Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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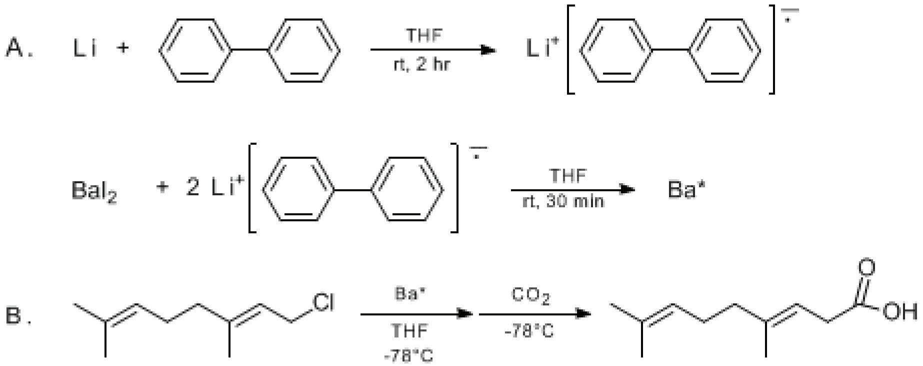
REGIO- AND STEREOSELECTIVE CARBOXYLATION OF ALLYLIC BARIUM REAGENTS: (E)-4,8-DIMETHYL-3,7-NONADIENOIC ACID

[3,7-Nonadienoic acid, 4,8-dimethyl-, (E)-]



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Checked by D. Scott Coffey and William R. Roush.

1. Procedure

A. *Active barium*. An oven-dried, three-necked, round-bottomed, 300-mL flask, equipped with a Teflon-coated magnetic stirring bar, is flushed with argon (Note 1). Freshly cut lithium (210 mg, 30.3 mmol) and biphenyl (4.7 g, 30.5 mmol) are placed in the apparatus and covered with dry tetrahydrofuran (THF) (80 mL) (Note 2), and the mixture is stirred for 2 hr at room temperature (Note 3). In a separate, oven-dried, three-necked, round-bottomed, 500-mL flask, equipped with a Teflon-coated magnetic stirring bar and a 100-mL addition funnel, is placed anhydrous barium iodide (BaI_2) (6.0 g, 15.3 mmol) ((Note 4), (Note 5)) under an argon atmosphere; this is covered with dry THF (80 mL), and stirred for 5 min at room temperature. To the resulting yellowish solution of BaI_2 in THF is added at room temperature a solution of the lithium biphenylide through a stainless steel cannula under an argon stream. The reaction mixture is stirred for 1 hr at room temperature, and the resulting dark brown suspension of active barium thus prepared is ready for further use.

B. *(E)-4,8-Dimethyl-3,7-nonadienoic acid*. To the suspension of active barium in THF is added dropwise over 20 min a solution of geranyl chloride (1.19 g, 6.89 mmol) (Note 6) in THF (40 mL) from the 100-mL dropping funnel at −78°C (Note 7), and the mixture is stirred at this temperature for 30 min (Note 8). An excess of dry ice (ca. 10 g) (Note 9) is added at −78°C and stirring continued for 10 min. The reaction mixture is quenched with 1 N hydrochloric acid (HCl) (40 mL) at −78°C, warmed to room temperature, and poured into a mixture of water (H_2O) (200 mL) and ethyl acetate (EtOAc) (200 mL). After the organic layer is shaken vigorously, it is separated and washed with dilute sodium thiosulfate solution (200 mL). The two aqueous layers are combined, acidified (pH <3) with concd HCl, and extracted twice with EtOAc (2 × 100 mL). The combined organic extracts are washed with H_2O (200 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue is then dissolved in methanol (MeOH) (10 mL) by gentle heating and placed in a freezer (0°C) for over 1 hr to crystallize the biphenyl. The white solid is filtered off (Note 10), washed with cold MeOH (0°C, 40 mL), and the filtrate is concentrated under reduced pressure. The residual oil is purified by flash-column chromatography on silica gel (70 g, (Note 11)) using 2% EtOAc/hexane (500 mL), 20% EtOAc/hexane (600 mL), and then 30% EtOAc/hexane (1 L) as eluant, to afford the crude β,γ-unsaturated carboxylic acid (1.43 g). An additional vacuum distillation (106°C/0.4 mm, (Note 12)) provides pure (E)-4,8-dimethyl-3,7-nonadienoic acid (0.91–0.96 g, 72–76% yield, (Note 13), (Note 14), (Note 15)) as a colorless oil. The isomeric purity is determined to be ≥ 97 : 3 [(E/Z) of 98 : 2 and α:γ of

>99 : 1] by GC analysis after conversion to the corresponding methyl ester (Note 16).

