Table I. Comparison of Intrinsic Gas-Phase Equilibrium Acidities and Solution Equilibrium Acidities

| Acid | p$K$ (DMSO)[a] | $\Delta G°$ (DMSO)[b] | $\Delta\Delta G°$ (DMSO)[c] | $\Delta G°$ (g)[d] | $\Delta\Delta G°$ (g)[c] |
|---|---|---|---|---|---|
| $CH_3COCH_3$ | 26.7 | 36.4 | (0.0) | 50.1 | (0.0) |
| $CH_3COPh$ | 24.7 | 33.9 | 3.5 | 45.6 | 4.5 |
| $CH_3COCH_2Ph$ | 19.4 | 26.6 | 9.8 | 36.2 | 13.9 |
| $(CH_3CO)_2CH_2$ | 13.4[e] | 18.3 | 18.1 | 28.0 | 22.1 |
| $CH_3COCH_2COPh$ | 12.7[f] | 17.4 | 19.0 | 24.2 | 25.9 |
| $CH_3CN$ | 31.2 | 42.7 | (0.0) | 47.6 | (0.0) |
| $PhCH_2CN$ | 21.9 | 30.0 | 12.7 | 35.0 | 12.6 |
| $CH_2(CN)_2$ | 11.1[g] | 15.1 | 27.6 | 17.2 | 30.4 |
|  | 18.1 | 24.8 | | 39.1 | |
| $(Ph)_2CH_2$ | 32.3 | 43.2 | | 47.0 | |

[a] Absolute acidities. As a result of anchoring our p$K$ scale to absolute measurements in the 7–12 p$K$ region the values reported earlier[4] have been adjusted upward by slightly more than 2 p$K$ units; the p$K$ of fluorene, which was previously used as a reference standard, is now 22.6. [b] At 25°. [c] Not statistically corrected. [d] Data of J. B. McMahon and P. Kebarle (ref 3) obtained at 327°. [e] Lit. p$K$ 13.4.[5] [f] Lit. p$K$ 12.1.[5] [g] Lit. p$K$ 11.0.[5]

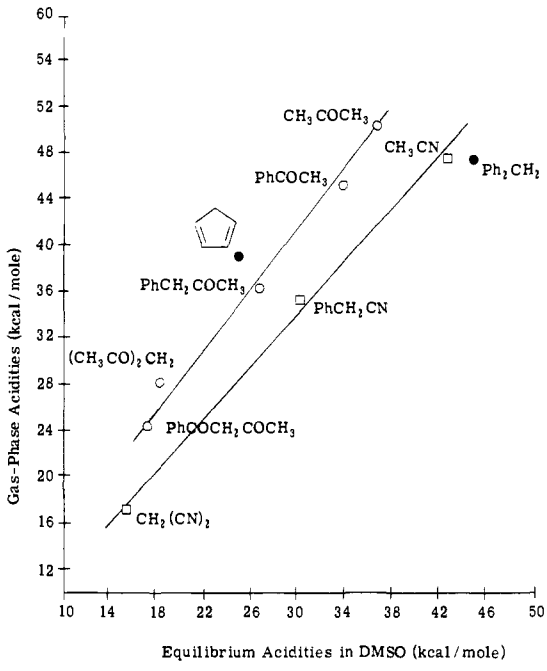


**Figure 1.** Equilibrium acidities of carbon acids in dimethyl sulfoxide (DMSO) solution plotted against intrinsic gas-phase acidities.

surprising degree to the intrinsic substituent effects revealed by gas-phase acidities. In other words, the solvent is exerting a relatively constant effect in both the nitrile series and the ketone series. The failure of substituent effects to be attenuated appreciably here is probably associated with the fact that the negative charge is delocalized in each instance essentially over the entire anion. This contrasts with the situation with meta- and para-substituted benzoic acids, where the charge is localized largely on the carboxylate ion. Solution substituent effects of a magnitude comparable to gas-phase substituent effects have also been observed for other highly delocalized ions, namely, aromatic radical anions,[6] and aryl carbocations.[7]

Although the substituent effects within the ketone and nitrile families are comparable in solution and in the gas phase (Figure 1), there is some indication of specific solvation effects. In the gas phase acetonitrile is a stronger acid than acetone by 2.5 kcal/mol,[8] whereas in DMSO solution acetonitrile is the weaker acid by 6.3 kcal/mol (Table I).

