[Chem. Pharm. Bull. 30(6)2051—2060(1982)]

Synthesis of Adamantane Derivatives. LVIII.[1] Reaction of 1-Adamantyl Chloride with Some Heterocyclic Unsaturated Silanes

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(Received November 27, 1981)

Various silylated heterocycles having amide functionality were treated with 1-adamantyl chloride (**1**) in the presence of a Lewis acid to give the corresponding *N*-adamantylated heterocycles. If α-position to the reacting lactim nitrogen was substituted, the reaction no longer occurred, or the adamantylation occurred at the position other than the expected nitrogen. These facts are attributed to a steric blocking effect of the α-substituent. While the same treatment of the thioamide **46** gave the *S*-adamantylated product, **48** and **51** afforded in contrast the *N*- and *S*-adamantylated products, respectively; this result can be explained in terms of steric effect. Analogously, silylated 2-pyrazolines and triazoles were adamantylated at nitrogen. The reactions of 2-trimethylsilylthiophene, furan and -pyridine with **1** failed to give site-selective monoadamantylation.

Keywords——adamantane; heterocyclic unsaturated silane; substitution reaction, Lewis acid catalysis; steric effect

Applications of adamantane derivatives in the field of pharmacology have given added impetus to research adamantane chemistry. Numerous derivatives have been shown to have antiviral activity,[2] ranging from the original amine hydrochloride to recent α-cyclohexanone derivatives.[3] Of particular interest are adamantane-substituted heterocycles, which we have been investigating.

Recently we have developed the Lewis acid-catalyzed substitution reaction of 1-adamantyl chloride (**1**) with $\alpha\beta$- and $\beta\gamma$-unsaturated silanes under mild conditions to give bridgehead-substituted adamantane derivatives.[4] When the unsaturated silyl moiety is contained in a cyclic system, this reaction can afford various adamantane-heterocycles in a single step (Chart 1).

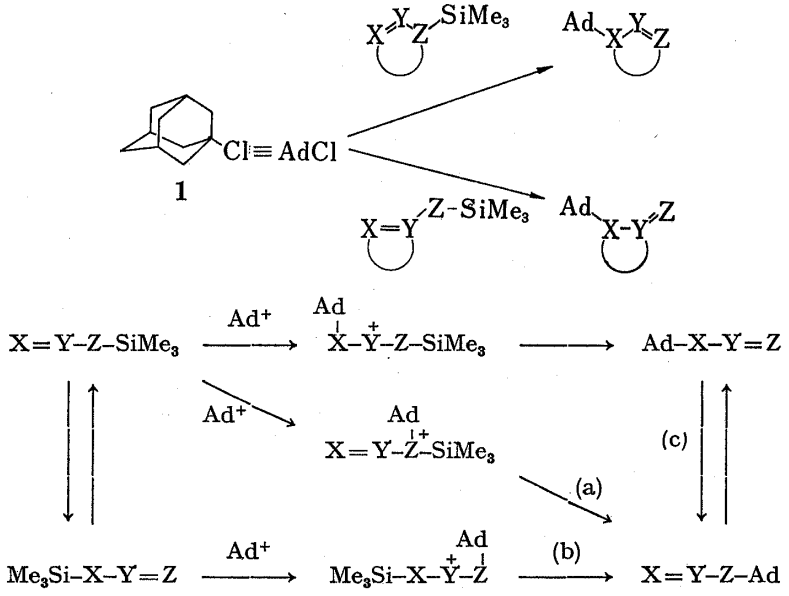


Chart 1

The reaction of this type involving bond formation between a glycoside and heterocyclic base is known as the silyl Hilbert–Johnson reaction.[5] Though it involves an electrophilic attack of a sugar cation, **1** is also capable of generating a stable tertiary carbocation, and hence of reacting substantially in the same manner as a sugar acetal; in fact, our preceding work[4b] indicated that silylated pyridone and uracil underwent such a substitution reaction with **1** smoothly.

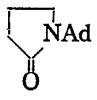
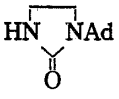
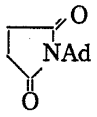
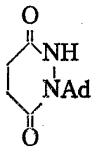
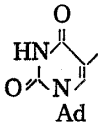
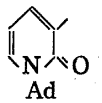
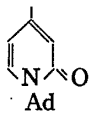
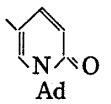
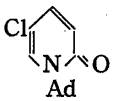
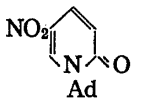
With these results in mind, an extension of this procedure was envisaged to various heterocycles bearing (**1**) CONH (**2**) CSNH and (**3**) miscellaneous unsaturated units. Starting heterocycles were trimethylsilylated by the standard method; treatment with hexamethyldisilazane with or without 10% trimethylsilyl chloride at reflux temperature, or with trimethylsilyl chloride and triethylamine in an intert solvent at reflux or room temperature. Thus prepared silylated heterocycles were used without purification, or otherwise, after trap-to-trap distillation. The results are summarized in Table I, together with the reaction conditions, products and analysis.

