Reagents for the Stepwise Functionalization of Spermidine, Homospermidine, and Bis(3-aminopropyl)amine

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A high-yield synthesis of reagents for the selective mono-, di-, or tri-N-functionalization of the polyamines spermidine, homospermidine, and norspermidine is described. The polyamine protecting groups utilized in these reagents are each easily removable under different conditions: hydrogenolysis, acid, and base. The versatility of these systems was demonstrated by a stepwise deprotection and refunctionalization of the spermidine reagent to yield N^8-acetyl-N^4-benzoyl-N^1-(2,3-dimethoxybenzoyl)spermidine (12). These reagents offer, for the first time, easy access to regioselective mono-, di-, and trifunctionalization of spermidine and its analogues.

In the past decade there has been considerable interest in the polyamines, an interest which can be attributed to both their ubiquitous nature and the role they play in proliferative processes.[1-3] Their latter function is largely responsible for the recent surge in the synthesis of the polyamines and their derivatives. Many of the synthetic systems have been evaluated as antineoplastics[4] and used in studies of polyamine receptors[5] and metabolism.[6] The most extensively studied of these amines, spermidine, has been found to be an essential segment of a wide variety of naturally occurring compounds including sugars,[7] steroids,[8] alkaloids,[9] and siderophore[10] systems. Many of these natural products have shown interesting biological properties and, accordingly, have been the target of synthetic chemists for years. Not surprisingly, therefore, several reagents designed for the synthesis of selectively functionalized polyamines have been developed.[11-15]

In previous papers we have reported on the synthesis of two such reagents for the selective acylation of spermidine and its symmetrical homologues, homo- and norspermidine. The first of these, N^4-benzylspermidine,[14] was designed to allow for selective acylation of spermidine's primary nitrogens while the second reagent N^1,N^8-bis(*tert*-butoxycarbonyl)spermidine[15] allowed for the selective secondary N-acylation. We now report on spermidine reagents and homologues capable of selective functionalization of triamines with one, two, or three different groups. These reagents utilize three different protecting groups: benzyl, *tert*-butoxycarbonyl, and trifluoroacetyl. Each of these protecting groups can be easily and efficiently removed in the presence of the others. This, for example, allows for the selective functionalization of any or all of spermidine's three nitrogens in any order with any three different acylating agents. It is because the protecting groups can be removed in any order that an enormous number of polyamine derivatives can be generated.

Although the reagent N^4-tosyl-N^8-phthaloylspermidine designed by Eugster[12] is already available for fixing three different substituents to the spermidine backbone, the eight steps required for its synthesis and the harsh conditions required for protecting group removal make it somewhat impractical. The synthesis of our spermidine reagent, for example, proceeds in five facile high-yield steps, starting from the commercially available 3-(benzylamino)propionitrile. Furthermore, both the homo- and norspermidine tris-protected reagents can also be synthesized and used similarly.

Results and Discussion

The choice of protecting groups used in the polyamine reagents described below is based on our experience with secondary N-benzylated and primary amino *tert*-butoxycarbonylated triamines.[14,15] We determined that debenzylation required only mild hydrogenolysis, and removal of the *t*-Boc groups only required brief exposure to trifluoroacetic acid. These conditions, of course, dictated that the third protecting group be stable to acid and hydrogenolysis and we thus chose a base-labile protecting group for the "last" nitrogen. The *N*-trifluoroacetyl group fulfills these requirements as it is easily removed by refluxing the corresponding amide with methanolic sodium bicarbonate.[16]

The synthesis of the polyamine reagents begins with the appropriate *N*-benzyl-protected amine, Scheme I. Thus, nitrile 1 (prepared previously in high yield)[17] was conveniently reduced to diamine 2 ($n = 3$) by utilizing a Raney nickel catalyst recently reported for moderate-scale reductions of this type.[18] Unfortunately, the analogous diamine 2 ($n = 4$) was not readily available and attempts to monoalkylate benzylamine met with limited success. The commercial availability of 1,4-diaminobutane, putrescine, prompted attempts to selectively functionalize

