# Synthesis of a series of novel 2,3-dihydrofurano-γ-lactone derivatives using DABCO as catalyst in an aqueous medium

**Maryam Salari[a], Mohammad H. Mosslemin[a*] and Alireza Hassanabadi[b]**

[a]*Department of Chemistry, Yazd Branch, Islamic Azad University, Yazd, Iran*
[b]*Department of Chemistry, Zahedan Branch, Islamic Azad University, Zahedan, Iran*

A one-pot, green and efficient synthesis of twelve *trans*-2-(4-chlorobenzoyl)-3-aryl-3,6-dihydrofuro[3,4-*b*]furan-4-ones has been achieved *via* a three-component condensation of 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide with furan-2,4-dione and an araldehyde in the presence of catalytic amounts of 1,4-diaza-bicyclo[2.2.2]octane (DABCO) in water under reflux conditions.

**Keywords:** 2,3-dihydrofurano-γ-lactone derivatives, aryl aldehydes, 4-chlorophenacyl bromide, furan-2,4-dione, DABCO, green chemistry

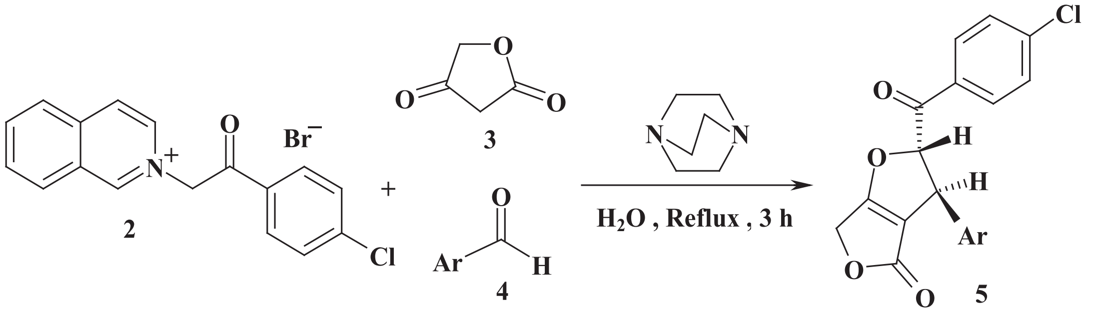
Multi-component reactions are useful and efficient methods in organic synthesis. The major advantages of these reactions are a single purification step, higher yields than stepwise assembly, the use of simple and diverse precursors to construct complex molecules and the use of only a single promoter or catalyst. Thus, the development of new multi-component reactions is a popular area of research in organic chemistry and from a green chemistry point of view.[1–3] Dihydrofurans are important heterocycles commonly found in a large variety of naturally occurring substances.[4] The development of new and efficient methods for their synthesis remains an area of current interest and a whole series of new synthetic methods have appeared in the literature.[5–8] The synthesis of dihydrofurans was reported by reaction of an aryl aldehyde, a cyclic 1,3-diketone, and 2-bromo-1-phenylethanone or 4-nitrobenzyl bromide in pyridine in the presence of 10 mol% sodium hydroxide in refluxing aqueous solution.[9] Recently, organic reactions in aqueous media have attracted a great deal of attention[10] as a result of increasing interest in the concepts of sustainability and green chemistry.[11] Also the latter synthesis used a procedure first described by Wang *et* al.[12] and Khan *et* al.[9], in which they synthesised a series of dihydrofurans *via* the pyridine-catalysed reaction of phenacyl bromides with a series of aromatic aldehydes and 4-hydroxycoumarin in presence of catalytic amounts of NaOH or $Et_3N$. Although many of the reported methods are effective, some of them suffer from disadvantages such as harsh reaction conditions, use of hazardous solvents, long reaction times, complex work-ups and purification procedures, high catalyst loadings and moderate yields. Therefore, the development of a simple, mild and efficient method is still needed. In the present work, we used 1,4-diaza-bicyclo[2.2.2]octane (DABCO) as an efficient catalyst to overcome these limitations.

