J IRAN CHEM SOC (2013) 10:565–575
DOI 10.1007/s13738-012-0190-4

ORIGINAL PAPER

Selective formation of spiro dihydrofurans from one-pot reaction of dimedone with BrCN and aldehydes in the presence of Et_3N

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Received: 17 September 2012 / Accepted: 16 November 2012 / Published online: 8 December 2012

Abstract Reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone), aldehydes and cyanogen bromide in the presence of triethylamine leads to the selective formation of spiro dihydrofurans in moderate to good yields at room temperature.

Keywords Dimedone · Spiro 2,3-dihydrofuran · Cyanogen bromide · One-pot · Aldehyde

Introduction

The development of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. Substituted dihydrofurans in numerous natural compounds, showing important biological activities and wide variety pharmaceutical applications [2]. Large variety of 2,3-dihydrofuran compounds are of interest because they constitute important class of compound and natural products, many of which exhibit useful biological activities and clinical applications (Fig. 1) [3, 4].

Electronic supplementary material The online version of this article (doi:10.1007/s13738-012-0190-4) contains supplementary material, which is available to authorized users.

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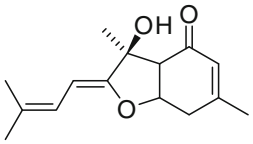
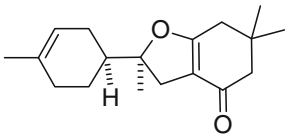
Dimroth and Pasedach [5] have presented a methodology to synthesize 2,3-dihydrofurans from the dehydration of 1,4-diols under high temperature and pressure conditions. The intramolecular cyclization of alkynyl alcohols to generate 2,3-dihydrofurans was performed by the promotion of a pentacarbonylmolybdenum/triethylamine complex [6]. The dihydrofuran moiety was prepared by Rh-catalyzed reactions of diazo compounds or iodonium ylides with alkenes [7–9]. Metal salts, such as cerium(IV) ammonium nitrate and manganese(III) acetate, catalyzed the cyclization of active methylene compounds with alkenes to generate the dihydrofurans [10–14]. Recently, Wang et al. [15] reported an efficient methodology for the oxidative addition reaction of aldehydes with 5,5-dimethylcyclohexane-1,3-dione (dimedone) and 1,3-indandione to selectively afford spiro dihydrofuran and cyclopropane derivatives, promoted by molecular iodine and dimethylaminopyridine (DMAP) under mechanical milling conditions. Yan et al. [16]. reported the synthesis of spiro dihydrofurans using DABCO catalysis.

Dimedone have been used in several reaction conditions with various aldehydes for the synthesis of 1,8-dioxo-octahydroxanthenes such as 1-butyl-3-methylimidazolium hydrogen sulfate [bmim]HSO_4 as an acidic ionic liquid [17], in the presence of selectfluor^{TM} 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2, 2, 2]octane bis(tetrafluoroborate) as catalyst under solvent-free conditions [18], in the presence of ferric hydrogen sulfate as an efficient heterogeneous catalyst [19] and etc.

Although the cyanogen bromide (BrCN) is a capable reagent for the synthesis of cyanamides [20], cyanates [21] and it is used for selective cleavage of the methionyl peptide bonds in ribonuclease [22]. This compound is used as brominating and cyanating agent for bromination and cyanation of imidazoles [23], free-radical reaction with



Bisabolangelone (anti-ulcer) [3a]



Anti-bacterial and anti-fungal [3b]

Fig. 1 Structures of some biological compounds containing substituted dihydrofurans

alkanes that result in bromination of alkanes [24] and α-bromination of β-aminoenones [25].

Here in, we report the synthesis of spiro 6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivatives by applying the reaction of dimedone with cyanogen bromide and aldehydes in the presence of triethylamine.

Experimental

General

Melting points were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra were determined in the region 4,000–400 cm^{-1} on a NEXUS 670 FT IR spectrometer by preparing KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). ^{1}H and ^{13}C NMR spectra were obtained on solution in DMSO-d_6 and/or in $CDCl_3$ as solvents using TMS as internal standard. The data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad singlet, coupling constant(s) in Hz, integration. All reactions were monitored by TLC with silica gel-coated plates (EtOAc: n-hexane/8:10/v:v). The mass analysis performed using mass spectrometer (Agilent Technology (HP) type, MS Model: 5973 network Mass selective detector Electron Impact (EI) 70 eV), ion source temperature was 230 °C (Tehran University, Tehran, Iran). Cyanogen bromide was synthesized based on reported references [26]. Compounds **1**, all aldehydes, triethylamine and used solvents purchased from Merck and Aldrich without further purification.

General procedures for the preparation of 3a–z, 3A and 3B

The physical and spectral data of the selected compounds from **3a–z, 3A and 3B** are follows.

In a 25 mL round bottom flask equipped by a magnetically stirrer, dissolved 0.05 g (0.48 mmol) cyanogen bromide (BrCN) in 2 mL methanol at 0 °C. Then separately, 0.13 g (0.96 mmol) dimedone and 0.028 g (0.48 mmol) propionaldehyde were dissolved in 10 mL methanol in an Erlenmeyer, 0.04 g (0.63 mmol) triethylamine was added into solution and then was transferred it into a separatory funnel, then it was added drop wise into solution of BrCN in round bottom flask at 0 °C to room temperature. (*Caution! The cyanogen bromide is toxic. Reactions should be carried out in a well-ventilated hood*). The progression of reaction was monitored by thin layer chromatography (TLC). After outstanding 24 h, the crystalline solid precipitate, filtered off, washed with few mL methanol and dried.

*Triethylammonium-2-bromo-5,5-dimethylcyclohexane-1,3-dione-2-ide (**4**)*

Colorless crystalline solid, mp 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (bs, 1H), 3.02 (q, $J = 7.5$ Hz, 6H), 2.18 (s, 4H), 1.17 (t, $J = 7.5$ Hz, 9H), 0.87 (s 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 8.7, 28.3, 31.7, 46.2, 50.2, 96.7, 186.0; FTIR (KBr, cm^{-1}) ν_{max}: 3,417, 2,958, 2,870, 2,678, 2,495, 1,644, 1,610, 1,509, 472.

*4′,4′,6,6-Tetramethyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3a**)*

Colorless crystalline powder in a 58 % yield; mp 208–210 °C (Lit.: 208–209 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.13 (s, 2H), 2.78 (d, $J = 13.9$ Hz, 2H), 2.65 (d, $J = 13.9$ Hz, 2H), 2.47 (s, 2H), 2.21 (s, 2H), 1.16 (s, 3H), 1.11 (s, 6H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.9, 28.7, 29.8, 30.8, 34.2, 34.4, 37.4, 51.0, 98.2, 109.2, 176.0, 194.2, 199.8; FTIR (KBr, cm^{-1}) ν_{max}: 2,957, 2,871, 1,731, 1,690, 1,500, 1,398, 1,144.

