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New Syntheses of α-N-Alkylacetamidomethylated Carbonyl Compounds

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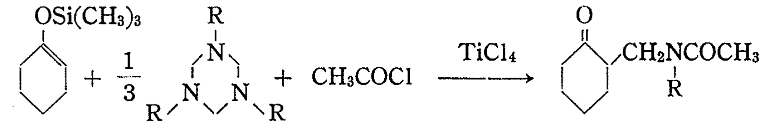
Reaction of silyl enol ethers of ketones and aldehydes with 1,3,5-trialkylhexahydro-1,3,5-triazines in the presence of acetyl chloride and titanium tetrachloride afforded α-N-alkylacetamidomethylated carbonyl compounds. Thus, the reaction provides a convenient, general method for introduction of the N-alkylacetamidomethyl moiety at a position α to a carbonyl group.

Keywords——N-alkylamidomethylation; 1,3,5-trialkylhexahydro-1,3,5-triazine; acetyl chloride; titanium tetrachloride; silyl enol ether

In the light of our previous report[1] on N-alkylamidomethylation by the use of the 1,3,5-trialkylhexahydro-1,3,5-triazine–acetyl chloride system, we were interested in the possibility of introducing an N-alkylamidomethyl unit at a position α to a carbonyl group. Subsequent hydrolysis can afford an N-monoalkylaminomethylated carbonyl compound, while the usual Mannich reaction is effective only for the introduction of an N,N-dialkylaminomethyl unit. Although a method of ureidoalkylation by the reaction of a silyl enol ether with N-(chloromethyl)carbamate in the presence of titanium tetrachloride has been reported with a few examples very recently,[2] N-alkylamidomethylation at a position α to a carbonyl group has independently been found to be feasible by the reaction of a silyl enol ether in the 1,3,5-trialkylhexahydro-1,3,5-triazine–acetyl chloride–titanium tetrachloride system.

The investigation was initiated by allowing 1-trimethylsilyloxy-1-cyclohexene (**2**) to react with 1,3,5-trialkylhexahydro-1,3,5-triazines, where R is methyl (**1a**), isopropyl (**1b**) or *n*-butyl (**1c**), in the presence of acetyl chloride and titanium tetrachloride in dichloromethane at 0—10°, whereupon the corresponding N-alkyl-N-[(2-oxocyclohexyl)methyl]acetamides (**3a**—**c**) were obtained in 32—48% yields.



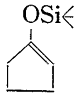
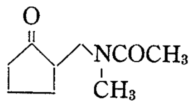
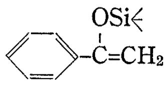
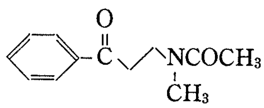
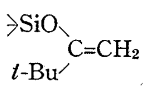
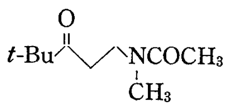
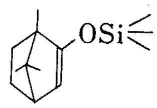
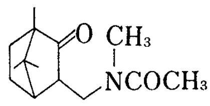
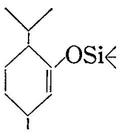
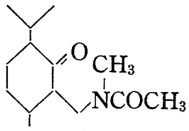
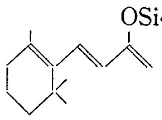
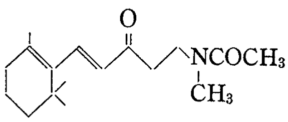
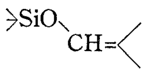
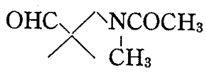
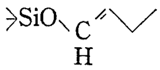
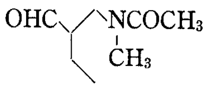
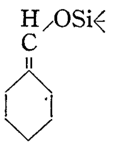
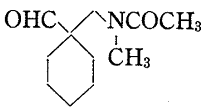
2 **1a—c** **3a—c**

		yield
1a, 3a:	R=CH_3	44%
1b, 3b:	R=iso-C_3H_7	48%
1c, 3c:	R=n-C_4H_9	32%

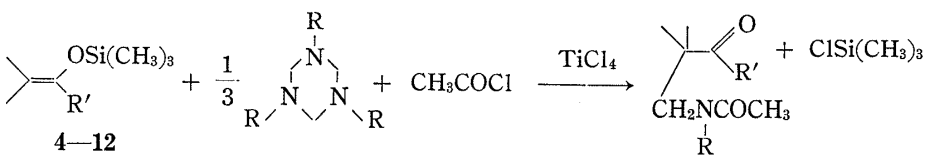
We next investigated the generality of this N-alkylamidomethylation. Various silyl enol ethers of not only ketones (**4**—**9**) but also aldehydes (**10**—**12**) were allowed to react with **1a**, acetyl chloride and titanium tetrachloride under the conditions described above for **2**. The results of these experiments are summarized in Table I; the N-methylacetamidomethylation worked well in every run, providing considerable yields of the products.

