Solubilizing Influence of 2,7-Bis(trimethylsilyl) Substitution on the Fmoc Residue†

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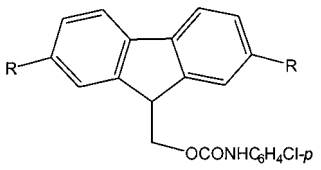
Recently Nowick and co-workers[1] described the synthesis of the 2,6-di-*tert*-butyl-9-fluorenemethyloxycarbonyl group (Fmoc* or Dtb-Fmoc) as a substitute for the Fmoc function[2] in cases where the latter led to highly insoluble derivatives. It was shown for some systems that such substitution enhanced solubilities by 1−2 orders of magnitude.[3]

Faced with a similar problem, we also examined the Dtb-Fmoc group with analogous results. In addition, we investigated the related 2,7-bis(trimethylsilyl) (Bts) systems and found some Bts-substituted carbanilates to be about 3 times more soluble than the Dtb analogues. The synthesis of key alcohol **5** is outlined in Scheme 1.

Solubilities were examined for the *p*-chlorophenyl carbanilates derived from **5** and the Fmoc and Dtb-Fmoc analogues **6**. For **6a**−**c** solubilities per 100 mL of DCM were 3.34, 6.74, and 22.3 g, respectively. While the Dtb-Fmoc group was more sluggishly deblocked than the Fmoc function, presumably due to a combination of inductive and steric factors, the Bts-Fmoc and Fmoc groups were nearly balanced, perhaps because steric factors were opposed by anionic stabilization[4] provided by the silicon residues. Comparisons are given in Table 1.



6a, R =H
b, R = *t*-Bu
c, R = Me_3Si

Table 1. Time for Complete Deblocking of Substituted Urethanes (U−PCA) by Various Amines[a]

	deblocking time		
base	U = Fmoc	Bts-Fmoc	Dtb-Fmoc
piperidine[b]	<3 min	<3 min	12 min
ethanolamine	45 min	90 min	4 h
morpholine[b]	75 min	190 min	10 h
tert-butylamine	5 h	4.5 h	20 h

[a] A mixture of urethane (0.05 mmol) in a solution prepared from an equal volume of base (2.5 mmol, 50 equiv) and dichloromethane was stirred at room temperature. The course of the reaction was monitored by TLC with an eluant consisting of Skelly B−ether (3:1) [b] For these amines, a significant amount of the amine−dibenzofulvene adduct had formed during the periods indicated.

The Bts-Fmoc function was also subject to deblocking under conditions of catalytic hydrogenolysis as previously reported[5] for the Fmoc function. Although stable toward acetic acid, the Bts-Fmoc function was converted, as expected,[6] to the Fmoc function itself, upon treatment with trifluoroacetic acid.

In summary, substitution of the 2,7-di-*tert*-butyl- and especially the 2,7-bis(trimethylsilyl)-Fmoc functions for the Fmoc group itself is shown to significantly enhance the solubility in a solvent such as methylene dichloride. In addition, in the Bts-Fmoc case the rate of deblocking by piperidine followed closely that of the Fmoc group, whereas deblocking of the Dtb-Fmoc was somewhat slower. These properties could be of practical importance in the manipulation of highly insoluble Fmoc derivatives, as already shown by Nowick[1] for the Dtb-Fmoc function.

Experimental Section

2,7-Di-*tert*-butyl-9-fluorenemethyl *p*-Chlorocarbanilate (Dtb-Fmoc-PCA), 6b. A mixture of 0.916 g of 2,7-di-*tert*-butyl-9-fluorenemethanol[7] and 0.456 g of *p*-chlorophenyl isocyanate in 4.0 mL of dry benzene was treated as described for the silyl analogues. Workup gave, after recrystallization from Skelly B/acetone (4:1), 1.08 g (81.2%) of the pure carbanilate as white crystals, mp 193−4 °C. IR (KBr): 3400 (NH), 1735 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (s, 18), 4.22 (t, 1), 4.60 (d, 2), 6.63 (b, 1), 7.18−7.55 (m, 10). Anal. Calcd for $C_{29}H_{32}NO_2Cl$: C, 75.39, H, 6.98; N, 3.03. Found: C, 75.36, H, 6.87; N, 3.01.

