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Synthesis of highly functionalized 9,10-anthraquinones

Issa Yavari[a,b,*], Ali R. Alborzi[a], Bita Mohtat[a]

[a] Department of Chemistry, Science and Research Campus, Islamic Azad University, Ponak, Tehran, Iran
[b] Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran

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Abstract

The reaction of dialkyl acetylenedicarboxylates with ethyl 9,10-dihydro-2-methyl-9,10-dioxo-anthracen-1-yl-carbamoyl-formate in the presence of triphenylphosphine produces dialkyl 2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-ethoxy-5-oxo-1*H*-pyrrole-2,3-dicarboxylates in fairly good yields.

Keywords: Pigment modification; Atropisomerism; Dye modification; Intramolecular Wittig reaction

1. Introduction

From the earliest days of modern structural theory of organic chemistry, quinones have been intimately associated with the chemistry of aromatic compounds [1–3]. Their importance in dye industry, in medicinal chemistry, in biological electron transport processes, and in other fields has been documented over the years [1–3]. 9,10-Anthraquinone is the parent compound for a large palette of anthraquinone dyes and so is the most important starting material in their production. 9,10-Anthraquinone derivatives, have been the subjects of many studies. The importance of the pyrrole nucleus in organic chemistry, especially in natural products such as hemoglobin, chlorophyll and mold metabolites is obvious [4,5].

In continuation of our current interest in the development of new routes to heterocyclic and carbocyclic systems [6–10], we report here a simple one-pot synthesis of highly functionalized 9,10-anthraquinone derivatives **3a–c** Thus, the reaction of ethyl-9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl-carbamoyl-formate (**2**) with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine leads to dialkyl 2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-ethoxy-5-oxo-1*H*-pyrrole-2,3-dicarboxylates **3a–c** in fairly good yields (see Fig. 1).

2. Results and discussion

Compound **3** is readily prepared via an intramolecular *Wittig* reaction [11–13]. The reaction of **2** with dimethyl acetylenedicarboxylate (**1a**) in the presence of triphenylphosphine proceeded spontaneously at room temperature in CH_2Cl_2 and was finished within 24 h. ^1H and ^{13}C NMR clearly indicated the formation of **3a**. Any product other than **3a** could not be detected by NMR spectroscopy. The structures of compounds **3a–c** were deduced from their elemental analyses and their high-field ^1H and ^{13}C NMR and IR spectral data.

Although, we have not yet established the mechanism of the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of **2** in an experimental manner, a plausible explanation is proposed

* Corresponding author. Department of Chemistry, Tarbiat Modarres University, PO Box 14115-175, Tehran, Iran. Tel.: +98 21 8006631; fax: +98 21 8006544.
E-mail address: isayavar@yahoo.com (I. Yavari).

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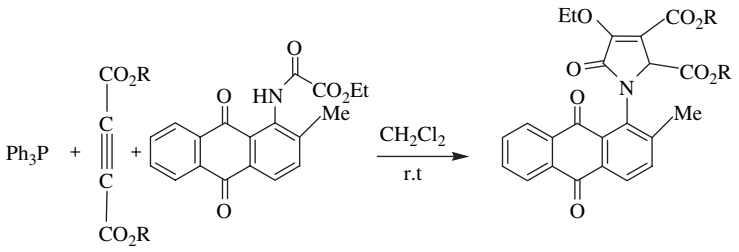

1, 3	R	Yield (%) of 3
a	Me	70
b	Et	75
c	*t*-Bu	70

Fig. 1. Synthesis of some dialkyl 2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-ethoxy-5-oxo-1*H*-pyrrole-2,3-dicarboxylates.

in Fig. 2. It is reasonable to assume that **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH–acid. Then, the positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH–acid to form the phosphorane **5**, which undergoes intramolecular Wittig reaction [11–13] to produce **3**.

