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Trifluoromethanesulfonic Acid-Promoted Reaction of Hexahydro-1,3,5-triazines. Introduction of a Secondary Aminomethyl Grouping into Carboxylates at the α-Position through Ketene Silyl Acetals

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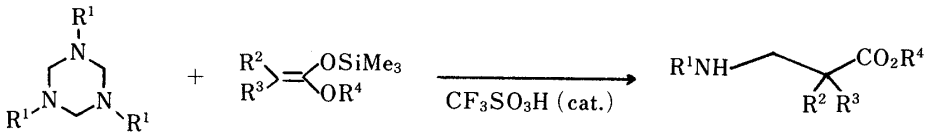
Introduction of the secondary aminomethyl grouping $RNHCH_2$ into carboxylates at the α-position has been achieved by reaction of hexahydro-1,3,5-triazines with ketene silyl acetals in the presence of a catalytic amount of trifluoromethanesulfonic acid.

Keywords——*N*-alkylaminomethylation; 1,3,5-trialkylhexahydro-1,3,5-triazine; ketene silyl acetal; trifluoromethanesulfonic acid; catalysis; β-lactam

Methods for synthesizing β-aminocarboxylates are of particular interest in connection with naturally occurring nocardicin A, sulfazecin, and related monobactam antibiotics. The reactivities[1] of 1,3,5-trialkylhexahydro-1,3,5-triazines (**1**) as *N*-alkylmethylenimine synthons[2] were shown by us to permit the *N*-alkylacetamidomethylation of electron-rich carbons by using **1** with acetyl chloride in the absence or in the presence of titanium tetrachloride. One of these papers reported the synthesis of *N*-alkyl-*N*-ureido-β-aminocarboxylates by the titanium tetrachloride-aided reaction of *N*-(chloromethyl)carbamate, derived from **1**, with ketene silyl acetals (**2**).

As communicated later, the *in situ* *N*-alkylaminomethylation of carboxylates at the α-position was found[3] to be readily achievable by the reaction of **1** with **2** in the presence of a catalytic amount of trifluoromethanesulfonic acid (**3c**). This reaction constitutes an important means for the introduction of the secondary aminomethyl grouping $RNHCH_2$ into carboxylates at the α-position, since no existing method can do this in a satisfactory way.

The previously known methods[4] have been limited to the introduction of the tertiary aminomethyl grouping $R'RNCH_2$ into carbonyl compounds at the α-position. We now wish to describe the details of our work.



1 **2** **3c** **4**

Preliminary experiments included examination of the relative efficiencies of various trifluoromethanesulfonate catalysts such as $Me_3SiOSO_2CF_3$ (**3a**), n-$Bu_2BOSO_2CF_3$ (**3b**), and $HOSO_2CF_3$ (**3c**). The reaction of ketene silyl acetal (**2a**), derived from methyl isovalerate, with one-third molar equivalent of 1,3,5-tribenzylhexahydro-1,3,5-triazine was carried out in dichloromethane at room temperature for 3 h using 0.05 molar equivalent of the catalyst. Under uniform conditions **3a**, **3b**, and **3c** gave methyl 2,2-dimethyl-3-(benzylamino)propionate in nearly the same yield (83—85%). The mechanistic rationale for the reaction is illustrated in

Chart 1. It is considered that **3a** may be the true catalyst which initiates formation of the *N*-silylated methyleniminium salt by reaction with **1**, and this intermediate attacks **2** as an electrophile to give *N*-silylated *N*-alkyl-*β*-aminocarboxylate with the stimultaneous generation of **3a**. In the reaction with **3b** or **3c**, a catalytic amount may initially be converted into **3a** by reacting with **2**, and thus enter the catalytic cycle.

