

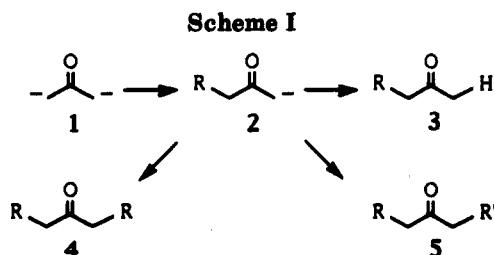
Dialkylation of Ketone Dianions

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α,α' -Dianions 1 from ketones were first prepared by Hubbard and Harris¹ by the metalation of potassium enolates with *n*-butyllithium. They reacted these dianions with 1 equiv of an electrophile at $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ and protonated the resulting mono-enolates 2 to give monoalkylated ketones 3 (Scheme 1). They knew they had prepared dianions since mono-enolates did not react readily with their electrophiles at these low temperatures. They ruled out α,α -dianions since 2,2-dimethyl-3-pentanone did not react and thus deduced that they had prepared α,α' dianions 1. They reported no dialkylations of dianions 1, presumably because dianions 1 cannot be cleanly dialkylated with alkyl halides due to rapid proton exchange processes (e.g., $2 \rightarrow 6$).



We wish to report that when the second electrophile is an alkyl triflate (known to react with secondary and tertiary enolates at low temperatures with virtually no exchange²), the desired dialkylation products 4 and 5 are accompanied by only very small amounts of byproducts from exchange. We have investigated the scope of these one-pot α,α' -bis-alkylations of ketones, which strongly support α,α' structures for the Hubbard and Harris¹ dianions.



We prepared the primary,primary dianion from acetone, the secondary,secondary dianions from 3-pentanone and cyclohexanone, the primary,secondary dianions from 2-butanone and 2-hexanone, and the primary,tertiary dianion from 3-methyl-2-butanone, but were unable to make the secondary,tertiary dianion from 2-methylcyclohexanone and the tertiary,tertiary dianions from 2,4-dimethyl-3-pentanone and 2,6-dimethylcyclohexanones in synthetically useful yields.

Hexane and (sometimes) ether were suitable solvents for the alkylations with triflates. THF was unsuitable since the ring-opening polymerization of THF is catalyzed by alkyl triflates.³ Diethyl ether, the solvent used for making the enolate with KH, was satisfactory unless the

exchange between diethyl ether and methyl triflate⁴ was competitive with the desired alkylation (in some cases where methyl triflate was used in diethyl ether, considerable ethylation was observed; we measured the half-life for this exchange to be 14 h at $25\text{ }^{\circ}\text{C}$). These reactions of alkyl triflates with ethers were avoided by evaporating the ether after the metalation and adding hexane as the solvent for the alkylation. The TMEDA used by Hubbard and Harris was omitted to avoid problems with its alkylation by alkyl triflates and to simplify the workup.

The dialkylation results are shown in Table 1. The best yields (shown) were obtained when the reactions were warmed to $25\text{ }^{\circ}\text{C}$ at the end, which sometimes resulted in small amounts of exchange products. Quenching without warming at the end gave slightly lower yields but with the advantage that there were virtually no exchange byproducts to separate.

Dianions 1 were all α,α' -dialkylated with excess methyl and/or ethyl triflate. The yields were 58–78% except for the dianion from acetone, which gave only 30% of the desired product under the best conditions for the other ketones, and 49% under the best conditions found for acetone dianion. These lower yields with acetone dianion are apparently related to faster exchange with primary enolates 2 than secondary enolates 6 or tertiary enolates 7.⁵ The higher yields in the dialkylations of other 2-alkanones suggest that their dianions react first mainly at their primary site. This was supported by alkylating the primary,tertiary-dianion from 3-methyl-2-butanone with methyl iodide followed by protonating to give a 2:1 mixture favoring 2-methyl-3-pentanone (from alkylation at the primary site) over 3,3-dimethyl-2-butanone (from reaction at the tertiary site). Hopefully other reagents and conditions will give regioselectivity >2:1 and thus make these unsymmetrical dianions more useful.

The dialkylation of dianions 1 with two different alkylating agents was investigated using acetone and cyclohexanone. The first alkylating agent could not be an alkyl triflate since they react too rapidly with intermediate enolate 2. Instead, an alkyl halide was used at low temperature for the first alkylation and then an alkyl triflate for the second. Yields of the mixed dialkylation products 5 were 58% from cyclohexanone and 28% from acetone. Again, faster proton abstraction by the intermediate primary enolate 2 was probably responsible for the lower yield from acetone than from cyclohexanone.

