Adventures in Silicon–Organic Chemistry†

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A. Nucleoside Syntheses

1. Silyl-Hilbert–Johnson Reaction in the Presence of $SnCl_4$. On joining the pharmaceutical research laboratories of Schering AG in 1966, I started a research program in antiviral chemotherapy and became thus interested in the synthesis and modification of nucleosides. From all the methods of nucleoside synthesis available at that time the silyl-Hilbert–Johnson method introduced by Birkofer[1,2] and further developed by Nishimura[3,4] and Wittenburg[5,6] seemed to be the most practical one.

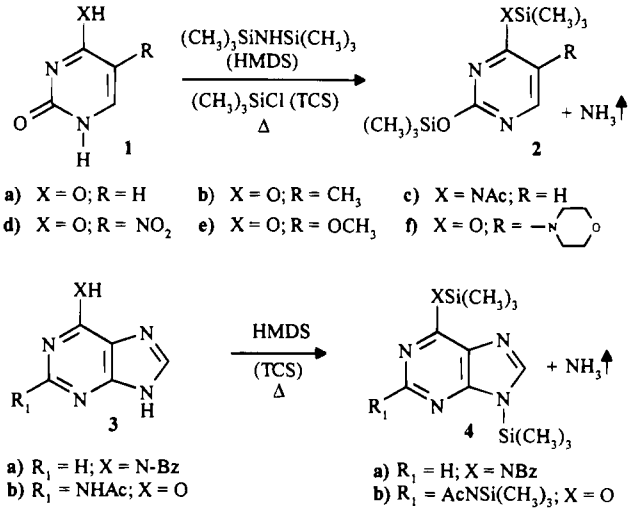
Polar and rather insoluble heterocyclic pyrimidine bases such as uracil (**1a**), thymine (**1b**), or N^4-acetylcytosine (**1c**) are converted by silylation with hexamethyldisilazane (HMDS) and traces of acidic catalysts such as trimethylchlorosilane (TCS) into the lipophilic, thermally quite stable basic and volatile bis-(silyl) compounds **2** (Scheme 1). Due to the mobility of the trimethylsilyl groups the most stable O-trimethylsilylated aromatic heterocycles **2** are always formed, which are rapidly hydrolyzed by water to the starting bases **1**. The even more polar purine bases N^6-benzoyladenine (**3a**) or N^2-acetylguanine (**3b**) afford analogously the stable lipophilic and volatile silyl compounds **4**.

The silylated bases **2** (or **4**) react either on heating to 100 °C or in the presence of catalysts such as $HgBr_2$ at 20–80 °C in benzene with protected 1-halogen sugars such as **6a** (X = Cl) to give the corresponding protected nucleosides such as **7**.

When we heated persilylated 6-azauracil **5** with **6a** in the presence of $HgBr_2$ in benzene, we obtained after workup and chromatography only a 60% yield of the desired 6-azauridine 2′,3′,5′-tri-*O*-benzoate (**7**), along with a number of colored, presumably mercury-containing impurities[7,8] (Scheme 2).

Since Lewis acids such as $SnCl_4$ or $TiCl_4$ had been demonstrated to convert peracylated sugars into the corresponding protected 1-halo sugars, which gave moderate yields of the corresponding protected purine nucleosides[9,10] *in situ* with free purine bases, we reacted persilylated 6-azauracil **5** with the crystalline and stable standard sugar **6b** in 1,2-dichloroethane in the presence of $SnCl_4$ and obtained after workup crystalline **7** in 93% yield.[7,8] We could subsequently demonstrate that a large variety of silylated pyrimidine bases **2** and protected 1-*O*-acyl or 1-*O*-methyl sugars gave good to excellent yields of the corresponding nucleosides with $SnCl_4$ or other Friedel–Crafts catalysts. Lichtenthaler[11] later demonstrated that persilylated purines **4** give likewise high yields of the corresponding protected purine nucleosides.

Scheme 1



On investigating the influence of 5-substituents in silylated uracils, we found that persilylated 5-nitrouracil **2d** reacted rapidly with the standard sugar **6b** in the presence of only catalytic amounts of $SnCl_4$ to afford protected 5-nitrouridine in nearly quantitative yield, whereas the much more basic persilylated 5-methoxyuracil **2e** reacted only with excess $SnCl_4$ to give, besides the anticipated protected 5-methoxyuridine, considerable amounts of the protected undesired N^3-nucleoside as well as of the N^1,N^3-bis-N-glycoside.[12]

These results led us to postulate the formation of σ-complexes between the basic persilylated uracils[12–14] and $SnCl_4$ slowing down the Friedel–Crafts type synthesis between the generated sugar cations and the persilylated uracils, explaining the much faster and smoother reaction of the less basic **1d** versus **1c, 1e,** or **1f** (cf. the subsequent discussion).

† Dedicated to H. J. Bestmann on the occasion of his 70th birthday.

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(2) Birkofer, L.; Ritter, A.; Kühlthau, A. *Chem. Ber.* **1964**, *97*, 934.
(3) Nishimura, T.; Shimizu, B.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 1470.
(4) Nishimura, T.; Iwai, I. *Ibid.* **1964**, *12*, 352.
(5) Wittenburg, E. *Z. Chem.* **1964**, *8*, 303.
(6) Wittenburg, E. *Chem. Ber.* **1968**, *101*, 1095.
(7) Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461.
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(10) Furukawa, Y.; Honjo, M. *Chem. Pharm. Bull.* **1968**, *16*, 1076.
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(12) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1976**, *41*, 2084.
(13) Vorbrüggen, H.; Niedballa, U.; Bennua, B.; Höfle, G. In *Chemistry Biol. Nucleosides, Nucleotides*; Harmon, R. E., Robins, R. K., Townsend, L. B., Eds.; Academic Press: New York, 1978; p 251.
(14) Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256.

Helmut Vorbrüggen received his scientific education at the University of Göttingen working on antibiotics with Professor H. Brockmann. Subsequent postdoctoral work on natural products with Professor H. Erdtman in Stockholm in 1958–1959 was followed by studies on alkaloids and terpenes with Professor C. Djerassi at Stanford in 1959–1963. He then moved to the Woodward Institute in Basel in June 1963 to participate in the first total synthesis of cephalosporin C. After joining central research at Schering AG in 1966, he worked on nucleic acids followed by synthetic studies on new potent prostaglandin and prostacyclin analogs. In addition to his work at Schering AG he has been teaching courses in modern synthetic chemistry as adjunct professor at the Technical University in Berlin.

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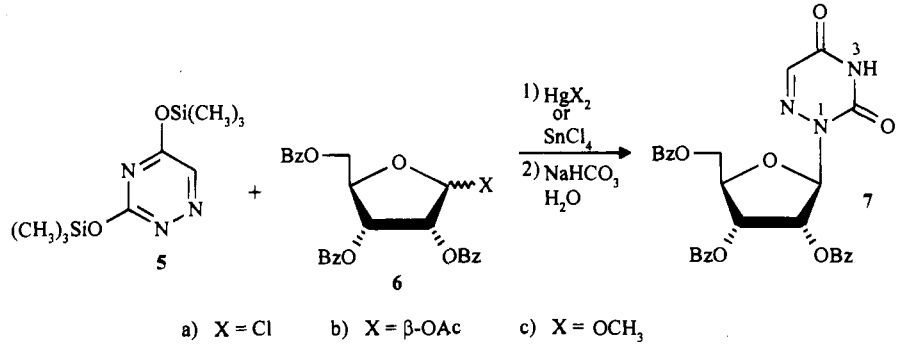
Scheme 2



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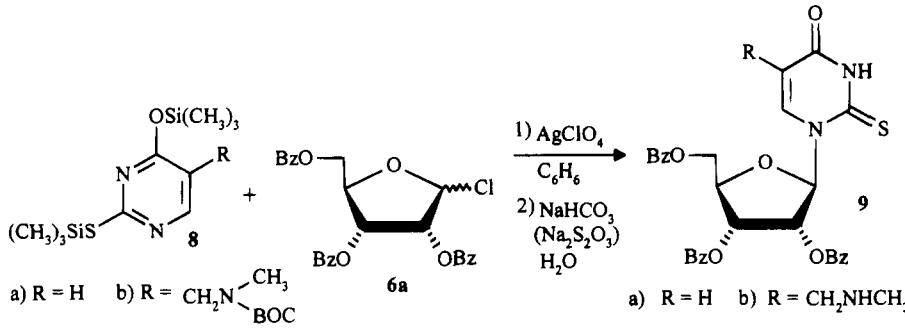

2. Discovery of Trimethylsilyl Triflate as a New Selective Lewis Acid for the Cleavage of *N*-Boc Groups and for Nucleoside Synthesis. Since protected 2-thiouridines **9** can be readily obtained by the reaction of silylated 2-thiouracil **8a** with 1-halo sugars such as **6a** in the presence of $AgClO_4$ in absolute benzene,[15] we reacted the silylated substituted 2-thiouracil **8b** with **6a** and obtained the O-acylated nucleoside **9b**, in which surprisingly the *N*-Boc protecting group had been lost (Scheme 3). Saponification gave the desired crystalline rare nucleoside from t-RNA 5-methylaminomethyl-2-thiouridine.[16,17] The only Lewis acid, which could have presumably cleaved the *N*-Boc group, was trimethylsilyl perchlorate, $(CH_3)_3SiClO_4$, (**10**), which had already been postulated as an intermediate in such reactions of 1-chloro sugars with silylated bases in the presence of $AgClO_4$ by Birkofer and Wittenburg.[2,6]