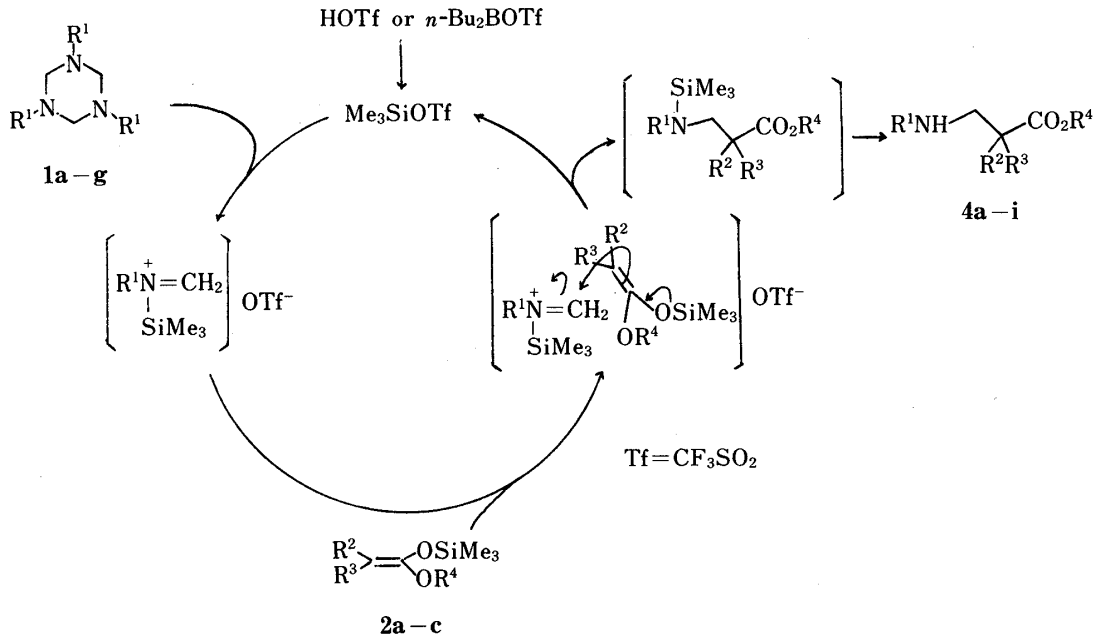
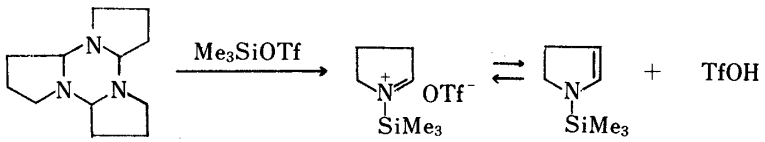


Chart 1

With **3a** as a catalyst, the reaction was extended to a number of derivatives of **1** and **2**, and the results are summarized in Table I. As can be seen, secondary aminomethylation of carboxylates at the α-position generally proceeds at room temperature in fair yield. *N*-(α-Methoxycarbonyl)benzyl-substituted *β*-aminocarboxylate (entry 8), which may be converted into a *β*-lactam structurally related to nocardicin A, was produced in considerable yield. The reaction of tetracyclic hexahydro-1,3,5-triazine is exemplified by the use of the trimer of 1-pyrroline; an alicyclic *β*-aminocarboxylate was formed but in rather low yield. This is probably because there exists an equilibrium (Chart 2) of the intermediary iminium salt which thermodynamically favors the less reactive enamine form.

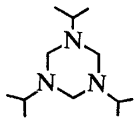
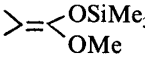
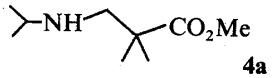
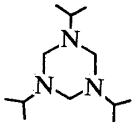
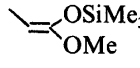
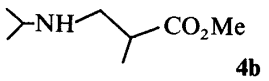
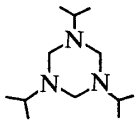
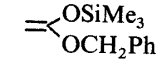
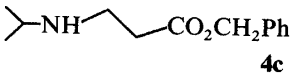
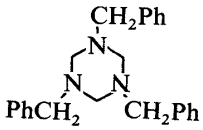
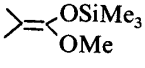
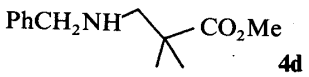
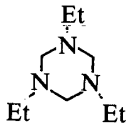
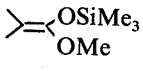
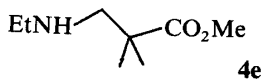
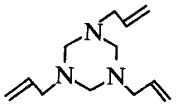
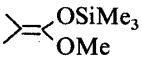
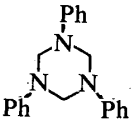
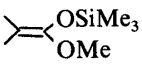
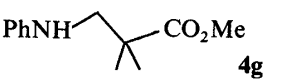
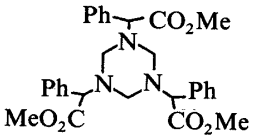
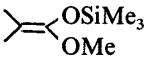
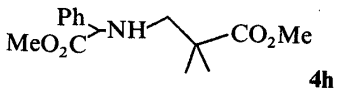
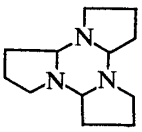
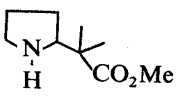