Although the literature contains **3a**,[3] **14**[4] and **19**[5] among these products, the reported syntheses of these compounds are very limited and virtually no general method for N-alkylamidomethylation of carbonyl compounds has been previously available. All the products gave

Table I. Production[a)] of α-N-Methylacetamidomethylated Carbonyl Compounds

Substrate	No.	Product	No.	Yield[b)] (%)
	4		13	35
	5		14	40
	6		15	42
	7		16	55
	8		17	23
	9		18	27
	10		19	54
	11		20	40
	12		21	44

a) Reaction conditions: molar ratio of substrate: $(CH_3NCH_2)_3$: CH_3COCl: $TiCl_4$=1.0:0.4:1.2:1.2; solvent, CH_2Cl_2; 0—10° for 1 hr.
b) Based on the product actually isolated.



4—12
R′=H, alkyl

13—21

nuclear magnetic resonance (NMR) and infrared (IR) spectra and elemental analyses consistent with their structures, as shown in Table II. In the NMR spectra of the products, methyl protons of the acetyl group and of the N-methyl group appeared as two singlets, except for **3b**, **3c**, **19** and **21**, due to the partial double bond character of the nitrogen–carbonyl carbon bond.

The reaction may be interpreted in terms of an interaction of the silyl enol ether with N-alkyl-N-chloromethylamide formed *in situ* from **1** and acetyl chloride. Silyl enol ethers are known to be effective for nucleophilic reactions in the presence of titanium tetrachloride.[6)] The path of the N-alkylacetamidomethylation may be as illustrated in Chart 1.

Table II. Analytical and Spectral Data for N-Methylacetamidomethylation Products

Compd. No.	bp °C or (mm Hg) mp °C	Formula	Analysis (%) Calcd (Found) C	H	N	IR $\nu_{max}^{liq.}$ cm^{-1} >NCO-	C=O	NMR[a] ($CDCl_3$) δ ppm (J=Hz) CH_3CO (3H, s)	CH_3N (3H, s)	$-CH_2N$ (2H, m)
3a	125—126	$C_{10}H_{17}NO_2$	65.54	9.35	7.64	1624	1709	2.04	2.85	3.30—3.70
	(0.25)		(65.17	9.34	8.04)			2.09	3.04	
3b	53—54	$C_{12}H_{21}NO_2$	68.21	10.02	6.63	1632	1701[b]	2.12		2.90—3.60
			(68.20	10.22	6.61)					
3c	134—135	$C_{13}H_{23}NO_2$	69.29	10.29	6.22	1630	1710	2.05		3.10—3.60
	(0.20)		(69.34	10.40	6.57)					
13	112—113	$C_9H_{15}NO_2$	63.88	8.94	8.28	1621	1735	2.08	2.88	3.30—3.70
	(0.25)		(63.52	8.94	8.48)			2.07	3.00	
14	78—79	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	1626	1680[b]	2.04	2.94	3.72
			(70.09	7.33	6.81)			2.12	3.06	(t, J=6.0)
15	107—108	$C_{10}H_{19}NO_2$	64.83	10.34	7.56	1644	1706	2.04	2.86	3.53
	(0.50)		(64.74	10.42	7.51)			2.10	3.00	(t, J=6.0)
16	74—75	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	1640	1739[b]	2.08	2.95	3.10—4.10
			(70.85	10.06	5.98)			2.15	3.05	
17	122—123	$C_{14}H_{25}NO_2$	70.25	10.53	5.85	1644	1708	1.99	2.91	3.20—4.50
	(0.15)		(70.67	10.86	5.69)			2.02	3.06	
18	169—170	$C_{17}H_{27}NO_2$	73.60	9.81	5.05	1650	1686	2.05	2.93	3.64
	(0.15)		(73.91	9.94	4.75)			2.13	3.06	(t, J=6.0)
19	65—67	$C_8H_{15}NO_2$	61.12	9.62	8.91	1625	1725[b]	2.06	3.03	3.47
			(60.79	9.73	8.88)					(s)
20	118—119	$C_8H_{15}NO_2$	61.12	9.62	8.91	1634	1724	2.06	2.91	3.10—4.00
	(5.0)		(60.57	9.71	9.34)			2.12	3.05	
21	99—100	$C_{11}H_{19}NO_2$	66.97	9.71	7.10	1629	1722[b]	2.04	3.02	3.43
			(66.78	9.69	7.13)					(s)

a) s=singlet, t=triplet, m=multiplet. *b*) KBr disk.