The 2,6-dialkylcyclohexanones were found in roughly 2:1 *Z/E* ratios which were readily changed to *Z/E* 4:1 by equilibrating with methanolic sodium methoxide.

Experimental Section⁶

Methyl and ethyl triflates from Aldrich Co. were used immediately after opening. Ketones from Aldrich were dried over molecular sieves before use. Reactions were carried out under purified argon. Products were purified by GC on a GE SE-30 silicone oil column and characterized by NMR on a Bruker WM-250 instrument in CDCl_3 with TMS as an internal standard. The NMR spectra of most of the products and byproducts have been reported.^{2,7}

(1) Hubbard, J. S.; Harris, T. M. *J. Am. Chem. Soc.* 1980, 102, 2110. They report dianions from acetone, 2-butanone, 3-pentanone, and cyclohexanone. We used modifications of their procedure to make the same and other dianions.

(2) Bates, R. B.; Taylor, S. R. *J. Org. Chem.* 1993, 58, 4469.

(3) Howells, R. D.; McCown, J. D. *Chem. Rev.* 1977, 77, 69.

(4) Gramstad, T.; Haszeldine, R. N. *J. Chem. Soc.* 1957, 4069. Burdon, J.; McLoughlin, V. C. R. *Tetrahedron* 1965, 21, 1.

(5) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972.

(6) For details, see Taylor, S. R. Ph.D. Dissertation, University of Arizona, 1993.

Table 1. Dialkylation of Ketones with Alkylating Agents RY

reaction	starting ketone	RY	product	% yield
1	acetone	EtOTf	4-heptanone	49
2	acetone	MeI/EtOTf	3-hexanone	28
3	2-butanone	MeOTf ^a	2-Me-3-pentanone	60
4	2-hexanone	MeOTf ^a	4-Me-3-heptanone	66
5	3-Me-2-butanone	MeOTf ^a	2,2-di-Me-3-heptanone	78
6	3-pentanone	MeOTf ^a	2,4-di-Me-3-pentanone	58
7	cyclohexanone	MeOTf ^a	2,6-di-Me-cyclohexanone	71
8	cyclohexanone	EtOTf ^a	2,6-di-Et-cyclohexanone	70
9	cyclohexanone	MeI ^a /EtOTf	2-Et-6-Me-cyclohexanone	58

^a Inverse addition.

α,α' -Dianion from Acetone. In a side-arm round-bottom flask fitted with septa was washed potassium hydride (6.5 mmol, 1.0 eq) as a 35% suspension in mineral oil via cannula with pentane (2 \times 10 mL). Dry ether (40 mL) and then acetone (6.5 mmol) were added at 0 °C, and the mixture was stirred for 1 h at 25 °C. *n*-Butyllithium (1.6 M, 1.1 equiv) in hexane was added to the potassium enolate suspension in ether at 0 °C, and the mixture was stirred for 10 min at 0 °C and 40 min at 25 °C.

α,α' -Dianions from Other Ketones. These differed from the above as follows. An amount of 1.3 equiv of KH was used. For cyclohexanone, the enolate generation time was increased to 4–7 h. After generation of the enolates, the ether was evaporated to dryness through a cannula by warming with a gentle argon flow. *n*-Butyllithium (1.2 equiv) in hexane was added to the potassium enolate suspension in hexane (40 mL) at 25 °C. An ultrasound cleaning bath was sometimes used for several minutes to aid mixing. The mixture was refluxed for 2–4 h.

4-Heptanone from the α,α' -Dianion from Acetone (Reaction 1). To dianion in ether at 0 °C was added 2.0 equiv of ethyl triflate, and the mixture was stirred 1 h at 0 °C and 16 h at 25 °C. Ice-water (20 mL) was added, the mixture was made slightly acidic with dilute HCl, and the pH was adjusted to 7–8 with solid NaHCO₃. After stirring for 16 h to destroy excess alkyl triflate, the pH was again adjusted to 7–8 with NaHCO₃. Extraction 3 \times 20 mL of ether, drying of the combined ether layers over magnesium sulfate, and fractional distillation of the ether left an oil which was 49% 4-heptanone, 37% 3-ethyl-2-pentanone, 7% 3-ethyl-4-heptanone, and 7% acetone.

3-Hexanone from the α,α' -Dianion from Acetone (Reaction 2). To dianion in ether at 0 °C was added slowly 1.0 equiv of methyl iodide. After stirring 10 h at 0 °C, 1.3 equiv of ethyl triflate was added slowly at 0 °C, and the mixture was stirred for 16 h as it warmed to 25 °C. The byproducts were 28% 3-methyl-4-heptanone [¹H NMR δ 0.84 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.10 (sextet, *J* = 7.2 Hz, 1H)]; ¹³C NMR δ 11.2, 13.5, 15.4, 16.9, 26.2, 42.7, 47.4], 19% 2-pentanone, 15% acetone, and 10% 3-ethyl-2-pentanone.