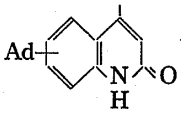
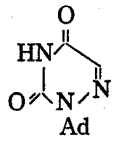
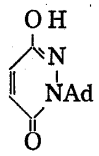
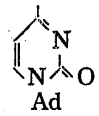
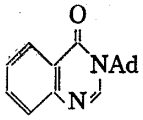
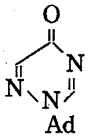
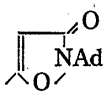
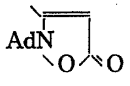
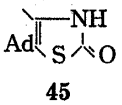
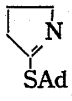
Reaction of Heterocycles with CONH Unit

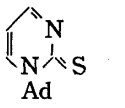
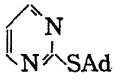
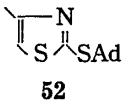
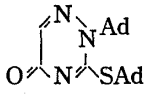
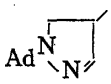
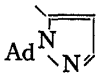
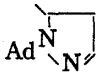
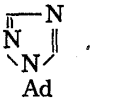
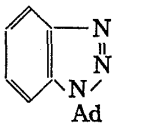
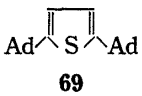
As exemplified in the reaction of acylic *N*-methylacetamide,[4] heterocycles with a CONH unit such as 2-pyrrolidone (**2**), 2-imidazolidone (**4**), succinimide (**6**), and perhydropyridazine-3,6-dione (**8**) were found to react with **1** after silylation in the presence of 2 equiv. of Lewis acid at room temperature to give the corresponding *N*-adamantyl derivatives. The products were characterized on the basis of spectral and elemental analyses. While these reactions were usually well-catalyzed by aluminum chloride, titanium tetrachloride catalysis gave better results for **2** and **4**. However no adamantane-substituted product was isolated from the same reaction of hydantoin (**10**). The fact that *N*-trimethylsilylpyrrolidine never reacted with **1** under the same conditions indicates that $\beta\gamma$-unsaturation, *i.e.*, conjugation with a carbonyl group in this case, is required for the substitution at nitrogen. The possible reaction course is either *ipso*-substitution (path a), or allylic substitution in the equilibrated *O*-silyl imidate form (path b) or in the *N*-silyl amide form followed by O,N rearrangement (path c) (X=O, Y=C, Z=N in Chart 1). The amide functionality of pyridone (**11**) and uracil (**12**) takes a lactim structure on silylation, possibly following reaction path b, whereby the expected *N*-adamantylpyridone and -uracil can be obtained.[4b] We have now attempted the reaction of their substituted derivatives **13**—**21**, and found that the steric bulkiness of an adamantyl group is reflected in their reactivity: thymine (**13**) could be adamantylated in a moderate yield, while 6-methyluracil (**14**) did not give any adamantane-substituted product under the same conditions. Similarly, in a series of pyridones, substituents at 3-, 4- and 5-positions did not influenced the reactivity (as can be seen in **15**—**19**), but a substituent at the 6-position showed a blocking effect; **20** did not react, and the substitution of 4-methylcarbostyril (**21**) took place at the benzene ring instead of nitrogen, although the substitution position was not determined. The observed lack of reactivity is attributed to steric congestion around the target nitrogen. The reaction of positional isomers, 3- and 4-trimethylsilyloxypyridines resulted in recovery of more than 60% of **1**.

To gain further insight into the mode of electrophilic attack of adamantyl cation, related aza analogs were treated with **1** under the above conditions. 6-Azauracil (**29**) was converted to the 1-adamantyl derivative (**30**) in only 9% yield by this procedure. The same type of reaction for maleic hydrazide (**31**), which is in equilibrium with pyridazine-3,6-diol, gave a monoadamantylated product, which showed the same features as the reported *N*-alkyl derivatives[6] in the infared (IR) [ν_{max}^{KBr} C=O (1650 cm^{-1}), ring (1490 cm^{-1})], ultraviolet (UV) [λ_{max}^{EtOH} 317 nm (log ε 3.47)], and nuclear magnetic resonance (NMR) spectra [δ(DMSO-d_6) 6.72 and 7.02 (each 1H, AB q, J=10 Hz, HC=CH], supporting the existence of the hydroxy-oxo form **32**. The reaction of the silyl derivatives of 4-methylpyrimidin-2-one (**33**), 3*H*-quinazolin-4-one (**35**), and 1,2,4-triazin-5-one (**37**) proceeded more slowly to give the corresponding *N*-adamantylated

TABLE I. Silylation, Reaction Conditions, Products, and Analysis Data for the Substitution Reaction of 1-Adamantyl Chloride with Some Heterocycles

