A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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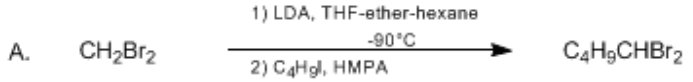
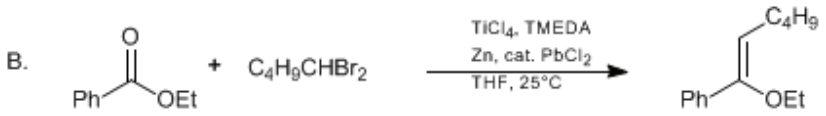
ALKYLIDENATION OF ESTER CARBONYL GROUPS: (Z)-1-ETHOXY-1-PHENYL-1-HEXENE





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1. Procedure

Caution! Hexamethylphosphoric triamide (HMPA) is toxic and must be handled with gloves.

A. *1,1-Dibromopentane*(Note 1). A dry, 3-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet, rubber septum, and a 200-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. After placing the system under a nitrogen atmosphere, the flask is charged with 280 mL of dry tetrahydrofuran (Note 2), 400 mL of dry diethyl ether (Note 2), and 20 g (0.20 mol) of dry diisopropylamine (Note 3). Stirring is initiated, and the contents of the flask are cooled to −10°C (dry ice-acetone bath). After transfer of 120 mL (0.20 mol) of 1.7 M butyllithium in hexane (Note 4) to the addition funnel by syringe, the solution of alkyllithium is slowly added to the stirred solution at such a rate as to maintain a temperature of −10°C. After the addition is complete, 10 mL of dry THF is introduced via syringe to rinse the walls of the addition funnel and then added to the reaction mixture. The mixture is stirred at −10°C for 15 min and cooled to −90°C (toluene-liq. nitrogen bath). The addition funnel is charged by syringe with a solution of 15 mL (38 g, 0.22 mol) of dibromomethane (Note 5) in 100 mL of dry THF, which is then added at such a rate that the temperature does not exceed −85°C (Note 6). The mixture is stirred for 15 min. A solution of 22 mL (37 g, 0.20 mol) of 1-iodobutane (Note 7) in 100 mL of THF, and 120 mL of hexamethylphosphoric triamide (Note 8) are successively added by syringe at such a rate (over an ~25 min period) that the temperature of the reaction mixture does not exceed −85°C (Note 6). After the addition is complete, the reaction mixture is stirred at −90°C (toluene-liq. nitrogen bath) for 2 hr, −78°C (dry ice-acetone bath) for 1 hr, −48°C (dry ice-acetonitrile bath) for 2 hr, and −23°C (dry ice-carbon tetrachloride bath) for 3 hr (Note 6) and (Note 9). The solution is poured into 200 mL of 1 M hydrochloric acid solution and transferred to a 2-L separatory funnel. The resulting mixture is extracted with three 100-mL portions of hexane. The organic extracts are combined and washed with three 300-mL portions of water, 100 mL of saturated aqueous sodium sulfite solution, and 100 mL of brine. The organic layer is dried over anhydrous magnesium sulfate and then concentrated with a rotary evaporator (0°C water bath, trapping at −78°C with a dry ice-acetone condenser) at aspirator pressure. The brown liquid residue is distilled to afford 27–32 g (59–70%) of 1,1-dibromopentane as a colorless liquid, bp 70–72°C (15 mm) (Note 10).

B. *(Z)-1-Ethoxy-1-phenyl-1-hexene*. A dry, 3-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet, rubber septum, and a 200-mL, pressure-equalizing addition funnel that is sealed with rubber septum. After placing the system under a nitrogen atmosphere, the flask is charged with 350 mL of dry tetrahydrofuran (Note 2). The contents of the flask are cooled to 0° C with an ice bath, and 140 mL (0.28 mol) of a 2.0 M solution of titanium tetrachloride in dichloromethane (Note 11) is added slowly by syringe to the stirred THF over a period of 10 min. To

