

THE SYNTHESIS OF AROMATIC 3-CARBOXY- δ -DIKETONES

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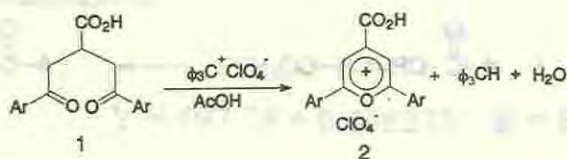
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ABSTRACT. The reaction of β -benzoylacrylic acid with acetophenones in ethanol in the presence of NaOEt led to δ -diketones (1) in good yields compared to the known methods for synthesising such compounds. The synthesis of 1,5-diaryl-3-carboxy-1,5-pentanediones are reported in this paper.

INTRODUCTION

1,5-Diaryl-3-carboxy-1,5-pentanediones (1) are important intermediates for the synthesis of heterocyclic compounds such as pyrylium salts (Scheme 1) and pyridines [1]. Thus such compounds react with triphenylmethyl perchlorate in acetic acid, leading to 2,6-diaryl-4-carboxypyrylium perchlorates (2).

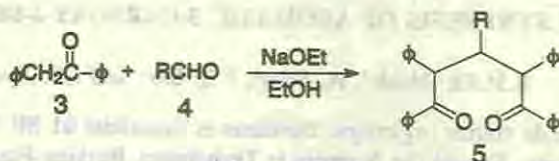


Scheme 1

The synthesis of diketones such as 1 is not very well developed. We report herein a general method of synthesising diketones of the type 1 and their homologs.

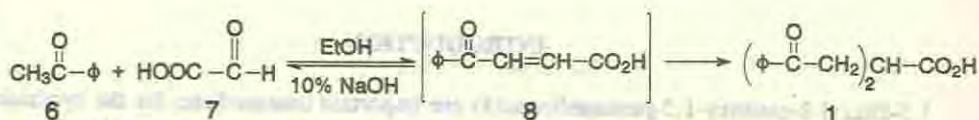
RESULTS AND DISCUSSION

Among the various methods reported in the literature [2-6] on the synthesis of δ -diketones the one proposed by Bagavant [6] was of particular interest to us. According to this method, symmetrical 1,5-diketones could be synthesised in satisfactory yields (> 60%) through reaction of two equivalents of a benzyl phenyl ketone (3) and one equivalent of an aldehyde (4) in basic medium (Scheme 2).

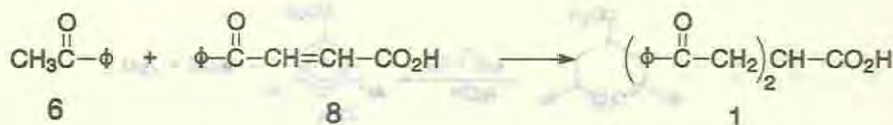


Scheme 2

The reaction of two equivalents of acetophenone (6) with one equivalent of glyoxylic acid (7), in a manner similar to that described by Bagavant [6] resulted in aromatic 3-carboxy- δ -diketones (1) as shown in Scheme 3. The formation of 1 presumably involves condensation of acetophenone (6) with glyoxylic acid (7) to lead to the intermediate β -benzoylacrylic acid (8) which further undergoes a Michael addition with a second molecule of acetophenone.



Scheme 3



Scheme 4

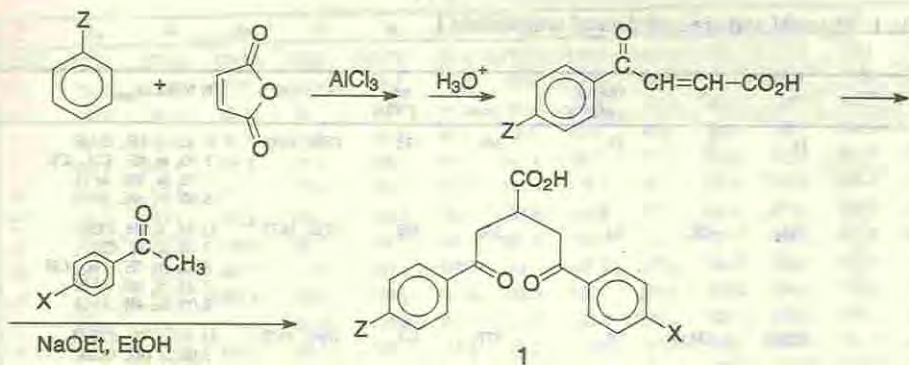
Our synthetic strategy towards preparing diketones involved the synthesis of intermediate 8 in order to make it react with substituted acetophenones.

All of our attempts to isolate intermediate 8 following the experimental conditions described by Bagavant [6] failed. We therefore synthesised 8 by employing the Friedel-Crafts reaction of maleic anhydride (9) with substituted benzenes (10) (Z is an activating group) as shown in Scheme 5.

