

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–Vollhard–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

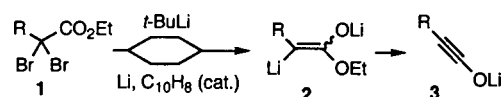


Chart 1

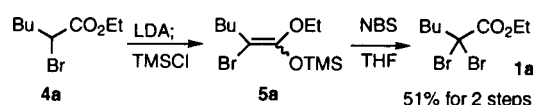


Chart 2

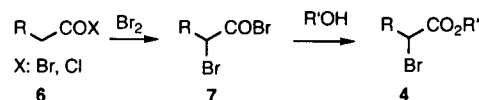
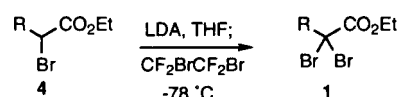


Chart 3



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

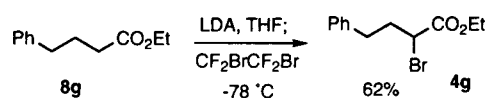
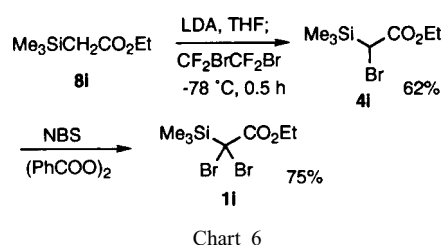


Chart 5

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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 ^1H - 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 literature⁵⁾ 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 $85\text{--}90^\circ\text{C}$ 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% ($49^\circ\text{C}/2.2$ mmHg). ^1H -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 $\text{C}_5\text{H}_8\text{Br}_2\text{O}_2$: C, 23.10; H, 3.10. Found: C, 23.19; H, 3.08.

Ethyl 2,2-Dibromoheptanoate (**1c**)⁷⁾: Colorless oil. Yield 86% ($96\text{--}102^\circ\text{C}/2.2$ mmHg). ^1H -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 $\text{C}_9\text{H}_{16}\text{Br}_2\text{O}_2$ (M^+) 313.9517, Found: 313.9551.

Ethyl 2,2-Dibromocyclohexanoacetate (**1d**)⁹⁾: Colorless oil. Yield 89%. ^1H -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 $\text{C}_{10}\text{H}_{16}\text{Br}_2\text{O}_2$: 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% ($53\text{--}60^\circ\text{C}/1.0$ mmHg). ^1H -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 $\text{C}_7\text{H}_{12}\text{O}_2\text{Br}_2$ (M^+) 285.9204, Found: 285.9206.

Ethyl 2,2-Dibromo-3,3-dimethylbutanoate (**1f**)⁶⁾: Colorless oil. Yield 84% ($88\text{--}90^\circ\text{C}/3.0$ mmHg). ^1H -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 $\text{C}_8\text{H}_{14}\text{Br}_2\text{O}_2$ (M^+) 299.9361, Found: 299.9367.

Ethyl 2-Bromo-4-phenylbutanoate (**4g**): Colorless oil. Yield 62% (bulb-to-bulb distillation, bp $160\text{--}180^\circ\text{C}$ at 2.0 mmHg). ^1H -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 $\text{C}_{12}\text{H}_{15}\text{BrO}_2$ (M^+) 270.0255, Found: 270.0256.

Ethyl 2,2-Dibromo-4-phenylbutanoate (**1g**)⁶⁾: Colorless oil. Yield 74% (bp $121\text{--}123^\circ\text{C}/0.8$ mmHg). ^1H -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 $\text{C}_{12}\text{H}_{14}\text{Br}_2\text{O}_2$ (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 $60\text{--}62^\circ\text{C}$ 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 $73\text{--}77^\circ\text{C}$ at 3 mmHg) to yield 3.0 g (75%) of **1i** as a colorless oil. ^1H -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 $\text{C}_7\text{H}_{14}\text{Br}_2\text{O}_2\text{Si}$ (M^+) 315.9130, Found: 315.9097.

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