Notes

Conversion of Macrocyclic Polyamines into Carbon-Substituted Derivatives. Synthesis of Derivatives of 1,5,9-Triazacyclododecane-2-carbonitrile

Philippe Brunet*,[1] and James D. Wuest

Département de Chimie, Université de Montréal, Montréal, Québec H3C 3J7, Canada

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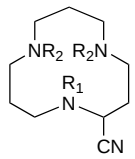
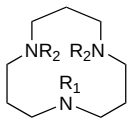
Introduction

A large number of macrocyclic polyamines have been synthesized as ligands for the chelation of metals.[2] They are widely used in coordination chemistry, and their complexes have found many applications as diagnostic agents for magnetic resonance imaging, therapeutic conjugates, sequestering agents, mimetics of metalloenzymes, and reagents for inducing NMR shifts and relaxation. Substituted derivatives of simple macrocyclic polyamines are typically prepared by functionalizing atoms of nitrogen, and few carbon-substituted derivatives are available.[3] In this paper, we show that carbon-substituted macrocyclic polyamines can be made directly from the unsubstituted parent compounds. Specifically, we describe the preparation of derivatives of 1,5,9-triazacyclododecane-2-carbonitrile (**1**) starting from 1,5,9-triazacyclododecane (**2**).



1 ($R_1 = R_2 = H$)
4 ($R_1 = OH$, $R_2 = Ts$)
5 ($R_1 = H$, $R_2 = Ts$)
8 ($R_1 = H$, $R_2 = Boc$)
13 ($R_1 = OH$, $R_2 = Boc$)



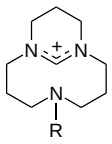
2 ($R_1 = R_2 = H$)
3 ($R_1 = H$, $R_2 = Ts$)
6 ($R_1 = R_2 = NO$)
7 ($R_1 = R_2 = Boc$)
9 ($R_1 = H$, $R_2 = Boc$)
11 ($R_1 = CH_2Ph$, $R_2 = H$)
12 ($R_1 = CH_2Ph$, $R_2 = Boc$)

Results and Discussion

Bis[(4-methylphenyl)sulfonamide] **3** was prepared in 68% yield by the selective ditosylation of 1,5,9-triazacyclododecane (**2**).[4] Tungstate-catalyzed oxidation of compound **3** with H_2O_2, followed by addition of excess KCN to the intermediate nitrone, then provided protected α-cyanohydroxylamine **4** in 75% yield.[5] Reduction of compound **4** with $TiCl_3$ in the presence of ammonium acetate as buffer gave the corresponding protected α-cyanoamine **5** in 98% yield.[6] Although similar sequences of oxidation, cyanide addition, and reduction have been used previously to convert simple acyclic and cyclic secondary amines into α-cyanoamines,[5] it is noteworthy that this procedure can also be used to synthesize macrocyclic derivatives. This observation indicates that macrocyclic nitrones, α-cyano hydroxylamines, and α-cyanoamines are stable enough to serve as useful intermediates in synthesis. It is also noteworthy that other methods for synthesizing simple α-substituted secondary amines failed to yield carbon-substituted derivatives of 1,5,9-triazacyclododecane.[7] For example, various attempts to monometalate and functionalize *N*-nitrosamine **6** and carbamate **7** were unsuccessful.

We did not expect the cyano group to survive the vigorous procedures required for hydrolyzing (4-methylphenyl)sulfonamides under acidic conditions, so we attempted to deprotect compound **5** by using reductive methods. Unfortunately, treatment with sodium in ammonia effected reductive decyanation to give 1,5,9-triazacyclododecane (**2**) in 70% yield,[8] while milder reductants such as aluminum amalgam,[9] SmI_2,[10] and calcium in ammonia[11] left the protected α-cyanoamine **5** unchanged.

To facilitate deprotection, we therefore decided to prepare the corresponding Boc-protected α-cyanoamine **8** from dicarbamate **9** by a similar series of reactions. Bicyclic formamidinium salt **10** was prepared from 1,5,9-triazacyclododecane (**2**) in two steps by the published method[12] and was then converted into monoprotected *N*-benzyl derivative **11** by basic hydrolysis in 99% yield.



