Conversion of 3-arylphthalides into anthrones with a methylcarbonyl substituent at the C-10 position.

Adam Bieniek*, Monika M. Bartczak and Jan Epsztajn

Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, 90-136 Łódź, Narutowicza 68, Poland

The ortho-lithiation of a benzoic acid anilide followed by condensation with an aryl aldehyde gave a 3-arylphthalide. Reductive alkylation with 1-methoxy-1-trimethylsilyloxyethene gave a substituted aromatic carboxylic acid which was cyclised to an anthrone bearing a methoxycarbonyl methylene unit at C-10.

Keywords: Mukaiyama reaction, benzoic acids, acetoacetic esters, 6-methyl-1,3-dioxin-4-one, anthrones

Recently there has been increased activity directed towards the preparation of anthrones alkylated at the C-10 position. Some members of this family have been found in nature and possess a variety of biological properties.[1-5] For example it has been observed that anthrones bearing alkl and carbonyl substitutents at C-10 are potent inhibitors of leukotriene B_4 biosynthesis.[1] A compound with an acetic acid methyl ester connected to the C-10 carbon atom was isolated from *Rubus ulmifolius* and showed antimicrobial activity against *Staphylococcus aureus*.[4] Our attention has been focused on obtaining a synthetic methodology leading to anthrone derivatives in which a methylcarbonyl group is attached to the C-10 position.

Consequently, we now report an efficient strategy for the transformation of aromatic carboxylic acids **A** into the desired anthrones **B** (as is depicted in Scheme 1) in three steps, starting from the benzoic acid anilides **1**.

Recently we have reported[6] that a secondary carboxamide moiety provides an excellent possibility for a regioselective synthesis of 3-arylphthalides, which are the key starting materials here.

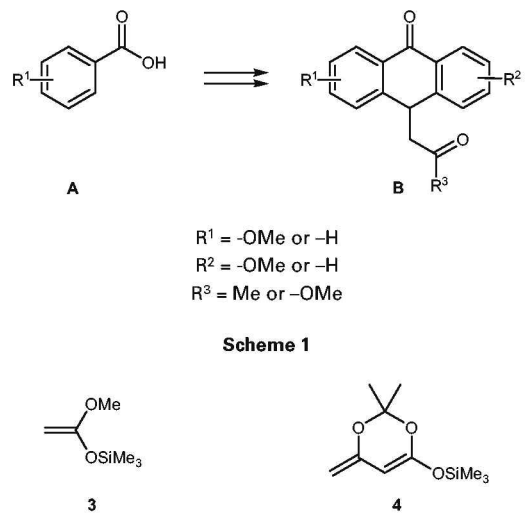
3-Arylphthalides **2** were obtained by the lithiation of benzoic acids anilides **1** using *n*-BuLi in THF[7,8] followed by the reaction of the resultant bis(*N*-and *C-ortho*)lithiated anilides with aromatic aldehydes. The *ortho*-hydroxymethylated anilides which were formed gave the corresponding phthalides **2** (Scheme2) as a result of acid-catalysed cyclisation.

In the following step the phthalides **2** were reductively alkylated at the C-3 position by reaction with 1-methoxy-1-trimethylsilyloxyethene (**3**) or 2,2-dimethyl-6-methylene-4-trimethoxysilyloxy-4*H*-[1,3]diox-4-ene (**4**) (Fig. 1) in the presence of $TiCl_4$ (Mukaiyama reaction conditions[9,10]). In the first case, the esters **5a**, **5b** were formed.[7] On the other hand, reaction of the phthalide **2** with compound **4** gave the corresponding dioxins **6** which on hydrolysis in boiling toluene furnished the ketones **5c**, **5d** and **5e**[11] (Scheme 2).

It was anticipated that treatment of the compounds (**5**), with trifluoroacetic acid anhydride (TFAA) (Friedel–Crafts cyclisation[12]) would provide an effective route to the desired C10-substituted anthrones **7**. In practice, compounds **5** when treated with TFAA in methylene chloride produced the corresponding anthrones **7** in satisfactory yield (Scheme 2). The IR and proton NMR data indicated that the compounds which were formed were pure keto-forms. No enols were detected.

In conclusion, we have developed a novel general strategy for the preparation of C10-substituted anthrones. The procedure is useful particularly because of its efficiency, the ready availability of the starting materials and the ease of operation.