The pyrrole moiety in compounds **3a–c** is not coplanar with the anthraquinone system. In fact, these molecules possess a conformational stereogenic axis and, in addition, a configurational stereogenic center [14]. As a result of restricted rotation around the Ar–N bond, these compounds adopt two distinct *syn*, *anti* conformational diastereomers (see Fig. 3). The ^{1}H and ^{13}C NMR spectra of **3a** and **3b** at room temperature are consistent with the presence of two rotamers. Only one rotamer was observed for the di-*tert*-butyl derivative **3c**, presumably, because of the bulky *tert*-butyl groups.

Selected ^{1}H NMR chemical shifts and the ΔG^{0} values [15] in the major and minor rotamers of compounds **3a** and **3b** are shown in Table 1.

The presented reaction provides a simple one-pot entry into the synthesis of functionalized 9,10-anthraquinone derivatives of potential synthetic interest.

3. Experimental

1-Amino-2-methyl-anthraquinone, dialkyl acetylenedicarboxylates and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and used without further purifications. Melting points were measured with an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were measured at 300, and 75 MHz, respectively, with a Bruker 300-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded with a Hewlet-Packard MSD 5973 mass spectrometer. IR spectra were measured with a Bomen MB-100 IR spectrometer.

3.1. Preparation of ethyl (9,10-dihydro-2-methyl-9,10-dioxo-anthracen-1-yl-carbamoyl)-formate

To a stirred solution of 0.46 g 1-amino-2-methyl-anthraquinone (2 mmol) in 20 mL of acetone was added dropwise, a solution of 0.28 g of ethyl oxalyl chloride (2 mmol) in 5 mL of acetone at room temperature. The reaction was completed after 1 h. The solvent was removed and the product was obtained as yellow crystals; yield: 0.60 g (70%) m.p. 212–215 °C.

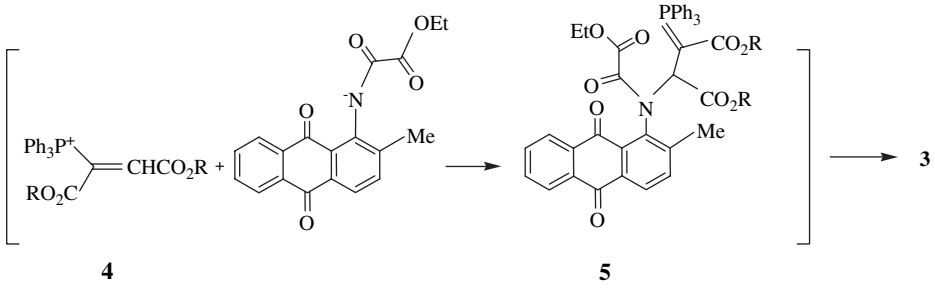

Fig. 2. Plausible mechanism for formation of **3**.

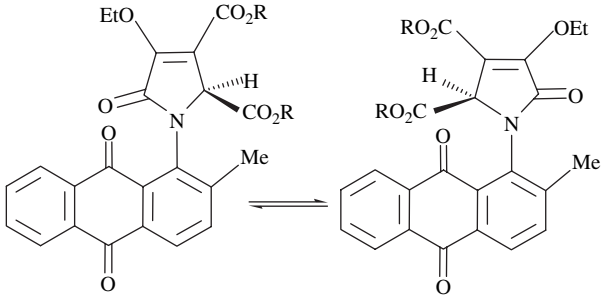

Fig. 3. The *syn* and *anti* atropisomers of **3**.

IR (KBr) (ν_{max}/cm^{-1}): 1736, 1720, 1668, and 1645 (C=O).

^{1}H NMR ($CDCl_3$): $\delta = 1.51$ (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 2.44 (3H, s, CH_3), 4.52 (2H, q, $^3J_{HH} = 7$ Hz, OCH_2), 7.73 (1H, d, $^3J_{HH} = 8$ Hz CH), 7.80–7.83 (2H, m, 2CH), 8.24 (1H, d, $^3J_{HH} = 8$ Hz CH), 8.27–8.33 (2H, m, CH), 11.76 (1H, s, NH) ppm.

^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (CH_3), 21.0 (CH_3), 64.2 (OCH_2), 125.3 (C), 126.1 (CH), 127.3 (CH), 127.9 (CH), 132.9 (C), 133.0 (C), 134.5 (C), 134.7 (CH), 134.8 (CH), 136.3 (C), 137.7 (CH), 142.7 (C), 154.9 and 160.7 (2C=O, amide and ester), 182.6 and 186.6 (2C=O) ppm.

