directly from the high-pressure cycloaddition was reduced and desulfurized in one step over Raney nickel in refluxing ethyl acetate, and cantharidin was isolated in 63% from **2** by one recrystallization (EtOAc).

Not surprisingly, in view of the previously cited thermal instability of furan Diels–Alder reaction products, this present reaction sequence could not be achieved by thermal activation. The heating of furan and dienophile **2** at 110 °C led to no reaction, while heating to 200 °C resulted in decomposition of **2** to give a black tar with a strong sulfur odor. The adduct **3** also decomposed in less than 15 min at 200 °C. Therefore, it must be concluded that the production of adduct **3** is only possible at elevated pressures.

The scale on which this cycloaddition can be performed is limited by the solubility of **2** (less than 60 mg/mL in CH_2Cl_2) and the size of the high-pressure apparatus. The Berkeley apparatus is capable of holding a 70-mL volume at 15 kbar; however, the employment of lower pressures allows the use of equipment with much larger usable volume. Furthermore, the solubility of **2** is approximately twice as great in acetonitrile and in acetone as it is in methylene chloride. A survey of the high-pressure cycloaddition of **2** and furan in three solvents at three pressures was made, and the results are given in Table I.

The reaction proceeded cleanly at all pressures in methylene chloride which is still liquid at 15 kbar.[12] The reaction is also clean in acetone at 4 and 8 kbar; however, at 15 kbar, the NMR spectrum of the crude reaction mixture could not be interpreted quantitatively, due to large amounts of unidentified reaction products. In acetonitrile, the same unidentified products were produced at 15 kbar, and, in addition, 12% of the dicarboxylic acid of **2** was formed at 8 kbar. This same diacid was formed in many of the reactions run in acetonitrile, and this hydrolysis, accelerated by pressure, is ascribed to traces of water which are difficult to remove from the solvent. The unidentified products formed at the higher pressures may be the result of the addition of furan to the initially formed adducts **3** and **4**; analogous results have been observed in the high-pressure reaction of furan with quinones.[13] Since both pure acetone and acetonitrile are solid at 15 kbar,[12] the formation of the products may be due to reaction in the solid state.

This work represents the first total synthesis of cantharidin which would be feasible on a large scale. Forty years after the first synthesis, the utilization of high-pressure acceleration of reactions which possess a $-\Delta V^{*}$ combined with careful selection of reactants and reaction conditions to achieve maximum utilization of the volume parameter has allowed the achievement of a simple synthesis of cantharidin in accord with its simple structure.

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(11) An authentic sample of cantharidin was kindly supplied by Dr. J. Muchowski.

(12) Bridgeman, P. W. "The Physics of High Pressure", Bell and Sons: London, 1949.

(13) Dauben, W. G.; Moreland, D. W., unpublished results.

(14) NIH Postdoctoral Fellow, 1979–present.

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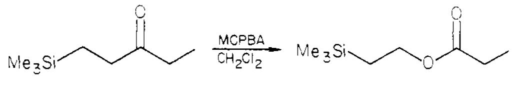
Silicon-Directed Baeyer–Villiger Reactions. Stereospecific Synthesis of Olefinic Acids and Esters[1]

Sir:

A considerable body of evidence indicates that cations β to silicon in organosilicon compounds are considerably stabilized by the silicon.[2,3] We have been interested in the possibility that this stabilization can be used to direct some types of carbon–carbon bond cleavage reactions. We have therefore been investigating the Baeyer–Villiger reactions of β-silyl ketones (γ-ketosilanes), as the migratory aptitude in Baeyer–Villiger reactions appears to be related to the ability of a group to bear a positive charge.[4] Here we report that Baeyer–Villiger reactions of a number of β-trimethylsilyl ketones are directed by the trimethylsilyl group to give esters of β-hydroxysilanes in accord with this rationale, and that this reaction is useful for the synthesis of olefinic acids and esters.

In a preliminary observation, we found that the Baeyer–Villiger reaction of 1-(trimethylsilyl)-3-pentanone[5] with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 produced what appeared (by NMR) to be β-(trimethylsilyl)ethyl propionate,[6] the ester of a β-hydroxysilane (eq 1). Since β-hydroxysilanes are readily convertible to olefins by β-elimination reactions,[3,7] the silicon-substituted lactones resulting from Baeyer–Villiger reactions of *cyclic* β-silyl ketones should be useful precursors to olefinic acids and, in principle, other olefinic compounds. We have therefore studied the Baeyer–Villiger reactions of silyl ketones **1**, **5a**, and **5b**.



