# Polystyrene-Based Deblocking–Scavenging Agents for the 9-Fluorenylmethyloxycarbonyl Amino-Protecting Group

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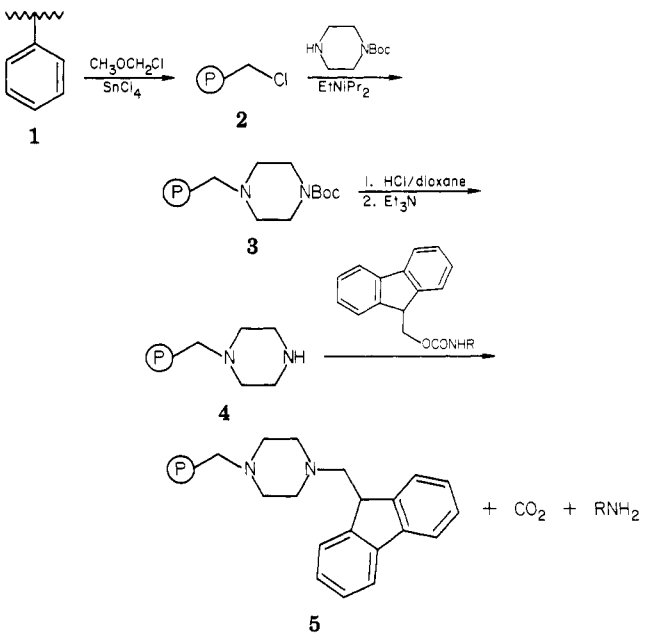
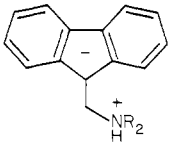
Piperazino- and piperidino-functionalized polystyrenes have been examined as deblocking–scavenging agents for the 9-fluorenylmethyloxycarbonyl (Fmoc) amino-protecting group. Both commercial and synthesized polystyrenes have been used as supports. In order to introduce the active functional groups, (chloromethyl)-polystyrene **2** was treated with *tert*-butyl piperazine-1-carboxylate followed by acidic deblocking (HCl/dioxane) or, alternatively, was directly aminated by means of a 10 molar excess of piperazine or 1,3-bis(4-piperidino)propane. Compounds **7–9** were examined as cross-linking agents in the preparation of appropriate reagents. Most suitable were reagents prepared from commercial macroreticular resins (XE-305) or those cross-linked via DVT (**8**). Proof that the DBF liberated in the deblocking process was scavenged (partially) by the active secondary amine reagents **4** came from (a) a study of the successful regeneration of an active agent from **5** by treatment with alkali ($H_2O$–dioxane) and (b) liberation of 9-methylfluorene from **5** by hydrogenation ($NH_4OCHO$/Pd-C).

Previously[1] it was reported that insoluble cross-linked polystyrene reagents **4** bearing piperazino functionality acted as novel deblocking–scavenging agents for the 9-fluorenylmethyloxycarbonyl (Fmoc)[2] amino-protecting group. In the initial studies (J.R.W.)[3] the active reagent was synthesized (Scheme I) from a commercially available sample of a microreticular polystyrene which had been cross-linked by polymerization with 1–2% of divinylbenzene (DVB).[4] By use of this reagent three Fmoc derivatives, $FmocNHC_6H_4Cl$-*p*, Fmoc-Leu-OH, and Fmoc-Trp-OH, were converted to the corresponding free amines simply by stirring in dichloromethane or, in the case of the amino acid derivatives, with the two-phase system dichloromethane–water. Complete scavenging of the dibenzofulvene (DBF) liberated in the deblocking process[5] occurred after periods of 8–24 h.

Subsequent work in another laboratory (A.Ł.) confirmed these results with $FmocNHC_6H_4Cl$-*p* by using a sample of **4** still available from the earlier work and in addition extended the reaction to a reagent prepared from a second commercial polystyrene (XE-305, a macroreticular resin of 4% DVB content).[7] However, in the case of reagents derived from XE-305, while deblocking occurred normally, complete scavenging was not observed until 15–20% methanol or formamide was added to the dichloromethane solvent. This hinted at a possible steric effect for the more highly cross-linked resin. The acceleration of the scavenging process by polar media was in line with a mechanistic rationale for a Michael-like addition process proceeding via a transition state resembling the dipolar species **6**.[8] In the process of completing these initial studies all of the original samples of polystyrene were consumed, and upon returning to this work after a lapse of several years, we obtained new samples of resins from the same suppliers but were surprised to find that both new batches of

Scheme I

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(1) Carpino, L. A.; Williams, J. R.; Łopusiński, A. *J. Chem. Soc., Chem. Commun.* **1978**, 450. For earlier references to the general use of the Fmoc protecting group see: Carpino, L. A. *J. Org. Chem.* **1980**, *45*, 4250.

