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Monoprotection of Diols as a Key Step for the Selective Synthesis of Unequally Disubstituted Diamondoids (Nanodiamonds)†

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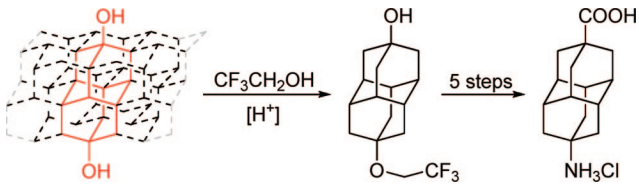

The monoprotection (desymmetrization) of diamondoid, benzylic, and ethynyl diols has been achieved using fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) under acidic conditions. This practical acid-catalyzed S_N1 reaction opens the door for the synthesis of novel bifunctional diamondoids. With diamantane as an example, we show that the resulting monoethers can be used to prepare selectively, for instance, amino or nitro alcohols and unnatural amino acids. These are important compounds in terms of the exploration of electronic, pharmacological, and material properties of functionalized nanodiamonds.

The naturally occurring[1] class of so-called diamondoids has received considerable attention during the past few years.[2] These nanometer-sized diamond-like molecules (nanodiamonds) possess a variety of different shapes (e.g., stick or pyramidal), and some of them are even chiral (Figure 1). Recently, our group was able to synthesize not only derivatives of diamantane (**2**), but also of triamantane (**3**), [121]tetramantane (**4**), and [1(2,3)4]pentamantane (**5**).[3−5] The synthesis of thiol derivatives[6] led to the preparation of diamondoid-SAMs, which display negative electron affinity (NEA) upon irradiation with X-rays.[7]

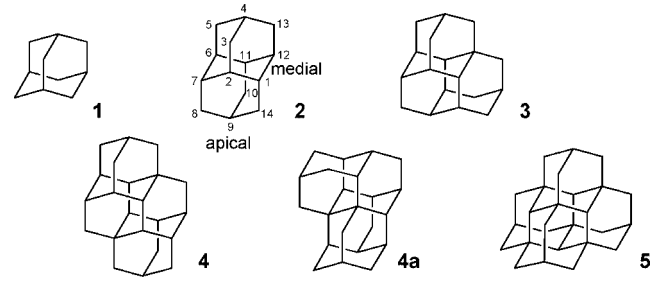

FIGURE 1. Examples of diamondoids: adamantane (**1**), diamantane (**2**), triamantane (**3**), [121]tetramantane (**4**), (*M*)-[123]tetramantane (**4a**), and [1(2,3)4]pentamantane (**5**).

Since the selective mono- and also the difunctionalization of diamondoids with equal substituents is now a straightforward task, we attempted to synthesize nanodiamonds with two different substituents. These building blocks would make the use of diamondoids even more interesting (e.g., to control and tune the NEA effect[7] or for the preparation of polymers). In our recent review,[2] we showed that besides **1** the derivatization of diamondoids having two different substituents at their tertiary positions has only been achieved for **2**. Burkhard, Janku, and Vodicka studied brominations of diamantanecarboxylic acids and their hydrolysis to hydroxy carboxylic acids.[8] Although the bromination route via the carboxylic acids leads to unequally disubstituted diamantane derivatives, these reactions either have low yields or the mixtures are hard to separate even with advanced HPLC techniques.[9] Recently, Padmanaban et al. treated diamantane-4,9-diol (**6**, Scheme 1) with equimolar amounts of reagent to obtain 4-hydroxy-9-diamantylmethacrylate, but this reaction proceeded in only 5% yield.[10]

Since it is possible to prepare the bisapical diol **6** in high yield directly from **2** using 100% nitric acid,[5] this linear

† Functionalized Nanodiamonds. 10. For part 9, see: Willey, T. M.; Fabbri, J. D.; Lee, J. R. I.; Schreiner, P. R.; Fokin, A. A.; Tkachenko, B. A.; Fokina, N. A.; Dahl, J. E. P.; Carlson, R. M. K.; Vance, A. L.; Yang, W.; Terminello, L. J.; van Buuren, T.; Melosh, N. A. *J. Am. Chem. Soc.* **2008**, *130*, 10536−10544.

