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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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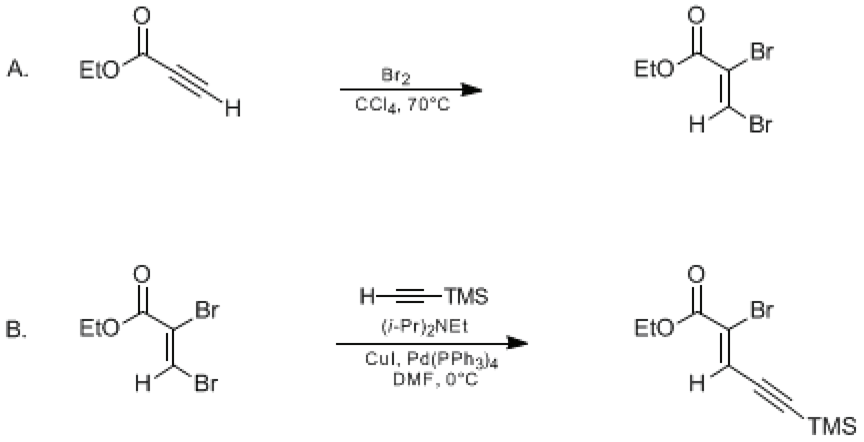
SYNTHESIS OF FUNCTIONALIZED ENYNES BY PALLADIUM/COPPER-CATALYZED COUPLING REACTIONS OF ACETYLENES WITH (Z)-2,3-DIBROMOPROPENOIC ACID ETHYL ESTER: (Z)-2-BROMO-5-(TRIMETHYLSILYL)-2-PENTEN-4-YNOIC ACID ETHYL ESTER

[2-Penten-4-ynoic acid, 2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)-]



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1. Procedure

A. *(Z)-2,3-Dibromo-2-propenoic acid ethyl ester.*[2] Ethyl propiolate (9.01 g, 91.8 mmol) and carbon tetrachloride (75 mL) are added in sequence to a 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (Note 1). The flask is fitted with a 30-mL, pressure-equalizing addition funnel to which elemental bromine (5.00 mL, 97.0 mmol) is added by transfer pipette (Note 2). The flask is partially immersed in an oil bath heated to 70°C. After 10 min for temperature equilibration, dropwise addition of bromine is initiated and completed within 10 min. Complete bromine transfer is achieved by rinsing the addition funnel with a 5-mL portion of carbon tetrachloride. The red-brown solution is heated at 70°C for 30 min, allowed to cool to ambient temperature, and carbon tetrachloride and excess bromine are removed by rotary evaporation. The pale yellow concentrate is applied to the top of a short column of flash-grade silica gel (150 g, 7-cm diam × 10 cm) loaded with 5% ethyl acetate-hexanes solution; the product dibromide elutes rapidly with this solvent system (< 1 L total solvent volume, 150-mL fractions, (Note 3)). Fractions containing the dibromide ($R_f = 0.66$, 5% ethyl acetate-hexanes) are combined and concentrated. The last traces of solvent are removed at 1 mm (0.5 hr) to afford (Z)-2,3-dibromo-2-propenoic acid ethyl ester (21.5–22.0 g, 91–93%) as a colorless liquid (Note 4), (Note 5).

