Regioselective Sonogashira Reactions of *N*-Methyltetrabromopyrrole: First Synthesis of Tri- and Tetra(1-alkynyl)pyrroles

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Abstract: *N*-Methyl-2,3,4,5-tetrabromopyrrole is transformed into a variety of alkynyl-substituted pyrroles by regioselective Sonogashira cross-coupling reactions. In this context, the synthesis of the first tri- and tetra(1-alkynyl)pyrroles is reported.

Key words: catalysis, palladium, carbon–carbon bond formation, regioselectivity, pyrroles

Hydrocarbons bearing multiple alkynyl groups have received considerable attention, due to their interesting physicochemical properties, as synthetic building blocks of new and interesting arenes and because of their æsthetic attraction (Figure 1).[1] For example, Vollhardt and coworkers reported the synthesis and characterization of hexaethynylbenzene **A** and its application to the first synthesis of the so-called archimedanes containing only benzene and cyclobutane moieties.[2] In contrast to their hydrocarbon counterparts, multiply alkynylated heterocycles are relatively rare. Whitesides et al. reported the synthesis of tetra(1-alkynyl)thiophenes **B** based on regioselective Sonogashira couplings of tetraiodothiophene.[3] Later, related reactions of tetrabromothiophene were reported.[4]

Pyrroles constitute an important class of heterocycles which are present in natural products (e.g., in the tetrapyrrole pigments porphobilinogen and bilirubin)[5] and in various synthetic drugs (e.g., zomepirac and atorvastatin).[6] Pyrroles and oligopyrroles show promising properties as new materials (e.g., as synthetic metals).[7] In recent years, syntheses of 2,5-[8] and 3,4-di(1-alkynyl)pyrroles[9] have been reported. These molecules have been used for the synthesis of polymers and fused heterocycles. The synthesis of tri- and tetra(1-alkynyl)pyrroles **C** has, to the best of our knowledge, not been reported to date.

Heterocycles have been widely functionalized by palladium(0)-catalyzed cross-coupling reactions.[10] In recent years, it has been shown that polyhalogenated heterocycles may be regioselectively functionalized in such reactions by selective activation of a single halogen atom – a process which is controlled by electronic and steric parameters.[11] Bach and Schröter reported regioselective Sonogashira reactions of ethyl 2,3,4-tribromopyrrole-5-carboxylate and of 2,3-dibromo-5-nitropyrrole.[12] Recently, we reported the synthesis of aryl-substituted thiophenes[13] and pyrroles[14] by Suzuki reactions of tetrabromothiophene and tetrabromo-*N*-methylpyrrole, respectively. Herein, we disclose our preliminary results related to what are, to the best of our knowledge, the first Sonogashira cross-coupling reactions of tetrabromo-*N*-methylpyrrole. These reactions allow a convenient synthesis of a variety of novel alkynylated pyrroles. In this context, we report what are, to the best of our knowledge, the first syntheses of tri- and tetra(1-alkynyl)pyrroles.

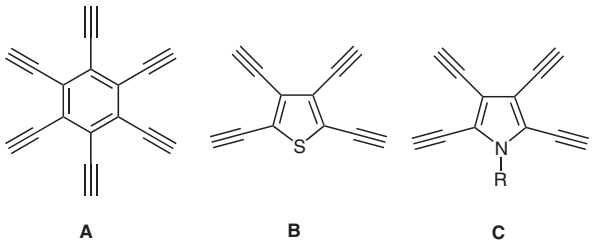

Figure 1 Molecules with multiple alkynyl groups

The reaction of *N*-methylpyrrole with *N*-bromosuccinimide (NBS) afforded tetrabromo-*N*-methylpyrrole (**1**). The synthesis was carried out following the procedure of Gilow and Burton,[15] but with some variations (related to the temperature, reaction time, and amount of NBS). Notably, we observed that it is crucial to isolate **1** in analytically pure form as colorless crystals. The oily form is generally slightly impure, tends to be considerably less stable and decomposes within a few days. The presence of impurities results in a failure of Pd(0)-catalyzed cross-coupling reactions. In contrast, the crystalline solid can be stored under argon atmosphere at –18 °C (in the dark) for a few weeks. Then, the compound starts to slightly darken and it cannot be successfully used anymore in Pd(0)-catalyzed reactions.