the yellow solution at 0°C is added slowly 84 mL (0.56 mol) of tetramethylethylenediamine> (Note 12) by syringe. After being stirred at 0°C for 20 min, 41 g (0.63 mol) of zinc dust (Note 13) is added to the reaction mixture at 0°C in five portions in such a manner that the temperature remains at 0°C (Note 14), followed by addition of 0.88 g (3.2 mmol) of lead (II) chloride (Note 13) and (Note 15), and then the resulting suspension is warmed to 25°C. The color of the suspension turns from brownish yellow to dark greenish blue while being stirred at 25°C for 30 min. The addition funnel is then charged by syringe with a solution of 11 g (70 mmol) of ethyl benzoate (Note 12) and 35 g (0.15 mol) of 1,1-dibromopentane (part A) in 100 mL of dry THF. The resulting solution is then added to the stirred reaction mixture over a period of 10 min at 25°C and stirring is continued for 3.5–4.5 hr. The color of the resulting mixture gradually turns dark brown as the reaction proceeds (Note 16),(Note 17),(Note 18). The reaction mixture is then cooled to 0°C and 70 mL of triethylamine (Note 12) and 91 mL of saturated aqueous potassium carbonate solution are successively added slowly at 0°C by syringe. After stirring at 0°C for an additional 15 min, 200 mL of ether-triethylamine (200/1, v/v) is added to the reaction mixture. The entire reaction mixture is then passed rapidly through a thin pad of activity III basic alumina (Note 19) on a 1-L glass filter using 500 mL of ether-triethylamine (200/1, v/v) as eluent. The filtrate is concentrated with a rotary evaporator (25°C, water bath). If a white solid appears at this point, the mixture is diluted with 100 mL of hexane-triethylamine (200/1, v/v) and the mixture is again filtered through a thin pad of basic alumina (Akt. III). The pad is washed with 100 mL of hexane-triethylamine (200/1, v/v) and the total eluent is concentrated again with a rotary evaporator. The resulting crude material is then vacuum distilled to give 11.0–11.4 g (77–80%) of a 93:7 mixture of (Z)- and (E)-1-ethoxy-1-phenyl-1-hexene, bp 73–75°C (0.20 mm) (Note 20) and (Note 21).

2. Notes

1. This procedure was reported by J. Villieras, C. Bacquet, and J. F. Normant.[3]
2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone just before use.
3. Diisopropylamine was distilled from calcium hydride, bp 84°C.
4. A 1.7 M hexane solution of butyllithium was obtained from Kanto Chemical Co. It may be standardized; however, the submitters chose to use a fresh reagent and forego the titration. The checkers employed a 1.6 M solution of n-butyllithium in hexane obtained from Lithco Inc., which was standardized before use.
5. Dibromomethane was freshly distilled, bp 96–97°C. The checkers noted some variability in the yield which in part appeared to be associated with the source of the dibromomethane.
6. The checkers monitored the internal temperature of the reaction mixture via thermocouple using an immersion well. The checkers observed that accurate temperature control is essential to obtain the reported yields reproducibly.
7. 1-Iodobutane was freshly distilled, bp 129°C.
8. Hexamethylphosphoric triamide is toxic and a cancer-suspect agent. It was distilled from calcium hydride, bp 68–69°C at 1 mm.
9. The color of the mixture changed from brown to white after 30-min stirring at −90°C. Then the color of the mixture changed gradually from white to light brown at −23°C.
10. The infrared spectrum (neat) has absorptions at 2956, 2930, 2860, 1465, 1431, 1238, 1158, 927, 732, 667, 596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3 H, J = 7.2), 1.28–1.61 (m, 4 H), 2.41 (dt, 2 H, J = 8.4, 6.2), 5.72 (t, 1 H, J = 6.2); ^{13}C NMR ($CDCl_3$) δ: 13.8, 21.4, 30.1, 45.1, 46.2.
11. Freshly distilled titanium tetrachloride (bp 136°C) was diluted with dichloromethane to afford a 2.0 M solution. All residues of titanium tetrachloride were destroyed with acetone from a wash bottle.
12. Tetramethylethylenediamine was freshly distilled from potassium hydroxide, bp 46–47°C (47 mm). Ethyl benzoate was distilled before use. Triethylamine was distilled from potassium hydroxide before use.
13. Zinc dust purchased from Wako Pure Chemical Industries, Ltd. (GR grade) was activated by washing several times with 5% hydrochloric acid washing in turn with water, methanol, and ether, and drying in vacuo according to Fieser and Fieser.[4] The lots employed by the submitters were found to contain ~0.05 mol% Pb based on the Zn content by X-ray fluorescence analysis (Note 15). The checkers employed Zn dust (−325 mesh, 99.998% purity) obtained from Aldrich Chemical Company, Inc.
14. The reduction is a slightly exothermic process.
15. Addition of a catalytic amount of $PbCl_2$ (Rare Metallic Co., 99.999% purity) to a commercial lot of Zn dust (Aldrich Chemical Company, Inc. (99.998% purity) or Rare Metallic Co. (99.999% purity)) has