(2) Abbreviations used: Boc, *tert*-butoxycarbonyl; Fmoc, 9-fluorenylmethyloxycarbonyl; DVB, divinylbenzene; DBF, dibenzofulvene; DVBP, 4,4′-divinylbiphenyl (**7**); DVT, 4,4′-divinyl-*p*-terphenyl (**8**); DVPD, 1,10-bis(4-vinylphenyl)decane (**9**); PZ, piperazino; PD, piperidino; DA, direct amination.

(3) Williams, J. R. Ph.D. Dissertation, University of Massachusetts, Amherst, MA, 1973.

(4) Obtained through the courtesy of the Dow Chemical Co., Midland, MI, in 1974.

(5) For liberation of DBF in reactions of Fmoc derivatives with amines see: Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748; *J. Org. Chem.* **1972**, *37*, 3404; **1973**, *38*, 4218. The spectral characteristics of DBF have been recorded.[6]

(6) Neuenschwander, M.; Vögeli, R.; Fahrni, H.-P.; Lehmann, H.; Ruder, J.-P. *Helv. Chim. Acta* **1977**, *60*, 1073.

(7) Obtained through the courtesy of Rohm and Haas Co., Philadelphia, PA, in 1975. Subsequent samples (1978) obtained from the same supplier were labeled XE-305A.

(8) Compare: Patai, S. "The Chemistry of Alkenes"; Interscience: New York, 1964; p 488.

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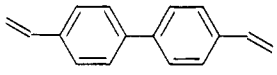
Table I. Deblocking of FmocNHC$_6$H$_4$Cl-*p* by Piperazino- and Piperidinopolystyrenes[a]

| entry | cross-linking agent | secondary amino[b] residue | mequiv of NH/g | solv | time for complete deblocking |
|---|---|---|---|---|---|
| 1 | 0.5% DVT | PZ | 2.02 | $CH_2Cl_2$ | 10-14 h |
| 2 | 0.5% DVT | PZ, DA | 2.02 | $CH_2Cl_2$ | 1-2 days |
| 3 | 0.5% DVT | PZ | 2.02 | dioxane | 3-3.5 h |
| 4 | 0.5% DVT | PZ | 2.02 | $Me_2SO$ | 3-4 days |
| 5 | 0.5% DVT | PD, DA | 1.46 | $CH_2Cl_2$ | 7-7.5 h |
| 6 | 0.5% DVT | PD, DA | 1.46 | dioxane | 3-3.5 h |
| 7 | 0.5% DVBP | PZ | 2.33 | $CH_2Cl_2$ | 12.5-13 h[c] |
| 8 | 0.5% DVBP | PZ, DA | 2.33 | $CH_2Cl_2$ | 3-4 days |
| 9 | 0.5% DVBP | PZ | 2.33 | dioxane | 3.5-6 h |
| 10 | 0.5% DVPD | PZ | 1.42 | dioxane | 8-10 h |
| 11 | DVB (XE-305A) | PZ | 1.69 | $CH_2Cl_2$ | 15-20 h |
| 12 | DVB (XE-305A) | PZ, DA | 1.69 | $CH_2Cl_2$ | 2-3 days |
| 13 | DVB (XE-305A) | PZ | 1.69 | dioxane | 0.5-1 h |
| 14 | DVB (XE-305A) | PZ | 1.69 | $Me_2SO$ | 1-1.5 h |
| 15 | DVB (XE-305A) | PD, DA | 1.46 | $CH_2Cl_2$ | 11.5-24 h |
| 16 | DVB (XE-305A) | PD, DA | 1.46 | dioxane | 3.5-4 h |
| 17 | *d* | | | | |

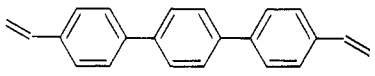
[a] Unless otherwise indicated a 10 molar excess of secondary amino residue was used per mole of urethane. [b] The reagents were prepared from (chloromethyl)polystyrenes bearing piperazino (PZ) or piperidino (PD) residues by the two-step method using *tert*-butyl piperazine-1-carboxylate except where indicated by DA (direct amination) where a 10-molar excess of piperazine or 1,3-bis(4-piperidino)propane was used directly on the chloromethyl derivative. [c] For an analogous sample prepared with 1% DVBP (1.77 mequiv of NH/g) reaction in $CH_2Cl_2$ gave complete deblocking within 24 h. At this point $^1$H NMR analysis showed 33% scavenging of DBF. After 36 and 48 h scavenging had increased to 40% and 50%, respectively. [d] With a commercial sample of gel-type polystyrene (Dow Chemical Co., 1978, 1-2% DVB) a piperazino-bearing reagent (0.7 mequiv of NH/g) prepared by the two-step method effected in $CH_2Cl_2$ only 59% deblocking within 24 h with a 25 molar excess of secondary amino residues over urethane. After 144 h, deblocking was 91% complete and scavenging less than 25%. If the molar excess of amino residue to urethane was increased to 100, the extent of scavenging after 144 h dropped to less than 10%. With a sample prepared by the two-step method from a commercial sample of (chloromethyl)-polystyrene (Bio-Beads S-X-1, 1.29 mequiv of Cl/g) having 0.96 mequiv of NH/g, deblocking in dichloromethane was complete in 24 h, but less than 5% scavenging had occurred by this time.

polymer behaved differently.[9] The new samples have given amino-functionalized reagents which effect deblocking at about the same rate as observed earlier but induce the scavenging step far more sluggishly. These systems have now been thoroughly investigated in an effort to accelerate the scavenging process and/or find some rationale for the lack of reproducibility encountered in the use of these polymeric reagents.

