Pergamon

Tetrahedron Letters 42 (2001) 5231–5233

TETRAHEDRON LETTERS

2-Alkylidene-benzo[1,3]dioxin-4-ones: a new class of compounds

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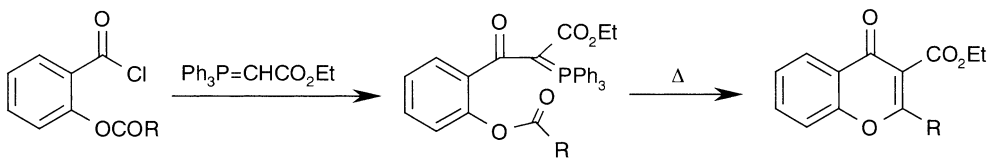
Received 2 April 2001; accepted 11 June 2001

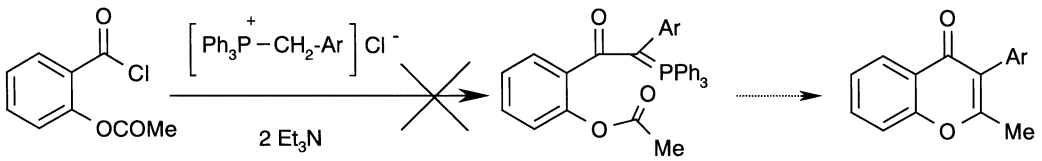
Abstract—A new class of compounds, 2-alkylidene-benzo[1,3]dioxin-4-ones, have been synthesised by cyclisation of the corresponding *o*-acyloxy benzoyl chlorides with triethylamine. The 2-methylene-benzo[1,3]dioxin-4-one acts as a prodrug for aspirin and is a useful intermediate in the synthesis of new aspirin prodrugs.

1. Introduction

In the past, we have described a synthesis of chromenes by thermal cyclisation of keto-ylids,[1] according to the following pathway.



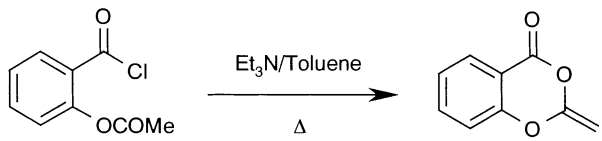
In the course of our studies on phyto-oestrogens,[2,3] we are pursuing the synthesis of new isoflavones intermediates containing a methyl group at C2. On the basis of our previous work, we attempted to obtain the required keto-ylid by reaction of acetoxy benzoyl chloride with a benzyltriphenylphosphonium salt in the presence of triethylamine to generate in situ the benzylidenetriphenylphosphorane:



Under these conditions, the expected keto-ylid could not be obtained.

2. Results

Instead of the keto-ylid, we isolated the methylene-benzo[1,3]dioxin-4-one **1** and the phosphonium salt was fully recovered. Another experiment under the same experimental conditions, but without the phosphonium salt, led to the same result.



1

Surprisingly, this product and the entire class of these 2-alkylidene-benzo[1,3]dioxin-4-ones are unknown in the literature. In order to evaluate the scope of the reaction, experiments were conducted with other acyloxy benzoyl chlorides.

All the reactions were performed in toluene,[4] at 110°C for 15 h, except for product **5**. The results are summarised in Table 1.

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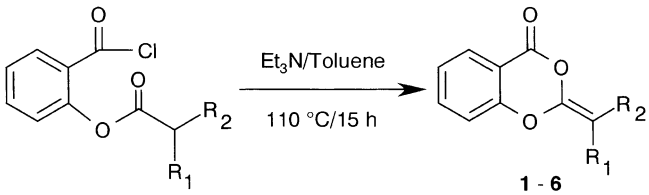
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00996-0

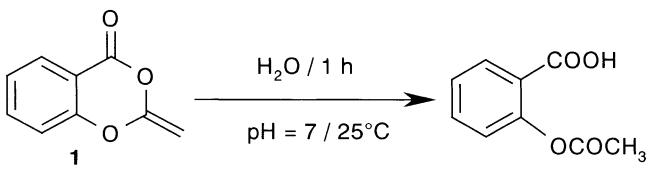
Table 1. 2-Alkylidene-benzo[1,3]dioxin-4-ones obtained



Product	R_1	R_2	Yield (%)[b]
1	H	H	60
2	CH_3	H	67 (*Z*/*E*)
3	$CH{=}CH_2$	H	33 (*Z*/*E*)
4	OCH_3	H	46 (*Z*/*E*)
5[a]	*m*-Tolyl	H	27 (*Z*/*E*)
6	$(CH_2)_5$	$(CH_2)_5$	58

[a] 100°C/2 h.
[b] Isolated yields.

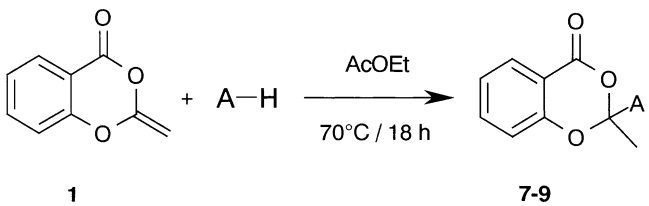
Preliminary experiments indicate that **1** is hydrolysed under mild conditions to yield aspirin.

