Preparation of 1,3-Functionalized Adamantanes by the Lewis Acid Catalyzed Electrophilic Cyclization of 7-Methylenebicyclo[3.3.1]nonan-3-one in the Presence of π- and N-Nucleophiles[1]

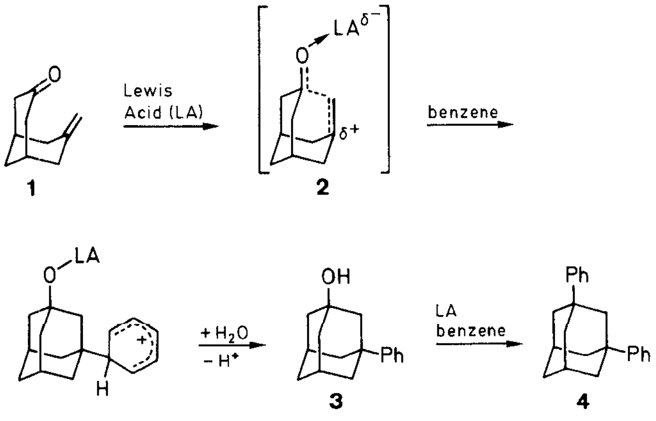
George A. Olah,* Ramesh Krishnamurti, G. K. Surya Prakash*

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1661, USA

Preparation of 1,3-difunctionalized adamantane derivatives from 7-methylenebicyclo[3.3.1]nonane-3-one (**1**) in the presence of nucleophiles under Lewis acid catalysis is described. Reaction of **1** with benzene using a variety of Lewis acid catalysts gave 1,3-diphenyladamantane (**4**) as the major product. Trimethylsilyl cyanide and azide efficiently reacted with **1** in the presence of zinc iodide as the catalyst to give good yields of the corresponding 3-trimethylsiloxyadamantyl isocyanide and azide, respectively. Trimethylsilyl isothiocyanate gave a 1:1 mixture of the thiocyanate and isothiocyanate derivatives. Silyl enol ethers, such as those of acetophenone and cyclopentanone, and allyltrimethylsilane also reacted with **1** to afford the corresponding 1,3-difunctionalized adamantanes.

Bicyclo[3.3.1]nonane systems possessing both methylene and carbonyl groups at the 3- and 7-positions are known to undergo transannular cyclization to afford adamantane derivatives. This process has been observed to occur in reactions with nucleophiles, such as amines, phenols, and thiols,[2] under catalytic hydrogenation over Group VIII metal catalysts,[3] and ionic hydrogenation using triethylsilane and acid initiators, such as sulfuric and trifluoroacetic acids.[4] We now report the Lewis acid mediated transannular cyclization reactions of readily available 7-methylenebicyclo[3.3.1]nonane-3-one (**1**)[5] in the presence of various nucleophiles, a methodology which substantially facilitates the preparation of 1,3-functionalized adamantanes.

In connection with our studies on 1,3-disubstituted adamantanes, we found that **1** could serve as a convenient precursor for reactions with a variety of nucleophiles to directly afford the corresponding 3-substituted adamantanols. Lewis acid complexation of the carbonyl group helps the formation of the intermediate **2** which subsequently reacts with benzene to give the phenylated adamantane (Scheme A).



Scheme A

A variety of Lewis acids were examined using benzene as the nucleophile. The results are summarized in Table 1. When titanium tetrachloride was employed, a 61 % isolated yield of 3-chloro-1-adamantanol (**5**) resulted after a 3.5 hour reaction period. Anhydrous ferric chloride also gave a similar result. However, in both cases, a longer reaction time resulted in the sole formation of 1,3-diphenyladamantane (**4**). With methylaluminum dichloride as the Lewis acid, 3-chloro-1-adamantanol (**5**) and 3-phenyl-1-adamantanol (**3**) were formed as minor products, and 1,3-diphenyladamantane (**4**) as the major product. From these results, it seems that when Lewis acid chlorides are used, the initial product is 3-chloro-1-adamantanol. However, the subsequent formation of 3-phenyl-1-adamantanol and 1,3-diphenyladamantane is competitive (as seen for example, in the reaction employing methylaluminum dichloride in Table 1). Stetter and co-workers have, in fact, previously observed a similar process when **1** was reacted with anisole in the presence of *p*-toluenesulphonic acid as catalyst; 1,3-bis(*p*-methoxyphenyl)adamantane was isolated in 58 % yield.[6] Using diethyl ether–boron trifluoride as catalyst results in a slower reaction with **3** and **4** obtained in about equal amounts in the reaction mixture. Trimethylsilyl trifluoromethanesulfonate (triflate) was next selected for this reaction, however, in order to obtain a more selective reaction a bulky Hunig base, such as diisopropyl-

