A New and Simple Synthesis of Fluoren-9-ones

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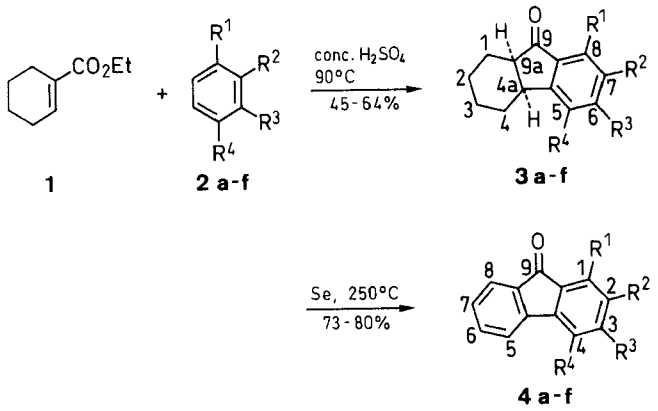
Ethyl cyclohexene-1-carboxylate (1) undergoes reaction with various aromatic substrates in presence of concentrated sulfuric acid to give *cis*-1,2,3,4,4a,9a-hexahydrofluoren-9-ones **3a–f** which on dehydrogenation afforded the corresponding fluoren-9-ones **4a–f** in good yield. Fluorenones with an alkoxy group in the *meta*-orientation with respect to carbonyl group have also been prepared.

Many fluoren-9-one derivatives are reported to exhibit varied biological activities. This includes antiviral,[1] antitumour,[2] local anaesthetic[3] and trypanocidal[4] activity. Recently, some of the fluoren-9-one derivatives have also been reported as natural products.[5–7]

A number of methods are known for the synthesis of fluoren-9-ones. Most of these methods utilise fluorene,[8] biphenyl-1-carboxylic acid[8] or benzophenone[9] derivatives as the starting substrate. A majority of these methods are characterised by limitations like the limited accessibility of the starting substrate, formation of more than one isomer and comparatively low yields. A perusal of the structure of naturally occuring fluoren-9-ones revealed that most of these have the carbonyl group in *meta*-orientation with respect to alkoxy or hydroxyl groups. Such an orientation of groups is rather difficult to attain by conventional methods of fluoren-9-ones synthesis. It was therefore felt desirable to develop a methodology for synthesising fluoren-9-ones. Towards this end, ethyl cyclohexene-1-carboxylate **(1)** obtained by esterification of readily accessible cyclohexene-1-carboxylic acid[10] was reacted with various aromatic substrates **2a–f** in concentrated sulfuric acid at 90°C (Table 1). These



2–4	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	OMe	OMe	H
c	OMe	H	H	OMe
d	H	OMe	H	H
e	H	OMe	H	OMe
f	H	NMe_2	H	H

Scheme

Table. Compounds **3** and **4** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	UV (MeOH) λ_{max} (nm) (log ε)	IR (KBr) (cm^{-1}) ν_{CH}, $\nu_{C=O}$, ν_{Ar}, ν_{C-O}	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	10	45	40	40–41[14]	–	–	–
3b	4	63	120	$C_{15}H_{18}O_3$ (246.3)	268.4 (2.340), 228.2 (2.599)	2910, 1700, 1600, 1265	1.25–2.05 (m, 8H, H-1,2,3,4), 2.35–2.75 (m, 1H, H-9a), 2.85–3.30 (m, 1H, H-4a), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.7 (s, 1H, H-5), 7.05 (s, 1H, H-8)
3c[c]	3.5	63	140	$C_{15}H_{18}O_3$ (246.3)	272.9 (4.992), 224.0 (4.818), 206.0 (4.874)	2910, 1700, 1600, 1260	0.82–1.92 (m, 8H, H-1,2,3,4), 2.32–2.68 (m, 1H, H-9a), 3.1–3.5 (m, 1H, H-4a), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.48–7.32 (m, $2H_{arom}$)
3d	2.5	59	98	98–99[12]	–	–	–
3e[c]	3	65	oil	$C_{15}H_{18}O_3$ (246.3)	258.7 (2.943), 220.1 (3.116), 210.8 (3.136)	2900, 1700, 1590, 1250	1.0–2.3 (m, 8H, H-1,2,3,4), 2.40–2.85 (m, 1H, H-9a), 3.1–3.5 (m, 1H, H-4a), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.75 (s, 1H, H-6), 7.05 (s, 1H, H-8)
3f	7	54	132	$C_{15}H_{19}NO$ (229.3)	259.4 (3.229), 209.6 (3.521)	2990, 1710, 1600	1.05–2.10 (m, 8H, H-1,2,3,4), 2.22–2.80 [m, 7H, H-9a + $(CH_3)_2$], 3.0–3.3 (m, 1H, H-4a), 6.35–7.10 (m, $3H_{arom}$)
4a	3	80	82	81–82[15]	–	–	–
4b	4	76	164	164[9]	–	–	–
4c	4	76	165	165–166[16]	–	–	–
4d	4	77	77	77–78[17]	–	–	–
4e[d]	3.5	74	116	$C_{15}H_{12}O_3$ (240.3)	273.2 (3.464), 251.0 (3.565), 207.4 (3.308)	2905, 1705, 1600, 1280	3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.05, 7.10 (m, $6H_{arom}$)
4f	4	78	159	159[18]	–	–	–

