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Photochemical Preparation of 1,3,5,7-Tetracyanoadamantane and Its Conversion to 1,3,5,7-Tetrakis(aminomethyl)adamantane

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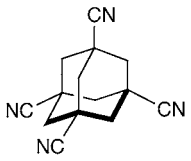
ABSTRACT



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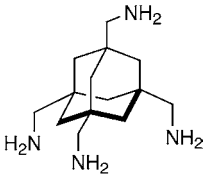

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New adamantane derivatives 1 and 2 that bear functionalized one-carbon extensions at all four bridgehead positions have been prepared. Radical nucleophilic substitution ($S_{RN}1$) reaction of 1,3,5,7-tetrabromoadamantane with cyanide produces 1,3,5,7-tetracyanoadamantane (1), which was reduced with borane reagents to 1,3,5,7-tetrakis(aminomethyl)adamantane (2). Improvements in the preparation of 1,3,5,7-tetrahaloadamantanes (halogen = Br, Cl, I) are also reported.

Tetra(bridgehead)-substituted adamantanes are valuable tetrahedral building blocks for the synthesis of engineered materials.[1] However, there are few examples of 1,3,5,7-carbon-substituted adamantane cores, and they are limited to tetraaryladamantanes[2] and adamantane tetracarboxylic acid [and its tetra(acid chloride),[3,4] tetraester,[3b,4] and tetraamide[3b,5] derivatives]. Our work on the synthesis of organic and mixed organic/inorganic dendrimers required the preparation of 1,3,5,7-tetracyanoadamantane (**1**) and 1,3,5,7-tetrakis(aminomethyl)adamantane (**2**). We report here their efficient synthesis from adamantane.

We initially prepared **2** (Scheme 1) by taking advantage of Bashir−Hashemi's photochemical conversion of either adamantane carboxylic acid (**3**) or 1,3-adamantane dicarboxylic acid (**4**) to 1,3,5,7-tetrakis(chlorocarbonyl)adamantane (**5**).[4] This was converted to the tetrabenzylamide **6b**,[6] which was subsequently reduced to tetraamine **2**, first by deoxygenation with lithium aluminum hydride to the tetrabenzylamine, followed by debenzylation by hydrogenolysis over Pd−C. Tetramine **2** was isolated in 4% overall yield

(1) (a) Wang, S.; Oldhman, J. W.; Hudack, R. A.; Bazan, G. C. *J. Am. Chem. Soc*. **2000**, *122*, 5695. (b) Martin, V. V.; Alferiev, I. S.; Weis, A. L. *Tetrahedron Lett*. **1999**, *40*, 223. (c) Menger, F. M.; Migulin, V. A. *J. Org. Chem*. **1999**, *64*, 8916. (d) Newkome, G. R.; Narayana, V. V.; Patri, A. K.; Grob, J. Moorefield, C. N.; Baker, G. R. *Polym. Mater. Sci. Eng*. **1995**, *737*, 222. (e) Reddy, D. R.; Craig, D. C.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun*. **1995**, *3*, 339. (f) Chen, S. H.; Mastrangelo, J. C.; Shi, H.; Bashir-Hashemi, A.; Li, J.; Gelber, N. *Macromolecules* **1995**, *28*, 7775.

(2) (a) Li, Q.; Rukavishnikov, A. V.; Petukhov, P. A.; Zaikova, T. O.; Keana, J. F. W. *Org. Lett*. **2002**, *4*, 3631. (b) Reichert, V. R.; Mathias, L. J. *Macromolecules* **1994**, *27*, 7015.

(3) (a) Stetter, H.; Bander, O. E.; Neumann, W. *Chem. Ber*. **1956**, *89*, 1922. (b) Newkome, G. R.; Nayak, A.; Behera, R. K.; Moorefield, C. N.; Baker, G. R. *J. Org. Chem*. **1992**, *57*, 358.

(4) Bashir-Hashemi, A.; Jianchang, L. *Tetrahedron Lett*. **1995**, *36* (8), 1236.

(5) Stetter, H.; Krause, M. *Tetrahedron Lett*. **1967**, *19*, 1843.

(6) **6b**: ^{1}H NMR (300 MHz, $CDCl_3$/MeOD-d_3) δ 1.72 (s, 12H), 4.16 (s, 8H), 6.85−7.02 (m, 20H), 7.41 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 38.66, 42.06, 42.95, 126.88, 126.99, 128.17, 137.99, 176.04; IR (cast) ν_{max} 3405, 2892, 1664, 1452 cm^{-1}.

