SYNTHESIS OF ADAMANTANE DERIVATIVES. 44.[1] FACILE SYNTHESIS OF SOME HOMOADAMANTANO[4,5]FUSED HETEROCYCLES BY THE 1,3-DIPOLAR CYCLOADDITION AND THE HOCH-CAMPBELL REACTION

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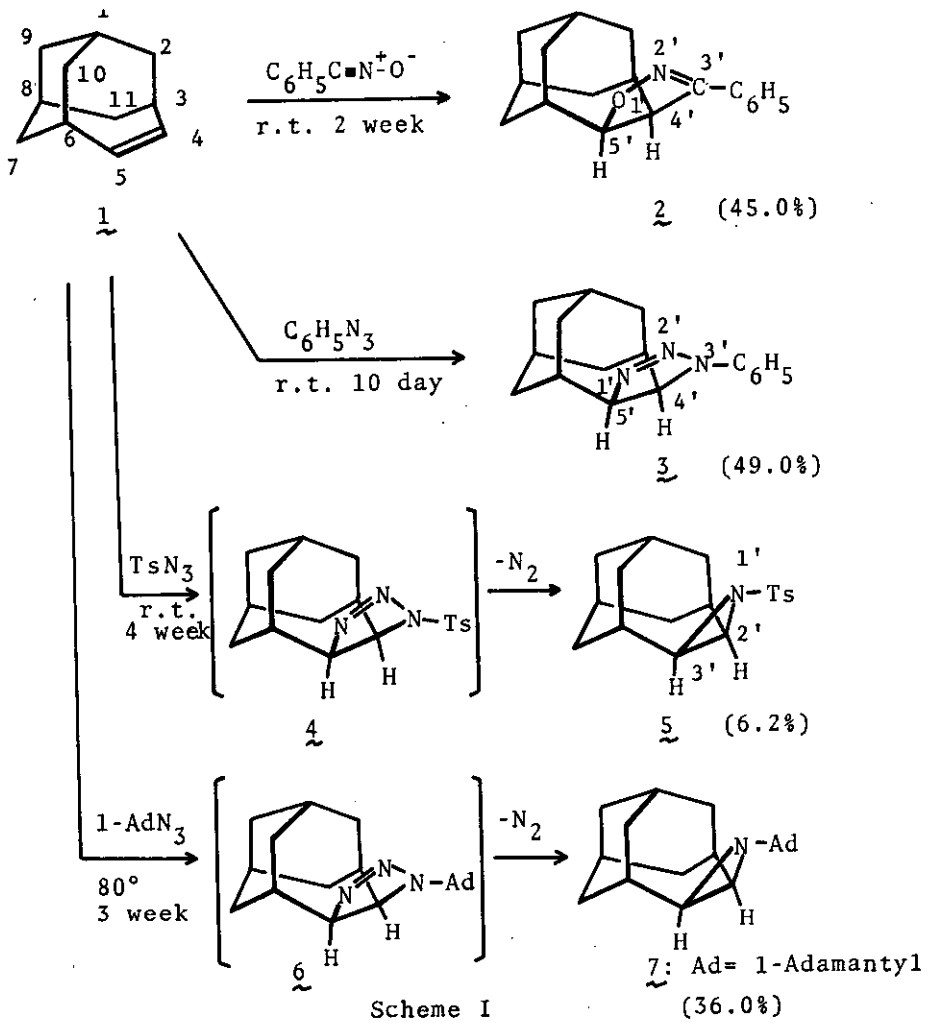
Homoadamantano[4,5]fused heterocycles 2, 3, 5 and 7 were obtained by the 1,3-dipolar cycloadditions of homoadamant-4-ene (1), and 2'-substituted homoadamantano-[4,5-b]aziridines 9a-c were obtained by the Hoch-Campbell reaction of homoadamantan-4-one oxime (8).

