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REGIOSPECIFIC SYNTHESIS OF UNSYMMETRICAL α-BROMOKETONES

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ABSTRACT
A convenient regiospecific preparation of unsymmetrical α-bromoketones, commencing from Meldrum's acid, has been developed. This procedure allows for preparation of α-bromoketones which are unobtainable in a pure state by other bromination methods and is compatable with introduction of a bromine atom in the presence of unsaturation using low-cost starting materials.

α-Bromoketones are valuable intermediates which are useful in the synthesis of a variety of heterocycles, including thiazoles,[1] imidazoles,[2] and pyran-2,5-diones,[3] as well as for other synthetic applications including cross aldol condensations,[4] enaminoketones,[5] and Favorskii rearrangements.[6] We required a number of regiospecifically α-brominated ketones as starting materials in order to complete a structure-activity study of a series of heterocyclic compounds with potential CNS activity.

While direct halogenation of symmetrical ketones offers no problem regarding regiospecificity, unsymmetrical ketones generally produce unusable mixtures of halogenated products. While a number of

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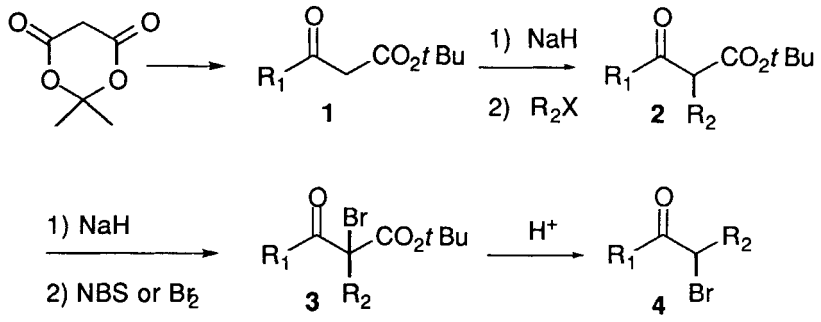
strategies to produce unsymmetrical α–haloketones have been reported including dianion chemistry,[7] organocadmium reagents,[8] hydrogen bromide decomposition of α-diazoketones,[3] sodium bromite oxidation of olefins,[9] and bromination of epoxides,[10] all have limited scope. Directing groups have also found some limited success in this area.[11-13] Of particular note is the synthesis of 3-chloro-2-alkanones which utilizes β-ketoesters to direct alkylation and chlorination prior to hydrolysis and decarboxylation.[13] In this instance, an ester moiety was successfully utilized as a directing group but the generality was limited to the formation of methyl ketones apparently as a result of higher homologues being unreactive toward ester hydrolysis and decarboxylation. Also of note is the synthesis of α-bromocarboxylic acid derivatives from acetoacetates wherein alkylation and bromination are directed by sequential anion formation and subsequent barium hydroxide deacetylation.[14]

To meet our needs for a more general synthesis of unsymmetrical α-bromoketones, we have extended these concepts to prepare regiospecifically brominated unsymmetrical ketones starting with Meldrum's acid (Scheme 1).

tert-Butyl-ß-ketoesters **1** (R_1 = Et, Bn) are readily available in generally good yields from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid).[15] Alkylation of **1** was accomplished by generation of the enolate using NaH in THF at 0°C, followed by addition of the appropriate alkyl halide (R_2X)[14] to give products **2a-e** in generally good yields (Table 1). Bromination of ß-ketoesters **2** was also accomplished by generating the enolate with NaH at 0°C, followed by rapid addition of bromine[14] in CH_2Cl_2 (Table 1). Bromination of the enolate with recrystallized NBS also gave acceptable results with the exception of **3e,** which could only be obtained in very modest yield by using Br_2. Bromination of the anion avoids the generation of by-product HBr which may catalyze bromine rearrangement[16] or other untoward results. Furthermore, this procedure allows selective bromination even in the presence of unsaturation[15] (Table 1, **3d, e**).



SCHEME 1

Table 1

Entry	R_1	R_2	%Yield[a] of **2**	bp °C (mm Hg) of **2**	%Yield of **3**
a	Me	Et	73[b]	89.5-90.5 (4.5)	54
b	Et	Et	79	91 (3.5)	69
c	Et	CH_2Ph	69	118-120 (0.3)	59
d	Me	$CH_2CH{=}CH_2$	76	100-101 (5)	53
e	CH_2Ph	$CH_2C{\equiv}CH$	47	----[c]	33

[a]Acceptable elemental analysis (C,H,Br) obtained for all new compounds except where indicated.
[b]Anal. calc. C, 64.49; Found C, 63.93.
[c]Purified by chromatography

Although most of the bromoketoesters **3** could be purified by chromatography on silica gel (4:1 hexane/CH_2Cl_2), the crude materials could be converted directly to bromoketones **4** with equally satisfactory results.

Final preparation of **4** was accomplished by decomposition of *t*-butyl esters **3** using either *p*-toluenesulfonic acid or Amberlyst® 15 strongly acidic resin in refluxing benzene and purification either by distillation or flash chromatography to give the desired α-

TABLE 2

Entry	R_1	R_2	%Yield[a,b]	bp°C (mmHg)
4a	Me	Et	39	50.5-52.5 (5)
4b	Et	Et	28	64-68 (4)
4c	Et	CH_2Ph	55	---[d]
4d	Me	$CH_2CH{=}CH_2$	25	67-69 (4.5)
4e	CH_2Ph	$CH_2C{\equiv}CH$	6[c]	---[d]
4f	CH_2Ph	H	40	---[d,e]

[a]Overall yield from **2**
[b]Satisfactory elemental analysis (C,H Br) was obtained for all new compounds, except where indicated.
[c]Insufficient sample for elemental analysis. Product characterized by NMR and Mass spectra
[d]Purified by chromatography.
[e]Attempts to purify this compound at an earlier stage led to dimerization as evidenced by spectral analysis.

bromoketones **4** in >90% purity.[18] (Table 2). As noted earlier hydrolysis and decarboxylation of methyl and ethyl esters with aqueous H_2SO_4 was successful only for R_1 = Me; our methodology significantly extends the utility of this approach.

