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REGIOSPECIFIC PREPARATION OF THERMODYNAMIC SILYL ENOL ETHERS USING BROMOMAGNESIUM DIALKYLAMIDES

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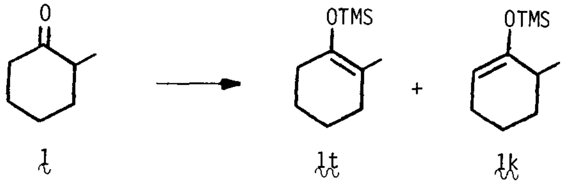
Abstract: Theromodynamic silyl enol ethers are regiospecifically generated in high yield from cyclic ketones, bromomagnesium diisopropylamide (BMDA) and trimethysilyl chloride.

There now exist a variety of mild and very selective procedures for the kinetic deprotonation of unsymmetrical ketones employing alkali metal dialkylamides. The "kinetic" enolates produced in this way may be efficiently trapped by trimethylsilyl chloride to regiospecifically provide the less substituted trimethylsilyl enol ethers.[1] Despite the recent introduction of several new methods, there are still no procedures available which allow direct[3] regiospecific preparation of the more substituted "thermodynamic" enolates or trimethylsilyl enol ethers.[4] The current state of this methodology is summarized in Table I.

We have found that the use of bromomagnesium dialkylamides provides a partial solution to this problem. These very mild reagents, known for several decades to be effective mediators

Table I. Preparation of Trimethylsilyl Enol Ethers from 2-methylcyclohexanone

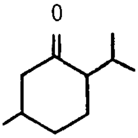
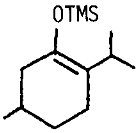
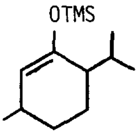
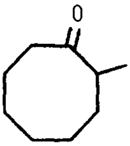
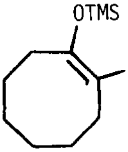
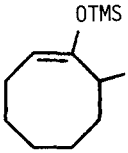
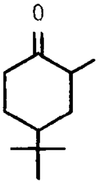
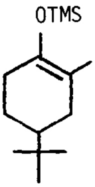
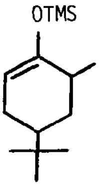


Reference	Reagents	Ratio (1t:1k)
2a	LDA/DME; TMSCl	1:99
2b	NaH/DME; TMSCl	73:27
2c	Et_3N/TMSCl/DMF, 130°	78:22
2d	$(nBu)_4NF/TMSCH_2CO_2Et$	82:18
2e	HMDS/TMSI	90:10
2f	KH/THF;TMSCl	67:33

of aldol type condensations,[5] may be used in conjunction with trimethylsilyl chloride to provide thermodynamic silyl enol ethers regiospecifically. This development now makes possible the preparation of thermodynamic enolates[6] under "kinetic" (non-equilibrating) conditions in aprotic media.

Bromomagnesium diisopropylamide (BMDA) may be conveniently prepared by treatment of an anhydrous[7] ethereal solution of diisopropylamine with an ethereal solution of methylmagnesium bromide at 25°C for 12h. Addition of an ethereal ketone solution to the resulting slurry (BMDA is essentially insoluble in ether) was followed by addition of trimethylsilyl chloride (TMSCl), triethylamine (Et_3N), and hexamethylphosphoramide (HMPA). Reaction times of 8-12h at 25°C were required for complete conversion to trimethylsilyl enol ethers. Results obtained using unsymmetrical cyclic ketones are listed in Table II.

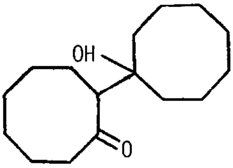
Table II. Formation of Trimethylsilyl Enol Ethers with BMDA/TMSCl/Et_3N

Ketone	Products	Ratio (t:k)[8]	Yield[9]
1	1t + 1k	97:3	95%
 2	 2t +  2k	97:3	97%
 3	 3t +  3k	95:5	85%
 4	 4t +  4k	97:3	95%

Substitution of other secondary amines for diisopropylamine led to different kinetic-thermodynamic enol ether ratios. Treatment of menthone (2) with bromomagnesium hexamethyldisilazide (BMHMDS) in ether produced a 96:4 ratio of **2t**:**2k** in 96% yield. Use of bromomagnesium dicyclohexylamide (BMDCA) was found to be less effective, leading to an 85:15 ratio of **2t**:**2k** in 88% yield. Tetramethylpiperidine was found to react very slowly with methylmagnesium bromide in ether. Addition of menthone (**2**) to this mixture after stirring for 12h at 25°C, followed by the TMSCl/Et_3N/HMPA trapping procedure as described above, provided tertiary alcohol (from addition of methylmagnesium bromide to menthone) as the major product (75%) along with 25% of a 1:1 mixture of **2t**:**2k**. Thus, it appears that BMDA and BMHMDS are the most effective of these bases for the preparation of thermodynamic enol ethers.