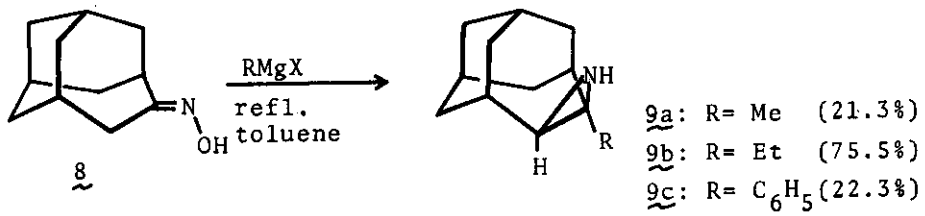
As a part of continuing efforts in our laboratories to synthesize adamantanoheterocycles[2] and in conjunction with our interest in their biological properties,[3] we initiated synthetic study of some heterocycles fused to homoadamantane ring system. We wish to report here facile synthesis of homoadamantano[4,5]-fused heterocycles 2, 3, 5 and 7 as well as 9a-c by the 1,3-dipolar cycloaddition and the Hoch-Campbell reaction.

As one of the most convenient routes to homoadamantano[4,5]-

fused 5-membered heterocycles, the 1,3-dipolar cycloadditions of homoadamant-4-ene (1)[4] were examined, and the results are summarized in Scheme I. The reaction of 1 with benzonitrile oxide[5] generated from phenylhydroximic acid chloride (1.5-fold excess to 1) with triethylamine in benzene for 2 weeks at room temperature (20-25°) afforded an adduct 2 in 45.0% yield as colorless crystals after recrystallization from n-hexane. The structure of 2 was determined as homoadamantano[4,5-d]-3'-phenyl-$\Delta^{2'}$-isooxazoline[6] on the basis of analytical and spectral data (see Table for physical data). In the nmr spectrum, 2 revealed characteristic signals assignable to C_4,H and C_5,H at δ 5.1 and 4.0 respectively, which supported the assigned structure. The reaction of 1 with phenylazide (1.3-fold excess to 1) in benzene for 10 days at room temperature afforded an adduct 3 in 49.0% yield as crystals after recrystallization from n-hexane. The adduct 3 had characteristic signals due to C_4,H and C_5,H at δ 4.76 and 4.12 (Table) and was characterized as homoadamantano-[4,5-d]-3'-phenyl-$\Delta^{1'}$-1',2',3'-triazoline. The reaction of 1 with p-toluenesulfonylazide (tosylazide) (1.5-fold excess to 1) in benzene for 4 weeks at room temperature gave a crystalline product 5 in 6.2% yield after recrystallization from methanol. Compound 5 was characterized as homoadamantano[4,5-b]-1'-tosyl-aziridine, a nitrogen extrusion product from the corresponding 1,3-dipolar cycloadduct 4. The reaction of 1 with 1-azido-adamantane[7] in 1:1 molar ratio at 80° for 3 weeks (in a sealed tube) afforded also a nitrogen extrusion product, 1'-adamantyl-aziridine derivative 7 in 36.0% yield. 7 may be produced via



Scheme I



Scheme II

1,3-dipolar cycloadduct 6 because 1-azidoadamantane was stable on heating at 100° for 1 week.

The other examined 1,3-dipoles such as diazomethane (20-fold excess to 1; 1 week at room temperature) and diphenylnitrone (1.2-fold excess to 1; 15 hr in refluxing toluene) did not give the corresponding adducts and only unreacted 1 was recovered. These results are summarized in Scheme I and Table.

Although homoadamantano[4,5-b]aziridine has been prepared by Schlatmann et al.,[8] no other homoadamantanoaziridine derivatives except ones described above seem to be not recorded, and therefore, the Hoch-Campbell reaction[9] of homoadamantan-4-one oxime (8)[8,10] was examined as a facile route to 2'-substituted homoadamantanoaziridines. The oxime 8 was treated with MeMgI (6.0-fold excess to 8) in refluxing toluene[11] and usual work-up and chromatography (Silica-gel, CH_2Cl_2-MeOH) afforded homoadamantano[4,5-b]-2'-methylaziridine 9a in 21.3% yield as an oil, which had a foul odor peculiar to aziridines and the assigned structure was supported by analysis and spectral data (Table). Similarly, the reaction of 8 with EtMgBr (3.0-fold excess to 8) afforded the corresponding 2'-ethylaziridine 9b in 75.5% yield. The reaction of 8 with C_6H_5MgBr (3.0-fold excess to 8) gave also 2'-phenylaziridine 9c as colorless crystals in 22.3% yield after chromatography (Alumina, Wako, basic, n-hexane-CH_2Cl_2-MeOH). In the nmr spectrum, 9c revealed a characteristic doublet signal assignable to an aziridine ring proton at δ 2.54, supporting the assigned structure.

