Bromomethyl Ketones and Enolates: Alternative Products from Ester Homologation Reactions

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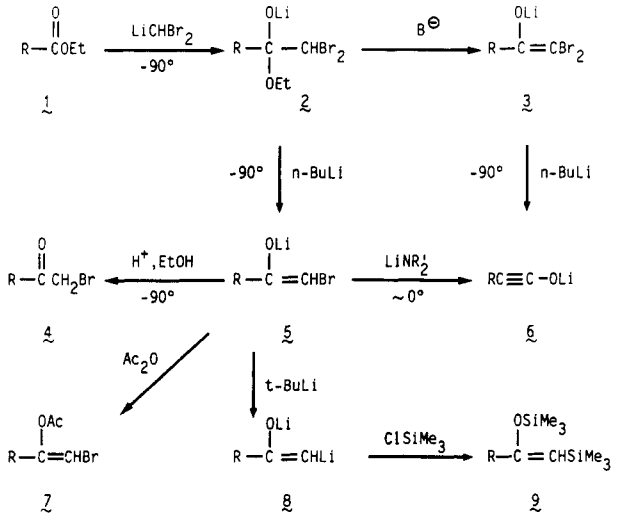
Esters 1, in which R represents a primary alkyl, alkynyl, alkenyl, or aromatic substituent, were reacted with (dibromomethyl)lithium, followed by *n*-butyllithium. Bromomethyl ketone enolate anions 5 resulted, which were quenched with acid to afford bromomethyl ketones 4, generally in 70–85% yields. Alternatively, enolate anions 5 could be quenched with acetic anhydride to afford bromo enol acetates 7 or treated with *tert*-butyllithium to produce α-keto dianions 8.

In our previous study on ester homologation,[1] it was found that transformation of esters 1, to alkynolate anions 6, occurred via two pathways. The esters were added to solutions of (dibromomethyl)lithium, prepared by treatment of methylene bromide with lithium tetramethylpiperidide. When the carbethoxy attachment was to a tertiary hydrocarbon (e.g., 1, R = $C(CH_3)_2CH_2Ph$), reaction occurred at −90 °C to afford dibromo ketone enolate 3.



Normant had previously reported formation of the enolate 3 (R = 2-propyl) under similar conditions.[2] Consistent with the presence of dibromo ketone enolate in our study was the fact that addition of *n*-butyllithium resulted in rapid metal–halogen exchange and rearrangement to alkynolate anion 6, even at −90 °C. Such exchange and rearrangement reactions of dibromo ketone enolates had previously been shown to occur with great facility, even at low temperatures.[3]

When a secondary hydrocarbon moiety (e.g., R = cyclohexyl) was attached in esters 1, much of the material was again converted to alkynolate anion 6 at −90 °C, upon sequential treatment with lithiodibromomethane and then *n*-butyllithium. In all other cases, however, addition of *n*-butyllithium in the second step did not result in formation of alkynolate anions 6 at low temperature but instead afforded monobromo ketone enolate anions 5. It seemed likely for these less hindered compounds that the tetrahedral intermediate 2 was stable under these conditions and upon addition of *n*-butyllithium underwent rapid metal–halogen exchange with loss of ethoxide to produce enolate 5. Such monobromo ketone enolates were known to be stable toward deprotonation at low temperatures,[3] and thus warming these reaction mixtures to room temperature proved to be crucial in effecting deprotonation/rearrangement (5 → 6) for the homologation sequence.[1]

Realization that the monobromo ketone enolate 5 was an intermediate in many of these homologations suggested the possibility of adapting this procedure to provide a method for bromomethyl ketone synthesis (i.e., 1 → 4). The homologation procedure could have been suitably modified simply by not warming the solution of enolate anion 5 prior to the acid quench. For the purpose at hand, however, there was no need to use lithium tetramethylpiperidide as base in forming the (dibromomethyl)lithium; this base had been used in the homologation procedure to avoid reaction of the amide base with the ketene derived from alkynolate anion 6 in the quench. Since ketenes were not expected intermediates in monobromo ketone formation, the more common and less expensive lithium diisopropylamide (LDA) was chosen as base.