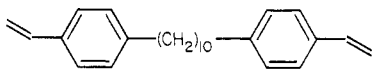
From parallel studies[10] of low molecular weight models it is now apparent that the insoluble polymeric secondary amines exhibit a reactivity of about that expected in the absence of any accelerating catalytic influences. The current study has included piperazino and piperidino resins derived from new (1978+) samples of polystyrenes made available by suppliers of the earlier resins as well as preformed (chloromethyl)polystyrene (Bio-Beads S-X-1) and homemade beaded polymers obtained via suspension polymerization.[11] The latter were obtained by radical polymerization in the presence of 0.5–2% of the novel cross-linking agents **7**,[12] **8**,[13] **9**.[14] Initially **7** and **8** were



**7** (DVBP)



**8** (DVT)




**9** (DVPD)

examined to determine whether the length of the rigid portion of the cross-linking agent affected swelling characteristics in a desirable manner. Lightly cross-linked "isoporous macronet" resins[15] were first examined, but they were not easily filtered and therefore not examined extensively. Flexible cross-linking agents for polymeric deblocking systems were also examined by Sheppard and co-workers.[16,17]

(9) Some changes in the polymerization techniques appear to have been made in the interim by both suppliers, but we have been unable to learn exactly what differences were involved. From the results reported in the present paper it is suspected that the presence of some residual material left over from the polymerization process might have had a catalytic effect on the scavenging process. Alternatively, in the earlier work the DBF might have undergone polymerization on the support. Generally DBF undergoes varying amounts of polymerization upon working up solutions containing the monomer. The early experiments were done without attempting to control laboratory lighting, access to sunlight, presence of oxygen, etc., all of which are known to have an effect on the homopolymerization of DBF. Generally, upon evaporation of a solution containing DBF a mixture of monomeric and polymeric DBF is obtained. On the other hand, under nitrogen, solutions of DBF in dichloromethane, chloroform, dioxane, etc. can be stored for weeks without any change in DBF content (UV, $^1$H NMR analysis). Indeed, it is the formation of unpredictable amounts of monomer and polymer following a deblocking reaction which is the main incentive to the development of practical scavenging agents. It is clear from the regeneration and hydrogenolysis experiments of the present work that loss of DBF is not due to homopolymerization.

(10) Carpino, L. A.; Mansour, E. M. E.; Knapczyk, J. *J. Org. Chem.*, accompanying paper in this issue.

(11) (a) Braun, D.; Brendlein, N. *Angew. Makromol. Chem.* **1973**, *31*, 137. (b) Braun, D.; Cherdron, D.; Kern, W. "Praktikum der Makromolekularen Chemie"; Hüthig: Heidelberg, 1966; p 174.

(12) Prepared according to: Drefahl, G.; Plötner, G; Rudolph, F. *Ber.* **1960**, *93*, 998. Difficulties were experienced until a large excess (2.5 mol) of lithium ethoxide was used to generate the enolate.

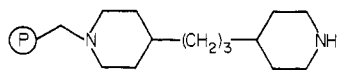
(13) 4,4′-Diacetyl-*p*-terphenyl was prepared according to: Baroni, E. E.; Kovyrzina, K. A. *J. Gen. USSR (Engl. Transl.)* **1963**, *33*, 577. The remainder of the method involved that of: Drefahl, G.; Winnefeld, K. *J. Prakt. Chem.* **1965**, *300*, 242.

(14) DVPD was obtained by the method of: Papukova, K. P.; Myagkova-Romanova, N. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, *3*, 600.

(15) Davankov, V. A.; Rogozhin, S. V.; Tsyurupa, M. P. *J. Polym. Sci., Polym. Symp.* **1974**, *47*, 95, 189.

(16) Arshady, R.; Atherton, E.; Sheppard, R. C. *Tetrahedron Lett.* **1979**, 1521.

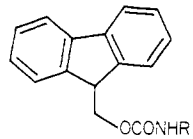
Following chloromethylation of the polystyrenes, introduction of the piperazino or piperidino unit was carried out by either of two methods. The first is outlined in Scheme I, with the formation of **3** and its conversion to **4** being followed by the buildup and disappearance of the carbamate absorption at 1695 $cm^{-1}$ in the infrared spectrum. As a simpler alternative, **4** was also obtained directly from **2** by treatment with a 10 molar excess of piperazine ["direct amination" (DA); see Table I]. With the piperidino derivative **10** the second method was adopted by



**10**

using 1,3-bis(4-piperidino)propane. Either method required treatment of the initially formed hydrochloride with triethylamine–dioxane for an extended period (2–3 days) in order to remove all contaminating chloride ion.