In general, the Sonogashira cross-coupling reactions reported herein only proved to be possible when tetrabromo-*N*-methylpyrrole was employed. The employment of benzyl-, carbamate-, and sulfonyl-protected tetrabromopyrroles was unsuccessful and resulted in the formation of complex mixtures and decomposition. In most of the Sonogashira reactions reported herein, the best

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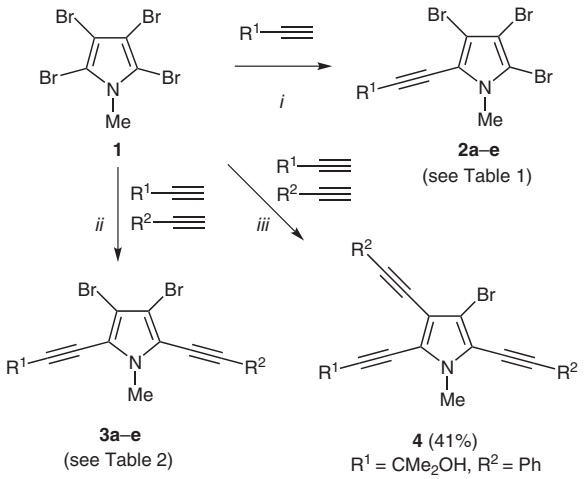
yields were obtained when (freshly prepared) $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), and (rigorously dried and freshly distilled) *i*-Pr_2NH were employed. The yields dramatically decrease when traces of water are present. The temperature and the reaction time also proved to be important parameters (vide infra). The yields of most products reported herein could be slightly increased when 20 mol% rather than 10 mol% of catalyst were employed. The best yields were generally obtained for nonvolatile alkynes, due to the high reaction temperatures.

The Sonogashira reaction of **1** with various alkynes (1.1 equiv) regioselectively afforded the novel 5-(1-alkynyl)-2,3,4-tribromopyrroles **2a–e** (Scheme 1, Table 1).[16,17] The formation of a 4-(1-alkynyl)-2,3,5-tribromopyrrole was not observed. The relatively low yields of **2a–e** can be explained by the formation of considerable amounts of 2,5-di(1-alkynyl)-3,4-dibromopyrroles. Therefore, it proved to be important during the optimization to use not more than 1.1 equivalents of the alkyne and to stir the solution at 90 °C for not more than 1 hour. Stirring for 3 h resulted in the formation of a mixture of 2,5-di(1-alkynyl)-3,4-dibromopyrroles and starting material **1**. Likewise, the yields of **2a–e** decreased when the reactions were carried out at temperatures lower than 90 °C. The yields could be slightly increased when 20 mol% rather than 10 mol% of catalyst were employed.

The Sonogashira reaction of **1** with two different alkynes (1.05 equiv each) afforded the unsymmetrical 2,5-(1-alkynyl)-3,4-tribromopyrroles **3a–e** (Scheme 1, Table 2).[16,18] During the optimization, it proved to be important that alkynes of considerably different reactivity were employed. In addition, it was crucial to add both alkynes at the same time to avoid the formation of symmetrical 2,5-di(alkynyl)pyrroles.