1g

Chart 2

Identification of the products was done on the basis of their spectral data (Table II). The infrared (IR) spectrum showed characteristic bands of a secondary amino group at 3312—3395 cm^{-1} and a carbonyl group at 1716—1740 cm^{-1}. The ^1H-nuclear magnetic resonance (NMR) spectrum showed the signal of a methylene proton (>N–CH_2–) at 2.06—3.19 ppm. In addition, the ^{13}C-NMR spectrum showed the signal of a carbonyl carbon (singlet) at 176.3—

TABLE I. Production of Alkyl *N*-Alkyl-*β*-Aminocarboxylates

Entry	Hexahydro-1,3,5-triazine No.	Ketene silyl acetal No.	Reaction[a] temp., time (h)	Product No.	Yield[b] (%)
1	 **1a**	 **2a**	r.t., 5	 **4a**	83
2	 **1a**	 **2b**	r.t., 1.5	 **4b**	87
3	 **1a**	 **2c**	r.t., 1.5	 **4c**	41
4	 **1b**	 **2a**	r.t., 3	 **4d**	83
5	 **1c**	 **2a**	r.t., 1	 **4e**	58
6	 **1d**	 **2a**	r.t., Overnight	 **4f**	76
7	 **1e**	 **2a**	r.t., 2	 **4g**	67
8	 **1f**	 **2a**	r.t., 2	 **4h**	69
9	 **1g**	 **2a**	r.t., Overnight	 **4i**	20

a) Triazine, ketene silyl acetal = 1 : 3 (molar proportion); CF_3SO_3H, 5 mol%; solvent, CH_2Cl_2. *b*) Based on the product isolated. r.t., room temperature.

177.9 ppm. In the ^{1}H-NMR spectrum of **4h**, the methylene proton ($>N-CH_2-$) signals appeared at 2.55 and 2.64 ppm (AB-quartet, $J = 12$ Hz).

Thus, the reaction provides an efficient method for direct introduction of the secondary aminomethyl grouping $RNHCH_2$ into a carboxylate at the α-position by simple procedures and in good yield.

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO A-202 spectrometer. ^{1}H-

