A Novel Method for Introduction of the Isoprene Skeleton into Chloromethylarenes and -heteroarenes via a Three-Step Sequence involving a Solvent-Assisted Claisen-Cope Rearrangement

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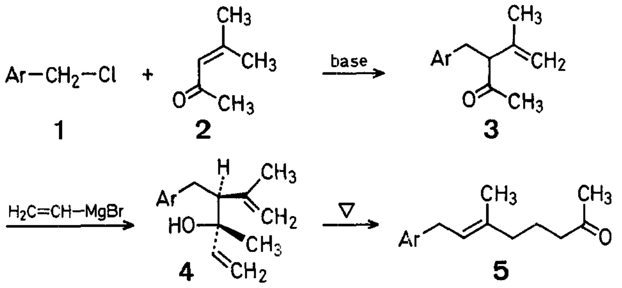
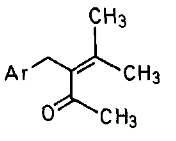
Cope rearrangement of hydroxy-group containing systems has been shown to be a useful method for carbon-chain elongation[1]. However, the applicability of this method is considerably reduced by the fact that β-hydroxyolefin cleavage may compete with the desired [3,3]sigmatropic rearrangement; in order to avoid the cleavage, several modifications such as that using siloxy compounds[2] or anionic processes[3] have been developed. On the other hand, no attention has been paid to solvent effects in Cope processes of hydroxy-group containing systems although such effects have repeatedly been studied in the case of other [3,3]sigmatropic rearrangements[4]. We describe here a new convenient modification of the chain elongation by Cope rearrangement using *N*-methyl-2-pyrrolidone as a solvent in which the selectivity of the [3,3] shift is increased. We applied the method to the introduction of the isoprene skeleton into the methyl group of chloromethylbenzenes (**1a–f**), 2-chloromethylthiophene (**1g**), and 2-chloromethylfuran (**1h**) using mesityl oxide (**2**) as a potential C_6 synthon[5].



The reaction of compounds **1** with an equivalent amount of the enolate prepared from mesityl oxide (**2**) and sodium amide in liquid ammonia/ether (1/1) affords predominantly the β,γ-unsaturated ketones **3** in ~65–70% yield, whereas the analogous reaction of compounds **1** with mesityl oxide (**2**) in 55% aqueous sodium hydroxide (1.5 equiv vs. **1**) at 50° (3 h) using a phase-transfer catalyst affords mixtures of ketones **3** and the isomeric α,β-unsaturated ketones **6** in 80% yield.



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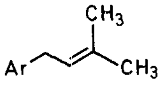

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The reaction of ketones **3** with vinylmagnesium bromide (1.3 equiv) in tetrahydrofuran at 35° (2 h) affords the tertiary alcohols **4** in ~80% yield. The predominant formation of **4** may be ascribed to nucleophilic approach of the vinyl group from the least hindered side according to Cram's rule[6]. Thermolysis of the neat compounds **4** at 170–190° gives 1-aryl-3-methyl-7-oxo-2-octenes (**5**) in ~55% yield, with the *E* isomer predominating. The main by-products

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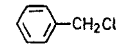
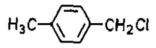
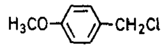
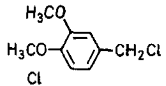
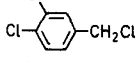
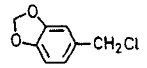
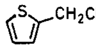
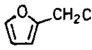
of the reaction are 1-aryl-3-methyl-2-butenes (**7**), butenone, and polymers. When the thermolysis is carried out in the double volume of *N*-methyl-2-pyrrolidone at 190°, the reaction rate is slightly accelerated, the yield of **5** is increased, and there is an increase in the selectivity of the [3,3]sigmatropic rearrangement to give a higher *E*/*Z* ratio. Further, the dependency of the selectivity of the [3,3] shift on the conversion which is observed to a low degree in the thermolysis of neat **4** disappears completely in the solvent-assisted process.

