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A Simple Approach to the Synthesis of Fluoren-9-Ones

M. M. V. Ramana [a] & Prashant V. Potnis [a]
[a] Department of Chemistry , University of Bombay , Vidyanagari, Santacruz (East), Bombay, 400 098, India

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A SIMPLE APPROACH TO THE SYNTHESIS OF FLUOREN-9-ONES.

M.M.V. Ramana*, Prashant V. Potnis

Department of Chemistry, University of Bombay.
Vidyanagari, Santacruz (East),
Bombay 400 098.
India

Abstract: Cyclohexene-1-Carboxylic acid (I) undergoes reaction with various aromatic substrates **(2a-i)** in presence of Polyphosphoric acid (PPA) at 100°c to give cis-1,2,3,4,4a,9a - hexahydrofluoren-9-ones **(3a-i)** in good yield. Dehydrogenation of **(3a-i)** with selenium powder afforded corresponding fluoren-9-ones **(4a-i)** in high yield.

Many fluoren-9-one derivatives are reported to exhibit varied biological activities. This includes antiviral[1], antitumour[2], local anaesthetic[3] and trypanocidal activity[4]. Recently, some of the fluoren-9-one derivatives have also been reported as natural products.[5,6,7].

A number of methods are reported for the synthesis of fluoren-9-ones. Most of these methods utilise fluorene[8], biphenyl-1-carboxylic acid[8], benzophenone[9], floranthene[8], cyclohexene[10,11], phen-

* To whom correspondence should be addressed.

anthrene[8] and phenylpropiolic acid[12,13] derivatives as the starting substrate. A majority of these methods are characterised by limitations like the limited accessibility of the starting substrate[8,10,12,13], formation of more than one isomer[8,9,13] and comparatively low yields.

It was therefore felt desirable to develop a simple methodology for synthesising fluoren-9-ones. Towards this end, cyclohexene-1- carboxylic acid **(1)** obtained[14] from readily accessible cyclohexanone was reacted with various aromatic substrates **(2a-i)** in PPA at 100°c (Table 1). These reactions resulted in the formation of 1,2,3,4,4a,9a-hexahydro fluoren-9-ones **(3a-i)** and have been characterised on the basis of their mp or bp, analytical and spectral data. For all hexahydrofluoren-9-ones **(3a-i)** one would expect them to possess thermodynamically more stable of the two possible hydrindanone ring junctions. House et al[15], have shown that for such compounds isomer with cis-fusion is more stable. This was also later confirmed by Kai et al[16] and Merchant et al[17]. It may be added that cis-hexahydrofluoren-9-ones derivatives have served as important intermediates in synthesis of β- norterpenoids[18], β- norsteroids[18], C-nor-D-homosteroids[19] and the gibberellins.[20] Further confirmation of hexahydrofluoren-9-one formation in

the above reactions was achieved by carrying out dehydrogenation in to their corresponding fluoren-9-ones **(4a-i)** (Table 1) by selenium. Both these sequences of reactions are depicted in scheme.

The method described is simple, short, convenient and yields are also reasonable.

Experimental

Melting points were determined in open capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H-NMP spectra were recorded on varian EM 360 L (60 MHZ) instrument with TMS as internal standard. IR spectra were recorded on Shimadzu UV-visible spectrophotometer UV-2100 using MeOH as solvent λmax in nm (log ϵ). Mass spectra were recorded on kratos MS-80 spectrometer.

Reaction of Cyclohexene-1-carboxylic acid (1) with various aromatic substrates (2a-i), General procedure. :

Cyclohexene-1-Carboxylic Acid (1.26 g, 0.01 mol) was reacted with various aromatic substrates **(2a-i)** (0.005 mol) in PPA (0.01 mol) at 100°C with intermittent shaking for a suitable period (Table-1). It was then poured into ice and extracted with

TABLE 1 - 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}, $\nu_{C=O}$ $\nu_{Ar.}$, ν_{C-O}	^{1}H NMR ($CDCl_3$/TMS) δ, J(Hz)
3a	8	40	40	40[21]	-	-	-
3b	4	59	Oil	$C_{15}H_{18}O$ (246.3)	260.5(4.472) 206.3(3.011)	2925,1720 1605	1.22 (m,8H,H-1,2,3,4) 2.12 [(S,6H, $(CH_3)_2$)] 2.6 (m,1H, H-9a) 3.28 (m,1H, H-4a) 6.88 (S,1H, H-5) 7.25 (S,1H, H-8)
3c	7	44	Oil	$C_{13}H_{13}ClO$ (220.5)	254.5(3.749) 212.3(3.200)	2910,1705 1610,740 (ν_{C-Cl})	1.71 (m,8H,H-1,2,3,4) 2.65 (m,1H,H-9a) 3.32 (m,1H,H-4a) 6.95 (m,3H,H-arom)