As shown in Table 1 this methods leads to symmetrical or dissymmetrical δ -diketones (1) in good yield compared to the known methods.

The β -benzoylacrylic acids (8) and the 1,5-diketones (1) were characterized based on their spectroscopic data (Tables 1-3). Assignment of the ^{13}C chemical shifts was assisted by DEPT spectra and by comparing experimental values with literature data [7].

The ^{13}C chemical shifts were found to be particularly sensitive to the change in substituent Z. In unsymmetrical diketones (Z \neq X) only C-3 and C-3' exhibited the same chemical shift (Table 3). The resonances of the carbonyl carbon groups (C-4 or C-4') showed some sensitive



Scheme 5

variation from symmetrical to dissymmetrical diketones. The resonance of the carbonyl carbon linked to an unsubstituted phenyl group (**1a**) shows an upfield shift (shielding) of *ca* 0.3 ppm as Z is changed from H to Cl (**1j**) and Br (**1k**), but if Z is changed from H to CH₃ (**1h**) and CH₃O (**1i**) the carbonyl carbon shows a downfield shift (deshielding) of *ca* 0.05 ppm. The resonance of the carbonyl carbon in **1d** (Z=X=Cl) experiences an upfield shift as X is changed from Cl to H (**1h**), CH₃ (**1l**) and CH₃O (**1m**). On the other hand the C-4 resonance shows a down-field shift (shielding) by *ca* 0.5 ppm in going from **1g** to **1k**.

We observed a good correlation between the chemical shifts of the carbonyl carbons and the Hammett σ_{p+} values (Figure 1) for the symmetrical diketones. This correlation does not exist for the unsymmetrical diketones.

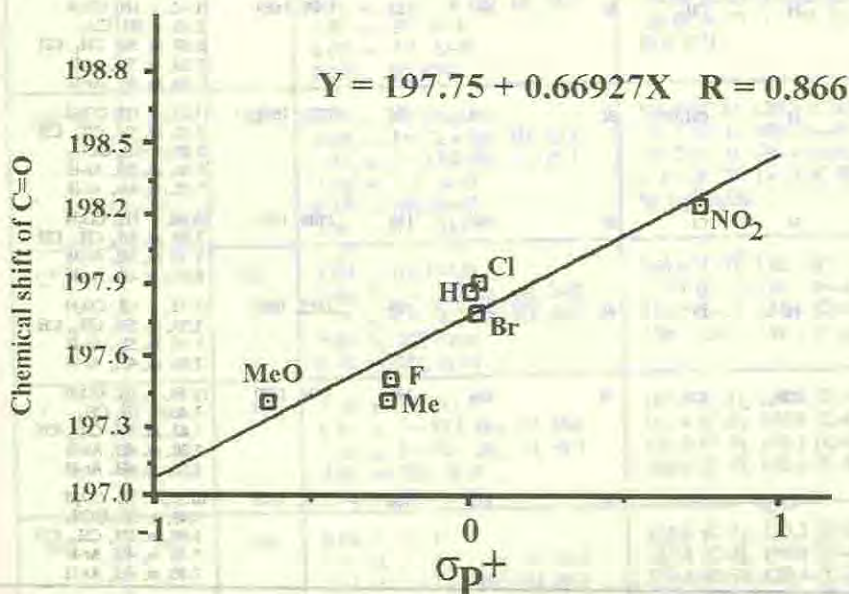
Figure 1. A plot of the chemical shift of the carbonyl carbon versus Hammett σ_{p+} constants.

Table 1. Physical and spectral data of compounds 1.