2-Methyl-3-(4-methylbenzyl)-4-oxo-1-pentene (3b):

To liquid ammonia (300 ml) is added a small amount of iron(III) nitrate. Then, sodium (8.1 g, 0.35 g-atom) is added, the mixture is stirred at −33° for 1 h to form sodium amide, mesityl oxide (**2**; 34.3 g, 0.35 mol) is added over a period of 10 min, and stirring is continued for 30 min. To this mixture, 4-methylbenzyl chloride (49 g, 0.35 mol) and ether (300 ml) are added over a period of 20 min, while the temperature is kept at −33°. Excess ammonia is then evaporated, the mixture is neutralized (at −10°) with ammonium chloride, poured into ice water, and extracted with ether. The extract is dried with magnesium sulfate, the ether

Table 1. Products of the Reaction of Chloromethylarenes (**1a–f**) and Chloromethylheteroarenes (**1g, h**) with Mesityl Oxide (**2**)

1 (mol)		Method[a]	Yield [%] (**3**+**6**)	Ratio (**3**/**6**)	**3**[b] b.p./torr
a 	(1.0)	A	80	69/31	66–69°/0.12
b 	(0.35)	B	70	94/6	85–89°/0.62
c 	(0.25)	B	66	87/13	113°/0.4
d 	(0.13)	B	63	91/9	118°/0.4
e 	(1.0)	A	80	64/36	107–112°/0.3
f 	(0.34)	B	65	84/16	130°/0.65
g 	(0.5)	B	66	88/12	92–98°/2.0
h 	(0.9)	A	79	68/32	54–56°/0.2

[a] Method A: reaction at 50° in the presence of trimethylstearylammonium chloride (1 mol % vs. **1**). Method B: reaction at −33° to −10° in ammonia/ether.

[b] All products gave satisfactory microanalyses: C, ±0.29; H, ±0.21. The N.M.R., I.R., and Mass spectral data were in agreement with the structure.

Table 2. Thermolysis of 4-Aryl(Heteroaryl)-3,5-dimethyl-3-hydroxy-1,5-hexadienes (**4**)

4	b.p./torr	Reaction conditions[a]	Yield [%] of **5**	*E*/*Z* Ratio of **5**[b]	b.p./torr	Molecular formula[c]
a	97°/0.25	190°, 1.5 h, S	80	75.0/25.0	107–113°/0.11	$C_{15}H_{20}O$ (216.3)
		N	58	65.0/35.0		
b	105–108°/0.1	190°, 1.5 h, S	83	73.5/26.5	121–124°/0.21	$C_{16}H_{22}O$ (230.3)
c	123–126°/0.3	180°, 3.0 h, S	83	71.3/28.7	127–131°/0.15	$C_{16}H_{22}O_2$ (246.3)
		N	59	64.5/35.5		
d	154–159°/0.3	180°, 2.5 h, S	79	70.0/30.0	172–175°/1.2	$C_{17}H_{24}O_3$ (276.3)
e	127–131°/0.2	185°, 1.5 h, S	78	73.0/27.0	168–170°/0.4	$C_{15}H_{18}Cl_2O$ (285.2)
		N	56	62.7/37.3		
f	141–144°/0.5	190°, 1.5 h, S	77	75.3/24.7	150–152°/0.2	$C_{16}H_{20}O_3$ (260.3)
g	105–110°/2.0	180°, 3.0 h, S	78	73.6/26.4	130–131°/1.1	$C_{13}H_{18}OS$ (222.3)
		N	55	60.0/40.0		
h	78–80°/0.4	180°, 3.5 h, S	78	70.0/30.0	105–106°/1.5	$C_{13}H_{18}O_2$ (206.2)

[a] S: Solvent-assisted reaction; thermolysis in *N*-methyl-2-pyrrolidone.
N: Thermolysis of neat **4**.

[b] Determined by G.L.C. analysis; PEG 20M 10% on Chromosorb W (AW).

[c] All products gave satisfactory microanalyses: C, ±0.23; H, ±0.18. The ^{1}H-N.M.R., I.R.-, and mass spectral data were in agreement with the structures.

evaporated, and the residue distilled in vacuo to give a mixture of **3b** and **6b** (94:6; 49.5 g); b.p. 83–90°/0.5 torr. Pure **3b** is obtained by fractional distillation using a column packed with SIBATA HP-9100-B having ~60 theoretical plates; yield: 41.9 g (59%); b.p. 85–89°/0.62 torr.

$C_{14}H_{18}O$	calc.	C 83.12	H 8.97
(202.2)	found	82.96	9.04

I.R. (neat): ν_{max} = 1718 (C=O); 1641 (C=C); 1519 cm^{-1} (aromatic).