DABCO has received considerable attention as an inexpensive, eco-friendly, highly reactive, easy to handle and non-toxic basic catalyst[13] for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The reactions are environmentally friendly and the catalyst can be recycled in some cases.[14] In continuation of our previous work on the synthesis of heterocyclic compounds[15,16] we decided to investigate the reaction of 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide **2** with furan-2,4-dione **3** and an aromatic aldehyde **4** in the presence of catalytic amounts of DABCO in water under reflux conditions (Scheme 1).

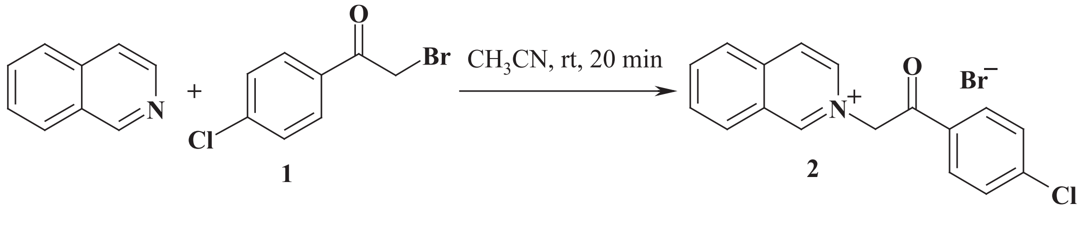
## Results and discussion

Using a previously reported method,[17] we prepared in nearly quantitative yield one of the starting materials, 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide **2** by treatment of isoquinoline with 4-chlorophenacyl bromide **1** in acetonitrile (Scheme 2).

As a test run, a three-component reaction of 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide



Scheme 1



Scheme 2

---

* Correspondent. E-mail: mhmosslemin@iauyazd.ac.ir

**2** with furan-2,4-dione **3** and benzaldehyde **4** (Ar = Ph) in the presence of catalytic amounts of DABCO in refluxing water gave the expected product **5a** (Ar = Ph) in an excellent yield of 92% (Table 1). Then 11 other araldehydes **4** (Ar = various) were then employed to prepare the corresponding analogues **5b–l** (Ar = various) (Table 1).

Yields were uniformly high, 90–96%, for both electron-donating and electron-withdrawing groups. The structures of compounds **5a–l** were deduced from their elemental analyses and their IR, $^1$H NMR and $^{13}$C NMR spectra. The mass spectra of compounds **5a–l** were fairly similar and displayed molecular ion peaks. In the $^1$H NMR spectra, the two protons at the 2,3-position of the dihydrofuran ring displayed two doublets at 4.32 and 6.08 ppm with a vicinal coupling constant $J$ = 5.2 Hz. It has been documented that in *cis*-2,3-dihydrofurans, the vicinal coupling constant of the two methine protons is 7–10 Hz, while in *trans*-2,3-dihydrofurans, the vicinal coupling constant is 2.8–6.0 Hz. Therefore, we concluded that the thermodynamically stable *trans* isomers of the 2,3-dihydrofuran derivatives were formed.[18]

**Table 1** Yields of a series of 2,3-dihydrofurano-γ-lactone derivatives **5** (Ar = various) prepared from 2-[2-(4-chlorophenyl)-2-oxoethyl)] isoquinolinium bromide **2**, furan-2,4-dione **3** and an araldehyde **4** (Ar = various) (Scheme 1)[a]