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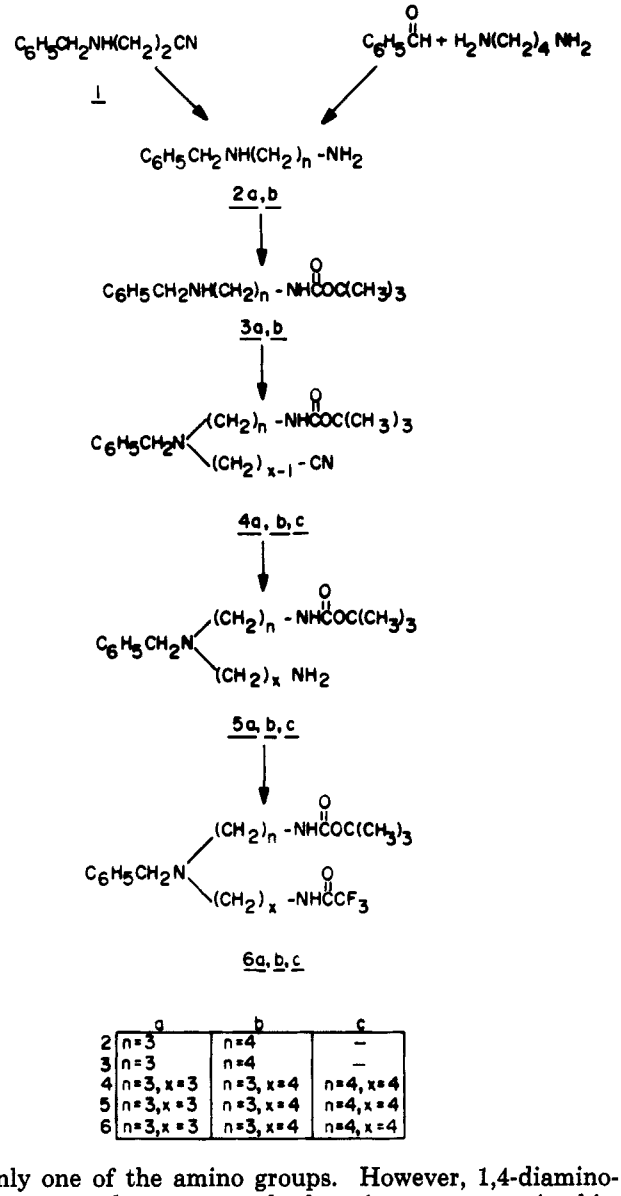
Scheme I. Synthesis of Triprotected Spermidine, Homospermidine, and Bis(3-aminopropyl)amine



	a	b	c
2	n=3	n=4	–
3	n=3	n=4	–
4	n=3, x=3	n=3, x=4	n=4, x=4
5	n=3, x=3	n=3, x=4	n=4, x=4
6	n=3, x=3	n=3, x=4	n=4, x=4

only one of the amino groups. However, 1,4-diaminobutane tends to react at both amino groups to give bis-functionalization even when the starting diamine is present in large excess relative to the functionalizing agent. For example, acylation of 1,4-diaminobutane (10 mmol) with benzoyl chloride (2 mmol) gave a 95% yield of the bis-acylated product. Additionally, treatment of putrescine (90.7 mmol) with benzaldehyde (22.7 mmol) gave a 67% yield of the corresponding bis-imine. This peculiar reactivity of putrescine apparently can be circumvented by the use of acidic conditions to give monofunctionalization as in the preparation of *N*-acetyl-1,4-diaminobutane from 1,4-diaminobutane and acetic anhydride in glacial acetic acid.[19] Successful monobenzylation of putrescine with benzaldehyde was effected under reductive amination conditions (formic acid) in high yields (81% distilled). Additionally, the excess amount of 1,4-diaminobutane required for monofunctionalization in this step is readily recovered (70% after distillation), making the procedure cost effective.

The diamines **2** are further protected by reacting them with 1 equiv of 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (BOC-ON). Although either of the amino groups can be protected by using this reagent,[11] we found that with 1 equiv of BOC-ON at 0 °C, regioselective acylation occurs quantitatively at the primary amine site. The resulting products **3** of this reaction were purified by vacuum distillation at less than 0.5 mmHg as at higher pressures the high temperature required promotes thermal decomposition of the Boc protecting group.

Cyanoethylation of **3a** with acrylonitrile gave the nitrile **4a** in quantitative yield. Alkylation of **3a** and **3b** with 4-chlorobutyronitrile gave the analogous nitriles **4b** and **4c**, respectively, also in high yields (95%). None of the nitriles required further purification and were subsequently reduced with Raney nickel as described earlier. The smooth, high-yield (91–100% crude yield) reductions allowed the amines **5a–c** to be acylated without further purification.

One note of interest is the inertness of the carbamate and the *N*-benzyl moieties to the reduction conditions employed, both of which can be cleaved with some hydrogenation procedures.[20,21] Finally, acylation with trifluoroacetic anhydride gave the desired triprotected spermidine and analogues (**6a–c**, respectively), again in good yield (91–96%).