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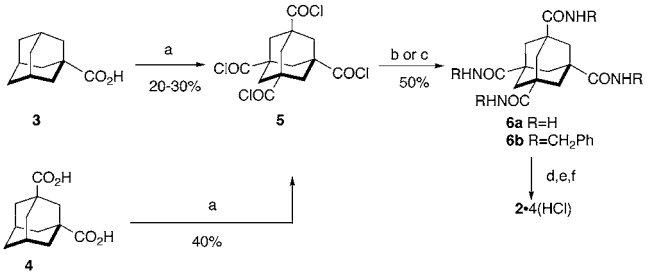
Scheme 1[a]



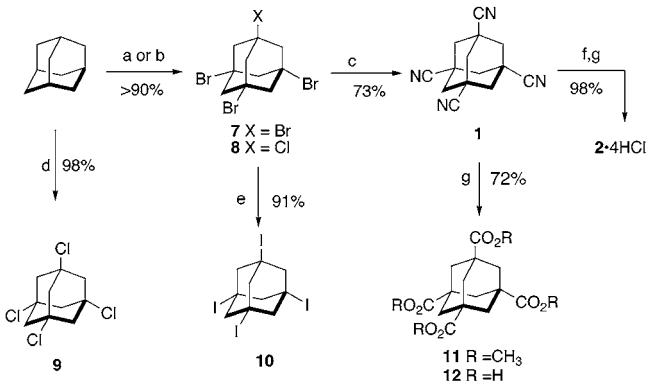
[a] Key: (a) $(COCl)_2$, hν; (b) NH_3; (c) $PhCH_2NH_2$; (d) $LiAlH_4$, THF; (e) H_2, Pd−C; (f) HCl.

from **3** as the tetrahydrochloride **2**•4(HCl).[7] This approach was unsatisfying for two reasons. The modest yield of the photocarbonylation step was aggravated by the considerable expense of adamantane monocarboxylic acid starting material (or by use of the even more costly 1,3-adamantanedicarboxylic acid, which gave higher, yet still modest, yields of product). Furthermore, the insolubility of parent tetrabenzamide **6a** necessitated the atom-inefficient introduction of nitrogen as benzylamine (rather than ammonia), which required an additional step to remove the four benzyl groups. We sought an alternative procedure.

Direct functionalization of adamantane through carbon−carbon bond formation at the bridgehead has previously resulted in limited success. Bridgehead monocyanation of adamantane has been reported by Olah to occur in high yield with trimethylsilylcyanide/$SnCl_4$,[8] yet even 1,3-dicyanation occurs only sparingly, as introduction of the first electron-withdrawing cyano group deactivates the molecule toward formation of subsequent carbocation intermediates. Replacement of halogen with other functional groups has been observed in bridgehead monohaloadamantanes under conditions that generate radical,[9] carbanionic,[10] or carbocationic[11] intermediates. Reactions of polyhaloadamantanes have generally been limited to arylation.[2] We report here that 1,3,5,7-tetrabromoadamantane (**7**) reacts photochemically with sodium cyanide to produce 1,3,5,7-tetracyanoadamantane (**1**) in good yield (Scheme 2).

Adamantane has been reported to react with 1 equiv of aluminum trichloride and excess bromine to provide 1,3,5,7-tetrabromoadamantane (**7**)[12] in 47−58% yields. We found a marked improvement in the yield (>90%) of tetrahaloadamantanes[13] with the use of greater amounts $AlCl_3$ (2, 3, or 4 equiv), but with the generation of not only **7** but also

Scheme 2[a]



[a] Key: (a) Br_2, $2AlBr_3$; (b) Br_2, $4AlCl_3$; (c) NaCN, DMSO, hν; (d) CCl_4, $AlCl_3$; (e) CH_3I, $AlBr_3$; (f) $BH_2Cl-SMe_2$; (g) HCl, MeOH

small amounts (3−12%) of 1-chloro-3,5,7-tribromoadamantane (**8**).[14] We sought to avoid halogen exchange in the synthesis of **7** by using aluminum tribromide.[15] We found that equimolar amounts of adamantane and $AlBr_3$ produced 1,3,5-tribromoadamantane in 86% yield. We also found that two equiv of $AlBr_3$ produced clean **7** in 85% yield, but manipulations involving this Lewis acid are experimentally more difficult.

