Novel 1*H*-2-benzopyran-1-one and 2,3-benzodiazepin-1-one derivatives

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A number of novel 1*H*-2-benzopyran-1-one derivatives have been synthesised using the readily obtainable starting material obtained from the Stobbe-type condensation of diethyl homophthalate with *p*-anisaldehyde. Bromination, followed by hydrazinolysis, produced the tetrahydro-2,3-benzodiazepin-1-one derivative **5**.

Keywords: isocoumarins, isoquinolinones, homophthalic esters, 2-benzopyran-1-ones

1*H*-2-Benzopyran-1-ones (isocoumarins) and their 3,4-dihydro derivatives are a class of natural products that occur as microbial metabolites and exhibit interesting biological properties.[1-12] The authors' objective was to construct the desired isocoumarin derivatives and study their behaviour towards different nucleophilic reagents.

Results and discussion

The condensation of *p*-anisaldehyde with dimethyl homophthalate in the presence of sodium hydride in dry benzene afforded the (*Z*)-half ester **1** (85%) together with the (*Z*)-diester **2** (15%). The preferential formation of the Z-configuration for the half ester **1** and the diester **2** may be rationalised by considering the strain associated with the (*E*)-isomer due to steric interference between the *o*-carboxyphenyl (or *o*-methoxycarbonylphenyl) and the bulky substituted aryl group.

4-Bromo-4-methoxycarbonyl-3-(4-methoxyphenyl)-3,4-dihydro-1*H*-2-benzopyran-1-one (**3**) was formed as the sole product via the treatment of the (*Z*)-half ester **1** with a mixture of bromine and acetic acid. The reaction of the isocoumarin derivative **3** with thiourea in ethanol yielded the thioisocoumarin derivative **4**. The primary element tests indicated the absence of nitrogen and showed the presence of sulfur and bromine. The IR spectrum of **4** revealed absorption bands at 1727 cm^{-1} and 1138 cm^{-1} corresponding to C=O ester and C=S groups, respectively, but no absorption band for the carbonyl group of a δ-lactone. The reaction of compound **3** with hydrazine hydrate afforded the benzodiazepine derivative **5** (Scheme 1).

Mild saponification of **1** and/or **2** yield the (*Z*)-dibasic acid **6**. Cyclisation of **6** using concentrated sulfuric acid at 0ºC yielded the ketolactone **7**, the IR spectrum of which shows strong absorption bands at 1748 cm^{-1} and 1706 cm^{-1} corresponding to δ-lactone and saturated five-membered ketone carbonyls, respectively. Moreover, cyclisation of **6** with acetyl chloride yielded (*Z*)-4-(4-methoxybenzylidene)-3-oxo-3,4-dihydro-1*H*-2-benzopyran-1-one (**8**), and its IR spectrum shows absorption bands at 1770 cm^{-1} and 1729 cm^{-1} expected for a six-membered anhydride (coupled vibrations) with α,β-conjugation. The same product **8** was obtained in fairly high yield upon treatment of **1** with acetic anhydride in the presence of zinc chloride (Scheme 1). Compound **8** is a useful intermediate for the synthesis of heterocyclic compounds, in particular isocoumarins and isoquinolinones, as will be revealed in a later paper.

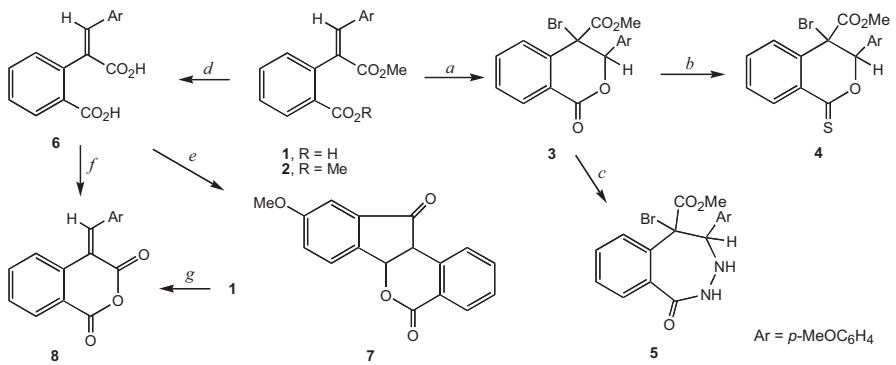
Experimental

Melting points were taken on Griffin & George melting point apparatus. IR spectra were recorded on a Pye-Unicam SP1200 spectrophotometer using the KBr wafer technique. The ^1H NMR spectra were determined on a Varian Gemini 200 MHz, Bruker AC-200 MHz using TMS as internal standard. The mass spectra were determined using HP model MS-5988 at electron energy 70 eV. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University using a Perkin-Elmer 2400 CHN Elemental Analyser**.**

