Piperazino-Functionalized Silica Gel as a Deblocking-Scavenging Agent for the 9-Fluorenylmethyloxycarbonyl Amino-Protecting Group

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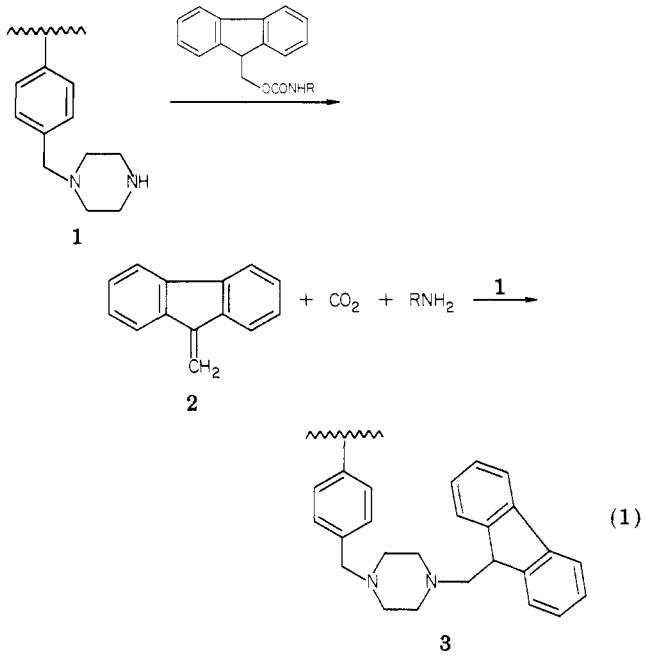
Bonding cyclic secondary amino residues to the surface of silica gel has given insoluble reagents capable of deblocking the 9-fluorenylmethyloxycarbonyl amino-protecting group and at the same time scavenging the dibenzofulvene (DBF) liberated in the deblocking process. A piperazino silica reagent **6** bearing approximately 1.1 mequiv of NH/g was easiest to prepare by reaction of trimethoxysilane **5** with chromatographic-grade silica. After use, spent reagent could be regenerated by treatment with excess piperidine. Piperidino silicas **14** and **15** were made similarly. For the amino-functionalized silica reagents and a variety of simple cyclic secondary amines (piperazine, piperidine, etc.) the existence of an equilibrium (eq 3) between DBF (**2**) and adduct **7** has been established with the position of equilibrium being dependent on the nature of the amine, solvent, etc. Both deblocking and attainment of equilibrium were faster in Me_2SO than in chloroform or dichloromethane. With piperazines in Me_2SO the equilibrium was shifted toward complete scavenging by precipitation of the adduct from the reaction medium.

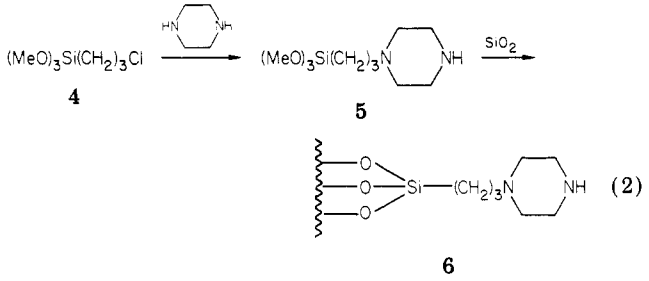
Previously[1] we showed that cross-linked polystyrenes bearing cyclic secondary amino functions of general structure **1** caused deblocking of the 9-fluorenylmethyloxycarbonyl (Fmoc) amino-protecting group[2] with the liberation of dibenzofulvene (DBF) **2** which is subsequently scavenged by the same insoluble reagent to give adduct **3** (eq 1). Filtration and evaporation of the solvent then



(1)

gave only the desired amine. Without removal of **2** the workup is often complicated by its gradual polymerization. In the earliest studies satisfactory reagents of this type were prepared from commercial samples of polystyrene of both microreticular (Dow Chemical Co., 1–2% DVB) and macroreticular (Rohm and Haas Co., XE-305) polystyrenes. Samples of reagent **1** made from polystyrenes obtained more recently from the same suppliers proved satisfactory only for the first step.[3]