For preliminary testing the Fmoc derivative **11a** of *p*-



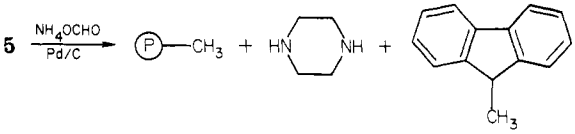
**11a**, R = *p*-$ClC_6H_4$
**b**, R = H

chloroaniline was treated with various samples of **4** in a number of solvents at room temperature, the extent of reaction being followed by TLC and $^1H$ NMR techniques. Generally a 10 molar excess of deblocking amine was taken relative to the urethane. Reactions run in dichloromethane, the solvent used exclusively in the earlier studies, were often inconsistent, possibly because of slow reaction of the solvent with the secondary amino function of the insoluble reagent. This might cause additional cross-linking as well as decreasing the number of active sites for the deblocking–scavenging process. Possibly for these reasons, as well as the polarity difference, deblocking is much slower in dichloromethane than in dioxane even though both are good swelling solvents. For a sample incorporating 0.5% DVT, deblocking was about 3 times as fast in dioxane. In dimethyl sulfoxide ($Me_2SO$) which does not swell the DVT-cross-linked polymer appreciably, deblocking requires 3–4 days for completion. This extremely sluggish reaction in $Me_2SO$ contrasts with the acceleration observed in $Me_2SO$ in the case of low molecular weight (piperazine, piperidine, morpholine, etc.) or silica-based analogues[10] of **4**. In the latter case reactivity is not dependent on swelling since the reactive functional groups extend from the surface as brushlike appendages.[18] Results collected in Table I.

In none of the solvents tested, even those in which rapid deblocking was observed, was complete scavenging noted. A measure of the extent of scavenging over a period of several days was therefore obtained by an ultraviolet technique.[19] For this purpose the *p*-chloroaniline derivative **11a** was replaced by the simple carbamate **11b** in order to avoid the presence of an additional chromophore. A mixture of **11b** and reagent **4** (0.5% DVT; 10 molar equiv of secondary amine vs. urethane) was stirred at room temperature until deblocking was complete (reaction was significantly slower than with **11a**). At this point the amount of free DBF in the solution was 64% of that expected, and its concentration slowly decreased until it leveled off at about 29% after 13 days. No further change occurred up to 15 days. Maximum scavenging was thus 71% under these conditions. With a 100:1 ratio of NH units to urethane maximum scavenging at equilibrium was 64%. With a sample of **4** obtained from a macroreticular resin (XE-305A) maximum scavenging of about 50% was reached after 9 days.

From these results it appears that an equilibrium is reached between **4** and DBF, the position of which is dependent on the nature and amount of **4** or **10** as well as the solvent used. Existence of such an equilibrium was confirmed by companion studies on low molecular weight models.[10] Also in line with such an equilibrium, it was possible to regenerate a sample of piperazino polystyrene **4** (XE-305A) which had been deliberately saturated with DBF by treatment with an excess of **11a**. Following saturation, a test showed that the recovered reagent effected complete deblocking of **11a** but little scavenging. Treatment of the saturated reagent with sodium hydroxide in aqueous dioxane[20] for 3 days gave a reagent which again effected scavenging at about the same level as the virgin material.

Further confirmation of the hypothesis that loss of DBF from solutions in contact with reagents such as **4** involves the formation of adducts **5** rather than homopolymerization of DBF or some other irreversible process came from experiments on the hydrogenolysis[21] of a sample of **4** (0.5% DVT) recovered from reaction with **11a**. Up to 10% of the secondary amino sites of this reagent should have been converted to the corresponding tertiary amino sites depicted in **5**. The initial reaction between **4** and **11a** was conducted in dioxane for 5 days. $^1H$ NMR analysis showed that 60% of the DBF had been scavenged. The spent reagent was then subjected to catalytic transfer hydrogenolysis[22] in the presence of Pd–C/$NH_4OCHO$ which liberated 85% of the expected amount of 9-methylfluorene (eq 1).



(1)

## Conclusions

While the various secondary amino-substituted polystyrenes synthesized in the course of this work can be used as deblocking–scavenging reagents for Fmoc systems, there are certain disadvantages inherent in their use. Due to the very tedious washing procedures required in the handling

(17) Compare: Morawetz, H. "Proceedings of the 4th American Peptide Symposium", Walter, R., Meienhofer, J., Eds.; Ann Arbor Science Publishers: Ann Arbor, MI, 1975; p 385.

(18) For reviews on the nature and reactivity of polymeric and silica-based reagents see: (a) Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557. (b) Akelah, A. *Br. Polym. J.* **1981**, 107.

(19) In certain cases $^1H$ NMR techniques were used to follow the extent of deblocking–scavenging processes. See footnotes *c* and *d* of Table I.