To illustrate the potential application of these reagents to the synthesis of selectively functionalized triamines, we chose to prepare a triacylated spermidine compound. The conditions employed would be identical for the nor- and homospermidine reagents. Furthermore, the order in which the deprotection and refunctionalization was carried out was random. Finally, the acylating agents employed were chosen simply because they were different. The sole purpose of synthesizing the final compound was to demonstrate the simplicity of the procedure. It is clear that we could have chosen a number of natural products to synthesize; however, this would not be any more effective at illustrating the potential of these reagents.

The benzyl protecting group was first removed by hydrogenolysis using palladium chloride to give bis-protected spermidine hydrochloride **7** (82% yield) with the secondary nitrogen available for functionalization (Scheme II). This secondary amine nitrogen was acylated with benzoyl chloride providing the N^4-benzoyl spermidine derivative **8** in 92% yield. Next, removal of the trifluoroacetyl group was effects in good yield (81%) by gentle heating in the presence of potassium carbonate in aqueous methanol. This selectively deprotected amine (**9**) was then acylated in quantitative yield with acetyl chloride to give **10**. The last protecting group, *tert*-butoxycarbonyl, was removed by brief exposure to trifluoroacetic acid (75% yield). The resulting amine salt was converted to the free amine **11** via a basic wash during workup. The free amine **11** was subsequently acylated with 2,3-dimethoxybenzoyl chloride to give an excellent yield (93%) of the target compound, a spermidine derivative with three different moieties attached to each of the amine sites, one to each nitrogen.

This type of stepwise deprotection–functionalization should work equally well for the other two triprotected spermidine analogues **6a** and **6c**, thus allowing for the first time easy access to selectively functionalized spermidine and its homologues. Additionally, these reagents provide access to large quantities of mono- and bis-protected putrescine (**2b** and **3b**, respectively) which can be envisioned in a number of ways as leading to a multiprotected spermine derivative. Work is now in progress in this area.

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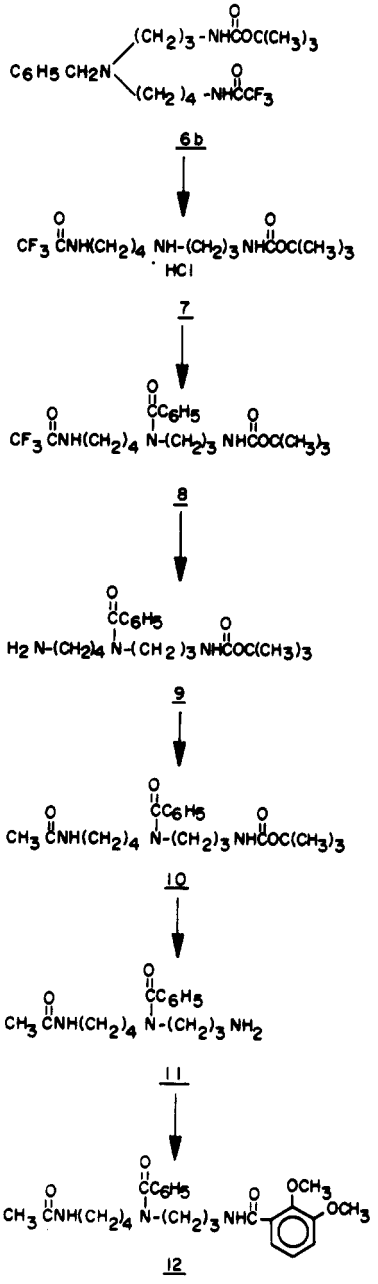
Scheme II. Stepwise Deprotection and Functionalization of Spermidine



Finally, we point out that each triprotected reagent is stable and may be stored for prolonged periods.

Experimental Section

Materials and Methods. ^{1}H NMR spectra were recorded on a Varian T-60, and, unless otherwise noted, in $CDCl_3$ solutions with chemical shifts given in parts per million downfield from an internal tetramethylsilane standard. The IR spectra were recorded on a Beckman Acculab 1 spectrophotometer. Preparative TLC was performed on Analtech 20 × 20 cm silica gel GF plates. Column chromatography was performed with silica gel 60, mesh 70–230, obtained from EM. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Raney nickel was obtained as a slurry with water from Aldrich and was used without further treatment. Hydrogenation was performed on a Parr hydrogenation–shaker apparatus.

