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ADDITION REACTION OF TRIMETHYLSILYL AZIDE TOWARDS KETONES AND FACILE FORMATION OF TETRAZOLE DERIVATIVES

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In the presence of Lewis acid such as $SnCl_2$, the reactions of trimethylsilyl azide with ketones readily gave 1:1- or 1:2-adduct, which reacted with Lewis acid to afford tetrazole.

For some time a great deal of attention has been focused on silyl azides because of their utilities for heterocycle synthesis.[1] There has been only a few reports concerning azide synthesis by silyl azide.[1,2] It has been well-known that silyl cyanides (≥SiCN)[3] and silyl thioethers (≥SiSR)[4] reacted with carbonyl compounds to give 1:1- or 1:2-adducts, while silyl azides did not react with these compounds[3,5] except for aliphatic aldehydes[2a,b] under the employed conditions. Vorbrüggen and his co-worker reported that the first reaction of silyl azide towards ketone,[6] in which chlorotrimethylsilane, sodium azide, and cyclohexanone in DMF gave 1-azido-1-trimethylsiloxycyclohexane in 58% yield. However, it is not clear whether this reaction involves prior *in-situ* formation of trimethylsilyl azide (TMSA) or not, because we could isolate only a trace amount of the compound in the reaction mixture of TMSA with cyclohexanone under the similar conditions. In this communication, we wish to describe the catalytic addition reaction of TMSA to ketones and a facile synthesis of tetrazole derivatives.

A typical reaction of ketone with TMSA was carried out as follows. To a mixture of acetone (22 mmol) and $SnCl_2 \cdot 2H_2O$ (2.2 mmol) *without solvent* was added TMSA (29 mmol) dropwise at 0 °C with stirring. And then the mixture was kept at room temperature for 20 h. The reaction mixture was poured into water and extracted with ether. The dried ether extract gave 38% of 2,2-diazidopropane [m/z 111.041 ($M^+ - CH_3$), ν_{max} 2100 cm^{-1}, ^1H NMR δ 1.5 (s), ^{13}C NMR δ 79.7 ($=\underline{C}(N_3)_2$) and 25.3 ($-\underline{C}H_3$), and bp 62-63 °C/85 mmHg (stable at this temperature)] as 1:2-adduct, while 1:1-adduct, *e.g.* 2-azido-2-trimethylsiloxypropane, could not be detected. With 3 equiv. of TMSA, the yield of the diazide increased to 82%. In stead of $SnCl_2$, zinc chloride ($ZnCl_2$) also catalyzed the reaction to give the azide in a moderate yield. When solvent such as ether, benzene, or dichloromethane was used, the yield of the azide was lowered to less than one third.

Other ketones reacted in a similar manner. The results are listed in Table 1. The diazides were confirmed with spectral analysis and by conversion into tetrazoles[7] as described below. The results show that TMSA was reactive towards

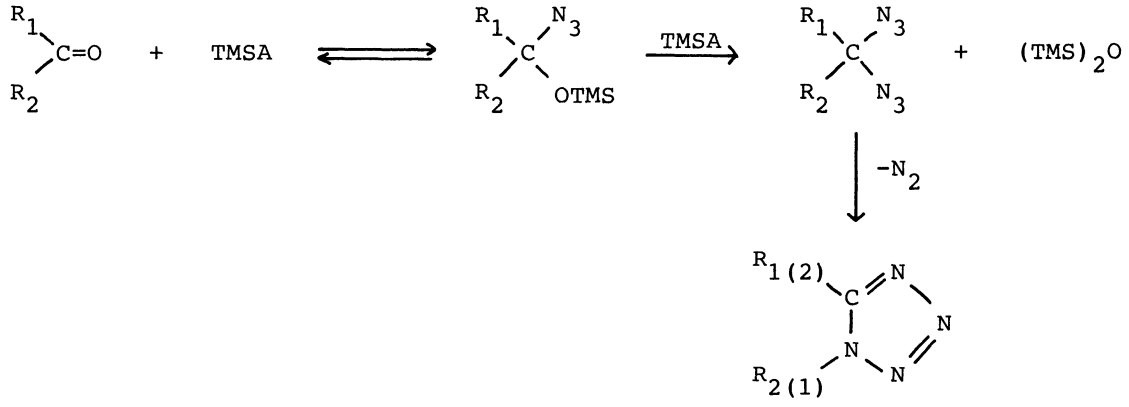
Table 1. The Reaction of TMSA with Ketones[a)]