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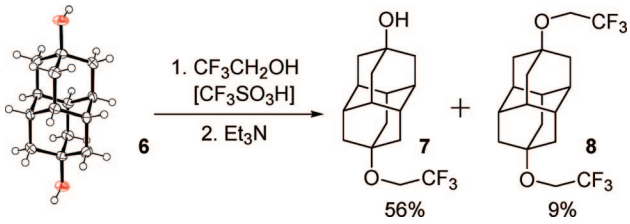
SCHEME 1. Monoprotection of Diamantane-4,9-diol (6, Crystal Structure Depicted), Using TFE and Catalytic Amounts of Triflic Acid Followed by Neutralization Using Triethylamine



dialcohol is a readily accessible precursor for the monoprotection. Even though there are many strategies for the monoprotection of diols, such reactions often require uncommon reagents, polymers, and/or dry solvents.[11] With regard to a suitable solvent, we first had to overcome the problem of solubility of the diamondoid diols. We found that 2,2,2-trifluoroethanol (TFE) is not only a good solvent in comparison to nonfluorinated simple alcohols but also exhibits its power as an excellent nucleophile upon addition of catalytic amounts of a nonnucleophilic acid such as triflic acid (Scheme 1). Therefore, we were able to isolate 9-(2,2,2-trifluoroethoxy)-diamantan-4-ol (**7**) in good yield (the crystal structure of **7** is available in the Supporting Information).

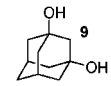
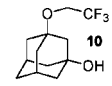
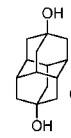
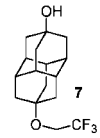
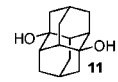
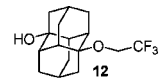
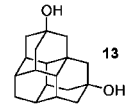
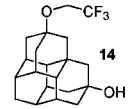
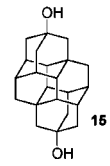
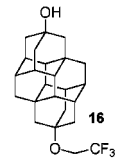
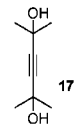
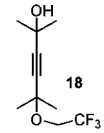
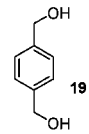
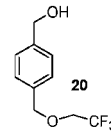
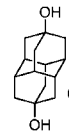
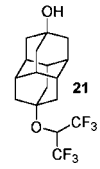
Fluorinated alcohols have long been known for their unique properties as solvents or cosolvents and can also be used in a whole variety of reaction types such as epoxidations, cycloadditions, metathesis, reductions, ring openings, and isomerization reactions,[12] but we found that they have not been used for the monoprotection of diols.

Encouraged by the results for the monoprotection of model compound **6**, we also examined other symmetrical diols for this reaction. Table 1 shows that this reaction is not only applicable to **6** but to all known symmetrical diamondoid diols. Furthermore, it can be applied to aromatic and ethynyl diols that stabilize the incipient tertiary cation in this S_N1 reaction. Other fluorinated alcohols, which are, however, more expensive, can also be used as shown for 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and they react with these diols in the same manner (entry 8, Table 1). Table 1 also shows that these results are in line with our earlier observations and computations regarding the reactivity of diamondoids.[3] Higher diamondoids are more reactive (decrease of reaction time and temperature) as compared to their smaller analogues. Also, the medial positions of **2** (and hence its corresponding diol) are more reactive than the apical ones.

The advantage of this protocol is the low boiling points of fluorinated alcohols in comparison to their nonfluorinated analogues. Thus, the reaction can be stopped by the addition of Et_3N and the solvent can easily be evaporated (and recycled), leaving the crude product behind. For the optimal quenching times and temperatures the reactions were monitored by GC/MS analysis. Preference for the monoether product is likely due to the destabilization of the intermediate carbenium ion through the trifluoroethyl group. Alternatively, the reaction can be quenched with water, and the crude product can be extracted with chloroform; this method requires more time and produces slightly lower yields.

To emphasize the practicality of the synthesized monoethers, we derivatized **7** to prepare an amino alcohol and an amino

TABLE 1. Yields, Temperatures, Times, and Selectivities for the Preparation of Fluorinated Monoethers Using TFE (HFIP for Entry 8) and Triflic Acid (3−37 mol %)[a]

	diol	monoether	yield %	selectivity mono vs. diether	T [°C]	time [h]
1			75	>75:1	40	3
2			56	6.2:1	40	4
3			64	4.3:1	40	0.33
4			53	2.0:1	RT	14
5			62	2.7:1	RT	2
6			57	>57:1	RT	0.5
7			64	>64:1	RT	14.5
8			32	1.9:1	RT	0.75

[a] All yields are preparative, and compounds are fully characterized. For entries 1, 6, and 7, only traces of the corresponding diethers were obtained.