It may be significant that cyclopentadiene, which gives a symmetrically delocalized anion, is more acidic in DMSO, relative to the gas phase, than either the nitrile or ketone families (Figure 1). One might have expected on this basis that diphenylmethane would also be relatively more acidic in DMSO than in the gas phase, but it is not (Figure 1). This is consistent with other data, however, which indicate that twisting of the phenyl groups is required in $(Ph)_2CH^-$ anion.[9]

We anticipate that additional comparisons of gas phase and DMSO solution acidities will reveal further significant information concerning the nature of substituent effects and the nature of solvent effects.

**Acknowledgment.** We are grateful to the National Science Foundation (GP 42725X) for support of this research.

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(9) J. E. Bares, unpublished results.
(10) National Science Foundation Postdoctoral Fellow, 1971–1972.

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## Consecutive 3,5 Shifts in Pyridine 1-Oxide Rearrangements. One-Step Furopyridine Synthesis

*Sir:*

When the 3- and 5-positions are blocked in a pyridine 1-oxide, reaction with benzyne gives, under conditions of kinetic control, products resulting from 1,3- and/or 1,5-sigmatropic shifts in the original 1,2-dihydropyridine 1,3-cycloadduct.[1] With 3,5-dihalogenated pyridine 1-oxides (**1**) elimination of hydrogen halide from the 1,5-sigmatropic shift product leads to benzofuro[3,2-*b*]pyridines in good yield.[1] Furopyridines are of interest since perhydro derivatives occur in the alkaloids febrifugine and jervine[2] and furo[2,3-*b*]quinolines are present in dictamnine and related alkaloids.[3] Little work has been carried out on the synthesis

Table I. Reaction of 1 with Some Acetylenes

| X | R,R' | Products | Mp, °C | Yield (%)[a] |
|---|---|---|---|---|
| Cl | R = Ph, R' = CN | 3a | 207–208 | 55.0 |
| | | 4a | 126–127 | 12.9 |
| Br | R = Ph, R' = CN | 3b | 200–201 | 22.4[b] |
| | | 4b | 137–138 | 20.6 |
| Cl | R = Ph, R' = $CO_2Me$ | 3c | 147–147.5 | 20.1[c] |
| | | 4c | 87–88 | 28.3 |
| Cl | R = R' = $CO_2Me$ | 3d | 102–103 | 60.0[d] |
| | | 4d | 133–134 | 5.0 |

[a] Isolated unoptimized yields. [b] Recovered 1, 33.5%. [c] Recovered 1, 38.4%. [d] Recovered 1 27.7%.

Table II. Reaction of 4-Substituted Pyridine 1-Oxides with Some Acetylenes

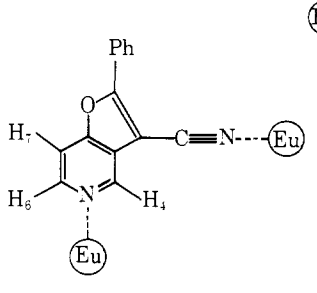
| $X_1$ and $X_2$ in 9 | R and R' in 2 | Product | Mp, °C | Yield (%)[a] |
|---|---|---|---|---|
| $X_1$ = H, $X_2$ = Cl | R = Ph, R' = CN | 5a | 134–135 | 96.5 |
| $X_1$ = H, $X_2$ = Cl | R = Ph, R' = $CO_2Me$ | 5b | Oil[b] | 70.8 |
| $X_1$ = H, $X_2$ = OMe | R = Ph, R' = CN | 5a | | 70.5 |
| $X_1$ = H, $X_2$ = OMe | R = Ph, R' = $CO_2Me$ | 5b | | 62.6 |
| $X_1$ = $X_2$ = Cl | R = Ph, R' = CN | 5c | 196–197 | 67.2[c] |
| $X_1$ = Cl, $X_2$ = $NO_2$ | R = Ph, R' = CN | 5c | | 45.7[d] |

[a] Reaction carried out in boiling toluene; products isolated by dry column chromatography on silica gel. [b] Picrate, mp 225–226°, dec. [c] Recovered 2, 11%. [d] Recovered 2, 13%.