* Correspondent. E-mail: bieniek@uni.lodz.pl



Scheme 1

Fig. 1

Experimental

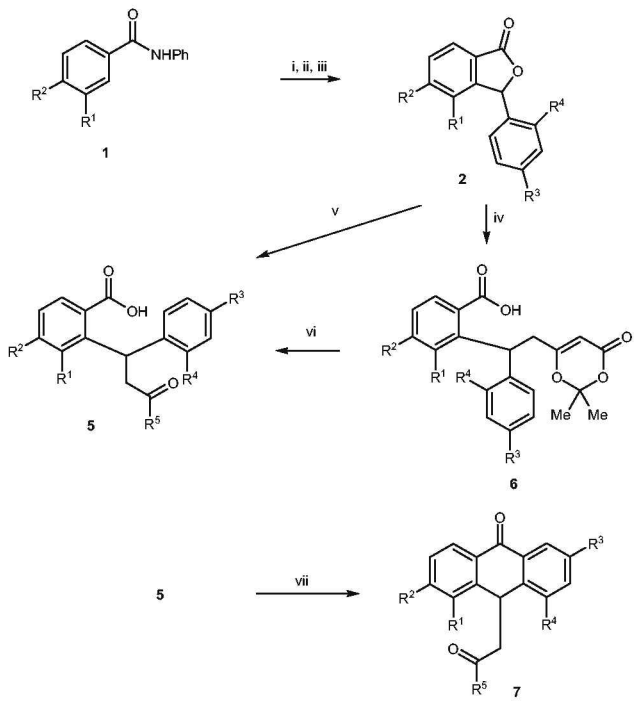
M.p.s were determined using a Boetius hot-stage apparatus and they are uncorrected. IR spectra were recorded on a NEXUS FT-IR (KBr pellets). NMR analyses were performed on a Varian-Gemini-200 (200 MHz) using TMS as an internal standard in $CDCl_3$; chemical shifts are quoted in ppm. Compounds were purified until observed as single spots on TLC (Kieselgel GF-254 type 60). Tetrahydrofuran was distilled before use from sodium-benzophenone ketyl, and dichloromethane was dried over molecular sieves, 3A. Other solvents and reagents were purified according to standard procedures where appropriate. *n*-Butyllithium (*n*-BuLi) (Aldrich) was titrated before use. Reaction temperatures were recorded as bath temperatures. Elemental analysis was carried out by the Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Łódź. Compounds **5a–c** and **5e** were obtained by known methods.[7,11]

4-Methoxy-2-[1-(2-methoxyphenyl)-3-oxobutyl]-benzoic Acid (**5d**): A solution of 0.01 mol of acid **6** in 20 cm^3 of toluene and 10 cm^3 of water was heated to boiling for 12 h. The mixture was extracted with chloroform (3 × 20 cm^3). Then the combined extracts were evaporated to dryness, crude products **5d** was purified by crystallisation.

Yield 68%; M.p. 139–140 °C (white needles from diisopropyl ether/ethyl acetate/hexane 6:2:1); IR (KBr): 1709, 1684, cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 7.89–7.85 (m, 1H, ArH), 7.26–7.19 (m, 2H, ArH), 6.80–6.66 (m, 4H, ArH), 5.72 (t, 1H, J = 7.0 Hz, CH), 3.74 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.36 (dd, 1H, J_1 = 8.7 Hz, J_2 = 17.0 Hz, CH_2), 3.15 (dd, 1H, J_1 = 7.1 Hz, J_2 = 17.0 Hz, CH_2), 2.19 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 209.3, 170.7, 162.2, 156.8, 146.3, 133.1, 130.9, 127.9, 126.5, 120.3, 114.6, 110.6, 110.5, 55.2, 49.1, 35.3, 29.6. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.09. Found: C, 69.60; H, 6.01%.

Cyclisation of compounds 5 using trifluoroacetic acid anhydride; general procedure

To the stirred solution of acids **5** (0.01 mol) in 10 cm^3 of CH_2Cl_2 was added of TFAA at 0 °C. The mixture was stirred for 10–72 h at room temperature. Next, the solvent was evaporated *in vacuo* and crude



a, $R^1 = R^4 = -OMe$; $R^2 = R^3 = -H$; $R^5 = -OMe$;
b, $R^1 = R^4 = -H$; $R^2 = R^3 = -OMe$; $R^5 = -OMe$;
c, $R^1 = R^2 = R^4 = -H$; $R^3 = -OMe$; $R^5 = -Me$;
d, $R^1 = R^3 = -H$; $R^2 = R^4 = -OMe$; $R^5 = -Me$;
e, $R^1 = R^3 = -OMe$; $R^2 = R^4 = -H$; $R^5 = -Me$;

Scheme 2

Step	Reagent	Molar ratios	Temperature	Reaction time
i	n-BuLi in THF/hexane	1:2.2	–78 °C → 0 °C	1 h
ii	Ar-CHO	1:1.2	–78 °C → 20 °C	1 h
iii	HCl (1:1)	excess		
iv–1	**4** in $CH_2Cl_2/TiCl_4$	1:1.1	-78 °C	7 h
iv–2	$KHSO_4$ 5% aq	excess	r.t	
v–1	**3** in $CH_2Cl_2/TiCl_4$	1:3	0°C → r.t.	4 h
v–2	$KHSO_4$ 5% aq	excess	r.t.	
vi	H_2O/toluene		reflux	10 h
vii	TFAA/0°°C		r.t.	10–72 h

products were purified by preparative TLC (chloroform/acetone 7:3), and the solid residue washed the mixture benzene/hexane 1:1.

