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VERSATILE PRECURSORS FOR THE SYNTHESIS OF ENYNES AND ENEDIYNES

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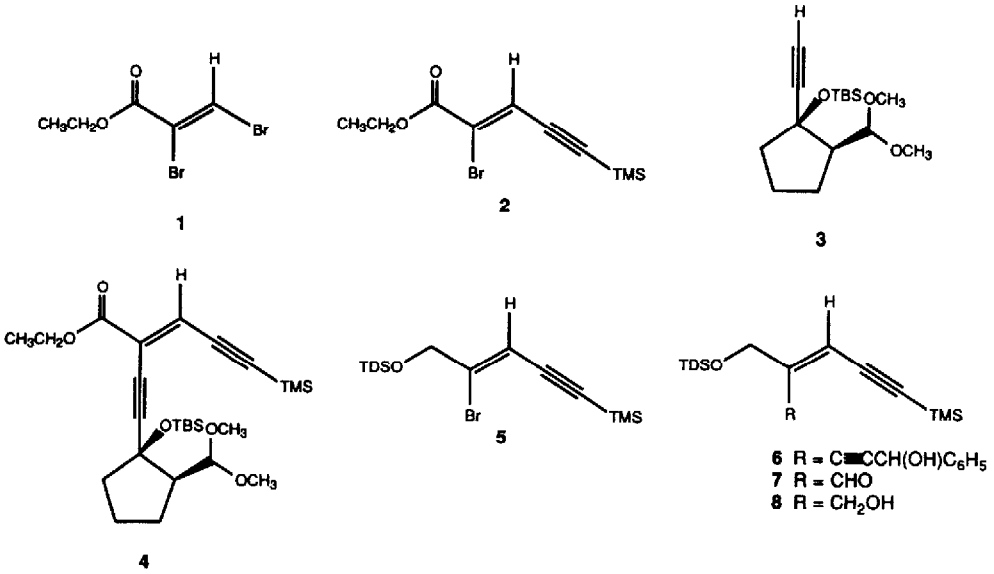
Summary: (*Z*)-Ethyl 2,3-dibromopropenoate, readily available in multigram quantities, undergoes selective replacement of the β-bromide in coupling reactions with trimethylsilylacetylene to produce the (*Z*)-enyne 2. This product may be further elaborated to various functionalized enynes of defined geometry or may be coupled with a second acetylenic reactant to produce (*Z*)-enediynes.

We describe simple and efficient procedures which have proven of value in the context of several ongoing projects in our laboratory requiring the synthesis of functionalized enynes and enediynes.

Hall and Trippett have shown that bromination of ethyl propiolate in carbon tetrachloride at 60-70 °C produces the (*Z*)-dibromide (1).[1] In a closer examination of this useful transformation we find that addition of slightly less than one equivalent of molecular bromine to ethyl propiolate in a variety of solvents (CCl_4, CH_2Cl_2, THF) at −78 to 23 °C produces a kinetically determined mixture of (*E*)- and (*Z*)-dibromides in a ratio of 2.5–5 : 1, respectively. This product distribution is unchanged upon heating at 70 °C, but undergoes rapid equilibration, even at 23 °C, in the presence of excess bromine to form pure (*Z*)-dibromide. We have found that the (*E*)-dibromide can be prepared in isomerically pure form in 97% yield by treatment of ethyl propiolate with a suspension of pyridinium bromide perbromide (1.3 equiv) in methylene chloride at 23 °C for 40 h (excess brominating agent does not lead to equilibration in this case).[2]

Through careful optimization of solvent, base and reaction temperature we have developed a protocol by which 1 and trimethylsilylacetylene are coupled in high yield with selective replacement of the β-bromide.[3] Thus, treatment of 1 with CuI (0.20 equiv), $Pd(PPh_3)_4$ (0.05 equiv), diisopropylethylamine (1.7 equiv) and trimethylsilylacetylene (1.7 equiv) in *N*,*N*-dimethylformamide at 0 °C for 10 h forms the (*Z*)-bromoenyne 2 in 86-90% yield after chromatographic purification. Other procedures lead to varying degrees of competitive α-coupling. Interestingly, the (*E*)-dibromide also produces the (*Z*)-coupling product 2 under the same conditions.



TMS = trimethylsilyl TBS = *t*-butyldimethylsilyl TDS = *t*-butyldiphenylsilyl

The (*Z*)-bromoenyne **2** may be elaborated in several ways. Replacement of the α-bromide with a second acetylene produces (*Z*)-enediynes in high yield. For example, **2** (1.2 equiv) and the cyclopentylacetylene **3** (1 equiv) are coupled in the presence of CuI (0.15 equiv), $Pd(PPh_3)_4$ (0.05 equiv) and propylamine (1.5 equiv) in toluene at 60 °C for 2 h to produce the (*Z*)-enediyne **4** in 83% yield. Reduction of the ester group of **2** (diisobutylaluminum hydride, 2.3 equiv in toluene, −78→0 °C) and protection of the resultant primary alcohol as its *t*-butyldiphenylsilyl ether (1.2 equiv *t*-butyldiphenylsilyl chloride, 5 equiv triethylamine, 0.3 equiv 4-dimethylaminopyridine, methylene chloride, 23 °C) gives **5** in 90% yield. This product also undergoes coupling reactions with acetylenes to produce geometrically defined trisubstituted enediynes. For example, 1-phenyl-2-propyn-1-ol (1.2 equiv) and **5** are coupled in tetrahydrofuran with CuI (0.20 equiv), $(PPh_3)_2PdCl_2$ (0.05 equiv) and propylamine (4.0 equiv) at 23 °C for 24 h to afford (*Z*)-enediyne **6** (74%). In another context, bromide **5** was metallated at −120 °C (2.5 equiv *t*-BuLi) and the resulting organolithium intermediate was trapped with *N*,*N*-dimethylformamide to form the (*Z*)-enal **7** in 71% yield. Reduction of **7** with sodium borohydride in methanol at −10 °C afforded the monoprotected diol **8** in 90% yield.

