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An efficient one-pot multi-component synthesis of 3,4,5-substituted furan-2(5*H*)-ones catalyzed by tetra-*n*-butylammonium bisulfate

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ABSTRACT

A facile one-pot synthesis of 3,4,5-substituted furan-2(5*H*)-one derivatives from a three-component reaction of aniline derivatives, dialkylacetylenedicarboxylates and aromatic aldehydes under mild conditions using tetra-*n*-butylammonium bisulfate as a catalyst has been developed.

1. Introduction

Highly substituted furans play an important role in organic chemistry, not only as the key structural units in many natural products, common subunits in pharmaceuticals [1–7] and flavors [8] but also as useful building blocks in synthetic chemistry [9–13]. They have also found utilities as synthetic intermediates or synthons for numerous functional groups, *inter alia*, carboxylic acids, α-keto-esters, and aromatics [14]. For this reason, the efficient syntheses of highly substituted furans continue to attract the interest of synthetic chemists [15,16]. Accordingly, many strategies have been developed for the preparation of furans [17–20]. The above-mentioned methodologies suffer from certain limitations such as long synthetic routes, use of costly metal catalysts and highly volatile solvents, *etc.* Recently Narayana *et al.* and Ramesh *et al.* developed a methodology for the synthesis of furan-2(5*H*)-ones *via* a reaction of aromatic amines, aldehydes and dialkyl acetylenedicarboxylate. Narayana *et al.* described the synthesis of 2(5*H*)-furanones in the presence of β-cyclodextrin [21]. Ramesh and Nagarajan reported the preparation of 2(5*H*)-furanones *via* a three-component reaction of a series of aldehydes (aromatic, heterocyclic), dialkylacetylenedicarboxylates and 9-alkyl-9*H*-carbazol-3-amines in the presence of KOH [22]. The synthesis of 2(5*H*)-furanones promoted by $SnCl_2$ has also been reported by Nagarapu *et al.* [23].

We have recently reported the synthesis of 2(5*H*)-furanones in the presence of acetic acid [24]. In continuation of our research work on the synthesis of furan derivatives [25–33], herein we describe a novel use of tetra-*n*-butylammonium bisulfate in a multi-component reaction of aldehyde, dialkyl acetylenedicarboxylates and aniline derivatives in generating furan-2(5*H*)-one derivatives under mild conditions (Scheme 1).

2. 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 ^{1}H NMR and ^{13}C NMR spectra were recorded 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 procedures for synthesis of furan-2(5H)-ones: A mixture of aldehyde (1 mmol), amine (1 mmol), dialkylacetylenedicarboxylate (1 mmol) and tetra-*n*-butylammonium bisulphate was stirred in ethanol at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtrated and washed with ethanol (10 mL × 3) to obtain a pure product.

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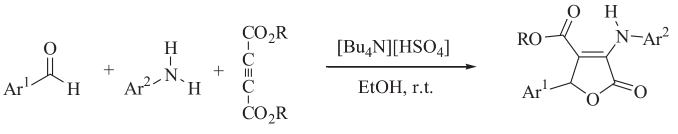

1 **2** **3** **4a-p**

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

Physical and chemical data of chosen products are demonstrated below.

Methyl 2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)furan-3-carboxylate (***4a***): White solid; 0.284 g (92%); mp 195–196 °C; IR (KBr, cm^{-1}): ν 3260, 3208, 1702, 1661; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3 H, OCH_3), 5.76 (s, 1H, benzylic), 7.13 (t, 1H, J = 7.3 Hz), 7.24–7.31 (m, 7H), 7.52 (d, 2H, J = 8 Hz), 8.90 (br, NH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 and 162.7 (ester CO), 156.3, 136.1, 134.9, 129.0, 128.7, 128.6, 127.4, 125.9, 122.3, 112.8 (aromatic C), 61.6 (methoxy C), 52.1 (benzylic C); MS (positive mode, m/z (%)): 57 (100), 97 (75), 152 (24), 213 (51), 240 (39), 250 (33), 309 (M^+, 44); Anal. calcd. for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53. Found: C 70.08, H 4.97, N 4.60.

