3,4-Bis(trimethylsilyl)-1*H*-pyrrole: a versatile building block for unsymmetrically 3,4-disubstituted pyrroles

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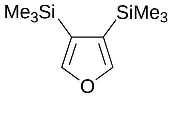
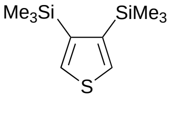
3,4-Bis(trimethylsilyl)-1*H*-pyrrole 1c functions as a versatile building block for the construction of unsymmetrically 3,4-disubstituted pyrroles through the use of stepwise regiospecific *ipso* mono-halogenation, Sonogashira cross-coupling reactions and Suzuki cross-coupling reactions; the advantages of this strategy lie in its stepwise manner as well as in its prospect of yielding 3,4-disubstituted pyrroles with diverse substitution patterns.

Pyrroles occur abundantly as structural units in many non-natural and natural molecules, including conducting poly(pyrroles),[1] antimitotics,[2] antitumour agents,[3] fungicides,[4] marine alkaloids[5] and porphyrins.[6] In the literature, several approaches to 3,4-disubstituted pyrroles have been recorded.[7–14] These approaches are generally not suitable for pyrroles containing elaborate substituents. With routes for the preparation of structurally diversified 3,4-disubstituted furans and thiophenes[15] from 3,4-bis(trimethylsilyl)furan **1a** and 3,4-bis(trimethylsilyl)thiophene **1b** now at our disposal, we focused our attention on the synthesis of 3,4-disubstituted pyrroles. Herein we report our strategy for synthesizing unsymmetrically 3,4-disubstituted pyrroles utilizing 3,4-bis(trimethylsilyl)-1*H*-pyrrole **1c** as a building block.



1a



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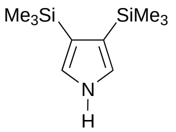


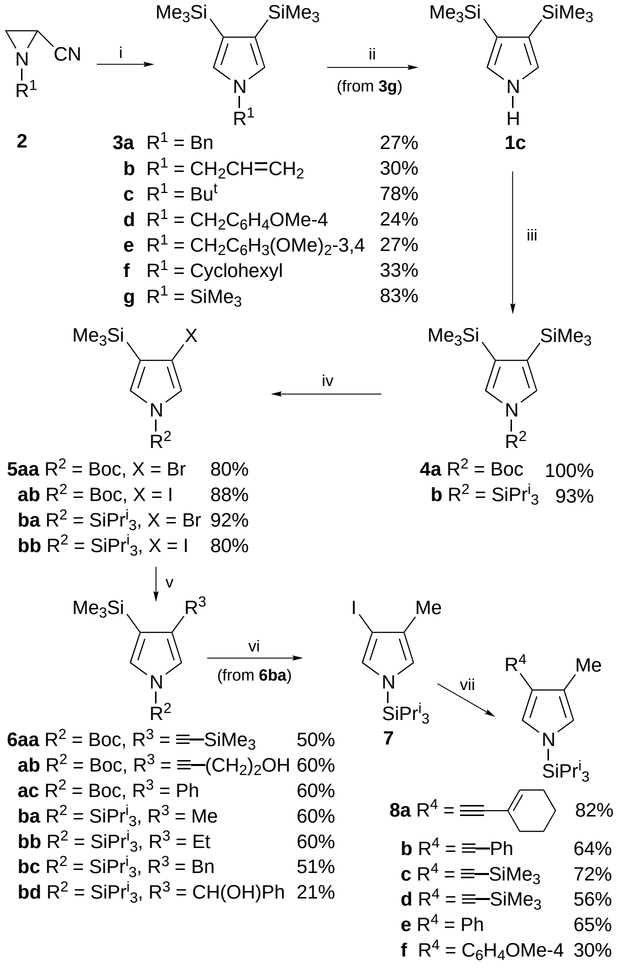
1c

By utilizing the [2 + 3] cycloaddition reported by La Porta *et al.*,[16] a number of *N*-protected 3,4-bis(trimethylsilyl)pyrroles were synthesized (Scheme 1) *via* thermal reactions of 2-cyanoaziridines **2**[17] with bis(trimethylsilyl)acetylene.† It is noteworthy that the preparation of **3c**, **3f** and **3g** did not require the use of sealed tubes. Amongst all the *N*-protected pyrroles prepared, only 1,3,4-tris(trimethylsilyl)pyrrole **3g** could be deprotected by a simple protodesilylation in MeOH, providing the desired molecule **1c** in good yield.