Thus, a convenient synthesis of regiospecifically brominated unsymmetrical α-bromoketones starting from Meldrum's Acid has been developed. To our knowledge, no previously reported method provides the flexibility or scope of our approach to obtain diverse examples of these synthetically useful intermediates. The advantages of our method include the flexibility of introducing bromine substitution in the presence of unsaturation as well as the low cost of starting materials. Our procedure allows the preparation of α-bromoketones which are unobtainable in a pure state by more conventional bromination procedures. The use of this techinique for the preparation of some novel CNS agents is the subject of a future report from our laboratories.[18]

EXPERIMENTAL

^1H NMR were recorded on a Bruker AC300 using TMS as the internal standard. Mass spectra were obtained using HP 5989 (CI), Finnigan TSQ70 or vg 7070E (FAB). Unless otherwise stated, chemicals and solvents were commercially available and used without further purification. Boiling points are uncorrected. The following procedures are representative.

***tert*-Butyl 2-ethyl- 3-oxo butyrate (2a).** An 80% dispersion of NaH (6.3 g, 0.21 mol) was washed 2x with hexane and suspended in dry THF (50 mL) and cooled in an ice bath. To this suspension, *tert*-butyl acetoacetate (31.6 g, 0.2 mol) in THF (200 mL) was added dropwise with stirring. After 30 min, ethyl iodide (32.8 g, 0.21 mol) was added in one portion. The mixture was allowed to warm to room temperature. After 48 hrs, the reaction mixture was diluted with Et_2O, the organic layer was washed with water (2x), and brine then dried over $MgSO_4$. The solution was concentrated *in vacuo* and the residue was distilled to give **2a**, 27.4 g (73%), bp 86-88°C (4 mmHg). An analytical sample was prepared by redistillation of an aliquot, bp 89.5-90.5°C (4.5mm). ^1H NMR ($CDCl_3$) δ 0.9-1.0 (t, J = 7.4 Hz, 3 H), 1.45-1.55 (s, 9 H), 1.85-1.95 (m, 2 H), 2.25-2.35 (s, 3 H), 3.25-3.35 (t, J = 7.4 Hz, 1 H). MS (FAB) MH^+ = 187 (15) , 131 (65), 58 (100); IR (neat) 1713 cm^{-1} (d). Anal. calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found C, 63.93; H, 9.65.

***tert*- Butyl 2-Bromo-2-ethyl-3-oxo butyrate (3a).** An 80% dispersion of NaH (0.78 g, 26 mmol) was washed 2x with hexane and suspended in dry THF (20 mL) and cooled in an ice bath. Compound **2a** (5.0 g, 26 mmol) in THF (50 mL) was added to the mixture dropwise with stirring. After 30 min, NBS (5.3 g, 30 mmol) was added in one portion and the mixture was allowed to warm to room temperature overnight. Et_2O was added and the organic layer was washed with water (3x) and brine then dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* to give **3a** which was used directly in

the next step. Chromatography on silica gel, eluting with 4:1 hexane CH_2Cl_2, provided an analytical sample of **3a**. ^1H NMR ($CDCl_3$) δ 0.95-1.05 (t, J = 7.3 Hz, 3 H), 1.45-1.55 (s, 9 H), 2.15-2.3 (m, 2 H), 2.35-2.45 (s, 3 H); MS (FAB) MH^+ = 263, 265, 208,210 (55), 191,193 (45), 148, 150 (65), 73 (100). IR (neat) 1723 cm^{-1} (d). Anal. calc. for $C_{10}H_{17}BrO_3$: C, 45.30; H, 6.42; Br 30.14. Found C, 45.33; H, 6.44; Br, 30.06.

3-Bromo-2-pentanone (4a). Compound **3a** (9.2 g, 35 mmol) was combined with 0.5 g of Amberlyst® 15 strongly acidic resin in dry benzene (75 mL) and the mixture was heated to reflux for 40 hrs. After cooling to room temperature, the mixture was diluted with some Et_2O and washed with dilute $NaHCO_3$ (2x) and brine then dried over $MgSO_4$. Filtration and solvent evaporation *in vacuo* gave a brown oil which was distilled to give **4a**, 2.6 g, 39 % for 2 steps, bp 50-52°C (5 mm Hg). An analytical sample was obtained by preparative TLC (95:5 hexane / Et_2O). ^1H NMR ($CDCl_3$) δ 1.0-1.1 (t, J = 7.3 Hz, 3H), 1.9-2.15 (2m, 2H), 2.35-2.4 (s, 3H), 4.15-4.25 (t, 1H). GC/MS MH^+ = 164,166. IR (neat) 1718 cm^{-1}. Anal. calc for C_5H_9BrO: C, 36.39; H, 5.50; Br, 48.42. Found C, 36.41; H, 5.36; Br, 48.27.

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17. In some cases, most notably **4e** and **4f** hydrolysis and decarboxylation was accompanied by some scrambling of the bromine. This could be minimized (<5%) by addition of the bromoketoester to a refluxing solution solution of benzene containing 1 eq. of TsOH or Amberlyst resin.

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