***N*-(3-Aminopropyl)benzylamine (2a).** Compound **2a** was prepared as previously described.[3]

***N*-(4-Aminobutyl)benzylamine (2b).** 1,4-Diaminobutane (32 g, 0.36 mol) was dissolved in 90% formic acid (120 mL) at 0.5 °C. This solution was treated with benzaldehyde (9.62 g, 90.62 mmol) also at 0–5 °C, and the reaction mixture was allowed to warm to room temperature and then brought to reflux. The progress of the reaction was monitored by TLC, and when all the benzaldehyde had disappeared the reaction mixture was cooled to room temperature and added slowly to 6 M hydrochloric acid (300 mL). The resulting pale yellow solution was then refluxed 18 h to hydrolyze any formamide, at which time the solution was concentrated almost to dryness. The semisolid was dissolved in water (200 mL), cooled to 5 °C, and basified (pH 10) with saturated sodium hydroxide. The cloudy solution was extracted with five 100-mL portions of chloroform. The combined chloroform extracts were dried over sodium sulfate, filtered, concentrated in vacuo, and finally distilled to yield 13.14 g (81%) of pure **2b**: bp 100–102 °C (0.2 mmHg); IR (neat) 3380, 3300, 1450, 1500, 1110, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.32–1.64 (m, 4 H), 2.42–2.74 (m, 4 H), 3.69 (s, 2 H), 7.18 (s, 5 H).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.04; H, 10.26.

The excess 1,4-diaminobutane used in this reaction was recovered by treating the basic aqueous layer from above (pH 10) with additional saturated sodium hydroxide until the cloudiness persisted. This solution was then extracted with four 100-mL portions of chloroform, dried over sodium sulfate, filtered, concentrated, and distilled under vacuum to give 16.5 g (69% recovery) of 1,4-diaminobutane, identical with starting material.

***N*-[*N*-(*tert*-Butoxycarbonyl)-3-aminopropyl]benzylamine (3a).** A solution of BOC-ON (6.9 g, 0.028 mol) in 20 mL of THF was slowly added dropwise to a solution of **2a** (5.0 g, 0.030 mol) in 30 mL of THF at 0 °C. After the addition was completed, the ice bath was removed and the reaction stirred for 8 h. The solvent was then evaporated, and the residue was dissolved in 100 mL of ether, washed with 5% NaOH (4 × 20 mL), dried, and concentrated. The product was further purified by distillation to afford 6.6 g (89%) pure **3a**: bp 150–151 °C (0.13 mmHg); ^{1}H NMR δ 1.53 (s, 9 H), 1.77 (m, 3 H), 2.72 (t, 2 H), 3.16 (quartet, 2 H), 3.70 (s, 2 H), 5.26 (br, 1 H), 7.23 (s, 5 H); IR ($CHCl_3$) 2950 (m), 1690 (s), 1490 (m), 1160 (s), 750 (s) cm^{-1}.

Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.14; H, 9.19; N, 10.55.

***N*-[*N*-(*tert*-Butoxycarbonyl)-3-aminopropyl]-*N*-(3-cyanopropyl)benzylamine (4b).** A solution of 4-chlorobutyronitrile (4.7 g, 0.095 mol) in 25 mL of BuOH was slowly added to a suspension of **3a** (10.0 g, 0.038 mol), Na_2CO_3 (4.4 g, 0.042 mol), and KI (1.4 g, 0.0095 mol) in 100 mL of BuOH. The reaction mixture was then refluxed for 48 h, cooled, and diluted with an equal volume of ether. The salts were filtered and washed with ether, and the filtrates were evaporated to give a yellow oil of sufficient purity to be used directly in the reduction step. A portion of the crude product was chromatographed on silica gel, eluted with 5% MeOH/$CHCl_3$, to afford 1.2 g (95%) of the desired product as an oil: ^{1}H NMR δ 1.43 (s, 9 H), 1.73 (m, 4 H), 2.43 (m, 4 H), 3.12 (quartet, 2 H), 3.47 (s, 2 H), 4.83 (br, 1 H), 7.23 (s, 5 H); IR (neat) 2990 (s), 2250 (w), 1710 (s), 1520 (s), 1180 (s), 740 (m) cm^{-1}.

Anal. Calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68. Found: C, 68.57; H, 8.85; N, 12.59.

***N*^{4}-Benzyl-*N*^{1}-(*tert*-butoxycarbonyl)spermidine (5b).** Raney nickel (3.0 g) was added to a solution of unpurified **4b** (13.6 g, 0.0409 mol) and NaOH (4.0 g, 0.10 mol) in 100 mL of 95% EtOH, and the resulting suspension was hydrogenated under 40 psi of H_2 for 28 h. The catalyst was then filtered (taking care that it did not become dry) and washed well with 95% EtOH, and the filtrates were concentrated. The residue was taken up in H_2O (250 mL), and the product was extracted into CH_2Cl_2 (4 × 50 mL), dried, and concentrated to afford 13.4 g (97%) of the desired product as a nondistillable oil. Thin-layer chromatography and NMR analysis indicated the purity of the product was in excess of 95% and could be used without further purification.