MS: *m*/*z* (%): 337 (M^+, 4), 265 (18), 264 (100), 237 (5), 236 (9), 208 (5), 165 (6), 152 (4), 83 (5), 57 (6), 43 (6).

Anal. Calcd for $C_{19}H_{15}NO_5$ (337.3): C, 68.63; H, 4.48; N, 4.15%. Found: C, 68.8; H, 4.5; N, 4.2%.

3.2. Preparation of **3** – typical procedure

To a stirred solution of 0.52 g of triphenylphosphine (2 mmol) and 0.66 g **2** (2 mmol) in 20 mL of CH_2Cl_2 was added a solution of the dialkyl acetylenedicarboxylate (2 mmol) in 5 mL of CH_2Cl_2 at room temperature. After 24 h the solvent was removed under reduced pressure and the viscous residue was purified by column chromatography (Merck silica gel 60, 230–400 Mesh ASTM) using *n*-hexane–EtOAc 2:3 as eluent. The solvent was removed under reduced pressure and the product was obtained.

3.2.1. Dimethyl 2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-ethoxy-5-oxo-1H-pyrrole-2,3-dicarboxylate (**3a**).

Golden crystals; yield: 0.64 g (70%); m.p. 139–142 °C.

IR (KBr) (ν_{max}/cm^{-1}): 1749, 1727, 1714, 1673, and 1645 (C=O).

^{1}H NMR ($CDCl_3$): $\delta = 1.52$ (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 2.35 (3H, s, CH_3), 3.63, 3.85 (3H, s, OCH_3), 4.80–4.98 (2H, m ABX_3, OCH_2), 5.05 (1H, s, NCH), 7.75 (1H, d, $^3J_{HH} = 8$ Hz, CH), 7.77–7.83 (2H, m, 2CH), 8.15–8.30 (2H, m, aromatic), 8.38 (1H, d, $^3J_{HH} = 8$ Hz, CH) ppm.

^{13}C NMR ($CDCl_3$): $\delta = 16.1$ (CH_3), 18.6 (CH_3), 52.4, 53.1 (OCH_3), 62.3 (NCH), 69.1 (OCH_2), 114.2 (O–C=*C*-3), 127.2 (CH), 127.9 (CH), 129.0 (CH), 129.4 (C), 132.8 (C), 134.4 (CH), 134.5 (C), 134.6 (C) 134.7 (CH), 137.0 (CH), 147.5 (N–C), 154.5 (O–*C*=C), 162.9, 165.2, and 168.8 (3 C=O, 2 ester, amide), 182.8 and 183.4 (2C=O) ppm.

MS: *m*/*z* (%): 463 (M^+, 6), 431 (25), 404 (25), 403 (41), 347 (25), 346 (100), 344 (23), 248 (69).

Anal. Calcd for $C_{25}H_{21}NO_8$ (463.4): C, 64.79; H, 4.57; N, 3.02%. Found C, 64.8; H, 4.6; N, 3.1%.

3.2.2. Diethyl 2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-methyl-5-oxo-1H-pyrrole-2,3-dicarboxylate (**3b**)

Yellow oil; yield: 0.74 g (75%).

^{1}H NMR ($CDCl_3$): $\delta = 1.08$ (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 1.32 (3H, t, $^3J_{HH} = 7$ Hz, CH_3), and 1.49 (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 2.35 (3H, s, CH_3), 3.98–4.18 (2H, m, ABX_3, OCH_2), 4.21–4.38 (2H, m, ABX_3, OCH_2), 4.78–4.98 (2H, m, ABX_3, OCH_2), 5.03 (1H, s, NCH), 7.74 (1 H, d $^3J_{HH} = 8$ Hz,), 7.77–7.81 (2H, m, 2CH), 8.18–8.28 (2H, m, 2CH), 8.37 (1H, d, $^3J_{HH} = 8$ Hz, CH) ppm.