On investigating the ^{29}Si shifts of a series of silylated strong acids, Marsmann and Horn had demonstrated that trimethylsilyl perchlorate, $(CH_3)_3SiClO_4$ (**10**), as well as trimethylsilyl triflate, $(CH_3)_3SiOSO_2CF_3$ (**11**), were indeed much stronger Lewis acids than, e.g., trimethylsilyl sulfate, $[(CH_3)_3Si]_2SO_4$.[18] We thus wondered whether **10** and **11**, which are readily accessible[18] (cf. the following equations), might not be very interesting new mild and selective Lewis acids.

$$(CH_3)_3SiCl + AgClO_4 \xrightarrow[C_6H_6]{24\ ^\circ C} \underset{\mathbf{10}}{(CH_3)_3SiClO_4} + AgCl\downarrow$$

$$(CH_3)_3SiCl + CF_3SO_3H \xrightarrow[\text{neat}]{\Delta} \underset{\mathbf{11}}{(CH_3)_3SiOSO_2CF_3} + HCl\uparrow$$

We subsequently demonstrated that solutions of the explosive trimethylsilyl perchlorate (**10**) as well as of the thermally stable trimethylsilyl triflate (**11**) do indeed cleave *N*-Boc groups in peptides.[19] This reaction was later taken up and expanded by Shioiri[20] and Ohfune.[21]

The apparent acidic properties of **10** and **11** induced us to apply **10** as well as **11** as catalysts to nucleoside synthesis. Gratifyingly, the reactions of persilylated pyrimidine or purine bases **2** or **4** with the crystalline and stable standard sugar **6b** afforded in the presence of **10** or **11** the corresponding protected nucleosides in excellent yields.[13,22,23] Thus the potentially explosive **10** as well as the stable **11**, which we later used exclusively, convert the sugar **6b** in 1,2-dichloroethane or acetonitrile into trimethylsilyl acetate (**13**) and the electrophilic sugar cation **12**, which reacts, e.g., with the nucleophilic silylated pyrimidine bases **2** to give the silylated protected intermediates **14** as well as regenerated **11**. As already discussed, in the case of the weakly basic silylated 5-nitrouracil **1d** only catalytic amounts of **11** (or $SnCl_4$) are necessary to afford protected 5-nitrouridine **15d** in high yields (Scheme 4).

In particular with the more basic silylated 5-methoxyuracil **2e** (or 5-morpholinouracil **2f**), however, the Lewis acid **11** (or analogously $SnCl_4$) reversibly forms σ-complexes **16**, thus decreasing the concentrations of available **11** (or $SnCl_4$) and of the free base **2**, which only can react with the sugar cation **12** to the desired natural N^1-nucleoside, **14** → **15** (Scheme 5). As a consequence the nucleoside formation slows down or stops completely until more than 1 equiv of **11** (or

(15) Vorbrüggen, H.; Strehlke, P.; Schulz, G. *Chem. Ber.* **1973**, *106*, 3039.
(16) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 255.
(17) Vorbrüggen, H.; Krolikiewicz, K. *Liebigs Ann. Chem.* **1980**, 1438.
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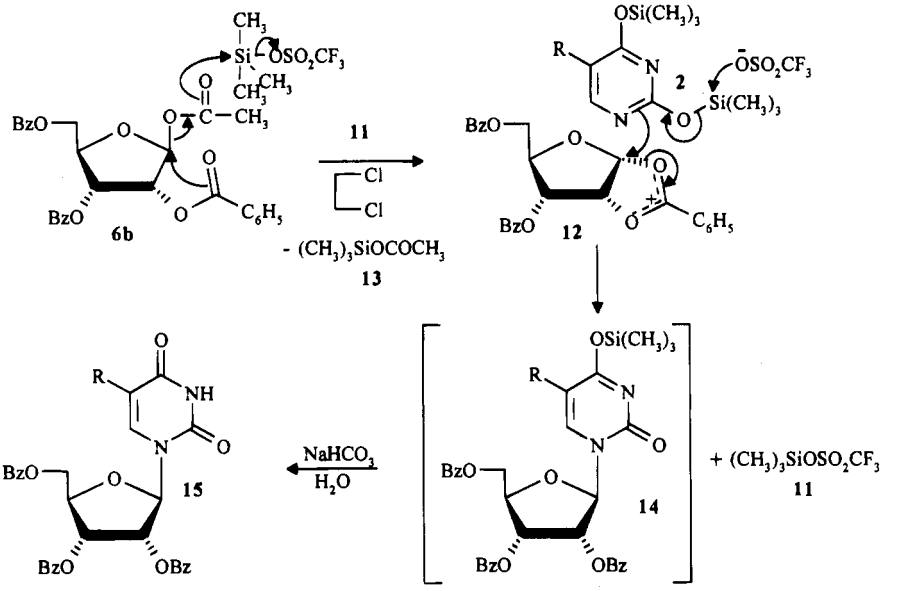
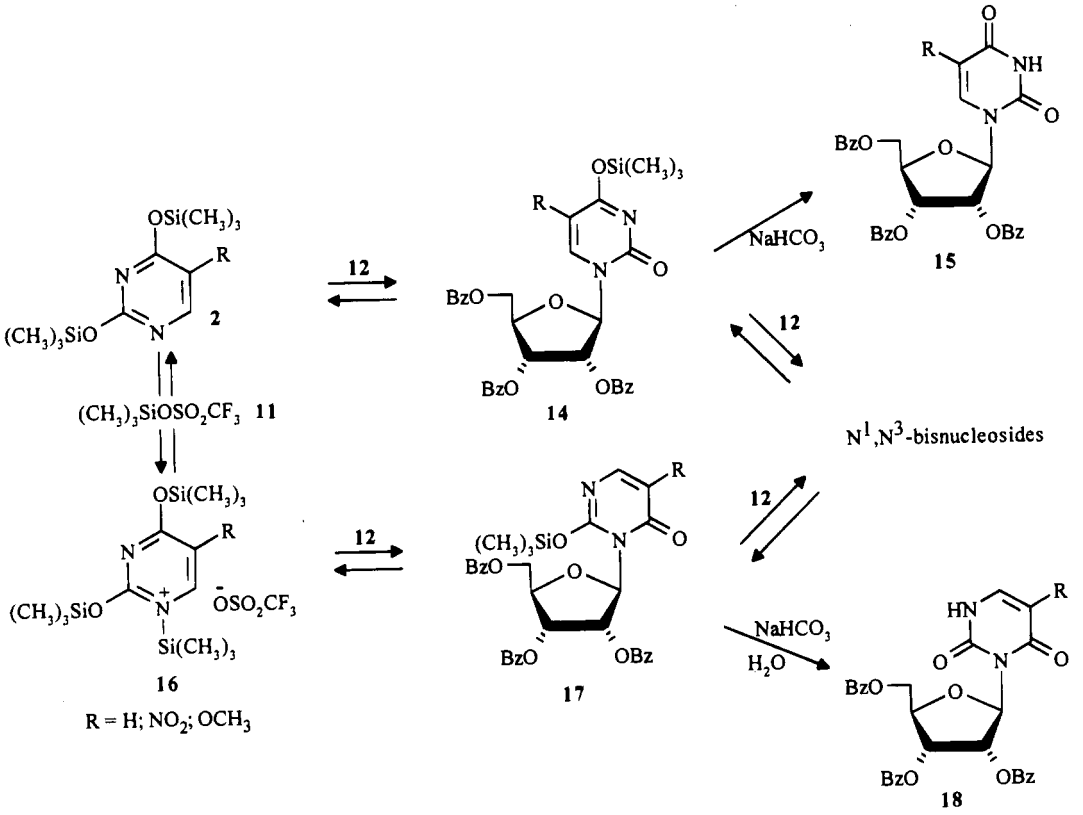
(20) Hamada, Y.; Kalo, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223.
(21) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543.
(22) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 421.
(23) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