Compd.	Silylation 1 reagent[a] 2 time (temp.)[b] 3 °C/mmHg[c]	Conditions 1 cat. (solv.)[d] 2 temp. 3 time [h]	Product	Yield [%]	mp [°C]	Formula	Analysis (%) Calcd (Found) C	H	N
2	H 4 (B) 120/2	T (M) rt 48	 **3**	54	98—99 (lit. 99.6—100.4)				
4	H 5 (B)	T (M) rt 12	 **5**	32	267—268	$C_{13}H_{20}N_2O$	70.87 (70.98	9.15 9.11	12.72 12.65)
6	TA (benzene) 10 (B) 150/2	A (C) rt 24	 **7**	33	118—119	$C_{14}H_{19}NO_2$	72.07 (72.14	8.21 8.17	6.00 5.97)
8	H 24 (B)	A (C) rt 48	 **9**	44	225—227	$C_{14}H_{20}N_2O_2$	67.71 (67.98	8.12 8.14	11.28 11.23)
13	HT 5 (B)	A (C) rt 12	 **22**	50	305—310	$C_{15}H_{20}N_2O_2$	69.20 (69.65	7.74 7.83	10.76 10.31)
15	TA (toluene) 12 (B) 120/2	A (C) rt 12	 **23**	25	101—103	$C_{16}H_{21}NO$	78.97 (79.17	8.70 8.71	5.76 5.66)
16	TA (toluene) 12 (B) 120/2	A (C) rt 12	 **24**	30	194—195	$C_{16}H_{21}NO$	78.97 (78.74	8.70 8.59	5.76 5.69)
17	TA (toluene) 12 (B) 120/2	A (C) rt 12	 **25**	30	164—166	$C_{16}H_{21}NO$	78.97 (79.10	8.70 8.69	5.76 5.67)
18	TA (toluene) 12 (B) 100/2	A (C) rt 12	 **26**	53	191—195	$C_{15}H_{18}NOCl$	68.30 (68.28	6.88 6.73	5.31 5.08)
19	H 5 (B)	A (C) rt 72	 **27**	77	195—199	$C_{15}H_{18}N_2O_3$	65.67 (65.46	6.61 6.62	10.21 10.41)

Compd.	Silylation 1 reagent[a] 2 time (temp.)[b] 3 °C/mmHg[c]	Conditions 1 cat. (solv.)[d] 2 temp. 3 time [h]	Product	Yield [%]	mp [°C]	Formula	Analysis (%) Calcd (Found) C	H	N
21	H 5 (B)	A (C) rt 12	 **28**	72	300>	$C_{20}H_{23}NO$	81.87 (81.80	7.90 7.89	4.77 4.85)
29	H 24 (B)	A (C) rt 12	 **30**	9	271—273	$C_{13}H_{17}N_3O_2$	63.14 (63.05	6.93 6.99	16.99 17.03)
31	H 3 (B)	A (C) rt 7	 **32**	61	292—297	$C_{14}H_{18}N_2O_2$	68.27 (68.37	7.37 7.42	11.37 11.22)
33	H 10 (B)	A (C) rt 72	 **34**	38	217—220	$C_{15}H_{20}N_2O$	73.73 (73.57	8.25 8.39	11.47 11.46)
35	H 15 (B)	A (C) rt 48	 **36**	50	210—212	$C_{18}H_{20}N_2O$	77.11 (77.08	7.19 7.20	9.99 9.98)
37	H 8 (B)	A (C) rt 72	 **38**	61	272—273	$C_{13}H_{17}N_3O$	67.50 (67.22	7.41 7.36	18.17 17.97)
39	TA (Et_2O) 5 (rt) 100/3	A (C) rt 1	 **43**	77	107—108	$C_{14}H_{19}NO_2$	72.02 (72.12	8.21 8.26	6.00 5.90)
40	TA (CH_3CN) 12 (rt) 120/3	A (C) rt 0.5	 **44**	64	133—135	$C_{14}H_{19}NO_2$	72.07 (71.82	8.21 8.23	6.00 5.79)
41	H 4 (B)	A (C) rt 1	 **45**	84	300>	$C_{14}H_{19}NOS$	67.43 (67.45	7.68 7.64	5.62 5.65)
46	TA (benzene) 10 (B) 150/2	A (C) rt 1	 **47**	85	104—105	$C_{14}H_{21}NS$	71.44 (71.46	8.99 8.98	5.95 5.94)

