Synthesis of New *N*-Aminoaziridine Derivatives by the Addition of Dibenzyloxycarbonylaminonitrene to Olefins

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In order to study the ring expansion of *N*-aminoaziridines into *N*-amino-5-membered heterocycles, *N*-(dibenzyloxycarbonylamino)aziridines were synthesized. *N,N*-Dibenzyloxycarbonylhydrazine was prepared. It was then oxidized with lead tetraacetate to a new diacylaminonitrene. This nitrene was added to various olefins to give the corresponding *N*-protected aminoaziridines. Cleavage of the protecting groups was realized for one example.

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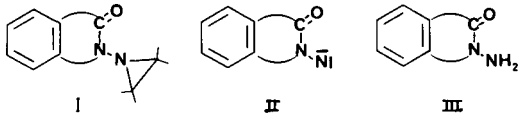
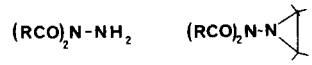
Synthesis of aziridines involving nitrene addition on olefins was reported by Lwowski [1] and Rees *et al* [2]. These second authors prepared heterocyclic derivatives of *N*-aminoaziridines I, by cycloaddition of aminonitrenes II with various olefins. Nitrenes were generated by oxidation with lead tetraacetate of *N*-amino heterocycles III. But no example has been reported in the literature for non cyclic *N,N*-diacylhydrazines IV.



I II III



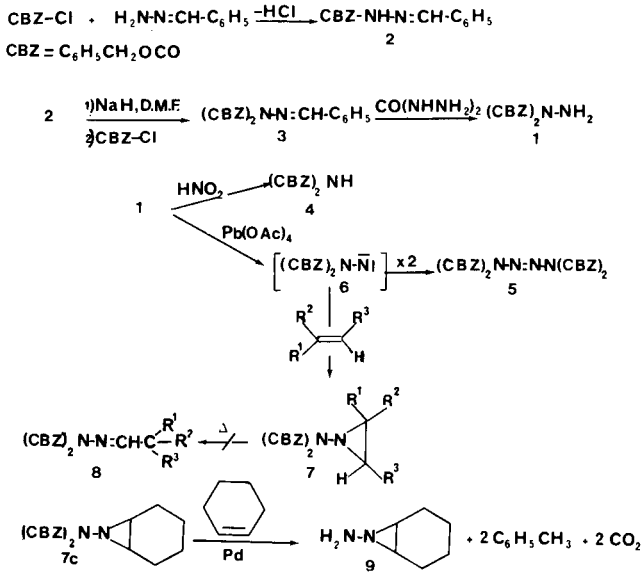
IV V

Our aim was the synthesis of protected *N*-aminoaziridines V from the *N,N*-dibenzyloxycarbonylhydrazine (**1**) by the same initial reaction, in order to study, afterwards, the ring expansion of these *N*-aminoaziridines into various *N*-amino-5-membered heterocycles [3]. The benzyloxycarbonyl (CBZ) was chosen because it is a well known protecting group of amine function.

Ten *N,N*-diacylhydrazines IV have been reported. The most usual methods of synthesis are action of an acid anhydride with the unstable chloromercuric complexe of hydrazine [4] or acylation of a benzaldehyde acylhydrazone followed by acid hydrolysis or hydrazinolysis [5].

Hydrazine **1** was prepared by this last method with several modifications. First, benzyl chloroformate reacted with the benzaldehyde hydrazone (prepared *in situ*) with the presence of sodium carbonate to give the benzaldehyde benzyloxycarbonylhydrazone (**2**) in anhydrous dimethylformamide at −20°. Formation of sodium derivative of **2** by sodium hydride action allowed a second acylation with a new molecule of benzyl chloroformate to give the benzaldehyde dibenzyloxycarbonylhydrazone (**3**). Classical hydrazinolysis of **3** with hydrazine or its derivatives afforded mixtures of hydrazine **1** and various compounds which were very difficult to separate. Some of them resulted from a deacylation of **3**. Hydrolysis with very dilute hydrochloric acid cleaved, as expected, the benzyloxycarbonyl protecting groups. Dilute sulfuric or organic acids gave a low yield of hydrazine **1**. After various attempts, we found a new method. Hydrazine **1** was isolated in good yield when **3** was treated with carbonohydrazide in ethanol with the presence of acetic acid. This new *N,N*-disubstituted hydrazine **1** should afford successful applications in heterocyclic synthesis.

