Chem. Pharm. Bull. 30(9)3167—3171(1982)

A 1,3-Dipolar Cycloaddition of Alicyclic Methylene Iminium Ylide to form Pyrrolizidine Nuclei and Its Application to Synthesis of Pyrrolizidine Alkaloids

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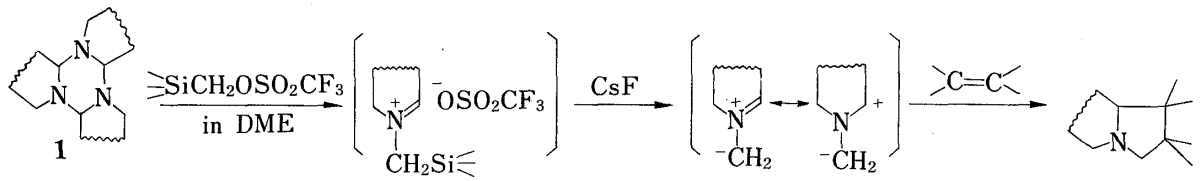
(Received March 3, 1982)

Efficient synthesis of pyrrolizidines and indolizidines has been achieved by reacting tetracyclic hexahydro-1,3,5-triazines with olefinic and acetylenic compounds in the presence of trimethylsilylmethyl trifluoromethanesulfonate and cesium fluoride. This reaction was applied to the synthesis of several pyrrolizidine alkaloids, (±)-trachelanthamidine, (±)-supinidine, and (±)-isoretronecanol.

Keywords——(±)-trachelanthamidine; (±)-supinidine; (±)-isoretronecanol; pyrrolizidine; indolizidine; methylene iminium ylide; trimethylsilylmethyl trifluoromethanesulfonate; trimer of alicyclic imine

Recently nonstabilized iminium ylides produced from intermediary *N*-(trimethylsilylmethyl)iminium trifluoromethanesulfonate by desilylation with cesium fluoride and their 1,3-dipolar cycloaddition to form pyrrolidines have been reported.[1] As a part of our continuing studies[2] on the reactions of hexahydro-1,3,5-triazines, their tetracyclic analogs (**1**) were found to be suitable precursors for synthesizing pyrrolizidine and indolizidine nuclei by a reaction with olefinic and acetylenic compounds in the presence of trimethylsilylmethyl trifluoromethanesulfonate and cesium fluoride. Furthermore, this reaction was applied to efficient syntheses of several pyrrolizidine alkaloids, (±)-trachelanthamidine (**2**), (±)-supinidine (**3**) and (±)-isoretronecanol (**4**).

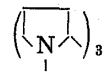
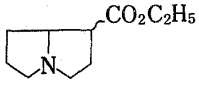
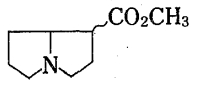
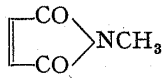
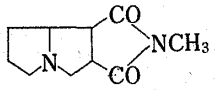
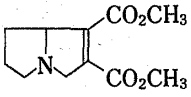
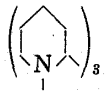
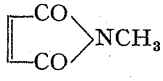
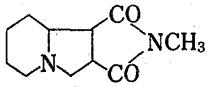
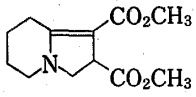


Formation of *N*-methylpyrrolinium ylide is expected by the reaction of the trimer of 1-pyrroline (**1a**), as a hexahydro-1,3,5-triazine, with trimethylsilylmethyl trifluoromethanesulfonate and cesium fluoride. Pyrrolizidines were obtained by 1,3-dipolar cycloaddition of the intermediary ylide to carbon-carbon multiple bonds. By using alkyl acrylate, *N*-methylmaleimide, and dimethyl acetylenedicarboxylate, one-pot synthesis of pyrrolizidine derivatives was achieved, as shown in Table I.

The products, **5**, **6** and **7** were obtained as mixtures of *endo*- and *exo*-isomers. Among them, **5** and **6** could be converted into nearly pure *exo*-isomers (**5b** and **6b**) by treatment with lithium diisopropylamide (LDA) in THF. Identification of the two isomers of **5** as well as those of **6** was achieved by comparison of their ^{13}C-nuclear magnetic resonance (CMR) and infrared (IR) spectra with those of authentic specimens of the isomers of **5** prepared according to the procedure reported by Pizzorno *et al.*[3]

Each of the isomers of **7** was isolated by column chromatography on silica gel with THF–EtOH. The *endo*-isomer (**7a**) was transformed into the *exo*-isomer (**7b**) by treatment with LDA in THF.