In view of these difficulties and in anticipation of carrying out such deblocking–scavenging reactions by column rather than batch techniques, we have now investigated analogous nonswelling silica-based reagents.[4] In fact, piperazino-functionalized silica gels proved to be superior to the polystyrene-based reagents. Since they are also far simpler to prepare, they are clearly reagents of choice for synthetic purposes. (Chloropropyl)trimethoxysilane (**4**)



(2)

was treated with excess piperazine and the resulting piperazino silane **5** used to bond the appropriate functional group to the surface of activated silica. For the resultant functionalized silica gel **6** loadings of about 1.1 mequiv of active NH per gram were achieved.

Upon treatment of a solution of 9-fluorenylmethyl *p*-chlorocarbanilate (Fmoc-PCA) in Me_2SO-d_6 with an amount of reagent **6** bearing a 10 molar excess of secondary amino residues, the extent of DBF scavenging gradually increased until after 24 h an equilibrium value of approximately 85% scavenging was attained as determined by NMR analysis. No further change occurred up to a period of 6 days. Removal of the spent silica by filtration and its replacement by a fresh batch removed the remaining DBF. On a preparative scale, using 40 g of **6** and 1.58 g of the Fmoc derivative of *p*-chloroaniline, after a single treatment pure *p*-chloroaniline was isolated in a yield of 75%. The small amount of residual DBF re-

(1) Carpino, L. A.; Williams, J. R.; Łopusinski, A. *J. Chem. Soc., Chem. Commun.* **1978**, 450.

(2) (a) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748; *J. Org. Chem.* **1972**, *37*, 3404. (b) Carpino, L. A. *J. Org. Chem.* **1980**, *45*, 4250.

(3) Carpino, L. A.; Mansour, E. M. E.; Cheng, C. H.; Williams, J. R.; MacDonald, R.; Knapczyk, J.; Carman, M.; Łopusiński, A. *J. Org. Chem.*, accompanying paper in this issue.

(4) Little effort has so far been invested in studies of silica-based synthetic organic *reagents* (as opposed to *catalysts*). For a brief review see: Akelah, A. *Br. Polym. J.* **1981**, 107. Among the few examples studied are peracids (Greig, J. A.; Hancock, R. D.; Sherrington, D. C. *Eur. Polym. J.* **1980**, *16*, 293) and tin hydride reducing agents (Schumann, H.; Pachaly, B. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1043). More common are uses as supports for repetitive reactions. A recent case involved polynucleotide synthesis (Caruthers, M. D. *J. Am. Chem. Soc.* **1981**, *103*, 3185). For phosphonium phase-transfer catalysts bonded to silica see the work of Tundo and Venturello (Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1979**, *101*, 6606), whose methods of synthesis and surface bonding were used as a guide in the present work.

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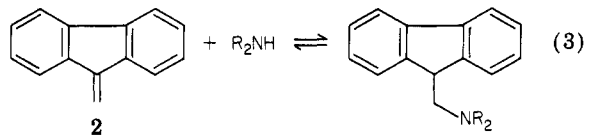
Table I. Deblocking-Scavenging of $FmocNHC_6H_4Cl$-p[a]

amine	solvent	approx half-lives, h: deblocking	approx half-lives, h: scavenging	% scavenging at equilibrium (time, h)
8	$CDCl_3$	24	90	62 (124)
9	$CDCl_3$	27	156	59 (168)
13	$CDCl_3$	13	48	85 (168)
10	$CDCl_3$	1	27	77 (144)
8	CD_2Cl_2	<0.25	1.5	100 (24)

[a] Reactions were carried out in NMR tubes as described in the Experimental Section.

maining did not interfere in the isolation procedure.

Following their use in typical deblocking–scavenging processes, spent reagents bearing varying amounts of DBF bound as depicted in **3** or the corresponding adduct of **6** were found, upon washing with dichloromethane, chloroform, or similar solvents, to suffer continuous sloughing off of small amounts of DBF. These observations suggested the existence of an equilibrium between the secondary amine and DBF (eq 3).



