Synthesis of α,α-Dibromo Esters as Precursors of Ynolates

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Aliphatic α,α-dibromo esters, precursors of ynolates, were synthesized *via* bromination of lithium α-bromo ester enolates with 1,2-dibromotetrafluoroethane in good yields. α-Trimethylsilyl-α,α-dibromo esters were synthesized *via* radical bromination.

Key words ynolate; α,α-dibromoester; bromination

Ynolates (**3**), multi-functional carbanions having a triple bond,[1—3] are finding increased use in organic synthesis. Our laboratory developed a novel synthetic method for the preparation of these compounds *via* cleavage of ester dianions (**2**) derived from α,α-dibromo esters (**1**) (Chart 1).[4—6] Since then, we have reported several new synthetic reactions such as the one-pot construction of carbocycles,[7,8] stereoselective olefination of carbonyl compounds,[9—11] and inverse electron-demand 1,3-dipolar cycloaddition of nitrones.[12]

In order for ynolates to become more widely used in organic synthesis, two important considerations have to be addressed: availability of the starting materials and convenience of the synthetic procedure. Although there have been very few reports on synthesis of α,α-dibromo esters, especially aliphatic esters, we published a synthetic method for α,α-dibromo esters (**1a**) by bromination of the bromo silyl ketene acetals (**5**) with *N*-bromosuccinimide (NBS), albeit in moderate yield (Chart 2). Herein, we describe an improved and efficient method for the synthesis of α,α-dibromo esters.

Aliphatic α-monobromo esters (**4**) can be easily prepared by the Hell–Volhard–Zelinsky reaction, *i.e.*, heating acyl chlorides or bromides (**6**) with bromine to afford α-bromo acyl bromides (**7**), followed by treatment with an alcohol (Chart 3).[5]

The electrophilic bromination of esters *via* silyl ketene acetals usually requires a two-step procedure, in which the intermediate silyl ketene acetals (**5**) are somewhat unstable and must be carefully isolated. Direct bromination of the ester enolates would be a much more efficient and convenient procedure for providing α,α-dibromo esters. Therefore, we reacted the lithium ester enolates, prepared from the esters and LDA in THF, with NBS at −78 °C. The reaction gave the dibromo ester in low yield probably due to decomposition of NBS in THF. After surveying brominating agents, we found that, in this system, 1,2-dibromo-1,1,2,2-tetrafluoroethane proved to be a much better brominating agent than NBS. Consequently, we added 1.5 eq of 1,2-dibromo-1,1,2,2-tetrafluoroethane in one portion at −78 °C to a vigorously stirred THF solution of the lithium enolate, prepared by treatment of the α-bromo ester (**4**) with LDA at −78 °C, and allowed the reaction mixture to stir for 30 min. After workup and distillation, the desired α,α-dibromo ester (**1**) was isolated in good yield. This method provided the desired α,α-dibromo esters in good yield with high generality, as shown in Chart 4.

α-Monobromo esters (*e.g.*, **4g**) can also be prepared by this method from the corresponding ester. This is useful for bromine sensitive compounds as shown in Chart 5. Ethyl α-bromo-α-phenylacetate, however, did not give the desired product, but rather decomposed. Ethyl α,α-dibromo-α-phenylacetate can be prepared instead by radical bromination according to the literature.[13] Although direct radical dibromination of ethyl trimethylsilylacetate (**8i**) failed, ethyl α-bromo-α-trimethylsilylacetate (**4i**), prepared by bromination of the lithium ester enolate with 1,2-dibromotetrafluoroethane, was converted to the desired dibromo product (**1i**) by radical bromination (Chart 6).

In conclusion, we have developed an efficient synthetic

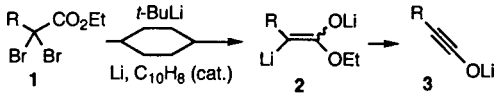


Chart 1

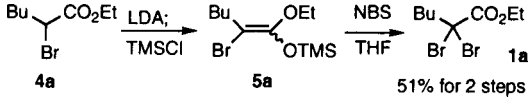


Chart 2

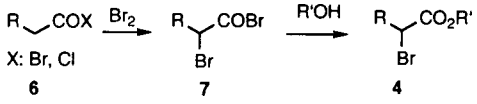
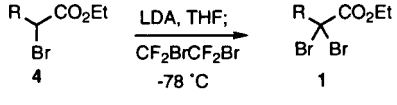


Chart 3



1a (R = Bu): 89%, **1b** (R = Me): 85%, **1c** (R = Pentyl): 86%, **1d** (R = Cyclohexyl): 89%, **1e** (R = *i*-Pr): 91%, **1f** (R = *t*-Bu): 84%, **1g** (R = $PhCH_2CH_2$): 74%, **1h** (R = Ph): 0%

