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1,3-Dipolar Cycloaddition of the Simplest *N*-Acylazomethine Ylide Leading to 3- or 3,4-Substituted *N*-Acylpyrrolidines

TOSHIAKI MORIMOTO, YOSHITAKA NEZU, and KAZUO ACHIWA*

Shizuoka College of Pharmacy, 2–2–1 Oshika, Shizuoka 422, Japan

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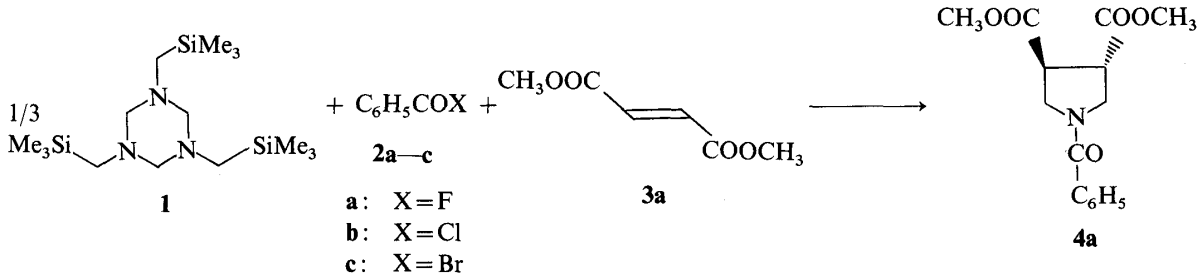
The 1,3-dipolar cycloaddition of intermediary *N*-acylazomethine ylides, formed from 1,3,5-tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine and acyl halides, to conjugated olefinic dipolarophiles has been found to give 3- or 3,4-substituted *N*-acylpyrrolidines in good yields.

Keywords——1,3-dipolar cycloaddition; *N*-acylazomethine ylide; 3,4-substituted pyrrolidine; 1,3,5-tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine; *N*-(halomethyl)amide; desilylation

As part of our studies to develop the chemistry of non-stabilized azomethine ylides[1] and to find a general synthesis of several types of pyrrolidines and 2,5-dihydropyrroles, we have previously reported[2] the trifluoroacetic acid-catalyzed 1,3-cycloaddition of *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine as a synthon for the simplest *N*-benzylazomethine ylide, leading to 3,4- or 3-substituted pyrrolidines and 2,5-dihydropyrroles. In this work, we show that 1,3,5-tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine (**1**) also behaves as a useful synthon for the simplest *N*-acylazomethine ylides (**6**) in the presence of acyl halides (**2**) and undergoes 1,3-cycloaddition to olefinic dipolarophiles (**3**) to afford the corresponding *N*-acylpyrrolidines (**4**) as shown below.

Preliminary experiments included examination of the relative activities of benzoyl halides (**2a—c**) using the triazine (**1**) and dimethyl fumarate (**3a**) in 1,1,2-trichloroethane or 1,1,2,2-tetrachloroethane by heating under reflux as shown in Table I. Table I indicates that benzoyl

TABLE I. Reaction of Dimethyl Fumarate (**3a**) with **1** in the Presence of Benzoyl Halides (**2a—c**)

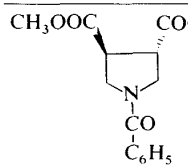
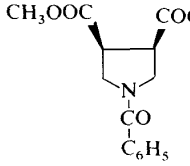
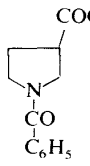
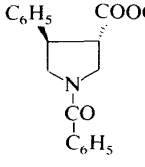
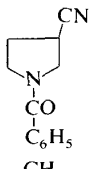
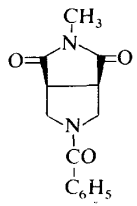


1 **2a—c** **3a** **4a**

a: X=F
b: X=Cl
c: X=Br

X	Molar ratio **1**:**2a—c**:**3a**	Solvent	React. temp. (°C)	React. time (h)	Yield (%)
F	1 :3 :3	$CHCl_2CH_2Cl$	110—115	24	55
F	1.3:3.9:3	$CHCl_2CH_2Cl$	110—115	20	80
Cl	1 :3 :3	$CHCl_2CH_2Cl$	110—115	48	41
Cl	1 :3 :3	$CHCl_2CHCl_2$	140—145	24	44
Br	1 :3 :3	$CHCl_2CH_2Cl$	110—115	24	43