An analytical sample was prepared by chromatography on silica gel, eluting with 30% MeOH/$CHCl_3$: ^{1}H NMR δ 1.50 (m, 17 H), 2.47 (m, 6 H), 3.10 (quartet, 2 H), 3.47 (s, 2 H), 5.33 (br, 1 H), 7.17 (s, 5 H); IR (neat) 3350 (br), 2940 (s), 1710 (s), 1510 (m), 1170 (s), 740 (m), 700 (m) cm^{-1}.

Anal. Calcd for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.91; N, 12.53. Found: C, 67.79; H, 9.96; N, 12.43.

***N*^{4}-Benzyl-*N*^{1}-(*tert*-butoxycarbonyl)-*N*^{8}-(trifluoroacetyl)spermidine (6b).** A solution of trifluoroacetic anhydride

(2.3 g, 11 mmol) in 10 mL of dry CH_2Cl_2 was slowly added to a cooled solution of unpurified **5b** (3.5 g, 10 mmol) in triethylamine (1.4 ml, 10 mmol) in 20 mL of dry CH_2Cl_2 under N_2. The reaction was allowed to warm to room temperature and stirred for 16 h, at which time additional CH_2Cl_2 was added (50 mL). The organic layer was washed with cold 3% HCl (2 × 5 mL), H_2O (1 × 25 mL), and 5% $NaHCO_3$ (2 × 25 mL), dried, and concentrated to afford 3.9 g (91%) of the desired product: ^1H NMR δ 1.42 (s, 9 H), 1.58 (m, 6 H), 2.43 (m, 4 H), 3.15 (m, 4 H), 3.50 (s, 2 H), 5.22 (br, 1 H), 7.25 (s, 5 H), 7.58 (br, 1 H); IR ($CHCl_3$) 3300 (m), 3020 (m), 1710 (s), 1620 (s), 1170 (s), 750 (s) 700 (m) cm^{-1}.

Anal. Calcd for $C_{21}H_{32}N_3O_3F_3$: C, 58.45; H, 7.47; N, 9.74. Found: C, 58.31; H, 7.49; N, 9.71.

N-[N-(*tert*-Butoxycarbonyl)-4-aminobutyl]benzylamine (3b). A solution of **2b** was treated and purified in a similar manner as described for **2a** to yield 10.96 g (92%) of pure **3b**: bp 146–148 °C (0.1 mmHg); ^1H NMR δ 1.31–1.61 (m, 14 H), 2.44–2.73 (m, 2 H), 2.86–3.22 (m, 2 H), 3.72 (s, 2 H), 4.78 (br, 1 H), 7.11 (s, 5 H); IR (neat) 3370 (br), 1710 (s), 1185 (s), 745 (m), 705 (m) cm^{-1}.

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03, H, 9.41; N, 10.06. Found: C, 69.12; H, 9.43; N, 10.01.

N-[N-(*tert*-Butoxycarbonyl)-3-aminopropyl]-N-(2-cyanoethyl)benzylamine (4a). A sealed vessel containing **3a** (6.0 g, 0.023 mol) and acrylonitrile (2.6 ml, 0.039 mol) under an argon atmosphere was heated in an oil bath at 100 °C for 24 h. The reaction mixture was cooled and purified via chromatography on silica gel, eluting with $CHCl_3$, to afford 7.06 g (98%) product as an oil: ^1H NMR δ 1.42 (s, 9 H), 1.6, (m, 2 H), 2.58 (m, 6 H), 3.13 (quartet, 2 H), 3.55 (s, 2 H), 4.73 (br, 1 H), 7.23 (s, 5 H); IR (neat) 3375 (br) 3000 (m), 2250 (w), 1715 (s), 1515 (s), 1180 (s), 740 (m), 700 (m) cm^{-1}.

Anal. Calcd for $C_{18}H_{27}N_3O_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 67.96; H, 8.55; N, 13.19.

N^4-Benzyl-N^1-(*tert*-butoxycarbonyl)norspermidine (5a). A solution of crude **4a** was reduced and purified in a similar manner as described for **4b**: yield 9.4 g (97%); ^1H NMR δ 1.40 (m, 11 H), 1.67 (m, 4 H), 2.53 (m, 6 H), 3.10 (quartet, 2 H), 3.48 (s, 2 H), 5.28 (br, 1 H), 7.18 (s, 5 H); IR (neat) 3380 (br), 2975 (s), 1710 (s), 1515 (s), 1180 (s), 740 (m), 705 (m) cm^{-1}.

