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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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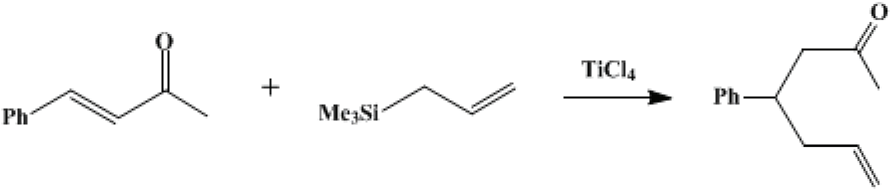
CONJUGATE ALLYLATION OF α,β-UNSATURATED KETONES WITH ALLYLSILANES: 4-PHENYL-6-HEPTEN-2-ONE

[6-Hepten-2-one, 4-phenyl-]



Submitted by Hideki Sakurai, Akira Hosomi, and Josabro Hayashi[1].
Checked by Todd A. Blumenkopf and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask is fitted with a dropping funnel (Note 1), mechanical stirrer, and reflux condenser attached to a nitrogen inlet. In the flask are placed 29.2 g (0.20 mol) of benzalacetone (Note 2) and 300 mL of dichloromethane (Note 3). The flask is immersed in a dry ice–methanol bath (−40°C) and 22 mL (0.20 mol) of titanium tetrachloride (Note 4) is slowly added by syringe to the stirred mixture. After 5 min, a solution of 30.2 g (0.26 mol) of allyltrimethylsilane (Note 5) and (Note 6) in 300 mL of dichloromethane is added dropwise with stirring over a 30-min period. The resulting red–violet reaction mixture is stirred for 30 min at −40°C (Note 7), hydrolyzed by addition of 400 mL of H_2O, and, after the addition of 500 mL of ethyl ether with stirring, allowed to warm to room temperature. The nearly colorless organic layer is separated and the aqueous layer is extracted with three 500-mL portions of ethyl ether. The organic layer and ether extracts are combined and washed successively with 500 mL of saturated sodium bicarbonate and 500 mL of saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. The residue is distilled under reduced pressure through a 6-in. Vigreux column to give 29.2–30.0 g (78–80%) of 4-phenyl-6-hepten-2-one, bp 69–71°C (0.2 mm), n_{D}^{20} 1.5156, as a colorless liquid (Note 8).

2. Notes

1. A 500-mL dropping funnel, with pressure-equalizing arm, is used.
2. Benzalacetone is purchased from Wako Pure Chemical Ind., Ltd. or Aldrich Chemical Company, Inc.
3. Dichloromethane is dried over anhydrous calcium chloride, distilled, and stored over Linde 5A molecular sieves before use. The checkers distilled dichloromethane from calcium hydride immediately before use.
4. Titanium tetrachloride, purchased from Junsei Chemical Co., Ltd. is distilled before use. The checkers purchased titanium tetrachloride from the Fisher Scientific Company and distilled it from copper powder before use.
5. The starting allyltrimethylsilane can be prepared in satisfactory yield by the procedure of Sommer.[2] It can also be purchased from PCR, Inc.; Aldrich Chemical Company, Inc.; Fluka A. G., Petrarch Systems, Inc.; and Tokyo Kasei Kogyo Co., Ltd. The checkers employed material from Petrarch.
6. The use of more than 1.2 equiv of allyltrimethylsilane is essential for shortening the reaction time as well as to avoid contamination of the product by unreacted benzalacetone.
7. Disappearance of benzalacetone and appearance of product can be readily monitored by thin-layer or gas chromatographic analysis on a 1-m column packed with 20% Silicone SE-30 at 180°C. The reaction should be stopped as soon as disappearance of benzalacetone is confirmed.
8. Gas chromatographic analysis of the product on a 1-m column packed with 20% Silicone SE-30 at 180°C should give a single peak. The product has the following spectral properties: IR (film) cm^{-1}: 1710, 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.97 (s, 3 H, CH_3CO), 2.35 (t, 2 H, $J = 7.5$, $CH_2C{=}C$), 2.72 (d, 2 H, $J = 7.5$, CH_2CO), 3.27 (quintet, 1 H, $J = 7.5$, PhCH), 4.8–5.1 (m, 2 H, $CH_2{=}C$), 5.4–5.9 (m, 1 H,

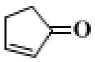
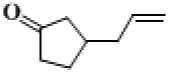
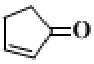
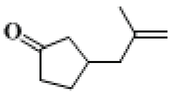
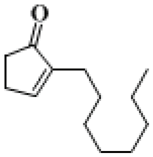
CH=C), 7.0–7.4 (m, 5 H, aromatic).

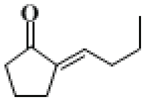
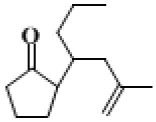
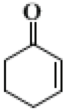
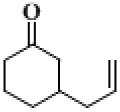
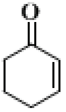
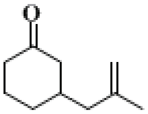
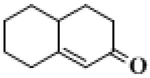
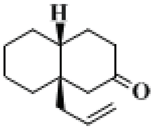
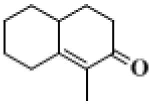
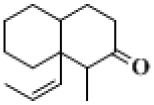
3. Discussion