(3)

2 **7**

In order to verify such an equilibrium, we examined the reactivity of a series of simple cyclic secondary amines with DBF. Among the amines used were those we have previously recommended as routine deblocking agents for Fmoc-protected amines.[2] The group of amines studied included piperazine (**8**), *N*-methylpiperazine (**9**), piperidine (**10**), pyrrolidine (**11**), morpholine (**12**), and 1-(*p*-isopropylbenzyl)piperazine (**13**), a low molecular weight model for insoluble reagent **1**.

Rather than separately synthesizing DBF (**2**) for these experiments, it was generated by deblocking Fmoc-PCA, with the base being studied.[5] Results observed with piperidine are typical. A solution in deuterated chloroform which was 0.5 M in piperidine and 0.05 M in Fmoc-PCA (10:1 molar ratio of amine to urethane) was contained in an NMR tube and the course of reaction monitored with time. Deblocking was essentially complete within 7 h. Scavenging was noticeable only after about 30 min, with the extent of uptake of DBF increasing gradually until after 6 days it leveled off at about 77%. With the less basic *N*-methylpiperazine deblocking was only 31% complete after 7 h, and equilibrium was reached after about 8 days with 59% scavenging. Other results are collected in Table I. Results for **13** correlated with expectations based on previous work with **1** in which the extent of scavenging at equilibrium under comparable conditions varied between 50% and 75%, depending on the precise nature of the polymer, solvent, etc.[3]

The equilibrium noted in eq 3 could also be approached from the side of the adduct. For example, when a purified sample of the piperidine adduct was allowed to stand in deuterated chloroform, ^1H NMR analysis showed that no significant change occurred up to 5 days although TLC analysis revealed the presence of small amounts of DBF. If 10 molar equiv of piperidine was present, the content of DBF gradually increased from 4.8% after 3 days to 17.6% after 8 days.

Table II. Deblocking-Scavenging of $FmocNHC_6H_4Cl$-p in Me_2SO-d[a]

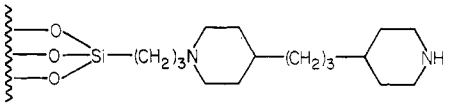
amine	approx half-lives for scavenging, min	% scavenging at equilibrium (time, h)
8	<5	100[b]
9	<10	100[c] (3)
10	<10	88 (1)
11	<10	78 (96)
12	<10	100 (72)
13	<20	100[d] (3)

[a] Reactions were carried out in NMR tubes as described in the Experimental Section. In every case deblocking is complete within 5–10 min. [b] Adduct begins to separate in 1 h. [c] Adduct begins to separate in 3 h. [d] Adduct begins to separate in 1.5 h.

In certain solvents, notably Me_2SO, these deblocking–scavenging reactions were markedly accelerated. Thus, in Me_2SO-d_6, with every amino compound studied, deblocking of Fmoc-PCA was complete within 5–10 min. For piperidine, equilibrium was established after 1 h (88% scavenging). With the less basic morpholine, equilibrium was reached more slowly, but the extent of scavenging was greater. Pyrrolidine gave at equilibrium only 78% scavenging after 4 days. Results are summarized in Table II. All of the piperazine derivatives examined showed special behavior in Me_2SO. Deblocking was again rapid (<10 min), but the adducts formed proved to be insoluble in the medium. By precipitating during the course of the reaction the equilibrium shifted, with the result that complete scavenging also occurred rapidly. For example, with piperazine itself complete scavenging occurred within 5 min, *N*-methylpiperazine and the benzylic model **13** required about 3 h, and *N*-phenylpiperazine required about 4.5 h. These relatively rapid scavenging reactions may eventually be of some practical interest in connection with the deblocking of certain urethanes. For piperazine itself both a mono and a bis adduct are possible. The initial precipitate appeared to be a mixture of the two since it was partially soluble in a variety of solvents although continued handling and recrystallization gave the highly insoluble bis adduct as the only isolable product.