Table I. Syntheses[a] of Pyrrolizidine and Indolizidine Derivatives

Substrate	or >C=C< >C≡C<	No.	Product	Yield (%)
 **1a**	$CH_2=CHCO_2C_2H_5$	**5**		28
	$CH_2=CHCO_2CH_3$	**6**		30
		**7**		31
	$CH_3O_2CC{\equiv}CCO_2CH_3$	**8**		20
 **1b**		**9**		15
	$CH_3O_2CC{\equiv}CCO_2CH_3$	**10**		20

a) Molar ratio: substrate/$(CH_3)_3SiCH_2OSO_2CF_3$/CsF/>C=C< or >C≡C<=1/3/3/3; solvent, DME.

Indolizidines were obtained by the same procedure using the trimer of 2,3,4,5-tetrahydropyridine (**1b**) instead of **1a**. The product (**9**) isolated was a single isomer, probably the *exo*-isomer. A double bond of the product (**10**) at the 1,9-position, which was assigned by CMR measurement, may be explained as a result of thermally favorable migration of the initially formed 1,2-double bond. The CMR signals of C–1 and C–2 of **10** were referred to as those of the carbon-carbon double bond of the cyclic enaminoketone system, since their chemical shifts are closely related to those of the corresponding double bond of *Aspidoperma* alkaloids reported by Wenkert *et al.*[4]

Attempts were made to apply the present reaction to the synthesis of pyrrolizidine alkaloids, which possess a wide range of physiological properties and are distributed in a number of plant families. The cycloaddition reaction has provided entries for simple syntheses of (±)-trachelanthamidine (**2**), (±)-supinidine (**3**) and (±)-isoretronecanol (**4**). Pure ethyl pyrrolizidine-1-*exo*-carboxylate (**5b**) was obtained by isomerization of the product **5** with LDA. Reaction of **5b** with lithium aluminum hydride afforded (±)-trachelanthamidine (**2**) quantitatively. The product have satisfactory physical and spectral data. Its CMR spectral data are given in Table II together with those of other pyrrolizidines obtained in this work.

For the synthesis of ethyl 1,2-dehydropyrrolizidine-1-carboxylate (**11**), a precursor of (±)-supinidine (**3**), the 1,3-dipolar cycloadditions of **1a** to ethyl propiolate and ethyl 2-chloroacrylate were examined under various conditions, but the reactions gave resinous mixtures; only the reaction with the latter was effective for the minor formation of **11**. However, isolation of the product **11** was unsuccessful because of contamination by resinous materials, and its formation was confirmed only by GLC–MS, the results of which were in good agreement with those for an authentic specimen synthesized below. Efficient synthesis of **11** was achieved

through phenylselenation of **5** according to the method reported by Robins *et al.*[5] (see Chart 1). (±)-Ethyl 1,2-dehydropyrrolizidine-1-carboxylate (**11**) has been converted to (±)-supinidine (**3**), which is also a precursor of (±)-isoretronecanol (**4**), as reported previously.[5]

