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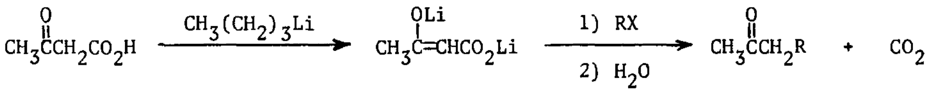
DILITHIO ACETOACETATE AS AN ACETONE ENOLATE EQUIVALENT

Richard A. Kjonaas* and Dhiren D. Patel
Department of Chemistry, Indiana State University
Terre Haute, Indiana 47809 USA

Summary: Dilithio acetoacetate, which can be generated from acetoacetic acid and n-butyllithium, undergoes alkylation followed by facile decarboxylation to give methyl ketones.

In connection with our studies involving the transition metal assisted stereo- and regiospecific formation of carbon-carbon bonds, we had need of a stabilized ketone enolate[1] which would not require hydrolysis, saponification, aluminum amalgam reduction, or other such treatment to remove the stabilizing group after alkylation had been achieved. Dilithio acetoacetate appeared to be the ideal candidate. Although there have been no reports of its use in the literature,[2] there have been reports of work done with an analogous compound, dilithio monoethyl malonate. McMurry[3] and Wierenga[4] and coworkers reported that dilithio monoethyl malonate can be alkylated[3] or acylated[4] then decarboxylated to give α-alkylated or α-acylated ethyl acetate.

We report here that dilithio acetoacetate can be generated from acetoacetic acid and n-butylithium in tetrahydrofuran (THF) at 0°C and then alkylated to give an adduct which decarboxylates at room temperature to give α-alkylated acetone as shown in the equation below.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2H} \xrightarrow{\mathrm{CH_3(CH_2)_3Li}} \mathrm{CH_3\overset{OLi}{\overset{|}{C}}{=}CHCO_2Li} \xrightarrow[\text{2) } \mathrm{H_2O}]{\text{1) RX}} \mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2R} + \mathrm{CO_2}$$

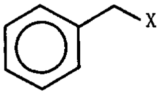
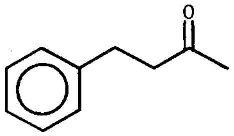
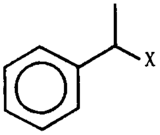
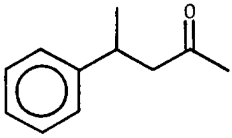
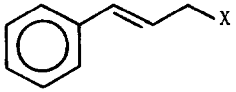
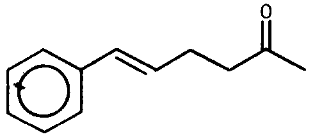
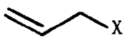
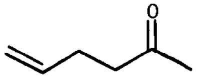
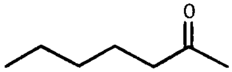
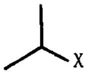
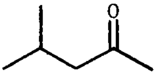
Benzyl bromide gave only a 45% yield when treated with one equivalent of dilithio acetoacetate. This yield was increased to 92% when 2.5 equivalents were used. Thus, 2.5 equivalents of dilithio acetoacetate were used in all of the examples in the table on the next page. As is the case when alkylating β-ketosulfoxides, low solubility of the lithiated species in THF impedes the reaction and necessitates the use of a cosolvent for the less reactive alkyl halides. The reactions were allowed to run 3 days. In almost all runs, some unreacted alkyl halide was recovered. No O-alkylation products could be detected in any of the reactions. Our acetoacetic acid was prepared by saponification of ethyl acetoacetate[5] but is also available in very high yield from diketene.[6] The methodology described herein constitutes experimental realization of a stabilized ketone enolate whose stabilizing group is removed without post-alkylation treatment. Further experiments with β-keto acids are in progress.

4-Phenyl-2-pentanone: To 2.5 mmole of dry crystalline acetoacetic acid[5] and approximately 1 mg of 2,2-bipyridine in 3.0 mL THF and 2.0 mL hexamethylphosphoric triamide (HMPA) at 0°C under an N_2 atmosphere was added enough n-butyllithium to produce a red color (slightly more than 5.0 mmoles). The resulting solution was then treated with 1.00 mmole of 1-bromo-1-phenylethane. After stirring at 25°C for 3 days, aqueous workup (5 mL diethyl ether and 2 X 10 mL water) gave the crude product contaminated with hydrocarbon impurities from the n-butyllithium solvent. The impurities were removed by column chromatography (silica gel eluted with hexane followed by diethyl ether).

5-Hexen-2-one: Following a procedure similar to the one above, THF (8 mL) was used but the HMPA was omitted. After the addition of 1.00 mmole of allyl bromide and stirring at 0°C for 3 days, 1.00 mmole of 2-heptanone was added as an internal standard. Aqueous workup (8 mL diethyl ether and 5 mL water) was followed by gas chromatographic analysis.

Acknowledgement: Financial assistance was provided by the Indiana State University Research Fund.

TABLE: Alkylation and Decarboxylation of Dilithio Acetoacetate

Substrate	Product[a]	Solvent	X	Yield (%)[b]
		THF	Br	92[c]
		THF/HMPA	Cl	81[c]
		THF/HMPA	Br	86[c]
		THF/HMPA	Cl	72[c]
		THF	Br	83
		THF/HMPA	I	73
		THF/HMPA	Br	54
		THF/HMPA	I	75
		THF/HMPA	Br	42

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[a] Spectral and chromatographic properties were consistent with that of authentic material. [b] Unless specified otherwise, yields were obtained by quantitative gas chromatographic analysis with an internal standard. [c] Yield of isolated product.

REFERENCES AND NOTES

1. For a discussion of some commonly used stabilized ketone enolates such as those generated from β-ketoesters, β-ketosulfoxides, and β-ketosulfones, see House, H.O., "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin Inc., 1972, pages 510-519.
2. However, the use of acetone enolate generated in situ by decarboxylation of acetoacetate ion has been reported: Yasuda, Michiko Chemistry Letters (1975), 89-90. Also, a dicuprous β-ketocarboxylate has been α-alkylated: Tsuda, T.; Chujo, Y.; Saegusa, T. J. Am. Chem. Soc. (1980), 102, 431-433.
3. McMurry, J.E.; Musser, J.H. J. Org. Chem. (1975), 40, 2556-2557.
4. Wierenga, W.; Skulnick, H.I. J. Org. Chem. (1979), 44, 310-311.
5. Krueger, R.C. J. Am. Chem. Soc. (1952), 74, 5536.
6. Grande, K.D.; Rosenfeld, S.M. J. Org. Chem. (1980), 45, 1626-1628.

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