Scheme 4



Scheme 5

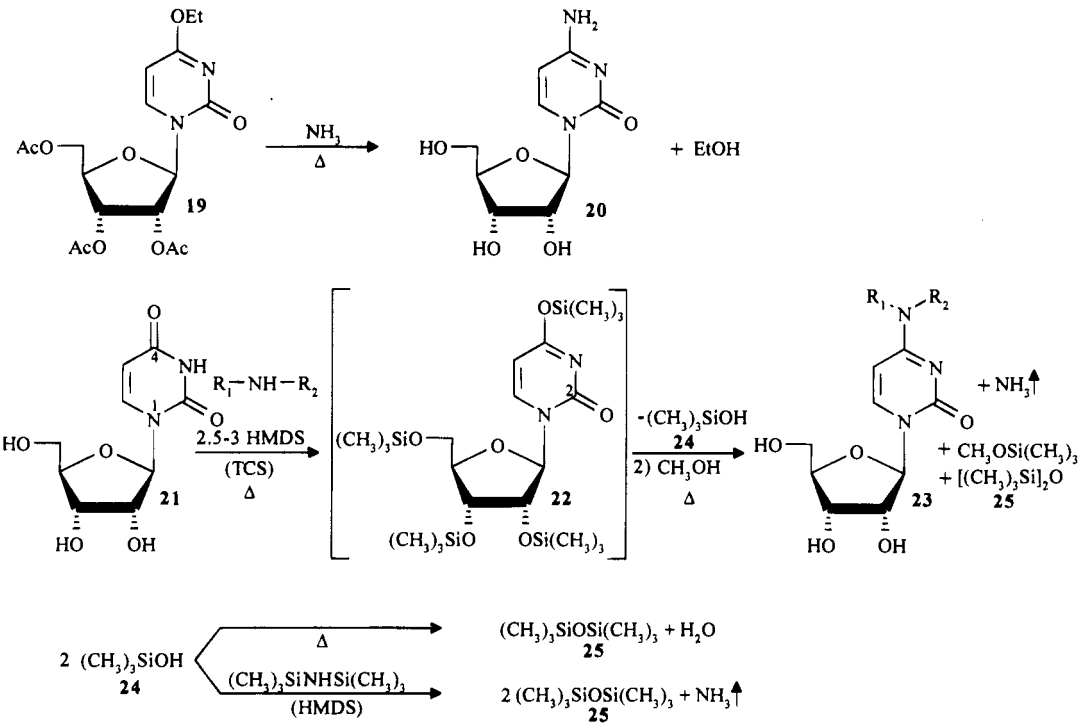


$SnCl_4$) is added to permit the formation of the sugar cation **12**. Furthermore, in the σ-complexes **16**, whose structure was determined by ^{13}C-NMR,[13,14] only the N^3-nitrogen is available for reaction with the sugar cation **12** to give the undesired protected N^3-nucleosides **18**. Both the silylated protected N^1-nucleosides **14** and the corresponding N^3-nucleosides **17** can react with the electrophilic sugar cation **12** to give the corresponding undesired protected N^1,N^3-bis(nucleosides). ^{13}C-NMR studies of these σ-complexes between silylated pyrimidines **1** and **11** (or $SnCl_4$) demonstrated that $SnCl_4$ is a much stronger Lewis acid or Friedel–Crafts catalyst than **11**.[13,14] Furthermore, the lipophilic **11** is a much weaker Lewis acid than triflic acid. These data explain why **11** as catalyst gives much more of the desired N^1-nucleosides **14** and consequently much less of the undesired N^3-nucleosides **18** than $SnCl_4$ with basic silylated pyrimidines such as silylated 5-methoxyuracil **2e**.

To decrease the basicity of silylated amino heterocycles such as of cytosine, adenine, or guanine, these amino groups should always be N-acylated as depicted in **2c**, **4a**, and **4b**. The probable mechanism of nucleoside synthesis with silylated N^6-benzoyladenine **4a** was also elucidated by ^{13}C-NMR investigations of their σ-complexes.[14]

Since the more polar solvent acetonitrile (compared

Scheme 6



to 1,2-dichloroethane) competes with the silylated bases for the Lewis acids **11** or $SnCl_4$, the more basic silylated pyrimidines **2** should always be reacted in acetonitrile.

Thus, **11** as the weaker Lewis acid compared to $SnCl_4$ is for most nucleoside syntheses the optimal catalyst, since it is just strong enough to convert protected 1-*O*-alkyl or 1-acyl sugars into their corresponding electrophilic cations such as **12**.

The $(CH_3)_3SiOSO_2CF_3$- or $SnCl_4$-catalyzed nucleoside synthesis has become a standard reaction. The different methods of nucleoside synthesis and their mechanisms will be summarized in a forthcoming review article.[24]

It is obvious that these reactive cations such as **12** can react also with other nucleophiles, e.g., with alcohols to form the corresponding β-glycosides, as was suggested by us, e.g., in a lecture in 1976.[25] This technique was put, however, into practice in 1981,[26] and we were subsequently occasionally given credit for introducing **11** to generate sugar cations such as **12**.[26-28] Following our first applications[13,19,22,23] of **11** as a selective new Lewis acid and Friedel–Crafts catalyst, many additional applications have been described and reviewed.[29-31]

B. Trimethylsilanol as a Leaving Group[32]

1. Silylation–Amination of Nucleosides and Heterocycles. During our studies on antiviral nucleosides we wanted to prepare a series of N^4-substituted cytidines **23** starting from uridine (**21**) and wondered whether we could not cut down the number of the hitherto necessary steps: (1) O-acylation of the alcoholic hydroxyl groups of the ribose moiety in uridine **21**; (2) subsequent activation of the 4-carbonyl moiety of the 2′,3′,5′-tri-O-acylated uridine either by heating with P_2S_5 in pyridine or dioxane[33,34] or by tris(1,2,4-triazolyl)phosphate;[35,36] and finally (3) treatment with a primary or secondary amine to give the desired N^4-modified cytidines **23**.

In the first synthesis of cytidine (**20**) protected 4-*O*-ethyluridine **19**, an intermediate in the classical Hilbert–Johnson nucleoside synthesis, had been heated in a closed vessel with NH_3 to give via an addition–elimination mechanism cytidine (**20**) and ethanol as a leaving group[37] (Scheme 6). Since we expected the corresponding 4-O-trimethylsilylated uridines to behave analogously, with formation of trimethylsilanol (**24**) instead of ethanol as a leaving group, except that trimethylsilanol (**24**) would dimerize to hexamethyldisiloxane (**25**) and H_2O, we persilylated **21** with hexamethyldisilazane (HMDS) and a catalytic amount of trimethylchlorosilane (TCS). We thus protected the alcoholic hydroxyl groups in the ribose moiety of **21** as well as activated the 4-position to the intermediate **22**, whose UV spectrum was practically identical to that of protected O^4-ethyluridine **19**.[38] Heating of uridine (**21**) with excess hexamethyldisilazane (HMDS) and primary or secondary amines R_1NHR_2 leads via an addition–elimination mechanism (cf. **27**) to persilylated N^4-substituted cytidine, **25**, and ammonia,

(24) Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React. (N.Y.)*, in preparation.
(25) Vorbrüggen, H. Lecture at Stanford Research Institute, Palo Alto, CA, September 1976.
(26) Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, 93, C6.
(27) Sliedregt, L. A. J. M.; van der Marel, O. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015.
(28) Teng, K.; Cook, P. D. *J. Org. Chem.* **1994**, *59*, 278.
(29) Emde, H.; Dornsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Kräkeloh, K.; Oesterle, T.; Steppau, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
(30) Simchen, G. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press Inc: Greenwich, CT, 1991, pp 89–301.
(31) Noyori, R. *Tetrahedron* **1981**, *37*, 3899.
(32) For a brief review, cf.: Vorbrüggen, H. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983.
(33) Fox, J. J.; van Praag, D.; Wempen, I.; Doerc, I. L.; Cheong, L.; Knoll, J. E.; Eidinoff, M. L.; Bendick, A.; Brown, G. B. *J. Am. Chem. Soc.* **1959**, *81*, 178.
(34) Fox, J. J.; Miller, N.; Wempen, I. *J. Med. Chem.* **1966**, *9*, 101.
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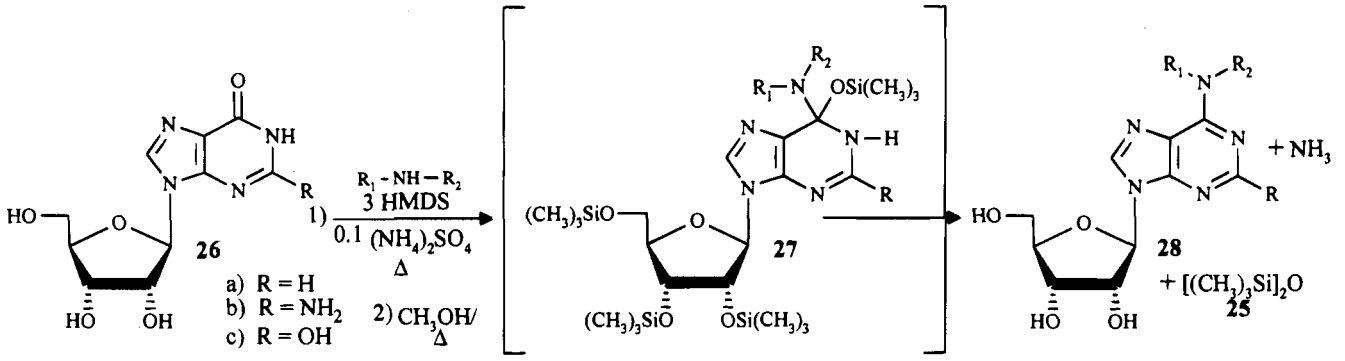
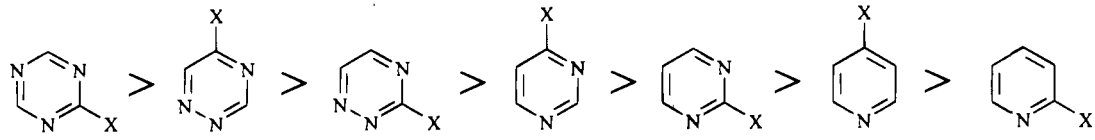
(36) Sung, W. L. *J. Org. Chem.* **1982**, *47*, 3623.
(37) Howard, G. A.; Lythgoe, B.; Todd, A. R. *J. Chem. Soc. (London)* **1947**, 1052.