| Product | Ar | Yield (%)[b] | M.p. (°C) |
|---|---|---|---|
| **5a** | $C_6H_5$ | 92 | 142–144 |
| **5b** | 2-$O_2NC_6H_4$ | 93 | 143–145 |
| **5c** | 4-$O_2NC_6H_4$ | 95 | 148–150 |
| **5d** | 2-$ClC_6H_4$ | 90 | 168–170 |
| **5e** | 4-$ClC_6H_4$ | 92 | 171–173 |
| **5f** | 2-$FC_6H_4$ | 94 | 140–142 |
| **5g** | 4-$CH_3OC_6H_4$ | 88 | 165–167 |
| **5h** | 4-$FC_6H_4$ | 96 | 174–176 |
| **5i** | 4-Cl-3-$O_2NC_6H_3$ | 91 | 177–179 |
| **5j** | 4-$NCC_6H_4$ | 92 | 167–169 |
| **5k** | 4-$CH_3C_6H_4$ | 90 | 170–172 |
| **5l** | 4-$BrC_6H_4$ | 93 | 163–165 |

[a] Reaction conditions: DABCO (15 mol%) was added to a stirred mixture of 2-[2-(4-chlorophenyl)-2oxoethyl)]isoquinolinium bromide **2** (1 mmol), furan-2,4-dione **3** (1 mmol) and an araldehyde **4** (Ar = various) (1 mmol) in water (10 mL) and the mixture heated at reflux for 3 h.

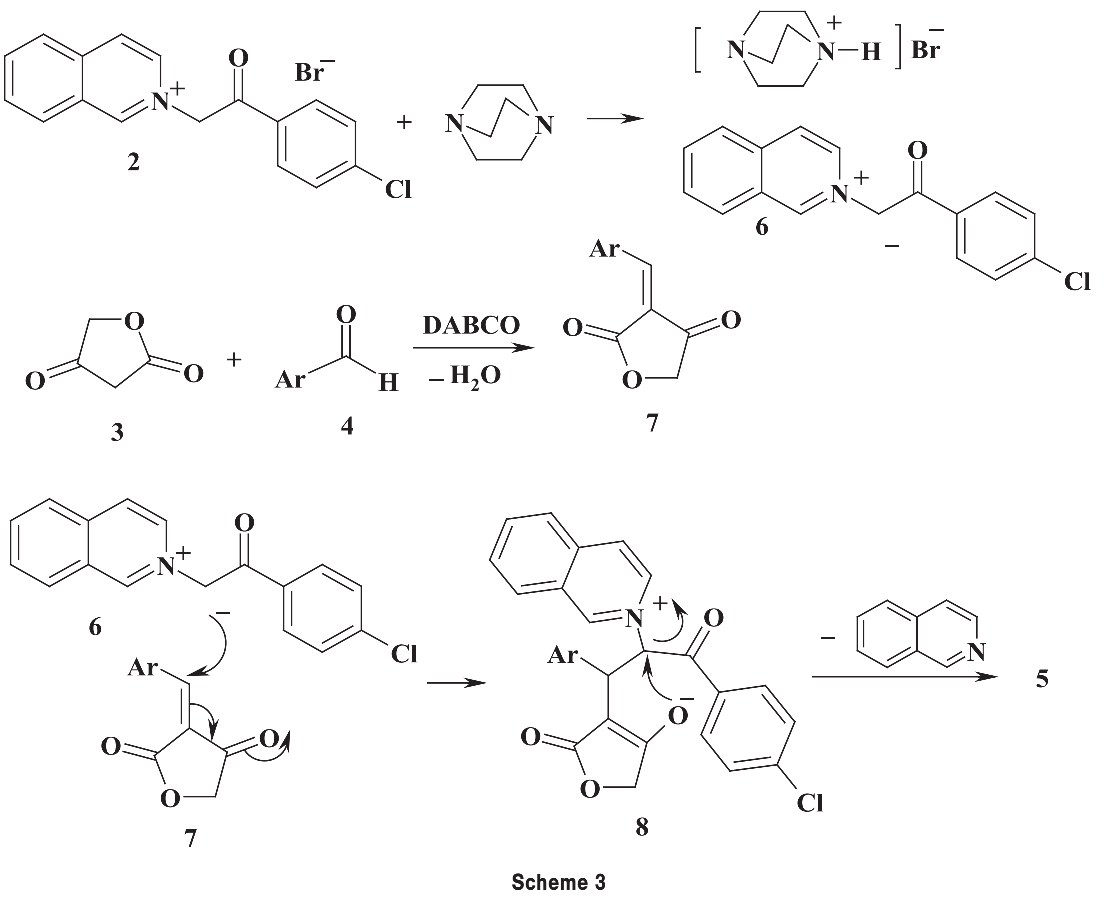
[b] Yields refer to the pure isolated products.