Compd.	Silylation 1 reagent[a] 2 time (temp.)[b] 3 °C/mmHg[c]	Conditions 1 cat. (solv.)[d] 2 temp. 3 time [h]	Product	Yield [%]	mp [°C]	Formula	Analysis (%) Calcd (Found) C	H	N
48	HT 15 (B)	A (C) rt 1	 **49**	41	202—204	$C_{14}H_{18}N_2S$	68.26 (68.32	7.36 7.37	11.37 11.35)
			 **50**	16	64—66	$C_{14}H_{18}N_2S$	68.26 (68.37	7.36 7.39	11.37 11.23)
51	H 8 (B)	A (C) rt 1	 **52**	60	105—107	$C_{14}H_{19}NS_2$	63.35 (63.43	7.21 7.32	5.28 5.00)
53	HT 5 (B)	A (C) −45°C 0.25	 **54**	50	289—290	$C_{23}H_{31}N_3OS$	69.48 (69.80	7.86 7.80	10.57 10.45)
57	TA 12 (rt) 100/20	A (C) 0°C 1	 **59**	60	oil	$C_{14}H_{22}N_2$	77.01 (77.02	10.16 10.10	12.83 12.80)
58	TA 12 (rt) 60/3	A (C) 0°C	 **60**	37	85—86	$C_{14}H_{20}N_2$	77.73 (77.68	9.32 9.39	12.95 12.93)
			 **61**	18		$C_{14}H_{22}N_2$	77.01 (76.93	10.16 10.26	12.83 12.82)
62	H 10 (B)	A (C) rt 4	 **64**	70	81—82	$C_{12}H_{17}N_3$	70.90 (71.14	8.43 8.47	20.67 20.74)
63	H 8 (B)	A (C) rt 2	 **65**	60	150—153	$C_{16}H_{19}N_3$	75.85 (75.68	7.56 7.51	16.59 16.47)
66	*e*)	S (M) rt 3	 **69**	65	198—200	$C_{24}H_{32}S$	81.76 (81.80	9.15 9.11)	

a) H: hexamethyldisilazane (3- to 4-fold molar excess). HT: hexamethyldisilazane containing 10% trimethylsilyl chloride (3-to 4-fold molar excess). TA: 1.1 equiv of mixture of trimethylsilyl chloride and triethylamine (1:1), with the solvent noted.

b) Reaction time in hour and temperature in parenthesis: B, boiling; rt, room temperature.

c) Trap-to-trap distillation of the silylated heterocycles at oven temperature/vacuum level (Shibata glass tube oven, model GTO-250). Note that the temperature does not mean "boiling point." The silylated heterocycles were used only after the removal of the excess silylating reagents by evaporation unless otherwise noted.

d) Catalyst: T, $TiCl_4$; A, $AlCl_3$: S, $SnCl_4$, and solvent in parenthesis: M, CH_2Cl_2; C, $CHCl_3$.

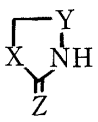
e) Prepared from trimethylsilyl chloride and 2-thienyllithium; R. A. Benkeser and R. B. Currie, *J. Am. Chem. Soc.*, **70**, 1780 (1948).

products. For **33**, adamantylation should occur at *N*-1 rather than *N*-3 nitrogen, considering the observed steric effect (*vide supra*). Similarly there are two possible reaction sites at *N*-1 and *N*-3 for **35** and **37**: for **35**, the C=O band in the IR spectrum appeared at 1660 cm^{-1}, suggesting the *ortho*-quinoid form **36**,[7] which was unequivocally determined by an independent synthesis from 1-adamantylamine and **35**.[8] The product from **37** was assignable as a *para*-quinoid structure since the UV spectrum [λ_{max}^{EtOH} 243 nm (log ε 4.22), 270 nm (sh, log ε 3.78)] is very similar to that of the ribosyl derivative [λ_{max}^{EtOH} 242 nm (log ε 4.13), 269 nm (sh, log ε 3.72)].[4] The reaction aptitude of **37** in adamantylation is in good agreement with that in ribosylation[4] which was explained in terms of steric effect of *N*-3 nitrogen by the bulky trimethylsilyl group. The contending *peri*-positional steric hindrance in **35** may lead to the preferential formation of the *ortho*-quinoid **36**, a thermodynamic product.

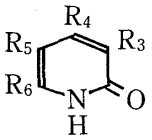
We next turned our attention to the five-membered rings, **39**—**42**. These are regarded as π-excessive ring systems, and therefore increased nucleophilicity made the reaction time shorter than 1 h. Thus 3-, and 5-trimethylsilyloxyisoxazoles derived from **39** and **40** yielded the expected *N*-adamantyl derivatives, whose structures were confirmed by the spectra: for the product **43**, the IR spectrum showed a C=O band at 1665 cm^{-1} and disappearance of the ring modes at 1620 and 1510 cm^{-1}.[9] For the product **44**, the IR spectrum showed a strong absorption at 1700 cm^{-1} due to a carbonyl group, and the NMR spectrum in $CDCl_3$ showed signals at 4.93 δ (1H, br s, C_4–H) and 2.32 δ (3H, s, C_3–CH_3), all of which are interpretable in terms of a 2*H*-isoxazol-5-one structure.[10] The formation of **44** was favored because the reaction at nitrogen is advantageous not only electronically but also sterically. In contrast, the reaction of the silyl derivative of **41** to give a C-5-adamantylated product (**45**), as indicated by the IR spectrum [ν_{max}^{KBr} NH/OH (3100—3600 cm^{-1}), C=O (1645 cm^{-1})] and the NMR spectrum [$\delta(CDCl_3)$ 9.39 (1H, br s, NH/OH), 2.15 (3H, s, C_4–CH_3)][11] was rather extraordinary since a typical electrophilic substitution reaction occurs at nitrogen or oxygen. Clearly the steric hindrance of the C-5-methyl substituent suppressed the reaction at nitrogen. Thus this is another case in which the steric effect altered the course of the reaction. The reaction using **42** was complex because thin-layer chromatography of the product mixture showed more than seven spots, even though the reaction was conducted at −50°C.

