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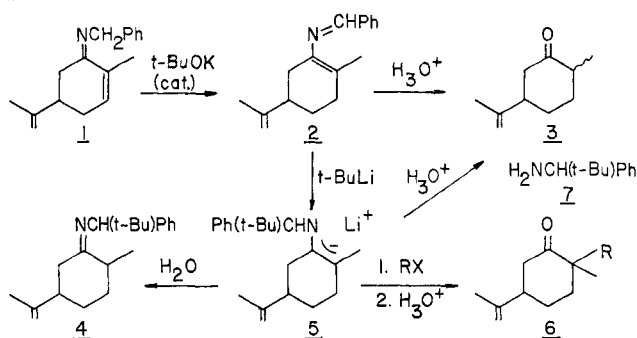
Received August 18, 1977

Regiospecific Generation of Lithioenamines from α,β -Unsaturated Imines. An Alternative Method for Reduction-Alkylation of Enones

Sir:

The demonstration¹ that ketone enolates can be regiospecifically generated from the dissolving metal reduction of enones has further enhanced the importance and utility of these organometallic intermediates in synthesis.² However, the adaptability of this reductive method to the preparation of regiospecifically alkylated ketones is often attenuated by the intrinsic reactivity of the enolate³ and its facile equilibration via proton transfer.⁴ Furthermore, since enolates generated in this fashion are more efficiently alkylated in a solvent other than liquid ammonia, a solvent exchange is frequently necessitated.⁵ In principle, these chemical and operational problems which lead to the formation of polyalkylated products, substrate over-reduction, and diminished regioselectivity could be circumvented by reduction of the imine derivatives of enones to the corresponding metaloenamines, intermediates of demonstrated versatility in synthesis.⁶ Our preliminary study of methods for effecting this unprecedented reduction-alkylation, processes which additionally represent the first ex-

Scheme I



amples of regiocontrolled metaloenamine preparations, is described herein.

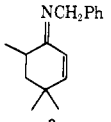
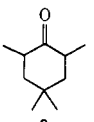
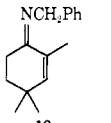
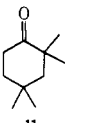
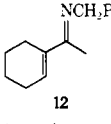
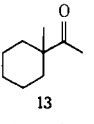
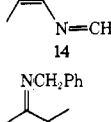
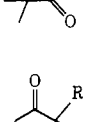
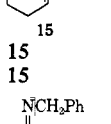
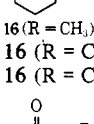
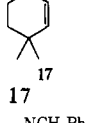
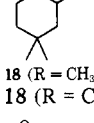
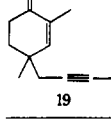
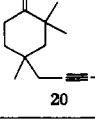
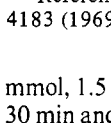
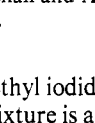
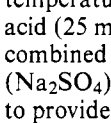
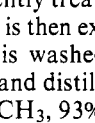
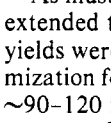
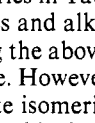
The present study is based on the finding⁷ that enones can be reduced to the corresponding ketones in yields of 40–77% via *N*-alkenylimine intermediates (Scheme I, **1** \rightarrow **2** \rightarrow **3**). Our anticipation that these intermediates could be nucleophilically trapped in situ, thereby regiospecifically generating metaloenamines, prompted our examination of this approach to the aforementioned objective.

Alkenylimine **2** is obtained in essentially quantitative yield by treatment of imine **1** with potassium *tert*-butoxide in anhydrous tetrahydrofuran (THF) at ambient temperature. When *tert*-butyllithium is added to the solution of imine **2**, metaloenamine **5** is readily formed as indicated by its conversion upon protonation (H_2O) to imine **4** and transformation (aqueous acid) to ketone **3** in >90% overall yield (distilled).^{8,9} Comparison of this result with the yield obtained using the previously reported imine isomerization-hydrolysis sequence (77%)⁷ or enone metal-ammonia reduction (66%,¹⁰ 61%^{4b}) illustrates the efficiency of this new variant. The crucial application of this concept to the reduction-alkylation objective was realized by the sequential addition of methyl iodide and aqueous acid to metaloenamine **5**, thereby providing the regiospecifically alkylated ketone **6** ($R = CH_3$) in an isolated yield of 93%. Trapping of imine **2** has also been effected with *sec*-BuLi, *n*-BuLi, and PhLi with only slight variation in overall efficiency (**1** \rightarrow **6** ($R = CH_3$); *sec*-BuLi, 90%; *n*-BuLi, 84%; and PhLi, 90%).