*3,4′,4′,6,6-Pentamethyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3b**)*

Colorless crystalline powder in a 62 % yield; mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.46 (q, $J = 6.6$ Hz, 1H), 3.15 (d, $J = 7.5$ Hz, 1H), 3.10 (d, $J = 7.2$ Hz, 1H), 2.18–2.99 (m, 6H), 1.22 (s, 3H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.09 (s, 6H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2, 26.0, 28.3, 28.6, 30.4, 34.2, 37.1, 43.3, 46.0, 50.0, 51.1, 54.4, 102.4, 114.0, 176.3., 194.1, 199.7, 199.8; FTIR (KBr, cm^{-1}) ν_{max}: 2,958, 2,877, 1,738, 1,714, 1,642, 1,396, 1,231, 1,041.

*4′,4′,6,6-Tetramethyl-3-ethyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3c**)*

Colorless crystalline powder in a 68 % yield; mp 130–131 °C (Lit.: 148–149 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (s, 1H), 3.61 (m, 1H), 3.12 (s, 1H), 2.82 (d,

$J = 14.4$ Hz, 2H), 2.63 (d, $J = 13.8$ Hz, 2H), 2.46 (m, 2H), 2.20 (s, 2H), 1.15 (s, 3H), 1.10 (s, 9H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.7, 27.9, 28.0, 28.3, 28.6, 29.6, 30.6, 34.1, 34.3, 37.2, 50.8, 50.9, 87.0, 97.0, 109.0, 176.2, 184.0, 194.3, 199.7; MS *m/z* (%): 319 ($M^+ + 1$, 20), 303 (20), 289 (50), 261 (5), 234 (15), 207 (8), 191 (15), 135 (5), 83 (100, base peak), 55 (12), 41 (7); FTIR (KBr, cm^{-1}) ν_{max}: 3,462, 2,955, 2,929, 2,875, 1,714, 1,634, 1,399, 1,245.

*4′,4′,6,6-Tetramethyl-3-propyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3d**)*

Colorless crystalline powder in a 60 % yield; mp 169–171 °C (Lit.: 168–170 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.42 (s, 1H), 2.43-3.03 (m, 7H), 2.22 (s, 2H), 1.56 (s, 3H), 1.29 (s, 3H), 1.13 (s, 6H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 19.7, 25.8, 28.5, 28.6, 30.5, 30.7, 33.7, 34.0, 37.3, 47.5, 49.9, 51.2, 54.7, 103.9, 113.5, 177.4, 194.2, 199.3, 200.0; FTIR (KBr, cm^{-1}) ν_{max}: 2,960, 2,874, 1,738, 1,710, 1,392.

*4′,4′,6,6-Tetramethyl-3-phenyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3e**)*

Colorless crystalline powder in a 65 % yield; mp 267–269 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (t, $J = 8.1$ Hz, 3H), 7.15 (d, $J = 6.6$ Hz, 2H), 4.44 (s, 1H), 3.08 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.54 (d, $J = 14.4$ Hz, 1H), 2.12-2.21 (m, 3H), 1.95 (d, $J = 14.1$ Hz, 1H), 1.16 (s, 6H), 1.12 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.4, 28.9, 30.49, 30.52, 34.2, 37.3, 50.0, 51.1, 53.7, 55.1, 103.8, 113.6, 128.5, 128.6, 129.0, 136.0, 176.6, 193.1, 198.8, 199.3; MS *m/z* (%): 366 (M^+, 50), 282 (50), 266 (25), 254 (85), 241 (15), 184 (10), 155 (6), 141 (7), 128 (32), 115 (12), 102 (11), 83 (100, base peak), 55 (40), 41 (25); FTIR (KBr, cm^{-1}) ν_{max}: 3,050, 2,957, 2,872, 1,737, 1,713, 1,642, 1,390.

*4′,4′,6,6-Tetramethyl-3-(4-nitrophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3f**)*

Yellow crystalline powder in a 70 % yield; mp 265–267 °C (Lit.: 265–266 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, $J = 6.9$ Hz, 2H), 7.36 (d, $J = 6.9$ Hz, 2H), 4.51 (s, 1H), 3.97 (d, $J = 8.1$ Hz, 1H), 3.06 (d, $J = 15.0$ Hz, 1H), 2.69 (s, 2H), 2.60 (d, $J = 15.0$ Hz, 1H), 2.17–2.25 (m, 3H), 1.92 (d, $J = 14.4$ Hz, 1H), 1.17 (s, 3H), 1.15 (s, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1, 28.4, 28.8, 30.4, 30.7, 34.4, 37.2, 49.9, 50.9, 53.9, 54.0, 103.2, 113.4, 125.3, 129.5, 143.4, 147.9, 177.4, 193.1, 198.2, 198.4; MS *m/z* (%): 411 (M^+, 40), 327 (18), 299 (40), 282 (7), 229 (7), 191 (5), 173 (5), 152 (5), 115 (7), 83 (100, base peak), 69 (6), 55 (23), 41 (13); FTIR (KBr, cm^{-1}) ν_{max}: 2,960, 2,871, 1,713, 1,641, 1,525, 1,396, 1,348.

*4′,4′,6,6-Tetramethyl-3-(3-nitrophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3g**)*

Yellow crystalline powder in a 60 % yield; mp 202–204 °C (Lit.: 201–203 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, $J = 7.7$ Hz, 1H), 8.07 (s, 1H), 7.45-7.54 (m, 2H), 4.56 (s, 1H), 3.13 (d, $J = 15.0$ Hz, 1H), 2.70 (s, 2H), 2.62 (dd, $J^3 = 15.0$, $J^4 = 2.7$ Hz, 1H), 2.29-2.13 (m, 3H), 1.96 (d, $J = 14.4$ Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.2, 28.4, 28.8, 30.4, 30.7, 34.4, 37.3, 49.9, 54.0, 53.7, 54.1, 103.0, 113.4, 123.5, 123.6, 130.0, 134.4, 138.4, 148.3, 177.6, 193.1, 198.3, 198.6; MS *m/z* (%): 411 (M^+, 13), 394 (15), 311 (12), 299 (6), 282 (8), 127 (8), 83 (100, base peak), 69 (5), 55 (25), 41 (13); FTIR (KBr, cm^{-1}) ν_{max}: 3,068, 2,959, 2,875, 1,741, 1,712, 1,645, 1,533, 1,391, 1,531.

*4′,4′,6,6-Tetramethyl-3-(2-nitrophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3h**)*

Pale yellow crystalline powder in a 70 % yield; mp 183–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, $J = 8.1$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 7.5$ Hz, 1H), 6.04 (s, 1H), 3.56 (d, $J = 15.3$ Hz, 1H), 2.54–2.73 (m, 4H), 2.03–2.22 (m, 3H), 1.21 (s, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.6, 28.3, 28.9, 30.2, 30.8, 34.4, 37.2, 46.6, 49.4, 50.7, 52.8, 102.9, 114.9, 124.3, 127.1, 129.2, 130.9, 133.2, 149.1, 176.6, 192.5, 198.97, 199.03; FTIR (KBr, cm^{-1}) ν_{max}: 3,064, 2,959, 2,875, 1,721, 1,649, 1,616, 1,523, 1,388, 1,347.

