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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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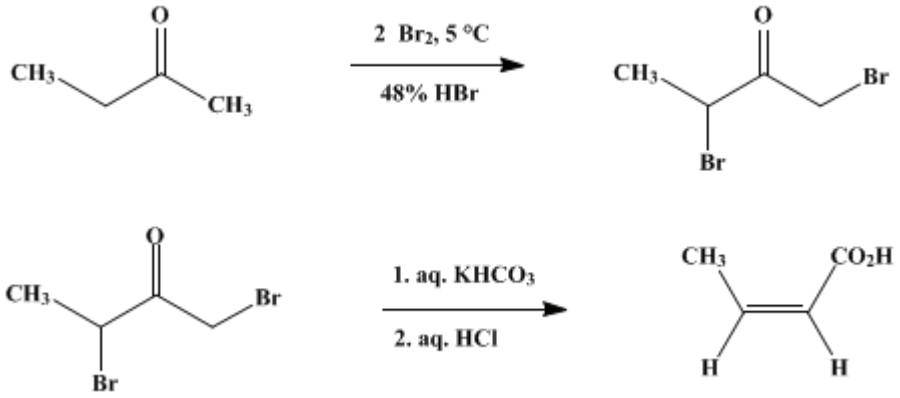
cis-α,β-UNSATURATED ACIDS: ISOCROTONIC ACID

[2-Butenoic acid, (Z)-]



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Checked by A. F. Kluge and J. Meinwald.

1. Procedure

Caution! 1,3-Dibromo-2-butanone is a powerful lachrymator and a vesicant. This preparation should be carried out in a hood and contact of this compound with the skin should be avoided.

A. *1,3-Dibromo-2-butanone*. A mixture of 72.1 g. (90.0 ml., 1.00 mole) of 2-butanone and 100 ml. of precooled (5°) 48% hydrobromic acid is prepared in a 1-l., three-necked, round-bottomed flask equipped with a dropping funnel, a condenser (Note 1), and a Teflon stirrer. The flask is immersed in ice water, and when the temperature of the mixture reaches 5°, 319.6 g. (102.5 ml., 1.998 moles) of bromine is added dropwise at a rate such that the temperature does not rise above 10° and unreacted bromine does not accumulate (Note 2). After addition of the bromine is complete, 400 ml. of water is added, and the heavier organic layer is separated and immediately (Note 3) fractionated under reduced pressure (Note 4) through a 25-cm. Widmer column, giving 115–134 g. (50–58%) of pure 1,3-dibromo-2-butanone, b.p. 91–94° (13 mm.), n_D^{25} 1.5252 (Note 5) and (Note 6).

B. *Isocrotonic acid*. A solution of 100 g. (1.00 mole) of potassium hydrogen carbonate (Note 7) in 1 l. of water is placed in a 2-l., three-necked, round-bottomed flask equipped with a condenser, a dropping funnel, and a Teflon stirrer. 1,3-Dibromo-2-butanone (46.0 g., 0.200 mole) is added over a 5-minute period (Note 8). The mixture is stirred thoroughly, and after 2–3 hours (Note 9) when constant titration values against methyl orange are obtained, the solution is extracted with two 100-ml. portions of diethyl ether (Note 10) and acidified to pH 1–2 by dropwise addition of dilute hydrochloric acid (Note 11). The aqueous solution is re-extracted with six 100-ml. portions of ether, and the ether phase is dried overnight in a refrigerator over magnesium sulfate.

The ethereal solution is filtered with suction, and the ether is removed with a rotary evaporator connected to a 500-ml., acetone–dry ice trap. A water bath maintained at 5–10° is used to facilitate the removal of the ether (Note 12) and (Note 13).

The yield of crude isocrotonic acid is 11.8–13.2 g. (69–77%). It is sufficiently pure for most purposes although NMR analysis (Note 14) shows that the crude acid contains a small amount of the stable *trans*-isomer (Note 15). The crude product cannot be stored without isomerization. For purification, 13.0 g. of the product is dissolved in 25 ml. of petroleum ether (b.p. 40–65°) at 5°. When left at −15° for days, crystals separate and are filtered at 5°, yielding 9.3 g. of product, m.p. 12.5–14°, n_D^{25} 1.4453, which can be stored in the dark at 30° for 3 weeks or at 5° for years with no detectable

isomerization (Note 16).

2. Notes

1. The hydrogen bromide evolved from the condenser should be absorbed in a gas trap.
2. Accumulation of bromine results in an uncontrolled reaction and a decrease in the yield. This step requires 6–8 hours.
3. The crude product soon begins to decompose if it is not distilled immediately.
4. Since corrosive vapor is evolved, a water pump should be used.
5. The distilled product might be highly colored (violet, green, and blue), but this has no effect on its further use.
6. The dihaloketone purified in this way is stable for years when stored at 5°.
7. The yield is slightly lower when other bases such as sodium hydrogen carbonate, sodium carbonate, or potassium carbonate are used.
8. The reaction is slightly exothermic.
9. Less time is required when stronger bases are used.
10. The nonacidic by-products are discarded.
11. Because of vigorous foaming, the addition must be made slowly and with care. The end-point can also be detected by a fading color of the reaction mixture. The checkers performed this acidification in the reaction flask with mechanical stirring which minimized the foaming.
12. The submitter used the following procedure for removal of ether. A 250-ml., two-necked, round-bottomed flask, fitted with a dropping funnel, is equipped for distillation under reduced pressure (water pump). The ethereal solution is added dropwise (Note 13) and, when all the solution is added and the pressure has dropped to 10 mm., the last traces of ether are removed with an oil pump (0.4 mm.) for a period of 30 minutes.
13. This is to avoid isomerization which is easily initiated at elevated temperature.
14. NMR spectroscopy is an excellent tool for distinguishing between the isomers.[2]
15. The checkers detected the presence of approximately 10% of the *trans*-acid by NMR analysis.
16. The crude acid could be distilled in 5–10 ml. portions at 1 mm. without isomerization (b.p. 36°), but these samples were found to be more sensitive to isomerization.