An analytical sample was prepared as for **5b**.

Anal. Calcd for $C_{18}H_{31}N_3O_2$: C, 67.25; H, 9.72; N, 13.07. Found: C, 66.98; H, 9.78; N, 13.04.

N^4-Benzyl-N^1-(*tert*-butoxycarbonyl)-N^7-(trifluoroacetyl)norspermidine (6a). A solution of **5a** and trifluoroacetic anhydride was reacted and purified in a similar manner as described for **5b**: yield 1.8 g (92%); ^1H NMR δ 1.43 (s, 9 H), 1.65 (m, 4 H), 2.44 (m, 4 H), 3.14 (m, 4 H), 3.52 (s, 2 H), 5.18 (br, 1 H), 7.21 (s, 5 H), 7.67 (br, 1 H); IR (neat) 3320 (m), 3000 (m), 1705 (s), 1620 (s), 1180 (s), 745 (m) cm^{-1}.

Anal. Calcd for $C_{20}H_{30}N_3O_3F_3$: C, 57.54; H, 7.24; N, 10.06. Found: C, 57.41; H, 7.29; N, 9.87.

N-[N-(*tert*-Butoxycarbonyl)-4-aminobutyl]-N-(3-cyanopropyl)benzylamine (4c). A solution of **3b** was reacted with 4-chlorobutyronitrile and purified in a similar manner as described in the preparation of **4b**: yield 3.42 g (89%); ^1H NMR δ 1.43 (m, 15 H), 2.47 (m, 6 H), 3.10 (m, 2 H), 3.47 (s, 2 H), 4.63 (br, 1 H), 7.17 (s, 5 H); IR (neat) 2990 (s), 2240 (w), 1700 (s), 1520 (s), 1190 (s), 750 (m), cm^{-1}.

Anal. Calcd for $C_{20}H_{31}N_3O_2$: C, 69.53; H, 9.04; N, 12.16. Found: C, 69.53; H, 9.04; N, 12.16.

N^5-Benzyl-N^1-(*tert*-butoxycarbonyl)homospermidine (5c). A solution of **4c** was reduced and purified as described for **4b**: yield 9.8 g (91%); ^1H NMR δ 1.50 (m, 19 H); 2.43 (m, 6 H), 3.02 (m, 2 H), 3.50 (s, 2 H), 4.74 (br, 1 H), 7.18 (s, 5 H); IR (neat) 3350 (br), 2970 (s), 1700 (s), 1515 (m), 1170 (s), 740 (w), 700 (w), cm^{-1}.

Anal. Calcd for $C_{20}H_{35}N_3O_2 \cdot H_2O$: C, 65.36; H, 10.14; N, 11.43. Found: C, 65.44; H, 10.13; N, 11.43.

N^5-Benzyl-N^1-(*tert*-butoxycarbonyl)-N^9-(trifluoroacetyl)homospermidine (6c). A solution of **5c** and trifluoroacetic anhydride was reacted and purified as previously described for **5b**: yield 1.8 g (96%); ^1H NMR δ 1.52 (m, 17 H), 2.38 (m, 4 H), 3.18 (m, 4 H), 3.43 (s, 2 H), 4.70 (br, 1 H), 7.18 (s, 5 H), 7.62 (br, 1 H); IR (neat) 3320 (m), 2975 (s), 1710 (s), 1520 (s), 1170 (s), 740 (m), 700 (w) cm^{-1}.

Anal. Calcd for $C_{22}H_{34}N_3O_3F_3$: C, 59.31; H, 7.69; N, 9.43. Found: C, 59.12; H, 7.69; N, 9.41.

N^1-(*tert*-Butoxycarbonyl)-N^8-(trifluoroacetyl)spermidine Hydrochloride (7). Palladium chloride (90 mg) was added to a solution of **6b** (1.0 g, 2.3 mmol) in 25 mL of MeOH containing 6 drops concentrated HCl. The resulting suspension was stirred under an H_2 atmosphere for 12 h at which time the catalysts were filtered off and washed with MeOH and the filtrates evaporated. The crude product was recrystallized from EtOH/ether to afford 710 mg (82%) of pure **7**: mp 140–141 °C; ^1H NMR (D_2O) δ 1.54 (s, 9 H), 1.80 (m, 6 H), 3.30 (m, 8 H); IR (KBr) 3380 (m), 2690 (m), 2800 (m), 1705 (s), 1530 (m), 1175 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{27}N_3ClF_3O_3 \cdot H_2O$; C, 42.50; H, 7.38; N, 10.62. Found: C, 42.55; H, 7.32; N, 10.64.