Methyl 4-(p-tolylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (***4b***): White solid; 0.287 g (89%); mp 173–175 °C; IR (KBr, cm^{-1}): ν 3228, 2950, 1706, 1677, 1513; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.72 (s, 1H, benzylic), 7.09 (d, 2H, J = 8 Hz), 7.22–7.270 (m, 5*H*, aromatic), 7.34 (d, 2H, J = 8.4 Hz), 8.86 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 and 162.8 (CO of ester), 156.4, 135.8, 135.0, 133.5, 129.6, 128.6, 128.5, 127.5, 122.4, 112.6 (C of aromatic), 61.3 (C of methoxy), 52.0 (benzylic C), 20.95 (C of methyl); MS (m/z (%)): 130 (96), 131 (21), 133 (19), 158 (39), 189 (34), 263 (14), 264 (33), 265 (12), 291 (24), 323 (M^+, 100); Anal. calcd. for $C_{19}H_{17}NO_4$: C 70.58, H 5.30, N 4.33. Found: C 70.77, H 5.38, N 4.35

Ethyl 2-(4-cyanophenyl)-2,5-dihydro-5-oxo-4-(phenylamino)-furan-3-carboxylate (***4e***): White solid; 0.324 g (93%); mp 188–189 °C; IR (KBr, cm^{-1}): ν 3293 (NH), 2977, 2225 (CN), 1731, 1684, 1666, 1500; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 7.2 Hz, CH_3), 4.24 (q, 2H, J = 7.2 Hz, CH_2), 5.82 (s, 1H, benzylic), 7.17 (t, 1H, J = 7.2 Hz), 7.32–7.47 (m, 6H, aromatic), 7.59 (d, 2H, J = 8 Hz), 9.03 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 162.5 (CO of ester), 156.89, 140.8, 135.7, 132.5, 129.2, 128.3, 126.3, 122.1, 118.1, 112.6 (aromatic C), 112.2 (C of CN), 61.6 (methoxy), 60.8 (benzylic), 14.02 (CH_3 of ethoxy). MS (m/z (%)): 93 (17), 119 (9), 155 (70), 183 (29), 228 (13), 275 (59), 302 (14), 348 (M+, 100); Anal. calcd. for $C_{20}H_{16}N_2O_4$: C 68.96, H 4.63, N 8.04. Found: C 69.10, H 4.69, N 8.11.

3. Results and discussion

We have discovered a one-pot three-component condensation reaction (MCR) for the synthesis of organic compounds using tetra-*n*-butylammonium bisulfate as a catalyst at room temperature in a single step. As previously mentioned, products can be easily separated and purified by simple filtration. Benzaldehyde, aniline, and dimethyl acetylenedicarboxylate were taken as model compounds for the optimization of the reaction conditions. For this purpose, the reaction was initially carried out in ethanol using different catalysts (Table 1). As can be seen, $[Bu_4N][HSO_4]$ was found to be the most effective catalyst for the reaction at room temperature.

Table 1
Optimization of catalyst for the synthesis of furan-2(5*H*)-ones from the reaction between benzaldehyde, aniline and dimethyl acetylenedicarboxylate at room temperature.

Entry	Catalyst	Time (h)	Isolated yield (%)
1	TiO_2	15	25
2	$Zn(SO_4)_2{\cdot}7H_2O$	15	25
3	$Zr(NO_3)_4$	12	30
4	$ZrCl_4$	12	50
5	$HClO_4–SiO_2$	12	20
6	$[Bu_4N][HSO_4]$	5	92
7	$KHSO_4$	15	26
8	NH_4HSO_4	15	40

Table 2
Optimization of solvent for the synthesis of furan-2(5*H*)-ones from the reaction of benzaldehyde, aniline and dimethyl acetylenedicarboxylate in the presence of $[Bu_4N][HSO_4]$ as an optimized catalyst.

Entry	Solvent	Time (h)	Isolated yield (%)
1	Ethanol	5	92
2	Ethylacetate	24	55
3	Acetonitrile	24	34
4	Diethylether	24	–
5	*n*-Hexan	24	59
6	Methanol	24	62
7	H_2O	24	80

In this work, various solvents were tested to optimize the conditions for the synthesis of compound **4a**. Ethanol was found to be the best solvent, in which the product was obtained in 92% yield (Table 2). Here, $[Bu_4N][HSO_4]$ and ethanol were finally selected as the suitable catalyst and the solvent, respectively.

