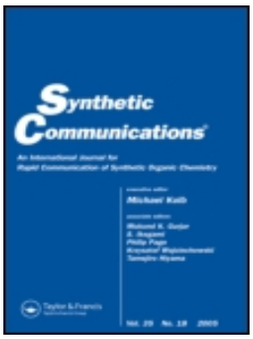

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Synthesis of 2-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-6,6-dimethyl-3-phenyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one Derivatives via Multicomponent Reaction

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SYNTHESIS OF 2-(4-HYDROXY-6-METHYL-2-OXO-2H-PYRAN-3-CARBONYL)-6,6-DIMETHYL-3-PHENYL-3,5,6,7-TETRAHYDRO-2H-BENZOFURAN-4-ONE DERIVATIVES VIA MULTICOMPONENT REACTION

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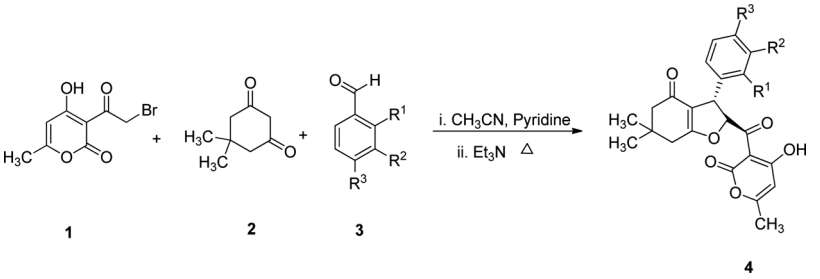
GRAPHICAL ABSTRACT



Abstract *A sequential one-pot, two-step reaction for an efficient preparation of 2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-6,6-dimethyl-3-phenyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one derivatives has been described. One-pot reaction of in situ–formed benzopyran-substituted pyridinium ylides with aromatic aldehydes and dimedone gives corresponding 2,3-dihydrofurans in good yields. The structures of all the newly synthesized compounds were confirmed from their analytical and spectral data.*

Keywords 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one; 2,3-dihydrofuran; dimedone; multicomponent reaction; pyridine

INTRODUCTION

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product.[1] The importance of multicomponent reactions in organic synthesis has been recognized, and considerable efforts have been focused on the design and development of one-pot procedures for the generation of libraries of heterocyclic compounds.[2,3] Wang et al. have reported a synthesis of 3,5,6,7-tetrahedro-2*H*-benzofuran-4-ones from reactions of phenacyl

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bromides, dimedone, and various substituted aromatic aldehydes.[4] The dihydrofuran moiety is a common structural feature of numerous natural products with great biological and pharmaceutical interest. Dihydrofuran derivatives are intensively studied. They are important subunits in many biologically active compounds[5] and are also important intermediates in organic synthesis.[6] 2,3-Dihydrofurans are subunits of a range of biologically active compounds[7] (e.g., aflatoxin B_1 and clerodin). Furthermore, they can be transformed with good stereoselectivity into an array of highly functionalized tetrahydrofurans.[8] The dihydrobenzo(naphtho)furans belong to an important class of heterocycles, principally because this ring system constitutes the core skeleton of an increasing number of pharmaceuticals and biologically active natural products. Remarkable examples of this class are the antileukemic agent megapodiol[9] and neolignan callislignan A, which exhibits antibacterial activity against *Staphylococcus aureus*.[10] On the basis of the aforementioned observations and as a part of our research program in the synthesis of novel heterocyclic systems,[11–13] we report in this article substituted dihydrofuran derivatives.

