Efficient and Chemoselective Methods for the Synthesis of Some Isobenzofuran and Spiro[isobenzofuran-1,2′-pyrrole] Derivatives

by **Mohammad R. Mohammadizadeh***, **Neda Firoozi**, and **R. Aradeh**

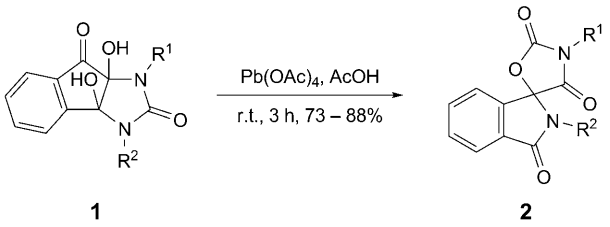
Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran (phone/fax: +98-771-4541494; e-mail: mrmohamadizadeh@pgu.ac.ir)

An efficient and practical one-pot procedure for the direct chemoselective synthesis of isobenzofuran and spiro[isobenzofuran-1,2′-pyrrole] derivatives is developed *via* oxidative cleavage of 3a,8b-dihydroxyindeno[1,2-*b*]pyrrol-4-ones with $Pb(OAc)_4$ at room temperature.

Introduction. – Substituted phthalides (= isobenzofuran-1(3*H*)-ones) represent an important class of natural products that possess significant biological properties [1]. In particular, 3-substituted phthalides are vital heterocyclic motifs in many bioactive compounds such as isocoumarins, anthraquinones, anthracyclines, and several alkaloids [2]. Their notable characteristics include antibacterial, anticonvulsant, anti-HIV, anti-asthmatic, antitumor, antiplatelet activities, anesthesia prolongation, and $PGF_{2\alpha}$ inhibitory properties [3]. Furthermore, the chemistry of isobenzofurans is of great importance, because they are 10π electron systems with a quinoid nature, which makes them attractive as unique building units for oligomeric and polymeric π-conjugated compounds [4][5].

Results and Discussion. – Recently, we reported a novel and simple method for the synthesis of spiro[isoindole-1,5′-oxazolidine] **2**, as part of our research program on the oxidative cleavage of 3a,8a-dihydroxyindeno[2,1-*d*]imidazole-2,8-diones **1** (*Scheme 1*) [6].

Scheme 1. *Our Previous Study* [6] *on Synthesis of Spiro[isoindole-1,5′-oxazolidine]* **2** via *Oxidative Cleavage of 3a,8a-Dihydroxyindeno[2,1-*d*]imidazole-2,8-diones* **1**



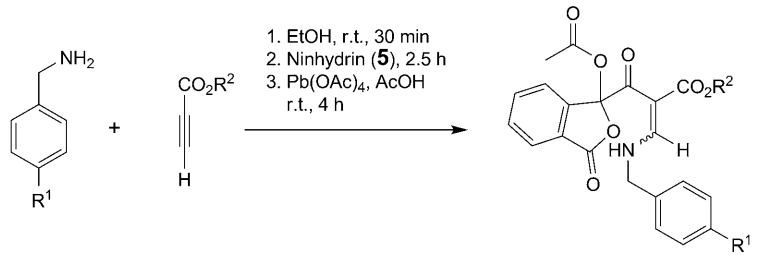
1 **2**

In continuation, we focused on the oxidation of some similar cyclic vicinal dihydroxy compounds, *e.g.*, 3a,8b-dihydroxy-3a,8b-dihydroindeno[1,2-*b*]pyrrol-4(1*H*)-

ones **8** (*cf. Scheme 3*), which could easily be prepared by the addition reaction of ninhydrin **5** and enamine esters **7** [7].

When $Pb(OAc)_4$ was added to a mixture of benzylamine **3**, prop-2-ynoate **4**, and ninhydrin **5**, 2-{[1-(acetyloxy)-1,3-dihydro-3-oxoisobenzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoates **6** were achieved in excellent yields (*Scheme 2*). Using this one-pot procedure, the reactions were completed after *ca.* 7 h as shown by TLC. However, the same results were obtained when pure **8** were exposed to $Pb(OAc)_4$.