Scheme 1



Two reactions were realized with hydrazine **1** before the synthesis of aziridines. Nitrous deamination of **1** gave the dibenzyloxycarbonylamine (**4**). This amine has just been studied as a possible starting material in a modified Gabriel synthesis. Oxidation of hydrazine **1** with lead tet-

Table I

N-(Dibenzyloxycarbonyl)aziridines **7**

7	R^1	R^2	R^3	Yield (%)	Mp °C		^{1}H NMR [a] δ ppm
a	COOMe	H	H	43	72	[b:c]	2.25-2.45 (m, 1H), 2.6-2.85 (m, 2H), 3.5 (s, 3H), 5.15 (s, 4H), 7.2 (m, 10H)
b	Ph	H	H	62	61	[d]	2.25-2.6 (m, 2H), 3-3.2 (2 d, 1H), 5.1 (s, 4H), 7.05-7.3 (m, 15H)
c	H	$(CH_2)_4$		73	74	[b:c]	1-1.45 (m, 4H), 1.6-1.9 (m, 4H), 2.2-2.35 (m, 2H), 5.25 (s, 4H), 7.3 (m, 10H)
d	Cl	H	H	67	64	[b:c]	2.95 (s, 2H), 5.2 (s, 4H), 7.25 (m, 10H)
e	Cl	H	Cl	41	55.5	[c]	4.35 (s, 2H), 5.15 (s, 4H), 7.2 (m, 10H)
f	COOMe	H	COOMe	30	105	[c:e]	3.38 (s, 2H), 3.42 (s, 3H), 3.52 (s, 3H), 5.1 (s, 4H), 7.2 (m, 10H)

[a] All compounds were measured in deuteriochloroform. [b] Diethyl ether. [c] Petroleum ether bp 40-60°. [d] Methanol. [e] Dichloromethane.

raacetate when olefin was absent gave the 1,1,4,4-tetrabenzyloxycarbonyltetrazene (**5**) besides small quantities of amine **4**. The formation of tetrazene **5** proceeded by coupling of two dibenzyloxycarbonylaminonitrenes **6**. In this reaction, hydrazine **1** behaves as some *N*-amino heterocycles III [2c].

Cycloaddition of diacylaminonitrene **6** with olefins gave *N*-(dibenzyloxycarbonylamino)aziridines **7** (Table I).

Small quantities of amine **4** and tetrazene **5** were obtained besides aziridines **7**. Liquid olefins (methyl acrylate, styrene, cyclohexene, 2-chloroacrylonitrile or *trans*-1,2-dichloroethylene) were used as reaction solvent to give the corresponding aziridines **7a-e** [6]. The synthesis of **7f** was carried in a saturated solution of methyl fumarate in dichloromethane. As already observed with nitrenes II [2c], unexpectedly, no aziridine was obtained with acrylonitrile; in this case, only tetrazene **5** and a few amine **4** were formed. However, aziridine **7d** was obtained in 67% yield from 2-chloroacrylonitrile.

With *cis* or *trans* isomers of 1,2-dichloroethylene, methyl maleate or fumarate, nitrene **6** added only to the *trans* isomer. Only one aziridine was formed in each case, respectively **7e** and **7f**; the reaction is stereospecific. The ^{1}H-nmr spectra show only one singlet for the two aziridine ring protons of **7e** (4.35 ppm) and **7f** (3.38 ppm). But a different singlet is observed for each ester methyl group of **7f** (3.42 and 3.52 ppm). This involves that the two esters groups are in *trans* position from each other. This agrees with a *cis* addition of nitrene **6**. At room temperature, no ^{1}H-nmr spectra of aziridines **7** showed the presence of invertomers.