The regioselectivity of the above alkylation is contrasted and synthetically complemented by the finding⁶ that alkylation of metaloenamines derived from unsymmetrically substituted imines using conventional deprotonation procedures occurs preferentially or exclusively at the less substituted carbon center. For example, in contrast to the exclusive formation of ketone **6** ($R = CH_3$) noted above, 2,6-dimethyl-3-isopropenylcyclohexanone is the main product obtained when metaloenamine **5** is heated under reflux (THF, 16 h) with 0.1 mol equiv of water and the resulting mixture submitted to standard alkylation and hydrolysis procedures.¹¹ The regioselectivity of the present method is further demonstrated with imines **8** and **10** (Table I), which would be expected to provide a common mixture of alkylated products if metaloenamine equilibration were to occur. Upon examination, imines **8** and **10** are cleanly converted to ketones **9** and **11**, respectively, without any evidence of crossover. Finally, reduction-alkylation of imine **12**, a system which tests equilibration between a primary and tertiary center, provides ketone **13**. Similarly, imine **14** is regiospecifically converted to 3,3-dimethyl-2-butanone.¹²

The efficiency and regiospecificity of this one-flask reduction-alkylation method is augmented by the ease with which it is performed as typified in the following procedure. Thus, imine **1** (13.2 mmol) is added dropwise (1 min) to a stirred solution (ambient temperature) of potassium *tert*-butoxide (1.4 mmol) in anhydrous THF (43 mL). After 30 min, the solution is cooled to $-78^\circ C$ and treated with *tert*-butyllithium (20.5

Table I. Reduction-Alkylation of α , β -Unsaturated Imines

Imine	Alkylating agent	Product	This study, % yield (isol)	Previous studies; enone reduction-alkylation, % yield
1	CH ₃ I	6 (R = CH ₃)	93	
1	PhCH ₂ Br	6 (R = CH ₂ Ph)	86	
1	<i>n</i> -Bul	6 (R = <i>n</i> -Bu)	89	
	CH ₃ I		65	57 ^a
	CH ₃ I		92	43 ^a
	CH ₃ I		55	29 ^b
	CH ₃ I		93	
	CH ₃ I		67	60 ^a
	PhCH ₂ Br		85	60 ^a
	CH ₂ CHCH ₂ Br		70	
	CH ₃ I		67	21 ^c
	PhCH ₂ Br		58	
	CH ₃ I		85	

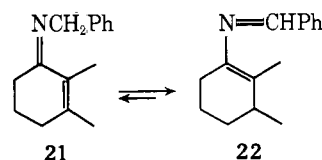
^aReference 4b. ^bJ. A. Marshall and A. E. Greene, *Tetrahedron*, 4183 (1969). ^cReference 4 c.

mmol, 1.5 M pentane). Methyl iodide (31 mmol) is added after 30 min and the resulting mixture is allowed to warm to ambient temperature and subsequently treated with 2 N hydrochloric acid (25 mL). The mixture is then extracted with ether and the combined organic phase is washed with dilute acid, dried (Na₂SO₄), concentrated, and distilled (bp 110 °C (27 mm)) to provide ketone **6** (R = CH₃, 93%).