Reaction of Heterocycles with CSNH Unit

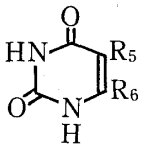
A typical cyclic thioamide (**46**) underwent the anticipated substitution reaction with **1** to give a lactim thioether (**47**), as indicated by the C=N band at 1595 cm^{-1} in the IR spectrum, in accord with our previous results in 2-mercaptothiazolines.[4b] In the case of pyrimidine-2-thione (**48**) and 4-methylthiazole-2-thione (**51**), their reactivity was contrasting although *N*-ribosylations were reported for both of them.[4,12] Treatment of **48** (Table I) gave rise to *N*-adamantylated **49** together with a smalla mount of **50**. Structural determination was performed by spectral inspections; for **49**, IR ν_{max}^{KBr} ring (1605 and 1540 cm^{-1}); UV λ_{max}^{EtOH} 218 nm (log ε 3.95), 296 nm (log ε 4.09), 371 (log ε 3.33);[13] NMR δ ($CDCl_3$) 6.65, 8.12 and 8.27 (each 1H, ABX, J=7 and 4 Hz, J=7 and 2 Hz, and J=4 and 2 Hz, respectively, ring H), and for **50**, IR ν_{max}^{KBr} ring (1565 and 1555 cm^{-1}); NMR δ ($CDCl_3$) 6.90 (1H, t, J=5 Hz, C_5–H), 8.48 (2H, d, J=5 Hz, C_4–H, C_6–H). These data unambiguously distinguish *N vs.* *S* substitution. The same treatment of **51** gave mainly *S*-adamantylated **52**, identified from the characteristic UV absorption at 264 nm (log ε 3.74) and the NMR signals at 6.93 δ (1H, q, J=1.5 Hz, C_5–H) and 2.46 δ (3H, d, J=1.5 Hz, CH_3).[11] This reactivity difference is seemingly surprising, but can be explained in terms of the foregoing results: after the substitution takes place at sulfur kinetically, the primarily formed *S*-product **50** rearranges to the thermodynamically more stable *N*-product **49** (path c, X=S, Y=C, Z=N in Chart 1), if catalyzed *S*,*N* rearrangement is allowed when the thiolate is stabilized by an aromatic ring, *i.e.*, in **48** and **51**. As a matter of fact, analogous *S*,*N* rearrangement is observed in the ribosylation.[14] Nevertheless, **52**, is forced to remain as the initial form because of the steric repulsion owing to the C-4 methyl group.



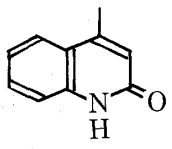
2 : X=CH_2, Y=CH_2, Z=O
4 : X=NH, Y=CH_2, Z=O
6 : X=CH_2, Y=CO, Z=O
10 : X=NH, Y=CO, Z=O
46 : X=CH_2, Y=CH_2, Z=S



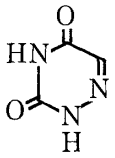
11 : R_3, R_4, R_5, R_6=H
15 : R_3=CH_3, R_4, R_5, R_6=H
16 : R_4=CH_3, R_3, R_5, R_6=H
17 : R_5=CH_3, R_3, R_4, R_6=H
18 : R_5=Cl, R_3, R_4, R_6=H
19 : R_5=NO_2, R_3, R_4, R_6=H
20 : R_5, R_6=$(CH_2)_4$, R_3=H, R_4=CH_3



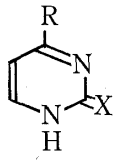
12 : R_5, R_6=H
13 : R_5=CH_3, R_6=H
14 : R_5=H, R_6=CH_3