Scheme 1 Synthesis of **2a–e**, **3a–e**, and **4**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), $R^1C{\equiv}CH$ (1.2 equiv), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 90 °C, 1 h; (*ii*) **1** (1.0 equiv), $R^1C{\equiv}CH$ and $R^2C{\equiv}CH$ (1.05 equiv each, addition at the same time), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 90 °C, 6–8 h; (*iii*) 1) **1** (1.0 equiv), $R^1C{\equiv}CH$ and $R^2C{\equiv}CH$ (1.05 equiv each, addition at the same time), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 100 °C, 6–8 h; 2) $R^2C{\equiv}CH$ (1.05 equiv), 12–16 h.

The reaction of **1** with 2-methylbut-3-yn-2-ol and phenylacetylene (1.05 equiv each) and, subsequently, with phenylacetylene (1.05 equiv) afforded the 2,4,5-tri(1-alkynyl)-3-bromopyrrole **4**.

Table 1 Synthesis of **2a–e**

Entry	Compd **2**	R^1	Yield (%)[a]
1	**2a**	*n*-Pr	30
2	**2b**	CMe_2OH	32
3	**2c**	$(CH_2)_3OH$	30
4	**2d**	$CH_2CH(OH)Me$	35
5	**2e**	4-MeC_6H_4	40

[a] Yields of isolated products.

Table 2 Synthesis of **3a–e**

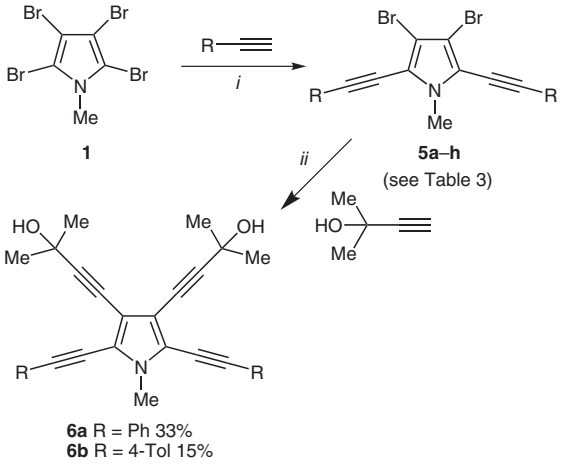
Entry	Compd **3**	R^1	R^2	Yield of (%)[a]
1	**3a**	4-MeC_6H_4	$CH_2CH(OH)Me$	40
2	**3b**	4-MeC_6H_4	$(CH_2)_3OH$	40
3	**3c**	4-MeC_6H_4	CMe_2OH	44
4	**3d**	4-MeC_6H_4	*n*-Hex	41
5	**3e**	CMe_2OH	*n*-Hex	37

[a] Yields of isolated products.

The Sonogashira reaction of **1** with 2.5 equivalents of various alkynes afforded the symmetrical 2,5-di(1-alkynyl)-3,4-dibromopyrroles **5a–k** in good yields and with very good regioselectivity (Scheme 2, Table 3).[16,19] Products **5a**,**b**,**d**,**g–k** were obtained in good yields when the reaction was carried out using $PdCl_2(MeCN)_2$, Ph_3P and HN*i*-Pr_2 (procedure A). The best yields were obtained when the reaction mixture was stirred at 100 °C for 6–8 hours. Longer and shorter reaction times resulted in a decrease in yield, due to decomposition and uncomplete conversion, respectively. However, product **5b** could be isolated in equally good yield after stirring for only 3 hours when the reaction was carried out in an autoclave (at 90 °C). The yields of products **5a**,**b** could be improved when $Pd(OAc)_2$, the novel ligand **L**[20] and Cs_2CO_3 were employed (procedure C). This method was also successfully applied to the synthesis of **5c**,**e**,**f**. The yields of **5a**,**b**,**i** considerably decreased when the (freshly prepared) carbene-ligated catalyst **7** (5 mol%, Figure 2) was employed (procedure B).

The structure of **5b** was independently confirmed by X-ray crystal structure analysis (Figure 3).[21]

The Sonogashira reaction of **5a**,**b** with 2-methylbut-3-yn-2-ol (4.0 equiv) afforded the tetra(1-alkynyl)pyrroles **6a**,**b** containing two different types of alkynyl substituents.



