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Note

One-pot synthesis of coumarin substituted dihydrofurans

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A sequential one-pot two-step tandem reaction for an efficient synthesis of 2,3-dihydrofurans substituted with 2*H*-benzopyrans has been developed. 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 the final compounds have been assigned as *trans*-2,3-dihydrofurans on the basis of their NMR spectra.

Keywords: 3-(2-Bromoacetyl)coumarins, *trans*-2,3-dihydrofurans, pyridinum ylides, one-pot reaction

Multi-component reactions (MCRs) play an important role in combinatorial chemistry, in which several different starting materials can be combined in one reaction to give a highly complex product. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation[1-4]. They offer significant advantages over conventional linear synthesis by reducing time and cost by saving energy and raw materials, thus providing both economic and environmental benefits. At the same time, diversity can be achieved from building up libraries by simply varying each component[5-8].

Dihydrofurans are an integral part of many natural and unnatural products which display a wide range of biological activities[9-13]. In the literature a number of synthetic methods appeared for the synthesis of dihydrofurans. The most common methods for the synthesis of dihydrofurans are oxidative coupling reactions which are catalyzed by metal salts such as manganese(III) acetate and cerium(IV) ammonium nitrate[14-17]. Aqueous iodine(III)-mediated stereoselective oxidative cyclization[18], diastereo- and enantioselective copper-catalyzed [4+1] cycloadditions of enones with diazo compounds using a planar-chiral bipyridine ligand[19], have also attracted much attention. Pyridinium ylides also play a major role in the synthesis of dihydrofurans[20].

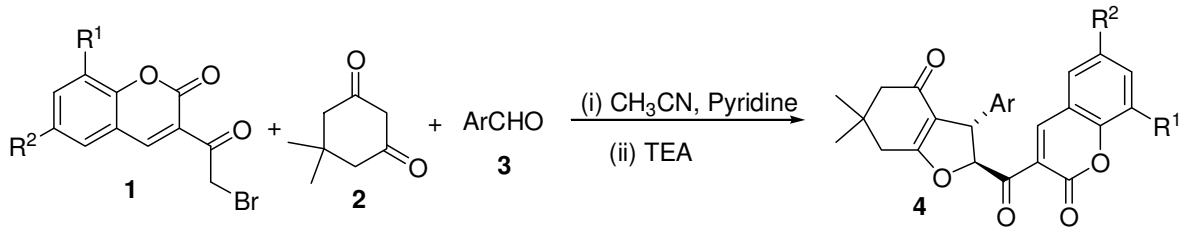
Coumarins are an important class of compounds that exist widely in nature and find numerous applications in medicine[21], and as fluorescent indicators[22]. A number of coumarin derivatives possess interesting biological activity, including anticancer, antifungal, and anti-HIV activities[23]. Coumarin derivatives and iminocoumarins have been reported to function as protein tyrosine kinase (PTK) inhibitors that are most valuable for the treatment of diseases involving excess cell proliferation as well as tumor forming processes[24].

Based on the above observations and in continuation of the earlier work on the synthesis of novel heterocyclic systems[25-27], herein is reported a new method for the synthesis of 2,3-dihydrofuran derivatives substituted with benzopyran-2-ones based on a pyridinium ylide assisted three-component tandem reaction.

Results and Discussion

Chang and Tsai[20] have developed a new method for the synthesis of 2,3-dihydro furans starting from enones and pyridinum salts. In the present study, a one-pot method for the synthesis of for the synthesis of benzopyran-2-one substituted 2,3-dihydrofurans has been developed using readily available starting materials 3-(2-bromoacetyl)coumarin, pyridine, cyclic 1,3-dicarbonyl compound and aromatic aldehyde. Reaction of 3-(2-bromoacetyl)coumarin, pyridine, dimedone aromatic aldehyde and triethylamine in acetonitrile at RT for about 12 hr gave fused system 3-(3-aryl-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydro-benzofuran-2-carbonyl)-chromen-2-one with good yields. This is a pyridinium ylide mediated one pot reaction. In the first step of the reaction, 3-(2-bromoacetyl)coumarin reacts with pyridine to give pyridinium ylide, and the dimedone reacts with aromatic aldehyde to give aryledene intermediate *via* Knoevengel reaction. In the second step, pyridinium ylide undergoes reaction with aryledene intermediate to give the zwitterionic salt[28]. Further, the zwitterionic salt cyclizes to *trans*-2,3-dihydrofuran by the elimination of pyridine (**Scheme I**).