Scheme 7



Scheme 8



which is evolved during silylation of **21**. Any hydroxy group in R_1NHR_2 as well as the leaving group **24** is silylated by HMDS to give, in the case of **24**, **25** (cf. the subsequent equations). The resulting persilylated N^4-substituted cytidines are converted into the corresponding free cytidines **23** by transsilylation with excess boiling methanol, from which the resulting free cytidines **23** often crystallize directly in 80–95% yields.[38] The weakly basic aniline reacts only in the presence of $(NH_4)_2SO_4$ as acidic catalyst facilitating the addition–elimination reaction of amines to the activated intermediate **22** by protonating the 2-carbonyl group.[38] Since intermediates with an activated 4-*O*-trimethylsilyl group (cf. **14** in the preceding section) are also obtained in the Friedel–Crafts catalyzed silyl-Hilbert–Johnson reaction starting with silylated uracils, these intermediates react also *in situ* with excess amines such as pyrrolidine to the corresponding protected cytidines![38] Thus in this one-pot reaction protection of the alcoholic hydroxyl groups in the ribose as well as in the amine moiety, activation of the 4-carbonyl group, and simultaneous amination is achieved in one step, followed only by the subsequent *in situ* transsilylation with excess methanol.

It is interesting to note that monosilylated water = trimethylsilanol (**24**), which is reasonably stable in pure form, boils at 99 °C,[39,40] whereas bissilylated water = hexamethyldisiloxane (**25**) boils at 101 °C. In contrast to the very polar solvent water, the bissilylated water = hexamethyldisiloxane (**25**) is a very unpolar volatile liquid, which does not mix with polar solvents such as acetonitrile, on which it floats as a clear colorless liquid.

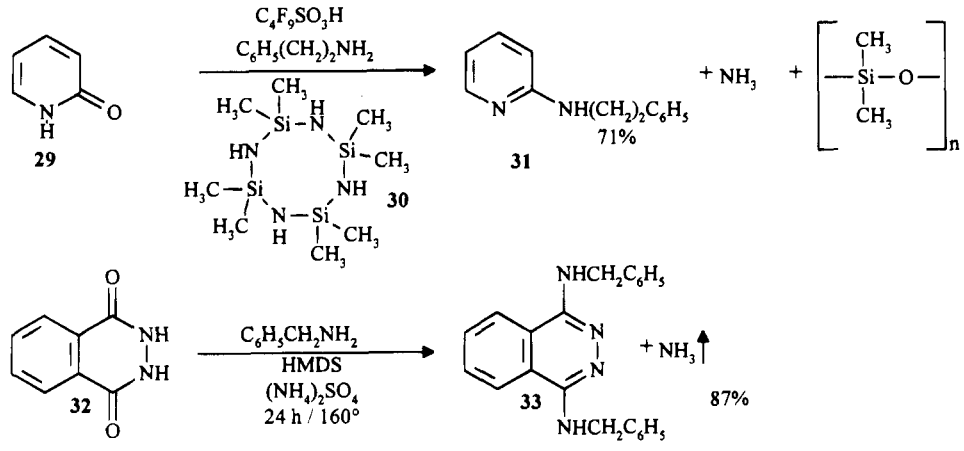
On extending this silylation–amination to the aromatic purine nucleosides lacking the conjugated carbonyl group to the (trimethylsilyl)imino ether system as in **22**, the silylation–amination of inosine (**26a**), guanosine (**26b**), or xanthosine (**26c**) proceeds *only* in the presence of Lewis acids such as $(NH_4)_2SO_4$, camphorsulfonic acid (CSA), *p*-toluenesulfonic acid hydrate ($TsOH{\cdot}H_2O$), or **11** to protonate the most basic N^1-nitrogen atom to facilitate the addition of R_1NHR_2 to the intermediate **27** leading after elimination of **24** to the N^6-substituted adenosines **28** in high yields[41] (Scheme 7).

In the case of dopamine hydrochloride as amine moiety an extra equivalent of HMDS has to be employed to silylate and protect the sensitive catechol system, using the hydrochloride as Lewis acid for silylation and amination. On working with volatile amines such as NH_3, the silylation–aminations of pyrimidine **21** or purine nucleosides **26** as well as of the subsequently discussed hydroxy N-heterocycles have to be carried out in an autoclave and take a much longer time in the case of the polar NH_3, since NH_3 or its more basic and bulky silylated derivatives $(CH_3)_3SiNH_2$ and $(CH_3)_3SiNHSi(CH_3)_3$ (HMDS) will form intermediates such as **27** much more slowly! Nevertheless the silylation–amination of guanosine (**26b**) into 2-aminoadenosine (**28**) (R = NH_2; $R_1 = R_2 = H$) is being carried out in 90% yield in 100–150 kg batches![42]

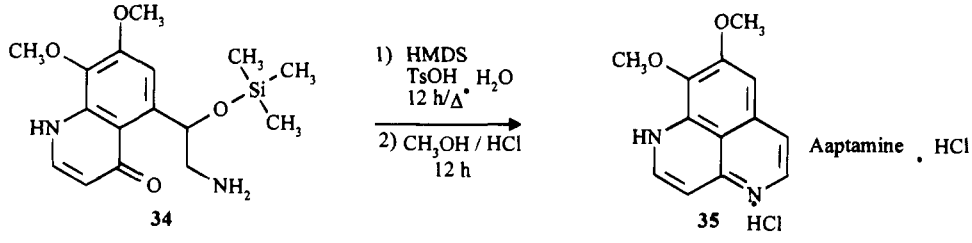
It is obvious that purines such as hypoxanthine or xanthine can also be silylated–aminated.[41] Furthermore, any of the aromatic hydroxy N-heterocycles investigated gave the corresponding amino derivatives[43,44] following in their reactivity the established order[45] (Scheme 8). In the depicted reactivity scale, in which a conjugated aromatic ring makes any heterocycle much more reactive, pyridin-2(1*H*)-one (**29**) is the least reactive one, demanding reaction temperatures of $T > 190$ °C for silylation–amination. These temperatures can only be reached at normal pressure by using the crystalline (mp. 97 °C) and high-boiling (bp 225 °C) tetramer octamethylcyclotetrasilazane (**30**) to give 2-(2-phenethylamino)pyridine (**31**) in 71% yield and silicon oil on silylation–amination with β-phenethylamine in the presence of perfluorobutanesulfonic acid after 24 h at 200 °C. The much more reactive 2,3-dihydro-4-phthalazinedione (**32**) is readily

(38) Vorbrüggen, H.; Krolikiewicz, K.; Niedballa, U. *Liebigs Ann. Chem.* **1975**, 988.
(39) Sommer, L. H.; Pietrusza, E. W.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 2282.
(40) Grubb, W. T. *J. Am. Chem. Soc.* **1954**, *76*, 3408.
(41) Vorbrüggen, H.; Krolikiewicz, K. *Liebigs Ann. Chem.* **1976**, 745.
(42) Krolikiewicz, K.; Vorbrüggen, H. *Nucleosides Nucleotides* **1994**, *13*, 673.
(43) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1976**, *11*, 305.
(44) Vorbrüggen, H.; Krolikiewicz, K. *Chem. Ber.* **1984**, *117*, 1523.
(45) Shephard, R. G.; Frederick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.

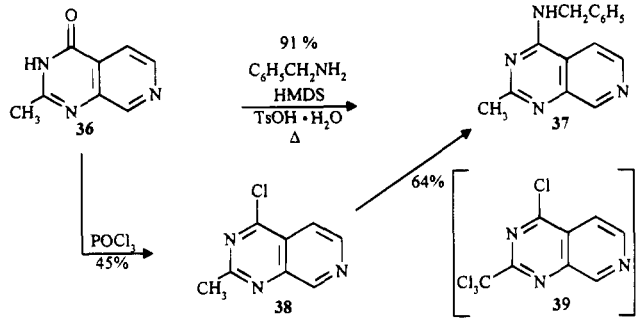
Scheme 9



Scheme 10



Scheme 11



bisaminated with benzylamine at 160 °C to give **33** in 87% yield[44] (Scheme 9).

Although the hitherto commonly used two-step procedure for the amination of hydroxy N-heterocycles, i.e., treatment with $POCl_3$, isolation of the corresponding chloro compounds, and subsequent amination,[45,46] has quite a number of drawbacks, such as the necessary protection of hydroxy groups in the heterocyclic or amine moieties or the frequently observed chlorination of any alkyl groups in the hydroxy N-heterocycle, the one-pot silylation–amination, which can be readily scaled up to multikilogram lots, to date has found relatively limited applications. Thus cyclization of **34** gave the alkaloid aptamine **35**[47] (Scheme 10). The silylation–amination of **36** with benzylamine afforded 91% of **37**, which is obtained in only 25% yield via the crystalline chloro compound **38**, since apparently larger amounts of chlorinated products such as **39** are formed during the reaction of **36** with $POCl_3$[48] (Scheme 11).

The different methods of aminations of hydroxy-N-heterocycles have been reviewed recently.[46]

(46) Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117.
(47) Andrews, R. G.; Raphael, R. A. *Tetrahedron* **1987**, *43*, 4803.
(48) Nishikawa, S.; Kumazawa, Z.; Kashinura, N.; Maki, S.; Nishikimi, Y. *Agric. Biol. Chem.* **1986**, *50*, 495.