Scheme 2 Synthesis of **5a**–**h** and **6a**,**b**. *Reagents and conditions*: (*i*) procedure A: **1** (1.0 equiv), RC≡CH (2.5 equiv), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 100 °C, 6–8 h; procedure B: **1** (1.0 equiv), **7** (5 mol%, structure see below), Ph_3P (5 mol%), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF; procedure C: $Pd(OAc)_2$ (5 mol%), **L** (15 mol%), Cs_2CO_3 (3.0 equiv), MeCN, reflux, 6 h; (*ii*) **5a**,**b** (1.0 equiv), RC≡CH (4.0 equiv), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 100 °C, 20 h.

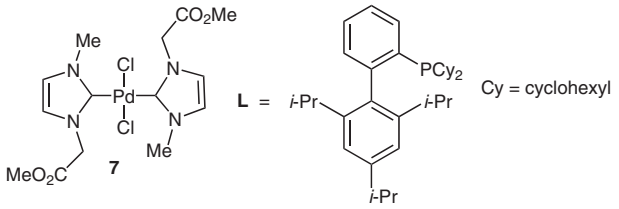


Figure 2

Table 3 Synthesis of **5a**–**h**

Entry	Compd **5**	Ar	Yield (%)[a]		
			Procedure		
			A	B	C
1	**5a**	Ph	59	17	84
2	**5b**	4-MeC_6H_4	71	19	79
3	**5c**	4-FC_6H_4			47
4	**5d**	*n*-Pr	45		
5	**5e**	*n*-Pent			67
6	**5f**	*n*-Oct			72
7	**5g**	*n*-Undec	65		
8	**5h**	$(CH_2)_3OH$	61		
9	**5i**	$CH_2CH(OH)Me$	70	15	
10	**5j**	CMe_2OH	74		
11	**5k**	TMS	67		

[a] Yields of isolated products using procedures A, B, and C (see Scheme 2).

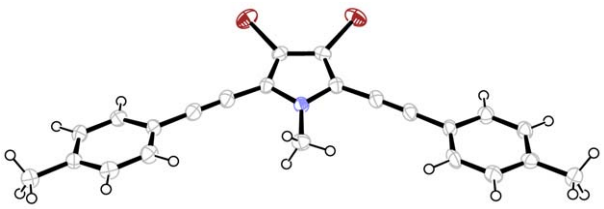
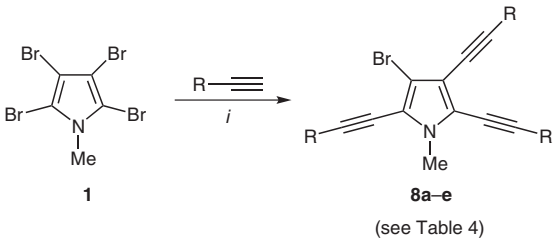


Figure 3 ORTEP plot of **5b** (50% probability level)

2,4,5-Tri(1-alkynyl)-3-bromopyrroles **8a**–**e**, containing three identical alkynyl groups, were selectively prepared by Sonogashira reaction of **1** with 3.3 equivalents of various alkynes (Scheme 3, Table 4).[16,22] The best yields were obtained when the reaction mixture was stirred at 100 °C for 12–16 hours. The success of these transformations relies on the fact that the formation of the fourth carbon–carbon bond is significantly slower than the formation of the third one. In fact, no competing formation of a tetra(1-alkynyl)pyrrole was observed.



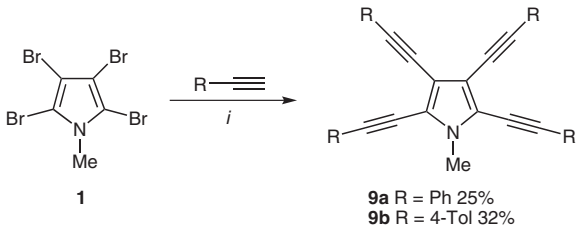
Scheme 3 Synthesis of **8a**–**e**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), RC≡CH (3.3 equiv), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 100 °C, 12–16 h.