In view of the cost of functionalized silica reagents it is important to be able to regenerate the secondary amino sites following use in a scavenging reaction. In the present case, taking advantage of the equilibrium between dibenzofulvene and cyclic secondary amines, this could be done by treatment with excess piperidine which readily removed dibenzofulvene as its piperidine adduct.

Silica reagents bearing the more basic piperidino function were also synthesized. Two methods were examined. In one approach S_N2 displacement by means of 1,3-bis(4-piperidyl)propane on the appropriate chloroalkyl-functionalized silica gave **14** or **15**. For **14** a method analgous



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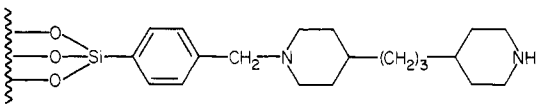

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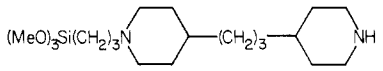
to that used for **6** was also successful although the pre-

(5) Dibenzofulvene generated in this way was characterized by means of its IR and ^1H NMR spectral characteristics. See: Neuenschwander, M.; Vögeli, R. Fahrni, H.-P.; Lehman, H.; Ruder, J.-P. *Helv. Chim. Acta* **1977**, *60*, 1073.

cursor trimethoxypiperidinosilane **16** could be obtained in



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only about 9% yield from (3-chloropropyl)trimethoxysilane and 1,3-bis(4-piperidyl)propane. As expected, the piperidino-bound silica reagents effected deblocking of Fmoc-protected amines more readily than the piperazino-bound reagents although in no case was complete scavenging observed.

Experimental Section[6]

(3-Chloropropyl)silyl-Functionalized Silica Gel. A suspension of 5.96 g of (3-chloropropyl)trimethoxysilane and 20 g of activated silica gel[7] in 100 mL of toluene was refluxed with stirring. After 1.5 h about 25 mL of methanol containing some toluene was distilled from the mixture. After an additional hour of refluxing an additional 25 mL of methanol–toluene was distilled out. Finally the mixture was refluxed for an additional 30 min, cooled, and filtered and the silica washed several times with Skelly F and air dried to give 21 g (91%) of chloropropyl silica. By elemental analysis for chlorine (3.38%) the loading was found to be 0.95 mequiv/g.

1-(Trimethoxysilyl)-3-(1-piperazyl)propane (5). To a solution of 25.8 g of anhydrous piperazine and 13 g of diisopropylethylamine in 90 mL of hot toluene was added in one portion of 20 g (3-chloropropyl)trimethoxysilane (**4**). A precipitate began to separate at once. The mixture was refluxed for 8 h under N_2, cooled in a refrigerator for 9 h, and filtered to remove excess piperazine along with precipitated amine hydrochlorides. Removal of solvent followed by distillation under N_2 gave 11.9 g (48%) of the piperazine: bp 108 °C (1.0 mm); ^{1}H NMR ($CDCl_3$) δ 0.5 (br t, 2 H, CH_2Si), 1.45 (m, 3 H, NH + $CH_2CH_2CH_2$), 2.25 (m, 6 H, CH_2N), 2.75 (m, 4 H, CH_2N), 3.5 (s, 9 H, CH_3O). Anal. Calcd for $C_{10}H_{24}O_3N_2Si$: C, 48.35; H, 9.74; N, 11.28. Found: C, 48.06; H, 9.57; N, 11.31.

Piperazino-Functionalized Silica Gel (6). To a solution of 10.4 g of **5** in 100 mL of toluene was added 28 g of activated silica gel.[7] The mixture was stirred mechanically under N_2 for 1.5 h at room temperature and then heated and distilled to remove two successive 25-mL portions of toluene–methanol as described for the corresponding chloropropylsilyl analogue. Filtration and washing with Skelly F gave 34.8 g (theory 34.4 g) of the piperazino silica which by elemental analysis for nitrogen (3.13%) showed a loading of 1.2 mequiv of NH/g.