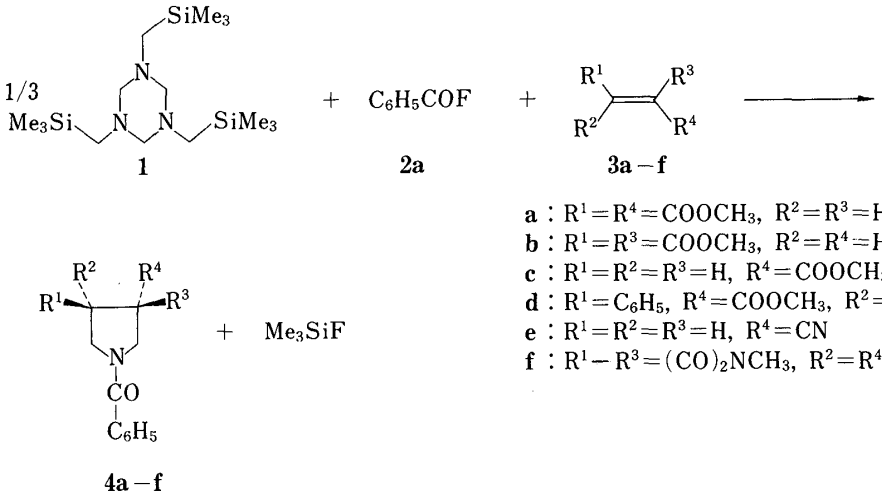
TABLE II. *N*-Benzoylpyrrolidines (**4a—f**)

Product		Yield (%)	bp[a] (C/mmHg) or mp (C)	IR (liq. or KBr) cm^{-1} (N–C=O)	IR (liq. or KBr) cm^{-1} (O–C=O)	^{1}H-NMR δ ($CDCl_3$)	Formula	Analysis (%) Calcd (Found) C	H	N
	**4a**	80	250/1	1630	1735	3.72 (6H, s, 2×CH_3) 3.30—4.30 (6H, m, 2×CH_2CH) 7.3—7.6 (5H, m, C_6H_5)	$C_{15}H_{17}NO_5$	61.85 (61.73	5.88 5.88	4.81 4.82)
	**4b**	71	—	1630	1735	3.72, 3.67 (6H, s, 2×CH_3) 2.85—4.2 (6H, m, 2×CH_2CH) 7.2—7.8 (5H, m, C_6H_5)	$C_{15}H_{17}NO_5$	61.85 (61.78	5.88 5.95	4.81 5.00)
	**4c**	81	240/5	1630	1735	2.10—2.32 (2H, m, CH_2) 2.83—3.32 (1H, m, CH) 3.66 (3H, s, CH_3) 3.32—4.08 (4H, m, 2×CH_2) 7.3—7.6 (5H, m, C_6H_5)	$C_{13}H_{15}NO_3$	66.93 (66.38	6.48 6.54	6.01 6.08)
	**4d**	49	—	1630	1735	3.60 (3H, s, CH_3) 2.9—4.35 (6H, m, 2×CH_2CH) 6.85—7.65 (10H, m, 2×C_6H_5)	$C_{18}H_{19}NO_3$	72.70 (72.94	6.44 6.26	4.71 4.71)
	**4e**	82	200/3	1630	2250 (C≡N)	1.87—2.36 (2H, m, CH_2) 2.78—3.94 (5H, m, 2×CH_2, CH) 7.16—7.52 (5H, m, C_6H_5)	$C_{12}H_{12}N_2O$	71.98 (71.56	6.04 6.09	13.99 13.75)
	**4f**	60	200—201 (EtOH)	1630	1695 1765 [N(C=O)$_2$]	2.99 (3H, s, CH_3) 3.25—4.35 (6H, m, 2×CH_2CH) 7.3—7.5 (5H, m, C_6H_5)	$C_{14}H_{14}N_2O_3$	65.10 (64.93	5.46 5.47	10.85 10.80)

a) Boiling point refers the bath temperature in a "Kugelrohr" short-path apparatus.

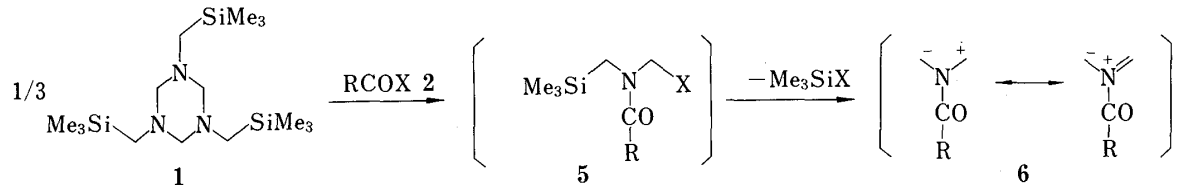
fluoride (**2a**) was most effective, and the best result was obtained by using 1.3 times the stoichiometric amount of **1** and **2a**.