^{13}C NMR ($CDCl_3$): $\delta = 14.1$ (CH_3), 14.5 (CH_3), 16.0 (CH_3), 18.9 (CH_3), 61.3 (OCH_2), 62.3 (OCH_2) 62.5 (NCH), 69.2 (OCH_2), 114.3 (O–C=*C*), 127.1 (CH), 127.9 (CH), 128.9 (CH), 129.5 (C), 132.8 (C), 133.5 (C), 133.6 (C)134.5 (CH), 134.7 (CH), 136.9 (CH), 147.62 (N–C), 154.4 (O–*C*=C), 162.2, 165.2, and 168.3 (3C=O, ester and amide), 182.8 and 183.3 (2C=O) ppm.

MS: *m*/*z* (%): 491 (M^+, 8), 445 (27), 418 (31), 417 (33), 388 (47), 361 (26), 360 (94), 344 (34), 264 (38), 248 (100).

Anal. Calcd for $C_{27}H_{25}NO_8$ (491.5): C, 65.97; H, 5.13; N, 2.85%. Found C, 65.9; H, 5.2; N, 2.9%.

Table 1
Selected ^{1}H NMR chemical shift (δ/ppm) for Ar–CH_3, 2-H, 2-CO_2R, 3-CO_2R in the major (M) and minor (m) rotamers and Gibbs free energy of compounds **3a–c**

Compound	Isomer (%)	^{1}H NMR				ΔG^0 (kJ/mole)
		Ar–CH_3	H-2	2-CO_2R	3-CO_2R	
3a	M (93%)	2.35	5.05	3.63	3.85	6.4
	m (7%)	2.37	5.12	3.50	3.86	
3b	M (94%)	2.35	5.03	3.98–4.18	4.21–4.38	6.8
	m (6%)	2.37	5.56	4.03–4.05	4.26–4.28	
3c	M (>99)	2.40	4.92	1.23	1.54	11.4

*3.2.3. Di-(tert-butyl)-2,5-dihydro-1-(9,10-dihydro-2-methyl-9,10-dioxoanthracen-1-yl)-4-methyl-5-oxo-1H-pyrrole-2,3-dicarboxylate (**3c**)*

Yellow oil; yield: 0.76 g (70%).

IR (neat) (ν_{max}/cm^{-1}): 1745, 1716, 1710, 1674, and 1644 (C=O).

^1H NMR ($CDCl_3$): $\delta = 1.23$ (9H, s, $OCMe_3$), 1.41 (3H, t, $^3J_{HH} = 7$ Hz, CH_3), 1.54 (9H, s, $OCMe_3$), 2.40 (3H, s, CH_3), 4.75–4.88 (2H, m, ABX_3, OCH_2), 4.92 (1H, s, NCH), 7.75 (1H, d, $^3J_{HH} = 8$ Hz, CH), 7.79–7.83 (2H, m, 2CH), 8.36 (1H, d, $^3J_{HH} = 8$ Hz CH) ppm.

^{13}C NMR ($CDCl_3$): $\delta = 16.0$ (CH_3), 19.4 (CH_3), 28.0 (CMe_3), 28.6 (CMe_3), 63.4 (NCH), 68.9 (OCH_2), 82.3 (CMe_3) 83.1 (CMe_3), 116.6 (O–C=*C*), 127.2 (CH), 128.0 (CH), 128.7 (CH), 129.6 (C), 132.8 (C), 134.2 (C), 134.6 (C), 134.7 (CH), 134.8 (CH), 136.8 (CH), 137.2 (C) 147.7(N–C), 153.6 (O–C=C), 161.6, 165.0, and 167.1 (3C=O, ester and amide), 182.9 and 183.2 (2C=O) ppm.

MS: *m*/*z* (%): 547 (M^+, 1), 435 (17), 391 (12), 390 (10), 389 (14), 388 (12), 360 (9), 344 (12), 264 (10), 248 (18), 57 (100).

Anal. Calcd for $C_{31}H_{33}NO_8$ (547.6): C, 59.77; H, 6.07; N, 2.56%. Found C, 59.8; H, 6.1; N, 2.6%.

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