*Methyl (Z)-2-(o-carboxyphenyl)-3-(4-methoxyphenyl)prop-2-enoate (**1**) and methyl (Z)-2-(o-methoxycarbonylphenyl)-3-(4-methoxyphenyl) prop-2-enoate* (**2**)

p-Anisaldehyde (8.16 ml, 0.06 mole) was added dropwise to a solution of dimethyl homophthalate (12.5 g, 0.06 mole) in dry benzene (100 ml) with stirring, then sodium hydride (1.9 g, 0.08 mole) was added. The whole mixture was stirred for 10 minutes (TLC). The solid deposited was filtered off and treated with 10% aqueous sodium carbonate. The alkaline filtrate was acidified and the solid deposited was filtered off, dried and recrystallised to give **1**. The part insoluble in sodium carbonate solution (neutral fraction) was separated by filtration, dried and recrystallised to give **2.**

Acid ester **1:** Colourless crystals (85%, ethanol), m.p. 145–146°C. IR: ν_{max} 3468–2960 br (OH), 1719 (C=O ester), 1687 cm^{-1} (C=O acid). NMR ($CDCl_3$): δ_H 11.2 (s, 1H, COOH), 8.3–6.6 (m, 9Harom + CH=), 3.75 (s, 3H, OMe), 3.6 (s, 3H, CO_2Me); MS: *m/z* (%) 312



Scheme 1 *Reagents: a,* Br_2/AcOH; *b,* $(H_2N)_2C=S$; *c,* $N_2H_4.H_2O$/pyridine; *d,* NaOH/H_2O; *e,* c.H_2SO_4, 0°C; *f,* AcCl; *g,* $Ac_2O/ZnCl_2$

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($M^{+\cdot}$, 58), 252 (17), 194 (5), 121 (100), 91 (5), 65 (4). Anal. Calcd. for $C_{18}H_{16}O_5$ (312.33): C, 69.22; H, 5.16, Found: C, 69.09; H, 5.40%.

Diester **2:** Pale grey crystals (15%, benzene), m.p. 50–51°C. IR: ν_{max} 1702 cm^{-1} (C=O). NMR ($CDCl_3$): δ_H 8.0-6.85 (m, 8H, arom), 6.6 (s, 1H, =CH), 3.8 (s, 3H, Ar-OMe), 3.7 (s, 3H, CO_2Me), 3.65 (s, 3H, CO_2Me). MS: *m/z* (%) 326 (M^+, 100), 252 (30), 165 (44), 91 (14), 77 (22), 65 (18). Anal. Calcd. for $C_{19}H_{18}O_5$ (326.36): C, 69.93; H, 5.56, Found: C, 70.28; H, 5.38%.

Methyl 4-bromo-3,4-dihydro-3-(4-methoxyphenyl)-1-oxo-1H-2-benzopyran-4-carboxylate (**3**)
To compound **1** (1 g, 3 mmol) in acetic acid (15 ml), bromine (1 ml) was added dropwise over 5 minutes with continuous stirring which was continued for a further 10 minutes (TLC). The deposited colourless crystals were filtered off, washed with acetic acid, dried and recrystallised (methanol) to give **3** as colourless crystals (82%), m.p. 180–181°C. IR: ν_{max} 1742 (C=O lactone), 1714 cm^{-1} (CO ester). NMR ($CDCl_3$): δ_H 8.2–6.8 (m, 8H, arom), 5.86 (s, 1H, C_3-H), 3.9 (s, 3H, Ar-OMe), 3.8 (s, 3H, Ar-CO_2Me). Anal. Calcd. for $C_{18}H_{15}BrO_5$ (391.20): C, 55.27; H, 3.86; Br, 20.42; Found: C, 55.19; H, 4.09; Br, 20.16%.

Methyl 4-bromo-3,4-dihydro-3-(4-methoxyphenyl)-1-thioxo-1H-2-benzopyran-4-carboxylate (**4**)
Compound **3** (1 g, 0.0025 mol) and thiourea (1 g, 0.013 mol) were added to a solution of sodium ethoxide [sodium metal (0.125 g) in absolute ethanol (30 ml)] and refluxed for 8 h (TLC). The excess of alcohol was distilled off, and the reaction mixture was poured on ice and hydrochloric acid to give the thionolactam **4**, yellow crystals (48%, recrystallised from benzene), m.p. 105–107°C. IR: ν_{max} 1717 (C=O), 1138 cm^{-1} (C=S). Anal. Calcd. for $C_{18}H_{15}BrO_4S$ (407.27): C, 53.10; H, 3.71; Br, 19.61; S, 7.87. Found: C, 52.96; H, 3.95; Br, 19.85; S, 7.53%.

Methyl 5-bromo-2,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-oxo-1H-2,3-benzodiazepine-5-carboxylate (**5**)
Compound **3** (1 g, 0.0025 mol) and hydrazine hydrate (1.6 ml, 0.05 mol) in pyridine (15 ml) were heated to reflux for 3 h (TLC). The cooled mixture was acidified with cold hydrochloric acid to give brown product which was filtered off, dried and recrystallised to give **5** as light brown crystals (39%), m.p. 95–96°C (from light petroleum ether, b.p. 80–100°C). IR: ν_{max} 1722 (C=O ester), 1651 cm^{-1} (C=O cyclic-imide). Anal. Calcd. for $C_{18}H_{17}BrN_2O_4$ (405.23): C, 53.35; H, 4.23; Br, 19.71; N, 6.91, Found: C, 53.18; H, 4.52; Br, 19.62; N, 6.63%.