A proposed mechanism for this reaction is shown in Scheme 3. The formation of the product can be explained as follows. The 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide **2** undergoes deprotonation in the presence of aqueous DABCO to give the reactive isoquinolinium ylide **6**. The furan-2,4-dione **3** reacts with aromatic aldehyde **4** in the presence of DABCO to give the Knoevenagel product **7**. Compound **7** reacts instantly with the isoquinolinium ylide **6** to form the zwitterionic intermediate **8**, which undergoes cyclisation with the elimination of isoquinoline to give **5**.

In summary, here we report a simple and efficient one-pot condensation of 2-[2-(4-chlorophenyl)-2-oxoethyl)] isoquinolinium bromide with furan-2,4-dione and an aromatic aldehyde in the presence of catalytic amounts of DABCO in water under reflux conditions to yield 2,3-dihydrofurano-γ-lactone derivatives. The advantages of this method are simply available starting materials, short reaction times, easy and clean work-up and excellent yields.

## Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT



Scheme 3

8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Bruker DRX-400 MHz spectrometer ($^1$H NMR at 400 Hz, $^{13}$C NMR at 100 Hz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in Hz. 2-[2-(4-Chlorophenyl)-2-oxoethyl)] isoquinolinium bromide **2** was prepared by a literature method.[17] Others chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

### *Synthesis of 2,3-dihydrofurano-γ-lactone derivatives; general procedure*

DABCO (15 mol %) in $H_2O$ (5 mL) was added to a magnetically stirred solution of 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide (1 mmol), furan-2,4-dione (1 mmol) and an aryl aldehyde (1 mmol) in $H_2O$ (10 mL). The mixture was then refluxed for 3 h. The progress of the reaction was monitored by TLC. After cooling to r.t., the solid product was filtered and recrystallised from ethanol to afford the pure products **5a**–**l**.

Trans*-2-(4-chlorobenzoyl)-3-phenyl-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5a**): White powder; m.p. 142–144 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2924, 2853, 1718, 1645, 1448, 1406, 1035, 754, 575; $^1$H NMR: δ 4.32 (d, *J* = 5.2 Hz, 1H, CH), 4.82 (s, 2H, $CH_2$), 6.08 (d, *J* = 5.2 Hz, 1H, CH), 7.27–8.04 (m, 9H, arom); $^{13}$C NMR: δ 38.5, 66.3, 84.7, 99.1, 1258, 127.8, 128.7, 130.2, 132.4, 138.5, 140.6, 168.2, 174.6, 188.3; MS *m/z* (%): 340 (5). Anal. calcd for $C_{19}H_{13}ClO_4$: C, 66.97; H, 3.85; found: C, 67.12; H, 3.72%.

Trans*-2-(4-chlorobenzoyl)-3-(2-nitrophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5b**): White powder; m.p. 143–145 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2924, 2839, 1728, 1644, 1512, 1415, 1026, 745, 570; $^1$H NMR: δ 4.56 (d, *J* = 5.1 Hz, CH, 1H,), 4.85 (s, $CH_2$, $OCH_2$), 6.12 (d, *J* = 5.1 Hz CH, 1H), 7.71–8.07 (m, 8H, arom); $^{13}$C NMR: δ 33.9, 66.3, 83.8, 99.1, 124.3, 126.8, 128.3, 128.6, 130.2, 132.3, 134.4, 138.7, 148.2, 170.8, 174.4, 186.4; MS *m/z* (%): 485 (8). Anal. calcd for $C_{19}H_{12}ClNO_6$: C, 59.16; H, 3.14; N, 3.63; found: C, 59.28; H, 3.29; N, 3.80%.