Chart 4

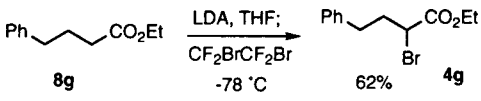


Chart 5

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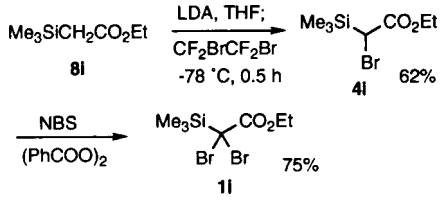

Chart 6

method for aliphatic α,α-dibromo esters, precursors of ynolates, *via* bromination of lithium α-bromo ester enolates with 1,2-dibromo-1,1,2,2-tetrafluoroethane. We have also synthesized trimethylsilyl dibromo esters *via* bromination of the lithium ester enolate of trimethylsilylacetate, followed by radical bromination in good yield. These results will contribute to the utility of ynolate chemistry.

Experimental

General ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM-AL 400 and an AL 300 spectrometer. Signals are given in ppm using tetramethylsilane as an internal standard. IR spectra were recorded on JASCO FT-IR 410. MS spectra were obtained on a JEOL JMS-DX303 and JMS-SX102A.

Materials 1,2-Dibromo-1,1,2,2-tetrafluoroethane was purchased from Tokyo Kasei Kogyo Co., Ltd. and purified by distillation. Anhydrous THF and butyllithium were purchased from Kanto Chemical Co., Inc. and used without further purification. α-Bromo esters were prepared according to the literature[5] except **4a**.

Representative Procedure for α-Bromination of Esters. Ethyl 2,2-Dibromohexanoate (**1a**)[5]: To a solution of diisopropylamine (9.90 ml, 70.6 mmol) in THF (200 ml) was added a butyllithium solution (1.34 M in hexane, 52.7 ml, 70.6 mmol) at −78 °C and the reaction was stirred for 15 min. A solution of ethyl 2-bromohexanoate (15.0 g, 67.2 mmol) in THF (20 ml) was added dropwise. After 30 min, 1,2-dibromo-1,1,2,2-tetrafluoroethane (12.0 ml, 101 mmol) was added in one portion. After 30 min, the reaction mixture was poured into a saturated $NaHCO_3$ solution and the resulting mixture was extracted with hexane. The organic phase was washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was distilled (bp 85—90 °C at 2.0 mmHg) to yield 18.1 g (89%) of **1a** as a colorless oil.

Ethyl 2,2-Dibromopropanoate (**1b**)[6]: Colorless oil. Yield 85% (49 °C/2.2 mmHg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.65 (3H, s), 4.34 (2H, q, J=7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.6 (q), 37.2 (q), 52.1 (t), 63.5 (s), 166.5 (s). IR (Neat) cm^{-1}: 1737. EI-MS *m/z*: 258 (M^+), 260 (M^++2). *Anal.* Calcd for $C_5H_8Br_2O_2$: C, 23.10; H, 3.10. Found: C, 23.19; H, 3.08.

Ethyl 2,2-Dibromoheptanoate (**1c**)[7]: Colorless oil. Yield 86% (96—102 °C/2.2 mmHg). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (3H, t, J=7 Hz), 1.29—1.42 (4H, m), 1.36 (3H, t, J=7 Hz), 1.59—1.64 (2H, m), 2.53—2.58 (2H, m), 4.33 (2H, q, J=7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.7 (q), 13.8 (q), 22.3 (t), 27.1 (t), 30.8 (t), 47.0 (t), 60.8 (s), 63.6 (t), 166.2 (s). IR (Neat) cm^{-1}: 1735. EI-MS *m/z*: 314 (M^+), 316 (M^++2). HR-MS (EI) Calcd for $C_9H_{16}Br_2O_2$ (M^+) 313.9517, Found: 313.9551.

Ethyl 2,2-Dibromocyclohexaneacetate (**1d**)[9]: Colorless oil. Yield 89%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.11—1.42 (5H, m), 1.35 (3H, t, J=7 Hz), 1.67—1.71 (1H, m), 1.78—1.99 (4H, m), 2.20 (1H, ddt, J=3, 3, 8 Hz), 4.34 (2H, q, J=7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8 (q), 25.6 (t), 25.8 (t), 29.6 (t), 50.5 (d), 63.8 (t), 70.3 (s), 166.2 (s). IR (Neat) cm^{-1}: 1732, 1749. EI-MS *m/z*: 326 (M^+), 328 (M^++2). *Anal.* Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.92. Found: C, 36.95; H, 4.94.