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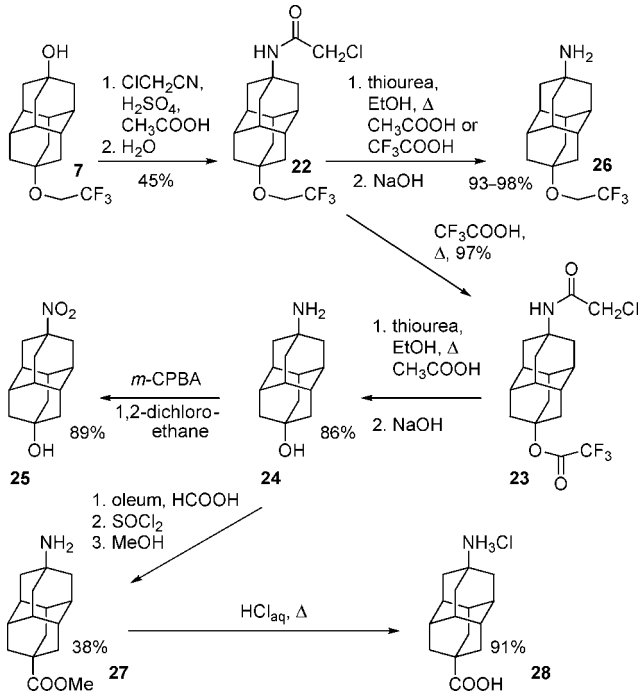
SCHEME 2. Ritter Reaction of Monoether 7 with Chloroacetonitrile Followed by Either Conversion of the Ether into the Corresponding Amino Ether or into Its Ester[a]



[a] The ester can be hydrolyzed into the amino alcohol from which the amino acid is prepared.

acid. However, we ran into the problem that all known procedures for the preparation of diamondoid amines either have low yields, use explosive azides, or employ the alkaline/acidic hydrolysis of acetamides, which is also low yielding.[13] Inspired by the work of Jirgensons et al.,[14] we attempted to prepare amines via Ritter reaction using chloroacetonitrile. With this approach, we were able to isolate the desired 2-chloro-*N*-[9-(2,2,2-trifluoroethoxy)diamant-4-yl]acetamide (**22**) in 45% yield. Structural proof of this compound was obtained from an X-ray measurement (Supporting Information). Along with this desired product, we isolated three other unequally disubstituted derivatives of **2** as side products (see the Supporting Information).

Since the conversion of the chloroacetamide into an amine is straightforward by using thiourea in acidic media,[14] we first turned our attention to converting the ether part back into an alcohol function. We attempted to synthesize the amino alcohol **24** in one step by using Jirgensons' protocol with acetic or trifluoroacetic acid, trying to convert the ether into a base labile ester, but this resulted in the preparation of the amino ether **26** (Scheme 2). Apparently, the use of thiourea with acetic or trifluoroacetic acid suppresses the conversion of the ether function into an ester. We bypassed the problem of the stable ether function by refluxing **22** with trifluoroacetic acid and obtained the corresponding trifluoroacetoxy ester **23** in high yield (Scheme 2). The following transformation of **23** into the amino alcohol **24** was achieved following a modified protocol by Jirgensons et al.[14] At this stage, we also attempted not only to prepare a diamondoid alcohol with an electron-donating function but also with an electron-withdrawing group. The easiest way to reach this goal was to oxidize **24** to a nitro alcohol. For this process, we followed a protocol by Gilbert et al.[15] and used *m*-CPBA in 1,2-dichloroethane to obtain the nitro alcohol **25** in high yield (Scheme 2).

The amino alcohol **24** is not only a suitable precursor for nitro derivatives but is also ideal for the preparation of amino acids. We found that the Koch−Haaf reaction in oleum with HCOOH gave the corresponding amino acid as the sulfate salt. Unfortunately, this product is insoluble in organic solvents and not pure. A better way to the amino acid is to prepare the methyl ester of the crude sulfate salt and to hydrolyze subsequently in concd hydrochloric acid (Scheme 2). Since the hydrochloride of the amino acid (**28**) is poorly soluble in aqueous HCl, we were able to grow crystals for structural proof by slowly cooling the reaction mixture (see the Supporting Information). It is very likely that this reaction sequence is also amenable to the other diols.

In conclusion, we have reported the first application of fluorinated alcohols for the monoprotection of various diamondoid as well as aromatic and ethynyl diols. The procedure employs only commodity chemicals and requires no special equipment. Using diamantane as a model, we showed that fluorinated diamondoid monoethers can be converted into unequally disubstituted derivatives such as amino- or nitro alcohols and even unnatural amino acids. No isomerization reactions were observed in these transformations.