Piperidine Cleavage of 2,7-Di-*tert*-butyl-9-fluorenemethyl *p*-Chlorocarbanilate, 6b. A solution of 0.3 g of Dtb-Fmoc-PCA in 6.5 mL of piperidine was stirred at room temperature for 30 min and poured into 50 mL of cold water. The suspended mixture was stirred for 20 min and the precipitate was removed by filtration, rinsed with water (2 × 5 mL), and dried in air to give 0.24 g (98.0%) of the crude ***N*-(2,7-di-*tert*-**

† Abbreviations used: Bts-Fmoc = 2, 7-bis(trimethylsilyl)-9-fluorenemethyloxycarbonyl; DCM = dichloromethane; Dtb-Fmoc = Fmoc* = 2, 7- di-*tert*-butyl-9-fluorenemethyloxycarbonyl; Fmoc = 9- fluorenemethyloxycarbonyl; NBS = N-bromosuccinimide; PCA = *p*-chloroaniline; Skelly B = saturated hydrocarbon solvent, bp range 60-70 °C; Skelly F = saturated hydrocarbon solvent, bp range 30-60 °C; TFA = trifluoroacetic acid.

(1) Stigers, K. D.; Koutroulis, M. R.; Chung, D, M.; Nowick, J. S. *J. Org. Chem.* **2000**, *65*, 3858.

(2) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

(3) In addition to the examples cited by Nowick and co-workers, the 2,7-di-*tert*-butyl substitution pattern was found effective in solubility enhancement in connection with thioxanthenes. See: Carpino, L. A.; Gao, H.-S.; Ti, G.-S.; Segev, D. *J. Org. Chem.* **1989**, *54*, 5887.

(4) (a) Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1968**, *90*, 4478. (b) Eaborn, C.; Eidenschink, R.; Jackson, P. M.; Walton, D. R. M. *J. Organomet. Chem.* **1975**, *101*, C40. (c) Zhang, S.; Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1995**, *117*, 602.

(5) (a) Carpino, L. A.; Tunga, A. *J. Org. Chem.* **1986**, *51*, 1930. (b) Martinez, J.; Tolle, J. C.; Bodanszky, M. *J. Org. Chem.* **1979**, *44*, 3596. (c) Atherton, E.; Bury, C.; Sheppard, R. C.; Williams, B. J. *Tetrahedron Lett.* **1979**, *20*, 3041.

(6) (a) Chan, T. H.; Fleming, I. *Synthesis*, **1979**, 761. (b) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.; (c) Gilman, H.; Marshall, F. J. *J. Am. Chem. Soc.* **1949**, *71*, 2066. (d) Gilman, H.; Nobis, J. F. *J. Am. Chem. Soc.* **1950**, *72*, 2629.; (e) Häbich, D.; Ettenberger, F. *Synthesis* **1978**, 755.

(7) In contrast to Nowick's method, our synthesis of 2,7-di-*tert*-butyl-9-fluorenemethanol involved modification of our earlier method[8] by substitution of KH for NaH and in situ reduction of the crude aldehyde by $NaBH_4$. The properties of the two samples were in agreement. For the fluorene precursor our method was the same as Nowick's, except that CH_2Cl_2 was used as solvent in place of CS_2 and the crude product was passed through a short column of alumina to remove inorganic byproducts prior to recrystallization.

(8) Carpino, L. A. *J. Org. Chem.* **1980**, *45*, 4250.