N^4-Benzoyl-N^1-(*tert*-butoxycarbonyl)-N^8-(trifluoroacetyl)spermidine (8). A solution of benzoyl chloride (240 mg, 1.7 mmol) was slowly added to a cooled solution of **7** (560 mg, 1.5 mmol) and triethylamine (280 μL, 2.0 mmol) in 25 mL of dry CH_2Cl_2 under N_2. The reaction was allowed to warm to room temperature and stirred for 18 h. Additional CH_2Cl_2 was added (50 mL) and the organic layer was washed with 3% HCl (3 × 15 mL), H_2O (2 × 15 mL), 5% $NaHCO_3$ (3 × 15 mL), and H_2O (2 × 15 mL), dried, and concentrated to afford 620 mg (92%) of the desired product as a fluffy solid. Thin-layer chromatography and NMR analysis indicated the product's purity was in excess of 95% and could be used without further purification.

An analytical sample was prepared by preparative TLC, eluting with 10% MeOH/$CHCl_3$: ^1H NMR δ 1.37 (s, 9 H), 1.68 (m, 6 H), 3.27 (m, 8 H), 5.18 (br, 1 H), 7.28 (s, 5 H), 7.62 (br, 1 H); IR ($CHCl_3$) 3310 (m), 3010 (m), 1710 (s), 1620 (s), 1170 (s), 750 (s) cm^{-1}.

Anal. Calcd for $C_{21}H_{30}N_3O_4F_3$: C, 56.62; H, 6.79; N, 9.43. Found: C, 56.50; H, 6.82; N, 9.20.

N^4-Benzoyl-N^1-(*tert*-butoxycarbonyl)spermidine (9). Potassium carbonate (660 mg, 4.6 mmol) was added to a solution of **8** (515 mg, 1.15 mmol) in 30 mL of MeOH and 2 mL of H_2O. The reaction mixture was refluxed for 2 h and cooled, and the solvent was evaporated. The residue was dissolved in 50 mL of CH_2Cl_2, washed with H_2O (2 × 10 mL), dried, and concentrated to afford the crude product. Further purification was effected by chromatography on silica gel, eluting with 20% MeOH/$CHCl_3$, to afford 325 mg (81%) product: ^1H NMR δ 1.20–1.94 (m, 17 H), 256 (m, 2 H), 3.30 (m, 6 H), 5.26 (br, 1 H), 7.33 (s, 5 H); IR (neat) 3000 (m), 1710 (s), 1625 (s), 1510 (s), 1175 (s), 760 (s) cm^{-1}.

Anal. Calcd for $C_{19}H_{31}N_3O_3 \cdot CH_3OH$: C, 62.96; H, 9.25; N, 11.01. Found: C, 62.77; H, 8.69; N, 10.89.

N^8-Acetyl-N^4-Benzoyl-N^1-(*tert*-butoxycarbonyl)spermidine (10). A solution of acetyl chloride (85 mg, 0.74 mmol) in 5 mL of dry CH_2Cl_2 was added to a cooled solution of **9** (215 mg, 0.62 mmol) and triethylamine (150 μL, 1 mmol) in 10 mL of dry CH_2Cl_2 under N_2. The reaction was allowed to stir for 18 h and then worked up and purified as described for **8**: yield 240 mg (98%); ^1H NMR δ 1.43 (s, 9 H), 1.70 (m, 6 H), 1.93 (s, 3 H), 3.27 (m, 8 H), 5.38 (br, 1 H), 6.44 (br, 1 H), 7.37 (s, 5 H), IR ($CHCl_3$) 2980 (m), 1710 (s), 1630 (br, s), 1180 (m) cm^{-1}.

Anal. Calcd for $C_{21}H_{33}N_2O_4$: C, 64.43; H, 8.50; N, 10.73. Found: C, 64.17; H, 8.50; N, 10.51.

N^8-Acetyl-N^4-benzoylspermidine (11). Trifluoroacetic acid (10 mL) was added to a flask containing **10** (320 mg, 0.82 mmol), and the resulting solution was allowed to stir for 20 min. The solvent was then quickly evaporated, and the residue was dissolved in 25 mL of MeOH and concentrated twice. The crude product was then treated with 15% Na_2CO_3 (10 mL), extracted with CH_2Cl_2 (3 × 25 mL), dried, and concentrated to afford 180 mg (75%) of product as a light yellow oil: ^1H NMR δ 1.66 (m, 8 H), 1.94 (s, 3 H), 2.61 (m, 2 H), 3.24 (m, 6 H), 6.41 (br, 1 H), 7.35 (s, 5 H); IR ($CHCl_3$) 2990 (m), 1650 (s), 1620 (s), 740 (s) cm^{-1}.