*4′,4′,6,6-Tetramethyl-3-(2-nitrocinamyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3i**)*

Yellow crystalline powder in a 70 % yield; mp 263–265 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, $J = 7.8$ Hz, 1H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.43 (m, 2H), 7.21 (d, $J = 15.3$ Hz, 1H), 5.70 (dd, $J^3 = 15.2$, $J^3 = 10.2$ Hz, 1H), 4.15 (d, $J = 9.9$ Hz, 1H), 3.12 (d, $J = 14.4$ Hz, 1H), 2.88 (d, $J = 15.0$ Hz, 1H), 2.49–2.58 (m, 4H), 2.25 (s, 2H), 1.27 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.6, 28.5, 28.6, 30.2, 30.7, 34.2, 37.4, 50.2, 51.3, 52.8, 54.2, 101.8, 110.7, 124.7, 128.4, 128.9, 129.8, 131.9, 132.1, 133.7, 147.4, 177.4, 193.5, 199.4, 200.0; MS *m/z* (%): 437 (M^+, 10), 420 (20), 392 (5), 360 (15), 336 (7), 318 (15),

302 (8), 287 (13), 266 (5), 231 (7), 206 (6), 178 (7), 152 (4), 120 (15), 83 (100, base peak), 55 (18); FTIR (KBr, cm^{-1}) ν_{max}: 3,109, 3,073, 2,960, 2,929, 2,870, 1,746, 1,715, 1,636, 1,523, 1,394, 1,350, 1,041.

*4′,4′,6,6-Tetramethyl-3-(4-cyanophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3j**)*

Colorless crystalline powder in a 75 % yield; mp 271–272 °C (Lit.: 248-250 °C [15]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, $J = 8.1$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 4.46 (s, 1H), 3.05 (d, $J = 14.7$ Hz, 2H), 2.52–2.67 (m, 3H), 2.11–2.26 (m, 3H), 1.90 (d, $J = 14.4$ Hz, 1H), 1.17 (s, 3H), 1.14 (s, 6H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1, 28.4, 28.8, 30.4, 30.6, 34.3, 37.2, 49.9, 50.9, 54.0, 54.2, 103.2, 112.7, 113.4, 118.1, 129.3, 132.7, 141.5, 177.3, 193.0, 198.2, 198.5; MS *m/z* (%): 391 (M^+, 65), 307 (45), 293 (20), 279 (70), 256 (12), 209 (7), 153 (12), 127 (5), 83 (100, base peak), 55 (20), 41 (13); FTIR (KBr, cm^{-1}) ν_{max}: 2,962, 2,928, 2,873, 2,230, 1,740, 1,709, 1,640, 1,395, 1,046.

*4′,4′,6,6-Tetramethyl-3-cinamyl-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3k**)*

Yellow crystalline powder in a 70 % yield; mp 284–285 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 6.73 (d, $J = 15.9$ Hz, 1H), 5.83 (dd, $J^3 = 15.5$, $J^3 = 9.6$ Hz, 1H), 4.08 (d, $J = 9.6$ Hz, 1H), 3.00 (d, $J = 14.7$ Hz, 1H), 2.51–2.65 (m, 5H), 2.22 (s, 2H), 1.20 (s, 3H), 1.15 (s, 6H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.4, 28.5, 28.6, 30.5, 30.6, 34.2, 37.4, 50.2, 51.3, 52.2, 54.4, 102.5, 111.4, 122.8, 126.8, 128.4, 128.6, 135.1, 135.6, 176.9, 193.4, 199.1, 199.3; FTIR (KBr, cm^{-1}) ν_{max}: 2,959, 2,871, 1,740, 1,711, 1,635, 1,389.

*4′,4′,6,6-Tetramethyl-3-(4-bromophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3l**)*

Yellow crystalline powder in a 75 % yield; mp 283–285 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, $J = 7.2$ Hz, 2H), 7.03 (d, $J = 7.2$ Hz, 2H), 4.38 (s, 1H), 3.03 (d, $J = 14.7$ Hz, 1H), 2.64 (s, 2H), 2.54 (d, $J = 14.1$ Hz, 1H), 2.16 (m, 3H), 1.96 (d, $J = 13.5$ Hz, 1H), 1.13 (s, 9H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.2, 28.4, 28.8, 30.5, 30.6, 34.3, 37.2, 50.0, 51.0, 53.9, 54.2, 103.4, 113.5, 122.8, 130.1, 132.2, 135.2, 176.8, 193.1, 198.6, 198.9; MS *m/z* (%): 447 (M^+ +2, 28), 445 (M^+, 30), 412 (15), 385 (5), 362 (25), 334 (60), 319 (7), 300 (10), 281 (45), 253 (6), 183 (6), 155 (5), 127 (10), 83 (100, base peak), 69 (5), 55 (24), 41 (15); FTIR (KBr, cm^{-1}) ν_{max}: 2,963, 2,870, 1,740, 1,710, 1,640, 1,392, 1,045.

*4′,4′,6,6-Tetramethyl-3-(3-bromophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3m**)*

Yellow crystalline powder in a 67 % yield; mp 228–229 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, $J = 7.8$ Hz, 1H), 7.32 (s, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 4.37 (s, 1H), 3.06 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.55 (dd, $J^3 = 14.7$, $J^4 = 3$ Hz, 1H), 2.13–2.24 (m, 3H), 1.98 (d, $J = 14.4$ Hz, 1H), 1.16 (s, 9H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.2, 28.4, 28.8, 30.5, 30.6, 34.3, 37.3, 49.9, 51.0, 53.9, 54.1, 103.5, 113.4, 123.0, 127.1, 130.5, 131.6, 131.8, 138.4, 177.0, 193.1, 198.4, 198.9; FTIR (KBr, cm^{-1}) ν_{max}: 3,072, 2,958, 2,871, 1,741, 1,713, 1,643, 1,392, 1,042, 692.

*4′,4′,6,6-Tetramethyl-3-(4-chlorophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3n**)*

Colorless crystalline powder in a 70 % yield; mp 271–273 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 4.41 (s, 1H), 3.05 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.55 (d, $J = 15.0$ Hz, 1H), 2.12–2.23 (m, 3H), 1.97 (d, $J = 14.4$ Hz, 1H), 1.16 (s, 3H), 1.15 (s, 6H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.2, 28.4, 28.8, 30.5, 30.6, 34.3, 37.3, 50.0, 51.0, 53.9, 54.2, 103.5, 113.5, 129.2, 129.8, 134.6, 134.7, 176.8, 193.1, 198.6, 198.9; MS *m/z* (%): 402 (M^+ +2, 27), 400 (M^+, 70), 372 (8), 341 (7), 316 (75), 302 (30), 288 (85), 274 (10), 218 (8), 191 (8), 162 (10), 127 (10), 83 (100, base peak), 55 (35), 41 (25); FTIR (KBr, cm^{-1}) ν_{max}: 2,962, 2,872, 1,742, 1,711, 1,641, 1,393, 1,044.

