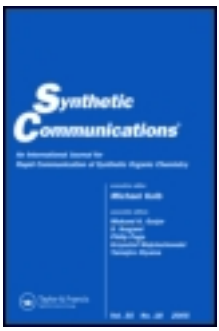

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SYNTHESIS OF α-MONOBROMINATED PYRROLE DERIVATIVES

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Abstract: Surprisingly stable N-*t*-BOC-2-bromo-4-hexyl-pyrrole is prepared from N-*t*-BOC-2-trimethylstannyl-4-hexyl-pyrrole using N-bromosuccinimide as reagent. The bromo-stannyl exchange reaction is performed quantitatively in THF at -70°C under inert atmosphere. Similarly, N-*t*-BOC-2-bromopyrrole and N-benzenesulfonyl-2-bromopyrrole have been synthesized from N-*t*-BOC-2-trimethylstannylpyrrole and N-benzenesulfonyl-2-trimethylstannylpyrrole, respectively.

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Introduction

Mono- and di-α-halogenated pyrrole derivatives are important building blocks in the synthesis of oligo- and polypyrroles. These oligomers and polymers are of interest with respect to research on conducting polymers[1] and porphyrin chemistry[2]. Unfortunately, the number of useful methods to prepare these compounds is limited.

In the early days several groups investigated the synthesis of N-unprotected halopyrroles[3], all of which appeared to be extremely unstable. Later Gilow et al.[4] investigated the chlorination and bromination of N-substituted pyrroles using N-chloro- and N-bromosuccinimide. Although the use of these reagents enhanced the selectivity, the partially halogenated compounds prepared, i.e. N-methyl-2-chloropyrrole or N-benzyl-2-bromopyrrole, were still not very stable under the conditions used and had to be stabilized by the addition of base.

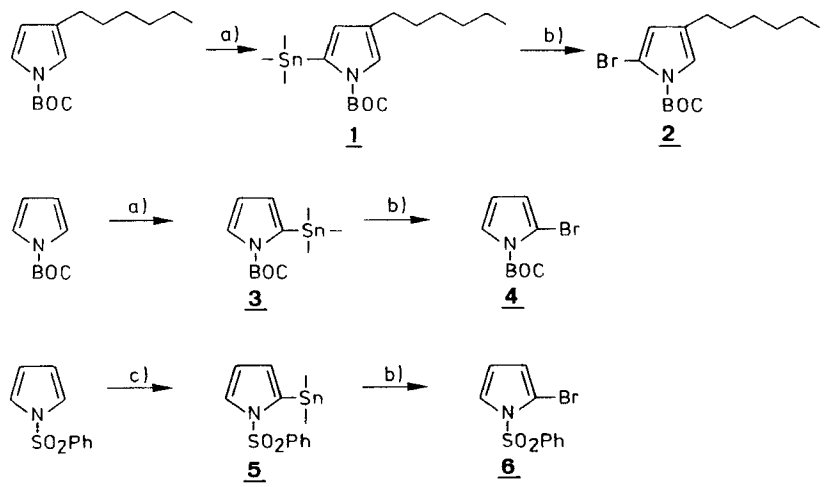
The introduction of the *tert*-butoxycarbonyl (*t*-BOC) protecting group[5] in pyrrole chemistry paved the way to prepare halogenated pyrrole building blocks. Cava et al.[6] reported on the synthesis of 2-mono- and 2,5-dibrominated N-*t*-BOC-pyrrole. They first brominated pyrrole using 1,3-dibromo-5,5-dimethylhydantoin, followed by protection with the *t*-BOC-group. Later Martina et al.[7] prepared 2,5-dibrominated N-*t*-BOC-pyrrole by first protecting pyrrole and then halogenating with N-bromosuccinimide. Only after exhaustive purification, a stable product was obtained. Unfortunately, this method was not applicable to N-*t*-BOC-2-bromo-pyrrole. Furthermore, no studies of

halogenated N-*t*-BOC-3-alkylpyrroles have been reported. In this paper we describe on a versatile synthesis of a number of N-protected 2-bromo-pyrroles, being stable starting compounds for oligopyrroles[8].

Results

N-*t*-BOC-3-hexyl-pyrrole, the precursor compound in the synthesis of N-*t*-BOC-2-bromo-4-hexyl-pyrrole **2** was synthesized following published procedures[9,10]. The trimethylstannylation of N-*t*-BOC-4-hexyl-pyrrole, using *t*-BuLi and trimethylstannyl chloride[11] yielded N-*t*-BOC-2-trimethylstannyl-4-hexyl-pyrrole **1**. The stannylation occurred at the 2-position only; no traces of the other isomer could be detected. NBS-bromination of **1** in THF at -70°C yielded **2** in quantitative yield after column chromatography (scheme 1). N-trimethylstannylsuccinimide was isolated as the byproduct. Much to our surprise **2** proved to be remarkably stable in the pure form after the isolation by column chromatography, this in sharp contrast to the products obtained from the direct NBS bromination of N-*t*-BOC-pyrrole derivatives.