Scheme 2. *Synthesis of 2-{[1-(Acetyloxy)-1,3-dihydro-3-oxo-2-benzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoate Derivatives* **6a**–**6c**



3a R^1 = MeO **4a** R^2 = Et
3b R^1 = H **4b** R^2 = Me

	R^1	R^2	Yield [%]	(*E*)/(*Z*) ratio
6a	MeO	Et	82	62:38
6b	H	Et	92	57:43
6c	H	Me	90	56:44

The NMR data and elemental analysis confirmed the proposed structures of the products **6a**–**6c**. The ^{1}H-NMR spectrum of products **6a**–**6c** indicated two diastereoisomeric (*E*)- and (*Z*)-compounds. For example, the ^{1}H-NMR spectrum of **6a** in $CDCl_3$ exhibited two *triplet*s at 0.94 and 1.20 ppm both with $J = 7$ Hz, which were attributed to the Me groups of esters, together with two sharp *singlet*s at 1.72 and 2.14 ppm, which were assigned to the Me groups of acetate moieties. *Fig. 1* shows the temperature-dependence of the ^{1}H-NMR spectrum of **6a**, recorded in (D_6)DMSO, for the Et resonance regions. The ester CH_2 group of the two diastereoisomers resonated as four *doublet*s of *quartet*s (two *AB* systems); two of them at 3.66 and 3.82 ppm, and two others overlapped at 3.98 ppm. The *multiplet*s at 3.98 ppm were separated into two $d \times q$ by recording the ^{1}H-NMR spectra in $CDCl_3$; the *multiplet*s at 1.06 and 4.13 ppm probably arise from a **6a**–DMSO complex, because it disappeared at elevated temperatures, as well as by recording the spectrum in $CDCl_3$. A ^{1}H-decoupled ^{13}C-NMR spectrum of **6a** showed distinct signal pairs for all aliphatic, spiro and C=O C-atoms indicating that the product is a mixture of diastereoisomers. The C=O groups of the isobenzofuran ring, esters, and enaminone resonated at 189.0, 168.9, 166.5, and 160.1 ppm, respectively.

However, only single crystals of the (*E*)-stereoisomer were formed during crystallization of **6a** from $CHCl_3$/hexane, which allowed determination of its structure unambiguously by an X-ray diffraction analysis[1]) (*Fig. 2*). The crystal structure of **6a**

[1]) CCDC-770133 contains the supplementary crystallographic data. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

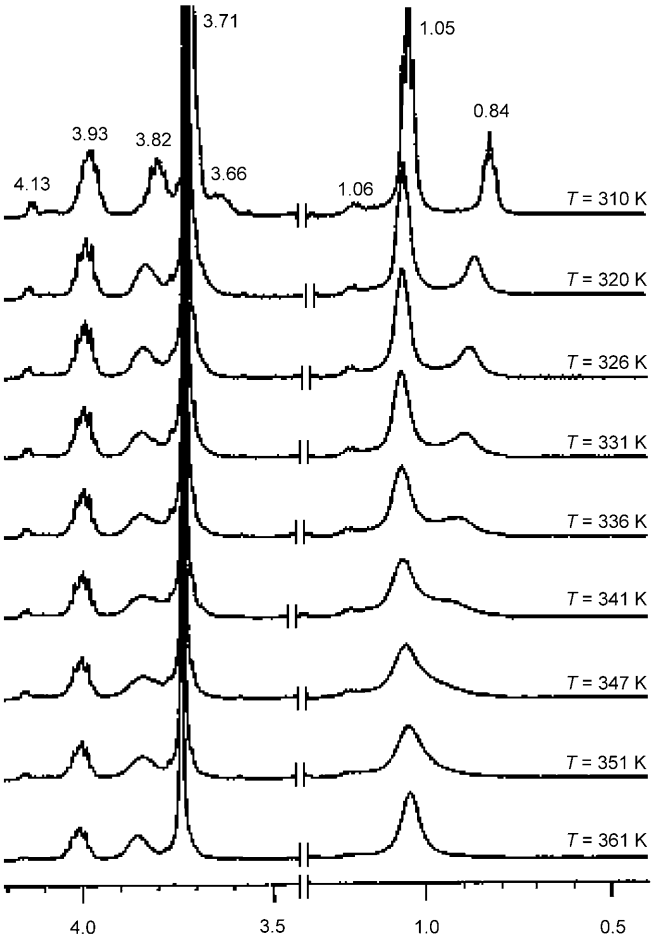


Fig. 1. *Aliphatic region of dynamic ^{1}H-NMR spectra of compound* **6a** *recorded in (D_6)DMSO*

also shows a H_2O molecule in its structure. This H_2O molecule, apparently, has been removed from the products **6** by drying at around 70°, to record the NMR spectra. Consequently, the recorded ^{1}H-NMR spectra of compounds **6** do not contain the signal of the H_2O of hydration.