10 ($R = CH_2Ph$)

Subsequent treatment of compound **11** with excess di-*tert*-butyl dicarbonate in the presence of triethylamine then afforded dicarbamate **12** in 99% yield. Hydrogenolysis of compound **12** provided the required dicar-

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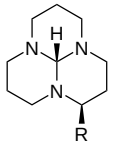
bamate **9** in quantitative yield. Although the synthesis of dicarbamate **9** from 1,5,9-triazacyclododecane (**2**) requires five steps, it proceeds in 85% overall yield, and no chromatographic purifications are needed.

Initial attempts to convert dicarbamate **7** into protected α-cyano hydroxylamine **13** by tungstate-catalyzed oxidation with H_2O_2 were unsuccessful. However, we eventually discovered that the use of H_2O_2 and *excess* sodium tungstate, followed by the addition of KCN and enough aqueous HCl to attain a pH of 7, gave compound **13** in 65% yield. Similarly, reduction of α-cyano hydroxylamine **13** to α-cyano amine **8** also required modification of the standard conditions. After extensive study, we found that the use of $TiCl_3$ without buffer in degassed CH_3OH/H_2O provided α-cyanoamine **8** in quantitative yield. Deprotection using trifluoroacetic acid in CH_2Cl_2 then gave the tris(trifluoroacetate) salt of 1,5,9-triazacyclododecane-2-carbonitrile (**1**), which was used without further purification in subsequent reactions analogous to those of 1,5,9-triazacyclododecane (**2**) itself. For example, condensation of unsubstituted compound **2** with formamidinium salts is known to give tricyclic orthoformamide **14a**.[13] Similarly, neutralization of the tris(trifluoroacetate) salt of nitrile **1** and subsequent condensation with formamidinium acetate provided cyanoorthoformamide **14b** stereospecifically.[14]



14a (R = H)
14b (R = CN)

Conclusions

Diprotected 1,5,9-triazacyclododecane **3** can be converted into carbon-substituted cyano derivative **5** in 73% overall yield by a simple procedure involving oxidation with Na_2WO_4/H_2O_2, addition of KCN, and subsequent reduction with $TiCl_3$. A similar procedure transformed diprotected 1,5,9-triazacyclododecane **9** into diprotected 1,5,9-triazacyclododecane-2-carbonitrile **8** in 65% overall yield. This strategy promises to be a useful general method for the direct conversion of macrocyclic polyamines into carbon-substituted derivatives that would otherwise not be readily available.

Experimental Section

Tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone, and $N(C_2H_5)_3$ was dried by distillation from CaH_2. Other commercial reagents were used without further purification. Flash chromatography was performed in the normal way.[15]

1,5-Bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane (3). A solution of 1,5,9-triazacyclododecane (**2**; 0.984 g, 5.74 mmol) and NaOH (0.284 g, 7.10 mmol) in H_2O (4.3 mL) was stirred at 0 °C and treated dropwise with a solution of (4-methylphenyl)sulfonyl chloride (2.05 g, 10.8 mmol) in ether (7.2 mL). The resulting mixture was stirred at 0 °C for 1 h. The precipitated solid was separated by filtration, washed thoroughly with H_2O, and dried *in vacuo* to give a mixture of di- and trisulfonamides.

Volatiles were removed from the combined aqueous phases by evaporation under reduced pressure, and the residue was subjected to ion-exchange chromatography (Dowex 2-X8, OH^- form, H_2O/CH_3OH). Solvent was removed from the eluent by evaporation under reduced pressure, and the residue was extracted with $CHCl_3$. Removal of volatiles from the extracts left a residue of recovered 1,5,9-triazacyclododecane (**2**; 0.186 g, 1.09 mmol).

