Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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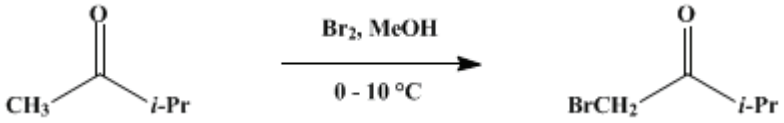
1-BROMO-3-METHYL-2-BUTANONE



Submitted by M. Gaudry and A. Marquet[1].
Checked by Diana Metzger and Richard E. Benson.

1. Procedure

Caution! This preparation must be carried out in an efficient hood. Bromomethyl ketones are highly lachrymatory and are skin irritants.

A 2-l., four-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a thermometer, a reflux condenser fitted with a calcium chloride drying tube, and a 100-ml., pressure-equalizing dropping funnel is charged with 86.0 g. (105 ml., 1.00 mole) of 3-methyl-2-butanone (Note 1) and 600 ml. of anhydrous methanol (Note 2). The solution is stirred and cooled in an ice–salt bath to 0–5°, and 160 g. (54.6 ml., 1.00 mole) of bromine (Note 3) is added in a rapid, steady stream from the dropping funnel (Note 4). During this time, the temperature is allowed to rise but not permitted to exceed 10°. The reaction temperature is maintained at 10° during the remaining reaction time (Note 5). The red color of the solution fades gradually in about 45 minutes (Note 6), 300 ml. of water is then added (Note 7), and the mixture is stirred at room temperature overnight (Note 8).

To the solution is added 900 ml. of water, and the resulting mixture is washed with four 500-ml. portions of diethyl ether. The ether layers are combined, washed with 200 ml. of aqueous 10% potassium carbonate and then twice with 200-ml. portions of water (Note 9), and dried for 1 hour over 200 g. of anhydrous calcium chloride (Note 10). The solvent is removed on a rotary evaporator at room temperature, yielding 145–158 g. of crude product (Note 11). Distillation under reduced pressure through a Vigreux column gives 115–128 g. of a fraction, b.p. 83–86° (54 mm.), n_D^{22} 1.4620–1.4640, containing 95% of 1-bromo-3-methyl-2-butanone as established by ^{1}H NMR measurements (Note 11).

2. Notes

1. The checkers used 3-methyl-2-butanone purchased from Eastman Organic Chemicals. One sample that gave a positive test for peroxides was purified by passage through a column of alumina before distillation. The material was distilled routinely before use.
2. The methanol was distilled twice from magnesium turnings. Alternately, it was dried overnight over molecular sieves then distilled. The checkers also found freshly opened reagent methanol (purchased from Fisher Scientific Company) to be satisfactory.
3. The submitters used R. P. bromine obtained from Prolabo, Paris, without further purification. The checkers used bromine available from Fisher Scientific Company.
4. It is very important to add the bromine in a single portion. When it is added dropwise, a mixture containing significant amounts of 3-bromo-3-methyl-2-butanone is obtained.
5. The temperature must be controlled carefully, especially at the end of the addition when the reaction becomes more exothermic. If the solution becomes warm, a mixture of the two isomeric bromoketones is obtained.
6. If a slight excess of bromine has been added, a light yellow color remains after reaction of one equivalent since dibromination is very slow under these conditions.
7. The quantity of water added is such that the brominated products do not separate from the aqueous methanol.
8. The water is added in order to hydrolyze the α-bromodimethyl ketals produced during the reaction. The ease of hydrolysis of these bromoketals depends on the structure of the ketone. With

acetylcyclohexane or acetylcyclopentane, stirring with water for 10 minutes is sufficient for complete hydrolysis. In contrast, with phenylacetone or methyl ethyl ketone, after dilution with water, the addition of 10 equivalents of concentrated sulfuric acid with respect to ketone and stirring for 15 hours at room temperature are necessary for complete hydrolysis.
9. The submitters state that the hydrobromic acid can also be neutralized before extraction by adding 75 g. of potassium carbonate (6 g. excess) in small portions.
10. Under these extraction conditions, the ether solution contains significant amounts of water and methanol which cannot be removed efficiently with anhydrous sodium sulfate.
11. In the crude product the ratio of 1-bromo-3-methyl-2-butanone to 3-bromo-3-methyl-2-butanone is estimated by ^{1}H NMR to be 95:5. The ^{1}H NMR properties of the two isomers are as follows; 1-bromo-3-methyl-2-butanone: ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 1.17 (d, *J* = 6.9, 6H, 2CH_3), 3.02 (m, 1H, C*H*), 4.10 (s, 2H, CH_2); 3-bromo-3-methyl-2-butanone. ($CDCl_3$): δ (multiplicity, number of protons, assignment): 1.89 (s, 6H, 2CH_3), 2.46 (s, 3H, COCH_3).

3. Discussion

Pure isomeric, monobrominated ketones substituted at the less substituted or at the more substituted α-carbon are not readily accessible by direct bromination of unsymmetrical ketones since the reaction often leads to a mixture of products, with the more substituted isomer usually predominating.[2] Radical bromination of unsymmetrical ketones in the presence of epoxides yields exclusively the monobromo ketone corresponding to bromination at the more substituted α-position.[3] The action of hydrobromic acid on diazo ketones has been, for a long time, the only method of preparing bromomethyl ketones.[4] Recently, some indirect routes involving halogenation of preformed isomeric enol silyl ethers[5] or enamines[6] have been described. The bromination of unsymmetrical ketals (e.g., dioxolanes or dimethyl ketals) occurs to a greater extent on the less substituted carbon atom, and this constitutes an efficient route to the corresponding α-bromo ketones.[7,8,9] Direct bromination of 2-substituted cyclohexanones[8] and various methyl ketones[10] in methanol leads to the same result.

This procedure, in contrast to methods mentioned above, has only one step and is readily adapted to large-scale preparative work. Furthermore, because dibromination is very slow in methanol, the crude reaction products contain only traces of dibromo ketones. This contrasts with the behavior in other solvents, such as ether or carbon tetrachloride, where larger amounts of dibromo ketones are always present, even when one equivalent of bromine is used. Methanol is thus recommended as a brominating solvent even when no orientation problem is involved. It should be noted that α-bromomethyl ketals are formed along with α-bromoketones and must be hydrolyzed during the workup (Note 8).[10]

The regiospecificity of bromination depends on the structure of the ketone.[10] This regiospecificity is very high for methyl ketones when the α'-position is tertiary, and not as high when it is secondary. For example, cyclohexyl methyl ketone and cyclopentyl methyl ketone lead to crude products containing 100 and 85%, respectively, of bromomethyl ketone, while 2-methylcyclohexanone, methyl ethyl ketone, and phenylacetone give 65,[8] 70,[10] and 40%,[10] respectively, of ketone brominated at the less substituted carbon. In these latter cases, bromination of the corresponding dimethyl ketal in methanol affords better yields of these bromo ketones.[10]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

methanol (67-56-1)

diethyl ether (60-29-7)

magnesium turnings (7439-95-4)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

phenylacetone (103-79-7)

methyl ethyl ketone (78-93-3)

3-methyl-2-butanone (563-80-4)

2-methylcyclohexanone (583-60-8)

Cyclohexyl methyl ketone,
acetylcyclohexane (823-76-7)

1-Bromo-3-methyl-2-butanone (19967-55-6)

3-bromo-3-methyl-2-butanone (2648-71-7)

acetylcyclopentane,

cyclopentyl methyl ketone (6004-60-0)