*4′,4′,6,6-Tetramethyl-3-(4-tolyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3o**)*

Yellow crystalline powder in a 60 % yield; mp 254–255 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (d, $J = 7.8$ Hz, 2H), 7.04 (d, $J = 7.8$ Hz, 2H), 4.42 (s, 1H), 3.08 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.53 (d, $J = 14.7$ Hz, 1H), 2.31 (s, 3H), 2.12–2.21 (m, 3H), 2.00 (d, $J = 14.4$ Hz, 1H), 1.16 (s, 6H), 1.13 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1, 26.3, 28.4, 28.9, 30.5, 34.2, 37.3, 50.0, 51.1, 53.8, 54.8, 103.8, 113.7, 114.4, 128.8, 129.7, 133.0, 138.4, 176.4, 193.1, 199.0, 199.4; MS *m/z* (%): 380 (M^+, 80), 365 (7), 352 (9), 337 (6), 321 (10), 296 (50), 281 (60), 265 (100, base peak), 255 (12), 212 (7),

198 (6), 141 (13), 115 (6), 83 (60), 55 (20), 41 (10); FTIR (KBr, cm^{-1}) ν_{max}: 2,964, 2,874, 1,743, 1,714, 1,640, 1,391, 1,041.

*4′,4′,6,6-Tetramethyl-3-(3-hydroxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3p**)*

Colorless crystalline powder in a 70 % yield; mp 238–240 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.43 (s, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 6.70 (d, $J = 6.9$ Hz, 1H), 6.63 (d, $J = 7.8$ Hz, 1H), 6.57 (s, 1H), 4.66 (s, 1H), 4.08 (d, $J = 5.1$ Hz, 1H), 3.58 (d, $J = 15$ Hz, 1H), 3.16 (d, $J = 5.1$ Hz, 1H), 2.36–2.59 (m, 5H), 1.08 (s, 3H), 1.06 (s, 6H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.4, 28.3, 28.6, 29.9, 30.6, 34.4, 36.8, 49.8, 51.1, 53.1, 53.4, 104.0, 113.4, 115.5, 116.1, 120.1, 129.6, 138.6, 157.7, 176.7, 192.6, 199.3, 200.7; MS *m/z* (%): 382 (M^+, 100, base peak), 367 (6), 323 (6), 298 (45), 270 (70), 256 (12), 214 (10), 200 (10), 144 (10), 115 (10), 83 (80), 55 (18), 41 (10); FTIR (KBr, cm^{-1}) ν_{max}: 3,444, 3,020, 2,961, 2,873, 1,738, 1,713, 1,625, 1,395.

*4′,4′,6,6-Tetramethyl-3-(2-hydroxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3q**)*

Colorless crystalline powder in a 65 % yield; mp 225–226 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.40 (bs, 1H), 7.05 (m, 1H), 6.93 (m, 3H), 5.01 (s, 1H), 1.95–2.52 (m, 8H), 0.84–1.02 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.6, 26.7, 28.1, 29.6, 31.8, 32.0, 32.04, 41.1, 50.9, 111.2, 115.7, 124.6, 126.0, 126.1, 127.3, 128.8, 150.1, 165.1, 192.0, 196.1, 196.2; FTIR (KBr, cm^{-1}) ν_{max}: 3,185, 2,955, 2,876, 1,642, 1,591, 1,377, 1,236, 756.

*4′,4′,6,6-Tetramethyl-3-(3-hydroxy-4-methoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3r**)*

Yellow crystalline powder in a 65 % yield; mp 241–242 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.94, 8.91 (2bs, 1H), 6.53–6.78 (m, 3H), 4.61, 4.58 (2 s, 1H), 3.71, 3.67 (2 s, 3H), 3.53 (m, 1H), 3.31, 3.27 (2 s, 1H), 2.31–2.55 (m, 6H), 1.04 (s, 6H), 1.02 (s, 3H), 0.66, 0.63 (2 s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.4, 28.2, 28.6, 29.9, 30.5, 34.3, 36.8, 49.8, 51.1, 52.9, 53.4, 55.8, 103.9, 111.9, 113.4, 116.3, 120.3, 129.5, 146.6, 147.8, 176.3, 192.6, 199.3, 200.8; MS *m/z* (%): 412 (M^+, 7), 328 (6), 313 (8), 300 (30), 287 (10), 191 (20), 178 (9), 165 (10), 152 (18), 128 (11), 115 (16), 102 (12), 83 (100, base peak), 69 (15), 55 (98), 41 (60); FTIR (KBr, cm^{-1}) ν_{max}: 3,442, 3,061, 3,008, 2,959, 2,898, 2,872, 1,739, 1,711, 1,640, 1,511, 1,388, 1,192, 1,037.

*4′,4′,6,6-Tetramethyl-3-(4-hydroxy-3-methoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3s**)*

Colorless crystalline powder in a 62 % yield; mp 278–279 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.04 (s, 1H), 6.76 (s, 1H), 6.65 (d, $J = 8.1$ Hz, 2H), 4.63 (s, 1H), 3.68 (s, 3H), 2.35-2.68 (m, 4H), 2.01–2.16 (m, 4H), 1.08 (s, 3H), 1.05 (s, 6H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.4, 28.1, 28.6, 29.9, 30.6, 34.3, 36.8, 49.8, 51.1, 53.3, 53.4, 56.1, 103.9, 113.9, 113.4, 115.7, 121.9, 127.9, 146.8, 147.6, 176.5, 192.7, 199.6, 200.9; FTIR (KBr, cm^{-1}) ν_{max}: 3,449, 2,960, 2,875, 1,737, 1,712, 1,639, 1,392, 1,280, 1,037.

*4′,4′,6,6-Tetramethyl-3-(2-methoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3t**)*

Colorless crystalline powder in a 78 % yield; mp 227–228 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20–7.25 (m, 1H), 6.89 (t, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 6.0$ Hz, 1H), 5.20 (s, 1H), 3.94 (s, 3H), 3.37 (d, $J = 14.4$ Hz, 1H), 2.66 (s, 2H), 2.48 (d, $J = 14.4$ Hz, 1H), 2.06–2.26 (m, 4H), 1.19 (s, 3H), 1.16 (s, 3H), 1.12 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.7, 28.8, 30.4, 30.6, 34.2, 37.3, 45.7, 49.7, 51.2, 52.7, 55.7, 102.9, 111.1, 113.2, 119.1, 121.6, 124.0, 129.6, 155.9, 177.0, 193.0, 199.4, 200.0; FTIR (KBr, cm^{-1}) ν_{max}: 3,075, 3,029, 2,957, 2,874, 1,742, 1,715, 1,647, 1,388, 1,235, 1,041.