All these results suggest that aminonitrene **6** behaves as aminonitrene II and is probably reacting in the singlet state [2c].

Aziridines **7** are stable at room temperature. Contrary to aziridines I [2c], they are not transformed into hydrazones **8** when they are heated at their melting point. In order to assure the structure of **7**, the deprotection of **7c** into the known aziridine **9** was attempted. As the aziridine ring is very sensitive to acid, the protecting groups cannot be cleaved by the classical method (reaction with a hydrobromic/acetic acids mixture [7]). Catalytic hydrogenolysis with palladium [8] is no more appropriate. However, the cleavage of the benzyloxycarbonyl groups was realized by a soft method using a hydrogen-donor solvent with the presence of palladium. With cyclohexene as such a solvent [9], we obtained the aziridine **9**.

Assignment for the structures of the new compounds was provided by elemental analysis and ir and ^{1}H-nmr spectra. Among the products with a dibenzyloxycarbonylamino group, the compounds **1**, **3**, **4**, **5** and aziridines **7a**, **7c**, **7d**, **7f** show two carbonyl absorption bands (1810-1745 cm^{-1} and 1770-1680 cm^{-1} regions); the other aziridines **7b** and **7e** show nevertheless a broad band (1745-1740 cm^{-1}). So the two carbonyl groups would have a *cis-trans* structure with respect to the N-N bond; this result is in concordance with ir work on -CO-NH-CO- structure [10]. Two N-H absorption bands (3265 and 3200 cm^{-1}) for amine **4** could be attributed to Fermi resonance.

EXPERIMENTAL

Melting points were taken with a Buchi oil heated apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer as potassium bromide disks. The ^{1}H-nmr spectra were obtained in deuteriochloroform on a Brucker WP 80 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

Benzaldehyde Benzyloxycarbonylhydrazone (**2**).

To a stirred mixture of 10 g (200 mmoles) of hydrazine hydrate in 60 ml of dimethylformamide, a solution of 21.2 g (200 mmoles) of benzaldehyde in 40 ml of dimethylformamide was added dropwise at 0°. The reac-

tion mixture was stirred at 0° for an additional one hour. Then 20 g of sodium bicarbonate and dropwise at −20°, 34.1 g (200 mmoles) of benzyl chloroformate were added successively. After stirring for 45 minutes, the mixture was poured onto ice-water. The precipitate was filtered and recrystallized from benzene:cyclohexane giving 48.3 g (95%) of **2**, mp 142°; ir: 3200, 1705 cm^{-1}; nmr: δ 5.25 (s, CH_2, 2H), 7.25-7.75 (m, aromatic, 10H), 7.85 (s, CH, 1H), 8.85 (s, NH, 1H).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.9; H, 5.5; N, 11.0. Found: C, 70.7; H, 5.6; N, 11.1.

Benzaldehyde Dibenzyloxycarbonylhydrazone (**3**).

Sodium hydride (50% in oil) (9.6 g, 200 mmoles) was added in small portions to a stirred mixture of 38.1 g (150 mmoles) of hydrazone **2** in 600 ml of anhydrous dimethylformamide at 0°. The reaction mixture was stirred for 2 hours (end of hydrogen evolution). Then 51.2 g (300 mmoles) of benzyl chloroformate in 60 ml of toluene was added dropwise at −20°. The reaction mixture was stirred for 2 hours at 0° and poured onto ice-water (6 liters). The product precipitated and was recrystallized from propanol giving 53.5 g (92%) of **3**, mp 78°; ir: 1745, 1700 (broad) cm^{-1}; nmr: δ 5.25 (s, 2 CH_2, 4H), 7.2-7.8 (m, aromatic, 15H), 8.3 (s, CH, 1H).

Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.1; H, 5.2; N, 7.2. Found: C, 71.3; H, 5.3; N, 7.2.

N,N-Dibenzyloxycarbonylhydrazine (**1**).