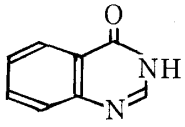
21



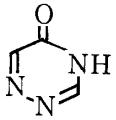
29



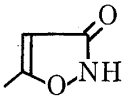
33 : X=O, R=CH_3
48 : X=S, R=H



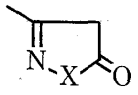
35



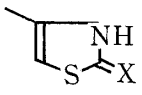
37



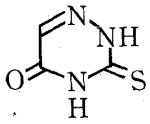
39



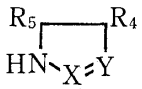
40 : X=O
42 : X=NH



41 : X=O
51 : X=S



53



56 : X=CCH_3, Y=N, R_4, R_5=H
57 : X=N, Y=CH, R_4=CH_3, R_5=H
58 : X=N, Y=CH, R_4=H, R_5=CH_3

Chart 2

When the reaction of the disilyl derivative of 3-thioxo-1,2,4-triazin-5-one (**53**) was conducted under milder conditions, two adamantyl groups were introduced. Since the substitution at N-4 is not favored on steric grounds, the positions substituted are probably N-2 and S; this view is supported by the following spectral data compared with those of the 2-methyl-3-methylthio derivative[15] of **53**; IR ν_{max}^{KBr} C=O (1640 cm^{-1}); UV λ_{max}^{EtOH} 232 nm (log ε 4.21), 319 nm (log ε 1.55); NMR δ ($CDCl_3$) 7.81 (1H, s, C_6–H). No product was obtained from the reaction of 5-methyl-1,3,4-thiazole-2-thiol (**55**) under the $AlCl_3$-catalyzed conditions.

Reaction of Miscellaneous Unsaturated Heterocycles

In an attempt to apply the above-mentioned reactions to heterocycles with NH–X=Y (X, Y=C, N), lysidine (**56**) and 3- and 4-methyl-2-pyrazolines, **57** and **58** were treated with **1** (Table I). While the silyl derivative of **56** was not reactive, those of **57** and **58** were adamantylated at *N*-1. The normal product (**59**) was obtained from **57**, but unexpectedly, the aromatized product (**60**) was obtained in 37% yield accompanied with **61** in 18% yield from **58**; a competitive diaproportionation reaction might be involved, because **60** was formed even under a

nitrogen atmosphere. In any event, *N*-1 adamantylation rather than C-3 adamantylation is explicable in terms of pathway b or c in Chart 1.

In imidazoles, we have observed C-adamantylation;[4b] however, the reaction of the silyl derivatives of 1,2,4-triazole (**62**) and benzotriazole (**63**) proceeded to give *N*-adamantyltriazoles, (**64**) and (**65**), respectively. The reason for this dissimilarity was not clarified. It shoud be noted that in contrast to the present mild conditions, the earlier method for preparing **64** required drastic conditions, *i.e.*, heating a mixture of 1-adamantyl bromide and **62** at 190—200°C.[16]

Finally we attempted the reactions of 2-trimethylsilylthiophene (**66**), -furan (**67**), and -pyridine (**68**), which might afford silyl-directed positional isomers if a well-known electronic effect of the silyl group works efficiently.[17] However, the $SnCl_4$-catalyzed reaction of **66** with **1** (1 : 1 ratio) at room temperature gave 2,5-diadamantylthiophene (**69**) in 65% yield after recrystallization from the product mixture. Moreover, **67** gave no appreciable amount of the desired product, and **68** did not react. The reaction of 2-trimethylsilyloxyfuran (**70**) with **1** also failed, suggesting that the products formed from **67** and **70** might be labile under the Lewis acid-catalyzed conditions.

In summary, adamantane-heterocycles were synthesized by the sequence of trimethylsilylation of the heterocycles with an NH–X=Y unit (X, Y=C, N, O, S) followed by adamantylation in the presence of a Lewis acid. In compounds with amide functionality, the substitution occurred exclusively at nitrogen. In some cases, a C=N bond in the ring system disturbed the reaction, for example, with **29** (low yield), **37** (prolonged reaction time), and **55** (no reaction). The steric bulkiness of the adamantyl group may inhibit the reaction or otherwise alter the course of the reaction.

Experimental

Infrared spectra were determined on a JASCO IRA-1 spectrophotometer, and data are reported in units of cm^{-1}. All of the crystalline products were scanned in KBr disks except for the oily product **59** (neat). Proton NMR spectra were determined at 60 MHz in a indicated solvent with a JEOL 60-HL spectrometer, and chemical shifts are reported in δ units downfield from internal tetramethylsilane. In all spectra, signals due to adamantane ring protons were usually recognized in the 1.5—2.2 δ region as a multiplet. Ultraviolet spectra were determined on a Hitachi model 200-10 spectrophotometer. Spectral patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder. Microanalyses were performed with a Perkin–Elmer 240 elemental analyzer. Melting points were determined on a Yanaco MP apparatus and are uncorrected.

General Procedure for the Substitution Reaction of 1 with Trimethylsilylated Heterocycles——A trimethylsilylated heterocycle (1 mmol) in $CHCl_3$ (or CH_2Cl_2) (2 ml) was added dropwise to a solution of **1** (1 mmol) containing $AlCl_3$ (or $TiCl_4$) (2 mmol) in $CHCl_3$ (or CH_2Cl_2) (5 ml) at the temperature designated in Table 1, and the mixture was stirred for the appropriate time. The reaction mixture was then poured into a saturated Na_2CO_3 solution containing ice, and products were extracted with $CHCl_3$ (or CH_2Cl_2). Occasionally Celite was used as a filter aid to remove undissolved precipitates. The combined extract was concentrated to give a solid or sometimes an oil, which was recrystallized or subjected to column chromatography on silica gel (Mallinckrodt 100 mesh with the solvent noted). The purified compounds were analyzed spectroscopically.