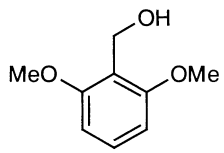
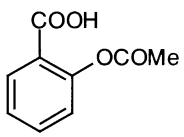


After 1 h, **1** is converted into aspirin quantitatively. The formation of aspirin is presumably due to the addition of water onto the exocyclic double bond, followed by opening of the heterocyclic ring. Therefore, the 2-methylene-benzo[1,3]dioxin-4-one **1** acts as a prodrug for aspirin[5] and can be seen as a 'dehydroaspirin'.

Addition of other protic compounds, such as an alcohol and carboxylic acids, to **1** occurs without subsequent ring opening. Moderate yields of the corresponding Markovnikov addition products are obtained (Table 2).

Table 2. Addition products



Entry	A–H	Product	Yield (%)[a]
1		**7**	60
2		**8**	57
3	H_3C–COOH	**9**	41

[a] Isolated yields.

The *ortho* ester **7** has already been described by Senning et al. and is obtained by reaction of 2-acetoxybenzoyl chloride with the corresponding alcohol.[6] The *ortho* ester **8** was also obtained by Senning et al., by treatment of aspirin with trifluoroacetic anhydride, then addition of triethylamine.[7] However, this method only allows synthesising the *ortho* esters corresponding to the condensation of two molecules of the starting *o*-acetoxy benzoic acid. In contrast, intermediate **1** allows the preparation of new original aspirin prodrugs by addition of carboxylic acids to the double bond[5] as illustrated by **9**.

In summary, we disclose here a new class of compounds: 2-alkylidene-benzo[1,3]dioxin-4-ones. Compound **1** acts as a new aspirin prodrug and is also a key intermediate for the design of new aspirin prodrugs. More detailed studies on the addition of protic derivatives to **1** and their pharmacological activities are in progress in our laboratory.

References

1. Babin, P.; Dunoguès, J.; Petraud, M. *Tetrahedron* **1981**, *37*, 1131.
2. Le Houérou, C.; Pelissero, C.; Lamothe, V.; Le Menn, F.; Babin, P.; Bennetau, B. *Tetrahedron* **2000**, *56*, 295.
3. Pelissero, C.; Le Houérou, C.; Lamothe, V.; Le Menn, F.; Babin, P.; Bennetau, B. *J. Agric. Food Chem.* **2000**, *48*, 305.
4. Typical procedure: Triethylamine (12 g, 0.12 mol) was added to a solution of 2-acetoxybenzoyl chloride (19.2 g, 0.1 mmol) in toluene (100 mL). The mixture was heated for 15 h at 110°C. After cooling, the organic layer was filtered and evaporated under reduced pressure. The crude product was purified by distillation to give the product **1**. New derivatives: Compound **1** solid (60%); bp 71–72°C/0.1 Torr; mp 46°C; IR (KBr) 3071, 1770, 1682, 1615, 1468. ^{1}H NMR (250 MHz, $CDCl_3$): 3.98 (s, 2H), 6.95 (dd, 1H, ^3J=7.8 Hz, ^4J=0.9 Hz), 7.10 (ddd, 1H, ^3J=7.8 Hz, ^3J=7.8 Hz, ^4J=0.9 Hz), 7.55 (ddd, 1H, ^3J=7.8 Hz, ^3J=7.8 Hz, ^4J=1.6 Hz), 7.82 (dd, 1H, ^3J=7.8 Hz, ^4J=1.6 Hz); with C_6D_6: 3.98 (dd, 2H, ^2J=2.3 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 73.1 (CH_2), 110.8 (C), 115.3–123.4–129.0–136.9 (4CH), 154.3–154.8 (2C), 156.2 (CO). Compound **2** was purified by distillation: oil (67%); bp 99–100°C/0.5 Torr; IR (KBr) 1770, 1709, 1613, 1594. ^{1}H NMR (250 MHz, $CDCl_3$): 1.64 and 1.67 (2d, 3H, *Z* and *E*, ^3J=7.1 Hz), 4.48 (q, 1H, ^3J=7.1 Hz), 6.98 and 7.07 (2d, 1H, *Z* and *E*, ^3J=8.4 Hz), 7.17 (m, 1H), 7.60 (m, 1H), 7.90 (dd, 1H, ^3J=7.8 Hz, ^4J=1.6 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 8.11 and 8.24 (CH_3), 84.9 and 85.0 (CH), 111.5 and 11.7 (C), 115.1 and 115.6 (CH), 123.3 and 123.5 (CH),