In the method which resulted, esters 1 were added to solutions of lithiodibromomethane (usually 2.2 equiv, prepared from LDA and methylene bromide in tetrahydrofuran), cooled with a dry ice/ether bath at about −90 °C. After 10 min, *n*-butyllithium (usually 1.5 equiv) was added to effect metal–halogen exchange (2 → 5), and 5 min later the reactions were quenched into cold, acidic ethanol. The procedure required little more than 30 min to complete. Good yields of bromomethyl ketones 4 were obtained for those esters 1 where R represented a primary alkyl, alkynyl, alkenyl, or aromatic substituent.

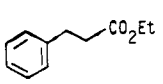
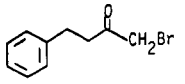
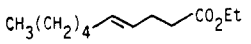
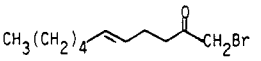
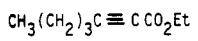
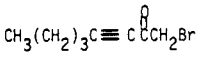
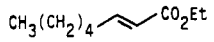
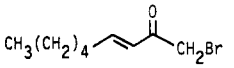
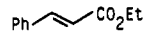
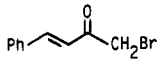
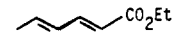
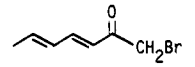
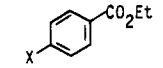
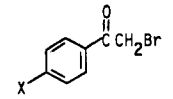
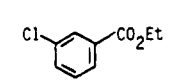
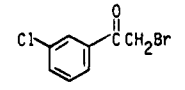
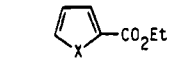
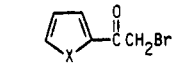
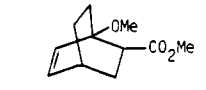
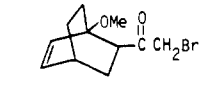
Listed in Table I are examples which illustrate the scope of this reaction. Of particular interest are those products containing either isolated (13) or conjugated olefins (17, 19, and 21). The preparation of such unsaturated α-bromo ketones by simple bromination of the methyl ketones is frequently problematic, since the olefins can also react; special reagents are usually required to achieve these transformations.[4] Similarly, the alkyne, furan, and thiophene moieties are compatible with this new methodology (examples 15, 27a, and 27b, respectively), as are other electron-rich (23b) as well as electron-deficient (25) aromatics. The only aromatic compound examined which did not afford bromo ketone in reasonable yield was the *p*-nitro ester 22c; extensive decomposition occurred in this case, possibly the result of electron-transfer processes.

As mentioned above, esters 1 bearing secondary or tertiary R groups were not expected to work well as bromo

(1) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429.
(2) Villieras, J.; Bacquet, C.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1975**, 1797.
(3) Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 321.
(4) For some examples of olefin vs. methyl ketone bromination, see: Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088. For special reagents to achieve selective bromination of methyl ketones in the presence of olefins, see ref 11 below and also: Bloch, R. *Synthesis* **1978**, 140.

0022-3263/85/1950-5140$01.50/0 © 1985 American Chemical Society

Table I

starting ester	bromo ketone (yield)
 10	 11[9] (75%)
 12	 13 (72%)
 14	 15[10] (78%)
 16	 17 (82%)
 18	 19[11] (76%)
 20	 21 (61%)
 22 a (X=H) b (X=OMe) c (X=NO_2)	 23 a (75%) b[6] (85%) c (0%)
 24	 25[12] (74%)
 26 a (X=O) b (X=S)	 27 a[13] (84%) b[14] (86%)
 28 a (exo) b (endo)	 29 a (80%) b (80%)

ketone precursors, since the competing pathway **2** → **3** → **6** predominates for such compounds even at low temperatures. One exception to this case proved to be the mixture of exo/endo esters **28a** and **28b**, which afforded only the bromomethyl ketones **29a** and **29b** (each in 80% yield). This result suggests the bridgehead methoxy group in **28** served to stabilize the tetrahedral intermediate **2**, either through induction, complexation, or both, such that low-temperature formation of **3** did not occur.[5]

Certainly there are numerous other methodologies for the preparation of bromomethyl ketones.[6] The procedure developed in this work offers a quick and straightforward alternative, starting from the corresponding ester, which should be particularly useful for compounds containing functionalities sensitive to electrophilic reagents. This chemistry has broader potential than just bromo ketone preparation, however, since the regiospecific bromo ketone enolate anions **5** are intermediates in these processes. Such bromo enolates can be trapped or used in reactions other than simple protonation. For example, in the case of ethyl benzoate, the intermediate solution of bromo enolate **5** (R = Ph) was treated with acetic anhydride to afford a mixture of bromo enol acetates **7** (R = Ph) in 83% yield after purification.

