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α-HALOCARBONYL COMPOUNDS, I. AN EFFICIENT PREPARATION OF α-BROMOESTERS AND α-BROMOACIDS

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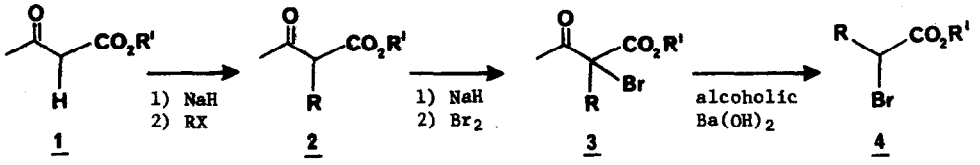
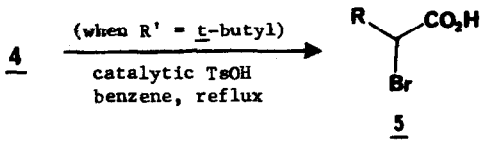
We wish to report a general, high-yield preparation of α-bromoesters 4 and α-bromoacids 5 from the corresponding α-alkylacetoacetates 2 (which are readily prepared by alkylation of the parent acetoacetates 1(1). Since the title compounds are well-known reagents useful in a number of synthetic transformations (2), this new procedure may be of considerable interest to synthetic organic chemists. Of particular note is the fact that t-butyl α-bromoesters containing oxidation-sensitive and acid/base-sensitive functionality may be prepared easily and in excellent yield (3). The procedure is schematically represented below:





Acetoacetic esters 1, available (4) commercially or by the action (5) of an appropriate alcohol on diketene, were converted to 2 usually in greater than 90% yield by alkylating solutions of the sodium enolate in tetrahydrofuran (from NaH on 1) with 1.1 equivalent primary alkyl iodide or primary allyl bromide. Use of these reactive halides substantially improved the yields of monoalkylated products obtained after one day at temperatures between 30°C and 55°C. In most cases, the crude products 2 obtained by normal aqueous work-up were sufficiently pure for use in the next steps (6).

In essentially quantitative yields, tetrahydrofuran solutions of 2 were brominated exclusively at the α-position by converting 2 to its sodium enolate (NaH on 2) and quenching this

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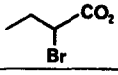
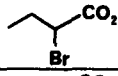
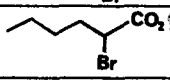
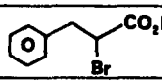
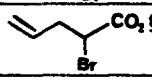
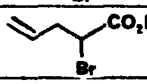
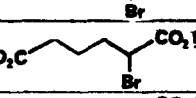
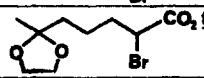
enolate with bromine (one equivalent, rapidly added as a solution in methylene chloride at 0°C or below). The α-bromo-α-alkylacetoacetates 3 (7) were directly transformed into α-bromoesters 4 by deacetylation using a suspension of anhydrous barium hydroxide in alcohol (8). Although use of excess barium hydroxide in wet alcohol was quite acceptable for the preparation of t-butyl esters 4, this deacetylation step gave poor results with other esters unless carried out under specific, non-aqueous conditions. However, when stoichiometric amounts of barium hydroxide (one equivalent, based on hydroxide ion, previously dried to constant weight under vacuum at 125°C) are used in absolute ethanol at 0° or below for thirty minutes, high yields of deacetylation without saponification or Favorskii rearrangement are obtained for all esters (9) investigated. After filtering insoluble barium salts, product esters 4 are isolated by partitioning the alcohol filtrate between pentane and brine. Results for a representative sample of α-bromoesters 4 prepared in this manner from 1 are indicated in Table 1.