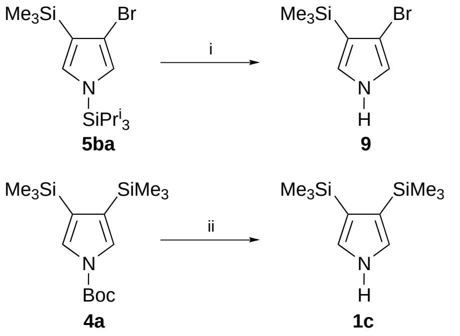
Due to the instability of **1c** as well as to the necessity for further transformation, **4a** and **4b** were synthesized by employing *tert*-butoxycarbonyl[18] and triisopropylsilyl groups[11*b,c*] as *N*-protecting groups. The role of a trimethylsilyl group in the *ipso*-directing substitution of aromatic compounds has been well documented.[19] In order to test the versatility of **4a** and **4b** in the realization of 3,4-disubstituted pyrroles, and the *ipso*-directing role of the trimethylsilyl groups, several halides **5** were regiospecifically prepared *via* literature procedures (Scheme 1).[20] Sonogashira reaction[21] was utilized to convert **5ab** into alkynes **6aa** and **6ab**. On the other hand, **5ab** was also successfully transformed to **6ac** by way of a Suzuki cross-coupling reaction.[22] A combined procedure involving lithiation and alkylation also converted **5ba** to **6ba**, **6bb**, **6bc** and **6bd**. In order to complete our initial plan of securing unsymmetrically 3,4-disubstituted pyrroles, **6ba** was allowed to undergo a regiospecific iodination, yielding iodide **7**. Sonogashira reaction of **7** again gave alkynes **8a–d**. Moreover, compounds **8e** and **8f** were also obtained from **7** *via* a Suzuki reaction pathway.

It is noteworthy that mild deprotection of **5ba** and **4a** was accomplished by using NaOMe in MeOH, affording 1*H*-pyrroles **9** and **1c**, respectively (Scheme 2).

In conclusion, making use of 3,4-bis(trimethylsilyl)-1*H*-pyrrole **1c** as a building block, an efficient and stepwise



Scheme 1 *Reagents and conditions*: i, (for **3a**, **3b**, **3d** and **3e**) Me$_3$SiC≡CSiMe$_3$, DBU, PhMe, sealed tube, 170 °C; (for **3c**, **3f** and **3g**) Me$_3$SiC≡CSiMe$_3$, xylene, reflux; ii, MeOH, 95%; iii, (for **4a**) BOC$_2$O, DMAP, CH$_2$Cl$_2$, 30 min; (for **4b**) BuLi, THF, −78 °C, 30 min, then Pr$^i_3$SiCl; iv (for **5aa**) NBS, THF, 0 °C, 1 h; (for **5ab**) I$_2$, CF$_3$CO$_2$Ag, THF, −78 °C, 1 h; (for **5ba**) NBS, THF, −10 °C, 1 h; (for **5bb**) I$_2$, CF$_3$CO$_2$Ag, THF, −78 °C, 1 h; v, (for **6aa** and **6ab**) R^{3}H, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_2$NH, 22–24 h; (for **6ac**) PhB(OH)$_2$, Pd(PPh$_3$)$_4$, 2 M Na$_2$Co$_3$, MeOH–PhMe; (for **6bb** and **6bc**) BuLi, THF, −20 °C, then R^{3}Br; (for **6bd**) Bu^{t}Li, THF, −78 °C, 15 min, then PhCHO, HMPA, −78 to 0 °C; vi, I$_2$, CF$_3$CO$_2$Ag, THF, 55%; vii, (for **8a–d**) R^{4}H, Pd(PPh$_3$)$_4$, CuI, Et$_2$NH, reflux; (for **8e** and **8f**) R^{4}B(OH)$_2$, Pd(PPh$_3$)$_4$, 2 M Na$_2$CO$_3$, MeOH–PhMe, 80 °C



Scheme 2 *Reagents and conditions*: i, NaOMe, MeOH, reflux, 1 h, 98%; ii, NaOMe, MeOH, THF, 80%

procedure for the synthesis of a number of unsymmetrically 3,4-disubstituted protected pyrroles has been established.