(1)

Silyl ketone **1**[8] was prepared from the cyclohexylamine imine of cyclohexanone by alkylation of the bromomagnesium salt[9] with Me_3SiCH_2Cl followed by hydrolysis of the product with aqueous acetic acid. Silyl ketones **5a** and **5b** were prepared from cyclohexenone by reaction with Me_3SiLi, followed by protonation (MeOH) or alkylation (MeI), respectively, as reported by Still.[10,11]

Treatment of silyl ketones **1** and **5a** with MCPBA in CH_2Cl_2 in the presence of Na_2HPO_4 buffer produced the silyl lactones **2**[8] and **6a**[8] in yields of 96% and 99%, respectively (Scheme I). The structures of the lactones were assigned from their spectra and from their conversion to olefinic acids and esters as discussed below. It should be noted that, in the absence of any directive effect of silicon, a mixture of two lactones would have been expected from silyl ketone **5a**. Only one lactone (**6a**) was obtained; the virtual absence of its regioisomer was shown by its conversion to silicon-free products as discussed below.

Saponification of the lactones yielded β-hydroxysilane acids **3a**[8a] (from **2**) and **7a**[8a] (from **6a**), which were treated (without

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[1] Portions of this work were presented at the 12th Organosilicon Symposium, Ames, IA, March 1978, and at the 178th National Meeting of the American Chemical Society, Washington, DC, September 1979, Abstr. ORGN 244.

(2) (a) A. W. P. Jarvie, *Organomet. Chem. Rev., Sect. A*, **6**, 153–207 (1970). (b) Cations β to other electropositive atoms in organometallic compounds also appear to be stabilized. The effectiveness of this stabilization is presumably related to the ability of the carbon–metal bond to overlap with the empty orbital of the cationic center—see T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton, and R. S. Brown, *J. Am. Chem. Soc.*, **93**, 5715–5725 (1971), and references cited therein.

(3) For recent reviews on the properties of organosilicon compounds and their use in organic synthesis, see (a) P. F. Hudrlik in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, 1976, pp 127–159; (b) E. W. Colvin, *Chem. Soc. Rev.*, **7**, 15–64 (1978); (c) P. F. Hudrlik and A. M. Hudrlik, "Silicon Compounds—Register and Review", Petrarch Systems, Inc., Levittown, PA, 1979, pp 25–32; (d) I. Fleming, "Comprehensive Organic Chemistry", Vol. 3, D. H. R. Barton, Ed., Pergamon Press, Oxford, 1979, pp 541–686.

(4) Reviews of the Baeyer–Villiger reaction: (a) C. H. Hassall, *Org. React. (N.Y.)*, 73–106 (1957); (b) P. A. S. Smith, "Molecular Rearrangements", Part 1, P. de Mays, Ed., Wiley-Interscience, New York, 1963, pp 577–589. Strongly electronegative groups γ to carbonyl have recently been found to partially direct the Baeyer–Villiger reaction: R. Noyori, T. Sato, and H. Kobayashi, *Tetrahedron Lett.*, 2569–2572 (1980).

(5) P. F. Hudrlik and G. P. Withers, *Tetrahedron Lett.*, 29–32 (1976).