B. *(Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester*. An oven-dried, 500-mL, modified Schlenk flask (Kjeldahl shape with 24/40 female top), equipped with a Teflon-coated magnetic stirring bar and rubber septum, is connected at the side-arm to a source of argon and vacuum. The flask is charged with (Z)-2,3-dibromo-2-propenoic acid ethyl ester prepared in part A (21.5 g, 83.4 mmol) and N,N-dimethylformamide (150 mL). With efficient stirring, it is alternately evacuated and flushed with argon at ambient temperature to deoxygenate the solution (Note 6), (Note 7). The flask is cooled in ice and (trimethylsilyl)acetylene (20.0 mL, 142 mmol) and N,N-diisopropylethylamine (24.7 mL, 142 mmol) are added in sequence (Note 8). The resulting pale yellow solution is deoxygenated as above. Cuprous iodide (3.18 g, 16.7 mmol) and tetrakis(triphenylphosphine)palladium (4.82 g, 4.17 mmol) are added, followed by a third deoxygenation cycle (Note 9). The brown reaction mixture is maintained at 0°C while the progress of reaction is monitored by thin layer chromatography (TLC), as follows: An aliquot (ca. 0.1 mL) of the reaction mixture is withdrawn with an argon-flushed hypodermic syringe and is injected into a small test tube containing ethyl ether (0.25 mL) and water (0.5 mL). After the biphasic mixture is swirled briefly, the ether layer is allowed to separate and is analyzed by TLC using 20% ethyl ether-hexanes as eluent (R_f of the starting dibromide = 0.67, of the product = 0.76, visualization with ultraviolet light). When TLC analysis indicates consumption of the starting dibromide, typically 3–6 hr at 0°C, the reaction mixture is poured into a 1-L separatory funnel containing water (300 mL), saturated aqueous ammonium chloride solution (75 mL), and the tetrasodium salt of ethylenediaminetetraacetic acid (4.50 g, (Note 10)). The resulting brown suspension is extracted with four 150-mL portions of 50% ethyl acetate-hexanes. The organic layers are combined and washed with three 100-mL portions of water, then dried over sodium sulfate and concentrated. The brown oil thus obtained is filtered through a short column of flash-grade silica gel (150 g, 7-cm diam × 10 cm), using 20% toluene-hexanes as eluent (< 1.5 L total solvent volume, 150-mL fractions). Fractions containing product (R_f = 0.23, 20% toluene-hexanes) are combined and concentrated. The light brown concentrate is combined with silicone oil (7.0 g) in a 250-mL, 14/20 round-bottomed flask. An insulated 6-in Vigreux column and a short-path distillation head are affixed for vacuum distillation. The system is evacuated (0.9 mm) and the pot is heated to 110°C whereupon bis(trimethylsilyl) butadiyne sublimes from the mixture. A heat gun is used to assist in the transfer of this component; the flow of condenser water is initiated only after this phase of the distillation. A liquid forerun is collected (ca. 0.5 mL, head temperature 94°C, pot temperature ∼125°C) prior to collection of the product. (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is collected (bp 105–108°C, 0.9 mm, pot temperature < 125°C) as a pale yellow oil (10.95–12.85 g, 48–56%) and is shown by capillary GC to be 87–94% pure (contaminants include bis(trimethylsilyl)butadiyne, <2% and (E)-2-[(trimethylsilyl) ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester, 6–11%; (Note 11),(Note 12),(Note 13)).

2. Notes

1. Ethyl propiolate was used as received from Aldrich Chemical Company, Inc. (pure by 400 MHz ^{1}H NMR analysis). Carbon tetrachloride was spectrophotometric grade and was used without purification.
2. Elemental bromine was used as received from EM Science.
3. Although the crude dibromide is essentially pure, the submitters found the subsequent coupling reaction to be more reproducible and to proceed in higher yield when this simple purification procedure is employed.
4. The purified compound displayed the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, 3 H, J = 7.1, CH_3), 4.31 (q, 2 H, J = 7.1, CH_2), 8.23 (s, 1 H, HC=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 63.0, 122.6, 126.4, 160.7; IR (thin film) cm^{-1}: 3072, 2983, 1732, 1569, 1253, 1213, 1037, 737; HRMS calcd for $C_5H_6Br_2O_2$: 255.8735, found: 255.8739. A trace impurity is visible in the ^{1}H NMR spectrum (δ 6.35, s). This impurity is tentatively identified as 2,2,3,3-tetrabromopropanoic acid ethyl ester and is estimated by integration to constitute less than 2 mol percent of the mixture.
5. The checkers found three distinct signals due to impurities at δ 7.74 (s), 7.14 (q), 6.34 (s) which totaled 4–7% by NMR integration.
6. N,N-Dimethylformamide was distilled from calcium sulfate under reduced pressure (40 mm) and was stored over 4 Å molecular sieves under argon.
7. Typically three to five evacuation/argon flush cycles are employed. This deoxygenation protocol is simpler and faster than a freeze-pump-thaw procedure.
8. (Trimethylsilyl)acetylene was used as received from Aldrich Chemical Company, Inc. N,N-Diisopropylethylamine was distilled from calcium hydride (atmospheric pressure) and stored over 4 Å molecular sieves under argon.
9. Cuprous iodide (EM Science) was purified by continuous extraction (12 hr) with tetrahydrofuran in a Soxhlet apparatus. The purified compound was stored in a brown bottle and was light grey in appearance. Tetrakis(triphenylphosphine)palladium, $Pd(PPh_3)_4$, was prepared according to a published procedure[3] and was stored in a dry box under a nitrogen atmosphere. It was a bright yellow solid. The purity of this reagent is crucial for the stoichiometry and reaction times reported to be observed. It must be handled with care to avoid exposure to air. Dark colored or yellow-green samples of $Pd(PPh_3)_4$ are not suitable.
10. For optimum results, it is important to monitor the reaction carefully. Extended reaction times lead to formation of bis-coupled product. Optimum results are obtained when the dibromide (Note 3) and the