1-[3-(Trimethoxysilyl)propyl]-1,3-bis(4-piperidyl)propane (16). A solution of 31 g of 1,3-bis(4-piperidyl)propane, 18 mL of diisopropylethylamine, and 20 g of (3-chloropropyl)trimethoxysilane in 70 mL of toluene was refluxed for 8.5 h under N_2. After the mixture was cooled and filtered, the solvent was removed in vacuo and the oily residue distilled. A forerun [bp 40–135 °C (0.5 mm)] was discarded and a fraction [bp 148–185 °C (0.05 mm)] collected. The second fraction was redistilled from a short-path distillation apparatus to give 3.5 g (9.3%) of the trimethoxysilane: bp 180–185 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 0.6 (m, 2 H, CH_2Si), 1.2–1.75 (m, 18 H, CCH_2C, CH), 2.2–3.2 (m, 10 H, NCH_2C), 3.05 (s, 9 H, CH_3O). Anal. Calcd for $C_{19}H_{40}N_2O_3Si$: C, 61.24; H, 10.82; N, 7.52. Found: C, 61.43; H, 11.01; N, 7.63.

Piperidine-Functionalized Silica Gel. (A) A solution of 1.25 g of **16**, 2 g of activated silica gel,[7] and 20 mL of toluene treated as usual gave 2.5 g of piperidino silica **14**. Elemental analysis for nitrogen (2.07%) showed a loading of 0.74 mequiv of active NH/g. (B) to 20.8 g of 1,3-bis(4-piperidyl)propane and 0.25 g of NaI dissolved in 50 mL of anhydrous Me_2SO was added 10 g of (3-chloropropyl)silyl-functionalized silica gel (0.67 mequiv of Cl/g), and the mixture was stirred and heated in a bath at 110 °C for 9 h. The functionalized silica **14** was filtered and washed successively with MeOH, H_2O, and MeOH and finally dried in vacuo at 60 °C for 10 h. Elemental analysis (1.62% N, <0.1% Cl) indicated a loading of 0.57 mequiv of NH/g. (C)[9] To a rapidly stirred solution of 60 mL of diisopropylethylamine and 60 mL of anhydrous methanol in 300 mL of anhydrous benzene was added 25 g of [4-(chloromethyl)phenyl]trichlorosilane in 100 mL of anhydrous benzene over a period of 30 min. Concentration in vacuo to 50 mL followed by filtration of the hydrochloride and washing with low-boiling ligroin gave a filtrate which upon evaporation and distillation of the oily residue gave 21.5 g (91%) of [4-(chloromethyl)phenyl]trimethoxysilane: bp 98–101 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 9, CH_3O), 4.55 (s, 2, CH_2), 7.6 (q, 4, aryl). Without further purification a solution of 5 g of this trimethoxysilane was added over a period of 30 min to a solution of 20.8 g of 1,3-bis(4-piperidyl)propane and 3.5 g of diisopropylethylamine in 40 mL of toluene which had been heated to 70 °C. Following complete addition, the mixture was stirred for 60 min at 50 °C, cooled to room temperature, and filtered. To the filtrate was added 6 g of activated silica gel, and bonding was carried out as previously described to give 8.03 g of functionalized silica **15**. Elemental analysis (2.11% N) showed a loading of 0.75 mequiv of NH/g.

Treatment of 9-Fluorenylmethyl *p*-Chlorocarbanilate with Piperazino Silica. A 0.5-g sample of functionalized silica **6** (1.12 mequiv of NH/g) was weighed into each of ten small vials[10] fitted with magnetic stirrers. There was added 1 mL of Me_2SO-d_6 and 0.0196 g of Fmoc-PCA,[3] and the contents were stirred at room temperature. At the desired time the contents of one of the vials was filtered, the silica washed with 0.5 mL of Me_2SO-d_6, and the filtrate subjected to analysis by ^{1}H NMR. Integration of peaks due to the original urethane, *p*-chloroaniline, and DBF at δ 4.2–4.65 (m, 3), 6.3 (s, 2), and 6.6 (d, 2), respectively, allowed the progress of the reaction to be followed. All of the urethane had disappeared within 15 min. The amount of DBF present at various times was determined relative to the *p*-chloroaniline doublet: 15 min, 100%; 3 h, 44%; 6 h, 25%; 10 h, 25; 12.5 h, 21.5%; 16.5 h, 18%; 20 h, 16%; 24 h, 16%, 5 days, 15%, 6 days, 15%. The decrease is the concentration of DBF was assumed to be due to scavenging by the silica reagent. This was confirmed by regeneration of the spent reagent (see below). When this experiment was repeated with a 1:1 ratio of urethane to silica, the results were as follows for urethane, *p*-chloroaniline, and DBF, respectively: 10 min, 52%, 48%, 48%; 30 min, 40%, 60%, 60%; 45 min, 25%, 75%, 75%; 3.5 h, 0%, 100%, 100%; 6 days, 0%, 100%, 50%; 7 days, 0%, 100%, 50%.