*4′,4′,6,6-Tetramethyl-3-(3-methoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3u**)*

Yellow crystalline powder in a 60 % yield; mp 214–216 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 (t, $J = 7.8$ Hz, 1H), 6.81 (dd, $J^3 = 8.1$, $J^4 = 1.8$ Hz, 1H), 6.76 (d, $J = 7.5$ Hz, 1H), 4.41 (s, 1H), 3.76 (s, 3H), 3.08 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.53 (dd, $J^3 = 14.7$, $J^4 = 3$ Hz, 1H), 2.00–2.27 (m, 4H), 1.17 (s, 6H), 1.12 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.3, 28.9, 30.5, 30.6, 34.2, 37.3, 50.0, 51.1, 53.7, 55.0, 55.2, 103.8, 113.5, 114.0, 114.4, 120.9, 130.0, 137.6, 159.9, 176.6, 193.1, 198.8, 199.3; MS *m/z* (%): 396 (M^+, 35), 312 (37), 296 (18), 284 (50), 271 (10), 228 (8), 214 (6), 191 (8), 158 (15), 128 (14), 115 (20), 83 (100, base peak), 69 (18), 55 (60), 41 (47); FTIR (KBr, cm^{-1}) ν_{max}: 3,050, 2,997, 2,962, 2,933, 2,872, 2,832, 1,740, 1,712, 1,639, 1,598, 1,392, 1,264, 1,041.

*4′,4′,6,6-Tetramethyl-3-(4-methoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3v**)*

Colorless crystalline powder in a 75 % yield; mp 236–237 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (d, $J = 8.1$ Hz, 2H), 6.83 (d, $J = 8.1$ Hz, 2H), 4.42 (s, 1H), 3.78 (s, 3H), 3.49, (s, 1H), 3.07 (d, $J = 14.7$ Hz, 1H), 2.66 (s, 2H), 2.54 (d, $J = 14.1$ Hz, 1H), 2.14–2.21 (m, 2H), 2.0 (d, $J = 14.4$ Hz, 1H), 1.16 (s, 6H), 1.13 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.4, 28.9, 30.4, 30.5, 34.2, 37.3, 50.1, 51.1, 53.8, 54.6, 55.2, 103.7, 113.5, 114.4, 127.9, 129.7, 159.6, 176.4, 193.0, 199.1, 199.4; MS *m/z* (%): 396 (M^+, 50), 337 (10), 312 (40), 298 (20), 284 (100, base peak), 270 (8), 228 (8), 167 (10), 149 (30), 135 (20), 115 (15), 83 (70), 69 (10), 55 (35), 41 (25); FTIR (KBr, cm^{-1}) ν_{max}: 2,960, 2,839, 1,739, 1,712, 1,639, 1,390, 1,036.

*4′,4′,6,6-Tetramethyl-3-(3,4,5-trimethoxyphenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3w**)*

Pale yellow crystalline powder in a 70 % yield; mp 227–228 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.36 (s, 2H), 4.37 (s, 1H), 3.83 (s, 3H), 3.82 (s, 6H), 3.06 (d, $J = 14.7$ Hz, 1H), 2.68 (s, 2H), 2.55 (dd, $J^3 = 14.4$, $J^4 = 2.7$ Hz, 1H), 2.15–2.30 (m, 2H), 2.01 (d, $J = 14.4$ Hz, 2H), 1.18 (s, 6H), 1.13 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.0, 29.1, 30.5, 30.6, 34.2, 37.3, 50.1, 51.1, 53.6, 55.6, 56.2, 60.8, 103.9, 105.8, 113.4, 131.8, 153.5, 168.0, 176.6, 193.2, 199.1, 199.2; MS *m/z* (%): 456 (M^+, 100, base peak), 428 (9), 397 (10), 372 (40), 357 (10), 341 (80), 317 (18), 289 (5), 273 (8), 168 (5), 83 (60), 55 (24), 41 (13); FTIR (KBr, cm^{-1}) ν_{max}: 2,959, 1,742, 1,714, 1,642, 1,393, 1,126.

*4′,4′,6,6-Tetramethyl-3-(4-dimethylaminophenyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3x**)*

Colorless crystalline powder in a 90 % yield; mp 298–299 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.07 (m, 4H), 4.41 (s, 1H), 3.05 (d, $J = 14.4$ Hz, 1H), 2.98 (s, 6H), 2.66 (s, 2H), 2.54 (d, $J = 13.5$ Hz, 1H), 2.02–2.26 (m, 3H), 1.16 (s, 6H), 1.14 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 25.9, 28.0, 28.6, 30.4, 30.5, 34.0, 37.0, 49.6, 50.7, 53.7, 54.0, 54.2, 106.0, 113.0, 120.0, 130.3, 132.0, 150.0, 176.0, 194.0, 198.4, 199.0; FTIR (KBr, cm^{-1}) ν_{max}: 2,957, 2,929, 2,874, 1,737, 1,712, 1,639, 1,390.

*4′,4′,6,6-Tetramethyl-3-(4-dimethylaminocinamyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3y**)*

Colorless crystalline powder in a 87 % yield; mp 278–279 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.14 (d, $J = 7.8$ Hz, 2H), 6.63 (d, $J = 7.8$ Hz, 2H), 5.54 (dd, $J = 14.7$, 9.3 Hz, 1H), 4.27 (d, $J = 8.7$ Hz, 1H), 3.50 (d, $J = 14.7$ Hz, 1H), 2.88 (s, 6H), 2.68 (d, $J = 14.7$ Hz, 2H), 2.05-2.53 (m, 6H), 1.12 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.5, 28.2, 28.5, 29.8, 30.7, 34.4, 36.9, 49.8, 50.9, 51.2, 53.8, 84.0, 103.0, 111.7, 112.6, 119.1, 124.0, 127.8, 134.6, 150.1, 176.7, 193.0, 200.0, 200.9; FTIR (KBr, cm^{-1}) ν_{max}: 3,094, 2,956, 2,874, 2,803, 1,735, 1,710, 1,637, 1,613, 1,525, 1,390.

*4′,4′,6,6-Tetramethyl-3-(2-hydroxy-1-naphthyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3z**)*

Colorless crystalline powder in a 60 % yield; mp 236–237 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.46 (bs, 1H), 8.18 (s, 1H), 7.71–7.79 (m, 2H), 7.37 (m, 2H), 7.17 (m, 1H), 5.54 (s, 1H), 2.59 (d, $J = 17.4$ Hz, 1H), 2.01–2.47 (m, 7H), 1.03 (s, 3H), 0.95 (s, 3H), 0.76 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 23.8, 24.0, 26.3, 27.5, 28.0, 29.8, 31.9, 32.1, 40.9, 44.0, 50.5, 51.0, 111.1, 117.1, 117.8, 124.1, 124.7, 126.8, 128.1, 128.6, 131.0, 132.0, 148.5, 164.8, 172.5, 195.0, 196.3; FTIR (KBr, cm^{-1}) ν_{max}: 3,180, 2,945, 2,892, 2,870, 1,717, 1,644, 1,593, 1,375, 1,234, 811, 748.

