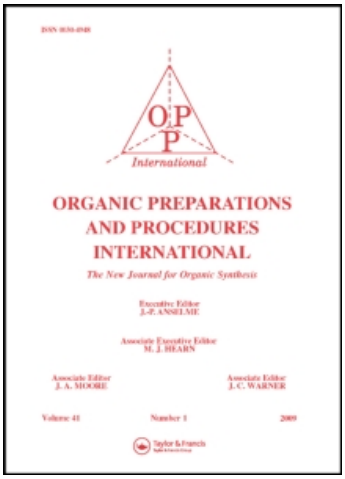

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MICHAEL REACTION OF FLUORENE AND INDENE BY PHASE-TRANSFER CATALYSIS

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MICHAEL REACTION OF FLUORENE AND INDENE BY PHASE-TRANSFER CATALYSIS

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(09/11/92)

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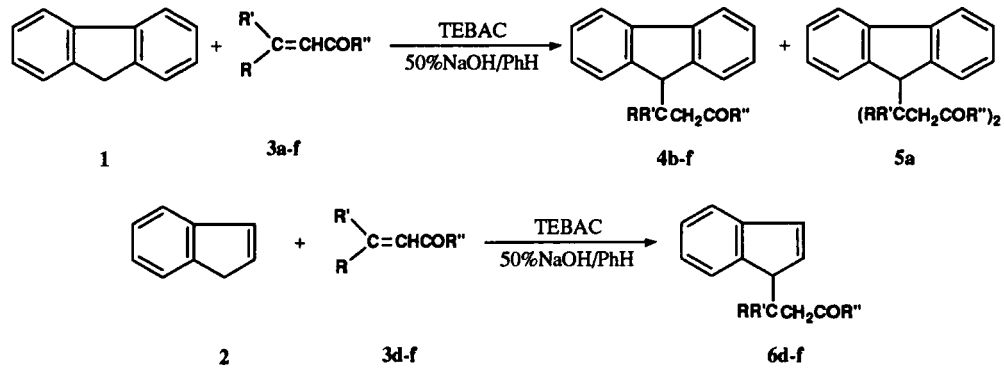
The Michael reaction is perhaps one of the most general methods for C-C bond formation.[1] Although fluorene and indene have active hydrogens and should be ideal for the Michael reaction, it has been reported that these substrates react only slowly or not at all.[2] Matsumato and coworkers have employed tetra-*n*-butylammonium fluoride as a catalyst in the Michael reaction of fluorene[3] and obtained moderate to good yields after *very long* reaction times (100-168 hrs). The precent communication describes the phase-transfer catalyzed Michael addition of fluorene (**1**) and indene (**2**) to α,β-unsaturated esters and ketones (**3**).



1 **3a-f** **4b-f** **5a**

2 **3d-f** **6d-f**

a) R = R' = H, R" = OEt b) R = H, R' = C_6H_5, R" = OEt c) R = R' = R" = Me
d) R = H, R' = C_6H_5, R" = C_6H_5 e) R = H, R' = *p*-ClC_6H_4, R" = C_6H_5
f) R = H, R' = *p*-$MeOC_6H_4$, R" = C_6H_5

The reaction was performed in a mixture of 50% sodium hydroxide and benzene in the presence of triethylbenzylammonium chloride (TEBAC). Although the yields are similar to those of Hashimoto,[3] the reaction time is much shorter (3-24 hrs) (see Table).

With ethyl acrylate (**3a**) as the Michael acceptor, a 1:1 molar ratio of ester to fluorene led to a mixture of single and double addition products. Because the single adduct is a liquid of very high boiling point, it was difficult to purify and was not studied further. A 3:1 molar excess of ester to fluorene led to double addition product (**5a**) as the sole product. Very little hydrolysis of the ester group of the adduct was observed. Ethyl cinnamate gave only a single adduct under similar reaction conditions. α,β-Unsaturated ketones also gave monoadducts. Acrolein did not give an adduct because of very rapid polymerization under these conditions.

TABLE. Michael Addition Product of Fluorene and Indene

Cmpd.	Time (hrs)	Yield (%)	mp (°C)	IR(CO) (cm^{-1})	Elemental Analyses (Found) C		H	
4b[3]	3	62	102-103[a]	1726	84.18	(84.08)	6.48	(6.45)
4c	12	64	72-73[a]	1711	86.32	(86.24)	7.62	(7.61)
4d[2]	20	70	116-118[a]	1671	89.81	(89.98)	5.92	(6.11)
4e	30	47	163-164[a]	1678	82.24	(81.93)	5.17	(4.98)
4f[2]	12	57	150-152[a]	1682	86.11	(85.82)	5.96	(5.94)
5a[3]	3	87	106-108[a]	1722	75.38	(75.17)	7.15	(7.18)
6d	24	55	108-110[b]	1672	88.55	(88.75)	6.21	(6.35)
6e	24	33	64-66[b]	1664	80.33	(80.46)	5.34	(5.52)
6f	24	40	102-103[b]	1676	84.78	(84.63)	6.25	(6.17)

a) Crystallized from ethanol. b) Crystallized from ethanol-benzene.