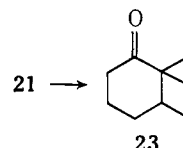
As illustrated by the entries in Table I, the method is readily extended to various enones and alkylating agents. The listed yields were obtained using the above procedure without optimization for each substrate. However, imines **8** and **17** require ~90–120 min for complete isomerization, although a larger amount of catalyst reduces this time substantially. As can be seen from the listings in the last two columns, the yields obtained using the present method compare favorably with those previously reported for the corresponding metal–ammonia reduction–alkylation of enones. Finally, it is important to note that *reduction* in the context of the present method is determined by an isomerization–trapping sequence rather than the

reduction potential of the enone as in the case of metal–ammonia-based processes. As such, certain functionalities such as nonterminal acetylenes, which would be reduced or require special experimental control¹³ with direct reduction, are compatible with the chemistry used in the present method (e.g., imine **19**).

The position of the α,β -unsaturated imine–alkenylimine equilibrium poses a potential limitation of the generality of the above method. For example, upon equilibration, imine **21** gives approximately a 1:2 mixture of imines **21** and **22**, respectively.



We have found in related studies that this problem can be circumvented by the prior introduction of substituents (e.g., OMe) on the aromatic moiety which further displace the equilibrium to the isomerized imine. However, a more straightforward solution to this problem is obtained by the direct reduction of the α,β -unsaturated imine.¹⁴ Thus, addition of imine **21** to lithium–ammonia followed by alkylation and hydrolysis directly provides ketone **23**. While this expedient



returns the reduction process to the dissolving metal milieu, it retains the conspicuous advantages of regiocontrolled metalloenamine generation and alkylation.

In addition to the features noted above, the present methods use new strategies for metalloenamine formation which allow for the generation of hitherto inaccessible systems and, as such, expand the repertoire of methods based on these intermediates.⁶ Further synthetic ramifications of this methodology include reduction–alkylation of the imines of epoxy ketones, α -halo ketones, and unsaturated aldehydes as well as isomerization–alkylation of *N*-allylimines of aryl aldehydes.¹² Studies in these and related areas are in progress.

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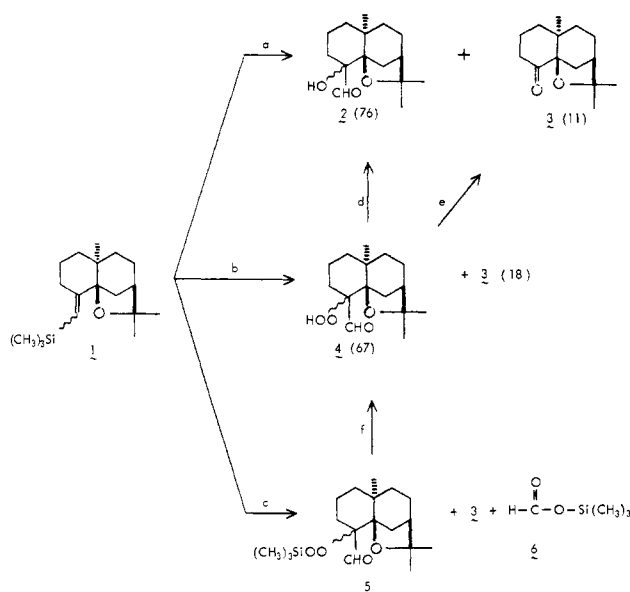
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Ozonolysis of Vinylsilanes

Sir:

Ozonolysis, discovered as early as 1855, remains one of the most efficient and economical methods to cleave carbon-carbon multiple bonds.¹ It appeared to be suitable for the degradation of vinylsilane **1**² to the norketone **3**,³ but ozonization in methanol followed by hydrolytic decomposition of intermediates afforded 67% α -hydroperoxy aldehyde **4** and only 18% anticipated ketone **3** (Scheme I). Reductive workup after ozonization gave mainly the α -hydroxy aldehyde **2** and again only minor amounts of the ketone **3**. In carbon tetrachloride ozonolysis of **1** produced some formic acid trimethylsilyl ester (**6**), an equivalent amount of ketone **3**, and an unstable substance that was not isolated in pure form. Tenta-