*4′,4′,6,6-Tetramethyl-3-(2-naphthyl)-3,5,6,7-tetrahydro-spiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3A**)*

Colorless crystalline powder in a 70 % yield; mp 278–279 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 (m, 3H), 7.70 (s, 1H), 7.50 (m, 2H), 7.21 (d, $J = 8.7$ Hz, 1H), 4.62 (s, 1H), 3.16 (d, $J = 15.0$ Hz, 1H), 2.72 (s, 2H), 2.58 (d, $J = 15$ Hz, 1H), 1.97–2.22 (m, 4H), 1.18 (s, 6H), 1.11 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3, 28.4, 28.9, 30.5, 30.6, 34.3, 37.3, 50.0, 51.1, 53.8, 55.1, 104.0, 114.0, 125.6, 126.5, 127.7, 127.9, 128.0, 129.0, 131.0, 133.0, 133.2, 133.5, 176.6, 194.0, 198.7, 199.2; MS *m/z* (%): 416 (M^+, 50), 357 (8), 332 (60), 316 (20), 304 (100, base peak), 291 (10), 277 (12), 248 (10), 205 (10), 191 (10), 178 (32), 165 (15), 149 (40), 127 (16), 83 (80), 69 (22), 55 (50), 41 (40); FTIR (KBr, cm^{-1}) ν_{max}: 3,054, 2,957, 2,873, 1,740, 1,713, 1,391.

*4′,4′,6,6-Tetramethyl-3-(1-naphthyl)-3,5,6,7-tetrahydrospiro[benzofuran-2(4H),1′-cyclohexane]-2′,4,6′-trione (**3B**)*

Colorless crystalline powder in a 60 % yield; mp 229–230 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.52–7.62 (m, 2H), 7.39 (t, $J = 7.2$ Hz, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 5.50 (s, 1H), 3.23 (d, $J = 15.0$ Hz, 1H), 2.73 (s, 2H), 2.56 (d, $J = 14.7$ Hz, 1H), 2.25 (d, $J = 16.2$ Hz, 1H), 2.16 (d, $J = 16.2$ Hz, 1H), 1.84 (d, $J = 13.8$ Hz, 1H), 1.59 (d, $J = 14.1$ Hz, 1H), 1.19 (s, 6H), 0.90 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1, 28.6, 28.8, 30.3, 30.4, 34.3, 37.4, 47.8, 50.5, 51.1, 52.8, 103.8, 114.9, 121.9, 125.6, 125.9, 127.2, 127.5, 128.9, 129.6, 131.2, 132.0, 133.9, 176.6, 192.9, 199.0, 199.7; FTIR (KBr, cm^{-1}) ν_{max}: 3,058, 2,959, 2,872, 1,741, 1,712, 1,645, 1,387.

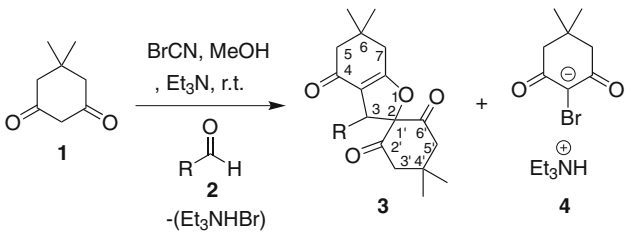
*2-Bromo-5,5-dimethylcyclohexane-1,3-dione (**6**)*

Colorless crystalline solid, mp 157–158 °C (Lit.: 156 °C [27]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.54 (s, 1H), 2.54 (s, 2H), 2.44 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.0, 32.0, 42.4, 50.8, 100.8, 190.2. (Equilibrium mixtures of two tautomers); MS *m/z* (%): 218 (M^+, 50), 220 ($M^+ + 2$, 50), 162 (95), 164 (100, base peak), 139 (25), 111 (27), 86 (90), 69 (27), 55 (45), 41 (40); FTIR (KBr, cm^{-1}) ν_{max}: 3,410, 2,958, 2,929, 1,732, 1,612, 1,384.

Results and discussion

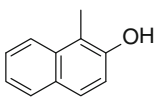
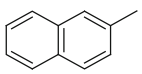
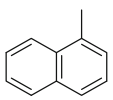
The reaction of dimedone (**1**) with BrCN and various aldehydes in the presence of Et_3N affords spiro 6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivatives (**3**) and salt of triethylammonium-2-bromo-5,5-dimethylcyclohexane-1,3-dione-2-ide (**4**) (Scheme 1; Table 1). The formation of salt **4** has interesting applications in many chemical transformations.

As a part of our current studies on dimedone **1** and its reaction with BrCN and our interest in the chemistry of



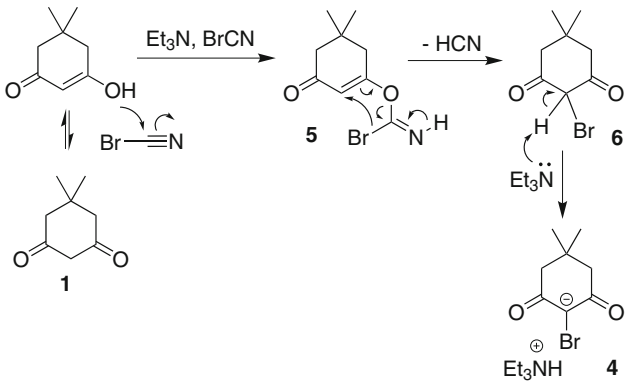
Scheme 1 Reaction of dimedone (**1**) with cyanogen bromide and aldehydes in the presence of triethylamine

Table 1 Reaction of dimedone **1** with various aldehydes mediated by BrCN in the presence of Et_3N

Entry	*R*	Product	Yield (%)
1	H (**2a**)	**3a**	58
2	CH_3 (**2b**)	**3b**	62
3	CH_3CH_2 (**2c**)	**3c**	68
4	$CH_3CH_2CH_2$ (**2d**)	**3d**	60
5	C_6H_5 (**2e**)	**3e**	65
6	*p*–NO_2–C_6H_4 (**2f**)	**3f**	70
7	*m*–NO_2–C_6H_4 (**2g**)	**3g**	60
8	*o*–NO_2–C_6H_4 (**2h**)	**3h**	70
9	*trans*–*o*–NO_2–$C_6H_4CH = CH$ (**2i**)	**3i**	70
10	*p*–CN–C_6H_4 (**2j**)	**3j**	75
11	*trans*–$C_6H_5CH = CH$ (**2k**)	**3k**	70
12	*p*–Br–C_6H_4 (**2l**)	**3l**	75
13	*m*–Br–C_6H_4 (**2m**)	**3m**	67
14	*p*–Cl–C_6H_4 (**2n**)	**3n**	70
15	*p*–CH_3–C_6H_4 (**2o**)	**3o**	60
16	*m*–OH–C_6H_4 (**2p**)	**3p**	70
17	*o*–OH–C_6H_4 (**2q**)	**3q**	65
18	3–OH–4–CH_3O–C_6H_3 (**2r**)	**3r**	65
19	4–OH–3–CH_3O–C_6H_3 (**2s**)	**3s**	62
20	*o*–CH_3O–C_6H_4 (**2t**)	**3t**	78
21	*m*–CH_3O–C_6H_4 (**2u**)	**3u**	60
22	*p*–CH_3O–C_6H_4 (**2v**)	**3v**	75
23	3,4,5–tri–CH_3O–C_6H_2 (**2w**)	**3w**	70
24	*p*–$(CH_3)_2N$–C_6H_4 (**2x**)	**3x**	90
25	*trans*–*p*–$(CH_3)_2N$–$C_6H_4CH = CH$ (**2y**)	**3y**	87
26	 (**2z**)	**3z**	60
27	 (**2A**)	**3A**	70
28	 (**2B**)	**3B**	60