The ^{1}H-NMR spectra of the single crystals of (*E*)-**6a** was also recorded, which shows the same signals as its initial uncrystallized compound. This shows that (*E*)- and (*Z*)-diastereoisomers are easily interconverted by dissolving the (*E*)-stereoisomer in a solvent.

Mechanistically, it is reasonable to propose that enaminones **7**, prepared from benzylamines **3** and acetylenic ester **4**, were added to ninhydrin **5** to form dihydroxyindeno[1,2-*b*]pyrrol derivatives **8** [7a]. Subsequently, oxidation of **8** gave the corresponding benz[*c*]azocine-1,5,6-triones **9a**, which were hydrolyzed to give benzoic acid derivative **10**. Finally, products **6** were formed *via* intramolecular

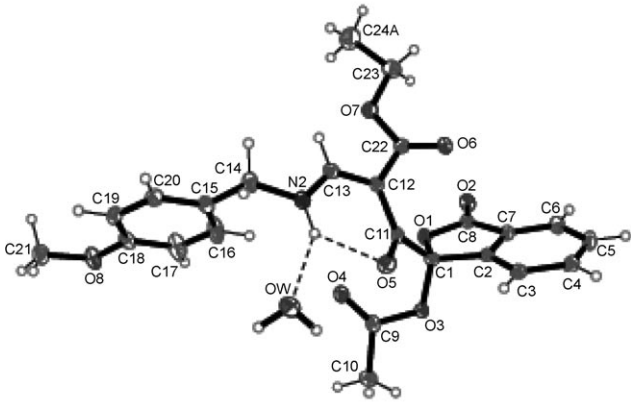
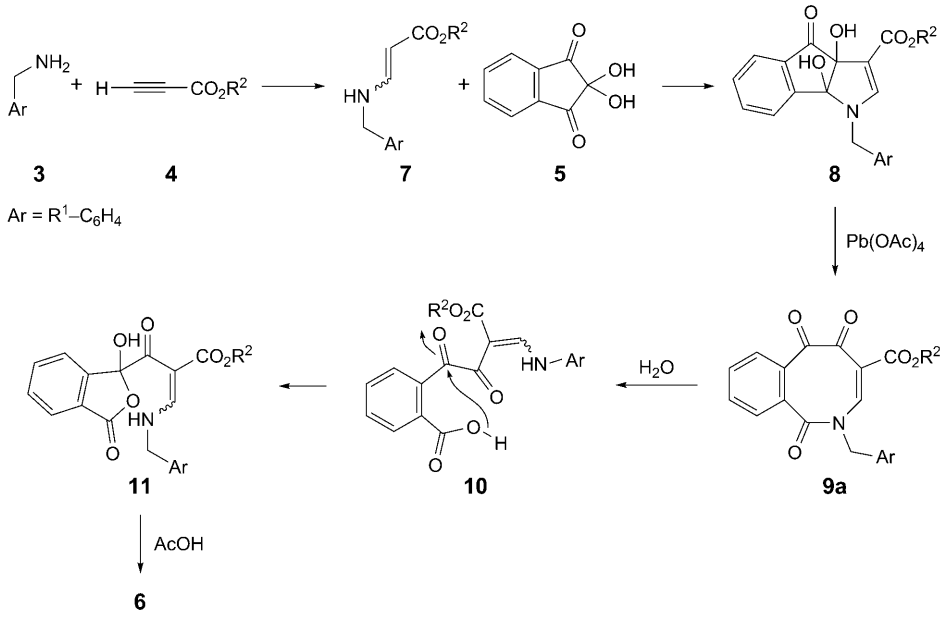