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Footnotes and References

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† All new compounds were identified by means of ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry, as well as elemental analyses.

1 J. M. Cooper, D. G. Morris and K. S. Ryderr, *J. Chem. Soc., Chem. Commun.*, 1995, 697; H.-H. Anh, F. Fache and M. Lemaire, *New J. Chem.*, 1992, **16**, 1017.
2 J. K. Groves, N. E. Cundasawmy and H. J. Anderson, *Can. J. Chem.*, 1973, **51**, 1089.
3 S. Halazy and P. Magnus, *Tetrahedron Lett.*, 1984, **25**, 1421.
4 N. E. Heard and J. Turner, *J. Org. Chem.*, 1995, **69**, 4302.
5 A. Fürstner, H. Weintritt and A. Hupperts, *J. Org. Chem.*, 1995, **60**, 6637; M. G. Banwell, B. L. Flynn, E. Hamel and D. C. R. Hockless, *Chem. Commun.*, 1997, 207.
6 B. Franck and A. Nonn, *Angew. Chem., Int. Ed. Engl.*, 1995, **43**, 1795.
7 N. P. Pavri and M. L. Trudell, *J. Org. Chem.*, 1997, **62**, 2649; R. ten Have, F. R. Leusink and A. M. van Leusen, *Synthesis*, 1996, 871; C. Dell'Erba, A. Giglio, A. Mugnoli, M. Novi, G. Petrillo and P. Stagnaro, *Tetrahedron*, 1995, **51**, 5181; D. van Leusen, E. van Echten and A. M. van Leusen, *J. Org. Chem.*, 1992, **57**, 2245; D. van Leusen, E. Flentge and A. M. van Leusen, *Tetrahedron*, 1991, **47**, 4639; S. P. J. M. van Nispen, C. Mensink and A. M. van Leusen, *Tetrahedron Lett.*, 1980, **21**, 3723; A. M. van Leusen, H. Siderius, B. E. Hoogenboom and D. van Leusen, *Tetrahedron Lett.*, 1972, **13**, 5337.
8 K. Ichimur, S. Ichikawa and K. Imamura, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1157.
9 D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587.
10 H. Seino, Y. Ishii, T. Sasagawa and M.Hidai, *J. Am. Chem. Soc.*, 1995, **117**, 12 181; H. Seino, Y. Ishii, T. Sasagawa and M. Hidai, *J. Am. Chem. Soc.*, 1994, **116**, 7433.
11 (*a*) A. Alvarez, A. Guzmán, A. Ruiz and E. Velarde, *J. Org. Chem.*, 1992, **57**, 1653; (*b*) B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis and J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317; (*c*) J. M. Muchowski and R. Naef, *Helv. Chim. Acta*, 1984, **67**, 1168.
12 N. W. Gabel, *J. Org. Chem.*, 1962, **27**, 301.
13 Y. Gao, M. Shirai and F. Sato, *Tetrahedron Lett.*, 1996, **37**, 7787.
14 T. J. Barton and G. P. Hussmann, *J. Org. Chem.*, 1985, **50**, 5881.
15 X.-S. Ye, P. Yu and H. N. C. Wong, *Liebigs. Ann.*, 1997, **3**, 459.
16 P. La Porta, L. Capuzzi and F. Bettarini, *Synthesis*, 1994, **5**, 287.
17 G. Bonteville, Y. Gelas-Mialke and R. Vessière, *Bull. Soc. Chim. Fr.*, 1971, 3264; B. A. Arbuzov and B. P. Lugovkin, *J. Gen. Chem. USSR (Engl. Trans,.)*, 1951, **21**, 99.
18 L. Grehn and U. Ragnarsson, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 296.
19 N. C. Cutress, A. R. Katritziky, C. Eaborn, D. R. M. Walton and R. D. Topsom, *J. Organomet. Chem.*, 1975, **43**, 131; B. Bennetau and J. Dunogues, *Synlett.*, 1993, 171; H. Ishibashi, H. Sakashita and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1953.
20 L. A. Jacob, B.-L. Chen and D. Stec, *Synthesis*, 1993, **4**, 611; S. R. Wilson and L. A. Jacob, *J. Org. Chem.*, 1986, **51**, 4833.
21 K. Sonogashira, Y. Tohda and N. Nagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.
22 A. Suzuki, *Pure Appl. Chem.*, 1991, **63**, 419.

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