When t-butyl esters are used in this sequence, the rapid conversion of 4 (R'=t-Bu) to the parent α-bromoacid 5 is readily effected by exposure to refluxing anhydrous benzene containing catalytic toluenesulfonic acid. Thus, from each of the t-butyl esters 4 described in Table 1, the corresponding acid 5 was isolated in greater than 80% yield (10). Although acid-catalyzed,

TABLE 1

	R	R'	2 percent isolated yield*	2 percent yield previously reported (ref.)	4 percent isolated yield* (over three steps from 1)	4	assignment of structure and purity based on: (ref.)
A	methyl	t-Bu	90	76 (1a)	82		authentic sample (2b)
B	ethyl	t-Bu	92	68 (1a)	85		authentic sample (2c)
C	ethyl	Et	92	not stated (1c)	70		available commercially
D	n-butyl	t-Bu	92	75 (1e)	87 (bp 93-94°C/ 3.5 mm)		footnote 13
E	benzyl	Et	90	89 (1d)	75 **		authentic sample (11)
F	allyl	t-Bu	91	62 (1a)	85 (bp 95-95.5°C/ 19 mm)		footnote 14
G	allyl	Et	90	40 (1b)	65		authentic sample (12)
H	γ-carboethoxy-propyl	t-Bu	92 **	footnote 6	85 **		footnote 13
I	δ,δ-(ethylene-dioxy)pentyl	t-Bu	92 **	footnote 6	85 **		footnote 14

*Yield shown indicates material isolated after purification by distillation or chromatography.

**Compound purified by chromatography on florisil or bulb to bulb distillation.

the mild conditions employed in this well-known ester cleavage appear to be compatible with acid-sensitive functionality as evidenced by the ready formation of 5F and 5I.

As shown in Table 1, the overall scheme offers a wide variety of possibilities for constructing α-bromoesters and α-bromoacids containing sensitive functionality within substituent R. Of particular interest in this respect are the several polyfunctional structures whose preparation is indicated. In general, such compounds are accessible only with difficulty by alternative, rather lengthy synthetic approaches (11, 12, 13) however, using this new scheme we have prepared them in excellent yield without special precautions. Note that all steps of the procedure are compatible with a terminal olefin (15) (cases F and G) or ketal (case I), and that mixed esters or mixed ester/acids (case H) can also be easily prepared (3). Finally, the preparation of homoallylic α-bromoesters and acids uncontaminated by by-products of thermal or base-catalyzed dehydrobromination is demonstrated (cases E, F, and G).

One last advantage of this scheme should be mentioned, which makes it desirable even for the preparation of simple α-bromoesters and acids. Brominated products 4 and 5 are obtained directly in a high state of purity; in particular, contamination by polybrominated materials is mechanistically unlikely. Simple purification procedures (distillation or rapid elution through florisil) generally produced pure samples of 4, which accounted for approximately 95% of the total crude material isolated in the deacetylation of 3.

Acknowledgements

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References and Footnotes

1. (a) S-O. Lawesson, S. Grönwall, and M. Anderson, Ark. Kemi., 17, 457 (1961).
   (b) Y. Gaoni, J. Chem. Soc., C, 2925 (1968).
   (c) S. T. Ioffe, K. V. Vatsuro, E. S. Kugucheva, and M. I. Kabachnik, Zh. Org. Khim., 2, 381 (1966).
   (d) H. Leuchs, Chem. Ber., 44, 1507 (1911).
   (e) W. B. Renfrow and G. B. Walker, J. Amer. Chem. Soc., 70, 3957 (1948).
2. (a) Use of these compounds as precursors to phosphoranes and phosphonates for Wittig olefin syntheses is well documented. See for example, A. Maercker, Org. React., 14, 270 (1965).
   (b) As precursors to α-amino acids and esters, see A. Wollman and M. S. Dunn, J. Org. Chem., 25, 387 (1960).
   (c) For direct use in Reformatsky reactions, see F. Gaudemar-Bardone and M. Gaudemar, Bull. Soc. Chim. Fr., 2088 (1969).
3. (a) Recent communications by Rathke and Lindert (3b) and by ourselves (3c) reported the preparation of α-haloesters by direct halogenation of lithium ester enolates. This method, however, requires the availability of the parent ester. In this communication we describe the facile direct construction of α-bromoesters from simple components, as well as the preparation of specifically brominated mixed esters (case H in Table I) not possible by a direct halogenation approach.
   (b) M. W. Rathke and A. Lindert, Tetrahedron Lett., 3995 (1971).
   (c) K. A. Hill and P. L. Stotter*, "γ-Halotiglates: Ubiquitous Reagents for Natural Products Synthesis", paper delivered before the Second International Symposium on Synthesis in Organic Chemistry, Cambridge, England (July, 1971).