In order to test the generality of the method and to investigate the origin of the stability of **2**, we subsequently synthesized N-*t*-BOC-2-bromo-pyrrole (**4**), being an interesting compound in the synthesis of oligopyrroles. Starting from N-*t*-BOC-pyrrole, we first synthesized N-*t*-BOC-2-trimethylstannyl-pyrrole **3** using *n*-BuLi, 2,2,6,6-tetramethylpiperidine and trimethylstannyl chloride, following the procedure of Martina et al.[7b] In the next step the same reaction as described for **1** was performed. Also in this



Scheme 1: a) 1. Li-TMP, THF, -70°C; 2. $(CH_3)_3SnCl$, THF, -70°C. b) NBS, THF, -70°C. c) 1. *t*-BuLi, THF, -70°C; 2. $(CH_3)_3SnCl$, THF, -70°C.

case a substitution of the trimethylstannyl-group by the bromo-group was observed in quantitative yield resulting in **4** and N-trimethylstannylsuccinimide. Again the mono-brominated N-*t*-BOC-pyrrole, prepared by this method, proved to be extremely stable.

We also investigated this mild substitution reaction on a trimethylstannyl substituted pyrrole bearing a N-benzenesulfonyl-group. Therefore, N-benzenesulfonyl-2-trimethylstannylpyrrole (**5**) was prepared by first making the anion using the procedure described by Levy et al[9], followed by reaction with trimethylstannyl chloride. From this compound N-benzenesulfonyl-2-bromo-pyrrole (**6**) could be isolated in high yields as a stable compound in analytically pure form .

Finally, we tried to use a 2-trimethylsilyl-substituted pyrrole for this reaction. Therefore N-*t*-BOC-2-trimethylsilyl- and N-benzenesulfonyl-2-trimethylsilyl-pyrrole were synthesized using *t*-BuLi and trimethylsilyl chloride[11]. Although these silylated compounds were more difficult to prepare (especially the *t*-BOC-substituted pyrrole derivative), they also gave the corresponding 2-monobrominated pyrroles.

Discussion

From the experiments described above, it is clear that the mild substitution reaction of a trimethylstannyl-pyrrole using NBS yields 2-monobrominated pyrrole derivatives under neutral conditions in quantitative yields. Although the same compound can be prepared from the trimethylsilyl derivatives, the synthesis of the latter is somewhat more difficult. Hence, the trimethylstannyl route is preferred. The compounds prepared exhibit a surprisingly good thermal stability and are much more stable than the compounds prepared from the direct bromination of N-protected pyrrole derivatives. This difference in stability is probably due to the formation of neutral trimethylstannyl-succinimide instead of the acidic succinimide. Small amounts of acid can give rise to an autocatalytic degradation of halopyrroles. Hence, neutral conditions to prepare these acid-labile halopyrrole derivatives is a prerequisite to synthesize these important building blocks for oligopyrrole chemistry in the area of conducting polymers and porphyrin chemistry.

Experimental

All materials and solvents were reagent grade and used as received unless otherwise indicated. Tetrahydrofuran (THF) was distilled over Na/benzophenone and directly used. Al_2O_3 (Merck, Al_2O_3-90 (neutral, act. I)) was deactivated with 8 %w of H_2O. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Bruker AM-400 spectrometer. IR data were recorded on a Perkin Elmer 1605 FTIR spectrometer. MS data were collected using a AMD mass spectrometer/data system (Beckeln, GFR). N-*tert*-Butoxycarbonyl-2-trimethylstannylpyrrole (3) was prepared according to the procedure described by Martina et al[7b].

N-*tert*-Butoxycarbonyl-2-trimethylstannyl-4-hexylpyrrole (1)

2,2,6,6-Tetramethylpiperidine (0.266 g, 1.58 mmol) was dissolved in THF (3 ml) and cooled to -70°C, blanketed by argon. Then *n*-BuLi (1.6 M in hexane, 2.52 ml, 1.58 mmol) was added dropwise after which the mixture was brought to -10°C. After 5 minutes at this temperature it was cooled to -70°C again and N-*t*-butoxycarbonyl-3-hexylpyrrole (0.3786 g, 1.51 mmol) in THF (2 ml) was added and the mixture was stirred at this temperature for another 45 minutes. Then trimethylstannyl chloride (0.30 g, 1.5 mmol) in THF (2 ml) was added dropwise. After another 4 hours at -70°C the mixture was allowed to warm to room temperature at which it was stirred for another 16 hours.