Ketones 4 from α,α' -Dianions from Other Ketones (Reactions 3–8). At –55 °C (–30 °C for Reactions 4 and 8), 3–4 equiv of methyl or ethyl triflate was added to the dianion and stirring was continued for 16 h as the reaction warmed to 25 °C. Byproducts were as follows. Reaction 3: 20% of alkenes from the addition of *n*-BuLi to ketones,⁶ 14% 2,4-dimethyl-3-pentanone, and 6% 2,2-dimethyl-3-pentanone. Reaction 4: 17% 3-heptanone, 16% 3-methyl-2-hexanone [¹H NMR δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 2.14 (s, 3H), 2.51 (sextet,

J = 7.0, 1H)]; ¹³C NMR δ 11.3, 16.0, 26.1, 29.3, 35.3, 44.4], and 1% 2-hexanone. Reaction 5: 12% *n*-BuLi addition products, 6% 2,4-dimethyl-3-pentanone, and 4% 2-methyl-3-pentanone. Reaction 6: 35% 2-methyl-3-pentanone, 4% 3-pentanone, and 3% products from *n*-BuLi addition. Reaction 7: 20% 2-methylcyclohexanone and 9% cyclohexanone. Reaction 8: 20% 2-ethylcyclohexanone and 10% 2,2-diethylcyclohexanone [¹H NMR δ 0.75 (t, *J* = 7.5 Hz, 6H); ¹³C NMR δ 7.1, 20.2, 26.7, 35.2, 41.3, 51.4]; (*E*)-2,6-diethylcyclohexanone [¹H NMR δ 0.87 (t, *J* = 7.4 Hz, 6H), 2.31 (m, 2H)]; ¹³C NMR δ 11.6, 23.1, 25.4, 32.7, 50.3]; (*Z*)-2,6-diethylcyclohexanone [¹H NMR δ 0.88 (t, *J* = 7.3 Hz, 6H), 2.16 (m, 2H)]; ¹³C NMR δ 11.6, 21.9, 25.4, 34.9, 52.6].

2-Ethyl-6-methylcyclohexanones from the α,α' -Dianion from Cyclohexanone (Reaction 9). At –30 °C, dianion was added to 5 equiv of methyl iodide. After stirring for 1 h as the mixture warmed to –10 °C, ethyl triflate (2.0 equiv) was added and stirring was continued for 16 h as the reaction warmed to 25 °C to give 39% (*Z*)-2-ethyl-6-methylcyclohexanone [¹H NMR δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H)]; ¹³C NMR δ 11.8, 14.5, 22.2, 25.6, 34.8, 37.5, 45.7, 52.4], 19% (*E*)-2-ethyl-6-methylcyclohexanone [¹H NMR δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H)]; ¹³C NMR δ 11.8, 15.4, 23.9, 25.6, 32.0, 35.5, 42.3, 51.0], 17% addition products, 8% 2,6-diethylcyclohexanones, 7% 2,6-dimethylcyclohexanones, 5% cyclohexanone, 4% 2-methylcyclohexanone, and 1% 2,2-diethylcyclohexanone.

Monomethylation of the Dianion from 3-Methyl-2-butanone. At –55 °C, 4 equiv of methyl iodide was added to the dianion. After stirring 30 minutes, the temperature was –30 °C. Stirring was continued at –30 °C for 1.25 h to give 54% 2-methyl-3-pentanone, 28% 3,3-dimethyl-2-butanone, 9% 2,2-dimethyl-3-pentanone, and 9% 3-methyl-2-butanone.

Equilibration of 2,6-Diethylcyclohexanones. A 2:1 mixture of (*Z/E*)-2,6-diethylcyclohexanones (0.4 g) was refluxed for 3 h with 0.54 g of NaOMe in 10 mL of methanol. ¹H NMR analysis showed that the *Z/E* ratio was now 4:1.

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Supplementary Material Available: ¹H NMR spectra of 3-methyl-4-heptanone, 3-methyl-2-hexanone; ¹H and ¹³C NMR spectra of 2,2-, (*E*)-2,6-, and (*Z*)-2,6-diethylcyclohexanones and (*E*)- and (*Z*)-2-ethyl-6-methylcyclohexanones (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) *Sadtler Standard Spectra*; Sadtler Research Laboratories: Philadelphia.