3-Furfuryl-2-methyl-4-oxo-1-pentene (3h):

To a solution of sodium hydroxide (54 g, 1.35 mol) in water (45 ml), mesityl oxide (**2**; 176.4 g, 1.8 mol) and trimethylstearylammonium chloride (3.1 g, 0.9 mmol) are added with stirring, followed by the dropwise addition at 40° over a period of 30 min of 2-chloromethylfuran (**2h**, furfuryl chloride; 104 g, 0.9 mol). The reaction temperature is then raised to 50° and stirring continued for 3 h. The mixture is extracted with ether, the extract dried with magnesium sulfate, and the ether evaporated. Distillation of the residue in vacuo gives a mixture of **3h** and **6h** (68:32; 126.5 g, 79%); b.p. 52–59°/0.2 torr. Pure **3h** is obtained by fractional distillation using a column packed with SIBATA HP-9100-B having ~60 theoretical plates; yield: 78.3 g (49%); b.p. 54–56°/0.2 torr.

$C_{11}H_{14}O_2$	calc.	C 74.13	H 7.92
(178.2)	found	74.08	8.01

I.R. (neat): ν_{max} = 1718 (C=O); 1640 (C=C); 1594, 1505, 733 cm^{-1} (furan).

3,5-Dimethyl-3-hydroxy-4-(4-methylbenzyl)-1,5-hexadiene (4b):

A solution of **3b** (48.5 g, 0.24 mol) in tetrahydrofuran (200 ml) is added dropwise with stirring to a solution of vinylmagnesium bromide (0.32 mol) in tetrahydrofuran (500 ml) under a nitrogen atmosphere while the reaction temperature is kept below 30°. Stirring is continued at 35° for 2 h, the mixture then poured into ice water, acidified with dilute acetic acid, and extracted with ether. The extract is dried with magnesium sulfate, the ether evaporated, and the residue distilled in vacuo; yield: 43.6 g (79%); b.p. 105–108°/0.1 torr.

$C_{16}H_{22}O$	calc.	C 83.43	H 9.63
(230.3)	found	83.36	9.77

I.R. (neat): ν_{max} = 3470 (OH); 1640 (C=C); 1518 cm^{-1} (aromatic).

^{1}H-N.M.R. (CCl_4, 100 MHz): δ = 1.20 (s, 3H, CH_3); 1.62 (s, 3H, CH_3); 2.21 (s, 3H, CH_3); ~2.10–2.80 (m, 3H, CH_2CH); 4.68, 4.82 (each broad s, 2H, CH_2); 5.07 (dd, 1H, J = 2 and 11 Hz, CH=); 5.28 (dd, 1H, J = 2 and 18 Hz, CH=); 6.02 (dd, 1H, J = 11 and 18 Hz, CH=); 6.97 ppm (s, 1 H_{arom}).

3-Methyl-1-(4-methylphenyl)-7-oxo-2-octene (5b):

A solution of **4b** (40 g, 0.174 mol) in *N*-methyl-2-pyrrolidone (100 ml) is purged with nitrogen and then heated at 190° for 90 min with stirring. The mixture is then poured into ice/water and extracted with ether. The extract is washed with saturated aqueous sodium chloride, dried with sodium sulfate, and evaporated. The residue is distilled in vacuo to give **5b** as a mixture of the two stereoisomers (E/Z = 73.5/26.5); yield: 33.1 g (83%); b.p. 121–124°/0.21 torr.

$C_{16}H_{22}O$	calc.	C 83.43	H 9.63
(230.3)	found	83.51	9.54

M.S.: m/e = 230 (M^+, 8%); 157 (38); 105 (41); 43 (100).

I.R. (neat): ν_{max} = 1710 (C=O); 1515 (aromatic).

^{1}H-N.M.R. (CCl_4): δ = 1.62, 1.65 (s, 3H, CH_3); 1.88 (s, 3H, CH_3); 2.20 (s, 3H, CH_3); ~1.70–2.40 (m, 6H, CH_2); 3.22 (d, 2H, CH_2, J = 7 Hz); 5.30 (t, 1H, CH=, J = 7 Hz); 7.00 ppm (s, 4 H_{arom}).

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