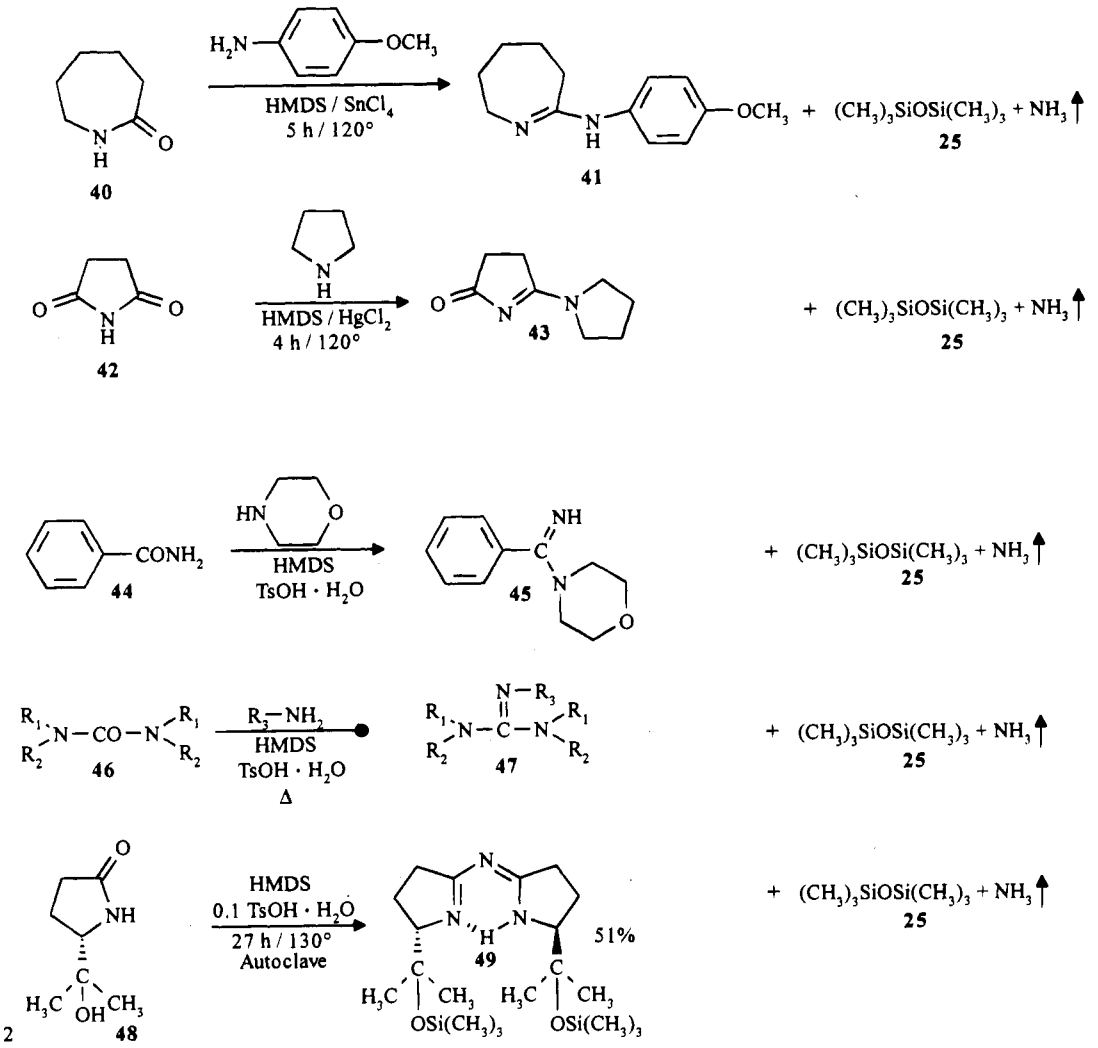
2. Amination of Amides and Lactams. Since the aminations of hydroxy N-heterocycles described in the previous section are all silylation–aminations of heterocyclic aromatic lactam systems, we have also applied the silylation–amination procedure to "normal" lactams and amides. Thus, caprolactam (**40**) reacts readily with *p*-anisidine to form the amidine **41** in 76% yield (Scheme 12). Succinimide (**42**) is converted by pyrrolidine into the cyclic acylated amidine **43** in 74% yield, whereas benzamide (**44**) reacts with morpholine to the amidine **45** in 75% yield.[49] It should be realized, however, that extended heating of bissilylated primary amides to 130–180 °C especially in the presence of Lewis acids leads to the formation of the corresponding nitriles and **25**[50–52]. Due to the limited number of examples, this simple amidine synthesis has not as yet been published in detail. Furthermore, the potential conversion of ureas **46** with amines R_1NHR_2 into their corresponding guanidines **47** has not been studied as yet.

A recently published simple silylation–amination of the chiral pyrrolidone **48** with HMDS and catalytic amounts of $TsOH·H_2O$ in an autoclave afforded in 51% yield the semicorrine system **49**, which is otherwise only accessible via a number of reaction steps, in 33% overall yield.[53] These results suggest that silylation–amination of cyclic acid imides such as phthalimides in the presence of metal templates might give ready access to phthalocyanine-like systems.

3. Cyanations of Pyridine *N*-Oxide and Quinoline *N*-Oxide. Pyridine *N*-oxide (**50**) can only be

(49) Vorbrüggen, H. Ger. Patent Appl. 2256755; *Chem. Abstr.* **1974**, *81*, 6341c.
(50) Dennis, W. *J. Org. Chem.* **1970**, *35*, 3253.
(51) Rigo, B.; Lespagnol, C.; Pauly, M. *Tetrahedron Lett.* **1986**, *27*, 347.
(52) Rigo, B.; Lespagnol, C.; Pauly, M. *J. Heterocycl. Chem.* **1986**, *23*, 183.
(53) Leutenegger, U.; Umbrecht, G.; Fahrni, C.; Matt, P. v.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.

Scheme 12



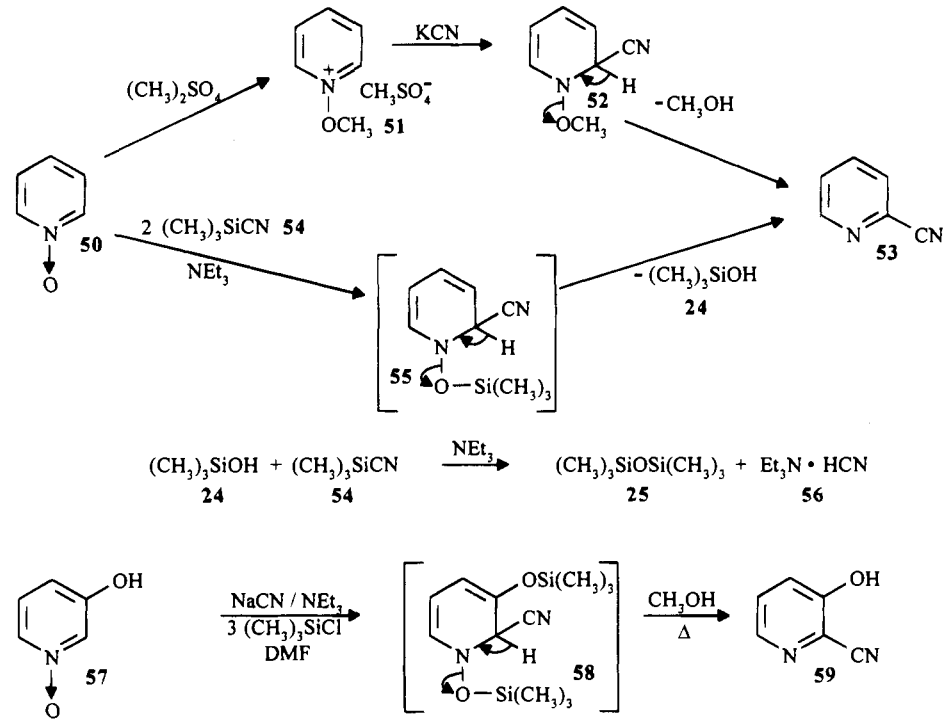
cyanated after O-alkylation with dimethyl sulfate to **51** followed by treatment with cyanide ion to give, via **52** and subsequent elimination of methanol, 2-cyanopyridine (**53**) as well as traces of 4-cyanopyridine[54,55] (Scheme 13). Due to the aforementioned similarity between an *O*-alkyl- and an *O*-trimethylsilyl group, we anticipated that treatment of **50** with trimethylsilyl cyanide (**54**), which can be considered as a combination of the "hard" trimethylsilyl cation and the "soft" cyanide anion, would add to **50** to give the intermediate **55**. This intermediate **55** would eliminate **24** to furnish 2-cyanopyridine (**53**) whereas the liberated **24** would react with excess **54** in the presence of equivalent amounts of triethylamine to give rise to **25** and triethylammonium cyanide (**56**).