R_1	R_2	$SnCl_2$ mol %	Yield/% $R_1(N_3)C(R_2)OTMS$	$R_1(N_3)C(R_2)N_3$	$R_{1(2)}$-tetrazole-$R_{2(1)}$
Me	Me	3	0	69	0
		10	0	82	0
Me	Et	3	0	52	0
		10	0	79	0
Me	n-Pr	3	0	47	0
		10	0	70	0
Me	i-Pr	3	0	40	0
		10	0	34	11
Me	Ph	3	0	26	0
		10	0	32	18
Me	CH_2Ph	3	0	28	0
		10	0	23	27
Et	Et	3	0	39	0
		10	0	45	5
$-(CH_2)_4-$		3	7	0	trace
$-(CH_2)_5-$		3	61	0	2

a) Reaction conditions are cited in text.

ketones to give 1:1- or 1:2-adduct under mild conditions in contrast to the reported investigations.[4,6)] Yields of the azides and tetrazole derivatives depend upon the bulkiness of alkyl group, structure of ketone, and the amount of catalyst. When acyclic ketone was employed, the sole adduct was not 1:1 but 1:2, as compared with cyclic ketone. That either 1:1- or 1:2-adduct could be isolated would be controlled by the azides' stability and/or their reactivities towards TMSA.

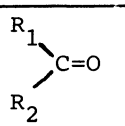
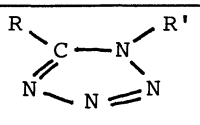
Treatment of 1-azido-1-trimethylsiloxycyclohexane with catalytic amounts of $SnCl_2$ gave cyclohexanone and TMSA together with the startting material. This indicates that the first step of the reaction of TMSA with ketone should be reversible.



The diazides would be stepwisely produced from the monoazides. The time dependency of the product distribution was remarkable; only the azide was detected at early stage, and both the azide (mono- or diazide) and the tetrazole were found at the long reaction time. On the basis of these findings, we propose the above reaction pathway.

Some of tetrazole derivatives have been known as biologically active compounds and their chemistry has been well established.[8] However, selective formation of tetrazoles required multi steps and/or complicated materials,[9] while the reaction of ketone with hydrazoic acid (HN_3), which has been known as a simple tetrazole formation, gave amide as a major product and tetrazole in a low yield because of the presence of water.[10] The confirmation of tetrazole derived from the azides led us to examine the direct reaction of ketone with TMSA in the presence of catalyst at elevated temperature. A mixture of acetone, 3 equiv. of TMSA, and 0.1 equiv. of $SnCl_2 \cdot 2H_2O$ was heated at 55 °C for 20 h with stirring. From the reaction mixture, 1,5-dimethyltetrazole was eluted quantitatively with benzene by column chromatography on alumina. Other ketones were treated with TMSA and $SnCl_2$ in a similar manner and the results are shown in Table 2. The known tetrazoles were identified by comparing with the authentic materials and all new compounds were determined by elemental analysis as well as spectroscopic analysis.

Table 2. Formation of Tetrazoles[a]

					
				^{1}H NMR (δ, ppm)	
R_1	R_2	Yield/% (R=Me : R'=Me)	mp/°C	1-position	5-position
Me	Me	99	72-73	4.00 (s, 3H)	2.50 (s, 3H)
Me	Et	69 (73 : 27)			
Me	n-Pr	96 (80 : 20)			
Me	i-Pr	80 (88 : 12)			
Me	t-Bu	40 (100 : 0)	76-77	1.70 (s, 9H)	2.65 (s, 3H)
Me	CH_2CMe_3	91 (100 : 0)	82-83	4.05 (s, 2H) 1.00 (s, 9H)	2.50 (s, 3H)
Me	Ph	80 (89 : 11)			
Me	CH_2Ph	93 (43 : 57)			
Et	Et	99	36	4.35 (q, 2H) 1.52 (t, 3H)	2.85 (q, 2H) 1.40 (t, 3H)
$-(CH_2)_4-$		71	115-116		
$-(CH_2)_5-$		71	57-58		
$-(CH_2)_6-$		86	66-67		
$-(CH_2)_7-$		60	oil		

a) Reaction conditions are cited in text.

With t-BuCOMe, Me_3CCH_2COMe, and cyclic ketones except for cyclohexanone, although the yield of the adduct (1:1- or 1:2-) was too low to isolate, the tetrazoles were obtained in a fairly good yield in all cases. As expected, two isomers of tetrazoles were obtained from unsymmetrical ketones. The isomer ratios were determined by ^1H NMR, which showed methyl resonance at about δ 2.5 or 4.0 ppm. The former was assigned to C-$C\underline{H}_3$ and the latter to N-$C\underline{H}_3$. The ratios can be explained by the steric effect and the migratory aptitude of the substituents, which are consistent with the Schmidt-type rearrangement;[11] Me< Et< i-Pr< t-Bu.

It has become clear that TMSA reversibly added to carbonyl group to give 1:1-adduct followed by formation of condensation product, 1:2-adduct, which was relatively stable diazide. The diazide was one of precursors of tetrazole derivatives. The reaction of TMSA with ketone readily gave tetrazole as one pot reaction product in good yield.

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