TABLE II. Spectral and Analytical Data for Alkyl *N*-Alkyl-β-Aminocarboxylates

Compd. No.	bp (°C) (mmHg) mp (°C)	IR $\nu_{max}^{liq.}$ cm^{-1} (C=O)	IR $\nu_{max}^{liq.}$ cm^{-1} (NH)	^{1}H-NMR ($CDCl_3$) δ ppm (J=Hz)	^{13}C-NMR ($CDCl_3$) δ ppm	Formula M_r	Analysis (%) Calcd (Found) C	H	N
4a	90—91 (75)	1740	3345	1.01 (6H, d, J=6.1, $\underline{Me}_2CH$), 1.18 (6H, s, Me_2C), 2.65 (2H, s, $\overline{NCH_2}$), 2.68 (1H, sept, J=6.1, $Me_2C\underline{H}$), 3.66 (3H, s, OMe)	23.1 (q, $\underline{Me}_2CH$), 23.7 (q, $\underline{Me}_2C$), 43.6 (s, $Me_2\underline{C}$), 49.1 (d, $Me_2\underline{C}H$), 51.5 (q, OMe), 56.3 (t, NCH_2), 177.7 (s, CO)	$C_9H_{19}NO_2$ 173.25	62.39 (62.15	11.05 11.08	8.09 7.78)
4b	84 (80)	1736	3312	1.09 (6H, d, J=4.4, $\underline{Me}_2CH$), 1.23 (3H, d, J=4.3, $\underline{Me}CH$), 1.83 (1H, br s, NH), 2.60—3.19 (4H, m, $Me_2C\underline{H}$ $MeC\underline{H}$ and NCH_2), 3.85 (3H, s, OMe)	15.4 (q, $\underline{Me}CH$), 23.0 (q, $\underline{Me}_2CH$), 40.4 (d, $\underline{Me}\underline{C}H$), 48.5 (d, $\underline{Me}_2\underline{C}H$), 50.4 (t, NCH_2), 51.5 (q, OMe), 176.3 (s, CO)	$C_8H_{17}NO_2$ 159.22	60.34 (60.35	10.76 10.82	8.80 8.69)
4c	90 (0.06)	1736	3320	0.99 (6H, d, J=6.1, $\underline{Me}_2CH$), 1.45 (1H, br s, NH), 2.48 (2H, t, J=6.4, CH_2CO), 2.83 (2H, t, J=6.4, NCH_2), 5.07 (2H, s, $C\underline{H}_2Ph$), 7.28 (5H, s, Ph)	22.9 (q, $\underline{Me}_2CH$), 30.0 (t, $\underline{C}H_2CO$), 42.6 (t, $\overline{NCH_2}$), 48.3 (d, $Me_2\underline{C}H$), 65.9 (t, $\underline{C}H_2Ph$), 128.0, 128.4 (d, Ph), 136.2 (s, Ph), 177.2 (s, CO)	$C_{13}H_{19}NO_2$ 221.29	70.55 (70.37	8.65 8.78	6.33 6.18)
4d	101—102 (0.15)	1735	3355	1.20 (6H, s, Me_2C), 1.53 (1H, br s, NH), 2.63 (2H, s, NCH_2), 3.63 (3H, s, OMe), 3.77 (2H, s, $C\underline{H}_2Ph$), 7.27 (5H, s, Ph)	23.6 (q, $\underline{Me}_2C$), 43.5 (s, $Me_2\underline{C}$), 51.4 (t, $\underline{C}H_2Ph$), 54.3 (q, OMe), 58.0 (t, NCH_2), 126.7, 127.9, 128.1 (d, Ph), 140.8 (s, Ph), 177.5 (s, CO)	$C_{13}H_{19}NO_2$ 221.29	70.55 (70.13	8.65 8.78	6.33 6.09)
4e	99—100 (65)	1735	3340	1.06 (3H, t, J=7.0, $C\underline{H}_3CH_2$), 1.17 (6H, s, Me_2C), 1.41 (1H, br s, NH), 2.61 (2H, q, J=7.0, $CH_3C\underline{H}_2$), 2.63 (2H, s, NCH_2), 3.62 (3H, s, OMe)	15.3 (q, $\underline{C}H_3CH_2$), 23.7 (q, $\underline{Me}_2C$), 43.6 (s, $Me_3\underline{C}$), 44.8 (t, $CH_3\underline{C}H_2$), 51.5 (q, OMe), 58.6 (t, $N\underline{C}H_2C$) 177.8 (s, CO)	$C_8H_{17}NO_2$ 159.22	60.34 (60.06	10.76 10.84	8.80 8.63)
4f	78 (30)	1740	3395	1.19 (6H, s, Me_2C), 1.47 (1H, br s, NH), 2.65 (2H, s, NCH_2), 3.22 (2H, br d, J= 5.9, $=CHC\underline{H}_2$), 3.66 (3H, s, OMe), 4.95—5.29 (2H, m, $C\underline{H}_2=CH$), 5.62—6.11 (1H, m, $CH_2=C\underline{H}$)	23.7 (q, $\underline{Me}_2C$), 43.6 (s, $Me_2\underline{C}$), 51.6 (q, OMe), 52.9 (t, $=CH\underline{C}H_2$), 58.1 (t, NCH_2), 115.4 (t, $\underline{C}H_2=CH$), 137.3 (d, $CH_2=\underline{C}H$), 177.7 (s, CO)	$C_9H_{17}NO_2$ 171.23	63.13 (62.53	10.00 10.10	8.18 7.93)
4g	97 (0.06)	1730	3415	1.23 (6H, s, Me_2C), 3.19 (2H, s, NCH_2), 3.60 (4H, s, br s, OMe and NH), 6.46—7.27 (5H, m, Ph)	23.5 (q, $\underline{Me}_2C$), 43.7 (s, $Me_2\underline{C}$), 51.8 (q, OMe), 52.8 (t, NCH_2), 113.0, 117.4, 129.2 (d, Ph), 148.6 (s, Ph), 177.3 (s, CO)	$C_{12}H_{17}NO_2$ 207.26	69.54 (70.09	8.27 8.28	6.76 7.18)
4h	36—37	1720 1740	3360[a]	1.17 (6H, s, Me_2C), 2.30 (1H, br s, NH), 2.55 (1H, d, J=12, $NC\underline{H}H$), 2.64 (1H, d, J=12, $NCH\underline{H}$), 3.64 (6H, s, OMe), 4.33 (1H, s, CHN), 7.32 (5H, s, Ph)	23.6 (q, $\underline{Me}_2C$), 43.6 (s, $Me_2\underline{C}$), 51.6 (q, OMe), 52.0 (q, OMe), 56.3 (t, NCH_2), 66.2 (d, CHN), 127.5, 127.9, 128.5 (d, Ph), 138.5 (s, Ph), 173.3 (s, CO), 177.4 (s, CO)	$C_{15}H_{21}NO_4$ 279.33	64.49 (64.92	7.58 7.41	5.01 5.24)
4i	120[b] (10)	1716	3352	1.17 (6H, s, Me_2C), 1.51—1.92 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.59 (1H, s, NH), 2.78—3.00 (2H, m, NCH_2), 3.16—3.43 (1H, m, NCH), 3.67 (3H, s, OMe)	21.1, 22.7 (q, $\underline{Me}_2C$), 26.2, 26.8 (t, $\underline{C}H_2\underline{C}H_2$), 45.9 (s, $Me_2\underline{C}$), 47.2 (t, NCH_2), 51.6 (q, OMe), 65.3 (d, NCH), 177.9 (s, CO)	$C_9H_{17}NO_2$ 171.23	63.13 (62.86	10.00 10.11	8.18 8.68)