Trans*-2-(4-chlorobenzoyl)-3-(4-nitrophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5c**): White powder; m.p. 148–150 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2933, 2856, 1726, 1642, 1523, 1413, 747, 575; $^1$H NMR: δ 4.36 (d, *J* = 4.8 Hz, CH, 1H), 4.92 (s, $CH_2$, $OCH_2$), 6.08 (d, *J* = 4.8 Hz, CH, 1H), 7.58–8.42 (m, 8H, arom); $^{13}$C NMR: δ 38.7, 66.3, 84.6, 99.1, 123.8, 128.6, 130.2, 132.3, 138.7, 145.1, 146.7, 170.8, 174.4, 186.4; MS *m/z* (%): 385 (6). Anal. calcd for $C_{19}H_{12}ClNO_6$: C, 59.16; H, 3.14; N, 3.63; found: C, 59.30; H, 3.32; N, 3.77%.

Trans*-2-(4-chlorobenzoyl)-3-(2-chlorophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5d**): White powder; m.p. 168–170 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2924, 2843, 1725, 1644, 1450, 1402, 1027, 754, 575; $^1$H NMR: δ 4.32 (d, *J* = 5.2 Hz, CH, 1H), 4.75 (s, $CH_2$, $OCH_2$), 5.98 (d, *J* = 5.2 Hz, CH, 1H), 7.16–8.06 (m, 8H, arom); $^{13}$C NMR: δ 33.4, 66.1, 84.5, 99.1, 126.6, 127.3, 128.8, 129.1, 130.2, 132.3, 133.1, 138.2, 138.6, 170.5, 174.6, 186.3; MS *m/z* (%): 374 (9). Anal. calcd for $C_{19}H_{12}Cl_2O_4$: C, 60.82; H, 3.22; found: C, 70.00; H, 3.39%.

Trans*-2-(4-chlorobenzoyl)-3-(4-chlorophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5e**): White powder; m.p. 171–173 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2934, 2826, 1723, 1646, 1414, 1024, 758, 536; $^1$H NMR: δ 3.91 (d, *J* = 5.2 Hz, CH, 1H), 4.92 (s, $CH_2$, $OCH_2$), 6.52 (d, *J* = 5.2 Hz, CH, 1H), 7.30–8.02 (m, 8H, arom); $^{13}$C NMR: δ 38.6, 66.4, 84.4, 99.1, 128.7, 129.1, 130.2, 131.5, 132.3, 138.7, 139.6, 170.8, 174.4, 186.4; MS *m/z* (%): 374 (7). Anal. calcd for $C_{19}H_{12}Cl_2O_4$: C, 60.82; H, 3.22; found: C, 60.97; H, 3.35%.

Trans*-2-(4-chlorobenzoyl)-3-(2-fluorophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5f**): White powder; m.p. 140–142 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2930, 2855, 1714, 1644, 1452, 1402, 1026, 755, 574; $^1$H NMR: δ 4.34 (d, *J* = 5.2 Hz, CH, 1H), 4.92 (s, $CH_2$, $OCH_2$), 6.10 (d, *J* = 5.2 Hz, CH, 1H), 7.07–8.10 (m, 8H, arom); $^{13}$C NMR: δ 31.7, 66.1, 84.5, 99.1, 115.3, 124.2, 127.2, 127.5, 128.7, 129.3, 132.3, 138.7, 160.2, 170.8, 174.4, 186.4; MS *m/z* (%): 358 (5). Anal. calcd for $C_{19}H_{12}ClFO_4$: C, 63.61; H, 3.37; found: C, 63.75; H, 3.50%.