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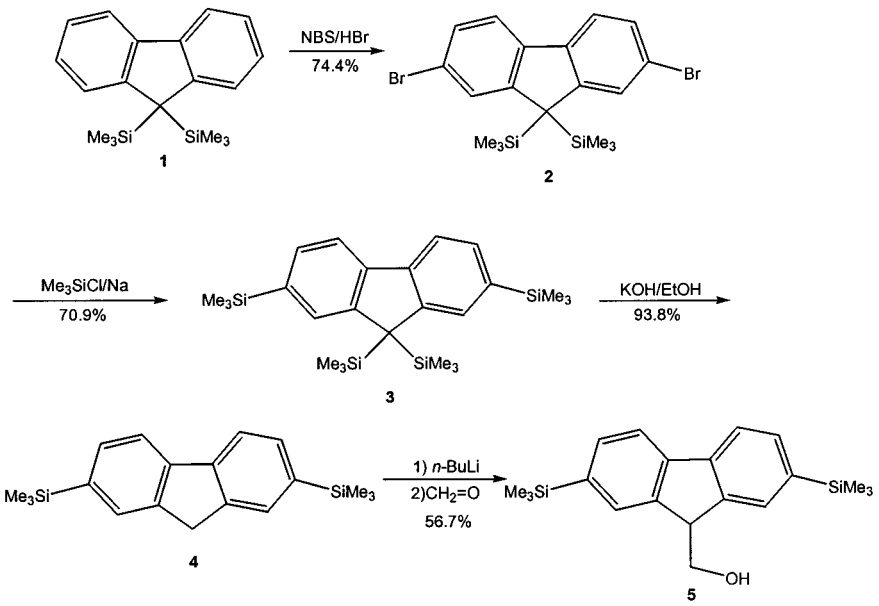
Scheme 1



butyl-9-fluorenemethyl)piperidine[9] as an off-white solid. Recrystallization from methanol/chloroform (2:1) afforded 0.20 g (82.01%) of the pure amine as colorless needles, mp. 159−160 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 18), 1.50−1.82 (m, 6), 2.55−2.70 (m, 6), 4.02 (t, 1), 7.34−7.82 (m, 6). Anal. Calcd for $C_{27}H_{37}N$: C, 86.34; H, 9.93. Found: C, 86.57; H, 9.84.

2,7-Dibromo-9,9-bis(trimethylsilyl)fluorene, 2. To a suspension of 4.0 g of 9,9-bis(trimethylsilyl)fluorene[10] and 5.0 g of *N*-bromosuccinimide in 90 mL of glacial acetic acid was added 1 mL of 48% hydrobromic acid over a period of 3 min. The reactants dissolved as a new solid separated. After 6 h, 200 mL of water was added slowly and the solid was filtered, rinsed with water, and dried in air to afford 6.04 g (99.6%) of the crude dibromide as a yellowish solid. Recrystallization from acetone gave 4.51 g (74.4%) of 2,7-dibromo-9,9-bis(trimethylsilyl)fluorene as white needles, mp 201−202 °C. ^{1}H NMR ($CDCl_3$): δ −0.07 (s, 18), 7.25−7.93 (m, 6). Anal. Calcd for $C_{19}H_{24}Br_2Si_2$: C, 48.75; H, 5.16. Found: C, 49.12; H, 5.27.

2,7,9,9-Tetrakis(trimethylsilyl)fluorene, 3. A mixture of 4.0 g of 2,7-dibromo-9,9-bis(trimethylsilyl)fluorene and 4.0 mL of freshly distilled chlorotrimethylsilane in 70 mL of toluene was added slowly to molten sodium (1 g of finely cut sodium in 40 mL of boiling toluene). The mixture was refluxed for 12 h and cooled in an ice bath. Ice chips were added slowly to destroy the excess sodium. The mixture was then washed with water (2 × 70 mL) and the pooled aqueous layer was extracted with ether (2 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo to give 3.63 g (93.6%) of the crude tetrasilane as an off-white solid. Recrystallization form methanol afforded 2.75 g (70.9%) of the pure silane derivative as white needles, mp 141−142 °C. ^{1}H NMR ($CDCl_3$): δ −0.10 (s, 18), 0.32 (s, 18), 7.20−8.00 (m, 6). Anal. Calcd for $C_{25}H_{42}Si_4$: C, 66.00; H, 9.31. Found: C, 66.04; H, 9.21.

2,7-Bis(trimethylsilyl)fluorene, 4. To a suspension of 0.5 g of 2,7,9,9-tetrakis(trimethylsilyl)fluorene in 15 mL of 95% ethanol was added 1.5 mL of 10% KOH. The mixture was refluxed for 2 h and cooled in an ice bath for 1 h. The precipitated crystals were removed by filtration, rinsed with water (2 × 5 mL), dried in air, and recrystallized from methanol to give 0.32 g (93.8%) of the pure fluorene derivative as colorless crystals, mp 117−118 °C. ^{1}H NMR ($CDCl_3$): δ 0.31 (s, 18), 3.90 (s, 2), 7.20−7.90 (m, 6). Anal. Calcd for $C_{19}H_{26}Si_2$: C, 73.48; H, 8.44. Found: C, 73.23; H, 8.43.