BrCN, we discovered the unexpected bromination of **1** by BrCN (in the presence and absence of aldehyde). Previously, dimedone has been α-brominated by bromodimethylsulfonium bromide (BDMS) [27]. Cyanation of compounds via BrCN are well known [20, 21, 28].

Although the mechanism of the reaction of **1** with BrCN has not yet been established experimentally, a possible explanation is proposed in Scheme 2. Previously, it was reported that the reaction of β-dicarbonyl compound with



Scheme 2 Proposed mechanism for the formation of **4**

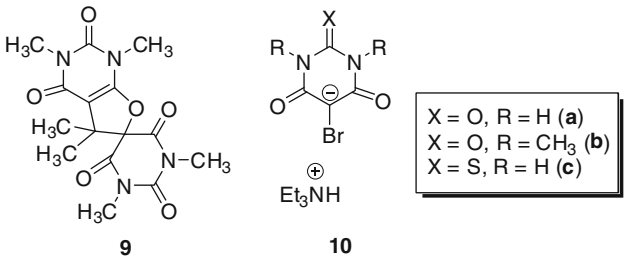
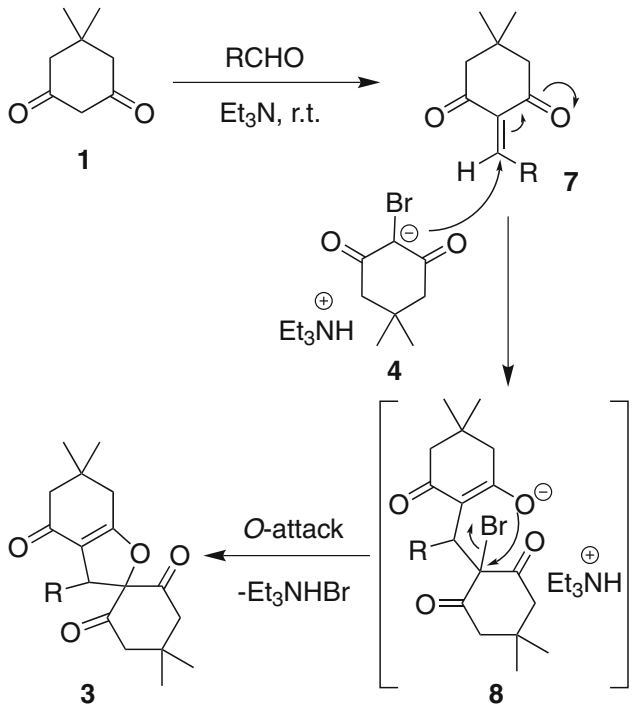


Fig. 2 Structures of spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine] derivative (**9**) [33], triethylammonium-5-bromo-(thio)barbiturates (**10**) [34–36]

iodine and bromine gave the α-iodinated [29–31] and α-brominated products [32], respectively. Recently, we reported the crystal structure of 1,1′,3,3′,5,5′-hexamethyl-1*H*,1′*H*-spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaone (**9**) that derived from the reaction of 1,3-dimethylbarbituric acid with BrCN and acetone in the presence of Et_3N [33]. We proposed that in these reactions the salts of triethylammonium-5-bromobarbiturates (**10**) are formed in the reaction of (thio)barbituric acids with aldehydes [34], aromatic dialdehydes [35] and ketones [36] in the presence of BrCN (Fig. 2). The salts of **10** plays a major role for the synthesis of spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine]2,2′,4,4′,6′(3*H*,3′*H*,5*H*)-pentaones. According to the mechanism of the bromination of 1-alkyl imidazoles by BrCN [23] and the mechanism of the formation of **10** [34–36], it was assumed that the enolic form of dimedone **1** reacted with BrCN was formed via intermediate **5**. Intramolecular rearrangement of **5** afforded **6** followed by the loss of HCN. Triethylamine as a base captured the acidic methylene proton of **6** forming salt **4** (Scheme 2). The salt of triethylammonium hydrobromide was filtered. Unfortunately, all attempts failed to separate or characterize **5** and **6** in the reaction with aldehydes. The structure of **4** was characterized by IR, ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **4** consists of a singlet at δ 0.87 ppm corresponding to geminal methyl groups, and a triplet at δ 1.17 ppm and a quartet at δ 3.02 ppm corresponding to methyl and methylene groups in triethylammonium salt moiety, respectively. A singlet at δ 2.18 ppm corresponds to cyclic methylene groups in dimedone ring moiety. Finally, a broad singlet at δ 7.27 ppm related to NH ammonium salt moiety. The ^{13}C NMR spectrum is in good agreement with the molecular structure and show seven distinct peaks. Two peaks at δ 8.70 and at 28.3 ppm correspond to three equivalent methyl groups on triethylammonium salt and two geminal methyl groups on dimedone ring moieties, respectively. Three peaks at δ 31.7, 46.2 and 50.2 ppm correspond to quaternary carbon atom on dimedone ring, three equivalent methylene groups on triethylammonium salt moiety and two equivalent methylene groups on dimedone ring moiety, respectively. Two peaks at δ 96.7 and 186.0 ppm correspond to C–Br and two equivalent carbonyl groups on dimedone ring moiety, respectively (see experimental and supplementary data). Other evidence for the formation of **4** (the existence of bromine atom in this molecule) was performed by Beilstein test and the wet silver nitrate test [37] (precipitate of pale yellow silver bromide).