Fig. 2. *X-Ray crystal structure of* **6a**

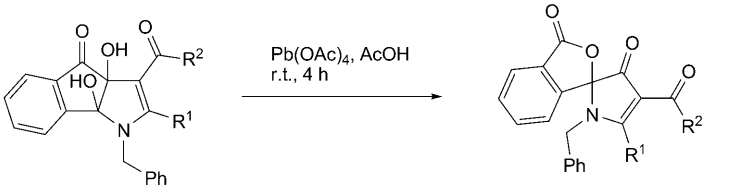
cyclization of **10** to 3-hydroxyisobenzofuran-1-one derivatives **11**, followed by esterification with AcOH (*Scheme 3*).

Scheme 3. *Proposed Mechanism for the One-Pot Synthesis of Prop-2-enoates* **6**



Interestingly, when the reaction was run for 3a,8b-dihydroxy-3a,8b-dihydroindeno[1,2-*b*]pyrrol-4(1*H*)-ones **12**, the corresponding 3*H*-spiro[isobenzofuran-1,2′-pyrrole]-3,3′(1′*H*)-diones **13** were obtained in good yields (*Scheme 4*). The structures of products **13a** and **13b** were unambiguously established based on their NMR, IR, and MS data, as well as CHN analysis. Contrary to compounds **6**, in the ^{1}H-NMR spectra of

Scheme 4. *Synthesis of Spiro[isobenzofuran-1,2′-pyrrole] Derivatives* **13a** *and* **13b**



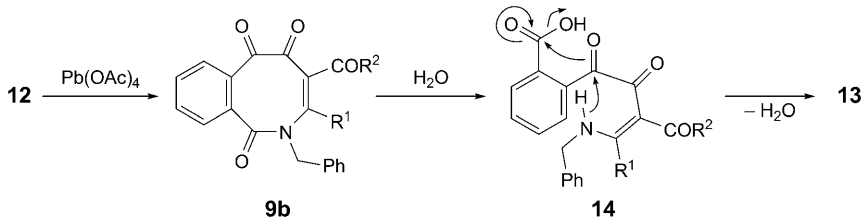
	R^1	R^2
12a	CO_2Me	MeO
12b	Ph	Ph

	R^1	R^2	Yield [%]
13a	CO_2Me	MeO	80
13b	Ph	Ph	84

products **13**, no signals for acetate moieties were detected, and diastereotopic CH_2 H-atoms resonated as two distinct *doublet*s, in the case of **13a** at 4.28 and 4.35 ppm with $J = 15.4$ Hz.

A mechanistic proposal for the formation of spiro[isobenzofuran-1,2′-pyrrole] derivatives **13** is presented in *Scheme 5*. It is reasonable to assume that benzo[*c*]azocine-1,5,6-triones **9b** could gave **13** *via* hydrolysis to benzoic acid derivatives **14**, which underwent cyclization by attack of the amino group on C=O, followed by intramolecular esterification with the carboxylic acid.

Scheme 5. *Proposed Mechanism for the Synthesis of Spiro[isobenzofuran-1,2′-pyrrole] Derivatives* **13**



In summary, we investigated the oxidative cleavage of dihydroxyindeno[1,2-*b*]pyrroles **8** and **12** with $Pb(OAc)_4$ in AcOH at room temperature, and developed novel and effective chemoselective procedures for the synthesis of 2-{[1-(acetyloxy)-1,3-dihydro-3-oxoisobenzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoate **6** and spiro[isobenzofuran-1,2′-pyrrole] derivatives **13**.

Experimental Part

General. Chemicals were of commercial grade and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-470* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$ on a *Bruker 500 DRX AVANCE* at 500 and 125 MHz, resp. EI-MS: *Shimadzu QP 1100EX* mass spectrometer operating at an ionization potential of 14 eV. Elemental analyses (CHN): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the One-Pot Synthesis of 2-{[1-(Acetyloxy)-1,3-dihydro-3-oxoisobenzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoate Derivatives **6a**–**6c**. A mixture of benzylamine **3** (1 mmol), acetylenic ester **4** (1 mmol), and EtOH (1 ml) was stirred at r.t. for 0.5 h. Then, ninhydrin (**5**; 1 mmol)

was added, and the mixture was stirred for 2.5 h. After addition of $Pb(OAc)_4$ (1.1 mmol) and AcOH (3 ml), stirring was continued for further 4 h, and then H_2O was added. The mixture was filtered, and the products **6a**–**6c** were purified by recrystallization from EtOH or by column chromatography (CC) with AcOEt/hexane 1:1.