The solid mixture of di- and trisulfonamides was separated by flash chromatography (silica, $CHCl_3$ (97%)/CH_3OH (2%)/$N(C_2H_5)_3$ (1%)). This provided 1,5-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane (**3**; 1.51 g, 3.15 mmol, 68% based on unrecovered 1,5,9-triazacyclododecane) as a colorless solid. An analytically pure sample was obtained by recrystallization from CH_3OH: mp 169°C; IR ($CHCl_3$) 3400, 1337, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (tt, 4H, ^3J = 6.6, 5.4 Hz), 1.89 (quint, 2H, ^3J = 6.9 Hz), 2.42 (s, 6H), 2.66 (t, 4H, ^3J = 5.4 Hz), 3.16 (t, 4H, ^3J = 6.9 Hz), 3.18 (t, 4H, ^3J = 6.6 Hz), 7.30 (d, 4H, ^3J = 7.9 Hz), 7.65 (d, 4H, ^3J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 24.1, 27.5, 43.9, 45.3, 46.2, 127.3, 129.6, 135.3, 143.2; MS (EI) *m/e* 480, 324. Anal. Calcd for $C_{23}H_{33}N_3O_4S_2$: C, 57.59; H, 6.93. Found: C, 57.15; H, 6.93.

1-Hydroxy-5,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane-2-carbonitrile (4). A solution of 1,5-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane (**3**; 1.22 g, 2.54 mmol) in a mixture of THF (17 mL) and H_2O (7 mL) was stirred at 0 °C and treated with $Na_2WO_4 \cdot 2H_2O$ (0.042 g, 0.13 mmol) and 30% aqueous H_2O_2 (0.61 mL, 6.0 mmol). The resulting mixture was kept at 25 °C for 18 h, cooled to 0 °C, and treated with KCN (0.307 g, 4.71 mmol) and 4 N aqueous HCl (0.91 mL, 3.6 mmol). The mixture was kept at 25 °C for 30 h, and then volatiles were removed by evaporation under reduced pressure. H_2O (30 mL) was added to the residue, and the basicity was adjusted to pH 8−9 by the addition of 2 N aqueous NaOH. The resulting mixture was extracted with CH_2Cl_2, and volatiles were removed from the combined extracts by evaporation under reduced pressure. Flash chromatography (silica, $CHCl_3$ (99%)/CH_3OH (1%)) of the residue provided 1-hydroxy-5,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane-2-carbonitrile (**4**; 0.987 g, 1.90 mmol, 75%) as a colorless solid. Recrystallization from benzene/CH_2Cl_2 yielded an analytically pure sample: mp 192−193 °C; IR (KBr) 3470, 1330, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50−1.65 (m, 1H), 1.76−1.87 (m, 1H), 2.00−2.11 (m, 2H), 2.18−2.29 (m, 1H), 2.30−2.42 (m, 1H), 2.44 (s, 3H), 2.45 (s, 3H), 2.79−2.94 (m, 2H), 2.95−3.18 (m, 5H), 3.21−3.37 (m, 3H), 4.01 (dd, ^3J = 11.5, 3.7 Hz, 1H), 5.38 (bs, 1H), 7.31−7.36 (m, 4H), 7.65−7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.4, 23.2, 26.2, 30.4, 42.5, 42.5, 46.3, 47.6, 54.7, 56.1, 117.0, 127.0, 127.3, 129.8, 129.9, 133.3, 135.4, 143.7, 144.1; MS (FAB) *m/e* 521, 494, 365; HRMS (FAB) calcd for $C_{24}H_{32}N_4O_5S_2$ + H 521.1892, found 521.1916.