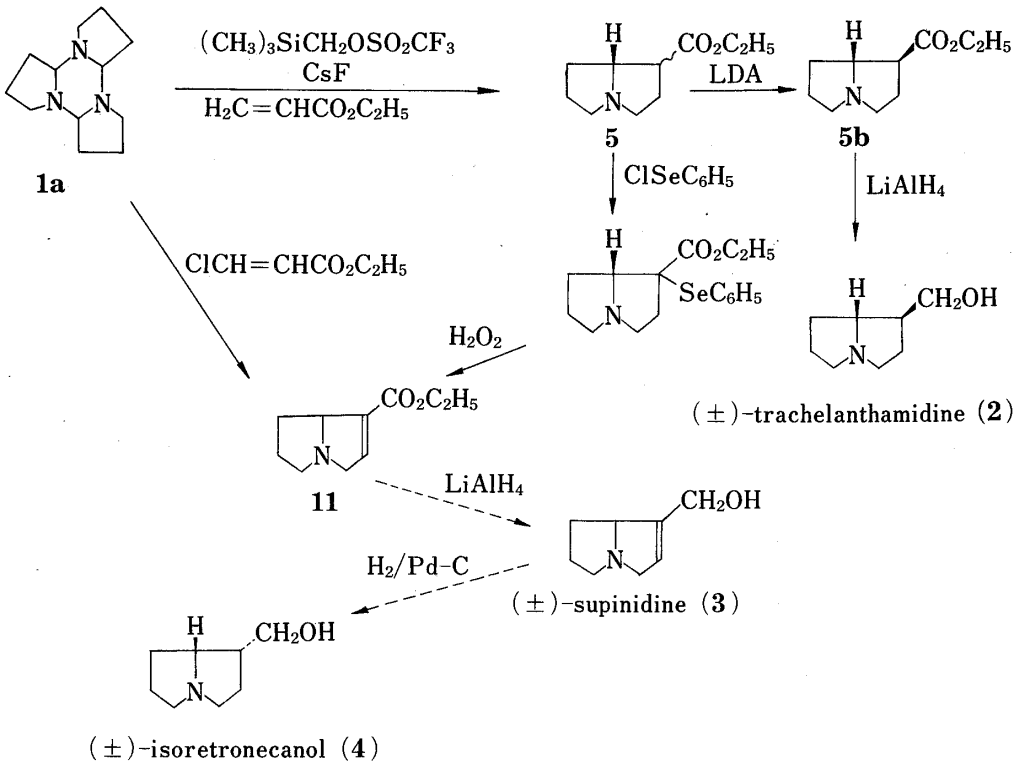
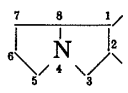
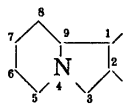


Chart 1. Synthesis of Pyrrolizidine Alkaloids

Table II. CMR Chemical Shifts of  or 

Compd. No.	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	Others
2	48.3	25.7	54.8 54.5		31.9 30.1		67.8	—	65.6
5a (*endo*)	50.4	25.7	55.0 54.5		31.5 30.6		68.3	—	174.2, 60.4, 14.3
5b (*exo*)	47.5	26.4	55.6 53.7		28.5 26.8		65.9	—	173.6, 60.3, 14.3
7a (*endo*)	50.0 45.9		54.5 51.8		29.5 23.5		68.7	—	178.9, 178.5, 23.5
7b (*exo*)	48.3 48.2		54.2 52.4		25.3 25.0		68.1	—	179.6, 177.7, 25.0
8	141.4 135.4		62.3 56.9		30.1 25.5		73.1	—	164.8, 164.0, 52.2 (2C)
9	47.7 43.3		57.2 52.9			27.7 24.9 24.8		65.8	179.5, 176.8, 24.3
10	94.9	56.5	47.0 44.9			24.8 24.5 23.0		162.9	175.4, 166.4, 52.2, 50.1

Table III. Pyrrolizidines and Indolizidines

Compd. No.	bp °C (mmHg)	IR ν_{max}^{neat} cm^{-1}	MS M$^+$ (*m/e*)	Formula	Analysis (%) Calcd (Found) C	H	N
2	95—96 (1)	3350 (OH)	141	$C_8H_{15}NO$	68.04 (67.78	10.71 10.75	9.92 9.92)
5	80—82 (10)	1735 (C=O)	183	$C_{10}H_{17}NO_2$	65.54 (65.30	9.35 9.10	7.64 7.76)
6	82—83 (10)	1735 (C=O)	169	$C_9H_{15}NO_2$	63.88 (63.49	8.94 9.70	8.28 8.60)
7a	121—123[a] (0.07)	1780 1705 (C=O)	194	$C_{10}H_{14}N_2O_2$	61.83 (61.42	7.27 7.36	14.42 14.26)
7b		1780 1705 (C=O)	194	$C_{10}H_{14}N_2O_2$	61.83 (61.45	7.27 7.36	14.42 14.02)
8	150—151 (1)	1740 (C=O) 1665 (C=C)	225	$C_{11}H_{15}NO_4$	58.65 (58.35	6.71 6.66	6.22 6.06)
9	145—148 (0.03)	1774 1705 (C=O)	208	$C_{11}H_{16}N_2O_2$	63.44 (63.10	7.74 7.70	13.45 13.61)
10	125—126	1740 (C=O) 1665 (C=C)	239	$C_{12}H_{17}NO_4$	60.24 (60.51	7.16 7.12	5.85 5.83)

a) A mixture of **7a** and **7b** (1: 1).