The structures of the prepared compounds were confirmed from their spectral and elemental analysis data. The structure of **4** is clearly assigned as the



4a: R^1=R^2=H, Ar=phenyl; **4b**: R^1=R^2=H, Ar=*p*-tolyl; **4c**: R^1=R^2=H, Ar=4-methoxy-phenyl; **4d**: R^1=R^2=H, Ar=3,4-dimethoxyphenyl; **4e**: R^1=R^2=H, Ar=4-dimethylamino; **4f**: 5,6-benzoanalouge of **4a** with Ar=phenyl; **4g**: 5,6-benzoanalouge of **4a** with Ar=4-methoxyphenyl; **4h**: R^1=R^2=Br, Ar=*p*-tolyl; **4i**: R^1=R^2=Br, Ar=4-methoxyphenyl; **4j**: R^1=R^2=Br, Ar=4-chlorophenyl; **4k**: R^1=R^2=Br, Ar=phenyl.

Scheme I — Synthesis of *trans*-2,3-dihydrofurans substituted with benzopyran-2-ones

trans-diastereomer from the analysis of the vicinal coupling constants of methine protons, which showed $J_{2,3}$=4-7 Hz, and from the literature[20,29-32]. For example, in the ^{1}H NMR spectra of **4a** the two protons at the 2,3-position of dihydrofuran ring show two doublets at δ 4.45 and 5.03 with vicinal coupling constant *J*=4.8 Hz and *J*=4.4 Hz respectively. Similarly, in the ^{1}H NMR spectra of **4j** the two methine protons were observed at δ 4.28 and 5.03 as doublets with coupling constant values *J*=5.2 Hz and 5.6 Hz respectively. This clearly indicates that the two methine protons are *trans* to each other. For all the synthesized compounds the coumarin 4th proton was observed between δ 9.6-10.1. Similarly, the ^{13}C NMR of compound **4a** showed three signals at δ 176.4, 190.8 and 192.4 for the carbons of three carbonyls which were present in the compound. The two methine carbons were observed at δ 46.8 and 50.6 respectively.

In conclusion, a one-pot reaction for the synthesis of *trans*-2,3-dihydrofurans has been developed using readily available starting materials. These highly functionalized derivatives may be of interest for pharmaceutical applications and are yet to be explored.

Experimental Section

All the reagents and solvents were pure, and purchased from commercial sources and used as received unless otherwise stated. 3-(2-Bromoacetyl) coumarins[33] were prepared according to the literature procedure. Melting points were determined in open capillaries with a Cintex (Mumbai, India) melting point apparatus, and are uncorrected. CHNS analysis was carried out on a Carlo Erba EA 1108 automatic elemental analyzer. The homogeneity of the compounds was checked by TLC (E. Merck, Mumbai, India). IR spectra (KBr) were recorded on a Bruker Optics (Model: Tensor 27) spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer (δ, ppm) using TMS as standard. Mass spectra (EI-MS) were recorded on a Perkin-Elmer instrument (SCIEX API- 2000, ESI) at 12.5 eV.

General procedure for the synthesis of 3-(3-aryl-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydro-benzofuran-2-carbonyl)-chromen-2-ones, 4a-k

A mixture of arylaldehyde (1.0 mmol), dimedone (1.0 mmol), 3-(2-bromoacetyl)coumarin (1.1 mmol) and pyridine (2.0 mmol) in acetonitrile (10 mL) was stirred at RT for about 2 hr. Triethylamine (2.1 mmol) was added to the reaction mixture and reaction was stirred at RT for about 8-9 hr. The solvent was distilled off and the resulting mixture was neutralized with dil. HCl. The solid obtained was filtered, washed with water and purified by recrystallization from ethanol to give the pure product.