Trans*-2-(4-chlorobenzoyl)-3-(4-methoxyphenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5g**): White powder; m.p. 165–167 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2924, 2843, 1728, 1694, 1642, 1617, 1514, 1418, 1258, 1210, 1235, 1176, 1080, 1022, 935; $^1$H NMR: δ 3.81(s, 3H, $OCH_3$), 4.34 (d, *J* = 4.8 Hz, 1H), 4.92 (s, 2H, $OCH_2$), 6.09 (d, *J* = 4.8 Hz, 1H), 6.85–8.05 (m, 8H, arom); $^{13}$C NMR: δ 38.6, 55.4, 66.2, 84.8, 99.1, 114.2, 128.6, 128.8, 130.2, 132.3, 132.9, 138.7, 157.6, 170.2, 174.7, 186.5; MS *m/z* (%): 370 (7). Anal. calcd for $C_{20}H_{15}ClO_5$: C, 64.79; H, 4.08; found: C, 64.95; H, 4.21%.

Trans*-2-(4-chlorobenzoyl)-3-(4-fluorophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5h**): White powder, m.p. 174–176 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2923, 2836, 1724, 1646, 1412, 1024, 754, 534; $^1$H NMR: δ 4.24 (d, *J* = 5.0 Hz, CH, 1H), 4.86 (s, 2H, $OCH_2$), 6.10 (d, *J* = 5.0 Hz, CH, 1H,), 7.16–8.06 (m, 8H, arom); $^{13}$C NMR: δ 39.2, 66.3, 84.6, 99.1, 115.4, 128.6, 129.8, 130.2, 132.3, 136.2, 138.7, 160.4, 170.9, 175.8, 187.7; MS *m/z* (%): 358 (3). Anal. calcd for $C_{19}H_{12}ClFO_4$: C, 63.61; H, 3.37; found: C, 63.78; H, 3.52%.

Trans*-2-(4-chlorobenzoyl)-3-(4-chloro-3-nitrophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5i**): White powder; m.p. 176–178 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2932, 2854, 1727, 1647, 1524, 1410, 747, 578; $^1$H NMR: δ 4.40 (d, *J* = 4.8 Hz, CH, 1H,), 4.89 (s, 2H, $OCH_2$), 6.12 (d, *J* = 4.8 Hz CH, 1H), 7.59–8.32 (m, 7H, arom); $^{13}$C NMR: δ 37.5, 66.7, 84.3, 99.4, 125.1, 125.6, 128.6, 130.2, 132.3, 132.8, 135.2, 138.7, 139.6, 147.5, 170.2, 174.6, 186.8; MS *m/z* (%): 419 (6). Anal. calcd for $C_{19}H_{11}Cl_2NO_6$: C, 54.31; H, 2.64; N, 3.33; found: C, 54.45; H, 2.80; N, 3.47%.

Trans*-2-(4-chlorobenzoyl)-4-oxo-2,3,4,6-tetrahydrofuro[3,4-b] furan-3-yl)benzonitrile* (**5j**): White powder; m.p. 167–169 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2935, 2854, 1725, 1645, 1526, 1412, 747, 575; $^1$H NMR: δ 4.35 (d, *J* = 4.8 Hz, CH, 1H), 4.94 (s, 2H, $OCH_2$), 6.08 (d, *J* = 4.8 Hz, CH, 1H), 7.60–8.07 (m, 8H, arom); $^{13}$C NMR: δ 38.7, 66.3, 84.8, 99.2, 109.8, 119.2, 128.6, 128.7, 130.2, 132.1, 132.3, 138.7, 144.6, 170.2, 174.6, 186.3; MS *m/z* (%): 365 (5). Anal. calcd for $C_{20}H_{12}ClNO_4$: C, 65.67; H, 3.31; N, 3.83; found: C, 65.84; H, 3.46; N, 3.70%.