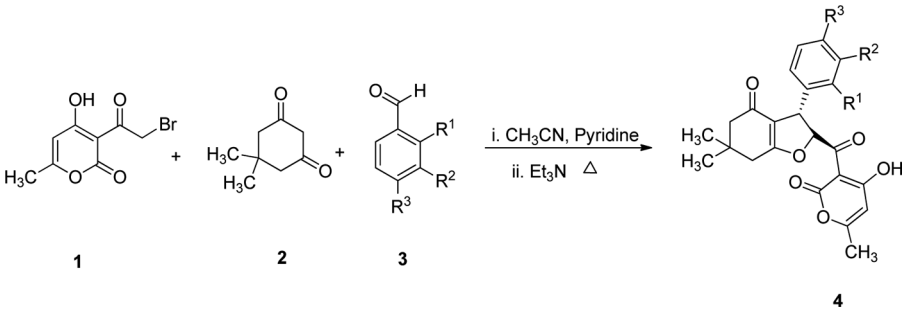
RESULTS AND DISCUSSION

Condensation of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one **1**, dimedone **2**, and substituted aromatic aldehyde **3** in acetonitrile under reflux for 9 h followed by addition of Et_3N and continuation of reflux gave fused system synthesis of 2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-6,6-dimethyl-3-phenyl-3,5,6,7-tetrahydro-2H-benzofuran-4-ones **4** (Scheme 1).

The results demonstrated that aromatic aldehyde carrying either electron-donating or electron-withdrawing group showed similar reactivity and reacted efficiently to yield the final products.

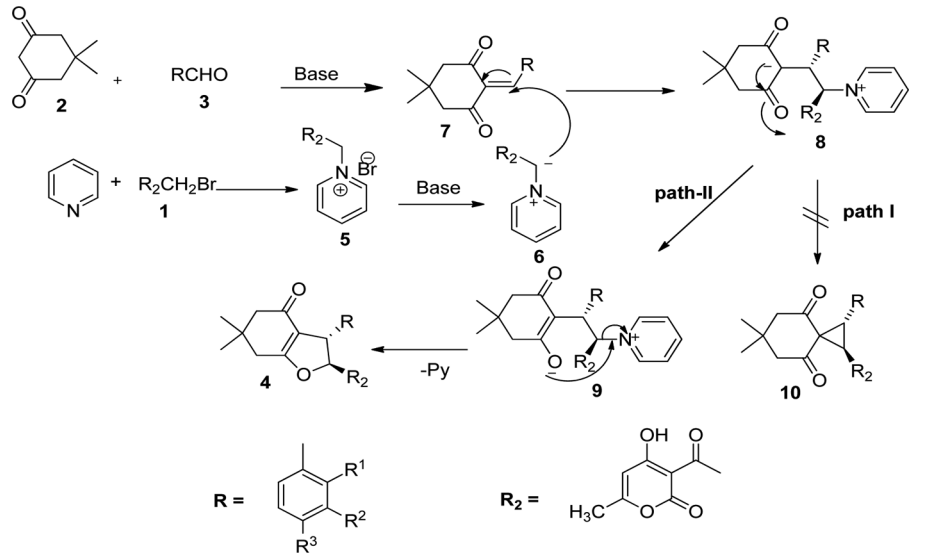
A plausible mechanism for the formation of product **4** is proposed in Scheme 2. The reaction is pyridinium ylide intermediate one-pot reaction. In the first step of the reaction dimedone **2** reacts with aromatic aldehyde **3** to give arylidene intermediate **7**.

The 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one **1** reacts with pyridine to give pyridinium salt **5**. In the second step of the reaction pyridinium ylide **6** reacts with arylidene intermediate **7** to give the zwitterionic salt **9** (path II). The zwitterionic salt **9** thus produced undergo cyclization to give trans-2,3-dihydrofurans **4**



1 2 3 4

Scheme 1. Synthesis of 2,3-dihydrofuran derivatives.



Scheme 2. Reaction mechanism of final compounds **4**.

by the removal of pyridine. In path I, there is a possibility for the formation cyclopropane **10** derivative. This involves intramolecular substitution of the carbanion displacing the pyridine, which is not observed here. In path II the more stable enolate replaces the pyridine to give the final product 2,3-dihydrofuran.

The structures of newly prepared compounds were confirmed from their analytical and spectral data.