2,7-Bis(trimethylsilyl)fluorene-9-methanol, 5. To an ice-cold solution of 6.0 g of 2,7-bis(trimethylsilyl)fluorene in 100 mL of dry ether was added dropwise 18 mL of 1.3 M *n*-butyllithium at 0 °C. The mixture was stirred at room temperature for 30 min and cooled in an ice bath. Gaseous formaldehyde, generated by heating 2.5 g of dried paraformaldehyde at 170 °C, was passed through a wide tube (8 mm) into the reaction mixture with the aid of a slow stream of nitrogen until the black color had disappeared. The mixture was washed with half-saturated NH_4Cl (50 mL) and water (50 mL). The pooled aqueous layer was extracted with ether (2 × 50 mL) and the combined organic extracts were dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (230−400 mesh, 5 × 60 cm packed column) with an eluant consisting of Skelly B/ether (3:1), to afford 3.73 g (56.7%) of the alcohol as a white solid. Recrystallization from Skelly B gave 3.30 g (50.16%) of the pure alcohol as colorless crystals, mp 112.5−113 °C. IR (KBr): 3250 cm^{-1} (br, OH). ^{1}H NMR ($CDCl_3$): δ 0.32 (s, 18), 1.57 (br s, 1), 4.03−4.17 (m, 3), 7.20−7.90 (m, 6). Anal. Calcd for $C_{20}H_{28}Si_2O$: C, 70.53; H, 8.29. Found: C, 70.44; H, 8.26.

2,7-Bis(trimethylsilyl)-9-fluorenemethyl *p*-Chlorocarbanilate (Bts-Fmoc-PCA), 6c. A mixture of 2.5 g of 2,7-bis(trimethylsilyl)fluorenemethanol and 1.13 g of *p*-chlorophenyl isocyanate in 20 mL of dry benzene was heated in an oil bath at 80 °C for 4 h. The mixture was cooled to room temperature, treated with 60 mL of Skelly B, and stirred for another 30 min. The precipitate was removed by filtration to give 3.60 g (99.3%) of the crude urethane as a white solid. Recrystallization from Skelly B gave 3.14 g (86.3%) of the carbanilate as white crystals, mp 162.5−163 °C. IR (KBr): 3240 (NH), 1710 (C═O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.30 (s, 18), 4.28 (t, 1), 4.58 (d, 2), 6.60 (b, 1), 7.15−7.90 (m, 10). Anal.Calcd for $C_{27}H_{32}NO_2Si_2Cl$: C, 65.62; H, 6.53; N, 2.83. Found: C, 65.80; H, 6.66; N, 2.80.

2,7-Bis(trimethylsilyl)-9-fluorenemethyl Carbanilate (Bts-Fmoc-aniline), 6c, Cl-p = H. A mixture of 0.71 g of 2,7-bis(trimethylsilyl)fluorene-9-methanol and 0.22 mL of phenyl isocyanate in 4 mL of dry benzene was treated as described for the *p*-chloro analogue. Workup gave 0.81 g (87.13%) of the urethane as white crystals, mp 178−179 °C. IR (KBr): 3240 (NH), 1710 (C═O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 18), 4.30 (t, 1), 4.58 (d, 2), 6.61 (b,1), 6.90−7.90 (m, 11). Anal. Calcd for $C_{27}H_{33}NO_2Si_2$: C, 70.54; H, 7.24; N, 3.05. Found: C, 70.40; H, 7.01; N, 2.92.

Piperidine Cleavage of 2,7-Bis(trimethylsilyl)-9-fluorenemethyl *p*-Chlorocarbanilate, 6c. A solution of 0.4 g of Bts-Fmoc-PCA in 7.6 mL of piperidine was stirred at room temperature for 30 min and poured into 125 mL of cold water. The precipitate was removed by filtration and the filtrate was extracted with ether (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evapo-

(9) Nowick and co-workers inferred the presence of this byproduct of the deblocking process but did not isolate and purify the material.