A reaction mixture of 24.8 g (64 mmoles) of hydrazone **3**, 2.9 g (32 mmoles) of carbonohydrazide and 4 ml of acetic acid in 150 ml of ethanol was stirred and heated at reflux for 90 minutes. After removal of the solvent *in vacuo* the resulting residue was dissolved in benzene. The solution was filtered and the benzene was evaporated. The product was first recrystallized from benzene:cyclohexane and then from ethanol:water giving 11.5 g (60%) of **1**, mp 83°; ir: 3370, 3320, 1760 (broad), 1680 cm^{-1}; nmr: δ 4.3 (s, NH_2, 2H), 5.2 (s, 2 CH_2, 4H), 7.4 (m, aromatic, 10H).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 64.0; H, 5.4; N, 9.3. Found: C, 63.9; H, 5.5; N, 9.1.

Dibenzyloxycarbonylamine (**4**).

To a stirred mixture of 3 g (10 mmoles) of hydrazine **1** in 30 ml of acetic acid and 10 ml of 1 *N* hydrochloric acid, a solution of 0.69 g (10 mmoles) of sodium nitrite in 10 ml of water was added dropwise at 5°. The reaction mixture was refluxed for 30 minutes. After removal of the solvents, the resulting residue was tritured with 50 ml of ice-water. The product was filtered and recrystallized from diethyl ether:petroleum ether 40-60 giving 2.4 g (84%) of **4**, mp 105.5-106.5°; ir: 3265; 3200, 1810, 1770 (broad) cm^{-1}; nmr: δ 5.1 (s, 2 CH_2, 4H), 7.1-7.4 (m, aromatic + NH, 11H).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3; N, 4.9. Found: C, 67.1; H, 5.2; N, 5.1.

1,1,4,4-Tetrabenzyloxycarbonyltetrazen (**5**).

To a stirred of 1.8 g (6 mmoles) of hydrazine **1** in 50 ml of anhydrous dichloromethane, a solution of 2.7 g (6.1 mmoles) of lead tetraacetate in 30 ml of anhydrous dichloromethane was slowly added at −5° (30 minutes). The reaction mixture was stirred for one hour, filtered and washed with water. The organic layer was dried (magnesium sulfate), concentrated *in vacuo* and the residue was recrystallized from dichloromethane:peteroleum ether 40-60 giving 1.1 g (61%) of **5**, mp 127°; ir: 3500, 1780, 1760, 1385, 1370 cm^{-1}; nmr: δ 5.35 (s, 4 CH_2, 8H), 7.4 (m, aromatic, 20H).

Anal. Calcd. for $C_{32}H_{28}N_4O_8$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.3; H, 4.6; N, 9.6.

N-(Dibenzyloxycarbonylamino)aziridines **7a-e**.

To a stirred mixture of 1.8 g (6 mmoles) of hydrazine **1** in 100 ml of the appropriate liquid olefin (methyl acrylate, styrene, cyclohexene, 2-chloroacrylonitrile or *trans*-1,2-dichloroethylene), a solution of 2.7 g (6.1 mmoles) of lead tetracetate in 30 ml of anhydrous dichloromethane was slowly added at −20° (1 hour). The reaction mixture was stirred for one hour, filtered and washed with water. The organic layer was dried (magnesium sulfate) and concentrated *in vacuo*. In order to eliminate **4** and **5**, the residue was generally recrystallized twice or more from appropriate solvent (Table I).

Methyl *N*-(Dibenzyloxycarbonylamino)aziridine-2-carboxylate (**7a**).

This compound had ir: 1745 (broad), 1720 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: C, 62.5; H, 5.2; N, 7.3. Found: C, 62.5; H, 5.3; N, 7.4.

N-(Dibenzyloxycarbonylamino)-2-phenylaziridine (**7b**).

This compound had ir: 1740 (broad) cm^{-1}.

Anal. Calcd. for $C_{24}H_{22}N_2O_4$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.6; N, 7.1.

N-(Dibenzyloxycarbonylamino)-7-azabicyclo[4.1.0]heptane (**7c**).

This compound had ir: 1750, 1730 cm^{-1}.