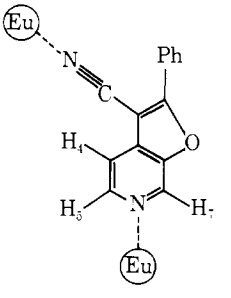
of the furo[3,2-*b*]pyridine ring system.[4-6] We now report a convenient one-step synthesis of furopyridines and a new molecular rearrangement.

Six-membered heteroaromatic *N*-oxides and suitable acetylenes gave β-alkylated products probably via a [$_\sigma 2_s$ + $_\pi 2_a$ + $_\pi 4_s$] rearrangement.[7] Reaction of 3,5-dichloropyridine 1-oxide (**1a**) with phenylpropiolonitrile (**2a**) in boiling toluene has now been found to give two isomeric chlorofuropyridines ($C_{14}H_7ClN_2O$, M·$^+$ *m/e* 254,256), resolved by preparative TLC. Thus were obtained **3a** (55%), mp 207–208° dec (NMR δ 8.64 (d, 1, $J_{5,7}$ = 2.1 Hz, $H_5$), 7.90 (d, 1, $J_{5,7}$ = 2.1 Hz, $H_7$), and aromatic protons), and **4a** (12.9%), mp 126–127° (NMR δ 8.94 (s, 1, $H_4$), 8.61 (s, 1, $H_6$)).[8] The spectral data for **4a** did not establish its structure unambiguously nor did those of its dechlorinated (zinc dust in acetic acid) product **5a** (57.7%), mp 134–135°. These could fit equally well the isomeric structure 2-phenyl-3-cyanofuro[2,3-*c*]pyridine (**6**).

A decision between **5a** and **6** could be made unambiguously by the use of Eu(fod)$_3$ shift reagent. The dechlorinated product exhibits the following NMR spectrum (excluding phenyl protons): δ 9.14 (s, 1, $H_4$ in **5a** or $H_7$ in **6**), 8.74 (d, 1, $J$ = 5.9 Hz, $H_6$ in **5a** or $H_5$ in **6**), 7.60 (d, 1, $J$ = 5.9 Hz, $H_7$ in **5a** or $H_4$ in **6**). Addition of up to 1 equiv of Eu(fod)$_3$ to a $CDCl_3$ solution of the compound resulted in shifting of all three pyridine protons (complexation at pyridine nitrogen atom), with the α-protons shifting most. As further shift reagent was now added formation of a linear complex at the nitrile nitrogen was expected.[9] No further