Table Physical and analytical data of 2, 3, 5, 7 and 9a-c

Compd (mp,°C or n_D, temp)	Ir,[a] cm^{-1}	Nmr ($CDCl_3$,60MHz),[b] δ	Formula	Analysis[c]		
				C	H	N
2 (132.5-133.5)	1585, 1575, 750	7.7-7.1(m,5), 5.1(d,d,5.3&14Hz,1), 4.0(d,d,3.7&14Hz,1), 2.7-1.1(m,14)	$C_{18}H_{21}ON$	F81.06 C80.86	8.16 7.92	5.32 5.24
3 (138-140)	1603, 1505, 755	7.4-6.8(m,5), 4.76(d,d,5.0&13.5Hz, 1), 4.12(d,d,3.5&13.5Hz, 1), 2.84(bs,1), 2.45(bs,1), 2.2-0.9(m,12)	$C_{17}H_{21}N_3$	F76.10 C76.37	7.91 7.92	15.71 15.72
5 (145-148)	1585, 1310, 1145, 760	7.87(d,8.0Hz,2), 7.39(d,8.0Hz,2), 3.35(d,3.8Hz,2), 2.80(bs,2), 2.43(s,3), 2.3-1.4(m,12)	$C_{18}H_{23}O_2NS$	F67.91 C68.10	7.31 7.30	4.59 4.41
7 (171-172)	1440, 1305, 1221, 1145, 840	4.2-3.7(bs,1),[d] 3.49(m,2), 2.73(bs,2), 2.5-1.1(m,27)	$C_{21}H_{31}N$	F84.80 C84.79	10.60 10.50	4.61 4.51
9a (1.5304, 23.0)	3270, 1252, 853	2.23(bs,1), 2.1-1.2(m,14), 1.32(s,3),[d] 0.89(bs,1)[d]	$C_{12}H_{19}N$	F81.47 C81.30	11.03 10.80	7.86 7.90
9b (1.5345, 23.0)	3270, 3070, 1220, 860	2.7-1.05(m,18),[e] 0.88(t,6.0Hz,3)	$C_{13}H_{21}N$	F81.70 C81.61	10.82 11.06	7.48 7.32
9c (74-75)	3270, 3060, 1600, 1270, 865, 760	7.45-6.9(m,5), 2.54(d,6.0Hz,1), 2.39(bs,2), 2.2-1.2(m,12), 0.90(bs,1)[d]	$C_{17}H_{21}N$	F85.51 C85.30	8.73 8.84	5.80 5.85

[a]In KBr for solids and film for oils. [b]The data of 7 were obtained in $CDCl_3$-CF_3COOH, and bs= broad singlet. [c]F=Found and C=Calcd. [d]Disappeared on shaking with D_2O. [e]The integration became 17H on shaking with D_2O.

EXPERIMENTAL

Homoadamantano[4,5-d]-3'-phenyl-$\Delta^{2'}$-isooxazoline (2).---To a stirred mixture of homoadamant-4-ene (1) (148 mg, 1.00 mmol) and phenylhydroximic acid chloride (227 mg, 1.50 mmol) in benzene (10 ml) was added a solution of triethylamine (152 mg, 1.50 mmol) in benzene (10 ml) during 2 hr. After the stirring was continued for 2 weeks at room temperature, the mixture was washed with water (10 ml x 3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure at 40° gave crude product which was purified by repeated recrystallizations from n-hexane to afford the adduct 2 as colorless crystals (120 mg, 45.0%). For physical and analytical data of 2, see Table.