Ethyl 2-{[1-(Acetyloxy)-1,3-dihydro-3-oxo-2-benzofuran-1-yl]carbonyl}-3-[(4-methoxybenzyl)amino]prop-2-enoate (**6a**; (*E*)/(*Z*) 62:38). Purified by CC (AcOEt/hexane 1:1). Yield: 0.37 g (82%). M.p. 115–117°. IR (KBr): 3243.7, 1770.5, 1695.4, 1656.2, 1581.4. ^{1}H-NMR ($CDCl_3$): 0.94 (*t*, *J* = 7.0, 1.14 H, *Me*CH_2); 1.20 (*t*, *J* = 11.9, 1.86 H, *Me*CH_2); 1.72 (*s*, 1.11 H, MeCO); 2.14 (*s*, 1.89 H, MeCO); 3.78–3.81 (*m*, 0.71 H, MeCH_2); 3.85 (*s*, MeO); 3.9–4.04 (*m*, 1.29 H, MeCH_2); 4.07–4.10 (*m*, 0.71 H, MeCH_2); 4.15–4.21 (*m*, 1.29 H, MeCH_2); 4.48–4.53 (*m*, NHCH_2); 6.93–6.95 (*m*, 2 arom. H); 7.21–7.24 (*m*, 2 arom. H); 7.63–8.04 (*m*, 4 arom. H); 9.30–9.33 (*m*, 0.35 H, NH); 10.12 (*m*, 0.65 H, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.4; 14.7; 21.2; 21.3; 53.7; 55.8; 60.3; 60.8; 98.9; 100.0; 114.9; 123.9; 124.5; 125.8; 125.9; 127.0; 127.7; 128.0; 128.5; 129.3; 129.4; 131.3; 131.4; 134.5; 135.0; 145.1; 145.4; 160.0; 160.1; 160.2; 166.6; 168.9; 169.2; 189.0; 189.5. Anal. calc. for $C_{24}H_{23}NO_8$ (453.44): C 63.57, H 5.11, N 3.09; found: C 63.49, H 5.04, N 3.17.

Ethyl 2-{[1-(Acetyloxy)-1,3-dihydro-3-oxo-2-benzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoate (**6b**; (*E*)/(*Z*) 57:43). Recrystallized from EtOH. Yield: 0.38 g (92%). M.p. 125–126°. IR (KBr): 3048.2, 3050.1, 1751.0, 1749.1, 1695.1, 1639.2, 1592.9. ^{1}H-NMR ($CDCl_3$): 0.95 (*t*, *J* = 7.1, 1.29 H, *Me*CH_2); 1.20 (*t*, *J* = 7.1, 1.71 H, *Me*CH_2); 2.14 (*s*, MeCO); 3.78–3.83 (*m*, 0.86 H, MeCH_2); 3.89–4.02 (*m*, 1.14 H, MeCH_2); 4.11–4.15 (*m*, 0.86 H, MeCH_2); 4.15–4.21 (*m*, 1.14 H, MeCH_2); 4.54–4.61 (*m*, NHCH_2); 7.29–7.43 (*m*, 4 arom. H); 7.65–7.80 (*m*, 3 arom. H); 7.96–7.99 (*m*, 2 arom. H); 9.35–9.39 (*m*, 0.37 H, NH); 10.13–10.20 (*m*, 0.63 H, NH). ^{13}C-NMR ($CDCl_3$): 14.4; 14.7; 21.2; 21.3; 54.2; 60.3; 60.8; 99.1; 100.3; 123.9; 124.5; 125.8; 125.9; 127.0; 127.7; 127.8; 127.9; 128.7; 128.8; 129.4; 129.5; 131.4; 131.5; 134.5; 135.0; 136.2; 136.5; 145.1; 145.2; 160.2; 160.4; 166.5; 167.7; 168.9; 169.2; 189.3; 189.5. Anal. calc. for $C_{23}H_{21}NO_7$ (423.42): C 65.24, H 5.00, N 3.31; found: C 65.14, H 5.00, N 3.39.