Ethyl 2,2-Dibromo-3-methylbutanoate (**1e**)[6]: Colorless oil. Yield 91% (53—60 °C/1.0 mmHg). ^{1}H-NMR (400 MHz, at 50 °C in $CDCl_3$) δ: 1.15 (6H, d, J=6 Hz), 1.34 (3H, t, J=7 Hz), 2.63 (1H, hept, J=6 Hz), 4.33 (2H, q, J=7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9 (q), 19.6 (q), 41.4 (d), 63.8 (t), 71.3 (s), 166.0 (s). IR (Neat) cm^{-1}: 1735, 1751. EI-MS *m/z*: 286 (M^+), 288 (M^++2). HR-MS (EI) Calcd for $C_7H_{12}O_2Br_2$ (M^+) 285.9204, Found: 285.9206.

Ethyl 2,2-Dibromo-3,3-dimethylbutanoate (**1f**)[6]: Colorless oil. Yield 84% (88—90 °C/3.0 mmHg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33—1.38 (3H, m), 1.36 (9H, s), 4.31 (2H, q, J=7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.9 (q), 27.3 (q), 43.4 (s), 58.5 (s), 63.7 (t), 165.8 (s). IR (Neat) cm^{-1}: 1739. EI-MS *m/z*: 300 (M^+), 302 (M^++2). HR-MS (EI) Calcd for $C_8H_{14}Br_2O_2$ (M^+) 299.9361, Found: 299.9367.

Ethyl 2-Bromo-4-phenylbutanoate (**4g**): Colorless oil. Yield 62% (bulb-to-bulb distillation, bp 160—180 °C at 2.0 mmHg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 2.25—2.42 (2H, m), 2.69—2.85 (2H, m), 4.16 (1H, dd, J=7, 8 Hz), 4.22 (2H, dq, J=2, 7 Hz), 7.17—7.32 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.0 (q), 33.2 (t), 36.3 (t), 45.4 (d), 62.0 (t), 126.3 (d), 128.4 (d), 128.5 (d), 139.7 (s), 169.5 (s). IR (Neat) cm^{-1}: 1739. EI-MS *m/z*: 270 (M^+), 272 (M^++2). HR-MS (EI) Calcd for $C_{12}H_{15}BrO_2$ (M^+) 270.0255, Found: 270.0256.

Ethyl 2,2-Dibromo-4-phenylbutanoate (**1g**)[6]: Colorless oil. Yield 74% (bp 121—123 °C/0.8 mmHg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.84—2.97 (4H, m), 4.33 (2H, q, J=7 Hz), 7.20—7.33 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8 (q), 33.9 (t), 48.8 (t), 59.6 (s), 63.7 (t), 126.3 (d), 128.4 (d), 128.4 (d), 139.4 (s), 165.8 (s). IR (Neat) cm^{-1}: 1733. EI-MS *m/z*: 348 (M^+), 350 (M^++2). HR-MS (EI) Calcd for $C_{12}H_{14}Br_2O_2$ (M^+) 347.9361, Found: 347.9375.

Ethyl 2,2-Dibromo-2-(trimethylsilyl)acetate (**1i**)[14]: To a solution of diisopropylamine (4.5 ml, 32.2 mmol) in THF (70 ml) was added a butyllithium solution (1.57 M in hexane, 20.5 ml, 32.2 mmol) at −78 °C and the reaction was stirred for 15 min. A solution of ethyl trimethylsilylacetate (4.30 g, 26.8 mmol) in THF (10 ml) was added dropwise. After 30 min, 1,2-dibromo-1,1,2,2-tetrafluoroethane (4.76 ml, 40.2 mmol) was added in one portion. After 2.5 h, the reaction mixture was poured into saturated NH_4Cl solution and then the resulting mixture was extracted with hexane. The organic phase was washed with water, saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford an oil, which was distilled (bp 60—62 °C at 3 mmHg) to give 3.95 g (62%) of **4i**[15] as a colorless oil. To a solution of **4i** (3.0 g, 12.5 mmol) in CCl_4 (50 ml) was added *N*-bromosuccinimide (3.35 g, 18.8 mmol) and a catalytic amount of benzoyl peroxide, and the resulting suspension was refluxed for 21 h. After filtration, the filtrate was concentrated *in vacuo* to afford a brown oil, which was distilled (bp 73—77 °C at 3 mmHg) to yield 3.0 g (75%) of **1i** as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.34 (9H, s), 1.33 (3H, t, J=7 Hz), 4.30 (2H, q, J=7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −2.4 (q), 14.0 (q), 51.5 (s), 63.5 (t), 167.6 (s). IR (Neat) cm^{-1}: 1718, 1740. EI-MS *m/z*: 316 (M^+), 318 (M^++2). HR-MS (EI) Calcd for $C_7H_{14}Br_2O_2Si$ (M^+) 315.9130, Found: 315.9097.

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