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.5; H, 6.4; N, 7.4. Found: C, 69.6; H, 6.3; N, 7.5.

N-(Dibenzyloxycarbonylamino)-2-chloro-2-cyanoaziridine (**7d**).

This compound had ir: 2250, 1760, 1710 cm^{-1}.

Anal. Calcd. for $C_{19}H_{16}ClN_3O_4$: C, 59.2; H, 4.2; N, 10.9. Found: C, 59.0; H, 4.2; N, 11.0.

N-(Dibenzyloxycarbonylamino)-*trans*-2,3-dichloroaziridine (**7e**).

This compound had ir: 1745 (broad) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_4$: C, 54.7; H, 4.1; N, 7.1. Found: C, 54.6; H, 4.2; N, 7.2.

Dimethyl *N*-(Dibenzyloxycarbonylamino)aziridine-*trans*-2,3-dicarboxylate (**7f**).

To a stirred mixture of 0.9 g (3 mmoles) of hydrazine **1** and 36 g (250 mmoles) of dimethyl fumarate in 125 ml of anhydrous dichloromethane, a solution of 1.37 g (3.1 mmoles) of lead tetraacetate in 15 ml of anhydrous dichloromethane was very slowly added (2 hours) at 25°. The reaction mixture was filtered and washed with water. The organic layer was dried (magnesium sulfate), concentrated, cooled at −30° and filtered to eliminate a major part of the dimethyl fumarate. The filtrate was evaporated to a residue which was chromatographed on silica gel 60 0.05-0.2 mm (Macherey-Nagel) using diethyl ether:petroleum ether 40-60 (1:1) as the eluent. The compound **7f** was recrystallized and had ir: 1750 (broad), 1730 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}N_2O_8$: C, 59.7; H, 5.0; N, 6.3. Found: C, 59.8; H, 5.0; N, 6.4.

N-Amino-7-azabicylco[4.1.0]heptane (**9**).

To a stirred mixture of 25 ml of cyclohexene and 50 ml of ethanol, were added 1 g of 10% palladium on calcium carbonate (oxidized form) and 2.3 g (6 mmoles) of aziridine **7c**. The stirred reaction mixture was refluxed for 2 hours. After filtration and removal of the solvents, was obtained 0.56 g (83%) of an oily product which crystallized slowly; it was recrystallized from petroleum ether 40-60: diethyl ether and had mp 48°; lit [11] mp 48° and same ir and nmr spectra.

REFERENCES AND NOTES

[1] W. Lwowski, *Angew. Chem.*, **79**, 922 (1967).

[2a] D. J. Anderson, T. L. Gilchrist, D. C. Horwell and C. W. Rees, *Chem. Commun.*, 146 (1969); [b] R. S. Atkinson and C. W. Rees, *J. Chem. Soc. (C)*, 772 (1969); [c] D. J. Anderson, T. L. Gilchrist, D. C.

Horwell and C. W. Rees, *J. Chem. Soc. (C)*, 576 (1970).

[3] H. C. Van Der Plas, "Ring Transformations of Heterocycles", Vol **1**, Academic Press, London, 1973, p 51.

[4] K. A. Hoffmann and E. C. Marburg, *Ann. Chem.*, **305**, 218 (1899).

[5] O. Diels and E. Borgwardt, *Ber.*, **53**, 150 (1920).

[6] A very large excess of olefin was necessary to obtain the aziridines **7**. With only 5 moles of olefin for 1 mole of **1** (as in Rees works [2c]), the major product was tetrazene **5**.

[7] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

[8] M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

[9] A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976).

[10] R. A. Abramovitch, *J. Chem. Soc.*, 1413 (1957); R. Uno and O. Machida, *Bull. Chem. Soc. Japan*, **34**, 545 (1961); R. Uno and O. Machida, *ibid.*, **34**, 551 (1961).

[11] D. Felix, J. Schreiber, K. Piers, U. Horn and A. Eschenmoser, *Helv. Chim. Acta*, **51**, 1461 (1968).