Regeneration of Spent Piperazino Silica. A 10-g sample of piperazino silica **6** (1.12 mequiv of NH/g) was added to a solution of 7.83 g of Fmoc-PCA[3] in 20 mL of Me_2SO and the mixture agitated by rotation[11] for a period of 24 h. The silica was filtered, washed first with Me_2SO and then with ether until a TLC test no longer showed the presence of DBF and *p*-chloroaniline. The resulting silica was dried in a vacuum oven at 40 °C overnight. A portion of the saturated silica was tested with a solution of the

(6) Melting and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 237B spectrometer and NMR spectra on a Perkin-Elmer R-12 instrument with Me_4Si as an internal standard. Elemental analyses were carried out by the University of Massachusetts Microanalytical Laboratory under the direction of Greg Dabkowski. TLC was performed on aluminum-backed silica gel 60 plates (Merck 5534) with hexane–ethyl acetate as the eluent.

(7) The silica gel was obtained from Merck (Catalog No. 7734, 70–230 mesh, specific surface area 500 m^2/g, pore diameter 60 Å). It was activated by the method of: Fritz, J. F.; King, J. N. *Anal. Chem.* **1976**, *48*, 570. The procedure for bonding was adapted from that of Tundo and Venturello.[4]

(8) Previously mentioned as having been obtained in this way but experimental details were not available. See: Lukevics, E.; Popova, E. P. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1978**, *2*, 207; *Chem. Abstr.* **1978**, *89*, 109669.

(9) The method of Parr and, Grohman (Parr, W.; Grohman, K. *Tetrahedron Lett.* **1971**, 2633) was modified by conversion of the trichlorosilane to the trimethoxysilane prior to fixation on the silica surface.

(10) Pierce Chemical Co., Rockford, IL.

(11) The shaft of a simple rotary evaporator (Rinco) was used. With extensive magnetic stirring in a round-bottomed vessel the silica was eventually crushed to a less easily filtered fine powder. This powdering was apparently accompanied by some degradation since material regenerated in this way was less effective as a scavenging agent for dibenzofulvene than virgin material or material generated via the rotation method. Because of the design of the Pierce vials used in the NMR tests in Me_2SO-d_6 no such powdering or degradation occurred even after continued stirring for 8–10 days.

Fmoc derivative of *p*-chloraniline by the NMR technique previously described. Deblocking occurred readily, but 85% of the theoretical amount of DBF remained in the solution. The dibenzofulvene-saturated sample of silica (9 g) was added to a solution of 8.6 g of piperidine in 20 mL of Me_2SO and the mixture agitated by rotation for 48 h. The mixture was filtered and washed first with Me_2SO and then with ether until a TLC test for DBF, and its piperidine adduct was negative. The silica was dried in a vacuum oven overnight at 40 °C. Testing of the regenerated silica with Fmoc-PCA showed it to be nearly as active as the virgin material (after 24 h, scavenging of DBF amounted to 80–84%).