Table 4 Products and Yields

Entry	Compd **8**	R	Yield (%)[a]
1	**8a**	Ph	36
2	**8b**	4-MeC_6H_4	42
3	**8c**	CMe_2OH	40
4	**8d**	$(CH_2)_3OH$	40
5	**8e**	$CH_2CH(OH)Me$	44

[a] Yields of isolated products.

Tetra(1-alkynyl)pyrroles **9a** and **9b**, containing four identical alkynyl groups, were prepared by reaction of **1** with an excess (6.0 equiv) of phenylacetylene and 4-tolylacetylene, respectively (Scheme 4).[16,23] The best yields were obtained when the reaction mixture was stirred at 100 °C for 20 hours. Although the yields of **9a**,**b** are relatively low, it should be taken into account that four carbon–carbon bonds are formed in one reaction. A theoretical yield of 71% for each C–C bond formation would result in a 25% overall yield. Notably, products derived from alkyl-substituted alkynes proved to be rather unstable and could not be isolated in pure form. We have not yet tried to prepare the unsubstituted parent compound, tetraethy-



1

9a R = Ph 25%
9b R = 4-Tol 32%

Scheme 4 Synthesis of **9a**,**b**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), RC≡CH (6.0 equiv), $PdCl_2(MeCN)_2$ (10 mol%), CuI (10 mol%), Ph_3P (20 mol%), *i*-Pr_2NH, 100 °C, 20 h.

nyl-*N*-methylpyrrole, as its thiophene analogue has been reported to be highly explosive.[3]

In conclusion, we have studied the synthesis of a variety of alkynyl-substituted pyrroles based on the first regioselective Sonogashira cross-coupling reactions of tetrabromo-*N*-methylpyrrole (**1**). In this context, the synthesis of what are, to the best of our knowledge, the first tri- and tetra(1-alkynyl)pyrroles has been reported. The Sonogashira reactions of **1** first occur at carbon atoms C2 and C5 which are more electron deficient than C3 and C4. In fact, the formation of 2,5-di(1-alkynyl)pyrroles is relatively fast. Therefore, the best yields were obtained for the synthesis of symmetrical di(alkynyl)pyrroles **5**. In contrast, the synthesis of the monoalkynylated pyrroles **2** was more difficult and required a thorough optimization of the reaction time. Unsymmetrical di(alkynyl)pyrroles **3** could be directly prepared from **1** when two alkynes of different reactivity were employed and added at the same time. The first tri(1-alkynyl)pyrroles were prepared. Their successful synthesis relies on the fact that the formation of the fourth carbon–carbon bond is significantly slower than the formation of the third one. Finally, we reported the synthesis of what are, to the best of our knowledge, the first tetra(1-alkynyl)pyrroles.

