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

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Abstract: 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: ynone; 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 acetal (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 acetal usually requires a two-step procedure, in which the intermediate silyl ketene acetal (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-bromo-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 (4j), prepared by bromination of the lithium ester enolate with 1,2-dibromotetrafluoroethane, was converted to the desired dibromo product (1j) by radical bromination (Chart 6).

In conclusion, we have developed an efficient synthetic method for the preparation of α,α-dibromo esters. This method is applicable to a wide range of esters and alcohols, and provides a convenient route to ynolates, which are useful multi-functional carbanions.

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method for aliphatic α,α-dibromo esters, precursors of yno-lates, 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 trimethylsilylacetal, followed by radical bromination in good yield. These results will contribute to the utility of ynoolate chemistry.

**Experimental**

**General** H- and 13C-NMR spectra were obtained on a JEOL JNM-AL 400 and an AL 300 spectrometer. Signals are given in ppm using tetramethyilsilane 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 was distilled to bulb-bulb distillation, bp 160—180 °C at 2.0 mmHg. 1H-NMR (300 MHz, CDCl3) δ: 1.33—1.38 (3H, m), 1.36 (9H, s), 4.31 (2H, q, J = 7 Hz). 13C-NMR (75 MHz, CDCl3) δ: 13.9 (q), 27.3 (q), 43.4 (3s), 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) Caled for C₇H₁₅BrO₂ (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). 1H-NMR (400 MHz, CDCl3) δ: 1.30 (3H, t, J = 7 Hz), 2.25—2.24 (2H, m), 2.69—2.85 (2H, m), 4.16 (1H, dd, J = 7, 8 Hz), 4.22 (2H, q, J = 7, 2 Hz), 7.17—7.32 (5H, m). 13C-NMR (100 MHz, CDCl3) 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) Caled for C₇H₆BrO₂ (M⁺): 270.0255, Found: 270.0256.

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