Experimental Section

General Procedure for the Preparation of Fluorinated Monoethers. As a representative procedure, diamantan-4,9-diol (**6**) (2.5 mmol, 551 mg), which was prepared according to the literature procedure[5] and recrystallized from methanol, was dissolved in 100 mL of TFE and heated to 40 °C. After the addition of 50 μL of triflic acid, the clear solution was stirred for 4 h at the same temperature. Thereafter, the reaction mixture was quenched with 100 μL of Et_3N and the solvent was completely evaporated. Column chromatography on silica gel (ethylacetate/hexane 8:2) gave 426.3 mg (56%) of the pure, colorless monoether **7** (R_f 0.36): mp 149 °C; IR (KBr) 3278, 2925, 2904, 2889, 2855, 1445, 1418, 1350, 1301, 1278, 1146, 1104, 1008, 962, 836, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (2H, q, J = 8.8 Hz), 2.01−1.90 (6H, m), 1.83−1.72 (12H, m), 1.33 (1H, OH, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.3 (q, J = 277.7 Hz), 73.1, 67.1, 59.3 (q, J = 35.2 Hz), 44.5, 40.3, 38.8, 38.3; ^{19}F-NMR (376 MHz, $CDCl_3$) δ −74.55; HRMS (*m/z*) found 302.1489, calcd for $C_{16}H_{21}F_3O_2$ 302.1494. Anal. Calcd for $C_{16}H_{21}F_3O_2$ (302.32): C, 63.56; H, 7.00. Found: C, 63.30; H, 6.90. Furthermore, 82.5 mg (9%) of the pure diether **8** (R_f 0.73) and 165.9 mg (30%) of the diol **6** (R_f 0.15) were obtained.

Preparation of 2-Chloro-*N*-[9-(2,2,2-trifluoroethoxy)diamantan-4-yl]acetamide (22). 9-(2,2,2-trifluoroethoxy)diamantan-4-ol (**7**) (1.96 g, 6.48 mmol) was dissolved in a mixture of 30 mL of acetic acid and 9 mL (0.1 mol) of chloroacetonitrile. The solution was cooled in an ice bath, and 4.5 mL of concd H_2SO_4 was added. After the solution was stirred for 30 min, the ice bath was removed and the solution was stirred for 17 h at rt. The addition of 120 mL of distilled water produced a white precipitate which could be extracted with $CHCl_3$ (4 × 50 mL). After being washed with distilled water (2 × 75 mL), the product was dried with Na_2SO_4. The obtained crude product was purified using column chromatography on silica gel (DCM/ethyl acetate 85:15 (R_f 0.57) and diethylether/pentane 2:1 (R_f 0.38), for a mixed fraction). The combined yield was 1.11 g (45%) of **22** as a colorless solid: mp

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148 °C; IR (KBr) 3294, 2932, 2894, 2862, 1691, 1664, 1555, 1445, 1411, 1353, 1292, 1172, 1110, 965, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, br s, NH), 3.94 (2H, s), 3.79 (2H, q, $J = 8.8$ Hz), 2.10−2.00 (9H, m), 1.91 (3H, br s), 1.81−1.76 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 124.3 (q, $J = 277.7$ Hz), 73.1, 59.3 (q, $J = 34.2$ Hz), 50.8, 42.9, 40.50, 40.46, 38.4, 37.4; ^{19}F-NMR (376 MHz, $CDCl_3$) δ −74.55; HRMS (*m*/*z*) found 377.1346, calcd for $C_{18}H_{23}ClF_3NO_2$ 377.1369. Anal. Calcd for $C_{18}H_{23}ClF_3NO_2$ (377.83): C, 57.22; H, 6.14; N, 3.71. Found: C, 56.91; H, 6.04; N, 3.40. For side products, see the Supporting Information.

Preparation of 9-Aminodiamantan-4-ol (24). Compound **23** (1.62 g, 4.12 mmol) was mixed with 474 mg (6.23 mmol) of thiourea and dissolved in a mixture of 20 mL of ethanol and 15 mL of acetic acid. The solution was refluxed for 4 h and diluted with 60 mL of a 20% aqueous NaOH solution after being cooled to rt (caution: solution heats up very quickly upon addition). Extraction with $CHCl_3$ (4 × 80 mL), washing with distilled water (2 × 80 mL), and drying over anhydrous Na_2SO_4 gave 781.3 mg (86%) of a colorless solid which proved to be amino alcohol **24**: mp 240−244 °C; IR (KBr) 3241, 2920, 2887, 2849, 1584, 1470, 1439, 1352, 1254, 1122, 1082, 1045, 1032, 970, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89−1.79 (6H, m), 1.74−1.68 (6H, m), 1.61−1.55 (6H, m), 1.42 (3H, br s, OH + NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.2, 45.8, 45.7, 44.8, 38.8, 37.9; HRMS (*m*/*z*) found 219.1628, calcd for $C_{14}H_{21}NO$, 219.1623. Anal. Calcd for $C_{14}H_{21}NO$ (219.32): C, 76.67; H, 9.65; N, 6.39. Found: C, 76.57; H, 9.65; N, 6.33.

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Supporting Information Available: Detailed experimental data for the remaining fluorinated monoethers and for the other obtained products, including all ^1H and ^{13}C NMR spectra as well as the crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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