Experimental

All boiling points are uncorrected. IR spectra were measured with a Hitachi EPI-G2 infrared spectrometer. CMR spectra were taken on a JEOL JNM90Q spectrometer (90 MHz) and all chemical shifts are given in downfield from TMS. Mass spectra were recorded on a JEOL JMS-D100 spectrometer.

Syntheses of Pyrrolizidines and Indolizidines (see Table I)——General Procedure: A solution of trimethylsilylmethyl trifluoromethanesulfonate (8.4 mmol) was added gradually to an ice-cooled solution of the trimer (2.8 mmol) of 1-pyrroline (**1a**) or 2,3,4,5-tetrahydropyridine (**1b**) in DME (20 ml) under a nitrogen atmosphere with stirring. After 10 min of stirring, a conjugated olefin or acetylene (8.4 mmol) and then cesium fluoride (8.4 mmol) were each added in one portion. The mixture was stirred for 2 h at room temperature. After removal of DME, benzene was added to the residue and insoluble material was filtered off. The filtrate was concentrated under reduced pressure to give an oily residue, which was subjected to distillation. A pure sample was obtained by thin layer chromatography (TLC) on silica gel using THF–hexane (2: 1) as an eluent.

The product **7** was chromatographed on a silica gel column with THF–EtOH (97: 3) to give **7a** and **7b** in nearly equimolar proportion.

Isomerization of **5**, as a mixture, to **5b** and of **7a** to **7b** was achieved by treatment of the THF solution with an equimolar amount of LDA at room temperature.

Physical and spectral data for the products are recorded in Tables I, II, and III.

Reduction of Ethyl Pyrrolizidine-1-*exo*-carboxylate (5b) with $LiAlH_4$——A solution of **5b** (183 mg, 1 mmol) in dry ether (5 ml) was added slowly to a cooled suspension of $LiAlH_4$ (95 mg, 2.5 mmol) in dry ether (5 ml) under a nitrogen atmosphere. The mixture was stirred for 2 h at room temperature. After the addition of a small amount of water and 10% NaOH with cooling, insoluble material was filtered off and washed with $CHCl_3$. The filtrate and washing were combined and dried over $MgSO_4$, then concentrated under reduced pressure to yield a pale yellow oil (130 mg), which was confirmed to be almost pure by GLC and TLC analyses. Further purification was carried out by distillation. The boiling point and spectral data for the product (**2**) are recorded in Tables I, II, and III. Picrate: mp 173—174°C (EtOH) (lit., mp 174—175,[6] 174—175.5°C[7]).

Reaction of the Trimer of 1-Pyrroline (1a) with Ethyl 2-Chloroacrylate——The same procedure as described above was repeated with **1a** (621 mg, 3 mmol), trimethylsilylmethyl trifluoromethanesulfonate (2.13 g, 9 mmol), cesium fluoride (1.35 g, 9 mmol), and ethyl 2-chloroacrylate (1.23 g, 9 mmol). The mixture was

stirred at room temperature for 30 min. After removal of DME, CH_2Cl_2 was added to the residue and insoluble material was filtered off. The filtrate was concentrated under reduced pressure to give a brown oil, which was carefully chromatographed on an alumina column with CH_2Cl_2–EtOH (4: 1). Ethyl 1,2-dehydropyrrolizidine-1-carboxylate (**11**) was present as a small fraction of the concentrate (100 mg), as determined by GLC–MS measurement. Its mass spectrum pattern was in good agreement with that of an authentic specimen prepared from **5** according to the method reported by Robins *et al.*[5] MS (*m/e*): 181 (M^+), 153, 150, 136, 134, 108, 80.

Acknowledgement The authors are indebted to Dr. K. Narita and the staff of the analysis center of this college for microanalyses. Thanks are also due to Dr. M. Uchida for mass spectral measurements.

References and Notes

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