Compound	X ^a	Z	Overall yields (%)	λ_{max} (nm)	mp (°C)	$\nu_{\text{C=O}}$ (cm ⁻¹)	¹ H NMR (δ_{ppm})
1a	H	H	83	248	133	1708, 1681	11.42, s, 1H, CO ₂ H 3.50, m, 5H, CH ₂ , CH 7.50, m, 4H, Ar-H 8.00, m, 6H, Ar-H
1b	CH ₃	CH ₃	80	260	185	1710, 1677	11.84, s, 1H, CO ₂ H 2.40, s, 6H, CH ₃ 3.48, m, 5H, CH ₂ , CH 7.20, m, 4H, Ar-H 8.00, m, 4H, Ar-H
1c	CH ₃ O	CH ₃ O	79	277	121	1691, 1679	11.80, s, 1H, CO ₂ H 3.90, s, 6H, OCH ₃ 3.48, m, 5H, CH ₂ , CH 7.00, m, 4H, Ar-H 7.90, m, 4H, Ar-H
1d	Cl	Cl	81	259	177	1741, 1665	11.40, s, 1H, CO ₂ H 3.50, m, 5H, CH ₂ , CH 7.60, m, 4H, Ar-H 8.00, m, 4H, Ar-H
1e	NO ₂	NO ₂	55	240	225	1730, 1681	11.72, s, 1H, CO ₂ H 3.50, m, 5H, CH ₂ , CH 7.70, m, 4H, Ar-H 8.20, m, 4H, Ar-H
1f	F	F	80	252	165	1732, 1692	11.68, s, 1H, CO ₂ H 3.45, m, 5H, CH ₂ , CH 7.60, m, 4H, Ar-H 7.85, m, 4H, Ar-H
1g	Br	Br	82	262	173	1728, 1684	11.70, s, 1H, CO ₂ H 3.30, m, 5H, CH ₂ , CH 7.60, m, 4H, Ar-H 7.90, m, 4H, Ar-H
1h	H	CH ₃	83	261	112	1709, 1684	11.42, s, 1H, CO ₂ H 2.40, s, 3H, CH ₃ 3.50, m, 5H, CH ₂ , CH 7.20, m, 5H, Ar-H 7.80, m, 4H, Ar-H
1i	H	CH ₃ O	82	274	164	1732, 1681	11.23, s, 1H, CO ₂ H 3.52, m, 5H, CH ₂ , CH 3.85, s, 3H, OCH ₃ 7.00, m, 5H, Ar-H 7.70, m, 4H, Ar-H
1j	H	Cl	80	260	155	1708, 1675	10.80, s, 1H, CO ₂ H 3.60, m, 5H, CH ₂ , CH 7.40, m, 5H, Ar-H 8.00, m, 4H, Ar-H
1k	H	Br	81	263	149	1722, 1683	11.13, s, 1H, CO ₂ H 3.50, m, 5H, CH ₂ , CH 7.10, m, 5H, Ar-H 7.90, m, 4H, Ar-H
1l	CH ₃	Cl	79	266	175	1724, 1690	11.52, s, 1H, CO ₂ H 2.40, s, 3H, CH ₃ 3.42, m, 5H, CH ₂ , CH 7.30, m, 4H, Ar-H 8.00, m, 4H, Ar-H
1m	CH ₃ O	Cl	78	272	166	1730, 1675	10.56, s, 1H, CO ₂ H 3.45, s, 3H, OCH ₃ 3.50, m, 5H, CH ₂ , CH 7.20, m, 4H, Ar-H 7.90, m, 4H, Ar-H

^a 1e was synthesised according to ref. [6]

Table 2. ^{13}C NMR data of compounds 1.

C	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m
1	176.3	175.3	176.6	175.8	175.4	177.2	175.9	175.5	176.4	176.0	175.9	175.1	175.5
2	36.5	35.5	36.7	36.4	36.4	37.5	36.3	36.1	36.5	36.4	36.2	35.5	36.0
3	39.3	39.2	40.3	40.5	40.9	41.2	40.0	40.3	40.2	40.2	39.7	39.2	40.2
3'	39.3	39.2	40.3	40.5	40.9	41.2	40.0	40.3	40.2	40.2	39.7	39.2	40.2
4	197.9	197.4	197.4	197.9	198.2	197.5	197.8	197.9	197.9	198.6	198.3	196.7	197.2
4'	197.9	197.4	197.4	197.9	198.2	197.5	197.8	197.2	197.1	197.6	197.5	197.1	197.8
5	132.7	133.9	130.8	136.3	142.3	160.1	127.9	131.8	133.2	137.3	137.1	134.8	135.0
5'	132.7	133.9	130.8	136.3	142.3	160.1	127.9	133.0	132.2	135.7	133.5	133.8	129.8
6	128.2	128.8	131.3	130.7	130.2	132.6	132.3	129.0	129.2	130.2	132.1	129.3	128.8
6'	128.2	128.8	131.3	130.7	130.2	132.6	132.3	129.7	129.9	129.3	130.2	128.8	130.4
7	127.6	127.6	114.8	129.8	124.8	132.2	130.3	126.4	127.5	129.2	128.3	128.4	128.3
7'	127.6	127.6	114.8	129.8	124.8	132.2	130.3	126.6	115.1	128.4	129.0	127.6	116.5
8	136.5	143.4	164.8	140.0	151.6	173.2	136.1	142.8	141.1	139.2	136.0	143.4	140.0
8'	136.5	143.4	164.8	140.0	151.6	173.2	136.1	137.0	135.3	133.7	127.9	138.3	153.7
CH ₃	-	20.4	-	-	-	-	-	20.3	-	-	-	20.6	-
CH ₃ O	-	-	56.3	-	-	-	-	-	56.2	-	-	-	56.2

Table 3. Physical and spectroscopic data of compounds 8.