The methods outlined above have been used in the preparation of multigram quantities of the products described and should be readily extendible to the synthesis of a variety of enynes and enediynes. Experimental details follow for the syntheses of **1**, **2**, **4** and **7**.

Experimental

(*Z*)-Ethyl 2,3-dibromopropenoate (1)[1]

Bromine (4.80 mL, 93.2 mmol, 1.05 equiv) was added dropwise over 5 min to a stirring solution of ethyl propiolate (9.00 mL, 88.8 mmol, 1 equiv) in carbon tetrachloride (50 mL) at 70 °C. After 30 min, the deep orange solution was allowed to cool and was then concentrated *in vacuo*. The residue was purified by filtration through a pad of flash grade silica gel (4 cm diam. x 8 cm) eluting with ethyl acetate-hexanes (400 mL 5%, then 100 mL 10%). Solvents were removed under reduced pressure to afford 1 as a pale yellow liquid (22.66 g, 99%).

Bromide 2

Cuprous iodide (1.48 g, 7.76 mmol, 0.20 equiv) and tetrakis(triphenylphosphine)palladium (2.24 g, 1.94 mmol, 0.05 equiv) were added sequentially to a deoxygenated solution of trimethylsilylacetylene (9.32 mL, 66.0 mmol, 1.70 equiv), diisopropylethylamine (11.5 mL, 66.0 mmol, 1.70 equiv) and (*Z*)-ethyl 2,3-dibromopropenoate (1, 10.0 g, 38.8 mmol, 1 equiv) in *N*,*N*-dimethylformamide (60 mL) at 0 °C. After 10 h at 0 °C, saturated aqueous ammonium chloride (50 mL) was added and the mixture was stirred in the air at 23 °C for 30 min and then extracted with ethyl acetate-hexanes (1 : 1, 3 x 100 mL). The combined organic layers were dried with sodium sulfate and concentrated *in vacuo*. The product was purified by filtration through a pad of flash grade silica gel (4 cm diam. x 4 cm) eluting with 5% ethyl acetate-hexanes to afford, after removal of solvents, bromide 2 as a light brown liquid (9.19 g, 86%).

(*Z*)-Enediyne 4

Bromide 2 (8.35 g, 30.3 mmol, 1.20 equiv) and tetrakis(triphenylphosphine)palladium (1.45 g, 1.26 mmol, 0.05 equiv) were incubated in oxygen-free toluene (18 mL) at 23 °C for 45 min. In a separate flask, propylamine (3.10 mL, 37.7 mmol, 1.49 equiv) was injected into a deoxygenated suspension of cuprous iodide (0.72 g, 3.78 mmol, 0.15 equiv) and acetylene 3 (7.56 g, 25.3 mmol, 1 equiv) in toluene (10 mL) at 23 °C and the mixture was stirred for 15 min prior to its transfer, via cannula, to the solution of bromide 2. The reaction mixture was heated at 60 °C for 2 h and then cooled. The product solution was poured into saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bicarbonate (20 mL) and the biphasic mixture was stirred in air for 1 h. The layers were separated and, after further extraction of the aqueous layer with ethyl acetate-hexanes (1 : 1, 2 x 100 mL), the com-

bined organic layers were dried with sodium sulfate and concentrated. Purification of the residue by flash column chromatography eluting with 3% ethyl acetate-hexanes afforded (*Z*)-enediyne **4** (10.2 g, 83%) as a pale yellow liquid.

Aldehyde 7

A solution of bromide **5** (1.00 g, 2.12 mmol, 1 equiv) in tetrahydrofuran (7.5 mL)-ether (1.9 mL)-pentane (1.9 mL) was added dropwise via cannula over 20 min to a well-stirred solution of *t*-butyl lithium (3.01 mL, 1.76 M in pentane, 5.30 mmol, 2.5 equiv) in tetrahydrofuran (22.5 mL)-ether (5.6 mL)-pentane (5.6 mL) at −120 °C.[4] The flask containing the bromide solution was rinsed with a 2-mL portion of tetrahydrofuran and this was added to the reaction mixture. Immediately thereafter, addition of a solution of *N*,*N*-dimethylformamide (0.41 mL, 5.30 mmol, 2.5 equiv) in tetrahydrofuran (2 mL) was begun and completed within 5 min. The reaction mixture was allowed to warm to −40 °C over 3 h and was then partitioned between brine (30% saturated, 70 mL) and ethyl acetate-hexanes (1 : 1, 3 x 75 mL). The combined organic layers were dried over sodium sulfate and concentrated and the liquid residue was purified by flash column chromatography (toluene-hexanes, 5 → 50% graded elution) to afford aldehyde **7** as a colorless oil (0.63 g, 71%). A similar experiment conducted on a 6.5-g sample of bromide **5** provided 3.19 g of pure **7** (55%).

Acknowledgment

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References and Notes

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2. Reported yields refer to products of ≥95% purity.

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