This procedure is general for the conjugate allylation of α,β-unsaturated ketones with allysilanes.[3] Some representative examples are listed in Table I. The main advantages of the method are its wide generality and the ready availability of the necessary starting materials. The procedure is often useful for the preparation of δ,ε-unsaturated ketones that cannot be obtained in satisfactory yield by the use of allylcuprate (e.g., entry 13) reagents.[4] Another useful aspect of the reaction is the regiospecific coupling of the allyl group. Examples of this feature can be seen in entries 2 and 5. Although cyclic as well as acyclic α,β-unsaturated ketones give satisfactory results, the reaction is slower in sterically hindered systems (entries 13 and 14). However, even in these cases, good yields are obtained by using excess allylsilane and by conducting the reaction at higher temperature. Since the allyl group can be modified by the regioselective addition of various reagents to the double bond,[5,6] the method is applicable to the synthesis of a wider variety of compounds than are shown in the Table. By oxidation of the double-bond 1,5-diketones may be obtained.[7] Conjugate allylation with allylsilanes can be used in conjunction with a suitable electrophile to achieve "one-pot" double alkylation at the adjacent vinyl position of an α,β-unsaturated ketone.[8] The method has also been utilized in the synthesis of perhydroazulenones.[9] Allylsilanes also undergo regioselective, Lewis acid-catalyzed reaction with carbonyl compounds,[10] acetals,[11] α,β-unsaturated acetals,[12] acyl halides,[13] tertiary alkyl halides,[14] and oxiranes.[14] Such allylations can also be achieved by using allystannanes.[15]

TABLE I

CONJUGATE ALLYLATION OF α,β-ENONES WITH ALLYLSILANES PROMOTED BY TITANIUM TETRACHLORIDE[a]

Entry	Allylsilane	α,β-Enone	Conditions Temp., °C, time	δ,ε-Enone	Yield (%)[b]
1	I[c]	$CH_2{=}CHCOCH_3$	−78, 1 min	$CH_2{=}CH(CH_2)_3COCH_3$	59
2	II[d]	$CH_2{=}CHCOCH_3$	−78, 3 hr	$CH_2{=}C(CH_3)_2CH_2CH_2COCH_3$	79
3	I	$(CH_3)_2C{=}CHCOCH_3$	25, 5 min	$CH_2{=}CHCH_2C(CH_3)_2CH_2COCH_3$	87
4	III[e]	$PhCH{=}CHCOCH_3$[f]	−78, 0.5 min	$CH_2{=}C(CH_3)CH_2CH(Ph)CH_2COCH_3$	69
5	IV[g]	$PhCH{=}CHCOCH_3$	−78, 5 hr	$CH_2{=}CHCH(CH_3)CH(Ph)CH_2COCH_3$	76
6	I	$PhCH{=}CHCOPh$	−78, 1 min	$CH_2{=}CHCH_2CH(Ph)CH_2COCH_3$	96
7	I		−78, 2 hr		70
8	III		−78, 10 min		70
9	I		−78, 2 hr		54

10	III		−78, 30 min		82[h]
11	I		−78, 1 hr		80[i]
12	III		−78, 10 min		99[j]
13	I		−78, 18 hr then −30, 5 hr		85[k]
14	I		−78, 2 hr then 0, 15 min		88

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[a] The reaction was carried out on a 1–20-mmol scale in dichloromethane.

[b] Yields after isolation by distillation or thin-layer chromatography.

[c] I = $Me_3SiCH_2CH{=}CH_2$.

[d] II = $Me_3SiCH_2CH{=}C(CH_3)_2$.

[e] III = $Me_3SiCH_2C(CH_3){=}CH_2$.

[f] Three equivalents of the allylsilane were used.

[g] IV = *trans*-$Me_3SiCH_2CH{=}CHCH_3$.

[h] A [2 + 2] cycloadduct assigned the structure 1-methyl-1-trimethylsilylmethyl-3-*n*-propylspiro[3,4]octan-5-one was obtained in 19% yield.

[i] BP 56–60°C (3 mm), n_D^{20} 1.4719.

[j] Two equivalents of the allylsilane were used.

[k] Bp 83–85°C (0.6 mm), n_D^{20} 1.5111. A diallylated product, assigned the structure 2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene, was obtained as a forerun in less than 5% yield.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

H_2O

perhydroazulenones

$Me_3SiCH_2CH=CH_2$

$Me_3SiCH_2CH=C(CH_3)_2$

$Me_3SiCH_2C(CH_3)=CH_2$

trans-$Me_3SiCH_2CH=CHCH_3$

$CH_2=CHCOCH_3$

$CH_2=C(CH_3)_2CH_2CH_2COCH_3$

$(CH_3)_2C=CHCOCH_3$

$CH_2=CHCH_2C(CH_3)_2CH_2COCH_3$

$PhCH=CHCOCH_3$

$CH_2=C(CH_3)CH_2CH(Ph)CH_2COCH_3$

$CH_2=CHCH(CH_3)CH(Ph)CH_2COCH_3$

$PhCH=CHCOPh$

$CH_2=CHCH_2CH(Ph)CH_2COCH_3$

calcium chloride (10043-52-4)

ether,
ethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

copper powder (7440-50-8)

Benzalacetone (122-57-6)

dichloromethane (75-09-2)

titanium tetrachloride (7550-45-0)

calcium hydride (7789-78-8)

4-Phenyl-6-hepten-2-one,
6-Hepten-2-one, 4-phenyl- (69492-29-1)

allyltrimethylsilane (762-72-1)

allylcuprate

allylsilane (18191-59-8)

2,8a-diallyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene

1-methyl-1-trimethylsilylmethyl-3-n-propylspiro[3,4]octan-5-one