[a] Yield of pure isolated product. Solvent used for chromatographic elusion: petrolcum ether (bp 60–80°C)/benzene, 50 : 50 for **3a, b, e, f** and **4d**; 60 : 40 for **3c, d**; 40 : 60 for **4b, c, e, f** and 30 : 70 for **4a**.

[b] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.12.

[c] MS: $m/z = 246$ (M^+).

[d] MS: $m/z = 240$ (M^+).

reactions resulted in the formation of 1,2,3,4,4a,9a-hexahydrofluoren-9-ones **3a–f** (Scheme) and have been characterised on the basis of their mp, analytical and spectral data. For all hexahydrofluoren-9-ones **3a–f** one would expect them to possess the thermodynamically more stable of the two possible hydrindanone ring junctions. House et al.[11] have shown that for such compounds, the isomer with *cis*-fusion is more stable. This was also later confirmed by the Kai et al.[12] and Merchant et al.[13] Further confirmation of hexahydroflouren-9-one formation, in the above reactions, was achieved by dehydrogenation into their corresponding fluoren-9-ones **4a–f** with selenium Scheme).

Thus, when ethyl cyclohexene-1-carboxylate **(1)** was reacted with aromatic substrates **2a–f** in concentrated sulfuric acid the initial step should be alkylation followed by cyclisation instead of acylation as the first step and then cyclisation when polyphosphoric acid was used as the reaction medium.[13] This is evident in case of reaction of **1** with an unsymmetrical substrate like anisole **2d**. Reaction with concentrated sulfuric acid resulted in the formation of 7-methoxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one[12] **(3d)** (mp 98 °C), while polyphosphoric acid yielded 6-methoxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one[12] (mp 67 °C). Further 2-methoxyfluoren-9-one[17] **4d** has a mp 77 °C, while 3-methoxyfluoren-9-one[19] has a mp 99 °C. In this way, fluorenones with alkoxy groups in *meta*-orientation with respect to the carbonyl group can be synthesised, which are otherwise difficult to synthesise. The method described is simple, short, convenient and yields are also reasonable.

Melting points (uncorrected) were determined on Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-4200 spectrometer. UV spectra were recorded on a UV-visible spectrophotometer UV-2100 using MeOH as a solvent, λ_{max} in nm (log ε). ^{1}H NMR spectra were recorded on Varian EM 360L (60 MHz) spectrometer with TMS as internal standard. Mass spectra were recorded on Kratos MS-80 spectrometer.

***cis*-1,2,3,4,4a,9a-Hexahydrofluoren-9-ones 3a–f, General Procedure:**
Ethyl cyclohexene-1-carboxylate (**1**; 1.54 g, 10 mmol) was reacted with various aromatic substrates **2a–f** (5.0 mmol) in conc. H_2SO_4 (15 mL) at 90 °C with intermittent shaking. It was poured into ice and extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were washed with H_2O (50 mL) and dried (Na_2SO_4). The solvent was evaporated and the product was chromatographed on a silica gel column (50 g) using the eluents given in the Table.

Fluoren-9-ones 4a–f, General Procedure:
cis-1,2,3,4,4a,9a-Hexahydrofluoren-9-one **3a–f** (5.0 mmol) was fused with Se powder (1 g) at 250 °C. The fused mass was extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were washed with H_2O (50 mL) and dried (Na_2SO_4). The solvent was evaporated and the product was chromatographed on a silica gel column (50 g) using the eluents given in the Table.

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