In the event **50** reacted with excess **54** and triethylamine in acetonitrile at 80 °C to give **53** in 80% yield.[32,56] From the many different applications to pyridine *N*-oxides, quinoline *N*-oxide, or isoquinoline *N*-oxide, the reaction of 3-hydroxypyridine *N*-oxide (**57**) may suffice. Treatment of a suspension of **57**, triethylamine, and sodium cyanide in DMF with trimethylchlorosilane (TCS) for 1 h at 24 °C generated **54** *in situ*. Subsequent heating for 12 h to 100 ° gave, via **58**, in which the phenolic 3-hydroxy group is protected by silylation, after transsilylation with methanol, 2-cyano-3-hydroxypyridine (**59**) in 90% yield. It is noteworthy that all these reactions with trimethylsilyl cyanide can be efficiently catalyzed by tetrabutylammonium fluoride trihydrate in THF at 5 °C.[32,56]

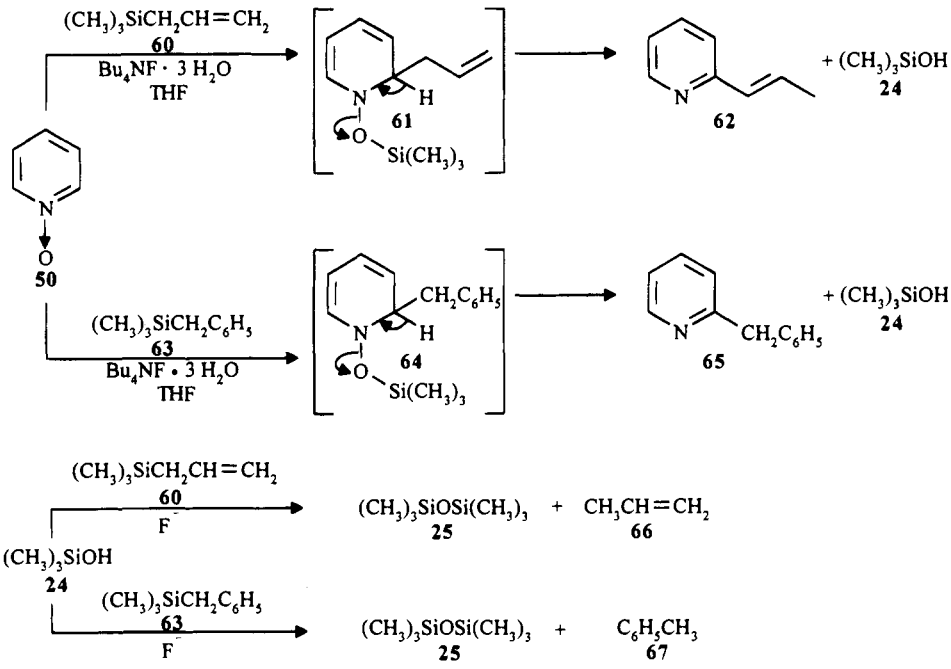
Other heterocyclic *N*-oxides such as pyrimidine *N*-oxides[57,58] as well as pyrazine *N*-oxides[59] or quinoxalines[60] were subsequently converted with trimethylsilyl cyanide (**44**) into their corresponding cyano compounds. Following our publications, a modification of this methodology was described using instead of **54**/triethylamine a combination of **54** with methyl- or ethyl carbonochloridate.[61,62] A critical comparison of the reactions of pyridine *N*-oxides with trimethylsilyl cyanide/NEt_3 or trimethylsilyl cyanide/alkyl carbonochloridate demonstrated,[58] however, that the addition of alkyl carbonochloridates gives in most cases diminished yields of the desired cyanoheterocycles.

(54) Okamoto, T.; Tani, H. *Chem. Pharm. Bull.* **1959**, *7*, 130, 925, 930.
(55) Feely, F.; Beavers, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 4004.
(56) Vorbrüggen, H.; Krolikiewicz, K. *Synthesis* **1983**, 316.
(57) Yamanaka, H.; Nishimura, S.; Kaneda, S. I.; Sakamoto, T. *Synthesis* **1984**, 681.
(58) Sakamoto, T.; Kaneda, S. I.; Nishimura, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 565.
(59) Sato, N.; Shimomura, Y.; Takeuchi, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2877.
(60) Iijima, C.; Miyashita, A. *Chem. Pharm. Bull.* **1990**, *38*, 661.
(61) Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375.
(62) Fife, W. K.; Boyer, B. D. *Heterocycles* **1984**, *22*, 1121.

Scheme 13



Scheme 14



Whereas we failed to achieve any reaction of **50** with trimethylsilyl azide, which is a combination of the "hard" trimethylsilyl cation and the neither "hard" nor "soft" azide anion, the much more reactive pyrazine *N*-oxide system was recently converted by trimethylsilyl azide into the corresponding 2-azidopyrazines.[63]

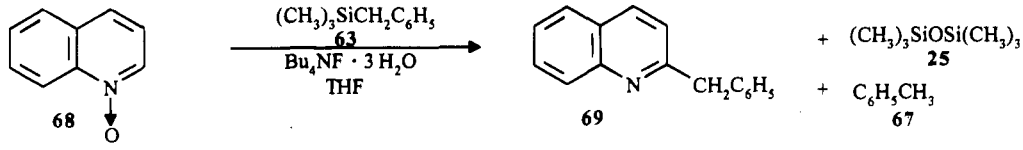
4. Alkylations of Pyridine *N*-Oxide and Quinoline *N*-Oxide. Since allyltrimethylsilane (**60**) or benzyltrimethylsilane (**63**) can be considered a combination of the "hard" trimethylsilyl cation and the "soft" allyl or benzyl anion we reacted **50** and other pyridine, quinoline, or isoquinoline *N*-oxides with excess **60** or **63** in the presence of catalytic amounts of tetrabutylammonium fluoride trihydrate.[32,64] **50** gave **62** as the *only* reaction product in 53% yield with excess **60** in the presence of catalytic amounts of tetrabutylammonium fluoride trihydrate in THF via the potential intermediate **61**, whereas **63** converted **50** in 70% yield via **64** into 2-benzylpyridine (**65**) (Scheme 14).

The elimination of **24** from **61** is apparently followed by fluoride-catalyzed isomerization of 2-allylpyridine into 2-propenylpyridine (**62**). The generated **24** reacts subsequently under fluoride catalysis with **60** or **63**

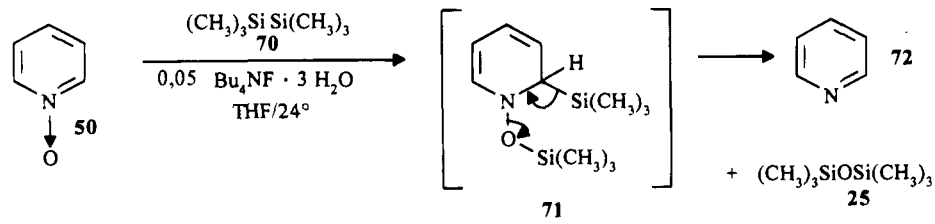
(63) Sato, N.; Matsuura, T.; Mira, N. *Synthesis* **1994**, 931.

(64) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1983**, *24*, 889.

Scheme 15



Scheme 16



to **25** and propylene (**66**) or toluene (**67**). Analogously quinoline *N*-oxide (**68**) affords 2-benzylquinoline (**69**) in 65% yield with **63**[64] (Scheme 15).

Although these reactions are formulated as ionic reactions via **61** or **64**, the color changes, the apparent formation of polymers, and the inhibition[65,66] of the fluoride-catalyzed reaction of **50** with **63** with sulfur and galvinoxyl but *not* with Tempo, point to a radical mechanism.

5. Reduction of Pyridine *N*-Oxides with Hexamethyldisilane (70). Hexamethyldisilane (**70**), which is produced industrially on a large scale, can be considered to be a combination of the "hard" trimethylsilyl cation and the "soft" trimethylsilyl anion. We, therefore, anticipated that **70** might react with **50** to give intermediates such as **71**. We thus treated **50** and **70** in THF with 0.05–0.1 equiv of a commercial tetrabutylammonium fluoride trihydrate solution in THF as a catalyst. After ca. 20–30 min of stirring at ambient temperature the colorless reaction mixture suddenly turned dark and the **reaction mixture exploded**.[67] We rationalized that the explosion might have been caused by the gradual removal of the water from the tetrabutylammonium fluoride trihydrate to result after a time in a *very reactive fluoride catalyst* and a sudden onset of the reaction! We thus stirred **50** and the catalytic amount of tetrabutylammonium fluoride trihydrate in THF and added slowly within 2–3 h a solution of ca. 1.5 equiv of **70** in THF to result in an apparent addition of hexamethyldisilane to **71** and subsequent elimination of **25** to give pyridine (**72**), which was isolated in 90% yield as its crystalline picrate (Scheme 16). Alternatively, elimination of **24** from the intermediate **71** might give 2-(trimethylsilyl)pyridine, which would, however, react with fluoride to generate the pyridyl α-anion. To trap this anion we added equivalent amounts of benzaldehyde but isolated in more than 70% yield a mixture of D,L- and *meso*- pinacol. Acetophenone was analogously converted into the corresponding mixture of pinacols by **70** in the presence of fluoride. This conversion of benzaldehyde by hexamethyldisilane in the presence of so-called "anhydrous" tetrabutylammonium fluoride in HMPA–THF into the same mixture of pinacols was reported at the same time by Hiyama.[68]

This smooth reduction of heterocyclic *N*-oxides with **70** was extended to a variety of pyridine, quinoline, and isoquinoline *N*-oxides, and we anticipate that nitrones might be reduced analogously to their corresponding Schiff bases.