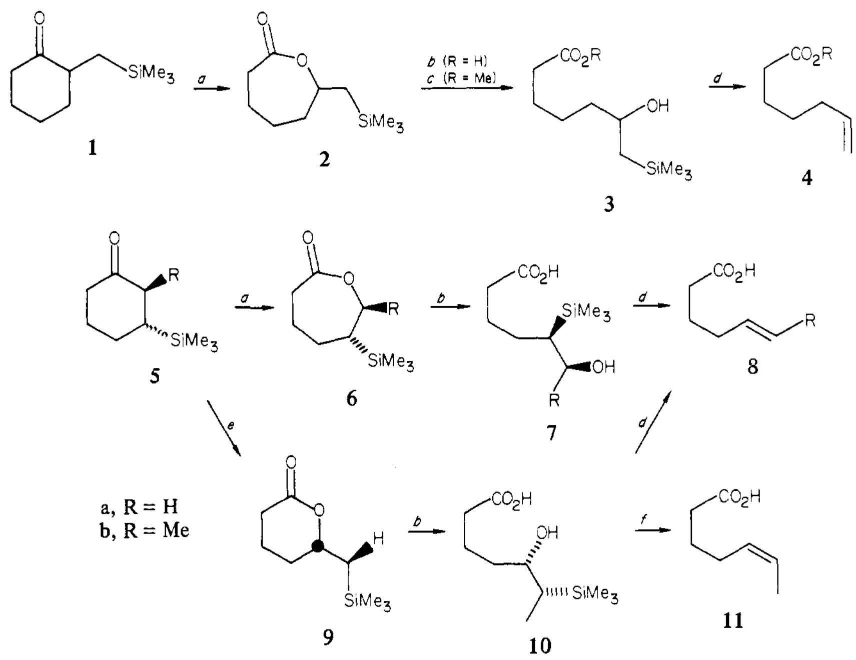
(6) The pertinent features of the NMR spectrum (CH_2Cl_2) were a triplet at δ 4.13 (J = 7 Hz, $-CH_2-O$) and a quartet at δ 2.25 (J = 7 Hz, $-CH_2CO$).

(7) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464–1468 (1975); P. F. Hudrlik, D. Peterson, and R. J. Rona, *J. Org. Chem.*, **40**, 2263–2264 (1975).

(8) The (a) IR and NMR spectra and (b) high-resolution mass spectrum were in agreement with the proposed structure.

(9) For the alkylation of imine salts, see G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178–2180 (1963). See also P. F. Hudrlik and C.-N. Wan, *J. Org. Chem.*, **40**, 2963–2965 (1975).

Scheme I



^{a} MCPBA, Na_2HPO_4, CH_2Cl_2, 4 h, room temp. ^{b} KOH, MeOH, H_2O, 4-12 h, room temp. ^{c} NaOMe, MeOH, 1 h, room temp. ^{d} $BF_3{\cdot}Et_2O$, CH_2Cl_2, 1-2 h, 0 °C. ^{e} (R = Me) MCPBA, CH_2Cl_2, 4 h, room temp. ^{f} KH, THF, 5 h, room temp.

purification) with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (causing β elimination) to give the olefinic acids **4a**[12] (85.5% from **2**) and **8a**[12,13] (80.5% from **6a**). The NMR spectra of olefinic acids **4a** and **8a** before distillation showed essentially no Me_3Si protons, indicating the Baeyer–Villiger reactions were highly (>99%) regioselective.[14] A test of the possibility of opening the lactones with other nucleophiles was made by treating lactone **2** (crude) with NaOMe in MeOH producing β-hydroxysilane **3b**,[8a] which was treated (without purification) with $BF_3{\cdot}Et_2O$ to give olefinic ester **4b**[15] in 75% overall yield from silyl ketone **1**.

We have studied the Baeyer–Villiger reaction of the α-substituted β-silyl ketone **5b** to determine the stereospecificity of the reaction sequence. We found that the initial silyl lactone product was too unstable to be a useful precursor to olefinic carbonyl compounds of defined geometry. However, it underwent a novel stereospecific rearrangement to yield an isomeric silyl lactone which is an efficient precursor to olefinic carbonyl compounds. Thus, treatment of silyl ketone **5b** with MCPBA under the above conditions (i.e., with Na_2HPO_4 buffer) yielded lactone **6b** as an unstable product frequently contaminated with the isomeric lactone **9**.[16] Saponification of the crude product yielded β-hydroxysilane acid (contaminated with olefin, presumably **8b**, by NMR). Treatment (without purification) with $BF_3{\cdot}Et_2O$ (to effect anti-β elimination)[7] yielded trans olefinic acid **8b**[17] (~100% trans, 75% yield from silyl ketone **5b**), but treatment with KH (to effect syn-β elimination)[7] produced mixtures of cis and trans olefinic acids **11** and **8b** (in varying ratios).[18,19]