Table 1. Reaction of **1** with Benzene in the Presence of Various Lewis Acids[a]

Lewis Acid	Reaction Conditions Temperature (°C)/ Time (h)	Composition of Reaction Mixture (%)[b] **1**	**3**	**4**	**5**
$TiCl_4$	0 → r.t./3.5				61[c]
$MeAlCl_2$	0 → r.t./20		17	80	3
$Et_2O \cdot BF_3$	0 → r.t./2.5	10	45	45	
BF_3	0/0.25			98	
Me_3SiOTf	reflux/7			98	
Me_3SiOTf	reflux/5	no reaction			
$AlCl_3$	0 → r.t./18			98	
$FeCl_3$	0 → r.t./1				90
$FeCl_3$	0 → r.t./20			92	

[a] One molar equiv of the Lewis acid was used in all cases. The solvent employed was benzene/CH_2Cl_2 (1:1) unless otherwise specified.

[b] Yields were determined by gas chromatography unless otherwise indicated.

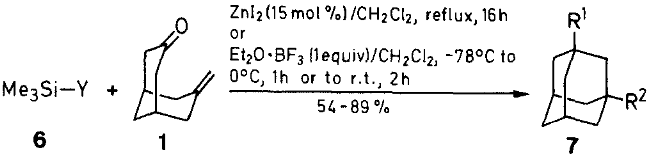
[c] Isolated yield.

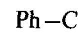
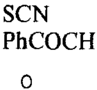
[d] Plus 1 equiv i-Pr_2EtN.

[e] Plus 1 equiv collidine.

ethylamine, was used in connection with this Lewis acid. After refluxing for 7 h, however, GC analysis showed the presence of only 1,3-diphenyladamantane in the reaction mixture. With collidine as the base, only unreacted starting material **1** remained.

Besides reactions with aromatics (i.e. π-nucleophiles), *N*-donor nucleophiles, such as trimethylsilyl cyanide, azide, and silyl enol ethers were also examined Scheme **B**. Anhydrous zinc iodide and diethyl ether–boron trifluoride were used to promote the reactions. The results are shown in Table 2. Satisfactory to good yields of 1,3-adamantane derivatives were obtained. It is interesting to note that with trimethylsilyl cyanide only the isocyanide derivative **7a** was obtained. This was evident from the ^{13}C-NMR spectrum which showed the isocyanide carbon as a triplet at $\delta = 152.4$ with $^1J_{^{13}C-^{14}N} \approx 4.9$ Hz. The ring carbon bearing the isocyanide group also appeared as a triplet with $J_{^{13}C-^{14}N} \approx 6$ Hz. Additionally, the IR spectrum showed an absorption for the N=C group at 2131 cm^{-1} which is in accordance with previous observations on related isocyanides.[7]



6	Y	7	R^1	R^2
a	CN	a	OSiMe$_3$	NC
b	N$_3$	b	OSiMe$_3$	N$_3$
c	S=C=N	c	OH	NCS
		d	OH	SCN
d	Ph–C(=CH$_2$)Oe	e	OH	PhCOCH$_2$
e		f	OH	
f	H$_2$C=CHCH$_2$	g	OH	CH$_2$=CHCH$_2$

Scheme **B**

Alternatively, trimethylsilyl cyanide can exist in equilibrium with the isocyanide, and it is the isocyanide form that reacts with the enone.[8] The ambident nature of trimethylsilyl cyanide is also evident from the reported titanium tetrachloride catalyzed reaction with 1-adamantyl chloride where the sole product was the isonitrile derivative.[9] Trimethylsilyl azide also afforded an excellent yield of the azido derivative **7b**. With trimethylsilyl isothiocyanate however, a 1:1 mixture of the isothiocyano and the thiocyano derivatives, **7c** and **7d**, respectively, were obtained. GC-MS analysis of the product mixture also showed a very small amount (ca. 2%) of adamantyl-1,3-diisothiocyanate (or the dithiocyanate) derivative. Again, one can visualize a rapid equilibrium between trimethylsilyl isothiocyanate and the thiocyanate form, however, both species can react equally well with the enone to produce a 1:1 mixture of **7c** and **7d**. Sasaki and co-workers observed that 1-chloroadamantane reacted with trimethylsilyl isothiocyanate in the presence of titanium tetrachloride at -78 °C to afford only 1-adamantyl thiocyanate.[9] However, when the reaction was conducted at 0 °C, a mixture of the thiocyanate and the isothiocyanate resulted in a ratio of 6:4. Control experiments indicated that 1-adamantyl thiocyanate isomerized catalytically to the isothiocya-