(Z)-2-(o-Carboxyphenyl)-3-(4-methoxyphenyl)prop-2-enoic acid (**6**)
Compound **1** (1 g, 3 mmol) or **2** (1 g, 3 mmol) was heated under reflux with aqueous sodium hydroxide (10%, 10 ml) for 3 h (TLC). The reaction mixture was allowed to cool and then poured onto ice/hydrochloric acid. The deposited solid was filtered off, dried and recrystallised to give the acid **6** as white crystals (84%), m.p. 185–186°C (from light petroleum ether b.p. 80–100°C). IR: ν_{max} 2964 (OH), 1680 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 12.6 (br, s, 2H, $2CO_2H$), 8.05–7 (m, 8H, arom.), 6.7 (s, 1H, olefinic H), 3.69 (s, 3H, OMe). MS: *m/z* (%) 298 (M^+, 87), 280 (37), 252 (19), 121 (100), 77 (39). Anal. Calcd. for $C_{17}H_{14}O_5$ (298.30): C, 68.45; H, 4.73, Found: C, 68.28; H, 5.06%.

4b,10b-Dihydro-2-methoxyindeno[1,2-c][2]benzopyran-6,11-dione (**7**)
Compound **6** (0.9 g, 3 mmol) was stirred at 0°C with concentrated sulfuric acid (10 ml) for 30 minutes, then cooled overnight in a refrigerator. The reaction mixture was poured onto ice/cold water and the obtained solid was filtered off, dried and recrystallised (ethanol) to give **7** as buff crystals (86%), m.p. 250–251°C. IR: ν_{max} 1748 (C=O lactone), 1706 cm^{-1} (C=O ketone). MS: *m/z* (%) 280 (M^+, 38), 279 (12), 235 (28), 207 (17). Anal. Calcd. for $C_{17}H_{12}O_4$ (280.29): C, 72.85; H, 4.32. Found: C, 73.11; H, 4.07%.

(Z)-4-(4-Methoxybenzylidene)[2]benzopyran-1,3(4H)-dione (**8**)
The dicarboxylic acid **6** (1 g, 3 mmol) and acetyl chloride (10 ml) were heated to reflux for 10 minutes on water bath. The reaction mixture allowed to cool and the obtained solid was collected by filtration, washed with petroleum ether (80–100°C), dried and recrystallised (benzene) to give **8** as orange crystals (79%), m.p.124–125°C. IR: ν_{max} 1770, 1729 (cyclic anhydride). NMR ($CDCl_3$): δ_H 8.1–7.0 (m, 8H, arom), 6.9 (s, 1H, olefinic H) and 3.9 (s, 3H, OMe). MS: *m/z* (%) 280 (M^+, 84), 252 (24), 236 (7), 193 (52), 165 (100). Anal. Calcd. For $C_{17}H_{12}O_4$ (280.29): C, 72.85; H, 4.32. Found: C, 72.63; H, 4.42%.

Received 7 July 2007; accepted 29 December 2007
Paper 07/4750 doi: 10.3184/030823408X291514

References

1 P.S. Waters and M.C. Koslowski; *Tetrahedron Lett.*, 2001, **42**, 3567.
2 A. Hajipour, S. Mallakpour and G. Imanzadeh, *Indian J. Chem.*, 2001, **40B**, 250.
3 M. Chinworrungs, P. Kittakoop, M. Isaka, R. Chanphen, M. Tanticharoen and Y. Thebtaranonth, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2473.
4 F. Karina, M. Devienna, G. Stela Raddi, A. Eliana and Z. Varand, *Z. Naturforsch.*, 2002, **57**, 85.
5 I.D. Kozekov, R.I. Koleva and M.D. Palamareva, *J. Heterocyclic Chem.*, 2002, **39**, 229.
6 M.P. Stephen, I.D. Kozekov and M.D. Palamareva, *J. Heterocyclic Chem.*, 2003, **40**, 795.
7 J.S. Yadav, B.V.S. Reddy, K. Saritha Raj and A.R. Prasad, *Tetrahedron*, 2003, **59**, 1805.
8 Z. Zalan, T.A. Martink, L. Lazar and F. Fülöp, *Tetrahedron*, 2003, **59**, 9117.
9 T.R. Kane, C.Q. Ly, D.E. Kelly and J.M. Denner, *J. Combin. Chem.*, 2004, **6**, 564.
10 R. Gitto, M. Barreca, E. Francica, R. Caruse, L. De Luca, E. Russo, G. De Sarro and A. Chimirri, *Arkivoc*, 2004, 170.
11 J. Azizian, A.A. Mohammadi, A.R. Karami and M.R.A. Mohammadizadeh, *J. Org. Chem.*, 2005, **70**, 350.
12 M.I. Kandinska, I.D. Kozekov and M.D. Palamareva, *Molecules*, 2006, **11**, 403.