(20) Compare: Kelly, R. P.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans 2* **1979**, 681. More recently it has been found that regeneration by treatment with excess piperidine is simpler.[10]

(21) Parallel studies have shown that simple 9-fluorenylmethylamines undergo hydrogenolysis over Pd/C catalysts with C–N bond cleavage. Analogous C–O bond cleavage was first reported by Sheppard and Bodanszky and their co-workers [(a) Atherton, E.; Bury, C.; Sheppard, R. C.; Williams, B. J. *Tetrahedron Lett.* **1979**, 3041. (b) J. Martinez, J. C. Tolle and M. Bodanszky, *J. Org. Chem.* **1979**, *44*, 3596], although with (apparently) less active catalysts both carbobenzoxy and benzyl ester functions [Chang, C.-D.; Waki, M.; Ahmad, M.; Meienhofer, J.; Lundell, E. O.; Haug, J. D. *Int. J. Pept. Protein Res.* **1980**, *15*, 59] have been selectively hydrogenolyzed in the presence of the Fmoc group. Whether this selectivity will be generally observable for both C–O and C–N bond cleavage is now the subject of an extensive study.

(22) Anwer, M. K.; Spatola, A. F. *Tetrahedron Lett.* **1981**, 4369.

of these resins, we have switched to the use of analogous silica-based systems.[10] Not only are the washing protocols simpler with silica-bound reagents but the reactions are also faster, cleaner, and more reproducible. In addition the silica derivatives are far easier to synthesize. Where advantages are found for the polystyrene-based systems the macroreticular types (e.g., XE-305) are recommended.

## Experimental Section[23]

***tert*-Butyl Piperazine-1-carboxylate.** A solution of 14.3 g of *tert*-butyl azidoformate in 150 mL of dry $CH_2Cl_2$ was added dropwise over a period of 20 min to a stirred solution of 17.2 g of anhydrous piperazine in 500 mL of dry $CH_2Cl_2$. The precipitated solid was removed by filtration and washed with three 200-mL portions of $CH_2Cl_2$. Removal of solvent at a water aspirator gave a colorless oil which was dissolved in 300 mL of water, and the mixture was filtered to remove the insoluble bis(*tert*-butoxycarbonyl) derivative. The aqueous filtrate was saturated with anhydrous $K_2CO_3$. Extraction with three 100-mL portions of ether followed by evaporation gave 15 g (80%) of mono-Boc-substituted piperazine as a viscous oil which was pure enough for most purposes. Recrystallization from ether gave the carbamate as a white solid; mp 70–76 °C. Sublimation gave a white solid: mp 42.5–45 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.41 (s, 9, $CH_3$), 2.14 (s, 1, NH, erasable by $D_2O$), 2.75 (m, 4 $CH_2NH$), 3.35 (m, 4, $CH_2NCO$). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.10; H, 9.67; N, 15.05. Found: C, 58.10; H, 9.70; N, 15.05.

**Polymerization of Styrene Cross-Linked by 0.5% *p,p'*-Divinylterphenyl.** While a solution of 220 mg of polyvinylpyrrolidone (K-90) in 98 mL of water held at 60 °C by means of an oil bath was stirred and purged with a gentle stream of nitrogen, there was added a mixture of 19.9 g of freshly distilled styrene, 270 mg of *p,p'*-divinylterphenyl, 220 mg of dibenzoyl peroxide, and 6.75 mL of *n*-amyl alcohol. After the addition to the aqueous solution the temperature of the mixture was gradually raised to 90 °C over a period of 1 h and maintained at this temperature with continued stirring and $N_2$ purging for a period of 10 h. The resulting mixture was cooled and filtered through paper (Whatman No. 41), and the beaded polymer was washed twice with 200-mL portions of $H_2O$ and twice with 200-mL portions of MeOH. The beads were then stirred with 200-mL portions of dioxane until no turbidity formed on dilution of the dioxane filtrate with $H_2O$ (five washings). Finally the polymer was washed with three 200-mL portions of $CH_2Cl_2$ and dried overnight in a vacuum oven at 80 °C to give 19.1 g (94.6%) of polymer (swelling capacity 8.64 g of toluene/g of polymer). Swelling capacity was generally determined by immersion of a 2-g sample contained in a sintered-glass funnel in the solvent for up to 72 h, suction filtration for 1 min, and determination of the weight gain. Polymerization of styrene in the same way with 0.5% and 1% DVPD gave nonbeaded polymers with either benzoyl peroxide or AIBN as the catalyst.

**[[4-(*tert*-Butoxycarbonyl)-1-piperazino]methyl]polystyrene.** A mixture of 50 g of (chloromethyl)polystyrene[24] (0.5% DVT, 2.29 mequiv of Cl/g), 42.84 g of *tert*-butyl piperazine-1-carboxylate, and 14.86 g of diisopropylethylamine was refluxed with vigorous stirring in 750 mL of $CH_2Cl_2$ for 5 days. The resin was filtered and washed with three 300-mL portions of the following solvents in the order given: $CH_2Cl_2$, dioxane, $H_2O$, dioxane, $CH_2Cl_2$, toluene. It was necessary to allow about 10 min for each wash solvent to penetrate the beads. Following the last dichloromethane washing, the resin was dried overnight in a vacuum oven at 40 °C to give 61 g of polymer, IR (KBr) 1695 $cm^{-1}$ (C=O). Anal. Calcd (for complete displacement of chloride): N, 4.76. Found: N, 4.34; Cl, 0.05.