Acknowledgment

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(16) **General Procedure for Sonogashira Reactions**
Tetrabromo-*N*-methylpyrrole (**1**, 750 mg, 1.87 mmol), Ph_3P (98 mg, 20 mol%), $PdCl_2(MeCN)_2$ (49 mg, 10 mol%), and CuI (36 mg, 10 mol%) were added to an oven-dried Schlenk flask, evacuated for 10 min, and then flushed with argon. To the mixture was added thoroughly dried, freshly distilled and oxygen-free diisopropylamine (20 mL). The clear yellow solution was stirred for 15 min at 20 °C for the generation of the catalyst. The solution was subsequently cooled to 0 °C, and the alkyne was dropwise added by syringe. The solution was stirred for 1 h at 0 °C and for 3 h at 20 °C. The dark brown mixture was heated at 90 °C. The solution was allowed to cool to ambient temperature, filtered, and the filtrate was concentrated in vacuo. To the residue was added CH_2Cl_2, and the solution was extracted with H_2O. The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (neutral silica gel, *n*-hexane). For the synthesis of products **3**, the two alkynes were added at the same time.
(17) **Synthesis of 2a**
Starting with **1** (500 mg, 1.25 mmol) and 2-pentyne (1.3 mmol), **2a** was isolated (134 mg, 30%) as a brownish highly viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.5 Hz, 3 H, Me), 1.64 (sext, ^3J = 7.2 Hz, 2 H, CH_2), 2.47 (t, ^3J = 7.0 Hz, 2 H, CH_2), 3.64 (s, 3 H, NCH_3). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 13.5 (CH_3), 21.6, 22.0 (CH_2), 35.6 (NCH_3), 70.1, 98.8 (C≡C), 100.4, 102.93, 104.19, 118.34 (C, pyrrole). IR (KBr): 3436 (br, s), 2958 (s), 2932 (m), 2872 (m), 2228 (w), 1717 (m), 1529 (m), 1456 (s), 1431 (m), 1378 (m), 1330 (s), 1092 (m) cm^{-1}. MS (EI, 70 eV, 85 °C): *m/z* (%) = 381 (19) [M$^+$, ^{79}Br, ^{79}Br, ^{79}Br], 356 (67), 354 (58), 275 (14), 224 (54), 194 (60), 115 (100). HRMS: *m/z* calcd for $C_{10}H_{10}Br_3N$ [M$^+$, ^{79}Br, ^{79}Br, ^{79}Br]: 380.83579; found: 380.83501.
(18) **Synthesis of 3c**
Starting with **1** (500 mg, 1.25 mmol), 2-methyl-3-pentyne-2-ol (1.3 mmol), and *p*-tolylacetylene (1.3 mmol), **3c** was isolated (238 mg, 44%) as a red to brown solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.65 (s, 6 H, CH_3), 2.36 (s, 3 H, Me-tolyl), 3.72 (s, 3 H, CH_3), 7.16 (d, ^3J = 8.1 Hz, 2 H, tolyl), 7.43 (d, ^3J = 8.1 Hz, 2 H, tolyl). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 21.6 (CH_3, tolyl), 31.3 (CH_3), 34.4 (NCH_3), 65.9 (C, *C*Me_2OH), 71.7, 71,6 (C≡C), 97.5, 97.7 (C, pyrrole), 102.2, 103.9 (C≡C), 116.9, 117.9 (C, pyrrole), 119.1, 131.4 (CH, *p*-tolyl), 139.2 (C, *p*-tolyl). IR (KBr): 3324 (br, s), 2983 (s), 2929 (s), 2865 (w), 2249 (m), 1906 (w), 1728 (s), 1534 (m), 1509 (m), 1440 (s), 1232 (s), 1160 (br, s), 910 (s), 815 (s), 730 (br, s) cm^{-1}. MS (EI, 70 eV, 110 °C): *m/z* (%) = 433 (49) [M$^+$, ^{79}Br, ^{79}Br], 418 (40) [M$^+$ – CH_3, ^{79}Br, ^{79}Br], 417 (11), 405 (17), 377 (18), 356 (15) [M$^+$ – ^{79}Br].