Conversion of tetrabromoadamantane **7** to tetracyanoadamantane **1** appears to occur by an $S_{RN}1$ process.[10b,16] No reaction occurs in the dark, yet photolysis at 254 nm of a 0.03 M solution of **7** and 16 equiv of sodium cyanide in DMSO (in quartz) in a Rayonet reactor produced a mixture where tetracyanoadamantane **1** was the predominant product. This was accompanied by small amounts of hypocyanated haloadamantanes (mass spectrometric analysis was consistent with the production of dibromodicyanoadamantane and bromotricyanoadamantane) and others that appear to be the result of decomposition of **1** under the reaction conditions. Indeed, a sample of pure tetracyanoadamantane **1** decomposed slowly on photolysis to several unidentified products that gave rise to ^{1}H NMR signals comparable to those seen in the reaction mixture of the photolysis of **7** and NaCN. Our best yields in converting **7** to **1** resulted from photolysis until only a small amount of **7** remained as indicated by TLC (generally 5−6 h). The residue, after distillation of DMSO at reduced pressure and removal of excess cyanide,[17] was chromatographed on silica gel. Removal of unreacted **7** by elution with hexanes, followed by mixtures of dichloromethane and acetone, allowed isolation of **1** in 63% yield. Alternatively, recrystallization of the crude residue from

(7) **2**•4HCl: mp > 400 °C.; ^{1}H NMR (300 MHz, D_2O) δ 1.27 (s, 8H), 2.77 (s, 12H); ^{13}C NMR (D_2O) δ 39.00, 33.39, 48.98; IR (KBr) ν_{max} 2923, 1596, 1520, 1459, 1376 cm^{-1}.

(8) Olah, G. A.; Wang, Q. *Synthesis* **1992**, 1090.

(9) (a) Santiago, A. N.; Stahl, A. E.; Rodriguez, G. L.; Rossi, R. A. *J. Org. Chem.* **1997**, *62*, 4406. (b) Kraus, G. A.; Siclovan, T. M. *J Org. Chem.* **1994**, *59*, 22.

(10) (a) Wu, T.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045. (b) Lukach, A. E.; Rossi, R. A. *J. Org. Chem.* **1999**, *64*, 5836.

(11) Olah, G. A.; Farooq, O.; Prakash, S. *Synthesis* **1985**, 1140.

(12) (a) Murray, R. W.; Rajadhyaksha, S. N.; Mohan, L. *J. Org. Chem.* **1989**, *54*, 5783. (b) Sollot, G. P.; Gilbert, E. E. *J. Org. Chem.***1980**, *45*, 5405.

(13) **7**: mp = 246−248 °C (lit.[12] 245−247 °C); ^{1}H NMR ($CDCl_3$) δ 2.71; ^{13}C NMR (300 MHz, $CDCl_3$) δ 54.62, 54.78; IR (KBr) ν_{max} 487 cm^{-1}; UV λ_{max}= 262 nm.

(14) **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55, 2.68; ^{13}C NMR (DMSO) δ 56.69, 55.69, 52.00, 51.00.

(15) It has been reported that catalytic amounts of $AlBr_3$ and Br_2 react with adamantane to produce 1,3,5-tribromoadamantane in low yield: (a) Tolstikov, H. A.; Lerman, B. M.; Aref'eva, Z. *Tetrahedron Lett.* **1972**, *31*, 3191. (b) Baughman, G. L. *J. Org. Chem.* **1963**, *29*, 238.

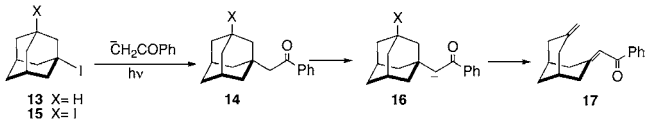
(16) Lukach, A. E.; Santiago, A. N.; Rossi, R. A. *J. Org. Chem.* **1997**, *62*, 426.

acetone−water gave **1** as an off-white powder in 73% yield and of similar purity as the chromatographed material. Although DMSO absorbs in the photolysis region, and the toxicity of cyanide in this solvent requires extreme care, we have been unable to identify other solvents useful for this transformation, largely because of the insolubility of the cyanide and tetracyanoadamantane **1**.

Useful photocyanation under these conditions appears to be limited to tetrabromoadamantane (**7**). We prepared tetrachloroadamantane **9** in 98% yield by a modified literature procedure,[18] and tetraiodoadamantane **10** in 91% yield from **7** and iodomethane/$AlBr_3$.[19] Photolysis of **9** and NaCN produced essentially no conversion to **1** after more than 10 h. On the other hand, tetraiodoadamantane **10** reacted within 1 h but led to a complex mixture of products, among which was **1**.