5,9-Bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane-2-carbonitrile (5). A solution of 1-hydroxy-5,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane-2-carbonitrile (**4**; 0.485 g, 0.932 mmol) and ammonium acetate (1.75 g, 22.7 mmol) in a deoxygenated mixture of THF (14 mL) and H_2O (4.2 mL) was stirred at 25 °C under N_2 and treated dropwise with a solution of $TiCl_3$ (0.878 g, 5.69 mmol) in deoxygenated H_2O (7.5 mL). The mixture became deep green and then deep blue, and it was stirred at 25 °C for 22 h. A second portion of $TiCl_3$ (0.451 g, 2.92 mmol) in H_2O (3.8 mL) was added, and the mixture was stirred at 25 °C for an additional 9 h. The mixture was then made strongly basic by the addition of 10% aqueous NaOH, diluted with H_2O, and extracted with CH_2Cl_2. Evaporation of volatiles from the combined extracts left a residue of 5,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclododecane-2-carbonitrile (**5**; 0.461 g, 0.913 mmol, 98%) as a colorless waxy solid. Flash chromatography (silica, $CHCl_3$ (99%)/CH_3OH (1%)) provided an analytically pure sample: IR ($CHCl_3$) 1342, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (bs, 1H), 1.49−1.68 (m, 2H), 1.71−1.83 (m, 2H), 1.95−2.08 (m, 1H), 2.44 (s, 3H), 2.45 (s, 3H), 2.50−2.62 (m, 1H), 2.66−2.75 (m, 2H), 2.91−2.98 (m, 2H), 3.07−3.26 (m, 3H), 3.30−3.38 (m, 2H), 3.40−3.48 (m, 1H), 3.76 (dd, ^3J = 11.7, 2.6 Hz, 1H), 7.31 (d, ^3J = 8.3 Hz, 2H), 7.34 (d, ^3J = 8.3 Hz, 2H), 7.64 (d, ^3J = 8.3 Hz, 2H), 7.67 (d, ^3J = 8.3 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.4, 21.4, 23.4, 26.8, 32.6, 42.6,

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42.7, 43.9, 45.2, 46.4, 47.3, 120.0, 127.1, 127.4, 129.7, 129.8, 133.6, 136.0, 143.3, 143.9; MS (FAB) *m/e* 505, 478, 351; HRMS (FAB) calcd for $C_{24}H_{32}N_4O_4S_2$ + H 505.1943, found 505.1962. Anal. Calcd for $C_{24}H_{32}N_4O_4S_2$: C, 57.12; H, 6.39. Found: C, 57.08; H, 6.53.

1-(Phenylmethyl)-1,5,9-triazacyclododecane (11). A solution of 5-(phenylmethyl)-5,9-diaza-1-azoniabicyclo[7.3.1]tridec-1(13)-ene (**10**; 1.94 g, 5.51 mmol)[12] and NaOH (7.1 g, 180 mmol) in a mixture of C_2H_5OH (192 mL) and H_2O (64 mL) was heated at reflux for 16 h. After partial evaporation under reduced pressure, more H_2O was added and the mixture was extracted with CH_2Cl_2. Removal of volatiles from the combined extracts by evaporation under reduced pressure left a residue of 1-(phenylmethyl)-1,5,9-triazacyclododecane (**11**; 1.43 g, 5.47 mmol, 99%) as a colorless solid. Recrystallization from benzene/CH_2Cl_2 provided an analytically pure sample: mp 192−193 °C; IR ($CHCl_3$) 3348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65−1.77 (m, 6H), 2.52 (t, ^3J = 5.9 Hz, 4H), 2.70 (t, ^3J = 5.5 Hz, 4H), 2.84 (t, ^3J = 5.5 Hz, 4H), 3.13 (bs, 2H), 3.49 (s, 2H), 7.21−7.41 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) 25.7, 26.4, 46.9, 49.2, 52.4, 57.2, 126.6, 127.9, 128.8, 139.0; MS (FAB) *m/e* 262; HRMS (FAB) calcd for $C_{16}H_{27}N_3$ + H 262.2283, found 262.2273.