Scheme I



^a O₃, CH₃OH, -20 °C; KI, AcOH. ^b O₃, CH₃OH, -20 °C; H₂O, 24 h, 20 °C. ^c O₃, CCl₄, -15 °C. ^d P(OCH₃)₃, CH₃OH, 20 min, 20 °C. ^e VPC, 260 °C. ^f H₂O. NMR spectra in CCl₄, chemical shifts in δ ; IR spectra in CHCl₃. **2**: mp 53 °C. **3**: mp 55 °C; [α]_D²⁵ -115° (CHCl₃). **4**: mp 152 °C; IR 3250, 1735 cm⁻¹. **5**: IR 1740 cm⁻¹; NMR 9.50 (1 H, s), 0.17 (9 H, s). **6**: IR 1710 cm⁻¹; NMR 7.90 (1 H, s), 0.32 (9 H, s). Yields are given in parentheses.

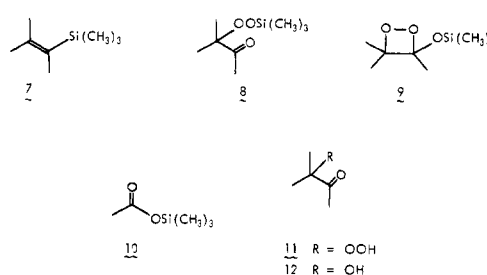
Table I

Silane	Conditions	Product	Yield, %
	a		73
	b		74
	c		70
	b		73
	c		33 ^e
	b		69
	d		64
	a		54
	a		30

^a O₃, 9:1 CH₃OH-CH₂Cl₂, -20 °C; (CH₃)₂S, 3 h, 20 °C. ^b O₃, EtOH, -15 °C; NaBH₄. ^c O₃, 9:1 CH₃OH-CH₂Cl₂, -20 °C; H₂O, 24 h, 20 °C. ^d O₃, 9:1 CH₃OH-CH₂Cl₂, -15 °C; (CH₃)₂S, HCl-(OCH₃)₃, *p*-TSA, 24 h, 20 °C. ^e Also formed in low yields were 2-hydroxycyclohexanone, 6-oxoadipic acid, and adipic acid monomethyl ester.

tive evidence in favor of structure **5** is based on spectra obtained of the original reaction mixture and hydrolysis to **4**. To gain insight into the mechanism of these unforeseen ozonizations and to determine the structures of intermediates, we studied the behavior of trimethyl(1,2-dimethyl-1-propenyl)silane (**7**) toward ozone in some detail. This substance was prepared from the corresponding vinyl chloride⁴ and trimethylsilyl chloride with sodium in ether (35% yield).⁵

In carbon tetrachloride solution vinylsilane **7** was stable to oxygen (6 h, 20 °C), but in methylene chloride solution at -5 °C it was rapidly consumed by ozone. Distillation (bp <20 °C (0.1 mm)) served to separate substances of low molecular weight from polymeric material. Acetic acid trimethylsilyl ester (**10**, 17%) was isolated from the lowest boiling fraction



and rapid chromatography on silica gel at -30 °C using 98:2 pentane-ether as eluent allowed the separation of two less volatile compounds. The less polar (15%; IR (CHCl₃) 1250, 860 cm⁻¹; ¹H NMR (CCl₄) δ 0.22 (s, 9), 1.37 (s, 3), 1.48 (s, 3), 1.51 (s, 3); ¹³C NMR (CDCl₃) δ 109.43, 91.80, 23.46, 22.01, 1.33) was identified as the dioxetane **9**. Its thermolysis⁶ (CCl₄, 75 °C, 45 min) proceeded with chemiluminescence⁶ which was particularly striking in the presence of 9,10-dibromoanthracene as a fluorescer.⁷ Acetone and acetic acid trimethylsilyl ester (**10**) were the almost exclusive products formed.

The more polar substance produced in the ozonolysis of **7** turned out to be the α -trimethylsilylperoxy ketone **8**: 25%; IR (CHCl₃) 1720, 1250, 900, 860 cm⁻¹; ¹H NMR (CCl₄) δ 0.18 (s, 9), 1.23 (s, 6), 2.15 (s, 3); ¹³C NMR (CDCl₃) δ 211.79, 87.64, 23.91, 21.21, -1.50. In contrast to the dioxetane **9**, the