3-(6,6-Dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl)-chromen-2-one, 4a

Yield 74%; m.p. 120-22°C; colour: light yellow; IR (KBr): 3062, 1729, 1699, 1645, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.21-2.22 (m, 2H, CH_2), 2.50-2.54 (m, 2H, CH_2), 4.45 (d, 1H, *J*=4.8Hz, CH), 5.03 (d, 1H, *J*=4.4Hz, CH), 7.09-7.70 (m, 7H, ArH), 7.88 (m, 1H, ArH), 8.07 (m, 1H, ArH), 10.03 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35. Found: C, 75.30; H, 5.31%.

3-(6,6-Dimethyl-4-oxo-3-*p*-tolyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl)-chromen-2-one, 4b

Yield 69%; m.p. 158-60°C; colour: light yellow; IR (KBr): 3027, 1731, 1694, 1640, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.18-

2.20 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.53-2.56 (m, 2H, CH_2), 4.32 (d, 1H, *J*=4.8Hz, CH), 4.99 (d, 1H, *J*=4.4Hz, CH), 7.12-7.16 (m, 4H, ArH), 7.38-7.40 (m, 2H, ArH), 7.69 (d, 2H, *J*=7.6Hz, ArH), 9.96 (s, 1H, C_4 of coumarin); ^{13}C NMR (DMSO-d_6): δ 20.6, 27.8, 28.1, 33.9, 36.6, 46.8, 50.6, 92.3, 114.4, 116.2, 118.1, 121.7, 125.0, 127.0, 128.4, 130.8, 134.9, 135.8, 139.1, 149.3, 154.7, 158.0, 176.4, 190.8, 192.4; ESI-MS: *m/z* 429 $[M+H]^+$. Anal. Calcd for $C_{27}H_{24}O_5$: C, 75.68; H, 5.65. Found: C, 75.64; H, 5.61%.

3-[3-(4-Methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-chromen-2-one, 4c

Yield 73%; m.p. 118-20°C; colour: light yellow; IR (KBr): 3061, 1731, 1702, 1640, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 2.20-2.22 (m, 2H, CH_2), 2.50-2.59 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.48 (d, 1H, *J*=4.8Hz, CH), 5.04 (d, 1H, *J*=4.4Hz, CH), 6.86 (d, 2H, *J*=8.8Hz, ArH), 7.01 (d, 2H, *J*=8.4Hz, ArH), 7.21 (d, 2H, *J*=8.8Hz, ArH), 7.84 (d, 2H, *J*=8.8Hz, ArH), 9.89 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.91; H, 5.40%.

3-[3-(3,4-Dimethoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-chromen-2-one, 4d

Yield 78%; m.p. 154-56°C; colour: light yellow; IR (KBr): 3068, 1730, 1702, 1638, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.15 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.20-2.23 (m, 2H, CH_2), 2.48-2.53 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.46 (d, 1H, *J*=4.8Hz, CH), 4.98 (d, 1H, *J*=4.4Hz, CH), 6.80 (d, 2H, *J*=7.2Hz, ArH), 7.28-7.42 (m, 3H, ArH), 7.70 (m, 2H, ArH), 9.86 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{28}H_{26}O_7$: C, 70.87; H, 5.52. Found: C, 70.81; H, 5.48%.

3-[3-(4-Dimethylaminophenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-chromen-2-one, 4e

Yield 70%; m.p. 160-62°C; colour: light yellow; IR (KBr): 3057, 1729, 1700, 1650, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H, CH_3), 2.04-2.09 (m, 2H, CH_2), 2.22-2.25 (m, 2H, CH_2), 3.09 (s, 6H, N,N-dimethyl), 4.34 (d, 1H, *J*=4.8Hz, CH), 4.98 (d, 1H, *J*=4.4Hz, CH), 6.70 (d, 2H, *J*=8.8Hz, ArH), 7.73-7.90 (m, 6H, ArH), 9.74 (s, 1H, C_4 of coumarin); ESI-MS: *m/z* 458 $[M+H]^+$. Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.47; H, 5.91; N, 3.01%.

2-(6,6-Dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl)-benzo[*f*]chromen-3-one, 4f

Yield 72%; m.p. 165-67°C; colour: light yellow; IR (KBr): 3060, 1726, 1701, 1624, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.19-2.28 (m, 2H, CH_2), 2.48-2.51 (m, 2H, CH_2), 4.53 (d, 1H, *J*=4.4Hz, CH), 5.01 (d, 1H, *J*=4.4Hz, CH), 7.21-7.90 (m, 11H, ArH), 10.02 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{30}H_{24}O_5$: C, 77.57; H, 5.21. Found: C, 77.51; H, 5.18%.