1-(1-Adamantyl)pyrrolidone (**3**)——This was separated by chromatography with $CHCl_3$ and compared with an authentic specimen.[18] IR ν_{max}: 1640 (C=O). NMR ($CDCl_3$): 2.35 (2H, t, J=6 Hz, $COCH_2$), 3.46 (2H, t, J=6 Hz, NCH_2).

1-(1-Adamantyl)imidazolidin-2-one (**5**)——This was chromatographed with $CHCl_3$/MeOH (10/1). IR ν_{max}: 3250 (NH), 1665 (C=O). NMR ($CDCl_3$): 3.35 (4H, m, NCH_2).

***N*-(1-Adamantyl)succinimide** (**7**)——This was obtained by recrystallization from hexane. IR ν_{max}: 1690 (C=O). NMR ($CDCl_3$): 2.55 (4H, s, CH_2).

***N*-(1-Adamantyl)perhydropyridazine-3,6-dione** (**9**)——This was chromatographed with $CHCl_3$/MeOH (95/5). IR ν_{max}: 3150 (NH), 1690 and 1630 (C=O). NMR ($CDCl_3$): 2.55 (4H, br s, CH_2), 10.58 (1H, br s, NH).

1-(1-Adamantyl)thymine (**22**)——This was obtained by recrystallization from $CHCl_3$–hexane. IR ν_{max}: 1660 (C=O). NMR ($CDCl_3$): 1.93 (3H, s, CH_3), 7.29 (1H, s, C_6–H), 8.92 (1H, br s, NH).

1-(1-Adamantyl)-3-methyl-1,2-dihydropyridin-2-one (**23**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1640 (C=O). NMR (CCl_4): 2.01 (3H, s, CH_3), 5.85 (1H, t, J=7 Hz, C_5–H), 7.00 and 7.27 (each 1H, dd, J=7 and 2 Hz, C_4–H and C_6–H).

1-(1-Adamantyl)-4-methyl-1,2-dihydropyriridin-2-one (**24**)——This was obtained by recrystallization from hexane. IR ν_{max}: 1650 (C=O). NMR ($CDCl_3$): 2.12 (3H, s, CH_3), 5.91 (1H, dd, $J=7$ and 2 Hz, C_5–H), 6.23 (1H, d, $J=2$ Hz, C_3–H), 7.35 (1H, d, $J=7$ Hz, C_6–H).

1-(1-Adamantyl)-5-methyl-1,2-dihydropyridin-2-one (**25**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1660 (C=O). NMR ($CDCl_3$): 2.07 (1H, s, CH_3), 6.36 (1H, d, $J=8$ Hz, C_3–H), 7.07 (1H, dd, $J=8$ and 2 Hz, C_4–H), 7.26 (1H, d, $J=2$ Hz, C_6–H).

1-(1-Adamantyl)-5-chloro-1,2-dihydropyridin-2-one (**26**)——This was obtained by recrystallization from CH_2Cl_2–Et_2O. IR ν_{max}: 1640 (C=O). NMR ($CDCl_3$): 6.38 (1H, d, $J=9$ Hz, C_3–H), 7.17 (1H, dd, $J=9$ and 3 Hz, C_4–H), 7.49 (1H, d, $J=3$ Hz, C_6–H).

1-(1-Adamantyl)-5-nitro-1,2-dihydropyridin-2-one (**27**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1670 (C=O), 1560 and 1350 (NO_2). NMR ($CDCl_3$): 6.11 (1H, d, $J=10$ Hz, C_3–H), 8.00 (1H, dd, $J=10$ and 3 Hz, C_4–H), 8.34 (1H, d, $J=3$ Hz, C_5–H).

Adamantylated 4-Methylcarbostyril (**28**)——This was obtained by recrystallization from $CHCl_3$–EtOH. IR ν_{max}: 3200—2400 (NH/OH), 1650 (C=O). NMR ($CDCl_3$): 2.53 (3H, s, CH_3), 6.57 (1H, s, C_3–H), 7.5 (3H, m, benzene ring H), 11.88 (1H, br s, NH).

1-(1-Adamantyl)-6-azauracil (**30**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1660 (C=O). NMR ($CDCl_3$): 7.35 (1H, s, C_5–H), 8.96 (1H, br s, NH).

***N*-(1-Adamantyl)maleic Hydrazide** (**32**)——This was chromatographed with $CHCl_3$/MeOH (10/1). IR and NMR: see text.