The proposed mechanism for the formation of **3** is shown in Scheme 3. First, the Knoevenagel condensation of **1** [17–19] with an aldehyde afforded 2-alkylidene and/or 2-arylidene-5,5-dimethylcyclohexane-1,3-dione (**7**) then Michael addition of the compound **7** with **4** as the key



Scheme 3 Knoevenagel condensation, Michael addition and cyclization mechanism for the formation of **3**

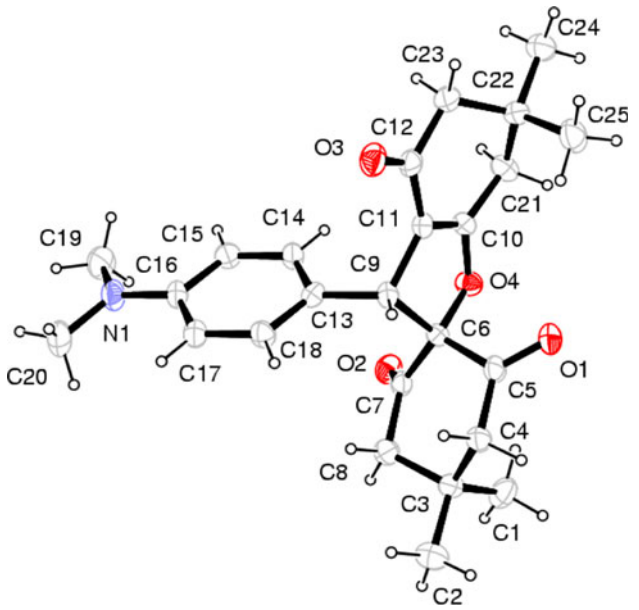


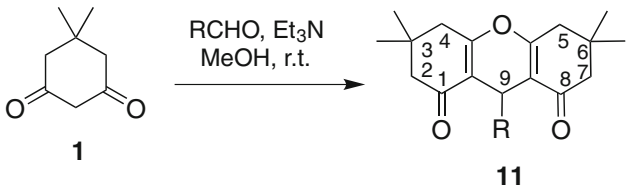
Fig. 3 Molecular structure of compound **3x**. Thermal ellipsoids are shown at 30 % probability level

intermediate gave the intermediate (**8**). Finally, an intramolecular nucleophilic *O*-attack via **8** followed by elimination of Et_3NHBr afforded spiro 6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-ones **3** in good yield. Unfortunately, all attempts failed to separate or characterize **8**.

Crystallographic analysis of **3x**

To analyse the structural peculiarities of the synthesized compound **3x**, its molecular structure was determined by single crystal X-ray diffraction. A perspective view of molecule **3x** is given in Fig. 3. The compound crystallizes in the monoclinic space group $P2_1/c$, with four molecules in the unit cell. p–$(CH_3)_2N$–C_6H_4 substituted stereogenic center possess the *R*-configuration.

For the crystal structure determination, the single crystal of the compound **3x** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two dimensional area IP detector). The graphite-monochromatised Mo Kα radiation (λ = 0.71,073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2,005) software [38]. The structures were solved by direct methods using SHELXS-97 [39] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [39] H-atoms were positioned geometrically and refined using a riding model. The final difference



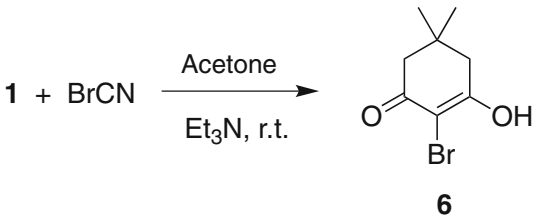
Scheme 4 Formation of xanthene derivatives (**11**) from the reaction of dimedone **1** with various aldehydes in the absence of BrCN

Fourier maps showed no peaks of chemical significance. *Crystal data for* ***3x***: $C_{25}H_{31}NO_4$, crystal system, space group: monoclinic, $P2_1/c$; (no:14); unit cell dimensions: a = 18.8,941(7), b = 6.0,009(6), c = 20.3,990(5) Å; volume: 2,236.01(2) $Å^3$; $Z = 4$; calculated density: 1.22 mg cm^{-3}; absorption coefficient: 0.082 mm^{-1}; $F(000)$: 880; θ-range for data collection 2.1–26.6°; refinement method: full-matrix least-square on F^2; data/parameters: 4,606/276; goodness-of-fit on F^2: 1.048; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.087$, w$R_2 = 0.239$; R indices (all data): $R_1 = 0.275$, w$R_2 = 0.245$; largest diff. peak and hole: 0.446 and –0.581 e$Å^{-3}$. Crystallographic data were deposited in CSD under CCDC registration number: 848718 and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (fax: +44-1,223-336,033, e-mail: deposit@ccdc.cam.ac.uk).

Dimedone and its derivatives were most often studied as C-nucleophiles. This compound gives mono- and bis-condensation products with aldehydes [40–42]. Therefore, according to Scheme 2, the BrCN plays a major role in these reactions through intermediates **5** and **6** to form **4**. We believe the compound **4** is the key reactant for the synthesis of **3a–z, 3A** and **3B**. No **4** and **3a–z**, **3A** and **3B** were observed in the absence of BrCN and/or Et_3N under the same condition!

We performed the reaction of **1** with BrCN and Et_3N in the absence of aldehyde so we only obtained the salts of **4** and triethylammonium hydrobromide. For understanding about the role of BrCN, reaction of **1** with aldehydes was performed in the absence of BrCN under the same condition. In this reaction, 9-alkyl- and/or 9-aryl-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-diones (**11**) was obtained (Scheme 4) [16–19, 43–45]. The formation of **11** confirms the important role of the BrCN in the formation of **4**.

Next, a variety of aldehydes (aromatics and aliphatics) were selected (under optimum condition) to react with dimedone (Table 1). Various aromatic aldehydes possessing electron-donating and electron-withdrawing substituent reacted smoothly and efficiently under the basic condition, affording the corresponding spiro 6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one derivatives **3** in good yields. The aldehyde with an electron-withdrawing



Scheme 5 Formation of **6** from the reaction of **1** with BrCN in acetone

substituent gave a higher yield than those bearing an electron-donating substituent. Aliphatic aldehydes, including formaldehyde (**2a**), acetaldehyde (**2b**), propionaldehyde (**2c**) and butyraldehyde (**2d**) were also investigated (see "Experimental" and Table 1).

The reaction of **1** with BrCN with less hindered ketone (acetone) was explored under the same condition producing exclusively α-monobrominated **6** in moderate yield (Scheme 5). Surprisingly, the proton of carbon atom of α-brominated **6** was observed in ^{1}H NMR time scale and the IR spectrum showed carbonyl and hydroxyl bonds stretching (see "Experimental"). Interestingly, this intermediate in the solid state does exists as enol form [27].

Conclusion

In summary, a versatile one-pot reaction of dimedone with aldehydes selectively affords spiro dihydrofurans in the presence of cyanogen bromide and triethylamine in good yields. The BrC-mediated oxidative cycloaddition provides an efficient route to the preparation of a wide variety of spiro dihydrofuran derivatives. The experimental results indicated that the aromatic aldehydes possessing electron-withdrawing are more reactive than those with electron-donating substituent or aliphatic aldehydes. The notable advantages of this protocol are mild, clean, good yields, simple reaction conditions and no need of chromatographic separations. The synthesis of spiro dihydrofuran derivatives was not successful using ketones.

Acknowledgments We gratefully acknowledge financial support by the Research Council of Urmia University (Grant Research no. #9-10,523). The authors also gratefully acknowledge to Prof. Dr. Dabbagh H. A. of Isfahan University of Technology (IUT) from Iran for his helpful discussion and guidance.

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