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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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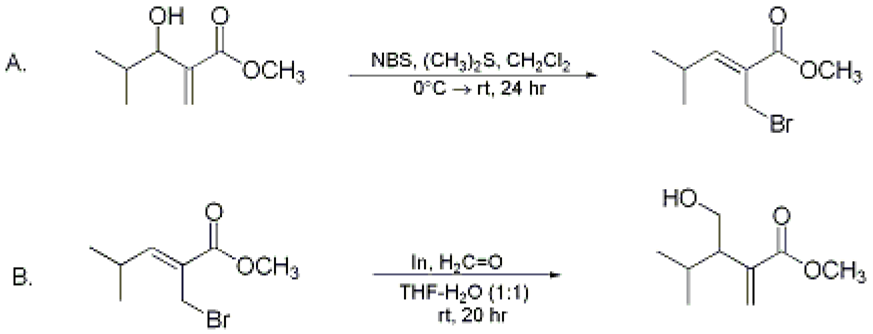
ALLYLINDATION IN AQUEOUS MEDIA: METHYL 3-(HYDROXYMETHYL)-4-METHYL-2-METHYLENEPENTANOATE



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1. Procedure

Caution! These reactions should be carried out in a fume hood because dimethyl sulfide is a stench compound, the bromo ester product is a lachrymator, and formaldehyde is a cancer suspect agent.

A. *Methyl Z-2-(bromomethyl)-4-methylpent-2-enoate* .[2] [3] [4] A dry, 250-mL, three-necked, round-bottomed flask fitted with an overhead stirrer and nitrogen inlet is charged with 100 mL of dichloromethane (CH_2Cl_2, (Note 1)) and 25.9 g (0.15 mol) of N-bromosuccinimide (Note 2). The stirred suspension is cooled to 0°C and 9.29 g (0.15 mol) of dimethyl sulfide (Note 3) is added (Note 4), followed by 15.8 g (0.10 mol) of methyl 3-hydroxy-4-methyl-2-methylenepentanoate (Note 5). The resulting mixture is allowed to warm to room temperature, stirred for 24 hr, recooled to 0°C, diluted with 150 mL of pentane (Note 6), and poured into 200 mL of saturated brine and ice. The separated aqueous phase is extracted with three 75-mL portions of pentane and the combined organic extracts are washed with 75 mL of brine , dried over magnesium sulfate (Note 7), gravity filtered, and concentrated on a rotary evaporator. The pale yellow residue is purified by column chromatography (Note 8) and (Note 9) to give 14.5 g (66%) of the bromo ester (Note 10) as a colorless oil.

B. *Methyl 3-(hydroxymethyl)-4-methyl-2-methylenepentanoate* . A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar is charged with 11.0 g (0.05 mol) of methyl Z-2-(bromomethyl)-4-methylpent-2-enoate , 110 mL of tetrahydrofuran (Note 11), 110 mL of distilled water, 4.1 mL of a 37% w/w solution (0.05 mol) of aqueous formaldehyde (Note 12), and 6.32 g (0.06 mol) of indium powder (Note 13). The mixture is stirred vigorously at room temperature for 20 hr and diluted with 110 mL of ethyl acetate (Note 14) and (Note 15). The separated aqueous phase is extracted with three 75-mL portions of ethyl acetate and the combined organic extracts are washed with 75 mL of brine , dried over sodium sulfate (Na_2SO_4, (Note 16)), gravity filtered, and concentrated on a rotary evaporator. The pale yellow residue is purified by column chromatography (Note 8) and (Note 17) to give 6.45 g (75%) (Note 18) of the hydroxy ester as a colorless oil (Note 19).

2. Notes

1. Dichloromethane was freshly distilled under nitrogen from calcium hydride .
2. N-Bromosuccinimide was used as purchased from the Aldrich Chemical Company, Inc.
3. Dimethyl sulfide was used as purchased from the Aldrich Chemical Company, Inc.
4. Dropwise addition via syringe successfully avoids such problems as rapid precipitation of the NBS·$(CH_3)_2S$ complex, high exothermicity, and loss of stirring efficiency.
5. Methyl 3-hydroxy-4-methyl-2-methylenepentanoate [5] was obtained by the means of a Baylis-Hillman

reaction[6] [7,8] as follows. To a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar were added 82.3 g (1.14 mol) of isobutyraldehyde , 109.2 g (1.27 mol) of methyl acrylate , 7.28 g (0.057 mol) of 3-hydroxyquinuclidine , and 20 mL of chloroform (to predissolve the catalyst). The mixture was stirred at room temperature for 48 hr and concentrated to give the hydroxy ester (50.0 g, 28%) as a pale yellow oil. The product can be distilled (bp 83-87°C at 3 torr) or used in Part A without further purification. In the latter event, yields are 10-20% lower.