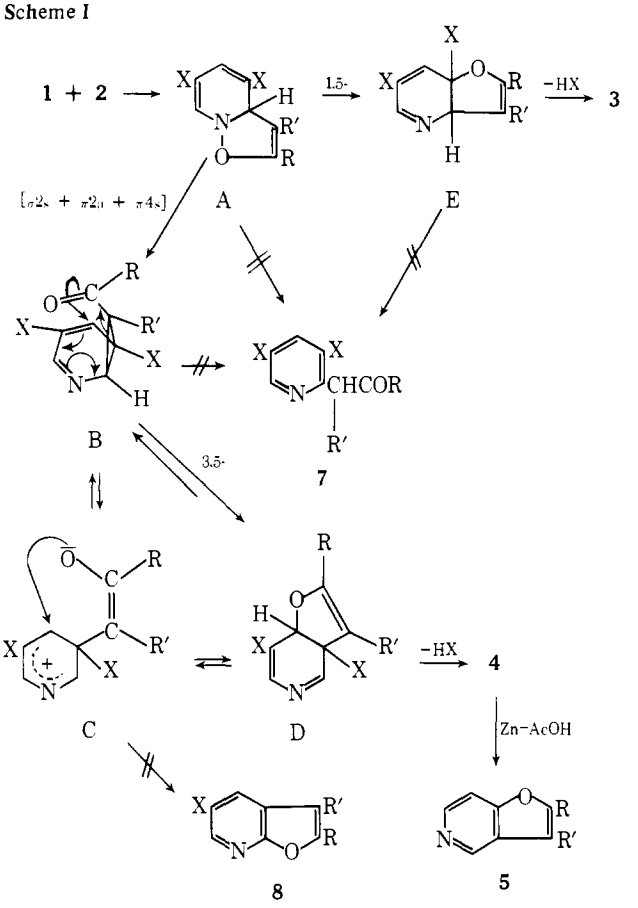



complexed **5a**

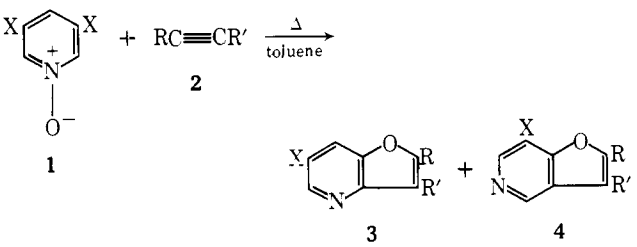



complexed **6**

Scheme I




shift was observed in the protons giving rise to a doublet, but the singlet proton peak suffered an even greater shift (Δδ = 25 ppm), compatible only with structure **5a.** The reaction appears to have general application as seen from the results in Table I.

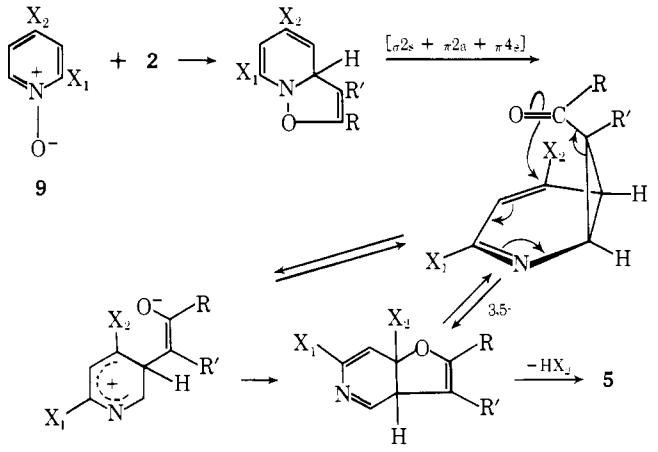



Formation of **3** probably proceeds by the 1,5 shift previously postulated for the 1,2-dihydro intermediates.[1] It is interesting to note that *no* 2-alkylated products (**7**) were observed in any of these reactions. **4** could arise by [$_\sigma 2_s$ + $_\pi 2_a$ + $_\pi 4_s$] rearrangement[1,7] of A (Scheme I) to B followed either by ring-opening to C[7] and ring closure to D or by another concerted 3,5-sigmatropic shift B → D followed by loss of hydrogen halide. Speaking against the stepwise process (B → C → D) is the fact that no furo[2,3-*b*]pyridines (**8**) were ever detected. A 1,5-sigmatropic shift similar to A → E has recently been observed in the reactions of **1a**[10] and 3-bromoquinoline 1-oxide[11] with phenyl isocyanate.

On the basis of this scheme, we anticipated that the above new rearrangement would be even more facile if a halogen or pseudo-halogen were present at $C_4$ of the pyridine ring. This is indeed found to be the case. Thus, treatment of 4-chloropyridine 1-oxide (**9a**) with **2a** gave an excellent yield (96.5%) of **5a.** Some extensions of this reaction are summarized in Table II.

Possible routes to **5** are sketched in Scheme II.

Scheme II



Extension of the synthetic scope of this reaction and investigation of aspects of the mechanisms of the rearrangements observed are under study.