Anal. Calcd for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 65.88; H, 8.46; N, 14.05.

N^8-Acetyl-N^4-benzoyl-N^1-(2,3-dimethoxybenzoyl)spermidine (12). A solution of 2,3-dimethoxybenzoyl chloride (95 mg, 0.47 mmol) in 10 mL of dry CH_2Cl_2 was slowly added to a cooled solution of **11** (125 mg, 0.43 mmol) and trimethylamine (70 μL, 0.5 mmol) in 10 mL of dry CH_2Cl_2. The reaction was allowed to stir for 18 h and purified as described for **10**: yield 180 mg (93%); ^1H NMR δ 1.68 (m, 6 H), 1.95 (s, 3 H), 3.24 (m, 8 H), 3.87 (s, 6 H), 6.45 (br, 1 H), 6.93–8.12 (m, 9 H); IR ($CHCl_3$) 3310 (m), 2980 (m), 1650 (br, s), 1530 (s), 740 (m) cm^{-1}.

Anal. Calcd for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30. Found: C, 65.67; H, 7.61.

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General Treatment of Periselectivity†

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Procedures to treat the competitions between most thermal pericyclic reactions have been developed and implemented in the CAMEO program. The algorithms are based on analyses of a large amount of kinetic data reported in the literature for cycloadditions, electrocyclic and cheletropic reactions, and sigmatropic rearrangements. For reaction types which have been extensively studied kinetically, approximate expressions are used to estimate energies of activation. More qualitative approaches are required to gauge reactivity for less well-studied reactions. The outcome of the analyses is the assignment of each possible competing pericyclic reaction to rate ranges which may then be compared.

I. Introduction

The computer program CAMEO, which predicts the products of organic reactions given starting materials and conditions, is being continually extended and refined.[1] The original efforts on anionic chemistry[1a] were expanded to include reactions of ylides and the organometallic chemistry of lithium, magnesium, and lithium cuprates.[1b] Subsequently, the treatment of organosilicon compounds was enhanced[1c] and a comprehensive module for electrophilic processes involving carbonium ion intermediates was added.[1d] Thermal pericyclic chemistry has also now been implemented including cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.[1e,f] This addition raises the important issue, addressed in the present paper, of periselectivity. That is, once all thermal pericyclic pathways available to a set of reagents are recognized by CAMEO, the program must determine which of the alternate pathways yields the predominant products that should be output.

Many obvious uses can be envisioned for a program capable of making sophisticated predictions on the outcome of organic reactions. However, as emphasized previously, the program development itself is highly beneficial because it necessitates the thorough analysis and organization of experimental data on reactivity.[1] This is well illustrated by the present work which provides a general treatment of periselectivity for all three classes of pericyclic reactions.

The CAMEO program has been set up so that the user may specify one of five temperature ranges (<0, 0–100, 100–200, 200–300, and >300 °C). The algorithms dealing with periselectivity then decide whether a particular reaction would have a rate constant above prescribed limits in the indicated temperature range. The chosen rate constant standards are 1.0×10^{-5} s^{-1} for first-order reactions (e.g., electrocyclic and Cope rearrangements) and 2.2×10^{-5} L/mol s for second order reactions (e.g., cycloadditions). These values are consistent with typical experimental conditions and correspond to 75% conversion in approximately 38 h.

The relationship between the rate constant and temperature is expressed by the Arrhenius equation:

$$k = A \exp(-E_a/RT) \text{ or } E_a = RT(\ln A - \ln k)$$

where A is the preexponential factor, E_a is the energy of activation, and R is the gas constant. If log A is known, the E_a required to achieve rate constant k at temperature T can be determined. Fortunately, log A tends to be relatively constant for a reaction type. Thus, given an average log A for each reaction type, it is simple to determine the range of E_a's required to achieve rate constant k for each of the above five temperature classes.

Clearly, the development of complete algorithms to predict activation energies for pericyclic reactions is a difficult undertaking. It is particularly aggravated by the lack of kinetic data for some reaction types. Consequently, the above categorization is meant only as a framework. For reaction types which have been extensively studied kinetically, it is possible to develop approximate expressions to estimate the energies of activation. These empirical relations will of necessity contain some parameters which are approximations. A different approach must be taken for reaction types for which there are few or no kinetic data available. Characteristics of the reagents which activate or deactivate the reaction can be identified. Subsequently, the reaction can be placed into a temperature slot that reflects typical experimental conditions for the particular process. The present algorithms are intended as a starting

† Computer-assisted mechanistic evaluation of organic reactions. 8. For part 7, see ref 1e.

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