palladium catalyst (Note 9) are prepared as described.

11. Capillary gas chromatography is conducted with a cross-linked phenyl methyl silicone stationary phase (5%, 25 m × 0.2 mm × 0.5 µm film thickness, injector temp. 225°C, detector temp. 250°C, column temp. 40–200°C, 15°C/min after 1 min initial time). (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is observed to have a retention time of 14.0 min. GC data for bis(trimethylsilyl) butadiyne is as follows: retention time 10.0 min, response factor (GC area produced relative to an equimolar quantity of (Z)-2-bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester) 1.29. For (E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester the retention time is 17.0 min, the response factor 1.19.

12. The purified product displays the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.25 (s, 9 H, $SiCH_3$), 1.34 (t, 3 H, J = 7.1, CH_3), 4.30 (q, 2 H, J = 7.1, CH_2), 7.29 (s, 1 H, HC=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −0.6, 14.0, 62.6, 100.4, 111.9, 123.7, 124.6, 161.7; IR (CH_2Cl_2 solution) cm^{-1}: 2964, 1723, 1584, 1252, 1082, 1044, 850; HRMS calcd for $C_{10}H_{15}BrO_2Si$: 274.0025, found: 274.0024. Additional purification of the distilled product (1.09 g) by silica gel chromatography (5 cm diam × 14-cm column, 100 g of silica gel, eluent, 20% toluene-hexanes) provided an analytical sample (1.02 g, 94% recovery) that was shown to be >99% pure by capillary GC analysis. Anal. Calcd for $C_{10}H_{15}BrO_2Si$: C, 43.64; H, 5.49. Found: C, 43.74; H. 5.26.

13. The fractions containing the product were combined and analyzed by capillary GC, which showed them to be 87–94% pure with the major impurity (~6–11%) being the bis-coupled product.

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 outlined above describes the selective, retentive, β-coupling of (Z)-2,3-dibromopropenoic acid ethyl ester with (trimethylsilyl)acetylene employing the palladium-modified version of the Castro-Stephens reaction.[4,5,6,7] The dibromide starting material is readily available by bromination of ethyl propiolate (Procedure A), as described by Trippett and Hall.[2] The coupling product has been shown to be a versatile precursor for the synthesis of variously substituted enynes and enediynes. For example, a second acetylene may be introduced into the α-position under modified coupling conditions. Alternatively, reduction of the ester with diisobutylaluminum hydride and protection of the resultant alcohol with tert-butyldiphenylsilyl chloride affords a vinyl bromide that can be metalated and trapped with various electrophiles. These procedures have been used on the gram and multigram scale.[7]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

hexanes

phenyl methyl silicone

ethyl acetate (141-78-6)

ether,
ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

toluene (108-88-3)

palladium (7440-05-3)

cuprous iodide (7681-65-4)

Tetrahydrofuran (109-99-9)

N,N-dimethylformamide (68-12-2)

argon (7440-37-1)

calcium hydride (7789-78-8)

diisobutylaluminum hydride (1191-15-7)

ethyl propiolate (623-47-2)

N,N-diisopropylethylamine (7087-68-5)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

(Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester,
2-Penten-4-ynoic acid, 2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)- (124044-21-9)

(Z)-2,3-Dibromo-2-propenoic acid ethyl ester,
(Z)-2,3-dibromopropenoic acid ethyl ester (26631-66-3)

(E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester

2,2,3,3-tetrabromopropanoic acid ethyl ester

tert-butyldiphenylsilyl chloride (58479-61-1)

bis(trimethylsilyl)butadiyne (4526-07-2)

(Trimethylsilyl)acetylene (1066-54-2)

tetrasodium salt of ethylenediaminetetraacetic acid (10378-23-1)