It is interesting that a mixture of bromo enol acetates **7** (R = Ph) was obtained, since preparation of this compound via lithium hexamethyldisilazide enolization of the ketone had previously afforded only a single isomer.[7] Although the two isomers in this case could not be readily separated preparatively, the NMR spectrum of the purified mixture showed two singlets for the vinyl H (at 6.52 and 6.30 ppm) and two singlets for the acetate methyl H's (at 2.30 and 2.12 ppm). For each pair, the downfield signal predominated (with a ratio of 83:17), and these major signals corresponded to those observed for the isomer which had previously been obtained.[7] Capillary GC/MS confirmed the presence of the two isomers and the 83:17 ratio. In the NMR spectrum, NOE enhancement was observed for the aromatic region upon irradiation of the major vinyl singlet at 6.52, establishing the *Z* configuration for the major isomer.

Bromo enol acetates are known to be effective precursors of α-keto dianions.[8] It was found, however, that the solution of bromo enolate anions **5** used to prepare the enol acetate mixture **7**, could also be used directly for the preparation of α-keto dianions. Following addition of *n*-butyllithium in one preparation of **5** (R = Ph), *tert*-butyllithium was added, and metal–halogen exchange was successfully effected to form dianions **8** (R = Ph). The resulting dianions were quenched with chlorotrimethylsilane to afford the bis-silylated enol ethers **9** in about 68%

(5) This experiment was repeated on the corresponding mixture of ethyl esters derived from **28** by treatment with sodium ethoxide in ethanol. The results were the same, demonstrating that the methyl ester moiety in **28** was not the cause of any unusual reactivity.

(6) For other methods of bromomethyl ketone synthesis, see: Reutrakul, V.; Tiensripojamarn, A.; Kusamran, K.; Nimigirawath, S. *Chem. Lett.* **1979**, 209 and references therein.

(7) Kowalski, C. J.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

(8) Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411.

(9) Ackrell, J.; Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Heterocycl. Chem.* **1980**, *17*, 1081.

(10) Davis, R. B.; Scheiber, D. H. *J. Am. Chem. Soc.* **1956**, *78*, 1675.

(11) Forlani, L. *Synthesis* **1980**, *6*, 487.

(12) Blank, B.; DiTullio, N. W.; Deviney, L.; Roberts, J. T.; Saunders, H. L. *J. Med. Chem.* **1975**, *18*, 952.

(13) Arcoria, A.; Fisichella, S.; Maccarone, E.; Scarlata, G. *J. Heterocycl. Chem.* **1975**, *12*, 215.

(14) Kumar, G.; Rajagopalan, K.; Swaminathan, S.; Balasubramanian, K. K. *Indian J. Chem., Sect. B* **1981**, *20B*, 271.

yield. As with the enol acetates **7**, NMR and GC/MS indicated a mixture of two isomers (in an 80/20 ratio); the signals for the major isomer corresponded to those of the single isomer of **9** (R = Ph), previously obtained from the pure *Z* bromo enol acetate **7** (R = Ph).[8] These results strongly suggest that the intermediate α-keto dianions **8** in this transformation are geometrically stable under these conditions. Firm establishment of this fact, however, requires additional experiments beyond the scope of this paper.

In summary, a new and convenient method has been found for the conversion of various esters **1** to homologated bromomethyl ketones **4**. Since bromo enolate anions **5** are intermediates in this process, it can also be adapted for the preparation of bromo enol acetates **7** as well as for the direct formation of terminal α-keto dianions **8**.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. IR spectra were obtained on a Perkin-Elmer 283 or 783 spectrophotometer, as thin films for liquids or as dilute solutions in $CDCl_3$ for solids. ^1H NMR were measured on a Varian EM 360L (60-MHz) or 390 (90-MHz) spectrometer. Unless otherwise mentioned, all NMR measurements were done with tetramethylsilane as internal standard with $CDCl_3$ as solvent. Gas chromatographic analyses were performed on a Hewlett Packard 5890A gas chromatograph with a 25-m capillary column (0.20 mm internal diameter) coated with cross-linked methyl silicone. The mass spectral analyses were done on a Hewlett Packard 5790A GC/MS system. Elemental (C and H) analyses were obtained on a Perkin-Elmer 240 CHN analyzer. Separations and purifications were done by flash chromatography with Baker silica gel or an Analtech Uniplate silica gel GF preparative TLC plates. Starting esters were purchased from Alfa-Ventron or Aldrich.