3. Discussion

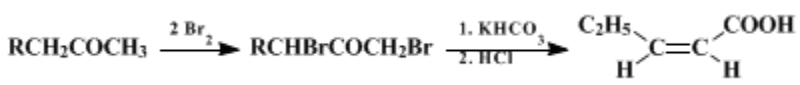
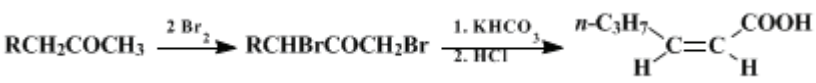
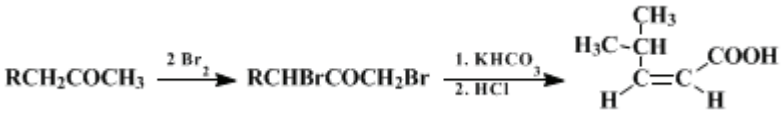
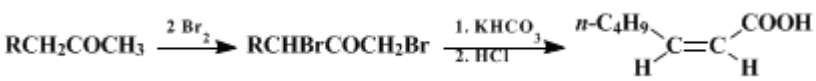
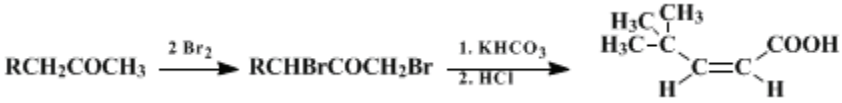
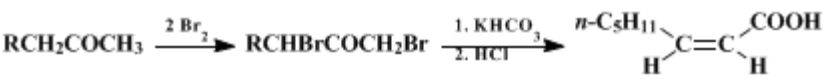
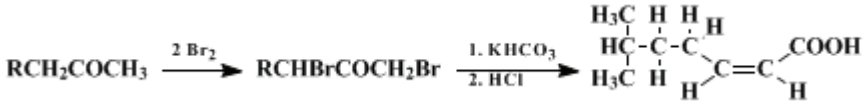
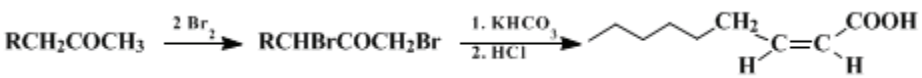
Isocrotonic acid can be prepared by the stereospecific *cis*-hydrogenation of tetrolic acid[3] or, mixed with the *trans*-isomer, by reduction of 3-chloro-*cis*-crotonic acid with sodium amalgam.[4] The *cis*-acid can also be prepared in small amounts by isomerization of the *trans*-acid.[5] The method described herein is much less laborious than the older procedures.[2]

The reaction is an example of a stereospecific Favorskii rearrangement,[6] and seems to have general applicability for the preparation of *cis*-α,β-unsaturated acids.[7] Only a limited number of the higher homologues have previously been prepared by the more laborious stereospecific *cis*-hydrogenation of the corresponding acetylenic acid,[1,8,9] and, moreover, in some cases, they seem to have been mixtures of the two geometric isomers. The rearrangements, starting with commercially available methyl ketones, yield the *cis*-isomer exclusively as determined by NMR spectroscopy.[7] The higher homologues can be purified by distillation with minimal losses. Purified in this manner, the samples can be stored at 5° for years without detectable isomerization. The yields and physical constants of the bromoketones and the *cis*-α,β-unsaturated acids are given in Table I.

TABLE I

PREPARATION OF BROMOKETONES AND *cis*-α,β-UNSATURATED ACIDS FROM METHYL

R	Bromoketone Yield, %	n_D^{25}	*cis*-α,β- Yield, %	Tim h

C_2H_5 	57	1.5176	68	3
n-C_3H_7 	51	1.5080	61	24
2-C_3H_7 	58	1.5099	85	24
n-C_4H_9 	65	1.5043	64	20
	49	1.5071	75	48
$tert$-C_4H_9 n-C_5H_{11} 	40	1.5001	50	48
$(CH_3)_2CH(CH_2)_2$ 	35	1.4997	58	48
n-C_6H_{13} 	41	1.4983	28	96

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 226

References and Notes

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

petroleum ether

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

HYDROBROMIC ACID,
hydrogen bromide (10035-10-6)

sodium carbonate (497-19-8)

bromine (7726-95-6)

sodium (13966-32-0)

magnesium sulfate (7487-88-9)

butanone,
2-butanone (78-93-3)

bromoketone (593-95-3)

potassium hydrogen carbonate (298-14-6)

Tetrolic acid (590-93-2)

Isocrotonic acid,
2-Butenoic acid, (Z)- (503-64-0)

1,3-Dibromo-2-butanone (815-51-0)

3-chloro-cis-crotonic acid