shown reproducible results as were previously reported.[5,6] The yield of (Z) and (E)-1-ethoxy-1-phenyl-1-hexene fell to 10–15% ((Z)/(E) = 92/8–95/5) without the addition of $PbCl_2$.[7]
16. The consumption of ethyl benzoate was checked by tlc analysis.
17. The following ratios of reactants, ester/1,1-dibromoalkane/zinc/$TiCl_4$/$PbCl_2$/TMEDA = 1/2.2/9/4/0.045/8, gave the best results. When the amount of the reagent was reduced to 1/1.1/4.5/2/0.023/4, only 44% of the 1-ethoxy-1-phenyl-1-hexene was isolated under the same reaction conditions and 44% of ethyl benzoate remained.
18. Under the reaction conditions for alkylidenation, compounds containing the following functional groups were found to be stable: trimethylsilyl ethers of alcohols, olefins, primary alkyl iodides, and ethylene acetals of aldehydes.
19. Basic alumina (ICN alumina B-Act. I) was purchased from ICN Biochemical GmbH and pretreated by shaking with 6% of water to change its activity (Act I → III).
20. The infrared spectrum (neat) has absorptions at 2924, 2870, 1649, 1492, 1446, 1266, 1072, 768, 696 cm^{-1}; ^1H NMR ((Z) isomer) ($CDCl_3$) δ: 1.00 (t, 3 H, J = 6.9), 1.23–1.45 (m, 7 H), 2.32–2.39 (m, 2 H), 3.76 (q, 2 H, J = 7.0), 5.38 (t, 1 H, J = 7.3), 7.23–7.50 (m, 5 H); ^1H NMR ((E) isomer) ($CDCl_3$) δ: 0.87 (t, 3 H, J = 7.0), 1.23–1.45 (m, 7 H), 2.00–2.13 (m, 2 H), 3.80 (q, 2 H, J = 7.0), 4.74 (t, 1 H, J = 7.4), 7.23–7.50 (m, 5 H); ^{13}C NMR ((Z) isomer) ($CDCl_3$) δ: 14.0, 15.3, 22.5, 25.4, 32.0, 65.8, 115.4, 125.8, 127.5, 128.2, 136.7, 153.2. MS m/z (%): 204 (M^+, 48), 161 (100), 133 (55), 55 (49). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.47; H, 10.04.
21. The ratio of the geometric isomers of the product ((Z)/(E)) was determined by ^1H NMR since isomerization has been shown to occur under GLC conditions.[8]

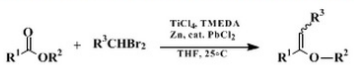
Waste Disposal Information

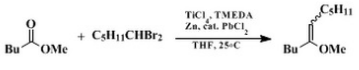
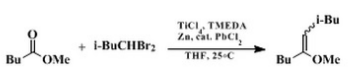
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