a) KBr. *b*) Bulb-to-bulb distillation.

NMR spectra (90 MHz) and ^{13}C-NMR spectra (22.5 MHz) were taken on a JEOL JNM-90Q NMR spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard, and the chemical shifts are given in δ values.

Preparation of 1,3,5-Trialkylhexahydro-1,3,5-triazines (1a—g)——The following 1,3,5-trialkylhexahydro-1,3,5-triazines were prepared according to the methods described in the literature; their boiling and melting points are as follows: **1a**, bp 125—126 °C/25 mmHg (lit.,[1] bp 87 °C/0.6 mmHg); **1b**, mp 50—51 °C (lit.,[1] mp 46—48 °C); **1c**, bp 82—92 °C/20 mmHg (lit.,[1] bp 53 °C/0.3 mmHg); **1d**, bp 88 °C/0.4 mmHg (lit.,[1] bp 92 °C/0.4 mmHg); **1e**, mp 135—139 °C (lit.,[5] mp 140—141 °C); **1f**, mp 167—168 °C (lit.,[6] mp 148—155 °C); **1g**, bp 92—98 °C (lit.,[7] bp 81—97 °C).

Preparation of Ketene Silyl Acetals (2a—c)——The ketene trimethylsilyl acetals were prepared from the corresponding carboxylic esters by the previously reported procedure[8]; their boiling points are as follows: **2a**, bp 76—77 °C/65 mmHg (lit.,[8] bp 35 °C/15 mmHg); **2b**, bp 68—69 °C/65 mmHg (lit.,[8] bp 70 °C/3 mmHg); **2c**, bp 98—99 °C/0.4 mmHg (lit.,[8] bp 63 °C/0.001 mmHg).

***N*-Alkylaminomethylation (Table I)**——General Procedure: Compound **3c** (0.3 mmol) was added as a catalyst to a stirred solution of 2 mmol of 1,3,5-trialkylhexahydro-1,3,5-triazine (**1a—g**) and 6 mmol of ketene silyl acetal (**2a—c**) in 10 ml of dry CH_2Cl_2, under cooling. After being stirred for the requisite time at room temperature, the reaction mixture was washed with 10% aqueous $KHCO_3$ solution. 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 (**4a—i**). Yields, and physical and analytical data for the products are listed in Tables I and II, respectively.

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References

1) *a*) D. D. Reynolds and B. C. Cossar, *J. Heterocycl. Chem.*, **8**, 597 (1971); *b*) *Idem, ibid.*, **8**, 605 (1971); *c*) *Idem, ibid.*, **8**, 611 (1971).
2) *a*) K. Ikeda, T. Morimoto, and M. Sekiya, *Chem. Pharm. Bull.*, **28**, 1178 (1980); *b*) K. Ikeda, Y. Terao, and M. Sekiya, *ibid.*, **29**, 1156 (1981); *c*) *Idem, ibid.*, **29**, 1747 (1981).
3) K. Ikeda, K. Achiwa, and M. Sekiya, *Tetrahedron Lett.*, **24**, 913 (1983).
4) *a*) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); *b*) A. Hosomi, S. Iijima, and H. Sakurai, *Tetrahedron Lett.*, **23**, 547 (1982) and references cited therein.
5) R. Carpignano, *Ann. Chim.* (Rome), **48**, 255 (1958).
6) T. Kamiya, H. Aoki, and Y. Mine, "Chemistry and Biology of β-Lactam Antibiotics," Vol. 2, ed. by R. B. Morin and M. Gorman, Academic Press, New York, 1982, pp. 166—226.
7) J. Martin Grisar and George P. Claxton, U. S. Patent 3853855 (1974) [*Chem. Abstr.*, **82**, 170690*k* (1975)].
8) C. Ainsworth, F. Chen, and Y.-N. Kuo, *J. Organomet. Chem.*, **46**, 59 (1972).