Bis(1,1-dimethylethyl) 9-(Phenylmethyl)-1,5,9-triazacyclododecane-1,5-dicarboxylate (12). A solution of 1-(phenylmethyl)-1,5,9-triazacyclododecane (**11**; 1.43 g, 5.47 mmol) and $N(C_2H_5)_3$ (1.34 g, 13.2 mmol) in dry THF (50 mL) was stirred at 25 °C under dry N_2, and a solution of di-*tert*-butyl dicarbonate (2.75 g, 12.6 mmol) in THF (10 mL) was added. The mixture was kept at 25 °C for 6 d, and then 15% aqueous NaOH (20 mL) was added. After 18 h, the mixture was concentrated by partial evaporation under reduced pressure, diluted with H_2O, and extracted with CH_2Cl_2. Removal of volatiles from the combined extracts by evaporation under reduced pressure left a residue of pure bis(1,1-dimethylethyl) 9-(phenylmethyl)-1,5,9-triazacyclododecane-1,5-dicarboxylate (**12**; 2.49 g, 5.39 mmol, 99%) as a pale yellow oil: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 18H), 1.78 (quint, ^3J = 6.4 Hz, 4H), 1.90 (quint, ^3J = 7.0 Hz, 2H), 2.41 (t, ^3J = 6.4 Hz, 4H), 3.32 (t, ^3J = 6.4 Hz, 4H), 3.36 (t, ^3J = 7.0 Hz, 4H), 3.51 (s, 2H), 7.19−7.31 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.7, 27.3, 28.4, 43.6, 44.9, 50.1, 58.7, 79.1, 126.8, 128.1, 128.8, 139.2, 156.1; MS (EI) *m/e* 462, 370, 270, 170; HRMS (EI) calcd for $C_{26}H_{43}N_3O_4$ + H 462.3332, found 462.3338. Anal. Calcd for $C_{26}H_{43}N_3O_4$: C, 65.11; H, 9.46. Found: C, 65.69; H 9.23.

Bis(1,1-dimethylethyl) 1,5,9-Triazacyclododecane-1,5-dicarboxylate (9). A mixture of bis(1,1-dimethylethyl) 9-(phenylmethyl)-1,5,9-triazacyclododecane-1,5-dicarboxylate (**12**; 2.6 g, 5.6 mmol) and 10% Pd on charcoal (5.0 g) in absolute C_2H_5OH (80 mL) was stirred at 25 °C for 4 d under H_2 (6 atm). The catalyst was separated by filtration, and volatiles were removed by evaporation under reduced pressure. This left a residue of bis(1,1-dimethylethyl) 1,5,9-triazacyclododecane-1,5-dicarboxylate (**9**; 2.1, 5.6 mmol, 100%) as a colorless solid. Flash chromatography (silica, $CHCl_3$ (95%)/CH_3OH (5%)) provided an analytically pure sample: mp 92−93 °C; IR ($CHCl_3$) 3430, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 18H), 1.77 (tt, ^3J = 5.9, 5.5 Hz, 4H), 1.88 (quint, ^3J = 6.9 Hz, 2H), 2.67 (t, ^3J = 5.5 Hz, 4H), 3.28 (t, ^3J = 6.9 Hz, 4H), 3.31 (t, ^3J = 5.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 28.0, 28.4, 45.9, 46.3, 46.9, 79.1, 156.3; MS (EI) *m/e* 372, 272, 172; HRMS (EI) calcd for $C_{19}H_{37}N_3O_4$ + H 372.2862, found 372.2903. Anal. Calcd for $C_{19}H_{37}N_3O_4$: C, 61.43; H, 10.04. Found: C, 61.25; H, 10.26.

Bis(1,1-dimethylethyl) 8-Cyano-9-hydroxy-1,5,9-triazacyclododecane-1,5-dicarboxylate (13). A solution of bis(1,1-dimethylethyl) 1,5,9-triazacyclododecane-1,5-dicarboxylate (**9**; 883 mg, 2.38 mmol) in THF (33 mL) was stirred at 25 °C and treated successively with $Na_2WO_4 \cdot 2H_2O$ (913 mg, 2.77 mmol), H_2O (37 mL), and 30% aqueous H_2O_2 (0.62 mL, 6.0 mmol). The resulting mixture was kept at 25 °C for 19 h and was then treated with KCN (309 mg, 4.75 mmol) and enough 4 N aqueous HCl (0.9 mL) to lower the pH to 7. After 22 h, the mixture was concentrated by partial evaporation under reduced pressure, 15% aqueous NaOH was added to adjust the basicity to pH 8−9, and the mixture was extracted with CH_2Cl_2. Volatiles were removed from the combined extracts by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, $CHCl_3$ (98%)/CH_3OH (2%)). This yielded bis(1,1-dimethylethyl) 8-cyano-9-hydroxy-1,5,9-triazacyclododecane-1,5-dicarboxylate (**13**; 639 mg, 1.55 mmol, 65%) as a colorless solid: IR ($CHCl_3$) 3414, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.47 (s, 9H), 1.85−2.38 (m, 5H), 2.75 (ddd, J = 13.3, 10.1, 3.2 Hz, 1H), 3.07−3.42 (m, 9H), 3.51 (dt, J = 14.2, 4.3 Hz, 1H), 3.77 (m, 1H), 5.07 (bs, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.3, 25.8, 28.2, 28.3, 29.9, 42.7, 43.4, 45.9, 46.4, 54.7, 56.5, 79.6, 80.0, 116.9, 156.3, 156.3; MS (FAB) *m/e* 413, 386, 313, 286, 213; HRMS (FAB) calcd for $C_{20}H_{36}N_4O_5$ + H 413.2764, found 413.2758.