Other dipolarophiles (**3b—f**) were also allowed to react with the triazine (**1**) and benzoyl fluoride (**2a**) in a molar ratio of 3 : 1.3 : 3.9 by heating in 1,1,2-trichloroethane. Table II shows that all the reactions gave the corresponding pyrrolidines (**4b—f**) in good yields. The spectral



and analytical data for the products (**4a—f**) are consistent with the proposed structures. The products **4a**, **b**, **d** were concluded to retain the configurations of olefinic dipolarophiles (**3a**, **b**, **d**), *i.e.*, 3,4-*cis* for **4b** and 3,4-*trans* for **4a**, **d** on the basis of the previous findings.[2] The similarity of nuclear magnetic resonance (NMR) spectra between **4a** and **4b** suggests that they are stereoisomers. When **4b** was distilled at 250 °C (1 mmHg), partial isomerization occurred to the thermodynamically stable isomer **4a** (detected by gas-liquid chromatographic analysis).

The present reaction can be rationalized in terms of the involvement of a reactive *N*-acylazomethine ylide (**6**) formed by 1,3-elimination of halosilane from an intermediary *N*-(halomethyl)amide (**5**).[3]



The advantages of this method are the stability of the reagent **1** to long storage and the potential availability of arbitrary acyl halides, although the present system is less reactive and requires higher temperatures than the *N*-(methoxymethyl)trimethylsilylamine–trifluoroacetic acid system.[2] Thus, this methodology provides a versatile procedure for synthesizing various *N*-acyl 3- or 3,4-substituted pyrrolidines by 1,3-dipolar cycloaddition of the simplest *N*-acylazomethine ylide (**6**), and may be applicable to the synthesis of azaprostacyclines.[4]

Experimental

All boiling and melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a JASCO IRA-2 spectrometer, and NMR spectra on a JEOL FX-90-Q spectrometer (with tetramethylsilane as an internal standard).

1,3,5-Tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine (1)——Aminomethyltrimethylsilane (5.16 g, 0.05 mol) was added dropwise to an ice-cooled 37% formaldehyde solution (4.46 g, 0.055 mol) with stirring. After 2 h of stirring at 0 °C, the reaction mixture was saturated with solid KOH and the organic layer was extracted with benzene (20 ml).

The aqueous layer was extracted with benzene (5 ml × 2). The benzene extracts were combined and dried over $MgSO_4$. Evaporation of the solvent left a liquid residue, which was distilled under reduced pressure on a "Kugelrohr" apparatus to give crude **1** (3.75 g) at a bath temperature of 170 °C (20 mmHg). The distillate was further purified by fractional distillation in a Claisen flask to yield pure **1**, 2.47 g (43%), bp 141—143 °C (24 mmHg). *Anal.* Calcd for $C_{15}H_{39}N_3Si_3$: C, 52.11; H, 11.37; N, 12.15. Found: C, 51.62; H, 11.40; N, 11.91. ^{1}H-NMR δ ($CDCl_3$): 0.06 (27H, s, 3 × Me_3Si), 1.91 (6H, s, $SiCH_2$), 3.10 (6H, br s, NCH_2N). ^{13}C-NMR δ ($CDCl_3$): −1.30 (q, Me_3Si), 44.1 (t, $SiCH_2$), 80.3 (t, NCH_2N).

Reaction of Olefinic Dipolarophiles (3a—f) with 1 in the Presence of Benzoyl Fluoride (2a)——General Procedure: A solution of benzoyl fluoride (**2a**) (484 mg, 3.9 mmol) in 1,1,2-trichloroethane (1 ml) was added to a stirred solution of an olefinic dipolarophile (**3a—f**) (3 mmol) and **1** (450 mg, 1.3 mmol) in 1,1,2-trichloroethane (5 ml) under nitrogen atmosphere. The stirred mixture was heated at 110—115 °C for 20 h. In the cases of **3c** and **3e**, the reaction was carried out at 90 °C for 3 h. After being cooled, the reaction solution was treated with saturated $NaHCO_3$ solution (6 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 ml). The organic layer and the extract were combined, washed with saturated NaCl (6 ml), and dried over $MgSO_4$. After evaporation of the solvent, the oily residue was purified by distillation or/and preparative thin-layer chromatography on Merck Silica-gel 60 (benzene : AcOEt = 4 : 1 for **4a—e** or 1 : 1 for **4f**). The yields of the products, **4a—f**, bp or mp, IR and NMR spectra, and analytical data are summarized in Table II.

References and Notes

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2) Y. Terao, H. Kotaki, N. Imai, and K. Achiwa, *Chem. Pharm. Bull.*, **33**, 2762 (1985).
3) In our previous paper, similar intermediary *N*-(halomethyl)amides derived from 1,3,5-trialkylhexahydro-1,3,5-triazines and acetyl chloride were used as amidomethylating agents. *Cf.* K. Ikeda, T. Morimoto, and M. Sekiya, *Chem. Pharm. Bull.*, **28**, 1178 (1980).
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