Methyl 2-(1,8-dimethoxy-10-oxo-9,10-dihydroanthracen-9-yl) acetate (**7a**): Reaction time: 24 h. Yield 68%; m.p. 198–200 °C (needles from benzene/hexane 1:1); IR (KBr): 1733, 1659 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.95–7.80 (m, 2H, ArH), 7.51–7.34 (m, 2H, ArH) 7.18–7.05 (m, 2H, ArH), 4.99 (m, 1H, CH), 3.97 (s, 6H, OCH_3), 3.27 (s, 3H, OCH_3), 3.07 (d, 2H, $J = 5.0$ Hz, CH_2); ^{13}C NMR ($CDCl_3$) 171.3, 156.1, 134.1, 131.8, 127.8, 119.0, 113.9, 102.9, 97.6, 55.7, 51.1, 38.3, 29.1. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.6. Found: C, 69.8; H, 5.7%.

Methyl 2-(2,6-Dimethoxy-10-oxo-9,10-dihydroanthracen-9-yl) acetate (**7b**): Reaction time: 24 h. Yield 46%; m.p. 264–266 °C (needles from benzene/hexane 1:1); IR (KBr): 1733, 1659 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.88–7.85 (m, 2H, ArH), 7.45–7.37 (m, 2H, ArH) 7.13–7.09 (m, 2H, ArH), 4.97 (m, 1H, CH), 3.95 (s, 6H, OCH_3), 3.26 (s, 3H, OCH_3), 3.06 (d, 2H, $J = 4.7$ Hz, CH_2); ^{13}C NMR ($CDCl_3$) 185.2, 171.3, 156.1, 134.1, 131.8, 127.8, 119.0, 113.9, 102.9, 97.6, 55.7, 51.1, 38.2, 29.0. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.5. Found: C, 69.8; H, 5.4%.

2-Methoxy-10-(2-oxopropyl)anthracen-9(10H)-one (**7c**): Reaction time: 24 h. Yield 52%; m.p. 202–203 °C (needles from benzene/hexane 1:1); IR (KBr): 1717, 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 8.29–8.25 (m, 2H, ArH), 7.79–7.73 (m, 3H, ArH) 7.38–7.29 (m, 2H, ArH), 4.85 (m, 1H, CH), 3.99 (s, 3H, OCH_3), 3.82 (dd, 2H, $J_1 = 9.2$ Hz, $J_2 = 18.6$ Hz, CH_2), 2.1 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 219.8, 178.4, 134.2, 133.7, 129.8, 127.2, 121.2, 110.0, 97.1, 95.6, 56.0, 55.5, 52.7, 36.3, 32.1. Anal. Calcd for $C_{18}H_{16}O_3$: C, 76.6; H, 6.4. Found: C, 76.8; H, 6.65%.

3,5-Dimethoxy-10-(2-oxopropyl)anthracen-9(10H)-one (**7d**): Reaction time: 72 h. Yield 69%; m.p. 168–170 °C (needles from benzene/hexane 1:1); IR (KBr): 1716, 1657 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.93–7.89 (m, 1H, ArH), 7.73–7.71 (m, 1H, ArH) 7.49–7.38 (m, 2H, ArH), 7.15–7.09 (m, 2H, ArH), 5.01 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.94 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 16.8$ Hz, CH_2), 2.68 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 16.6$ Hz, CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 206.4, 184.5, 158.7, 155.8, 137.9, 133.7, 133.0, 132.4, 129.8, 127.7, 121.5, 119.4, 114.1, 109.1, 55.7, 55.5, 52.8, 32.0, 30.5. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.4; H, 5.77%.

2,5-Dimethoxy-10-(2-oxopropyl)anthracen-9(10H)-one (**7e**): Reaction time: 72 h. Yield 75%; m.p. 124–26 °C (needles from benzene/hexane 1:1); IR (KBr): 1716, 1657 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.92–7.88 (m, 1H, ArH), 7.72–7.71 (m, 1H, ArH) 7.49–7.42 (m, 2H, ArH), 7.13–7.09 (m, 2H, ArH), 4.99 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.94 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 16.7$ Hz,

CH_2), 2.68 (dd, 1H, J_1 = 7.6 Hz, J_2 = 16.7 Hz, CH_2), 2.02 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 206.4, 184.5, 158.6, 155.8, 137.9, 133.7, 132.9, 132.4, 129.7, 127.7, 121.5, 119.4, 114.1, 109.1, 55.7, 55.5, 52.8, 32.0, 30.6. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.5; H, 5.8. Found: C, 73.5; H, 5.8%.

This work was supported by Grant-in-Aid for Research from University of Łódź, and is gratefully acknowledged.

Received 12 December 2008; accepted 28 January 2009
Paper 08/0344 *doi: 10.3184/030823409X416956*
Published online: 6 April 2009

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