2-[3-(4-Methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-benzo[*f*]chromen-3-one, 4g

Yield 75%; m.p. 130-32°C; colour: light yellow; IR (KBr): 3066, 1731, 1702, 1640, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 2.20-2.24 (m, 2H, CH_2), 2.47-2.53 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.34 (d, 1H, *J*=4.8Hz, CH), 4.96 (d, 1H, *J*=4.4Hz, CH), 6.83-7.85 (m, 10H, ArH), 9.90 (s, 1H, C_4 of coumarin); ESI-MS: *m/z* 495 $[M+H]^+$. Anal. Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.22; H, 5.25%.

6,8-Dibromo-3-(6,6-dimethyl-4-oxo-3-*p*-tolyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl)-chromen-2-one, 4h

Yield 80%; m.p. 140-42°C; colour: light yellow; IR (KBr): 3069, 1725, 1703, 1644, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.12-2.40 (m, 4H, CH_2), 2.44 (s, 3H, CH_3), 4.22 (d, 1H, *J*=4.8Hz, CH), 4.88 (d, 1H, *J*=4.8Hz, CH), 7.03-7.07 (m, 2H, ArH), 7.32-7.34 (d, 2H, *J*=8.8Hz, ArH), 7.77-7.79 (m, 2H, ArH), 9.96 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{27}H_{22}Br_2O_5$: C, 55.31; H, 3.78. Found: C, 55.29; H, 3.74%.

6,8-Dibromo-3-[3-(4-methoxyphenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-chromen-2-one, 4i

Yield 77%; m.p. 136-38°C; colour: light yellow; IR (KBr): 3070, 1726, 1682, 1644, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.19-2.30 (m, 2H, CH_2), 2.44-2.56 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.22 (d, 1H, *J*=4.8Hz, CH), 4.84 (d, 1H, *J*=4.8Hz, CH), 6.82-7.10 (m, 4H, ArH), 7.83-7.85 (m, 2H, ArH), 9.89 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{27}H_{22}Br_2O_6$: C, 53.84; H, 3.68. Found: C, 53.80; H, 3.62%.

6,8-Dibromo-3-[3-(4-chlorophenyl)-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl]-chromen-2-one, 4j

Yield 80%; m.p. 125-27°C; colour: light yellow; IR (KBr): 3029, 1722, 1704, 1644, 1599 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.29-2.44 (m, 4H, $2CH_2$), 4.46 (d, 1H, *J*=5.2Hz, CH), 4.99 (d, 1H, *J*=5.6Hz, CH), 7.09-7.34 (m, 4H, ArH), 7.76-7.78 (m, 2H, ArH), 9.96 (s, 1H, C_4 of coumarin). Anal. Calcd for $C_{26}H_{19}Br_2ClO_5$: C, 51.47; H, 3.16. Found: C, 51.42; H, 3.12%.

6,8-Dibromo-3-(6,6-dimethyl-4-oxo-3-phenyl-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl)-chromen-2-one, 4k

Yield 76%; m.p. 108-10°C; colour: light yellow; IR (KBr): 3066, 1730, 1700, 1645, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.20-2.30 (m, 2H, CH_2), 2.45-2.55 (m, 2H, CH_2), 4.28 (d, 1H, *J*=5.2Hz, CH), 5.03 (d, 1H, *J*=5.6Hz, CH), 7.52-7.57 (m, 5H, ArH), 7.88-7.90 (m, 2H, ArH), 10.03 (s, 1H, C_4 of coumarin); ^{13}C NMR (DMSO-d_6): δ 28.2, 28.8, 33.8, 36.5, 47.0, 50.0, 93.1, 110.6, 116.2, 126.7, 126.9, 128.3, 128.5, 128.6, 128.7, 129.1, 129.4, 133.2, 134.5, 141.7, 146.2, 165.7, 176.1, 193.1. Anal. Calcd for $C_{26}H_{20}Br_2O_5$: C, 54.57; H, 3.52. Found: C, 54.51; H, 3.47%.

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