4. The ready availability of 1 as starting materials makes this scheme superior to alternatives which require mixed malonate esters.

5. S-O. Lawesson, S. Grönwall, and R. Sandberg, Org. Syn., 42, 28 (1962).

6. (a) The excellent yields of α-alkylacetoacetates 2 reported in Table 1 seem to be the result of a combination of three factors: (1) use of aprotic solvent (THF) to suppress proton transfer from 2 to the enolate of 1, thus minimizing dialkylation; (2) use of reactive alkyl iodides and allyl bromides (rather than the corresponding alkyl bromides or chlorides and allyl chlorides) as alkylating agents; and (3) extended reaction times to insure complete alkylation.

   (b) Combustion analyses on purified samples of previously unreported acetoacetates 2H and 2I were not attempted, since such esters give notoriously non-reproducible analyses (see ref. 1a). Structural assignments, as well as standards of purity, were based on unexceptional spectral data and on high resolution mass spectra of chromatographically pure samples which showed single spot t.l.c. characteristics.

7. NMR spectra of 3, similar in most respects to 2, showed two characteristic differences: disappearance of α-proton absorption (6.65, triplet, J = 6Hz) and slightly lower field acetyl singlet (Δ0.15 ppm).

8. (a) A similar deacetylation of α-alkyl-α-chloro-β-diketones has been reported; however, reaction conditions were not described in detail. W. S. Johnson, et al., J. Amer. Chem. Soc., 90, 5277 (1968); ibid., 90, 6225.

   (b) It should be noted that anhydrous barium oxide in absolute ethanol was not suitable for conversion of 3 to 4.

9. Preliminary results indicate some transesterification occurs when methyl esters 3 are deacetylated in ethanol; however, use of methanol as solvent avoids this difficulty and gives satisfactory deacetylation.

10. α-Bromoacids 5 were identified by comparison with available authentic samples. Previously unreported acids 5F and 5I were somewhat unstable liquids whose structures were assigned from unexceptional spectral data and high resolution mass spectra.

11. J. R. Dice and J. N. Bowden, J. Amer. Chem. Soc., 71, 3107 (1949).

12. D. D. Phillips, ibid., 76, 5385 (1954).

13. Authentic samples of previously unreported t-butyl esters 4D and 4H were prepared from the parent α-bromoacids, using thionyl chloride followed by t-butanol and N,N-diethylaniline. The half ester acid 5H was prepared by the method of W. Treibs and H. Reinheckel, Chem. Ber., 87, 341 (1954).

14. Authentic samples of t-butyl esters 4F and 4I were not available for comparison since neither they nor their parent acids have been reported previously. Structural assignments, as well as standards of purity, were based on unexceptional spectral data and on high resolution mass spectra of purified samples which showed single-peak g.l.c. and single-spot t.l.c. characteristics, respectively.

15. (a) An early report (15b) suggests that direct bromination of ethyl α-allylacetoacetate 2G in carbon tetrachloride produces crystalline 3G. However, an attempt to reproduce this work gave a mixture of products containing little olefinic material (by NMR).

   (b) J. Parrod and M. Rahier, C. R. Acad. Sci., Paris, Ser. C, 224, 663 (1947).