In a related reaction pyridine *N*-oxides have been reduced by a combination of trimethylsilyl chloride (TCS) and NaI(=$(CH_3)_3SiI$) in acetonitrile.[69]

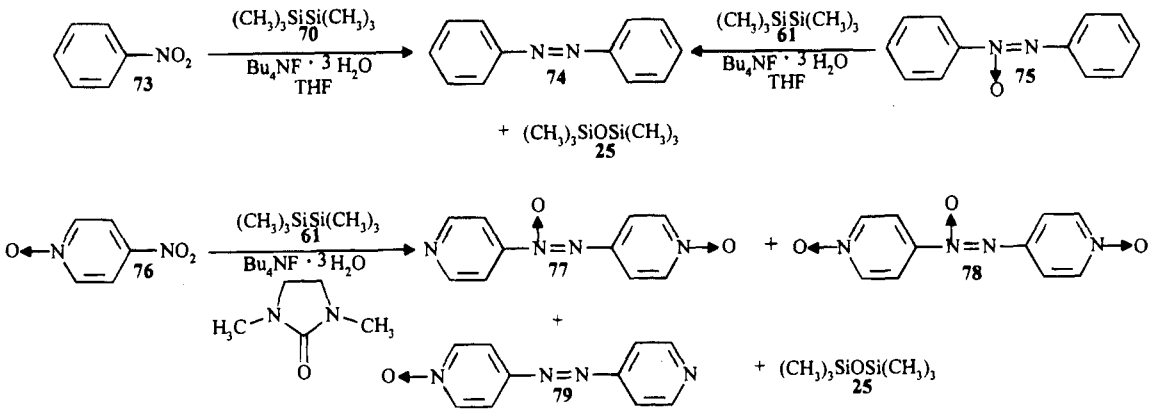
6. The Reduction of Aromatic Nitro Groups with Hexamethyldisilane (70). Since aromatic nitro compounds such as nitrobenzene (**73**) had been reduced by hexamethyldisilane (**70**) at 210 °C to give azobenzene (**74**) and aniline,[70] we anticipated that the same reduction might proceed at room temperature in THF in the presence of catalytic amounts of tetrabutylammonium fluoride trihydrate (Scheme 17). Thus we dissolved **73** and 0.05 equiv of tetrabutylammonium fluoride trihydrate in THF, added **70** within 2 h at 24 °C, and obtained **74** in 84% yield,[71] whereas azoxybenzene (**75**) gave **74** in 95% yield, making **75** a probable intermediate in the reduction of **73** to **74**. The reduction of 2-nitrodiphenyl did not give any carbazole, excluding thus any nitrene intermediates. The very polar, rather insoluble 4-nitropyridine *N*-oxide (**76**) could be reduced by **70** in the polar solvent *N,N'*-dimethylimidazolin-2-one to give 52% of precipitated **77** as well as 12% of a mixture of **78** and **79**. Thus the nitro groups in **76** appear to be reduced more rapidly by **70** than the heterocyclic *N*-oxide moiety (cf. the preceding section).

Mechanistically, the fluoride-catalyzed reduction of **73** with **70** to **74** can be rationalized to proceed via **80** → **81** → **82** → **75** and **74** (Scheme 18).

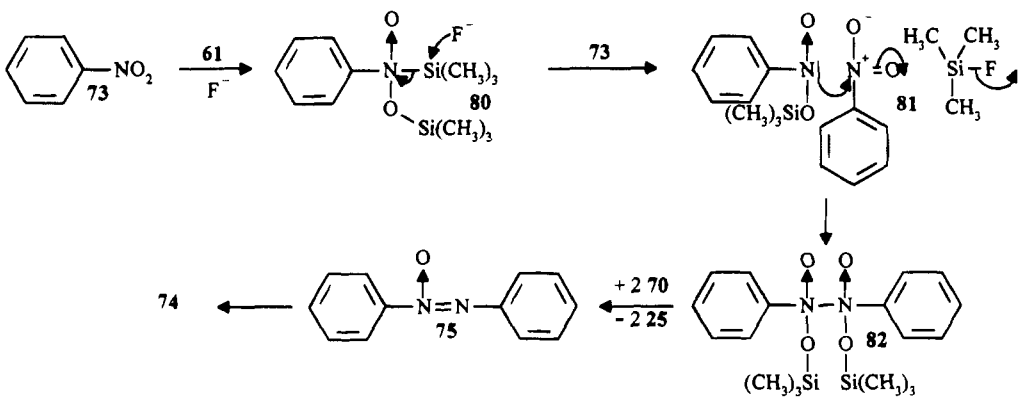
7. Generation of Anhydrous Tetrabutylammonium Fluoride and Its Properties. As indicated in the two preceding sections, a solution of commercial tetrabutylammonium fluoride trihydrate (**83**) in THF can be dehydrated on a preparative scale by gradual addition of **70** at $T \leq 10–15$ °C.[71,72] Mechanistically, **70** reacts probably with **83** under initial formation of trimethylsilyl fluoride (**84**) and the trimethylsilyl tetrabutylammonium salt (**85**), both of which interact with water to give **24**, trimethylsilane (**86**), and tetrabutylammonium fluoride (**87**) (Scheme 19). **24** is converted by **70** under fluoride catalysis to **25** and **86**. Alternatively, **24** can react with **86** to give **25** and

(65) Kitteringham, J.; Mitchel, M. B. *Tetrahedron Lett.* **1988**, *29*, 3319.
(66) Lewis, N.; Mitchell, M. B. *Chem. Ind.* **1991**, 374.
(67) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1983**, *24*, 5337.
(68) Hiyama, T.; Obayashi, M.; Mori; I.; Nozaki, H. *J. Org. Chem.* **1983**, *48*, 912.
(69) Morita, T.; Kuroda, K.; Okamoto, Y.; Sakurai, H. *Chem. Lett.* **1981**, 921.
(70) Tsui, F. P.; Vogel, T. M.; Zon, G. *J. Org. Chem.* **1975**, *40*, 761.
(71) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1984**, *25*, 1259.
(72) Marschner; M. Ph.D. Dissertation, Technical University Berlin, 1984.

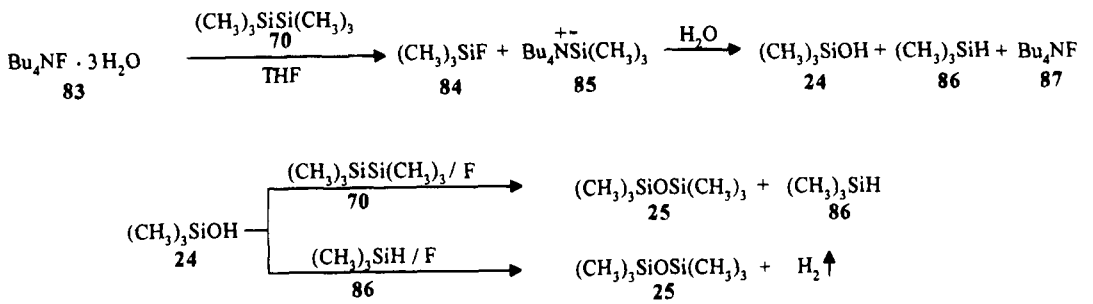
Scheme 17



Scheme 18



Scheme 19



hydrogen. Whatever the actual mechanism is, the formation of **84** and **86** as well as of **25** was readily demonstrated by GC/MS.

The preparation of larger amounts of practically anhydrous and very reactive tetrabutylammonium fluoride (**87**) (still containing, however, **25** as well as probably some **86**) is tricky, since the removal of the last traces of water by **70** by the different reactions depicted above takes many hours and any warming of the THF solution to temperatures $T > 15$ °C leads to rapid decomposition of **87** to give tributylamine hydrofluoride (**88**), butyl fluoride (**89**), and butylene (**90**). We found, however, that a solution of anhydrous **87** in THF can be kept at −28 °C for several months without decomposition.[71]

$$\underset{\mathbf{87}}{Bu_4NF} \xrightarrow{T > 15\text{–}17\ ^\circ C} \underset{\mathbf{88}}{BuN{\cdot}HF} + \underset{\mathbf{89}}{BuF} + \underset{\mathbf{90}}{\text{butylene}}$$

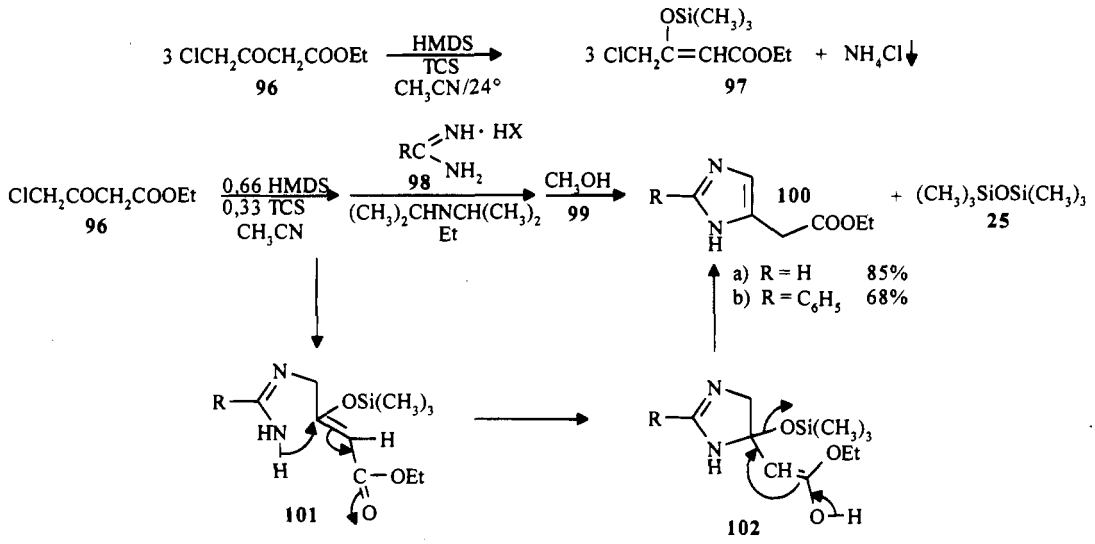
We could demonstrate in 1983 that anhydrous **87** can effect C−C-bond formation.[72] Thus benzyl chloride (**91**) reacts in THF in the presence of equivalent amounts of **87** with allyltrimethylsilane **60** to furnish butenylbenzene (**92**) in 53% yield as well as **84** (bp 17 °C) and tetrabutylammonium chloride (**93**), which precipitates. Furthermore, 1,6-dibromohexane (**94**) reacts with **60** to give 1,11-dodecadiene (**95**) in 61% yield.