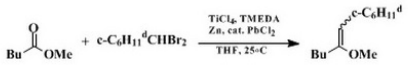
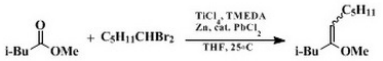
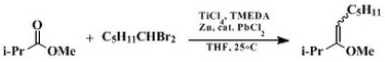
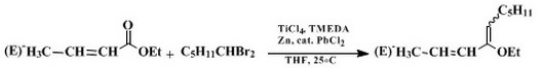
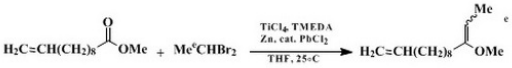
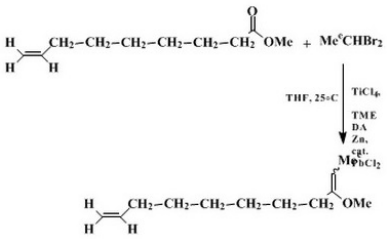
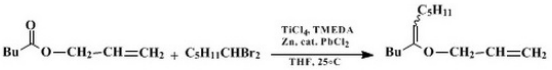
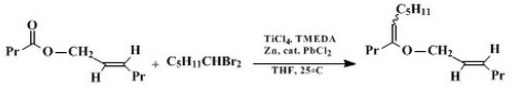
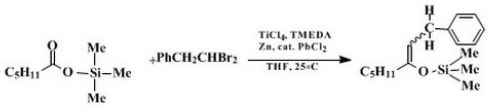
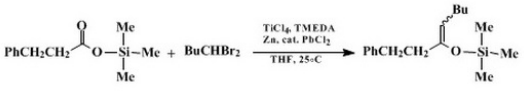
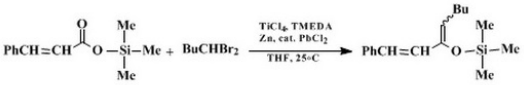
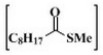
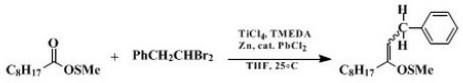
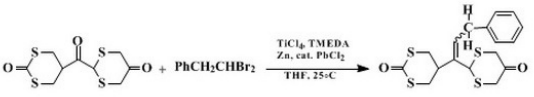
3. Discussion

The procedure described here provides a convenient method for the conversion of esters to Z-alkenyl ethers.[5] The results in the Table show the wide applicability and high Z selectivity of the process. As the substituents R^1 or R^3 become bigger, or R^2 becomes smaller, higher Z selectivity is observed. The stereochemistry of the isomers (Table, cases 1–10) was determined by ^{13}C NMR.[8] Since isomerization of alkenyl ethers has been reported to take place under GLC conditions, the remaining Z/E ratios were measured by ^1H NMR (200 MHz) analysis. Esters having terminal double bonds reacted to afford the corresponding alkenyl ethers in about 50% yield (cases 7 and 9). Esters with internal double bonds gave better yields and the stereochemistry of double bonds of the reactants was retained except in the instance of case 8 where partial isomerization of the isolated cis double bond occurred. Thus, the reaction provides a convenient and stereoselective access to allyl vinyl ethers (cases 9 and 10) and oxygen-substituted dienes (case 6). Z-Isomers of silyl enol ethers (cases 11–13) and an alkenyl sulfide (case 14) are also produced under good stereocontrol from the corresponding carboxylic acid derivatives.

TABLE
ALKYLIDENATION OF CARBOXYLIC ACID DERIVATIVES[a]



Case	R^1	R^2	R^3	Yield(%)[b]	Z/E[c]
1	Bu	Me	C_5H_{11}	 96	91/9
2	Bu	Me	i-Bu	 95	93/7

3	Bu	Me	c-C_6H_{11}[d]		93/7
				69	
4	i-Bu	Me	C_5H_{11}		92/8
				88	
5	i-Pr	Me	C_5H_{11}		100/0
				89	
6	(E)-MeCH=CH	Et	C_5H_{11}		94/6
				90	
7	CH_2=CH$(CH_2)_8$	Me	Me[e]		89/11
8		Me	Me[e]		90/10
				70[f]	
9	Bu	CH_2=$CHCH_2$	C_5H_{11}		92/8
				52	
10	Pr		C_5H_{11}		94/6
				85	
11	C_5H_{11}	Me_3Si	$PhCH_2$		89/11
				76[g]	
12	$PhCH_2CH_2$	Me_3Si	Bu		84/16
				80[g]	
13	PhCH=CH	Me_3Si	Bu		100/0
14			$PhCH_2$		90/10
				87[g]	
15			$PhCH_2$		—
				87[h]	