(10) Eaborn, C.; Shaw, R. A. *J. Chem. Soc.* **1955**, 1420.

rated under reduced pressure to give 0.10 g (96.9%) of yellow solid, identified by NMR spectroscopy as *p*-chloroaniline. The solid (0.31 g, 94.0%, mp 105−108 °C) precipitated from the original solution by the addition of water was recrystallized from methanol to give 0.25 g (75.8%) of ***N*-[2,7-bis(trimethylsilyl)-9-fluorenemethyl]piperidine**, mp 107−108 °C. ^{1}H NMR ($CDCl_3$): δ 0.32 (s, 18), 1.47−1.80 (m, 6), 2.50−2.68 (m, 6), 4.05 (t, 1), 7.43−7.96 (m, 6). Anal. Calcd for $C_{25}H_{37}NSi_2$: C, 73.64, H, 9.15; N, 3.44. Found: C, 73.38; H, 8.94, N, 3.35.

Hydrogenolysis of 2,7-Bis(trimethylsilyl)-9-fluorenemethyl Carbanilate, 6c, Cl-p = H. To a solution of 0.2 g of 2,7-bis(trimethylsilyl)-9-fluorenemethyl carbanilate in 15 mL of 100% ethanol and 15 mL of EtOAc was added 20 mg of 10% palladium on charcoal at 0 °C. The heterogeneous mixture was stirred under a hydrogen atmosphere (1 atm) for 20 h. The catalyst was filtered and rinsed with EtOAc (2 × 5 mL). The combined filtrate was washed with saturated NH_4Cl (2 × 20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. After evaporating the solvent in vacuo, the residue (0.14 g) was recrystallized from 95% ethanol to afford 0.11 g (78.0%) of **2,7-bis(trimethylsilyl)-9-methylfluorene** as white needles, mp 106.5−108 °C. ^{1}H NMR ($CDCl_3$): δ 0.34 (s, 18), 1.58 (d, 3), 3.96 (q, 1), 7.4−7.0 (m, 6). Anal. Calcd for $C_{20}H_{28}Si_2$: C, 74.00; H, 8.69. Found: C, 73.91; H, 8.51.

Protonolysis of 2,7-Bis(trimethylsilyl)-9-fluorenemethyl *p*-Chlorocarbanilate, 6c, in Trifluoracetic Acid. To a solution of 0.3 g of Bts-Fmoc-PCA in 8 mL of CH_2Cl_2 was added dropwise a solution of 0.5 mL (10.7 equiv) of trifluoroacetic acid in 3.0 mL of methylene chloride over a period of 10 min. The mixture was stirred at room temperature for 12 h, washed with water (2 × 10 mL), and neutralized with saturated $NaHCO_3$ (2 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated in vacuo to give 0.19 g (89.5%) of crude 9-fluorenemethyl *p*-chlorocarbanilate, **6a**. Recrystallization from EtOAc−Skelly B (2:1) gave 0.16 g (75.3%) of the pure Fmoc-PCA as colorless needles, mp 184−185 °C (lit.[11] mp 183.5−185 °C), identified by mixture melting point and IR and NMR spectral comparisons with an authentic sample.

2,7-Bis(trimethylsilyl)-9-fluorenemethyl Chloroformate, 5, H = COCl. To a stirred solution of 1 mL of liquid phosgene, condensed at −78 °C, in 10 mL of dry THF was added dropwise a solution of 2.0 g of 2,7-bis(trimethylsilyl)-9-fluorenemethanol in 20 mL of dry THF at 0 °C over a period of 30 min. The mixture was stirred for another hour at 0 °C. Excess phosgene along with the solvent was removed by a water aspirator in a hood to afford an oil which was triturated with Skelly F to give 2.3 g (97.1%) of the crude choroformate as white crystals. Recrystallization from Skelly F gave 2.02 g (85.23%) of the pure chloroformate as colorless crystals, mp 64−66 °C. IR (KBr): 1770 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ 0.37 (s, 18), 4.32 (t, 1), 4.57 (d, 2), 7.50−7.90 (m, 6). Anal. Calcd for $C_{21}H_{27}O_2Si_2Cl$: C, 62.58; H, 6.75. Found: C, 62.79; H, 6.74.

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