**(1-Piperazinomethyl)polystyrene. (A) Deblocking of Boc Derivative.** Gaseous HCl was bubbled through 1500 mL of dioxane at such a rate that the gas was just absorbed before the bubbles reached the surface of the liquid. The temperature rose to about 50 °C. Before use the temperature was allowed to fall to room temperature. To 61 g of [[4-(*tert*-butoxycarbonyl)-1-piperazyl]methyl]polystyrene (0.5% DVT, 4.34% N) was added in one portion 750 mL of the dioxane–HCl reagent. Gas evolution was noted immediately. The mixture was stirred for 1 h and filtered, and the resin was treated in the same manner with the second 750 mL of dioxane–HCl reagent. After being filtered and washed with three 300-mL portions of $CH_2Cl_2$ the resin was stirred with three 300-mL portions of $Et_3N$–$CH_2Cl_2$ (30/70) allowing 30–45 min for each washing. The filtered resin was then stirred with three 300-mL portions of the following solvents in the order given: $CH_2Cl_2$, dioxane, $H_2O$, dioxane, $CH_2Cl_2$, toluene. The resin was dried in an oven at 40 °C under reduced pressure overnight. Since elemental analysis showed considerable residual chloride (N, 4.72%; Cl, 5.12%), the resin was soaked again in $Et_3N$–dioxane (30/70) for 3 days and then washed in the usual manner three times with 300-mL portions of the following nonchlorinated solvents in the order given: dioxane, dioxane–$H_2O$ (70/30), $H_2O$, dioxane, toluene, MeOH. The resin (52 g) was dried in a vacuum oven at 40 °C overnight. Anal. Calcd for complete deblocking: N, 5.78. Found: N, 5.65; Cl, <0.1. A similar reaction carried out on a commercial sample of polystyrene (XE-305, 8.59% Cl, 2.42 mequiv of Cl/g) gave first the Boc derivative [4.19% N (calcd 4.98%), <0.1% Cl] and subsequently by HCl–dioxane treatment the secondary amine (4.74% N, <0.1% Cl).

**(B) Direct Amination.** A mixture of 10 g of (chloromethyl)polystyrene (0.5% DVT, 9.46% Cl, 2.66 mequiv of Cl/g) and 22.9 g of piperazine was heated under an atmosphere of $N_2$ in an oil bath at 60–70 °C with stirring in 300 mL of toluene overnight. The resin was filtered, and stirred for 2 days in 300 mL of $Et_3N$–dioxane (50/50), and then washed with the following solvents in the order given, allowing 10 min for each washing: 3 × 300 mL of dioxane, 3 × 300 mL of dioxane–$H_2O$ (75/25), 3 × 300 mL of dioxane, 3 × 300 mL of toluene, 3 × 300 mL of methanol. The resin (9.5 g) was dried in an oven at 40 °C under reduced pressure. Anal. Calcd (for complete displacement of chloride): N, 6.57. Found: N, 5.38; Cl, <0.1. A similar reaction carried out on a commercial sample of polystyrene (XE-305, 8.59% Cl, 2.42 mequiv of Cl/g) gave a reagent for which elemental analysis showed 4.97% N (calcd 6.05%) and 0.35% Cl. Related resins were made similarly (see Table I).

**Piperidino-Functionalized Polystyrene (10).** From 10 g of (chloromethyl)polystyrene (0.5% DVT, 9.46% Cl, 2.66 mequiv of Cl/g) and 55.86 g of 1,3-bis(4-piperidino)propane in 300 mL of toluene at 60–70 °C under $N_2$ according to the method described for the piperazino analogue (direct amination) there was obtained 11.6 g of the piperidino resin. Anal. Calcd for complete displacement of chloride: N, 5.09. Found: N, 4.1; Cl, <0.1.

**9-Fluorenylmethyl Carbamate.** To a stirred mixture of 5 g of 9-fluorenylmethanol and 3.3 g of NaOCN in 60 mL of benzene there was slowly added 3.9 g of $CF_3CO_2H$. The resulting mixture was stirred for 3 h, and the precipitate which separated was filtered and washed with Skelly B, $H_2O$, and again with Skelly B. Recrystallization of the air-dried solid from acetone gave 5.6 g (92%) of the carbamate as tiny white needles: mp 200–201 °C; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 4.07 (s, 3, $CHCH_2$), 6.48 (br s, 2 $NH_2$, erasable by $D_2O$), 7.18–7.85 (m, 8, aryl). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.58; N, 5.85. Found: C, 75.02; H, 5.75; N, 5.62.