Methyl 2-{[1-(Acetyloxy)-1,3-dihydro-3-oxo-2-benzofuran-1-yl]carbonyl}-3-(benzylamino)prop-2-enoate (**6c**; (*E*)/(*Z*) 56:44). Purified by CC (AcOEt/hexane). Yield: 0.37 g (90%). M.p. 135–137°. IR (KBr): 3309.2, 3286.1, 1766.5, 1760.7, 1683.3, 1600.6, 1592.9. ^{1}H-NMR ($CDCl_3$): 2.13 (*s*, OCOMe); 3.4 (*s*, 1.32 H, MeO); 3.6 (*s*, 1.68 H, MeO); 4.57–4.63 (*m*, CH_2); 7.29–7.30 (*m*, 2 arom. H); 7.34–7.43 (*m*, 3 arom. H); 7.60–7.81 (*m*, 3 arom. H); 7.96–8.06 (*m*, 1 arom. H); 9.38–9.43 (*m*, 0.45 H, NH); 10.11–10.19 (*m*, 0.55 H, NH). ^{13}C-NMR ($CDCl_3$): 21.2; 21.3; 41.3; 51.3; 52.0; 54.2; 98.8; 99.8; 123.8; 124.5; 125.6; 125.8; 127.0; 127.7; 127.8; 127.9; 128.7; 128.8; 129.5; 129.6; 131.4; 131.5; 134.6; 135.0; 136.1; 136.4; 145.0; 145.2; 160.5; 160.7; 166.9; 168.3; 168.9; 169.2; 189.2; 189.8. Anal. calc. for $C_{22}H_{19}NO_7$ (409.39): C 64.54, H 4.68, N 3.42; found: C 64.62, H 4.61, N 3.32.

*General Procedure for the One-Pot Preparation of 3*H*-Spiro[2-benzofuran-1,2′-pyrrole] Derivatives* **13a** *and* **13b**. A mixture of indeno[1,2-*b*]pyrrole-2,3-diol **12** (1 mmol) and $Pb(OAc)_4$ (1.1 mmol) in AcOH (3 ml) was stirred at r.t. for 4 h. Then, H_2O was added, and the precipitated products **13** were separated from the mixture by filtration and further purified by recrystallization from EtOH.

*Dimethyl 1′-Benzyl-1′,3′-dihydro-3,3′-dioxo-3*H*-spiro[2-benzofuran-1,2′-pyrrole]-4′,5′-dicarboxylate* (**13a**). Yield: 0.32 g (80%). M.p. 190–191°. IR (KBr): 1787.7, 1737.5, 1689.3, 1548.6, 1540.8. ^{1}H-NMR ($CDCl_3$): 3.77 (*s*, MeO); 3.86 (*s*, MeO); 4.28 (*d*, *J* = 15.4, 1 H of CH_2); 4.35 (*d*, *J* = 15.4, 1 H of CH_2); 7.01–7.03 (*m*, 2 arom. H); 7.15–7.21 (*m*, 4 arom. H.); 7.55–7.57 (*m*, 2 arom. H); 7.87–7.88 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 49.4; 52.2; 54.3; 94.8; 101.4; 122.7; 126.7; 127.0; 129.0; 129.1; 129.2; 131.9; 133.5; 135.5; 141.9; 161.4; 162.5; 167.4; 173.4; 187.5. Anal. calc. for $C_{22}H_{17}NO_7$ (407.37): C 64.86, H 4.21, N 3.44; found: C 64.77, H 4.31, N 3.40.

