

Notes

Alkylation of Enolates with Triflates

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Alkylations of enolates are among the most useful carbon-carbon bond-forming reactions. While in most such reactions the desired product is the main product, scrambling reactions involving proton exchange between the alkylation products and bases generally reduce the yield and produce difficultly separable byproducts similar to (sometimes isomeric with) the desired product.¹ Many indirect ways of bringing about clean monoalkylation of enolates have been developed.² We wish to report that when alkyl triflates³ are used as the alkylating agents, alkylation can be achieved directly without significant exchange.

Potassium hydride in ether was used to generate the potassium enolates of cyclohexanone⁴ and 2,6-dimethylcyclohexanone. (Metal amides were avoided since the equivalent of amine which forms during the metalation would react rapidly with alkyl triflates).

It was necessary to find a suitable solvent for the alkylations with triflates. THF is unsuitable since the ring-opening polymerization of THF is catalyzed by alkyl triflates.³ Ethyl ether, the solvent used for making the enolate with KH, is satisfactory for ethylations, and for other triflate alkylations unless the exchange between ethyl ether and alkyl triflate^{3a} is competitive with the desired alkylation (in some cases where methyl triflate was used in ethyl ether, more ethylation than methylation was observed). These reactions of alkyl triflates with ethers can be avoided by evaporating the ether after the metalation and adding hexane as the solvent for the alkylation.

Direct addition (electrophile added to enolate) was used except in the cases of MeI and Me₂SO₄ in ether, where for unknown reasons the yields were about 10% higher by inverse addition.

The results with potassiocyclohexanone are shown in Table I. Reactions 1-7 using alkyl halides or sulfates gave 2-41% of dialkylcyclohexanones, even though unreacted cyclohexanone (2-56%) was present in each case. The dialkylation product was in all cases largely 2,2-dialkylcyclohexanone, the product from the thermodynamic enolate, rather than the 2,6-dialkylcyclohexanones, suggesting that proton exchange to the thermodynamic enolate is faster than alkylation of the kinetic enolate of the intermediate 2-alkylcyclohexanone.² Reaction 8 shows that exchange (3%) can complicate alkyl triflate reactions if the reactants are mixed at 25 °C. The last four reactions, with triflate additions at -30 or 0 °C, went in the highest yields (85-91%) and avoided exchange products. No ethylation products were observed in reaction 10, indicating that in this case alkylation of the enolate was significantly faster than alkyl exchange between ethyl ether and methyl triflate.

Table I. Reactions of Potassiocyclohexanone with Alkylating Agents RY

reactn no.	RY	solvent	T, °C	time, h	% yields ^a		
					sm	mono	di
1	n-BuBr	Et ₂ O	25	18	56	42	2
2	n-BuI	Et ₂ O	0 → 25	18	48	44	8
3	PhCH ₂ Cl	Et ₂ O	0 → 25	18	2	57	41
4	Me ₂ SO ₄	Et ₂ O	25	6	30	62	8
5	MeI	Et ₂ O	0 → 25	0.3	27	60	13
6	MeI	Et ₂ O	0 → 25	4	15	70	15
7	MeI	hexane	-10 → 25	1	5	70	25
8	MeOTf	hexane	25	0.3	13	84	3
9	MeOTf	hexane	-30 → 25	1.2	9	91	0
10	MeOTf	Et ₂ O	-30	1	14	86	0
11	EtOTf	hexane	-30 → 25	1.2	15	85	0
12	EtOTf	Et ₂ O	0 → 25	18	12	88	0

^a sm = cyclohexanone, mono = 2-alkylcyclohexanone, di = mixture of 2,2- and (*E*)- and (*Z*)-2,6-dialkylcyclohexanones.

Table II. Reactions of Potassio-2,6-dimethylcyclohexanone with Methylating Agents MeY

reactn no.	MeY	solvent	T, °C	time, h	% yields ^a		
					di	tri	tetra
13	MeI	Et ₂ O	-30 → 25	1	8	63	29
14	MeOTf	hexane	-30 → 25	1	7	92	1
15	MeOTf	Et ₂ O	-30 → 25	1	1	98	1

^a di = 2,6-dimethylcyclohexanones, tri = 2,2,6-trimethylcyclohexanone, tetra = 2,2,6,6-tetramethylcyclohexanone.

The potassium enolate from 2,6-dimethylcyclohexanone was shown to react without significant exchange with methyl triflate in ether or hexane (Table II, reactions 14 and 15). The reaction is especially clean in ether (98% yield). Reaction 13 shows that much exchange can occur when methyl iodide is used.

In summary, alkylations of enolates from ketones with alkyl triflates in ether or hexane go in high yield (85-98%) and avoid the exchange products which occur when alkyl halides and sulfates are used.

Experimental Section

General. Cyclohexanones and electrophiles were used as purchased from Aldrich Co. Gas chromatography was carried out on a GE SE-30 silicone oil column. NMR spectra were obtained on a Bruker WM-250 instrument in CDCl₃ with TMS as an internal standard. Reactions were carried out under argon.

Potassiocyclohexanone⁴ and Potassio-2,6-dimethylcyclohexanone. In a round-bottom flask with a side arm fitted with two septa, potassium hydride (6.4 mmol) in mineral oil was washed with pentane (2 × 10 mL). Ethyl ether (40 mL) and cyclohexanone or 2,6-dimethylcyclohexanone (5.8 mmol) were added. The mixture was stirred for 1-3 h (5 h for 2,6-dimethylcyclohexanone) at 25 °C. For alkylations in ether, the resulting mixture was used directly. For alkylations in hexane, the ether was distilled through a cannula under a gentle argon flow.