3d	6	42	Oil	$C_{13}H_{12}Cl_2O$	268.0(2.230)	2920,1700	1.6 (m,8H,H-1,2,3,4)
				(255.0)	224.2(2.195)	1605,745	2.44 (m,1H,H-9a)
						(ν_{C-Cl})	3.1 (m,1H,H-4a)
							7.27 (m,2H,H-arom.)
3e	6	50	Oil	$C_{15}H_{19}NO$	312.9(2.122)	2945,1700	1.5 (m,8H,H-1,2,3,4)
				(229.3)	268.5(2.205)	1600	2.55[(m,7H,H-9a +
					230.5(2.486)		$(CH_3)_2$)], 3.15(m,1H,H
					207.2(2.500)		-4a),6.80 (m,3H,H_{arom})
3f	5	55	67	67[16]	-	-	-
3g	4	57	80	$C_{15}H_{18}O_3$	274.0(4.914)	2950,1705	1.77 (m,8H,H-1,2,3,4)
				(246.3)	226.4(4.988)	1605,1260	2.75 (m,1H, H-9a)
							3.32 (m,1H,H-4a)
							3.9 [(S,6H, $(OCH_3)_2$)]
							6.3 (S,1H, H-7)
							6.5 (S,1H, H-5)
3h	3	58	120	120[11]			
3i	3	59	140	140 [11]			
4a	3	80	82	82[22]	-	-	-

(continued)

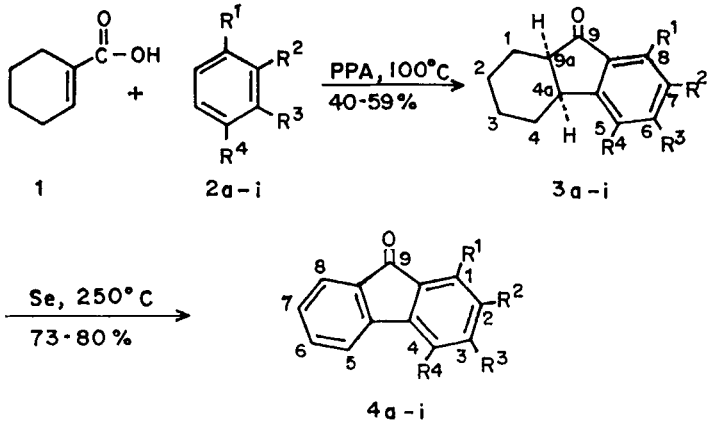
Table 1 Continued

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}, ν_{Ar}, $\nu_{C=O}$ ν_{C-O}	^{1}H NMR (CDCl$_3$/TMS) δ,J(Hz)
4b	5	74	109	109[23]	-	-	-
4c	3	74	157	157[24]	-	-	-
4d	4	76	162	162[25]	-	-	-
4e	3	76	Oil	($C_{15}H_{13}NO$) (223.0)	338.1(2.142) 253.6(2.296) 230.6(2.773) 206.9(2.596)	2990,1720 1610	2.3 [(S,6H,$(CH_3)_2$)] 7.35 (m,7H, H_{arom})
4f	5	78	99	99[26]	-	-	-
4g	5	73	144	144[27]	-	-	-
4h	4	76	164	164[9]	-	-	-
4i	4	76	165	165[28]	-	-	-

a Yield of pure isolated product, Solvent used for chromatographic elution: Petroleum ether (bp 60-80°C)/ benzene, 50:50 for 3a,d,f,h and 4c, 60:40 for 3e,i,40:60 for 3c, g and 4d,f,h,i, 30:70 for 4a,g, 100:0 for 3b and 80:20 for 4b.

b Satisfactory microanalysis obtained. C± 0.26, H±0.12, N±0.17

Scheme



1 2a-i 3a-i

4a-i

2-4	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	CH_3	CH_3	H
c	H	H	Cl	H
d	Cl	H	H	Cl
e	H	H	$N(CH_3)_2$	H
f	H	H	OCH_3	H
g	OCH_3	H	OCH_3	H
h	H	OCH_3	OCH_3	H
i	OCH_3	H	H	OCH_3

chloroform. The combined chloroform extracts were washed with $NaHCO_3$ solution (10%), water and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on a silica-gel column (50g) using the eluents mentioned in Table 1 to get the pure products (3a-i).

Fluoren-9-ones (4a-i), General procedure.

Cis-1,2,3,4,4a,9a - hexahydrofluoren-9-ones **(3a-i)** (0.005 mol)was fused with selenium powder (1g) (Table-1). The fused mass was extracted with chloroform. The combined extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on a silica-gel column (50g) using the eluents mentioned in Table 1 to get the pure products **(4a-i).**

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