General Procedure for Preparation of Bromomethyl Ketones from Esters. A stirred solution of 4.8 mmol of diisopropylamine (486 mg) in 6 mL of THF was cooled to 0 °C under a nitrogen atmosphere, and 4.4 mmol of *n*-butyllithium (2.5 M in hexanes, 1.76 mL) was added dropwise. A solution of 4.4 mmol of dibromomethane (766 mg) in 6 mL of THF was cooled to −90 °C (with a dry ice/diethyl ether bath) in another flask. The lithium diisopropylamide solution was added dropwise to the stirred dibromomethane solution. After 5 min, a solution of 2 mmol of the ester in 4 mL of THF was added dropwise to the reaction mixture, and after an additional 10 min, 3 mmol of *n*-BuLi solution in hexane (1.2 mL) was added. After 5 min, the reaction mixture was added, via cannula, to a rapidly stirring solution of 3 mL of acetyl chloride in 20 mL of absolute ethanol cooled to −78 °C. The mixture was diluted with 200 mL of ether, washed with aqueous solutions of cold 10% H_2SO_4 (40 mL × 2), 5% $NaHCO_3$ (40 mL), and brine (30 mL), dried over $MgSO_4$, and filtered. After solvent evaporation with a rotary evaporator, the crude product was purified by preparative TLC, with 5% ether in petroleum ether as eluting solvent, unless otherwise indicated. Yields of purified material, along with references to known compounds, are presented in Table I; characterization of purified new compounds is presented below.

(*E*)-1-Bromo-5-undecen-2-one (13) was obtained as an oil: IR 1718 and 968 cm^{-1}; NMR δ 5.52–5.30 (m, 2 H), 3.88 (s, 2 H), 2.85–2.60 (m, 2 H), 2.50–1.75 (m, 4 H), 1.50–1.20 (m, 6 H), 1.05–0.85 (m, 3 H). Anal. Calcd for $C_{11}H_{19}OBr$: C, 53.45; H, 7.75. Found: C, 53.35; H, 7.74.

(*E*)-1-Bromo-3-nonen-2-one (17) was prepared by using a slight modification of the general procedure. In the first step, 4.4 equiv of (dibromomethyl)lithium were used, followed in the second step by 6 equiv of *n*-BuLi. Purification afforded ketone **17** as an oil: IR 1695 and 1675 (doublet) and 1628 cm^{-1}; NMR δ 7.18 (td, *J* = 7 and 15 Hz, 1 H), 6.28 (br d, *J* = 15 Hz, 1 H), 4.00 (s, 2 H), 2.45–2.20 (m, 2 H), 1.55–1.15 (m, 6 H), 1.05–0.80 (m, 3 H). Anal. Calcd for $C_9H_{15}OBr$: C, 49.33; H, 6.9. Found: C, 49.34; H, 6.93.

(*E,E*)-1-Bromo-3,5-heptadien-2-one (21) was obtained as a pale yellow solid: IR 1680 (CO), 1635, 1592, 1338, and 1000 cm^{-1}; NMR δ 7.54–7.08 (m, 1 H), 6.44–6.10 (m, 3 H), 4.00 (s, 2 H), 1.92 (d, *J* = 5 Hz, 3 H). Anal. Calcd for C_7H_9OBr: C, 44.47; H, 4.79. Found: C, 44.44; H, 4.69.