Rossi has previously described the $S_{RN}1$ substitution of adamantane bridgehead halogen (Scheme 3).[20] Photochemical reaction of iodoadamantane (**13**) with acetophenone enolate resulted in good yields of **14** (X = H). However, attempted

Scheme 3



disubstitution of 1,3-diiodoadamantane (**15**) resulted in cage fragmentation products (presumably via the intermediacy of the enolate **16** (X = I) formed subsequently from the monosubstitution product **14** (X = I) and its elimination to form **17**. Our substitution of all four bridgehead positions in tetrabromoadamantane **7** with cyanide was possible as no enolizable intermediates could be formed, thus avoiding elimination pathways.

Reduction of tetranitrile **1** was best accomplished in our hands by monochloroborane−methyl sulfide in refluxing THF (with removal of methyl sulfide). Isolation of product was accomplished by decomposition of remaining hydride with multiple additions of excess methanol and evaporation to remove the volatile borate esters and solvent. Reaction with dry methanolic HCl produced the tetrakis(aminomethyl)adamantane tetrahydrochloride [**2**·4(HCl)] in 98% yield.[7] The parent tetraamine **2** was prepared by deprotonation of an aqueous solution of **2**·4(HCl) with NaOH.[21]

The present work also represents a (formal) new synthesis of the very useful 1,3,5,7-adamantanetetracarboxylic acid (**12**), which has been previously prepared by multistep processes that required assembly of the polycyclic-substituted adamantane cage from monocyclic precursors.[3b] A more efficient synthesis of derivatives of **12** has been reported to occur from the photocarbonylation of adamantane mono- or dicarboxylic acids, but the expense of starting materials and modest product yields are limitations.[4] We have converted tetracyanoadamantane **1** to 1,3,5,7-tetracarbomethoxyadamantane (**11**) in 72% yield by solvolysis with methanolic anhydrous HCl.[22]

In conclusion, we have synthesized new and useful 1,3,5,7-tetrasubstituted adamantanes **1** and **2** in good yields from (inexpensive) adamantane. Since **1** can be solvolyzed to 1,3,5,7-tetra(carbomethoxy)adamantane (**11**), this also represents a formal synthesis of 1,3,5,7-adamantane tetracarboxylic acid (**12**), which has previously found wide application. Finally, we have also improved procedures for making 1,3,5,7-tetrahaloadamantanes **7**, **9**, and **10**.

We will describe in other reports the incorporation of the tetrasubstituted adamantanes **1** and **2** into several designed materials.

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Supporting Information Available: Complete experimental details and data characterizing all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Excess NaCN is washed away with water and decomposed with bleach. **1**: mp > 400 °C.; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 12H); ^{13}C NMR (DMSO-d_6) δ 29.37, 36.19, 120.96; IR (KBr) ν_{max} 2240 cm^{-1}; HRMS-FAB (*m*/*z*) [M$^+$] calcd 236.1062, found 236.1630; UV λ_{max}= 257 nm.

(18) It has been reported that adamantane and catalytic $AlCl_3$ refluxed in CCl_4 for 3 days produce **9** in 55% yield: Bach, R. D.; Badger, R. C. *Synthesis* **1979**, *7*, 529. We refluxed 1:2 adamantane/$AlCl_3$ in CCl_4 for 1 h to produce **9**: mp = 191−193 °C (lit.[18] 194 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 46.56, 53.58; IR (KBr) ν_{max} 502 cm^{-1}.

(19) It has been reported that reaction of tetrabromoadamantane and Al foil with bromine in methylene iodide produced **10** in 65% yield: McKinley, J. W.; Pincock, R. E.; Scott, W. B. *J. Am. Chem. Soc*. **1973**, *95*, 2030. We stirred 1: 1 adamantane: $AlBr_3$ in iodomethane at room temperature for 15h to yield **10**: *mp* >360 °C (lit 370 °C[19]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 12H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 57.21, 59.22; IR (KBr) 479 cm^{-1}.

(20) Borosky, G.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem*. **1990**, *12*, 3705.

(21) **2**: ^{1}H NMR (300 MHz, D_2O) δ 0.89 (s, 8H), 2.11 (s, 12H); ^{13}C NMR (D_2O) δ 32.65, 38.99, 50.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 8H), 2.45 (s, 12H); IR (cast) ν_{max} 3646, 3444, 2914, 1556, 1320 cm^{-1}; HRMS-FAB (*m*/*z*) [M + H] $^+$ calcd 253.2391, found 253.2388.

(22) **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 12H), 2.66 (s, 12H); IR (cast) ν_{max} 2985, 2878, 1736, 1179 cm^{-1}.