Table 2. Compounds **7a–g** Prepared

Product	Yield	Molecular Formula[a]	MS[b] *m/z*	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ	^{13}C-NMR (CDCl$_3$)[g] δ, J(Hz)
7a	69[d]	C$_{14}$H$_{23}$NOSi (249.4)	249, 234, 73	2131, 1146	0.11 (s, 9H, Me$_3$Si), 1.49 (m, 2H), 1.70 (m, 4H), 1.86–2.04 (m, 6H), 2.23 (m, 2H)	2.7, 30.1, 34.1, 42.3, 44.1, 51.2, 56.0 (t, $J = 6.0$), 70.9, 152.4 (t, $J = 4.9$)
7b	86[d]	C$_{13}$H$_{23}$N$_3$OSi (265.4)	265, 223, 73	2089, 1252, 1139	0.11 (s, 9H, Me$_3$Si), 1.46–1.82 (m, 12H), 2.27 (m, 2H)	2.7, 30.8, 34.5, 40.2, 44.4, 49.6, 60.5, 72.2
7c + **7d**	75[e]	C$_{11}$H$_{15}$NOS (209.2)	209, 151	3248, 2146, 1123	1.46–1.56 (m, 4H), 1.60–1.67 (m, 8H), 1.83–1.96 (m, 12H), 2.20–2.32 (m, 6H)	30.3, 31.5, 33.9, 34.0, 42.1, 42.5, 43.2, 43.3, 50.9, 53.9, 59.9, 68.7, 69.9, 110.4 (SCN), 130.6 (NCS)
7e	65[f]	C$_{18}$H$_{22}$O$_2$ (270.4)	270, 252, 105, 77	3287, 3084, 1667, 1596, 1580, 1134	1.50–1.64 (m, 12H), 2.15 (br s, 2H), 2.55 (br s, 1H, OH), 2.79 (s, 2H, CH$_2$CO), 7.46 (m, 3H), 7.95 (m, 2H)	30.3, 34.9, 36.7, 41.1, 44.1, 49.7, 50.1, 68.3, 128.1, 128.3, 132.6, 138.2, 199.6
7f	55[f]	C$_{15}$H$_{22}$O$_2$ (234.3)	234, 151, 133, 84	3301, 1730, 1137	1.15–2.20 (m, 21H), 2.65 (br s, 1H, OH)	19.9, 24.5, 30.0, 30.2, 35.1, 37.8, 38.2, 40.2, 44.3, 47.0, 57.1, 67.9, 219.7
7g	54[f]	C$_{13}$H$_{20}$O (192.3)	192, 151, 133, 41	3349, 3073, 1639, 1453, 1141	1.30–1.94 (m, 15H), 2.17 (m, 2H), 4.90–5.06 (m, 2H), 5.68–5.92 (m, 1H)	30.5, 35.4, 36.0, 40.8, 44.5, 47.7, 49.6, 68.7, 116.8, 134.0

[a] Satisfactory microanalyses were obtained: C ±0.39, H ±0.36, N ±0.13.

[b] Obtained on a Finnigan MAT Model INCOS 50 spectrometer.

[c] Recorded on a Perkin-Elmer Model 1550 FT-IR spectrophotometer.

[d] 15 mole % ZnI$_2$ was employed as the Lewis acid catalyst.

[e] One molar equiv of ZnI$_2$ was used.

[f] One molar equiv of Et$_2$O · BF$_3$ was used.

[g] Recorded on a Varian VXR-200 spectrometer.

nate derivative at 0 °C. Therefore, the thiocyanate is the kinetic product, and its formation was explained by considering the preferential attack of the adamantyl cation on the γ-heteroatom (allylsilane-type reaction[10]) or alternatively on the heteroatom in the equilibrated form, $N{\equiv}C{-}S{-}SiMe_3$ (ipso substitution).

The Lewis acid mediated cyclization can also be effected with concomitant carbon–carbon bond formation to produce functionalized adamantane derivatives. Silyl enol ethers can serve as efficient nucleophilic substrates in this regard. For example, the trimethylsilyl enol ethers of acetophenone and cyclopentanone reacted with the enone **1** to afford the corresponding 3-alkylated adamantanols **7e** and **7f**, respectively, in fair yields. Allyltrimethylsilane also reacted as a carbon nucleophile to give 3-allyl-1-adamantanol (**7g**). Diethyl ether–boron trifluoride was found to be a more satisfactory Lewis acid than zinc iodide for the cyclizations involving the silyl enol ethers and allyltrimethylsilane. The reaction was found, however, not to work with vinyltrimethylsilane, benzyltrimethylsilane, cyclopropyltrimethylsilane, phenyltrimethylsilane, and ethylthiotrimethylsilane, either with zinc iodide or diethyl ether–boron trifluoride as catalyst.

In summary, the Lewis acid mediated cyclization of 7-methylenebicyclo[3.3.1]nonane-3-one in the presence of varied nucleophiles can be usefully employed to prepare otherwise difficult to obtain 1,3-difunctionalized adamantane derivatives.