Preparative-Scale Deblocking of 9-Fluorenylmethyl *p*-Chlorocarbanilate by means of Piperazino Silica. A 40-g sample of piperazino silica **6** (1.13 mequiv of NH/g) was added to a solution of 1.58 g of Fmoc-PCA[3] in 75 mL of Me_2SO, the reaction mixture was stirred for 24 h, and filtered, and the silica was washed several times with ether. The ether layer was separated, and the Me_2SO layer was diluted with water and extracted with three 50-mL portions of ether. The combined ether layer was washed twice with water, dried ($MgSO_4$), and evaporated, and the residue was recrystallized from *n*-hexane to give 0.43 g (74.1%) of *p*-chloroaniline (mp 70–73 °C), identified by IR and ^1H NMR comparison with an authentic sample.

1-(9-Fluorenylmethyl)-4-methylpiperazine. A solution of 0.6 g of $FmocNH_2$[3] and 2.5 g of *N*-methylpiperazine in 25 mL of DMF was stirred overnight at room temperature (crystals began to separate after 30 min). Dilution with H_2O and recrystallization from *n*-hexane gave 0.64 g (92%) of the adduct as white crystals: mp 157–159 °C; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3, CH_3), 2.5–2.75 (m, 10, CH_2N), 4.02 (t, 1, $CHCH_2$), 7.25–7.90 (m, 8, aryl). anal. Calcd for $C_{19}H_{22}N_2$: C, 82.01; H, 7.91; N, 10.07. Found: C, 82.03; H, 8.09; N, 10.03.

1,4-Bis(9-fluorenylmethyl)piperazine was obtained from piperazine as described for the *N*-methyl analogue in 80% yield: mp 208–210 °C (benzene); ^1H NMR (CF_3CO_2H δ 3.25 (s, 8, CH_2CH_2), 4.10–4.50 (m, 6, CH_2CH), 7.25–7.90 (m, 16, aryl). Anal. Calcd for $C_{32}H_{30}H_2$: C, 86.88, H, 6.79; N, 6.33. Found: C, 86.59; H, 6.81; N, 6.20.

1-(9-Fluorenylmethyl)-4-phenylpiperazine was obtained from *N*-phenylpiperazine as described for the *N*-methyl analogue: 95% yield; mp 168–170 °C (*n*-hexane); ^1H NMR ($CDCl_3$) δ 2.60–3.00 (m, 6, $CH_2NC_6H_5$, CH_2CH), 3.20–3.45 (m, 4, $CHCH_2NCH_2$), 4.08 (t, 1, $CHCH_2$), 6.90–7.90 (m, 13, aryl). Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.71; H, 7.06; N, 8.23. Found: C, 84.90; H, 7.00; N, 8.21.

1-(*p*-Isopropylbenzyl)piperazine. A mixture of 5 g of *p*-isopropylbenzyl chloride, 7.4 g of *tert*-butyl piperazine-1-carboxylate,[3] and 3.88 g of diisopropylethylamine in 75 mL of dichloromethane was refluxed overnight with stirring. The solution was extracted with three 50-mL portions of H_2O, dried ($MgSO_4$), and evaporated to an oil, presumably the Boc derivative: ^1H NMR ($CDCl_3$) δ 1.23 (d, 6, $CH(CH_3)_2$), 1.45 (s, 9, $C(CH_3)_3$), 2.25–2.4 (m, 4, $ArCH_2N(CH_2)_2$), 2.7–3.0 (m, 1, $CH(CH_3)_2$), 3.3–3.55 (m, 6, $ArCH_2N(CH_2)_2$), 7.2 (br s, 4, aryl). Without further purification the residue was refluxed in MeOH–concentrated HCl for 2 h. When the mixture cooled, the hydrochloride (mp 268–274 °C) was filtered and the salt treated with $NaCHO_3$. Extraction into ether followed by distillation gave a colorless liquid: bp 146–148 °C (2.75 mm); ^1H NMR ($CDCl_3$) δ 1.25 (d, 6, $CH(CH_3)_2$), 2.2–2.45 (m, 4, $ArCH_2N(CH_2)_2$), 2.6–2.95 (m, 5, $CH(CH_3)_2$, $(CH_2)_2NH$), 3.4 (s, 2, $ArCH_2$), 7.20 (s, 4, aryl).

The liquid was very sensitive to moisture which gave a crystalline solid, apparently a hydrate, mp 91–93 °C. Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.06; H, 10.09; N, 12.84. Found: C, 76.70; H, 10.27; N, 12.82.