(19) **Synthesis of 5b**
Procedure A[16]
Starting with **1** (750 mg, 1.87 mmol) and *p*-tolylacetylene (0.6 mL, 4.67 mmol), **5b** (620 mg, 71%) was isolated as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.36 (s, 6 H, CH_3, *p*-tolyl), 3.77 (s, 3 H, NCH_3), 7.14 (d, ^3J = 8.1 Hz, 4 H, *p*-tolyl), 7.56 (d, ^3J = 8.1 Hz, 4 H, *p*-tolyl). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 21.6 (CH_3, *p*-tolyl), 34.6 (NCH_3), 77.9 (C≡C), 97.7 (C, pyrrole), 104.1 (C≡C), 117.9 (C, pyrrole), 119.1 (C, *p*-tolyl), 129.2 (CH, *p*-tolyl), 131.3 (CH, *p*-tolyl), 139.1 (C, *p*-tolyl). IR (KBr): 3435 (br, m), 3023 (m), 2717 (s), 2206 (w), 1537 (s), 1441 (s), 1377 (s), 1345 (s), 817 (s), 809 (8 s), 535 (s), 520 (s) cm^{-1}. MS (EI, 70 eV, 320 °C): *m/z* (%) = 465.6 (51) [M$^+$, ^{79}Br, ^{79}Br], 403 (16), 306.5 (10), 292.5 (14), 277 (42). HRMS: *m/z* calcd for $C_{23}H_{17}Br_2N$: 464.97223; found: 464.97163.
(20) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358; and references cited therein.
(21) CCDC-689251 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.
(22) **Synthesis of 8c**
Starting with **1** (500 mg, 1.25 mmol) and 2-methyl-3-pentyne-2-ol (0.4 mL, 4.12 mmol), **8c** was isolated (198 mg, 40%) as a brownish solid. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.45, (s, 12 H, 4 CH_3), 1.48 (s, 6 H, 2 CH_3), 3.60 (s, 3 H, NCH_3), 5.42, 5.60, 5.61 (3 s, 3 OH). ^{13}C NMR (62.8 MHz, DMSO-d_6): δ = 31.35, 31.38, 31.8, (6 CH_3), 33.8 (NCH_3), 63.8, 63.9, (C, *C*Me_2OH), 69.8, 70.0, 72.4, (C≡C), 100.1, 102.6, 103.7 (C, pyrrole), 104.1, 110.0 (C≡C), 116.8 (C, pyrrole), 119.9 (C, pyrrole). IR (KBr): 3435 (br, s), 2980 (s), 2933 (s), 2226 (w), 1634 (m), 1452 (m), 1374 (s), 1374 (s), 1238 (s), 1164 (s), 1137 (s), 989 (w), 938 (s), 939 (m), 892 (w), 841 (m) cm^{-1}. MS (EI, 70 eV, 130 °C): *m/z* (%) = 405 (99) [M$^+$, ^{79}Br], 403 (16), 390 (14), 388 (28), 374 (65), 372 (71), 278 (40), 235 (23). HRMS: *m/z* calcd for $C_{20}H_{24}BrNO_3$ [M$^+$, ^{79}Br]: 405.09341; found: 405.09328.
(23) **Synthesis of 9a**.
Starting with **1** (500 mg, 1.25 mmol) and phenylacetylene (0.82 mL, 7.5 mmol), **9a** was isolated (150 mg, 25%) as an orange-red oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, NCH_3), 7.32 (br s, 4 H, Ph), 7.35 (m, 8 H, Ph), 7.56 (m, 8 H, Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 33.8 (NCH_3), 79.2, 82.3, 94.3 (C≡C), 112.7 (C, pyrrole), 120.6 (C, pyrrole), 122.5 (C, Ph), 123.9 (C, Ph), 127.9, 128.3, 128.46, 128.7, 131.46, 131.52 (CH, Ph). IR (KBr): 3435 (m), 3058 (w), 2959 (s), 2927 (s), 2871 (m), 2204 (s), 1728 (s), 1597 (s), 1478 (s), 1454 (s), 1376 (m), 1255 (m), 1067 (m), 910 (m), 754 (s), 688 (s) cm^{-1}. MS (EI, 70 eV, 85 °C): *m/z* (%) = 482 (10), 481 (39) [M$^+$], 480 (100), 476 (6), 401 (4), 338 (6), 239 (22), 230 (2). HRMS: *m/z* calcd for $C_{37}H_{23}N$; 481.18301; found: 481.18276.