**9-Fluorenylmethyl *p*-chlorocarbanilate** was obtained from 9-fluorenylmethanol and *p*-chlorophenyl isocyanate in benzene with 1 drop of $Et_3N$: 90% yield; white crystals ($C_6H_6$); mp 183.5–185 °C. Anal. Calcd for $C_{21}H_{16}ClNO_2$: C, 72.10; H, 4.61; N, 4.00. Found: C, 72.02; H, 4.85; N, 3.98.

**Deblocking–Scavenging of $FmocNH_2$ in Dioxane by Piperazinopolystyrene 4.** A 0.1-g sample of piperazinopolystyrene 4 (XE-305), 1.69 mequiv NH/g) was weighed into each of ten small vials[25] fitted with magnetic stirrers. There were added 1 mL of dioxane and 0.0040 g of $FmocNH_2$ and the contents stirred at room temperature. At the desired time the contents of one of the vials

(23) Melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 237B instrument and NMR spectra on Varian A-60 and Perkin-Elmer R-12 instruments 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. Dioxane was distilled over $LiAlH_4$ to remove peroxides. If peroxides were not removed, this solvent appeared to degrade the piperazino reagent 4.

(24) Stewart, J. M.; Young, J. D. "Solid Phase Peptide Synthesis"; W. H. Freeman: San Francisco, 1969; p 27.

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

was filtered and the resin washed with three 10-mL portions of dioxane. The combined filtrate was made up to a volume of 100 mL in a volumetric flask, 1 mL of this solution was diluted to 10 mL, and the concentration of remaining dibenzofulvene was determined by ultraviolet analysis. The urethane disappeared after 24 h, and thereafter the amount of dibenzofulvene remaining relative to the original amount at various times was found to be as follows: 2 days, 84.7%, 4 days, 75.9%; 6 days, 62.3%; 8 days, 52.8%; 9 days, 47.6%. A duplicate run showed 52.4% dibenzofulvene remaining after 9 days. The decrease in the concentration of dibenzofulvene was assumed to be due to scavenging by the polymeric reagent. This was confirmed by regeneration of the spent reagent (see below). With a sample of polymeric reagent 4 (0.5% DVT, 2.02 mequiv of NH/g) the extent of scavenging amounted to 71.5% after 13 days.

**Regeneration of Spent (1-Piperazinomethyl)polystyrene.** A mixture of 10 g of (1-piperazinomethyl)polystyrene (XE-305, 1.69 mequiv of NH/g) and 11.82 g of 9-fluorenylmethyl *p*-chlorocarbanilate in 100 mL of dioxane was stirred at room temperature for 5 days. The mixture was filtered and the resin was washed with the following solvents in the order given: 3 × 50 mL of dioxane, 3 × 50 mL of dioxane–$H_2O$ (50/50), 3 × 50 mL of $H_2O$, 3 × 50 mL of dioxane–$H_2O$ (50/50), 3 × 50 mL of dioxane. The resin was dried in a vacuum oven overnight at 40 °C. For confirmation that most of the available NH sites were occupied, a sample (0.1 g) of the saturated resin was added to a solution of 0.004 g of $FmocNH_2$ in 1 mL of dioxane and the mixture stirred at room temperature for 5 days. After this period the mixture was filtered, and the filtrate was diluted with dioxane to 100 mL and subjected to UV analysis for dibenzofulvene as described previously. Analysis revealed the presence of 86% dibenzofulvene. The small amount of scavenging which occurred (14%) could have arisen due to sloughing off of DBF during the extended washing procedure. In fact, DBF was detected in the filtrates from the washings by TLC and UV analysis. A 10-g sample of the DBF-saturated resin was added to a solution of 6.76 g of NaOH in 100 mL of dioxane–$H_2O$ (50/50) and the mixture stirred at room temperature for 3 days. A workup according to the solvent washing procedure described for the saturation step gave 10 g of regenerated secondary amine resin. As a test of its capacity, 0.2 g of regenerated resin was added to a solution of 0.0118 g of 9-fluorenylmethyl carbanilate in 1 mL of $Me_2SO$-$d_6$. After being stirred for 24 h, the mixture was filtered and washed with two 0.5-mL portions of $Me_2SO$-$d_6$ and the filtrate transferred to an NMR tube. Analysis revealed the presence of 50% dibenzofulvene (50% scavenging) relative to *p*-chloroaniline. A similar test on a virgin sample of the piperazino resin showed 50–65%; scavenging.

**Double Treatment of 9-Fluorenylmethyl *p*-Chlorocarbanilate with (1-Piperazinomethyl)polystyrene.** A sample (0.3 g) of (1-piperazinomethyl)polystyrene (XE-305, 1.69 mequiv of NH/g) was added to a solution of 9-fluorenylmethyl *p*-chlorocarbanilate in 1.5 mL of $Me_2SO$-$d_6$ and the mixture stirred at room temperature for 24 h. Filtration and washing with two 0.5-mL portions of $Me_2SO$-$d_6$ followed by transfer to an NMR tube showed by $^1H$ NMR analysis that scavenging had occurred to the extent of 65%. A new 0.3-g portion of polymeric reagent was added, and after a second 24-h period a workup in the same manner gave a solution which by $^1H$ NMR analysis showed the presence of no significant amount of dibenzofulvene (<5%).