The structure of **4** is clearly assigned as the *trans*-diastereomers from the analysis of the vicinal coupling constants of methine protons, which showed $J = 4$–7 Hz and from the literature.[14–16] For example, the infrared (IR) spectrum of compound **4a** displayed carbonyl at 1631, lactone carbonyl at 1720 cm^{-1}, and OH at 3436 cm^{-1}. The ^1H NMR spectrum of **4a** revealed singlet peaks at δ 1.04, 3.83, 3.87, and 6.15 for methyl, methoxy, and pyran protons. Two doublets at δ 4.45 ($J = 4.4$) and δ 4.94 ($J = 4.4$) assignable to the protons of furan (C_3−H), (C_2−H) respectively. The multiplet at δ 2.02–2.10 is assignable to the protons of methyl and methylene. Another multiplet at 2.51–2.55 is due to methylene protons. The multiplet at δ 6.69–6.83 is given to aromatic protons. The ^{13}C NMR spectrum of the product **4a** exhibited CH_3 carbon at δ 22.15, furan C-3 carbon at δ 36.26, and furan C-2 carbon at δ 88.16. Carbonyl carbon was exhibited at δ 192.12.

CONCLUSION

We have developed a simple, efficient, and one-pot, three-component synthesis of highly functionalized substituted dihydrofuran derivatives. The biological activity of these compounds is under investigation. The reaction conditions are mild, and the reaction gave excellent yields of products.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and used without further purification unless otherwise stated. Melting points were determined in open capillaries with a Cintex melting-point apparatus Mumbai, India, and were uncorrected. CHNS analysis was carried out by Carlo Erba EA 1108 automatic elemental analyzer (Italy). The purity of the compounds was checked using thin-layer chromatography (TLC) plates (Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 models). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as standard. Mass spectra (EI-MS) were determined on Perkin-Elmer instrument (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for the Synthesis of 3-(3,4-Dimethoxy-phenyl) -2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-carbonyl)-6,6-dimethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (4a)

In a typical experimental procedure, a mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1.1 mmol), dimedone (1 mmol), 3,4-dimethoxy benzaldehyde (1 mmol), and pyridine (2 mmol) in acetonitrile (10 mL) was refluxed for 3 h. To the reaction mixture triethylamine (2.1 mmol) was added and the reaction mixture was refluxed for the appropriate time (Table 1). After cooling to room temperature, the solvent was distilled and neutralized with diluted HCl. The solid obtained was filtered washed with water and recrystallized from ethanol to give excellent yields of products (Table 1). Yellow solid; mp 181–183 °C; IR (KBr) (υ_{max}/cm^{-1}): 3436, 1720, 1631; ^{1}H NMR (400 MHz, DMSO-d_6) 1.04 (s, 6H, $2 \times CH_3$), 2.02–2.10 (m, 5H, CH_2 & pyran CH_3), 2.51–2.55 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.87 (S, 3H, OCH_3), 4.45 (d, 1H, $J = 4.4$ Hz, furan C-3 proton), 4.94 (d, 1H, $J = 4.4$ Hz, furan C-2 proton), 6.15 (s, 1H, pyran proton), 6.70 (d, 1H, $J = 8.8$ Hz, ArH), 6.78 (d, 1H, $J = 8.0$ Hz, ArH), 6.83 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) 22.1, 27.9, 33.8, 36.2, 49.1, 51.6, 88.1, 99.8, 102.9, 110.7, 112.7, 116.1, 121.3, 136.1, 147.7, 150.0, 161.4, 163.8, 176.6, 185.3, 192.1, 198.8; Mass

Table 1. Synthesis of 2,3-dihydrobenzofuran derivatives **4a–l**

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)
1	H	OCH_3	OCH_3	**4a**	8	86
2	H	H	Br	**4b**	9	85
3	H	H	Cl	**4c**	9	87
4	H	H	OH	**4d**	10	87
5	H	OCH_3	OH	**4e**	10	75
6	H	H	NO2	**4f**	9	70
7	OCH_3	OCH_3	OCH_3	**4g**	9	76
8	OH	OCH_3	H	**4h**	10	69
9	H	H	OCH_3	**4i**	9	82
10	2-Hydroxynaphthaldehyde			**4j**	10	78
11	OH	H	H	**4k**	10	73
12	H	NO2	H	**4l**	10	71

spectrum m/z: 455 (M + H). Anal. calcd. for $C_{25}H_{26}O_8$: C, 66.05; H, 5.76. Found: C, 66.17; H, 5.68.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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