Baeyer–Villiger reaction of silyl ketone **5b**, carried out with MCPBA in the *absence* of the Na_2HPO_4 buffer, produced only silyl lactone **9**. In contrast to lactone **6b**, lactone **9** was stable to VPC analysis and to distillation (although it was normally used without purification). Saponification yielded a β-hydroxysilane acid which was readily converted to trans olefinic acid **8b**[18,19,20a] (~100% trans, 63% yield from silyl ketone **5b**) upon treatment with $BF_3{\cdot}Et_2O$, and to cis olefinic acid **11**[18,19,20b] (96.5% cis, 62% yield from silyl ketone **5b**) upon treatment with KH. The yields have not been optimized.

The structures of lactones **6b** and **9** were assigned on the basis of the above reactions, their spectra,[21] and their conversion to 6- and 5-ketoheptanoic acids, respectively [by saponification (KOH/MeOH) followed by oxidation (CrO_3/pyridine) and treatment with aqueous NaOH].[22]

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(10) W. C. Still, *J. Org. Chem.*, **41**, 3063–3064 (1976).

(11) For other routes to β-silyl ketones, see references cited in ref 5 and 10, and D. J. Ager and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 177–178 (1978).

(12) G. M. Rubottom, R. Marrero, D. S. Krueger, and J. L. Schreiner, *Tetrahedron Lett.*, 4013–4016 (1977). The IR and NMR spectra were essentially identical with those supplied by Professor Rubottom for this compound.

(13) The IR and NMR spectra and VPC retention time were identical with those of a commercial sample (Sapon Laboratories).

(14) In the β-elimination reactions **3a** → **4a** and **7a** → **8a**, the Me_3Si group ends up in volatile products such as $Me_3SiOSiMe_3$. The β-silyl acids expected to result from saponification of the regioisomeric lactones would not be expected to lose Me_3Si on treatment with $BF_3{\cdot}Et_2O$.

(15) R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4361–4364 (1977). The IR and NMR spectra were essentially identical with those supplied by Professor Smith for this compound.

(16) The proportion of the two lactones in the reaction product was found to be sensitive to the workup procedure. The usual procedure, decomposition of excess peracid with aqueous $NaHSO_3$ (followed by base wash of the organic layer), led to mixtures of **6b** and **9** of varying composition. Decomposition of excess peracid with aqueous $Na_2S_2O_3$ or aqueous Na_2SO_3 (followed by base wash) led predominantly to **6b**.

(17) *p*-Bromophenacyl ester mp 61–61.5 °C (lit.[18] mp 60–61 °C).

(18) Both *cis*- and *trans*-5-heptenoic acids and their *p*-bromophenacyl esters have been reported: M. F. Ansell, J. C. Emmett, and R. V. Coombs, *J. Chem. Soc. C*, 217–225 (1968).

(19) The isomeric purity of olefinic acids **8b** and **11** was determined by VPC analysis of their derived methyl esters,[8a] prepared by treatment of the acids with CH_2N_2. For a previous report of 5-heptenoic acid, methyl ester, see C. J. Albisetti, N. G. Fisher, M. J. Hogsed, and R. M. Joyce, *J. Am. Chem. Soc.*, **78**, 2637–2641 (1956).

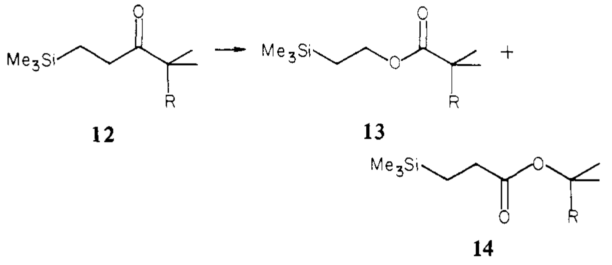
(20) (a) *p*-Bromophenacyl ester mp 62 °C (lit.[18] mp 60–61 °C); (b) *p*-bromophenacyl ester mp 49–50 °C (lit.[18] mp 49–50 °C).