2. Notes

1. The submitters used standard grade argon gas (oxygen <10 ppm) which was further purified by passing through a GAS CLEAN column (GC-RX, NIKKA SEIKO Co.) to remove traces of oxygen. The checkers used UHP/Zero grade argon that was passed through a tube of Dri-Rite before use. However, no special precautions were made to remove oxygen.
2. Lithium (wire, 99.9%) was purchased from Aldrich Chemical Company, Inc., (submitters) or EM Science (checkers). The wire was cut into 20–30-mg pieces that were rinsed with dry hexane before use. Biphenyl (guaranteed reagent) was used as purchased from Nacalai Tesque (submitters) or EM Science (checkers). The submitters used dry THF as purchased from Aldrich Chemical Company, Inc. (anhydrous, 99.9%). The checkers used THF (99.5%, EM Science) that was distilled from benzophenone ketyl.
3. The submitters reported that lithium was completely consumed within 2 hr at room temperature (20 ~ 25°C). However, the checkers found that a small amount of Li (ca. 20–40 mg) remained at the end of the reaction.
4. The submitters report that $BaI_2 \cdot 2H_2O$ purchased from Nacalai Tesque (extra pure reagent), Aldrich Chemical Company, Inc., Fluka Chemical Corp., Kishida Chemical, or Wako Pure Chemical can be used with equal efficiency. The checkers used $BaI_2 \cdot 2H_2O$ purchased from Aldrich Chemical Company, Inc.
5. The submitters prepared anhydrous BaI_2 by drying $BaI_2 \cdot 2H_2O$ at 150°C for 2 hr under reduced pressure (<10 mm). However, the checkers were unsuccessful in attempts to generate active barium from BaI_2 that was dried according to these specifications. The checkers obtained good results when finely ground $BaI_2 \cdot 2H_2O$ was dried at 150°C (1–2 mm) for 12–24 hr while being stirred (see (Note 13)). The color of the $BaI_2 \cdot 2H_2O$ changes from light yellow to white during the first 1–2 hr, with no subsequent color changes observed.
6. Geranyl chloride (95%, Aldrich Chemical Company, Inc.) was purified by distillation immediately before use.
7. A 5-L Dewar flask (I.D. 200 mm) was employed for the −78°C cooling bath (dry ice/methanol).
8. A dark red suspension or wine-red solution is obtained.
9. Dry ice was cut into appropriate size pieces and added from the middle inlet of the three-necked, round-bottomed flask. The checkers obtained good results (65–74%) by bubbling carbon dioxide (CO_2) gas (Air Products and Chemicals, Inc.) vigorously into the reaction mixture through an 18-gauge needle for 20 min. The CO_2 was dried by passing through sulfuric acid and then through a drying tube packed with Dri-Rite.
10. After recrystallization (methanol) ca. 2.8 g of biphenyl was recovered (60%).
11. Silica gel 60 (E. Merck 9385, 230–400 mesh) was used.
12. A bulb to bulb distillation apparatus was used. The checkers found the bp to be 104–110°C/0.4 mm.
13. The checkers obtained 0.93 g of product (74% yield) with isomeric purity of 97 : 3 from an experiment run with 210 mg of lithium (Li), BaI_2 that was dried for 24 hr (see (Note 5)), and CO_2 gas. The yield was 62–65% (isomeric purity 97 : 3) from experiments run with 230 mg of Li and BaI_2 that was dried for only 12–14 hr; one experiment was quenched with dry ice and the other with CO_2 gas.
14. The physical properties of (E)-4,8-dimethyl-3,7-nonadienoic acid are as follows: TLC $R_f = 0.50$ (1:1 ethyl acetate/hexane); bp 106°C/0.4 mm; IR (neat) cm^{-1}: 2969, 2919, 1713, 1416, 1300, 1225, 1156, 1109, 941, 831; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.60 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 2.07 (m, 4 H, 2 CH_2), 3.10 (d, 2 H, J = 7.0, CH_2), 5.05–5.13 (m, 1 H, vinyl), 5.31 (t, 1 H, J = 7.0, vinyl), 10.2–11.4 (br, 1 H, CO_2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.4, 17.7, 25.7, 26.4, 33.5, 39.5, 114.9, 123.9, 131.7, 139.8, 178.8; MS (EI) m/e (rel intensity): 170 (5.86, M-12), 149 (7.45), 139 (17.87), 122 (9.11), 69 (62.75); MS (FAB) m/e 183 (M^++1). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.20.
15. The checkers performed this procedure on five times the reported scale and obtained 2.6 g (41%) of crude (impure) (E)-4,8-dimethyl-3,7-nonadienoic acid following chromatographic purification.
16. GC analysis was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25 × 25000 mm) using nitrogen as carrier gas.