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian VXR-200 instrument in $CDCl_3$ solution with TMS as the internal standard. Infrared spectra of the compounds were obtained on a Perkin-Elmer Model 1550 FT-IR instrument using either a KBr pellet, or a nujol mull, or as neat films on KBr plates. Mass spectra were measured with a Finnigan MAT Model INCOS 50 instrument. Enone **1** was prepared using the procedure described in the literature.[5] All reactions were run under a fresh atmosphere of dry nitrogen. Dichloromethane was obtained dry by distillation from P_2O_5 after standing over 4 Å molecular sieves. Column chromatography was carried out with silica gel (60–200 mesh, J.T. Baker). Reaction with benzene was carried out under conditions specified in Table 1.

Preparation of 1,3-Difunctionalized Adamantanes (7a–d); General Procedure:

To a solution of enone **1** (10 mmol) in CH_2Cl_2 (20 mL) at r.t. is added an appropriate amount of anhydrous zinc iodide (as indicated in Table 2) followed by a solution of the appropriate trimethylsilyl derivative (TMS-Y) (12 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL). The resulting heterogeneous solution is heated under reflux for 16 h. After cooling to r.t., the reaction mixture is filtered, and the filtrate is concentrated to give the crude product. Compounds **7a–d** are obtained pure by column chromatography using silica gel and 95:5 hexanes/Et_2O as the eluent. No purification of the product (1:1 mixture of the thiocyanate and the isothiocyanate derivatives, **7c** and **7d**, respectively) from the reaction with trimethylsilyl isothiocyanate is necessary as it is spectroscopically and analytically pure. Yields of the isolated products and spectroscopic data are given in Table 2.

Preparation of 1,3-Difunctionalized Adamantanes (7e–g); General Procedure:

To a mixture of a solution of the enone **1** (10 mmol) and the appropriate trimethylsilyl derivative (TMS-Y, Table 2) (12 mmol) in CH_2Cl_2 (20 mL), cooled to -78 °C is added $Et_2O \cdot BF_3$ (10 mmol) *via* syringe. The dry ice bath is allowed to warm up to 0 °C over 1 h in the case of **6e** and **6f**, and to r.t. over 2 h in the case of **6d**. The reaction mixture is quenched with H_2O (5 mL), and extracted with Et_2O (2 × 30 mL). The combined Et_2O extracts are washed with H_2O (30 mL), dried ($MgSO_4$), and concentrated to give the crude products. Column chromatography using silica gel and a suitable eluent affords the pure products. Isolated yields and spectroscopic data are given in Table 2.

Support of our work by the National Institutes of Health is gratefully acknowledged.

Received: 11 October 1989; revised: 26 March 1990

(1) Synthetic Methods and Reactions Part 150. For Part 149 see: Olah, G.A.; Wu, A. *Synlett* **1990**, 54.

(2) Yamaguchi, R.; Yang, K.H.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 673.

(3) Ishiyama, J.; Senda, Y.; Imaizumi, S. *Chem. Lett.* **1983**, 771.

(4) Kratsutskii, P.A.; Ambrosienko, N.V.; Rodionov, V.N.; Yurchenko, A.G.; Parnes, Z.N.; Bolestova, G.I. *Zh. Org. Khim.* **1985**, *21*, 1465.

(5) Momose, T.; Muraoka, O. *Chem. Pharm. Bull.* **1978**, *26*, 1978.

(6) Stetter, H.; Gartner, J.; Tacke, P. *Chem. Ber.* **1965**, *98*, 3888.

(7) Sasaki, T.; Egushi, S. Katada, T. *J. Org. Chem.* **1974**, *39*, 1239.

(8) Booth, M.R.; Frankiss, S.G. *Spectrochim. Acta* **1970**, *26A*, 859.
Bither, T.A.; Knoth, W.H.; Lindsay, R.V.; Sharkey, W.H. *J. Am. Chem. Soc.* **1958**, *80*, 4151.
Seckar, J.A.; Thayer, J.S. *Inorg. Chem.* **1976**, *15*, 501.
Gassman, P.G.; Guggenheim, T.L. *J. Am. Chem. Soc.* **1982**, *104*, 5849.
Gassman, P.G.; Gremban, R.S. *Tetrahedron Lett.* **1984**, *25*, 3259.
Gassman, P.G.; Haberman, L.M. *J. Org. Chem.* **1986**, *51*, 5010.

(9) Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1981**, *46*, 5445.

(10) Fleming, I., in: Barton and Ollis *Comprehensive Organic Chemistry*, Vol. 3, Jones, D.N. (ed.), Pergamon Press, Oxford, **1979**, Part 13.