Z	Yield (%)	mp (°C)	^1H NMR (δ_{ppm})	^{13}C NMR (δ_{ppm})
H	93	110	9.60, s, 1H, CO ₂ H 6.88, d, $J = 12.3$ Hz, 1H, H-2 7.80, d, $J = 12.3$ Hz, 1H, H-3 7.90, m, 5H, Ar-H	167.1 (C-1), 143.8 (C-2), 133.4 (C-3), 190.5 (C-4), 133.2 (C-5), 129.4 (C-6), 128.8 (C-7), 131.9 (C-8)
CH ₃	90	174	9.50, s, 1H, CO ₂ H 6.88, d, $J = 11.4$ Hz, 1H, H-2 7.90, d, $J = 11.4$ Hz, 1H, H-3 7.80, m, 2H, Ar-H 8.00, m, 2H, Ar-H 2.39, s, 3H, CH ₃	166.95 (C-1), 130.28 (C-2), 130.01 (C-3), 189.25 (C-4), 133.26 (C-5), 130.42 (C-6), 120.88 (C-7), 133.71 (C-8), 20.6 (CH ₃)
CH ₃ O	89	149	9.70, s, 1H, CO ₂ H 6.80, d, $J = 12.4$ Hz, 1H, H-2 7.95, d, $J = 12.4$ Hz, 1H, H-3 7.80, m, 2H, Ar-H 8.10, m, 2H, Ar-H 3.90, s, 3H, CH ₃ O	166.5 (C-1), 129.3 (C-2), 128.6 (C-3), 189.2 (C-4), 131.2 (C-5), 129.4 (C-6), 118.2 (C-7), 134.2 (C-8), 56.5 (CH ₃ O)
Cl	92	163	9.70, s, 1H, CO ₂ H 6.80, d, $J = 12.0$ Hz, 1H, H-2 7.75, d, $J = 12.0$ Hz, 1H, H-3 7.60, m, 2H, Ar-H 8.10, m, 2H, Ar-H	166.6 (C-1), 136.9 (C-2), 133.4 (C-3), 189.5 (C-4), 140.2 (C-5), 131.1 (C-6), 129.7 (C-7), 142.7 (C-8)
F	90	159	9.60, s, 1H, CO ₂ H 6.82, d, $J = 12.0$ Hz, 1H, H-2 7.60, d, $J = 12.0$ Hz, 1H, H-3 7.60, m, 2H, Ar-H 8.00, m, 2H, Ar-H	167.0 (C-1), 133.2 (C-2), 132.4 (C-3), 191.9 (C-4), 135.0 (C-5), 133.1 (C-6), 128.9 (C-7), 138.2 (C-8)
Br	91	160	9.68, s, 1H, CO ₂ H 6.60, d, $J = 11.5$ Hz, 1H, H-2 7.65, d, $J = 11.3$ Hz, 1H, H-3 7.50, m, 2H, Ar-H 7.90, m, 2H, Ar-H	168.0 (C-1), 132.2 (C-2), 131.8 (C-3), 190.9 (C-4), 134.5 (C-5), 129.4 (C-6), 128.8 (C-7), 137.1 (C-8)

EXPERIMENTAL

General. IR spectra were recorded as KBr pellets on a Perkin-Elmer apparatus. UV-VIS spectra were measured in CH_2Cl_2 on a Perkin-Elmer 550S instrument. NMR spectra were run in a mixture of $\text{CD}_3\text{CN}/\text{DMSO}-d_6$ (3:1) on Bruker AC 80 and AMX 400 instruments.

Synthesis of 8

In a 500-mL three-necked flask fitted with a mechanical stirrer, 50 mL of freshly purified benzene (or its derivative) and 0.1 mol of AlCl_3 were placed. 0.1 mol of maleic anhydride, dissolved in benzene, was placed in a separatory funnel and added drop-wise into the stirred solution of AlCl_3 in benzene. The flask was cooled in an ice-bath. After the addition was complete the mixture was refluxed for 1 h. It was then cooled to r.t. and hydrolyzed in a beaker containing 200 g of ice and 50 mL of HCl . The product was filtered and recrystallized from EtOAc. The yields, mps ^1H and ^{13}C NMR data of the resulting β -benzoylacrylic acids (8) are summarized in Table 3.

Synthesis of δ -diketones

In a 250-mL round-bottomed flask containing 10 mL of anhydrous EtOH were added 0.01 mol of 8, 0.01 mol of acetophenone and 0.01 mol NaOEt. The mixture was refluxed and the progress of the reaction monitored by TLC over silica gel. At the end of the reaction, the mixture was acidified with 10% H_2SO_4 in which case a massive oil was formed which subsequently crystallized. The solid was filtered, dried and recrystallized from EtOH.

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