(21) The six-membered lactone **9** had the following data: IR (film) 2970, 1740, 1250, 835 cm^{-1}; NMR (CCl_4) δ 4.25 (m, 1 H, >CH–O), 2.25 (m, 2 H, $-CH_2CO$), broad absorption centered at 1.6 overlapping with broad singlet at 0.90 (total integration 8 H), –0.05 (s, 9 H, Me_3Si); mass spectrum, *m/e* (rel intensity) 204 (presumed impurity, 1), 200.12363 (M^+, 1) (calcd for $C_{10}H_{20}O_2Si$: 200.12326), 185 (9), 117 (68), 75 (100), 73 (79). The seven-membered lactone **6b** had an IR spectrum similar to that of lactone **9** with small differences in the fingerprint region, especially from 900–1300 cm^{-1}. The NMR spectrum (CCl_4) showed δ 4.37 (m, >CH–O), 2.47 (m, $-CH_2CO$), 1.30 (d, J = 6.5 Hz, CH_3), 0.00 (s, Me_3Si).

The formation of lactone **9**, although unexpected, is easily explained in terms of acid-catalyzed ring opening of lactone **6b** with 1,2-migration of Me_3Si and ring closure to the more stable **9**. 1,2-Shifts of Me_3Si groups to cationic centers are known in simple systems,[28] but their stereochemistry has not been investigated. The fact that both cis and trans olefinic acids were obtained in high purity from lactone **9** indicates that the silicon migration observed here was highly stereospecific.

The rearrangement of lactone **6b** to lactone **9** occurs under very mild conditions. A mixture of **6b** and **9** (approximately 3:2 by NMR) in CCl_4 solution (with $CHCl_3$ internal standard) was almost completely transformed into lactone **9** after 9 days at room temperature. The lability of lactone **6b** may in part be due to the fact that in a preferred conformation of **6b** (by analysis of molecular models) the C–Si and C–O bonds are in the anti conformation favored for acid-catalyzed β elimination. In lactone **9**, the Me_3Si group is not conformationally constrained, and the anti conformation, although easily achieved, should not be particularly favored. It should be noted that this rearrangement transfers the stereochemistry easily established in a cyclic system to a system having silicon attached to a side chain, which otherwise would not be easily prepared with defined stereochemistry.

In order to test the magnitude of the directive effect of silicon in the Baeyer–Villiger reactions of β-silyl ketones, we have studied the Baeyer–Villiger reactions of silyl ketones **12a** and **12b**.[29] Ketone **12a** gave a 2:1 ratio of esters **13a**[8] and **14a**[8] in 80% yield, while ketone **12b** gave a 1:2 ratio of esters **13b**[8] and **14b**[8] in 79% yield (eq 2).[31] Thus, in these compounds, the migratory aptitude of $Me_3SiCH_2CH_2$– is intermediate between that of secondary and tertiary alkyl groups.[32]



12 **13** **14**

a, R = H
b, R = Me

(2)

This work demonstrates that silicon can direct the Baeyer–Villiger reactions of β-silyl ketones[33] and that the products resulting from cyclic β-silyl ketones can be transformed into olefinic acids and esters. We expect these reactions will have a number of applications in organic synthesis, for example, for insect pheromones and for the olefinic acid side chain in many prostaglandins.

Acknowledgment. We thank the NIH Minority Biomedical Support Program, the National Science Foundation, Dow Corning Corporation, and the National Cancer Institute for their financial support, and we thank Professors A. B. Smith and G. M. Rubottom for comparison spectra. High-resolution mass spectral determinations were carried out at the MIT mass spectroscopy laboratory supported by NIH Grant RR00317 from the Biotechnology Resources Branch, Division of Research Resources (Principal Investigator: Professor K. Biemann).

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[22] The product obtained from lactone **9** was identified as 5-ketoheptanoic acid by comparison of its IR and NMR spectra with those of an independently prepared sample of 5-ketoheptanoic acid[23] and by its mp (50–51 °C) and the mp of its semicarbazone (179–180 °C, not depressed when mixed with an independently prepared sample[23]). The product obtained from lactone **6b** contaminated with lactone **9** (from the buffered Baeyer–Villiger reaction of **5b**) was identified as a mixture of 5- and 6-ketoheptanoic acids (with some olefinic acid) by comparison of its IR and NMR spectra and VPC retention times with those of independently prepared samples of 5-[23] and 6-ketoheptanoic[25] acids.

