results indicate the effectiveness of electron-withdrawing and electron-donating groups on the time and yield of the reaction. Benzaldehydes with electron-withdrawing groups react with aniline better than electron-donating groups for generation of furan-2(5H)-ones in good to high yields. In our research work, aliphatic aldehyde and amine such as propanal and 1-buthylamin did not tolerate the reaction.

Table 2: Optimization amount of formic acid for for the synthesis of furan-2(5H)-ones .under room tempreture conditions.

Entry	formic acid(gr)	Time (min)	Yield(%)[a]
1	0.02	240	90
2	0.05	60	89
3	0.09	20	98
4	0. 15	20	90

[a] Isolated yield.

The speculative proposed mechanism for the formation 4 is shown in Scheme **2**.



Scheme 2: The speculative proposed mechanism for the formation of furan-2(5H)-one derivatives.

The structures of new compounds in Table **3** were deduced on the basis of IR, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of Methyl 4-(4-chlorophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (Table **3**, Entry 1) displayed the molecular ion peak at *m/z* = 343, which is consistent with the proposed structure. The ^{1}H NMR spectrum of this product, exhibited a singlet at δ = 3.77 ppm for methyl protons of the carboxylate group and one sharp singlet arising from benzylic proton at δ = 5.72 ppm. The aromatic protons of product were observed at δ = 7.22 -7.46 ppm. A broad singlet for the NH group at δ = 8.97 ppm indicated intra-molecular hydrogen bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum of this product was showed 12 distinct resonances in agreement with the proposed structure. The IR spectrum indicated one sharp peak at 3218 cm^{-1} for NH within product.

Table 3: Synthesis of furan-2(5*H*)-one derivatives.

Entry	Ar^1	Ar^2	R	Time (min)	Yield(%)[a]	Ref.
1	Ph	4-Cl-C_6H_4	CH_3	170	82	*b*
2	4-NO_2-C_6H_4	Ph	CH_3	60	96	*b*
3	Ph	Ph	CH_3CH_2	20	95	23
4	Ph	4-Me-C_6H_4	CH_3CH_2	20	98	23
5	4-Me-C_6H_4	Ph	CH_3CH_2	20	89	23
6	4-Cl-C_6H_4	Ph	CH_3CH_2	40	86	23
7	4-OMe-C_6H_4	Ph	CH_3CH_2	80	83	23
8	1- naphtyl	Ph	CH_3CH_2	180	73	23

[a]Yields refer to the pure isolated products
[b]The new compounds synthesized in this work.

Experimental

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer respectively. The ^1H, ^{13}C NMR spectra were obtained on Bruker DRX-250 and 400 Avance instruments with $CDCl_3$ as a solvent. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. All reagents and solvents obtained from Fluka and Merck were used without further purification.

General procedure:

The mixture of aldehyde (1 mmol), amine (1 mmol), dialkylacetylenedicarboxylate (1 mmol) and formic acid (0.09g) were stirred under solvent free condition at room temperature. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was filtrated and washed with ethanol (10mL×3) to separate the catalyst and to obtain a pure product.

(Table **3**, Entry 1). *Methyl 4-(4-chlorophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate*:

White solid; 0.268g (82%); mp 165-166 °C; mp 165-166 °C; IR (KBr): 3218, 2951, 1715, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, OCH_3), 5.72 (s, 1H, benzylic), 7.22-7.32 (m, 7H, aromat), 7.46 (d, *J* = 8.8 Hz , 2H), 8.97 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 162.7 (ester C), 156.1, 134.8, 134.6, 131.2, 129.1, 128.8, 128.9, 127.4, 123.2, 113.0 (10 C aromatic), 61.5 (methoxy C), 52.1(benzylic C).; MS m/z (%): 121 (17), 130 (74), 158 (24), 189 (67), 284 (30), 286(10), 311 (10), 343 (M^+, 100), 345 (M^++2, 41), 347(M^++4, 8); Anal. calcd. for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.07. Found: C, 63.15; H, 4.14; N, 4.12

(Table **3**, Entry 2). *methyl 2,5-dihydro-2-(4-nitrophenyl)-5-oxo-4-(phenylamino)furan-3-carboxylate*:

White solid; 0.300 g (96%); mp 130-131 °C; IR (KBr): 3321, 2976, 1697, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, OCH_3), 5.89 (s, 1H, benzylic), 7.17 (t, *J* = 7.6, 1H), 7.30-7.34 (m, 3H, aromatic), 7.46 (d, *J* = 8 Hz, 4H), 8.15 (d, *J* = 8.8 Hz, 2H), 9.02 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 162.5 (ester CO), 156.4, 148.0, 142.6, 135.5, 129.3, 128.5, 126.5, 124.0, 122.1, 111.9 (10 C aromatic), 60.7(methoxy C), 52.3 (benzylic C). MS m/z (%): 69 (20), 81 (22), 83 (19), 84 (18), 93 (38), 96 (19), 97 (21), 98 (17), 175 (45), 203 (19), 295 (34), 354 (M^+, 100); Anal. calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.71; H, 5.36; N, 3.40.

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