Use of solvents other than ether in this process gave rise to synthetically unacceptable mixtures of regioisomers. Treatment of 2-methylcyclohexanone (**1**) with BMDA/TMSCl/Et_3N/HMPA in THF produced a 23:77 ratio of **1t**:**1k**. When the reaction was conducted in DME solution a 13:87 ratio of **1t**:**1k** was obtained. Use of other bromomagnesium amide bases in THF or DME solution was also found to give mixtures of regioisomers.

The effectiveness of magnesium enolates as nucleophilic agents in the aldol condensation limits the methodology we describe to the preparation of trimethylsilyl enol ethers of relatively hindered ketones. With less substituted substrates than **1**-**4** products of aldol condensation predominate. For example, treatment of cyclooctanone with BMDA in ether *with or without* TMSCl/Et_3N/HMPA leads to the isolation of aldol product **5** in 72% yield.



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Due to solubility limitations, we have been unable to directly ascertain by NMR the distribution of magnesium enolates present prior to silylation. We are therefore unable to determine whether the high t:k ratio of silyl enol ethers obtained accurately represents the magnesium enolate composition. It is also possible that the observed regiospecificity is due in part to more rapid silylation of thermodynamic magnesium enolate than kinetic magnesium enolate.[10] This phenomenon, operating simultaneously with enolate equilibration, would then serve to shift the equilibrium further in favor of the thermodynamic enolate.

Nonetheless, it is now possible for the first time to selectively prepare the thermodynamic silyl enol ether from an unsymmetrical ketone *free from contamination by its kinetic regioisomer.* In view of methodology available for rapid and quantitative regeneration[6] of enolates from silyl enol ethers, we expect BMDA to become a standard reagent for organic synthesis. We have found this methodology to be extremely effective in a total synthesis to be reported in due course.

A typical experimental procedure follows:

1-trimethylsiloxy-2-methylcyclohexene (1t). To a solution of 0.7 mL (5 mmol) of diisopropylamine in 65 mL of anhydrous ether under N_2 at 25°C was added 1.95 mL of a 2.5 M ethereal solution (4.9 mmol) of methylmagnesium bromide. The mixture was stirred for 12h at 25°C, during which time a white suspension formed. A solution of 448 mg (4 mmol) of 2-methylcyclohexanone (1) in 12 mL of anhydrous ether was subsequently added. After 10-15 min, 1.6 mL (12 mmol) of TMSCl, 1.8 mL (13 mmol) of Et_3N, and 0.35 mL (2 mmol) of HMPA were added in that order. After stirring for ca. 8h at 25°C, the solution was diluted with ether, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated. The resulting oil was filtered through a plug of silica gel (10% ethyl acetate/hexane) to remove HMPA and remaining amines. Concentration of the eluant yielded 697 mg (95%) of chromatographically (TLC) homogeneous oil. NMR analysis (90 MHz, $CDCl_3$) showed a trace of vinyl proton absorption (4.8δ,t,J = 3Hz) corresponding to 1k. GC analysis (OV-101, 95°C) showed the mixture to contain 97% 1t and 3% 1k. The mixture could be distilled (Kugelrohr, 0.1 mm, 55°C) to provide 670 mg of colorless oil with no apparent improvement in purity.

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References and Notes

1. Recent reviews: (a) enolates: J. d'Angelo, Tetrahedron 32, 2979 (1976); L. M. Jackman and B. C. Lange, ibid. 33, 2737 (1977); (b) silyl enol ethers: J. K. Rasmussen, Synthesis 91 (1977).

2. (a) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem. 34, 2324 (1969); (b) G. Stork and P. F. Hudrlik, J. Am. Chem. Soc. 90, 4462 (1968); (c) Reference 2(a); (d) E. Nakamura, T. Mruofushi, M. Shimizu, I. Kuwajima, J. Am. Chem. Soc. 98, 2346 (1976); (e) R. D. Miller and D. R. McKean, Synthesis 730 (1979); (f) C. A. Brown, J. Org. Chem. 39, 3913 (1974).

3. It is sometimes possible to adjust the 1t:1k ratio by acid catalyzed equilibration of the silyl enol ether mixture; see reference 2(b).

4. Professor E. Negishi has recently found that use of KH/BEt_3 produces enoxyborates in a higher t:k ratio than previously reported for KH alone (reference 2(f). The regioselectivity observed by these workers appears to be only slightly less than we have obtained using BMDA. We thank Professor Negishi for informing us of his results prior to their publication.

5. W. J. Houlihan, Organic Reactions 16 (1968).

6. Lithium enolates may be rapidly and quantitatively regenerated from silyl enol ethers (CH_3Li/DME, reference 2(b)).

7. We have found that anhydrous, peroxide-free ether may be obtained most effectively by refluxing over LAH in a continuous distillation apparatus for at least five days prior to use.

8. Ratios were determined by ^1H NMR and GC (OV 101).

9. Isolated yields of chromatographically (TLC) homogeneous material.

10. Such selectivity has been observed in the alkylation of the lithium enolates of 2-methylcyclohexanone with ethyl iodide; D. Caine and B. J. L. Huff, Tetrahedron Lett. 4695 (1966).

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