**Acknowledgment.** We wish to thank the National Institutes of Health (Grant No. GM-16626) for support of this work.

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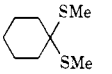
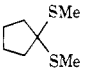
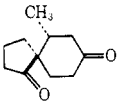
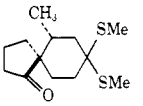
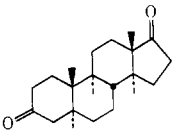
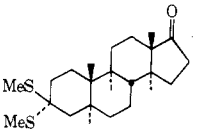
## Methylthiotrimethylsilane. A Versatile Reagent for Thioketalization under Neutral Conditions

*Sir:*

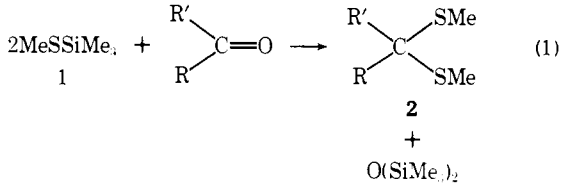
It is now well recognized that silicon is an excellent oxygenophile, and as such, a host of useful synthetic methods have been developed which exploit this property.[1] As a class, alkylthiosilanes[2] have gone virtually unrecognized as potentially useful reagents in organic synthesis[3] although such silicon derivatives are easily prepared by a variety of methods.[2,4]

During an investigation into the chemistry of organosulfur derivatives of silicon, we have developed an exceptionally mild procedure for thioketalization *which proceeds without the apparent requirement of acid catalysis* (eq 1). We have found that methylthiotrimethylsilane, TMS-SMe (**1**),[5] reacts spontaneously at 0° with aldehydes and ketones to give dimethylthioketals, **2**, in excellent yields (Table I). Reaction solvents such as $C_6H_6$, $CH_3CN$, $CH_2Cl_2$, and $Et_2O$ may be employed with equal success; however, the overall reaction rate of thioketalization appears to be proportional to solvent polarity. The following is a general procedure for thioketalization.

Table I. Thioketalization with TMS–SMe (eq 1)

| RRC=O | 2[a] | % yield[b] | bp (mp), °C |
|---|---|---|---|
| $C_6H_5CHO$ | $C_6H_5CH(SMe)_2$[c] | 90 | 35 (0.04 mm) |
| $CH_3(CH_2)_5CHO$ | $CH_3(CH_2)_5CH(SMe)_2$[d] | 88 | 48 (0.06 mm) |
|  |  | 90 | 35 (2.0 mm) |
|  |  | 93 | 39 (2.0 mm) |
|  |  | 93 | (70–71) |
|  |  | 92 | (156–158) |

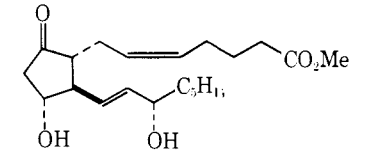
[a] Consistent spectral data and combustion analyses have been obtained on all compounds shown. [b] Isolated yields. [c] A. Schonberg and K. Praefcke, *Chem. Ber.*, **100**, 778 (1967). [d] J. M. Lalancette, Y. Beavregard, and M. Bhereur, *Can. J. Chem.*, **49**, 2983 (1971). [e] V. J. Morgenstern and R. Mayer, *J. Prakt. Chem.*, **34**, 116 (1966). [f] K. Grimm, P. S. Venkatrami, and W. Reusch, *J. Am. Chem. Soc.*, **93**, 270 (1971).



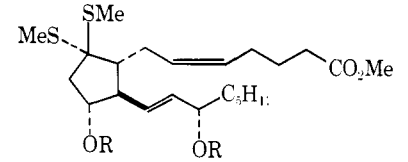
(1)

To a cooled (0°) solution of ketone or aldehyde in anhydrous ether is added dropwise 2 equiv of TMS-SMe (**1**) over a 15-min period. After the addition is completed, the reaction is allowed to stir at room temperature for 2 hr. Addition of water and extraction with ether or methylene chloride are followed by drying ($Na_2SO_4$), removal of solvents, and filtration through alumina (activity III) to remove minor impurities.

This mild carbonyl derivatization procedure may be further illustrated by the conversion of $PGE_2$ methyl ester (**3**) into the dimethylthioketal **4b** in 37% overall yield.[6] Treatment of **3** with 4 equiv of TMS-SMe in acetonitrile at 0° afforded **4a** which was hydrolyzed (MeOH, $H_2O$, HOAC; 20:2:1) to **4b** following literature precedent.[7]



**3**



**4a**, R = TMS
**b**, R = H