Bis(1,1-dimethylethyl) 8-Cyano-1,5,9-triazacyclododecane-1,5-dicarboxylate (8). A solution of bis(1,1-dimethylethyl) 8-cyano-9-hydroxy-1,5,9-triazacyclododecane-1,5-dicarboxylate (**13**; 530 mg, 1.3 mmol) in deoxygenated CH_3OH (20 mL) was added under Ar to a stirred solution of $TiCl_3$ (620 mg, 4.0 mmol) in deoxygenated H_2O (3 mL). The deep blue solution was kept at 25 °C for 15 min and was then poured into a separatory funnel containing cold CH_2Cl_2 (50 mL) and 15% aqueous NaOH (2 mL). The contents were shaken vigorously, the funnel was opened periodically to admit air, and 15% aqueous NaOH was added occasionally to maintain a strongly basic solution. When the blue color had disapeared and an abundant white precipitate had formed, the aqueous phase was extracted with CH_2Cl_2. The phases were separated by centrifugation, and volatiles were removed from the combined organic extracts by evaporation under reduced pressure. This yielded bis(1,1-dimethylethyl) 8-cyano-1,5,9-triazacyclododecane-1,5-dicarboxylate (**8**; 510 mg, 1.3 mmol, 100%) as a colorless oil: IR ($CHCl_3$) 3324, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.41 (s, 9H), 1.61−1.95 (m, 3H), 1.95−2.11 (m, 1H), 2.34 −2.48 (m, 1H), 2.51−2.62 (m, 1H), 2.99−3.55 (m, 12H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.4, 27.6, 28.2, 28.3, 32.3, 43.4, 44.3, 44.4, 46.0, 46.5, 47.2, 79.2, 79.7, 120.0, 156.0, 156.0; MS (FAB) *m/e* 397, 370, 297, 170; HRMS (FAB) calcd for $C_{20}H_{36}N_4O_4$ + H 397.2815, found 397.2841.

Tris(trifluoroacetate) Salt of 1,5,9-Triazacyclododecane-2-carbonitrile (1). A solution of bis(1,1-dimethylethyl) 8-cyano-1,5,9-triazacyclododecane-1,5-dicarboxylate (**8**; 336 mg, 0.847 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C and treated with CF_3COOH (3 mL). The cooling bath was removed, the mixture was stirred for 15 min, and then volatiles were removed by evaporation under reduced pressure. This yielded the tris(trifluoroacetate) salt of 1,5,9-triazacyclododecane-2-carbonitrile (**1**; 454 mg, 0.843 mmol, 100%) as a colorless hygroscopic oil that was used in subsequent reactions without further purification: ^1H NMR (300 MHz, D_2O) δ 1.55−1.72 (m, 1H), 1.73−2.19 (m, 4H), 2.41−2.53 (m, 1H), 2.82−3.30 (m, 10H), 3.76 (dd, ^3J = 11.2, 2.7 Hz, 1H); ^{13}C NMR (75.4 MHz, D_2O) δ 21.4, 24.2, 28.9, 42.8, 43.7, 45.8, 46.4, 46.5, 49.8, 117.1 (q, $^1J_{CF}$ = 290 Hz), 119.6, 162.9 (q, $^2J_{CF}$ = 36.5 Hz).

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