$$\underset{\mathbf{91}}{C_6H_5CH_2Cl} + \underset{\mathbf{60}}{(CH_3)_3SiCH_2CH{=}CH_2} \xrightarrow[THF]{BuNF\ (\mathbf{87})} \underset{53\%\ \mathbf{92}}{C_6H_5(CH_2)_2CH{=}CH_2} + \underset{\mathbf{84}}{(CH_3)_3SiF} + \underset{\mathbf{93}}{Bu_4NCl}$$

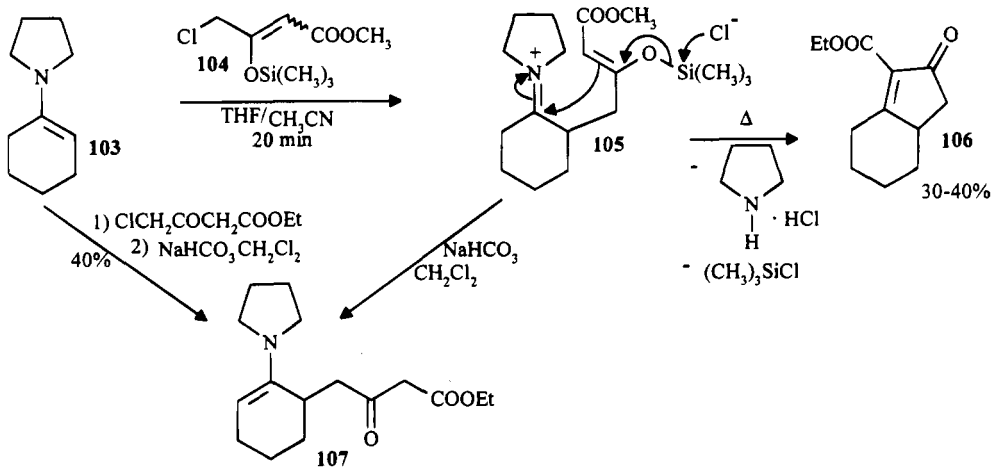
$$\underset{\mathbf{94}}{CH_2Br(CH_2)_4CH_2Br} + 2\underset{\mathbf{60}}{(CH_3)_3SiCH_2CH{=}CH_2} \xrightarrow[THF]{Bu_4NF\ (\mathbf{87})} \underset{61\%\ \mathbf{95}}{CH_2{=}CH(CH_2)_8CH{=}CH_2}$$

Similar reactions employing anhydrous phosphazenium fluorides were reported recently.[73]

Scheme 20



Scheme 21



8. Reactions of Silylated Alkyl 4-Chloroacetoacetate. Since we needed large amounts of imidazole (4,5)-acetic acid (**100a**), whose multistep synthesis via (4,5)hydroxymethylimidazole seemed to be quite awkward,[74] we wondered whether the commercial ethyl 4-chloroacetoacetate could be reacted with amidines **99** to **100**. Due to the low reactivity of the chloromethyl group in **96**, however, reaction with amidines affords exclusively 2-substituted 6-(chloromethyl)pyrimidin-4-ones.[75]

Since the chlorine in O-alkylated or silylated ethyl 4-chloroacetoacetate **97** is allylic and thus much more reactive, we silylated **96** with HMDS and TCS in more than 80% yield to a 4:1 mixture of (*E*)- and (*Z*)-ethyl 3-[(trimethylsilyl)oxy]-4-chlorocrotonate (**97**), which can be isolated and distilled.

Heating of **96** with amidines **98** in the presence of HMDS and Hünig base in acetonitrile afforded the corresponding ethyl imidazole(4,5)acetates **100** in up to 85% yield[32,76] via the probable intermediates **101** and **102**, in which the (*E*) and the (*Z*) isomer of **97** react the same way (Scheme 20).

Further reactions of **97** with *o*-phenylenediamine and the more complex reactions with ammonia and primary amines will be reported shortly.

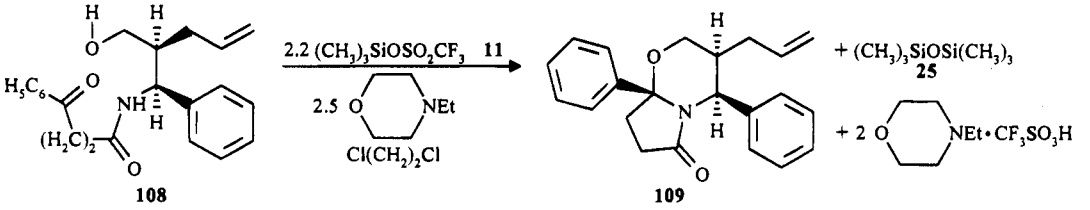
The pyrrolidine enamine of cyclohexanone **103** afforded with **104** via **105** the bicyclic keto ester **106** in 30–40% yield[32] (Scheme 21). Hydrolysis of the intermediate **105** gives the substituted enamine **107**, which is also obtained directly from **103** with ethyl 4-chloroacetoacetate. These yields have not been optimized as yet.

All the reactions of silylated alkyl 4-chloroacetoacetate and their subsequent ready cyclizations to the corresponding heterocyclic systems indicate that cyclizations with elimination of **24** (cf. also the cyclization of **34** → **35**) are especially facile and efficient due to the mobility[77] of the trimethylsilyl group. Thus after a facile alkylation of an enolate with methyl 4-chloro-3-methoxycrotonate, the enol ether had to be cleaved to the β-keto ester system followed by silylation and cyclization![78]

When we tried to cyclize the ω-keto-ω-hydroxyamide **108** by heating in toluene or xylene in the presence of camphorsulfonic acid (CSA), we observed only decomposition. But heating of **108** with 2.2 equiv of **11** in the presence of 2.5 equiv of *N*-ethylmorpholine in 1,2-

(73) Schweringer, R.; Link, R.; Thiele, G.; Rotter, H.; Honerl, D.; Limbach, H. H.; Mäusle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1372.
(74) Pyman, F. L. *J. Chem. Soc. (London)* **1911**, *99*, 668.
(75) Lonza AG. Ger. Pat. Appl. 2167194; *Chem. Abstr.* **1972**, *76*, 72539.
(76) To be published shortly.
(77) Klebe, J. F. *Acc. Chem. Res.* **1970**, *3*, 399.
(78) Shibazaki; M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090.

Scheme 22



dichloroethane afforded 46% of the desired cyclization product **109**[79] (Scheme 22).

On the basis of all these results we want to emphasize that, on planning any reaction implying the elimination of water, acid-catalyzed silylation and subsequent elimination of hexamethyldisiloxane (25) should always be considered!

Concluding Remarks. Although we were one of the first groups to investigate the elimination of water as **24** or **25** in a more systematic way,[32] quite a number of similar reactions, e.g., with sulfoxides,[80,81] aliphatic nitrocompounds,[82] or the aforementioned dehydration of primary amides to nitriles,[50-52] have been published and await a critical summary.[83]

I thank my colleagues at Schering AG for their help and support, but I am especially obliged to my very able and motivated technicians Mr. Konrad Krolikiewicz and Mrs. Bärbel Bennua-Skalmowski, who did most of the work described in these ventures with silicon organic chemistry. Finally I want to thank all of my various secretaries over the years, Mrs. H. Göritz, Mr. W. Becker, Miss C. Heinz, and Miss N. Schidniogrotzki, for their patient and able writing and rewriting of our manuscripts.

AR950014N

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(80) Chou, T. S. *Tetrahedron Lett.* **1974**, 725.
(81) de Koning, J. J.; Kooreman, H. J.; Tan, H. S.; Verweij, J. *J. Org. Chem.* **1975**, *40*, 1346.
(82) Torssell, K. B. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Verlag Chemie: Weinheim, Germany, 1988.
(83) Vorbrüggen, H. An extended review is in preparation.

Additions and Corrections

Vol. 28, 1995

Kanjai Khumtaveeporn* and Howard Alper*: Transition Metal Mediated Carbonylative Ring Expansion of Heterocyclic Compounds.

Page 416. The footnotes at the bottom of the page were incorrectly numbered. This error occurred during the production process. The Journals Department of the ACS was responsible for the error. The correct footnote numbers are 17–24.

(17) Chamchaang, W.; Pinhas, A. R. *J. Chem. Soc., Chem. Commun.* **1988**, 710.
(18) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943.
(19) Roberto, D.; Alper, H. *Organometallics* **1984**, *3*, 1767.
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(21) Reppe, W.; Kroper, H.; Pistor, H. J.; Weissbarth, O. *Justus Liebigs Ann. Chem.* **1953**, *582*, 87.
(22) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816.
(23) Nienburg, H. J.; Elschnigg, G. Ger. 1,066,572 (Oct 8, 1959); *Chem. Abstr.* **1961**, *55*, 10323h.
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