[23] A comparison sample of 5-ketoheptanoic acid was prepared from cyclopentanone by (1) treatment with EtMgBr, (2) dehydration of the product with oxalic acid, and (3) oxidation with $KMnO_4$. The final product had mp 50–51 °C (lit.[24] mp 51–52 °C); semicarbazone mp 180–181 °C (lit.[24] mp 186–188 °C).

[24] S. G. Levine, *J. Am. Chem. Soc.*, **82**, 2556–2559 (1960).

[25] A comparison sample of 6-ketoheptanoic acid was prepared from 2-methylcyclohexanone by (1) Baeyer–Villiger oxidation with MCPBA, (2) saponification with $KOH/MeOH/H_2O$, and (3) oxidation with CrO_3/pyridine. The final product had mp 31–32 °C (lit.[26] mp 33–34 °C); semicarbazone mp 142–143 °C (lit.[27] mp 144–145 °C).

[26] R. M. Acheson, *J. Chem. Soc.*, 4232–4237 (1956).

[27] G. Foster and W. J. Hickinbottom, *J. Chem. Soc.*, 215–218 (1960).

[28] M. A. Cook, C. Eaborn, and D. R. M. Walton, *J. Organomet. Chem.*, **24**, 301–306 (1970); A. J. Bourne and A. W. P. Jarvie, *ibid.*, **24**, 335–340 (1970); see also ref 2a, p 188.

[29] Ketones **12a**[8a,30] and **12b**[8] were prepared from the cyclohexylamine imines of methyl isopropyl ketone and pinacolone, respectively, by reaction with i-Pr_2NLi, Me_3SiCH_2Cl, and acetic acid (hydrolysis) (cf. the preparation of ketone **1**).

[30] D. N. Andreev and E. V. Kukharskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1397-1398 (1958); *Chem. Abstr.*, **53**, 6992 (1959); see also V. Bažant, V. Chvalovský, and J. Rathouský, "Organosilicon Compounds", Academic Press, New York, 1965, Volume 2, Part 1, p 347.

[31] The Baeyer–Villiger reaction of **12b** with MCPBA at room temperature was quite sluggish and was more conveniently carried out at reflux (in CH_2Cl_2) in the presence of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) to minimize decomposition of the peracid [cf. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64–65 (1972)]. We thank Dr. R. H. Ellison for bringing this reference to our attention and for a sample of this compound.

[32] Baeyer–Villiger reactions of methyl isopropyl ketone and pinacolone under similar conditions gave isopropyl acetate and *tert*-butyl acetate, respectively, as expected.

[33] The possibility that a β-trimethylsilyl group might accelerate the Baeyer–Villiger reaction is also of interest. Rate acceleration might be expected if rearrangement were rate determining. [This might be the case for some ketones under some conditions—see ref 4b, and B. W. Palmer and A. Fry, *J. Am. Chem. Soc.*, **92**, 2580–2581 (1970).] In our work, the Me_3Si group appears to have little effect on the rate of reaction. The reactivities of silyl ketones **1** and **5b** were quite similar to that of 2-methylcyclohexanone, and the reactivity of silyl ketone **12a** was quite similar to that of methyl isopropyl ketone. Silyl ketone **5a** was slightly more reactive than cyclohexanone (for example, after 10 min at room temperature, 65% and 18% reacted, respectively), and silyl ketone **12b** was somewhat less reactive than pinacolone.

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Competitive Condensation and Proton-Transfer Processes in the Reaction of t-$C_4H_9^+$ Ions with Ammonia in Gaseous Systems at Atmospheric Pressure

Sir:

The gas-phase reaction of alkyl cations with ammonia and amines has been recently developed into a general mechanistic model for a wide class of ion–polar molecule interactions, as a result of detailed mass spectrometric and theoretical studies.[1-5]

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[1] Hellner, L.; Sieck, L. W. *J. Res. Natl. Bur. Stand., Sect. A* **1971**, *75*, 487–492.

[2] Su, T.; Bowers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 7611–7613.

[3] Chesnavich, W. J.; Su, T.; Bowers, M. T. *J. Am. Chem. Soc.* **1977**, *100*, 4362–4366.

[4] Meot-Ner (Mautner), M. In "Gas Phase Ion Chemistry"; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 1, p 254.