*4′-Benzoyl-1′-benzyl-5′-phenyl-3*H*-spiro[2-benzofuran-1,2′-pyrrole]-3,3′(1′*H*)-dione* (**13b**). Yield: 0.39 g (84%). M.p. 207–208°. IR (KBr): 1788.5, 1690.8, 1655.2, 1590.6, 1553.4. ^{1}H-NMR ($CDCl_3$): 4.37 (*d*, *J* = 15.6, 1 H of CH_2); 4.42 (*d*, *J* = 15.6, 1 H of CH_2); 6.85 (*d*, *J* = 7.1, 2 arom. H); 7.06–7.12 (*m*, 3 arom. H); 7.33–7.36 (*m*, 3 arom. H); 7.44–7.60 (*m*, 8 arom. H); 7.74 (*dd*, *J* = 7.7, 0.9, 2 arom. H); 7.84 (*d*, *J* = 7.6, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 48.6; 95.1; 111.8; 122.5; 126.6; 127.2; 128.0; 128.3; 128.4; 128.5; 129.0; 129.4; 129.7; 129.9; 131.6; 131.7; 133.0; 134.7; 135.3; 138.5; 143.1; 167.8; 185.0; 188.9; 189.0. Anal. calc. for $C_{31}H_{21}NO_4$ (471.50): C 78.97, H 4.49, N 2.97; found: C 78.90, H 4.41, N 3.06.

The authors thank the *Research Council of the Persian Gulf University of Bushehr* for financial support for this work. We would like also to thank Dr. *M. Helliwell* at the University of Manchester, UK, for X-ray data.

REFERENCES

[1] S. M. Landge, M. Berryman, B. Török, *Tetrahedron Lett*. **2008**, *49*, 4505; R. Pedrosa, S. Sayalero, M. Vicente, *Tetrahedron* **2006**, *62*, 10400; X. Z. Zhu, X.-Y. Li, J. Liu, *Eur. J. Pharmacol*. **2004**, *500*, 221; G. Lin, S. S.-K. Chan, H.-S. Chung, S.-L. Li, 'Chemistry and Biological Action of Naturally Occurring Phthalides', in 'Studies in Natural Products Chemistry', Ed. Atta-ur-Rahman, Elsevier, Amsterdam, 2005, Vol. 32, p. 611.

[2] N. S. Narasimhan, R. S. Mali, *Synthesis* **1975**, 796; J. E. Baldwin, K. W. Bair, *Tetrahedron Lett.* **1978**, *19*, 2559; K. S. Kim, M. W. Spatz, F. Johnson, *Tetrahedron Lett*. **1979**, *20*, 331; P. Pahari, B. Senapati, D. Mal, *Tetrahedron Lett.* **2004**, *45*, 5109; D. Mal, P. Pahari, S. R. De, *Tetrahedron* **2007**, *63*, 11781.

[3] J. Safari, H. Naeimi, A. A. Khakpour, R. S. Jondani, S. D. Khalili, *J. Mol. Catal. A: Chem.* **2007**, *270*, 236; S. F. Brady, M. M. Wagenaar, M. P. Sing, J. E. Janso, J. Clardy, *Org. Lett*. **2000**, *2*, 4043; K. Yoganathan, C. Rossant, S. Ng, Y. Huang, M. S. Butler, A. D. Buss, *J. Nat. Prod*. **2003**, *66*, 1116; P. V. Ramachandran, G.-M. Chen, H. C. Brown, *Tetrahedron Lett*. **1996**, *37*, 2205; H. Yang, G.-Y. Hu, J. Chen, Y. Wang, Z.-H. Wang, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5210; S. Mor, S. N. Dhawan, M. Kapoor, D. Kumar, *Tetrahedron* **2007**, *63*, 594; E. W. Bousquet, M. D. Moran, J. Harmon, A. L. Johnson, J. C. Summers, *J. Org. Chem*. **1975**, *40*, 2208.

[4] A. O. Patil, A. J. Heeger, F. Wudl, *Chem. Rev.* **1988**, *88*, 183; J. Roncali, *Chem. Rev.* **1997**, *97*, 173.

[5] H. Zhang, A. Wakamiya, S.Yamaguchi, *Org. Lett.* **2008**, *10*, 3591, and refs. cit. therein.

[6] M. R. Mohammadizadeh, N. Firoozi, *Tetrahedron Lett*. **2010**, *51*, 2467.

[7] a) J. Azizian, F. Hatamjafari, A. R. Karimi, M. Shaabanzadeh, *Synthesis* **2006**, 765; b) A. Ziyaei-Halimehjani, M. R. Saidi, *Tetrahedron Lett*. **2008**, *49*, 1244.

Received June 26, 2010