[a]The carboxylic acid derivatives (1–2 mmol scale) are treated with 1,1-dibromoalkane (2.2 equiv), Zn (9.0 equiv), $TiCl_4$ (4.0 equiv), $PbCl_2$ (0.045 equiv), and TMEDA (8.0 equiv) in THF at 25°C for 0.5–3 hr. [b]Products are isolated by column chromatography on alumina unless otherwise noted. [c]See the text. [d]Prepared from cyclohexanecarbaldehyde[9] [e]Commercially available at Tokyo Kasei Kogyo Co., Japan. [f]The cis/trans ratio of the double bond at C-11 of the resultant ether was 87/13. [g]Isolated by column chromatograpy on silica gel (70–230 mesh ATSM, MERCK). [h]The product was isolated by Kugelrohr distillation.bp 150–152°C (bath temperature, 0.2 mm).

The preparation of alkenyl ethers is limited to methods which use as starting materials either acetals[10] or acetylenes.[11,12] It is usually difficult to prepare the alkenyl ethers, especially trisubstituted ones, in a regio- and stereoselective manner by these methods. Alkylidenation of carboxylic acid derivatives does not proceed with the Wittig reagent.[13] Methylene transfer (C=O → C=CH_2) of such electron-rich carbonyl compounds has been achieved with the Tebbe reagent[14] or dimethyltitanocene.[15,16] Alkylidenation by using the Schrock-type metal carbene complex of Ta, Ti, Zr, or W has been reported.[17 18 19] However, the method using the Schrock complexes has several drawbacks. For example, i) the preparation of the complex usually requires special techniques and some restrictions exist on the nature of the substitutents R^1 and/or R^2. ii) The alkylidenation reaction using the Schrock complexes does not provide alkenyl ethers with good control over olefin geometry. The present procedure offers an experimentally simple and stereoselective preparation of alkenyl ethers. The reactants, 1,1-dibromoalkanes, are readily prepared from either iodoalkanes (vide supra) or aldehydes[20 9,21 22] and it is not necessary to isolate the reactive organometallic compound.

References and Notes

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7. Professor R. K. Boeckman, Jr. and Dr. A. T. Johnson noted while attempting to check this procedure that this alkylidenation did not proceed with commercial samples of high purity zinc from Aldrich Chemical Company, Inc. However, the reaction proceeded normally with a sample of Wako Pure Chemicals zinc powder obtained from the submitters. Atomic absorption analysis by the checkers suggested the only significant impurities to be lead and cadmium. The presence of lead in active lots of zinc powder was also found by the submitters by X-ray fluorescence analysis (with the aid of Professor H. Takatsuki and Mr. Y. Honda of the Environmental Research Center, Kyoto University), and Auger electron spectroscopy (by Professor Z. Takehara and Dr. Y. Uchimoto of the Division of Energy and Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

alumina

brine

(Z) and (E)-1-ethoxy-1-phenyl-1-hexene

$PbCl_2$

Zn

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium sulfite (7757-83-7)

lead (II) chloride

nitrogen (7727-37-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

ethyl benzoate (93-89-0)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

cadmium (7440-43-9)

butyllithium,
n-butyllithium (109-72-8)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

titanium tetrachloride (7550-45-0)

triethylamine (121-44-8)

cyclohexanecarbaldehyde (2043-61-0)

calcium hydride (7789-78-8)

hexamethylphosphoric triamide (680-31-9)

diisopropylamine (108-18-9)

tetramethylethylenediamine (20485-44-3)

1-iodobutane (542-69-8)

(Z)-1-Ethoxy-1-phenyl-1-hexene (174866-87-6)

1,1-Dibromopentane (13320-56-4)

(E)-1-ethoxy-1-phenyl-1-hexene

1-ethoxy-1-phenyl-1-hexene