***exo*- and *endo*-2-(Bromoacetyl)-1-methoxybicyclo[2.2.2]-oct-5-ene (29a and 29b).** A commercially available (Aldrich) 20/80 mixture of *exo*- and *endo*-ethyl 1-methoxybicyclo[2.2.2]-oct-5-ene-2-carboxylate was used as the starting ester producing both compounds. The same modified general procedure was used as in the preparation of the ketone **17**, (i.e., 4.4 equiv of (dibromomethyl)lithium and 6.0 equiv of *n*-butyllithium). The exo (**29a**) and the endo (**29b**) ketones were formed in the same ratio (20/80) as that of the starting esters. The two isomeric ketones were separated and purified by preparative TLC, affording each compound as an oil in 80% yield. *exo*-**29a**: IR 1725 and 1710 (doublet), 1610 cm^{-1}; NMR δ 6.50–6.19 (m, 2 H), 4.10 (s, 2 H), 3.34 (s, 3 H), 3.10 (dd, *J* = 10 and 6 Hz, 1 H), 2.64–2.46 (m, 1 H), 2.08–1.50 (m, 2 H), 1.68–1.40 (m, 4 H). Anal. Calcd for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.83. Found: C, 51.08; H, 5.89. *endo*-**29b**: IR 1720 and 1710 (doublet), 1610 cm^{-1}; NMR δ 6.48–6.09 (m, 2 H), 4.10 (s, 2 H), 3.35 (s, 3 H), 3.28 (t, *J* = 8 Hz, 1 H), 2.72–2.53 (m, 1 H), 1.84–1.46 (m, 6 H). Anal. Calcd for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.83. Found: C, 51.09; H, 5.87.

(*Z*)- and (*E*)-2-Bromo-1-phenylethenyl Acetates ((*Z*)-7 and (*E*)-7, R = Ph). The general procedure was applied to 2 mmol of ethyl benzoate, but the solution of bromo enolates **5** was not quenched into acidic ethanol. Instead excess acetic anhydride was added to the stirred reaction mixture at −90 °C. The cooling bath was removed, and after 45 min the mixture was diluted with 200 mL of petroleum ether and then washed sequentially with aqueous solutions of cold, 2% sodium hydroxide (40 mL × 3), cold, 2% sulfuric acid (40 mL × 3), and 5% sodium bicarbonate (50 mL). After having been dried over magnesium sulfate and removal of solvent on a rotary evaporator, the remaining oil was purified by preparative TLC to afford in 83% yield an 83:17 mixture (by GC) of (*Z*)- and (*E*)-**7** (R = Ph) as an oil: IR 1768, 1620, 1495, 1370 cm^{-1}; NMR δ 7.36 (s, 5 H), 6.52 (s, $^{83}/_{100}$ H), 6.30 ($^{17}/_{100}$ H), 2.30 (s, 3 × $^{83}/_{100}$ H), 2.12 (s, 3 × $^{17}/_{100}$ H).

An NOE experiment was performed on this mixture on a Brucker 360-MHz NMR spectrometer. Irradiation of the major vinyl hydrogen singlet (δ 6.52) produced an enhancement of 2.1% in the aromatic region (5.2% considering only the ortho hydrogens); no change was observed in the intensity of any other peaks. The major isomer must therefore have the vinyl and phenyl groups cis to one another, being (*Z*)-**7** (R = Ph). The NMR peaks of this major isomer correspond to those of the single isomer previously reported.[7]

(*Z*)- and (*E*)-1-Phenyl-1-[(trimethylsilyl)oxy]-2-(trimethylsilyl)ethene ((*Z*)-9 and (*E*)-9, R = Ph). The general procedure was applied to 2 mmol of ethyl benzoate, but the solution of bromo enolate anions **5** was not quenched into acid ethanol. Instead 4 equiv of 2 M *tert*-butyllithium in pentane was added dropwise to the stirred solution. The −90 °C cooling bath was replaced by a 0 °C bath for 5 min, and then the original bath was returned. Chlorotrimethylsilane (9 equiv, distilled from calcium hydride) was added all at once, and after stirring for 40 min without cooling, the mixture was diluted with 200 mL of petroleum ether. After washing with water (50 mL × 3) and cold, 5% sodium bicarbonate solution (40 mL × 2), the solution was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator. Kugelrohr distillation of the remaining liquid afforded a mixture of the bis-silyl enol ethers (*Z*)- and (*E*)-**9** (R = Ph), still contaminated by some more volatile impurities, which was not purified further due to the sensitive nature of the product. GC analysis of the distilled material indicated the yield of **9** (R = Ph) to be about 68%, as an 80:20 mixture of isomers. NMR indicated the same ratio of isomers, with peaks for the major isomer corresponding to those of the single isomer of **9** (R = Ph) previously prepared[8] from the (*Z*)-enol acetate **7** (R = Ph). Key spectral data for the still somewhat impure mixture include the following: IR 1595, 1250, 1065, 835 cm^{-1}; NMR δ 7.45–7.20 (m, 5 H), 4.86 (s, $^4/_5$ H), 4.73 (s, $^1/_5$ H).

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