**Hydrogenolysis of 9-Fluorenylmethyl-Substituted (Piperazinomethyl)polystyrene.** To 20 mL of MeOH (cooled in an ice bath) were added 200 mg of 10% Pd/C catalyst (Pfaltz and Bauer) and 200 mg of $Pd(OAc)_2$. The mixture was stirred at room temperature and 660 mg of ammonium formate added. After a few minutes the yellow color due to $Pd(OAc)_2$ disappeared as highly active Pd metal precipitated on the commercial catalyst.[26] At this point 5 g of a sample of (1-piperazinomethyl)polystyrene (0.5% DVT, 2.02 mequiv of NH/g) which had been treated previously for 24 h with 0.35 g of 9-fluorenylmethyl *p*-chlorocarbanilate was added and the mixture stirred at room temperature for 5 days. TLC analysis showed the presence of both 9-methylfluorene and piperazine. The mixture was filtered and washed with MeOH, the filtrate evaporated, and the residue washed with water to give 0.095 g of 9-methylfluorene [mp 45–47 °C (lit.[21b] mp 44–45 °C)], identified by TLC, IR, and $^1H$ NMR comparison with an authentic sample. The amount of 9-methylfluorene obtained represents 85% of that expected on assuming 60% scavenging during the initial deblocking–scavenging process in dioxane as the solvent.

***tert*-Butyl 4-(*p*-Vinylbenzyl)piperazine-1-carboxylate.**[27] A solution of 15 g of *tert*-butyl piperazine-1-carboxylate and 9 mL of *N,N*-diisopropylethylamine in 18 mL of $CH_2Cl_2$ was heated to reflux and treated dropwise with a solution of 8.1 g of *p*-vinylbenzyl chloride[28] in 5 mL of $CH_2Cl_2$ to which a few milligrams of *tert*-butylcatechol had been added. After being refluxed for 5 h, the reaction mixture was cooled and extracted with three 20-mL portions of 5% NaOH and five 20-mL portions of $H_2O$. Drying ($K_2CO_3$) and evaporation of solvent gave an orange oil which crystallized on standing. Two recrystallizations from aqueous ethanol gave 14.1 g (88%) of the carbamate as white crystals: mp 78–80 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.44 (s, 9 H, $Me_3C$), 2.35 (br t, 4 H, $CH_2CH_2NCH_2$), 3.4 (m, 6 H, $CH_2NCO$, $ArCH_2N$), 5.25, 5.75, 6.6, 6.9 (ABX, 3 H, $CH{=}CH_2$, $J_{AB}$ = 18 Hz, $J_{BX}$ = 11 Hz, $J_{AB}$ = 2 Hz), 7.35 (br s, 4 H, aryl). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.25. Found: C, 71.26; H, 8.83; N, 9.16.

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**Registry No.** *tert*-Butyl azidoformate, 1070-19-5; piperazine, 110-85-0; *tert*-butyl piperazine-1-carboxylate, 57260-71-6; styrene-*p,p'*-divinylterphenyl copolymer, 84433-25-0; styrene, 100-42-5; *p,p'*-divinylterphenyl, 3365-22-8; 1,3-bis(4-piperidino)propane, 17252-51-6; 9-fluorenylmethanol, 24324-17-2; 9-fluorenylmethyl carbamate, 84418-43-9; *p*-chlorophenyl isocyanate, 104-12-1; 9-fluorenylmethyl *p*-chlorocarbanilate, 68089-94-1; *p*-vinylbenzyl chloride, 1592-20-7; *tert*-butyl 4-(*p*-vinylbenzyl)-piperazine-1-carboxylate, 84433-27-2.

(26) This simple in situ method of generating a highly active supported palladium catalyst has proved to be of general value in other transfer hydrogenolyses involving formic acid and 1,4-cyclohexadiene as well as ammonium formate.

(27) No improvement in the supported piperazino reagents was noted when they were prepared by co-polymerization of this vinyl monomer with styrene in the presence of 8 or DVB.

(28) Tanimoto, S.; Miyake, T.; Okano, M. *Syn. Commun.* **1974**, *4*, 193. For more recent techniques for the synthesis of this useful intermediate see: (a) Nishikubo, T.; Iizawa, T.; Kobayashi, K.; Okawara, M. *Tetrahedron Lett.* **1981**, 3873. (b) Kondo, S.; Ohtsuka, T.; Ogura, K.; Tsuda, K. *J. Macromol. Sci., Chem.* **1979**, *A13*, 767. (c) Arshady, R.; Kenner, G. W.; Ledwith, A. *Makromol. Chem.* **1976**, *177*, 2911. (d) Arshady, R.; Ledwith, A. *Ibid.* **1978**, *179*, 819.