Trans*-2-(4-chlorobenzoyl)-3-(4-methylphenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5k**): White powder; m.p. 170–172 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2932, 2864, 1726, 1647, 1453, 1406, 1025, 753; $^1$H NMR: δ 2.18 (s, 3H, $CH_3$), 4.44 (d, *J* = 5.4 Hz, CH, 1H), 4.84 (s, 2H, $OCH_2$), 6.05 (d, *J* = 5.4 Hz, CH, 1H), 7.02–8.05 (m, 8H, arom); $^{13}$C NMR: δ 21.3, 38.4, 66.4, 84.8, 99.1, 127.6, 1287, 128.9, 130.2, 132.4, 135.6, 137.6, 138.7, 170.1, 174.6, 186.2; MS *m/z* (%): 354 (7). Anal. calcd for $C_{20}H_{15}ClO_4$: C, 67.71; H, 4.26; found: C, 67.88; H, 4.40%.

Trans*-2-(4-chlorobenzoyl)-3-(4-bromophenyl)-3,6-dihydrofuro[3,4-*b*]furan-4(2*H*)-one* (**5l**): White powder; m.p. 163–165 °C; IR (KBr) ($\nu_{max}$ cm$^{-1}$): 2915, 2821, 1718, 1646, 1405, 1028, 754, 538; $^1$H NMR: δ 4.22 (d, *J* = 5.2 Hz, CH, 1H), 4.88 (s, 2H, $OCH_2$), 6.32 (d, *J* = 5.2 Hz, CH, 1H), 7.32–8.02 (m, 8H, arom); $^{13}$C NMR: δ 39.2, 66.3, 84.6, 99.1, 120.3, 128.6, 129.8, 130.2, 131.5, 132.3, 138.7, 139.6, 170.8, 174.4, 186.4; MS *m/z* (%): 419 (8). Anal. calcd for $C_{19}H_{12}BrClO_4$: C, 54.38; H, 2.88; found: C, 54.52; H, 3.02%.

*Received 21 June 2017; accepted 7 July 2017*
*Paper 1704844*
*https://doi.org/10.3184/174751917X15005654784030*

## References

1 A. Domling and I. Ugi, *Angew. Chem.*, 2000, **112**, 3300.
2 D.J. Ramon and M. Yus, *Angew. Chem.*, 2005, **117**, 1628.
3 A. Ulaczyk-Lesankom and D.G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266.
4 B.H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795.
5 G. Bar, A.F. Parson and C.B. Thomas, *Tetrahedron Lett.*, 2000, **41**, 7751.

6 P. Müller, Y.F. Allenbach and G. Bernardinelli, *Helv. Chim. Acta*, 2003, **86**, 3164.

7 H. Hagiwara, K. Sato, T. Suzuki and M. Ando, *Tetrahedron Lett.*, 1997, **38**, 2103.

8 W. Cao, W. Ding, J. Chen, Y. Chen, Q. Zang and G. Chen, *Synth. Commun.*, 2004, **34**, 1599.

9 A.T. Khan, M.S. Lal and R. Basha, *Synthesis*, 2013, **45**, 406.

10 C.-J. Li and T.-H. Chan, *Organic reactions in aqueous media*. Wiley. New York, 1997.

11 C. Jiménez-González and D.J.C. Constable, *Green chemistry and engineering: a practical design approach*. Wiley, Hoboken, 2011.

12 Q.F. Wang, H. Hou, L. Hui and C.G. Yan, *J. Org. Chem.*, 2009, **74**, 7403.

13 H. Yang, R. Tian and Y. Li, *Front. Chem. Chin.*, 2008, **3**, 279.

14 B. Baghernejad, *Eur. J. Chem.*, 2010, **1**, 54.

15 M. Salari, M.H. Mosslemin and A. Hassanabadi, *J. Chem. Res.*, 2017, **41**, 60.

16 M. Salari, A. Hassanabadi and M.H. Mosslemin, *J. Chem. Res.*, 2017, **41**, 271.

17 M. Anary-Abbasinejad, K. Charkhati and A. Hassanabadi, *J. Chem. Res.*, 2009, **2**, 95.

18 A.T. Khan, M.S. Lal and R. Basha, *Synthesis*, 2013, **45**, 406.