1-(1-Adamantyl)-4-methyl-1,2-dihydropyrimidin-2-one (**34**)——This was chromatographed with $CHCl_3$/MeOH (95/5). IR ν_{max}: 1655 (C=O). NMR ($CDCl_3$): 2.32 (3H, s, CH_3), 6.21 (1H, d, $J=7$ Hz, C_5–H), 7.82 (1H, d, $J=7$ Hz, C_6–H).

3-(1-Adamantyl)-3,4-dihydroquinazolin-4-one (**36**)——This was chromatographed with $CHCl_3$. IR: see text. NMR ($CDCl_3$): 7.3—7.8 and 8.2—8.4 (3H and 2H, m, ring H). A mixture of 1-adamantylamine and **35** (1 : 1) was heated at 200°C for 5 h and chromatographed with $CHCl_3$ to give mainly the unchanged amine and a solid which was identical with the obtained product in terms of the spectral and TLC analyses.

2-(1-Adamantyl)-2,5-dihydro-1,2,4-triazin-5-one (**38**)——This was chromatographed with $CHCl_3$/MeOH (95/5). IR ν_{max}: 1670 (C=O). NMR ($CDCl_3$): 7.84 (1H, d, $J=1$ Hz, C_6–H), 8.62 (1H, d, $J=1$ Hz, C_3–H).

2-(1-Adamantyl)-5-methyl-2,3-dihydroisoxazol-3-one (**43**)——This was chromatographed with $CHCl_3$. IR: see text. NMR ($CDCl_3$): 2.18 (4H, br s, CH_3), 5.37 (1H, br s, C_4–H).

2-(1-Adamantyl)-3-methyl-2,5-dihydroisoxazol-5-one (**44**)——This was chromatographed with $CHCl_3$. IR and NMR: see text.

5-(1-Adamantyl)-4-methyl-2,3-dihydrothiazol-2-one (**45**)——This was chromatographed with $CHCl_3$/MeOH (95/5). IR and NMR: see text.

2-(1-Adamantylthio)-1-pyrroline (**47**)——This was chromatographed with $CHCl_3$. IR: see text. NMR (CCl_4): 2.48 (2H, m, N=CCH_2), 3.80 (2H, m, CH_2N=C).

1-(1-Adamantyl)-1,2-dihydropyrimidine-2-thione (**49**)——Chromatographic separation with $CHCl_3$ gave **50** as the first fraction and **49** as the second fraction. IR and NMR: see text.

2-(1-Adamantylthio)-4-methylthiazole (**52**)——This was chromatographed with $CHCl_3$. Small amounts of by-products were obtained as a mixture but were not purified. IR ν_{max}: 1520 (ring). NMR: see text.

2-(1-Adamantyl)-3-(1-adamantylthio)-2,5-dihydro-1,2,4-triazin-5-one (**54**)——In this case only, the products were chromatographed on an alumina column (Woelm N, Akt 1) with $CHCl_3$. IR and NMR: see text.

1-(1-Adamantyl)-4-methyl-2-pyrazoline (**59**)——This was chromatographed with $CHCl_3$. IR ν_{max}^{neat}: 1580 (C=N). NMR ($CDCl_3$): 1.16 (3H, d, $J=6$ Hz, CH_3), 2.4—3.5 (3H, m, NCH_2 and C_4–H), 6.58 (1H, s, N=CH).

1-(1-Adamantyl)-5-methylpyrazole (**60**)——Chromatographic separation with $CHCl_3$ gave **60** as the first fraction and **61** as the second fraction. **60**: IR ν_{max}: 1520 (ring). UV λ_{max}^{EtOH}: 219 nm (log ε 3.70). NMR (CCl_4): 2.17 (3H, s, CH_3), 5.78 (1H, d, $J=1.5$ Hz, C_4–H), 7.21 (1H, d, $J=1.5$ Hz, C_3–H). **61**: IR ν_{max}: 1600 (C=N). NMR (CCl_4): 1.22 (3H, d, $J=6$ Hz, CH_3), 2.18 and 2.72 (each 1H, dq, $J=16$, 9 and 1.5 Hz and $J=16$, 10 and 2 Hz, respectively, C_4–CH_2), 3.52 (1H, m, C_5–H), 6.37 (1H, dd, $J=2$ and 1.5 Hz, N=CH).

1-(1-Adamantyl)-1,2,4-triazole (**64**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1520 (ring). NMR ($CDCl_3$) 7.94 and 8.14 (each 1H, s, ring H).

1-(1-Adamantyl)benzotriazole (**65**)——This was chromatographed with $CHCl_3$. IR ν_{max}: 1620 and 1590 (ring). NMR ($CDCl_3$): 7.2—8.2 (4H, m, benzene ring H).

2,5-di(1-Adamantyl)thiophene (**69**)——This was obtained by recrystallization from MeOH–Et_2O. IR ν_{max}: 1520 (ring). NMR (CCl_4): 6.45 (2H, s, ring H). An equivalent amount of $SnCl_4$ was used in the experiments with **66**, **67** and **70**.

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