Homoadamantano[4,5-d]-3'-phenyl-$\Delta^{1'}$-1',2',3'-triazoline (3).---A solution of 1 (148 mg, 1.00 mmol) and phenylazide (155 mg, 1.30 mmol) in benzene (2 ml) was stirred for 10 days at room temperature. Addition of n-hexane to the solution gave crude adduct as colorless crystals which were recrystallized from n-hexane-CH_2Cl_2 to afford the adduct 3 (131 mg, 49.0%). For physical and analytical data of 3, see Table.

Homoadamantano[4,5-b]-1'-tosylaziridine (5).---A solution of 1 (148 mg, 1.00 mmol) and tosylazide (295 mg, 1.50 mmol) in benzene (5 ml) was allowed to stand at room temperature for 4 weeks. Concentration of the solution under reduced pressure at 20° afforded colorless precipitates which were filtered and recrystallized from methanol to give 5 (20 mg, 6.2%). For physical and analytical data of 5, see Table.

Homoadamantano[4,5-b]-1'-(1-adamantyl)aziridine (7).---A mixture of 1 (148 mg, 1.00 mmol) and 1-azidoadamantane[7] (177 mg, 1.00 mmol) in a sealed tube was heated for 3 weeks at 80°. The crude product was purified on a silica gel column eluting with n-hexane-CH_2Cl_2 to afford the aziridine 7 as colorless prisms after recrystallization from CH_2Cl_2-MeOH (110 mg, 36.0%). For physical and analytical data of 7, see Table.

General Procedure for Preparation of Homoadamantano[4,5-b]-2'-substituted Aziridines (9a-c).---To a stirred solution of appropriate Grignard reagent (MeMgI for 9a, EtMgBr for 9b and C_6H_5MgBr for 9c) (6.0 mmol) in ether (5 ml) and toluene (5 ml) was added a solution of homoadamantan-4-one oxime (8) (2.0 or 1.0 mmol) in toluene (10 ml) at 100-105° and the mixture was kept at the same temperature for 3 hr. The cooled mixture was poured onto an ice-ammonium chloride mixture, and the organic layer was separated, and the water layer was extracted with ether (10 ml x 2). The combined organic layer and extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure at 40° gave crude product which was purified on a silica gel column eluting with CH_2Cl_2-MeOH to afford homoadamantano[4,5-b]-2'-methyl- (9a), -ethyl- (9b), and -phenylaziridine (9c) in 21.3, 75.5, and 22.3% yield, respectively. For physical and analytical data of 9a-c, see Table.

REFERENCES AND FOOTNOTES

1 Part 43: T. Sasaki, S. Eguchi, T. Esaki and T. Suzuki, submitted for publication.

2 For example, see T. Sasaki, S. Eguchi and N. Toi, J. Org. Chem., 43, 0000 (1978) and previous papers.

3 For a recent review, see R. C. Fort, Jr., "Adamantane: The Chemistry of Diamond Molecules," in "Studies in Organic Chemistry," Vol. 5, Ed by P. G. Gassmann, Marcel Dekker, Inc., New York, N. Y., 1976.

4 Homoadamant-4-ene (1) was prepared by the method of Black and Gill: R. M. Black and G. B. Gill, J. Chem. Soc. (C), 671 (1970).

5 For a review, see C. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer-Verlag, Berlin, 1971.

6 We used this nomenclature for convenience in this paper.

7 T. Sasaki, S. Eguchi, T. Katada and O. Hiroaki, J. Org. Chem., 42, 3741 (1977) and references cited therein.

8 J. L. M. A. Schlatmann, J. G. Korsloot and J. Schut, Tetrahedron, 26, 949 (1970).

9 For a review, see O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969 and also see ref 11.

10 T. Sasaki, S. Eguchi and T. Toru, J. Org. Chem., 36, 2454 (1971).

11 For detailed procedure, see S. Eguchi and Y. Ishii, Bull. Chem. Soc. Japan, 36, 1434 (1963).

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