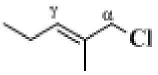
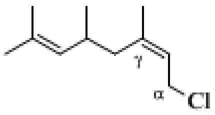
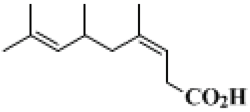
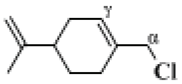
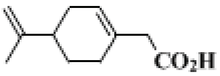
Waste Disposal Information

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

3. Discussion

β,γ-Unsaturated carboxylic acids and their derivatives are valuable synthetic intermediates for various natural products. Two typical multi-step processes for the synthesis of β,γ-unsaturated acids, Knoevenagel reaction/isomerization with base[2] [3] [4] [5] [6] and allylic cyanide/hydrolysis,[7] [8] [9] [10] [11] [12] are those most commonly used. Other new methods have been developed;[13,14,15] [16] [17] [18] [19] [20,21] however, there is a problem with E/Z stereoselectivity. One straightforward way to obtain β,γ-unsaturated acids is by the carboxylation of an allyl metal intermediate. In the substituted allylic series, the reaction usually occurs at the more sterically hindered terminus.[22] A stereospecific route for the synthesis of homogeranic acid and homoneric acid by carboxylation of the lithiated allylic sulfone has also been reported.[23] In contrast, we have found that allylic barium reagents are prepared directly by reaction of in situ generated barium metal with various allylic chlorides, and react with carbonyl compounds or allylic halides in a highly α-selective manner without loss of the double bond geometry.[24] [25] As illustrated in the present procedure, treatment of the allylic barium reagent with excess carbon dioxide results in α-carboxylation, whereas γ-carboxylation occurred with allylic magnesium reagent.[22] Results of carboxylation of allylic barium reagents are summarized in the Table.[26] [27] The characteristic features of the reaction are as follows: (1) Allylic barium reagents generated from a variety of γ-mono- and γ-disubstituted allyl chlorides showed high α-selectivities without exception. (2) The double-bond geometry of the allyl chloride precursor was completely retained in each case. (3) The alkyl substituent at the β-position of an allylic barium reagent had no effect on the regioselectivity.

TABLE
REGIO- AND STEREOSELECTIVE CARBOXYLATION OF ALLYLIC BARIUM REAGENTS

Allylic chloride[a]	Product	Yield, %[b]	α : γ[X]	E : Z[c]
 (E)-$\mathrm{C_7H_{15}\overset{\gamma}{C}H{=}CHC\overset{\alpha}{H}_2Cl}$	(E)-$\mathrm{C_7H_{15}CH{=}CHCH_2CO_2H}$	82	98 : 2	99 : 1
 (Z)-$\mathrm{C_7H_{15}\overset{\gamma}{C}H{=}CHC\overset{\alpha}{H}_2Cl}$	(Z)-$\mathrm{C_7H_{15}CH{=}CHCH_2CO_2H}$	65	82 : 18	1 : 99
		58	95 : 5	99 : 1
 $\mathrm{(CH_3)_2\overset{\gamma}{C}{=}CHC\overset{\alpha}{H}_2Cl}$	$\mathrm{(CH_3)_2C{=}CHCH_2CO_2H}$	59	>99 : 1	
		51	>99 : 1	<1 : 99
		79	98 : 2	

[a] Stereochemically pure (>99%) allylic chloride was used. [b] Isolated yield.
[c] Determined by GC analysis after conversion to methyl ester.

In conclusion, this is one of the most straightforward and practical methods available for the regioselective and stereospecific synthesis of β,γ-unsaturated carboxylic acids.

References and Notes

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

silica gel

benzophenone ketyl

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ethyl acetate,

EtOAc (141-78-6)

methanol (67-56-1)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

Biphenyl (92-52-4)

barium (7440-39-3)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

Geranyl chloride (5389-87-7)

Lithium biphenylide (34467-57-7)

diethyl oxomalonate (609-09-6)

(E)-4,8-Dimethyl-3,7-nonadienoic acid,
3,7-Nonadienoic acid, 4,8-dimethyl-, (E)- (459-85-8)

barium iodide (13718-50-8)