Under the optimized reaction conditions, the generality of the reaction was fully investigated with different aldehydes, anilines and dialkyl acetylenedicarboxylate to produce furan-2(5*H*)-one derivatives. The results are summarized in Table 3. These results show the effects of electron-withdrawing and electron-donating groups on the time required and the yield of the reactions. Benzaldehydes with electron-withdrawing groups react with aniline more efficiently than the benzaldehydes substituted with electron-donating groups. In our work, aliphatic aldehydes and amines such as propanal and 1-buthyl amine did not work well under the reaction conditions.

The structures of the new compounds in Table 3 were established on the basis of IR, ^1H NMR, ^{13}C NMR, MS and elemental analysis. The mass spectrum of ethyl 2-(4-cyanophenyl)-2,5-dihydro-5-oxo-4-(phenylamino)furan-3-carboxylate (Table 3, entry 5) displayed the molecular ion peak at m/z 348, which is consistent with the proposed structure. The ^1H NMR spectrum of

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

Entry	Ar^1	Ar^2	R	Compound	Time (h)	Yield (%)[a]	Ref.
1	Ph	Ph	CH_3	**4a**	5	92	23
2	Ph	$4-Me–C_6H_4$	CH_3	**4b**	4	89	23
3	$4-Me–C_6H_4$	Ph	CH_3	**4c**	14	83	23
4	$4-Cl–C_6H_4$	Ph	CH_3	**4d**	13	72	23
5	$4-CN–C_6H_4$	Ph	CH_3CH_2	**4e**	5	93	This work
6	Ph	$4-F–C_6H_4$	CH_3	**4f**	9	70	24
7	Ph	$4-Cl–C_6H_4$	CH_3	**4g**	7	75	24
8	Ph	$3-NO_2–C_6H_4$	CH_3	**4h**	10	85	24
9	$4-OMe–C_6H_4$	Ph	CH_3	**4i**	9	65	24
10	$4-NO_2–C_6H_4$	Ph	CH_3	**4j**	2	90	24
11	Ph	Ph	CH_3CH_2	**4k**	2	90	21
12	Ph	$4-Me–C_6H_4$	CH_3CH_2	**4l**	3	80	21
13	$4-Me–C_6H_4$	Ph	CH_3CH_2	**4m**	4	88	21
14	$4-Cl–C_6H_4$	Ph	CH_3CH_2	**4n**	4	89	21
15	$4-OMe–C_6H_4$	Ph	CH_3CH_2	**4o**	3	80	21
16	1-Naphtyl	Ph	CH_3CH_2	**4p**	10	67	21

[a] Yields refer to those of the pure isolated products.

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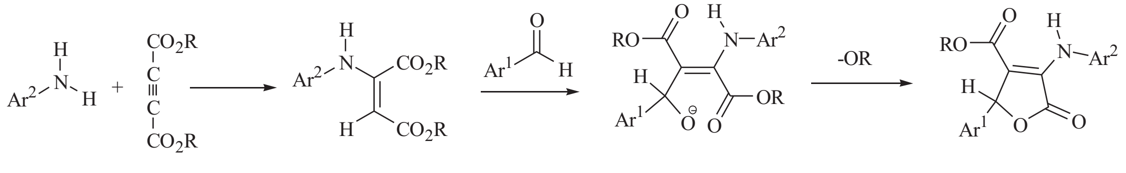

Scheme 2. The speculative proposed mechanism for the formation of furan-2(5*H*)-one derivatives.

this product, exhibited a triplet at δ 1.23 (J = 7.2 Hz) for the methyl protons and a quartet for the methylene protons of the carboxylate group at δ 4.24 and one sharp singlet arising from the benzylic proton at δ 5.82. The aromatic protons of the product were observed at δ 7.17–7.59. A broad singlet for the NH group at δ 9.03 indicated an intramolecular hydrogen bond formed with the vicinal carbonyl group. The ^{13}C NMR spectrum of this product showed 16 distinct resonances in agreement with the proposed structure. The IR spectrum contained one sharp peak at 3293 cm^{-1} for the NH group in the product.

A proposed mechanism for the formation of **4** is shown in Scheme 2.

4. Conclusion

In conclusion we have identified an efficient and simple one-pot reaction for the synthesis of furanone derivatives using tetra-*n*-butylammonium bisulfate as an economic catalyst in ethanol. This methodology has several advantages such as simplified workup procedures, mild conditions, and the use of green solvents.

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