6. Reagent grade pentane was used as purchased from Fisher Scientific Company .
7. Anhydrous $MgSO_4$ was used as purchased from Fisher Scientific Company .
8. ICN (230-400 mesh) silica gel was purchased from Bodman Industries .
9. Silica gel (300 g) was packed to form a column of dimensions 19 cm × 6.5 cm. Elution was accomplished with hexanes:ethyl acetate (19:1), both of which were used as purchased from Mallinckrodt Inc. The flow rate was 4 drops/sec. After collection of 300 mL of eluant, 20-mL fractions were collected. The pure, UV-active product (10.0 g) eluted in fractions 34-48 (R_f = 0.29; silica gel developed with p-anisaldehyde). Fractions 13-33 and 49-57 were combined and concentrated to give 6.9 g of material which was purified by chromatography over 200 g of silica gel to afford an additional 4.5 g of pure bromide.
10. Spectral data were as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.09 (d, 6 H, J = 6.6), 2.71-2.83 (m, 1 H), 3.80 (s, 3 H), 4.23 (s, 2 H), 6.77 (d, 1 H, J = 10.5) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 24.2, 28.5, 52.1, 127.0, 154.4, 166.3 ; IR (CH_2Cl_2) cm^{-1}: 3035 (w), 2980 (s), 2886 (m), 1740 (s), 1648 (m), 1470 (s), 1370 (m), 715 (s) ; MS (EI, 70 eV): m/z (M^+OCH_3) calcd 141.0915, obsd 141.0916 (100%) .
11. THF was used as purchased from Mallinckrodt Inc.
12. Formaldehyde solution was used as purchased from EM Science .
13. Indium powder (99.99%) was used as purchased from the Aldrich Chemical Company, Inc.
14. If the aqueous phase is cloudy because of polymeric formaldehyde at this time, 1% hydrochloric acid can be added to clarify the solution.
15. Technical grade ethyl acetate was used as purchased from Mallinckrodt Inc.
16. Anhydrous Na_2SO_4 was used as purchased from Fisher Scientific Company .
17. Silica gel (275 g) was packed to form a column of dimensions 16 cm × 6.5 cm. Elution was accomplished with technical grade hexanes:ethyl acetate (7:3), both of which were used as purchased from Mallinckrodt Inc. The flow rate was 4 drops/sec. After collection of 150 mL of eluant, 20-mL fractions were collected. The UV-active product eluted in fractions 17-34 (R_f = 0.30; developed with I_2/SiO_2).
18. The submitters indicate that yields are 5-10% higher on smaller scale. The use of excess formaldehyde solution led to polymerization and lower yields of the desired product.
19. Spectral data are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (d, 3 H, J = 6.9), 0.96 (d, 3 H, J = 6.9), 1.90 (m, 2 H), 2.45 (m, 1 H), 3.74 (dd, 1 H, J = 7, 3), 3.75 (s, 3 H), 3.77 (dd, 1 H, J = 7, 3), 5.60 (dd, 1 H, J = 0.75, 1.1), 6.29 (d, 1 H, J = 1.2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.1, 20.5, 27.6, 50.5, 51.6, 62.7, 126.2, 140.8, 168.3 ; IR ($CHCl_3$) cm^{-1}: 3619 (m), 3444 (w), 2964 (s), 1714 (s), 1624 (m), 1440 (m), 1159 (m) ; MS (EI): m/e 173 (MH^+) ; Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.59; H, 9.57.

Waste Disposal Information

The malodorous aqueous phase from the work-up of reaction A was treated with commercial bleach before disposal. Metallic indium from reaction B was treated with concd HCl and diluted before disposal.

3. Discussion

This procedure exemplifies a general method[9] [10] [11] [12] for effecting carbon-carbon bond formation between a wide range of reactive halides and aldehydes or appropriately activated ketones[13] [14] [15] in aqueous media. The properties of indium metal, most notably its first ionization potential (5.785 eV),[16] inertness to dissolution in hot alkali[17] and air oxidation,[18] and low toxicity contribute well to smooth coupling of the derived allylindium reagents. The latter are slow to hydrolyze, amenable to chelation control under the proper circumstances,[13,14,15,19] [20] and conducive to long-range asymmetric induction.[5,21] Significantly, indium(0) can easily be recovered from its salts by simple, conventional electrolysis.[22]

Indium-promoted organometallic reactions are greatly accelerated in water, especially when the coreactant carbonyl compound also has good water solubility. Otherwise, aqueous tetrahydrofuran can be used. To date, indium is the most effective metal for promoting Barbier-type reactions under aqueous conditions. As illustrated here, this is of particular value where formaldehyde is concerned, since the need to generate monomeric formaldehyde by thermal cracking is avoided.

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

Dimethyl sulfide:
Methyl sulfide (8);
Methane, thiobis- (9); (75-18-3)

Formaldehyde (8,9); (50-00-0)

Methyl Z-2-(bromomethyl)-4-methylpent-2-enoate:
2-Pentenoic acid, 2-(bromomethyl)-4-methyl-, methyl ester, (Z)- (12); (137104-39-3)

N-Bromosuccinimide:
Succinimide, N-bromo- (8);
2,5-Pyrrolidinedione, 1-bromo- (9); (128-08-5)

Methyl 3-hydroxy-4-methyl-2-methylenepentanoate:
Pentanoic acid, 3-hydroxy-4-methyl-2-methylene-, methyl ester (10); (71385-30-1)

Indium (8,9); (7440-74-6)

Isobutyraldehyde (8);
Propanal, 2-methyl- (9); (78-84-2)

Methyl acrylate:
Acrylic acid, methyl ester (8);
2-Propenoic acid, methyl ester (9); (96-33-3)

3-Hydroxyquinuclidine:
1-Azabicyclo[2.2.2]octan-3-ol (9); (1619-34-7)