129.6 (CH), 137.0 and 137.1 (CH), 149.1 (C), 155.6 and 155.9 (C), 157.4 and 157.5 (CO). Some peaks are split into two due to the presence of Z/E isomers. Compound **3** was purified by distillation: oil (33%); bp 103–104°C/0.5 Torr; IR (KBr): 1774, 1681, 1617, 1606. ^{1}H NMR (250 MHz, $CDCl_3$): 5.0 (m, 1H), 5.1–5.2 (m, 2H), 6.55 (m, 1H), 7.05 (m, 1H), 7.18 (m, 1H), 7.61 (m, 1H), 7.91 (m, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 91.9 and 92.2 (CH), 112.2 (C), 115.0 and 115.2 (CH_2), 118.7 and 118.8 (CH), 123.9 and 124.1 (CH), 127.7 and 127.8 (CH), 129.7 (CH), 137.4 (CH), 150.1 and 150.2 (C), 156.7 and 156.8 (C), 157.5 and 157.6 (CO). Some peaks are split into two due to the presence of Z/E isomers. **4** was purified by distillation: oil (46%); bp 108–109°C/0.5 Torr; IR (KBr): 1771, 1731, 1614, 1591. ^{1}H NMR (250 MHz, $CDCl_3$): 3.51 and 3.53 (2s, 3H), 5.7 and 5.72 (2s, 1H), 6.86–7.08 (m, 2H), 7.46 (m, 1H), 7.77 (dd, 1H, $^3J=7.8$ Hz, $^4J=1.7$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 60.8 and 60.9 (CH_3), 115.8 and 115.9 (C), 119.0 and 119.1 (CH), 123.7 and 124.2 (CH), 128.8 (CH), 130.0 and 130.1 (CH), 136.9 and 137.6 (CH), 142.6 and 142.8 (C), 156.1 (C), 157.4 (CO). Some peaks are split into two due to the presence of Z/E isomers. Compounds **5a**–**b** were purified by chromatography (SiO_2, pentane/dichloromethane 1:1): solid (27%). Compound **5a**: mp 93°C; IR (KBr): 1771, 1681, 1609, 1593. ^{1}H NMR (250 MHz, $CDCl_3$): 2.46 (s, 3H), 5.57 (s, 1H), 7.08–7.38 (m, 4H), 7.44 (s, 1H), 7.55 (d, 1H, $^3J=7.8$ Hz), 7.77 (ddd, 1H, $^3J=7.6$ Hz, $^3J=7.8$ Hz, $^4J=1.7$ Hz), 8.04 (dd, 1H, $^3J=7.8$ Hz, $^4J=1.6$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 21.2 (CH_3), 91.3 (CH), 111.2 (C), 115.8 (CH), 123.8 (CH), 125.2 (CH), 127.4 (CH), 128.5 (CH), 128.9 (CH), 129.8 (CH), 132.3 (C), 135.5 (CH), 138.1–149.4–155.9 (3C), 156.4 (CO). Compound **5b**: mp 102°C; IR (KBr): 1758, 1677, 1613, 1593. ^{1}H NMR (250 MHz, $CDCl_3$): 2.41 (s, 3H), 5.49 (s, 1H), 7.08 (d, 1H, $^3J=8.0$ Hz), 7.14–7.38 (m, 4H), 7.47 (d, 1H, $^3J=7.9$ Hz), 7.67 (ddd, 1H, $^3J=7.6$ Hz, $^3J=7.8$ Hz, $^4J=1.7$ Hz), 8.01 (dd, 1H, $^3J=7.8$ Hz, $^4J=1.6$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 21.5 (CH3), 91.7 (CH), 112.6–115.9–124.2–125.0–127.3–128.4–128.9–129.9 (8CH), 133.1 (C), 137.3 (CH), 138.3–149.9–156.2 (3C), 156.7 (CO). **6** was purified by distillation: solid (58%); bp 130–131°C/0.5 Torr; mp 30°C; IR (KBr): 1769, 1710, 1612, 1591. ^{1}H NMR (250 MHz, $CDCl_3$): 1.50 (s, 6H), 2.22 (s, 4H), 7.01 (dd, 1H, $^3J=8.3$ Hz, $^4J=0.6$ Hz), 7.10 (ddd, 1H, $^3J=7.7$ Hz, $^3J=7.8$ Hz, $^4J=0.6$ Hz), 7.54 (ddd, 1H, $^3J=8.3$ Hz, $^3J=7.7$ Hz, $^4J=1.7$ Hz), 7.88 (dd, 1H, $^3J=7.8$ Hz, $^4J=1.7$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 25.3–25.6–28.3–28.7–28.8 ($5CH_2$), 102.5–102.3 (2C), 115.6–123.2–129.8–136.8 (4CH), 141.7–156.7 (2C), 158.8 (CO).

5. Babin, P.; Bennetau B.; Dunoguès, J. Rhodia Chimie, **1999**, FR99/04656; **2000** WOFR0000974.
6. Ankersen, M.; Senning, A. *Acta Chem. Scand.* **1989**, *43*, 793.
7. Falborg, L.; Senning, A. *Acta Chem. Scand.* **1993**, *47*, 514.