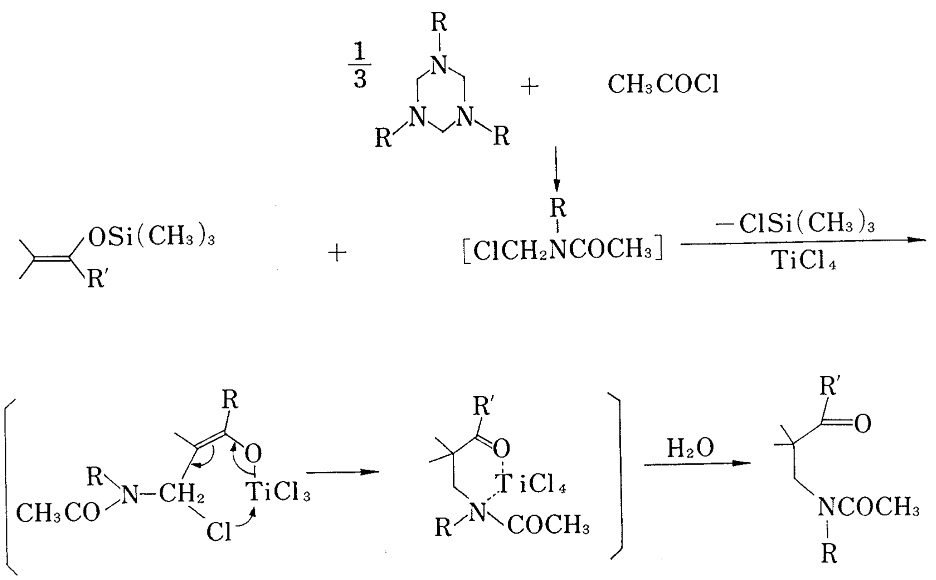


Chart 1

Experimental

All boiling and melting points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer. NMR spectra were recorded on a Hitachi R-24 spectrometer, and all chemical shifts are given in ppm downfield from TMS.

Preparation of Silyl Enol Ethers——The following trimethylsilyl enol ethers of carbonyl compounds were prepared according to the previously reported procedure:[7,8] **2**, bp 65—66° (12 mmHg) [lit.,[7] 74—75°

(20 mmHg)]; **4**, bp 84—85° (75 mmHg) (lit.,[8] bp 158—159°); **5**, bp 115—116° (40 mmHg) [lit.,[7] bp 89—91° (12 mmHg)]; **6**, bp 71—72° (80 mmHg) (lit.,[7] bp 140—142°); **7**, bp 100—101° (25 mmHg); **9**, bp 124—125° (5 mmHg); **10**, bp 53—54° (70 mmHg) (lit.,[7] bp 119°); **11**, bp 48—52° (46 mmHg) [lit.,[7] bp 56—62° (75 mmHg)]; **12**, bp 77—78° (15 mmHg) [lit.,[7] bp 75—76° (12 mmHg)]. A new compound, 3-trimethylsilyloxy-2-*p*-menthene (**8**), was prepared from menthone and trimethylsilyl chloride according to the procedure described in the literature,[8] and the physical data are as follows: **8**, bp 96—97° (15 mmHg), IR $\nu_{max}^{liq.}$ cm^{-1}: 1650 (C=C), NMR ($CDCl_3$) δ: 4.5—4.7 (1H, m, vinyl CH), 0.17 [9H, s, $Si(CH_3)_3$].

N-Alkylamidomethylation——General Procedure: A stirred solution of 0.03 mol of a 1,3,5-trialkyl-hexahydro-1,3,5-triazine (**1a**—**c**) in 200 ml of dry CH_2Cl_2 was treated dropwise with 7.1 g (0.09 mol) of acetyl chloride, with cooling, and stirring was continued for 1 hr at room temperature. To this solution, 0.082 mol of silyl enol ether (**2**—**12**) and 0.09 mol of $TiCl_4$ were added successively at 0—10°. After being stirred for 1 hr at 0—10°, the reaction mixture was washed with aqueous $KHCO_3$. The separated organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent gave an oily residue, which was fractionally distilled under reduced pressure to give the product (**3a**—**c**, **13**—**21**). Physical and analytical data for the products are listed in Table II.

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Reduction with Sodium Borohydride–Transition Metal Salt Systems. I.[1] Reduction of Aromatic Nitro Compounds with the Sodium Borohydride–Nickelous Chloride System

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The reduction of aromatic nitro compounds with the sodium borohydride–nickelous chloride system was examined.

Aromatic nitro compounds afforded primary amines in high yield without by-products. Similarly, nitroso-, azoxy-, azo- and hydroxylaminobenzene were reduced with sodium borohydride–nickelous chloride to give aniline.

Keywords——reduction; aromatic nitro compound; aromatic primary amine; sodium borohydride–nickelous chloride system; nitrosobenzene; azobenzene; azoxybenzene; phenylhydroxylamine

In recent years, significant advances have been made in the reduction of a variety of functional groups with sodium borohydride.[2] However, in general, sodium borohydride