The solvent was evaporated and Et_2O (10 ml) and H_2O (10 ml) were added. After extraction with Et_2O (3 x 10 ml) the combined organic fractions were

dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by chromatography (40 g Al_2O_3, hexane, R_f=0.57) resulted in a colourless liquid (0.38 g, 0.92 mmol, 61%).

^{1}H-NMR ($CDCl_3$): δ 7.13 (d, J=1.3 Hz, 1H, H-5), 6.23 (d, J=1.5 Hz, 1H, H-3), 2.41 (t, J=7.7 Hz, 2H, pyr-C<u>H</u>$_2$), 1.57 (m, 11H, H-methyl (BOC), pyr-CH_2-C<u>H</u>$_2$), 1.31 (m, 6H, C<u>H</u>$_2$), 0.89 (t, J=6.8 Hz, 3H, CH_2-C<u>H</u>$_3$), 0.23 (s, 9H, H-methyl (stannyl)) ppm. ^{13}C-NMR ($CDCl_3$): δ 150.5 (C=O), 134.6 (C-2), 129.2 (C-4), 123.5-120.0 (C-3, C-5), 82.9 (C-q (BOC)), 28.0 (C-methyl (BOC)), 31.7 (pyr-<u>C</u>H$_2$), 30.5-26.8 (CH_2-<u>C</u>H$_2$-CH_2), 22.6 (<u>C</u>H$_2$-CH_3), 14.1 (CH_2-<u>C</u>H$_3$), -7.8 (C-methyl (stannyl)) ppm.

N-*tert*-Butoxycarbonyl-2-bromo-4-hexylpyrrole (<u>2</u>)

N-*tert*-Butoxycarbonyl-2-trimethylstannyl-4-hexylpyrrole (<u>1</u>, 0.1571 g, 0,379 mmol) was dissolved in THF (2 ml) and cooled to -70°C, blanketed by argon. N-Bromosuccinimide (0.0682 g, 0,383 mmol) was added and the mixture was stirred for another 15 minutes at -70°C. Then it was warmed to 3°C at which temperature it was kept for 16 hours.

Na_2CO_3 (50 mg) was added and the solvent was evaporated. CCl_4 (10 ml) was added to the residue, the suspension was filtered and the filtrate was evaporated. After chromatography (10 g SiO_2, $CHCl_3$:hexane (1:1), R_f=0.75) a pale yellow liquid was obtained (0.1173 g, 0.355 mmol, 97%).

^{1}H-NMR ($CDCl_3$): δ 7.05 (dt, J=2.2 and 1.0 Hz, 1H, H-5), 6.17 (d, J=2.1 Hz, 1H, H-3), 2.35 (t, J=7.9 Hz, 2H, pyr-C<u>H</u>$_2$), 1.60 (s, 9H, H-methyl (BOC)), 1.51

(m, 2H, pyr-CH_2-$C\underline{H}_2$), 1.29 (m, 6H, $C\underline{H}_2$), 0.88 (t, J=6.9 Hz, 3H, CH_2-$C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$): δ 148.1 (C=O), 127.5 (C-4), 119.5-118.3 (C-3, C-5), 99.9 (C-2), 84.3 (C-q (BOC)), 28.0 (C-methyl (BOC)), 31.6 (pyr-$\underline{C}H_2$), 30.0-26.8 (CH_2-$\underline{C}H_2$-CH_2), 22.6 ($\underline{C}H_2$-CH_3), 14.1 (CH_2-$\underline{C}H_3$) ppm.

MS: m/z (%) = 329 (M^+, 1.3), 331 ($M+2^+$, 1.5), 161 (36.3), 160 (21.3), 159 (39.4), 158 (17.6), 57 (100).

IR (KBr): ν = 3136, 2928, 2856, 1757, 1741, 1321, 1243, 1158, 1022, 852, 809, 759 cm^{-1}.

N-*tert*-Butoxycarbonyl-2-bromopyrrole (4)

The reaction between N-*tert*-butoxycarbonyl-2-trimethylstannylpyrrole (3, 0.2494 g, 0.756 mmol) and N-bromosuccinimide (0.1350 g, 0.758 mmol) in THF (3 ml) was carried out as described for the preparation of 2. After chromatography (10 g SiO_2, $CHCl_3$:hexane (1:1), R_f=0.67) 2 was obtained as a colourless oil (0,1803 g, 0.733 mmol, 97%).