1-(9-Fluorenylmethyl)-4-(*p*-isopropylbenzyl)piperazine was obtained from 1-(*p*-isopropylbenzyl)piperazine and $FmocNH_2$[3] in DMF as described for the *N*-methyl analogue: 85% yield; mp 149–151 °C (*n*-hexane); ^1H NMR ($CDCl_3$) δ 1.25 (d, 6, CH_3), 2.6–3.0 (m, 11, CH_2N, $CHMe_2$), 3.55 (s, 2, NCH_2Ar), 4.05 (t, 1, $CHCH_2$), 7.25–7.90 (m, 12, aryl). Anal. Calcd for $C_{28}H_{32}N_2$: C, 84.85; H, 8.08; N, 7.07. Found: C, 84.58; H, 8.24; N, 7.11.

1-(9-Fluorenylmethyl)pyrrolidine was obtained from pyrrolidine and $FmocNH_2$[3] in DMF as described for *N*-methylpiperazine: 82% yield; white crystals; mp 90–91 °C (*n*-hexane); ^1H NMR ($CDCl_3$) δ 1.6–2.0 (m, 4, CH_2CH_2), 2.05–2.85 (m, 6, CH_2N), 4.0 (t, 1, $CHCH_2$), 7.25–7.90 (m, 8, aryl). Anal. Calcd for $C_{18}H_{19}N$: C, 86.75; H, 7.63; N, 5.62. Found: C, 87.13; H, 7.82; N, 5.60.

Treatment of 9-Fluorenylmethyl *p*-Chlorocarbanilate with Various Cyclic Secondary Amines. A solution of 0.0258 g of piperazine and 0.0105 g of Fmoc-PCA[3] in 0.6 mL of $CDCl_3$ contained in an NMR tube was allowed to stand at room temperature and examined by ^1H NMR at various times to follow the course of the deblocking–scavenging reaction. The extent of deblocking and scavenging at various times was recorded: 2 h, 15%, 0%; 4 h, 20%, 0%; 22 h, 43%, 0%; 24 h, 50%, 5%; 46 h, 88%, 34%; 96 h, 100%, 56%; 124 h, 100%, 62%. Similar reactions were carried out in Me_2SO-d_6 by using in each case a 10:1 ratio between amine (0.5 M) and urethane (0.05 M). Results are collected in Tables I and II. With *N*-phenylpiperazine it was difficult to follow the course of the reaction by ^1H NMR because of overlap of the *N*-phenyl protons with those of *p*-chloroaniline. However, after 2.5 h the adduct started to separate, and scavenging was complete in 4.5 h.

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Registry No. **2**, 4425-82-5; **4**, 2530-87-2; **5**, 40762-28-5; **16**, 84418-36-0; piperazine, 110-85-0; 1,3-bis(4-piperidyl)propane, 16898-52-5; 9-fluorenylmethyl *p*-chlorocarbanilate, 84418-37-1; 1-(9-fluorenylmethyl)-4-methylpiperazine, 84418-38-2; 1,4-bis(9-fluorenylmethyl)piperazine, 84418-39-3; 1-(9-fluorenylmethyl)-4-phenylpiperazine, 84418-40-6; 1-(*p*-isopropylbenzyl)piperazine, 23145-95-1; 1-(9-fluorenylmethyl)-4-(*p*-isopropylbenzyl)piperazine, 84418-41-7; 1-(9-fluorenylmethyl)pyrrolidine, 84418-42-8; 9-fluorenylmethyl carbamate, 84418-43-9; *N*-methylpiperazine, 109-01-3; *N*-phenylpiperazine, 92-54-6; *p*-isopropylbenzyl chloride, 2051-18-5; *tert*-butyl piperazine-1-carboxylate, 57260-71-6; pyrrolidine, 123-75-1; *tert*-butyl 4-(*p*-isopropylbenzyl)piperazine-1-carboxylate, 84418-44-0; 1-(*p*-isopropylbenzyl)piperazine hydrochloride, 84418-45-1.