Indene reacted with benzalacetophenone (**3d**), giving a black solution containing some tarry material. Chromatography gave a 55% yield of a yellow Michael adduct (**6d**). *p*-Methoxybenzalacetophenone (**3e**) and *p*-chlorobenzalacetophenone (**3f**) gave similar results.

EXPERIMETAL SECTION

Fluorene, indene and the unsaturated esters are commercial products. The unsaturated ketones were prepared by a reported procedure.[4] Melting points are uncorrected and were determined using the capillary tube method. The microanalyses were obtained using a Carlo Eba model 1106 Elemental Analyzer. IR spectra were recorded as KBr disks on a Nicolet 740 FT IR spectrometer. ^1H NMR were obtained on JEOL FX 90Q spectrometer in $CDCl_3$, using TMS as an internal reference.

Reaction of Fluorene with 4-Methyl-3-penten-2-one (3c). Typical Procedure.- A mixture of fluorene (10 mmol, 1.66 g) and 4-methyl-3-penten-2-one (10 mmol, 0.98 g) in a mixture of 50% sodium hydroxide (10 mL) and benzene (10 mL) containing TEBAC (0.2 g) was stirred at room temperature for 12 hrs, then water was added and the organic layer was separated and dried. The solvent was removed and the residual solid was recrystaillized from ethanol to give 1.70 g white crystals of **4c** (64%). IR: 2983, 2880, 1711, 1655, 1635, 1475, 1442, 1358, 743 cm^{-1}. ^1H NMR: δ 1.12 (6 H, s, 2 CH_3), 2.08 (3 H, s, $COCH_3$), 2.36 (2 H, s, CH_2), 4.18 (1 H, s, CH), 7.1-7.8 (8 H, m, Ar-H)

Reaction of Indene with Benzalacetophenone (3d). Typical Procedure.- A mixture of indene (15 mmol) and benzalacetophenone (10 mmol) were reacted as described above for 24 hrs. The solution was washed with water and the organic layer chromatographed on aluminum oxide (neutral) using benzene as eluent to give the crude product, which was purified by recrystallization from ethanol-benzene (1.2 g, 55%). IR: 3084, 3017, 2914, 1672, 1450, 1258, 774, 667 cm^{-1}. ^1H NMR: δ 3.36 (m, -CH_2-), 3.68(m, -CH-), 4.80 (m, CH), 6.82 (m, -CH=CH-), 7.0-8.0 (m, Ar-H)

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PREPARATION OF THE RACEMATE AND ENANTIOMERS OF 3-HYDROXY-5,5-DIMETHYLHEXANOIC ACID†

Submitted by (06/29/92)

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Carnitine (**6**) is important in mammalian systems as an acceptor (and donor) of acyl groups, which may vary in chain length from acetate to long chain fatty acids. Several carnitine acyltransferases, which differ in acyl chain length specificity, catalyze the acylation of the β-hydroxy group on carnitine.[1] As part of a study to compare the carnitine binding requirements for these related enzymes, we required the uncharged racemic carnitine analog **5** and each of its enantiomers, whose preparations have not been previously reported.

Racemic **5** was synthesized from commercially available 4,4-dimethyl-2-pentanone (**1**). The synthesis of intermediate **2** was previously reported by House[2] in three steps: the acid chloride of 3,3-dimethylbutanoic acid was prepared in 86% yield from the acid, and diethylmalonate was hydrolyzed to the half ester in 78% yield. The acid chloride and ethyl malonate (as the dianion) were then condensed to give **2** in 84% yield. We more conveniently prepared **2** in one step (79% yield after distillation) via the acylation of **1** with NaH and diethyl carbonate. Ketoester **2** was then reduced with $NaBH_4$ to give hydroxyester **3** (77% yield), which was hydrolyzed in HCl (aq) to give racemic **5** (82% yield; 50% overall isolated yield from **1**).

For careful comparisons in enzyme kinetics assays, we required both enantiomers of **5** in high optical purity. These were thus prepared via a conventional chromatographic resolution of