Alkylations of Potassiocyclohexanone and 2,6-Dimethylpotassiocyclohexanone. All reactions in Tables I and II except no. 10 were allowed to warm with stirring to 25 °C before

(1) House, H. O. *Rec. Chem. Prog.* 1967, 28, 98.(2) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; p 737.(3) (a) Howells, R. D.; McCown, J. D. *Chem. Rev.* 1977, 77, 69. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* 1982, 85.(4) Hubbard, J. S.; Harris, T. M. *J. Am. Chem. Soc.* 1980, 102, 2110.

workup. HCl (2.6 M) was added to pH 2, then solid NaHCO₃ to pH 7-8, and then solid NaCl until the aqueous layer was saturated. The organic layer was separated, and the aqueous layer was extracted 4 × 10 mL ether. The combined organic layers were dried (MgSO₄). The bulk of the solvent was removed by fractional distillation, and the residue was analyzed by analytical and preparative GC (except for reaction 3, where the products were not sufficiently volatile) and ¹H and ¹³C (APT) NMR. GC retention times for cyclohexanones at 225 °C were as follows: cyclohexanone, 2.5 min; 2-methyl, 3.0 min; 2-ethyl and 2,2- and 2,6-dimethyls, 3.5 min; 2,2,6-trimethyl, 3.8 min; 2,2,6,6-tetramethylcyclohexanone, 4.1 min; 2,2- and 2,6-diethyls, 6.0 min; 2-butyl, 6.5 min; 2,2-dibutyl, 17 min. The ¹H NMR spectra of cyclohexanone, 2-methylcyclohexanone, 2-ethylcyclohexanone, 2-*n*-butylcyclohexanone, and 2,2,6-trimethylcyclohexanone and the ¹³C NMR spectra of cyclohexanone, 2-methylcyclohexanone, and 2-*n*-butylcyclohexanone have been reported.⁵ NMR parameters used for the other compounds were as follows.

2-Ethylcyclohexanone: ¹³C NMR δ 11.0, 21.8, 24.2, 27.4, 32.9, 41.2, 51.6.

2-Benzylcyclohexanone: ¹H NMR δ 3.21 (dd, *J* = 13.5, 4.4 Hz, 1H); ¹³C NMR δ 24.8, 27.8, 33.2, 35.2, 41.9, 52.1, 125.6, 128.0, 128.8, 140.2, 212.0.

2,2-Dimethylcyclohexanone: ¹H NMR δ 1.11 (s, 6H); ¹³C NMR δ 21.4, 25.2, 27.6, 38.4, 41.1, 45.3, 213.7.

(*E*)-2,6-Dimethylcyclohexanone: ¹H NMR δ 1.10 (d, *J* = 6.9 Hz, 6H), 1.57 (m, 2H), 1.95 (m, 2H), 2.58 (sextet, *J* = 6.8 Hz, 2H); ¹³C NMR δ 15.9, 25.4, 34.6, 42.6.

(*Z*)-2,6-Dimethylcyclohexanone: ¹H NMR δ 1.01 (d, *J* = 6.4

Hz, 6H), 1.79 (m, 2H), 2.09 (m, 2H), 2.39 (sextet, *J* = 6.2 Hz, 2H); ¹³C NMR δ 14.5, 25.5, 37.2, 45.2, 214.4.

2,2-Di-*n*-butylcyclohexanone: ¹H NMR δ 0.89 (t, *J* = 7.1 Hz, 6H), 2.34 (br t, *J* = 6.7 Hz).

(*E*)- and (*Z*)-2,6-Di-*n*-butylcyclohexanone: ¹H NMR δ 0.89 (t, *J* = 7.1 Hz, 6H).

2,2-Dibenzylcyclohexanone: ¹H NMR δ 2.67 (d, *J* = 13.6 Hz, 2H), 3.08 (d, *J* = 13.6 Hz, 2H); ¹³C NMR δ 20.5, 25.5, 33.4, 34.6, 39.5, 53.7, 126.1, 127.7, 130.5, 137.3, 213.8.

(*Z*)-2,6-Dibenzylcyclohexanone: ¹³C NMR δ 52.6.

2,2,6-Trimethylcyclohexanone: ¹³C NMR δ 15.0, 21.6, 25.3, 25.7, 36.8, 40.8, 41.8, 45.2.

2,2,6,6-Tetramethylcyclohexanone: ¹H NMR δ 1.12 (s, 12H); ¹³C NMR δ 27.6, 40.2.

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Registry numbers supplied by authors: 2-ethylcyclohexanone, 64870-41-3; 2-*n*-butylcyclohexanone, 1126-18-7; 2-benzylcyclohexanone, 91603-45-1; 2,2-dimethylcyclohexanone, 1193-47-1; 2,6-dibenzylcyclohexanone, 36040-03-6.

Supplementary Material Available: ¹H and ¹³C (APT) NMR spectra of cyclohexanones (12 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.

(5) Sadtler Standard Spectra, Sadtler Research Laboratories, 3316 Spring Garden Street, Philadelphia, PA 19104.