^{1}H-NMR ($CDCl_3$): δ 7.31 (dd, J=3.5 and 1.9 Hz, 1H, H-5), 6.29 (dd, J=3.5 and 1.9 Hz, 1H, H-3), 6.15 (t, J=3.5 Hz, 1H, H-4), 1.61 (s, H-methyl (BOC)) ppm. ^{13}C-NMR ($CDCl_3$): δ 148.0 (C=O), 123.0 (C-5), 117.2 (C-3), 111.5 (C-4), 100.2 (C-2), 84.7 (C-q (BOC)), 27.9 (C-methyl (BOC)) ppm.

MS: m/z (%) = 245 (M^+, 3.4), 247 ($M+2^+$, 3.6), 147 (29.1), 145 (29.4), 57 (100).

IR (KBr): ν = 3156, 3129, 2980, 2934, 1746, 1322, 1156, 847, 804, 767, 720 cm^{-1}.

N-Benzenesulfonyl-2-trimethylstannylpyrrole (5)

N-Benzenesulfonylpyrrole (2.07 g, 9.99 mmol) was dissolved in THF (12 ml) and cooled to -70°C, blanketed by argon. Then *t*-BuLi (1.5 M in hexane, 7.70 ml, 11.55 mmol) was added over a 20-minute period after which the mixture was allowed to warm to room temperature. After 30 minutes at room temperature it was cooled to -70°C again and trimethylstannyl chloride (2.28 g, 11.44 mmol) in THF (6 ml) was added. After addition it was kept at this temperature for another 30 minutes after which the dark brown solution was stirred at room temperature over a night.

The solvent was evaporated and Et_2O (30 ml) and H_2O (30 ml) were added. After extraction with Et_2O (3 x 25 ml) the combined organic fractions were dried ($MgSO_4$), filtered and the solvent was evaporated. The resulting brown oil was purified by chromatography (200 g Al_2O_3, hexane, R_f=0.08) to afford a colourless oil (2.20 g, mmol, 59%).

^{1}H-NMR ($CDCl_3$): δ 7.63 (d, J=8.3 Hz, 2H, H-ortho), 7.57 (t, J=7.4 Hz, 1H, H-para), 7.47 (t, J=7.6 Hz, 2H, H-meta), 7.41 (dd, J=3.1 and 1.8 Hz, 1H, H-5), 6.47 (dd, J=3.1 and 1.4 Hz, 1H, H-3), 6.43 (t, J=3.0 Hz, 1H, H-4), 0.30 (s, 9H, H-methyl(stannyl)) ppm. ^{13}C-NMR ($CDCl_3$): δ 140.1 (C-ipso (phenyl)), 135.8 (C-2), 133.4 (C-para), 129.2 (C-ortho), 126.0 (C-meta), 125.7-124.3 (C-3, C-5), 114.6 (C-4), -7.3 (C-methyl (stannyl)) ppm.

N-Benzenesulfonyl-2-bromopyrrole (6)

Using N-benzenesulfonyl-2-trimethylstannylpyrrole (5, 0.3372 g, 0.911 mmol), THF (3 ml) and N-bromosuccinimide (0.1622 g, 0.911 mmol), the reaction was

carried out as described for **2** and **4**. After chromatography (10 g SiO_2, $CHCl_3$:hexane (1:1), R_f=0.56) a white solid was obtained (0.2576 g, 0.900 mmol, 99%). Mp.: 86-87°C.

^{1}H-NMR ($CDCl_3$): δ 7.92 (d, J=8.5 Hz, 2H, H-ortho), 7.63 (t, J=7.5 Hz, 1H, H-para), 7.53 (t, J=7.8 Hz, 2H, H-meta), 7.48 (dd, J=3.6 and 1.9 Hz, 1H, H-5), 6.28 (dd, J=3.6 and 1.9 Hz, 1H, H-3), 6.25 (t, J=3.5 Hz, 1H, H-4) ppm.

^{13}C-NMR ($CDCl_3$): δ 138.0 (C-ipso (phenyl)), 134.2 (C-para), 129.2 (C-ortho), 127.7 (C-meta), 124.3 (C-5), 118.0 (C-3), 112.7 (C-4), 110.0 (C-2) ppm.

MS: m/z (%) = 285 (M^+, 17.5), 287 ($M+2^+$, 18.0), 141 (73.8), 77 (100).

IR (KBr): ν = 3132, 3087, 1367, 1266, 1186, 1169, 1141, 727, 681, 611 cm^{-1}.

$C_{10}H_8BrNO_2S$	calc.:	C 41.97	H 2.82	N 4.90
	found:	C 42.08	H 2.79	N 4.79

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