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Site-selective Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole

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ABSTRACT

The first Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole are reported. These reactions proceed with very good site-selectivity in favour of position 5 which is more reactive than position 2, due to steric reasons. The second attack occurs at position 2 which is more electron deficient than position 3.

The pyrrole system is of great importance in organic chemistry, due to its occurrence in many natural products and pharmacologically active molecules.[1] For example, a pyrrole core structure is present in marine natural products, such as the lamellarines, storniamide A, ningalin A and halitulin, which show considerable potential for the treatment of various cancers and AIDS.[2] Pyrroles also occur in the structure of atorvastatin (lipitor), an oral drug which lowers the level of cholesterol in the blood.[3] They are also found in the natural product porphobilinogen, a trisubstituted pyrrole which is a biosynthetic precursor of many natural products such as haemoglobin.[4] Structurally more simple pyrroles have been also isolated as natural products, for example, pyrrolnitrin, isolated from *Pseudomonas pyrrocinia*, which possesses potent antifungal and antibiotic activities (Chart 1).[5]

Site-selective palladium(0)-catalyzed cross-coupling reactions of polyhalogenated heterocycles provide an efficient approach to more complex substituted derivatives.[6,7] This methodology has been applied also to the synthesis of natural products and pharmaceuticals.[8] Schröter and Bach studied Suzuki–Miyaura (S–M) reactions of 2,3,4-tribromopyrrole-5-carboxylate and of 2,3-dibromo-5-nitropyrrole and observed site-selectivity in favour of position 2.[9] Handy and co-workers reported site-selective one-pot double S–M reactions of 4,5-dibromopyrroles using ligand free conditions.[10] Beaumard and co-workers reported one-pot S–M reactions of 2,5-dibromo-*N*-Boc-pyrrole.[11]

Recently, we have reported site-selective S–M reactions of various polyhalogenated heterocycles, such as tetrabromo-*N*-methylpyrrole, tetrabromothiophene, tetrabromo–selenophene, tribromopyrazoles, and tribromothiophenes. The site-selectivity of such reactions is controlled by electronic and steric effects. Directing groups at sites neighbouring the reactive position also play a significant role in the selectivity. Herein, we report what are, to the best of our knowledge, the first site-selective Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole. These reactions provide a convenient approach to novel 5-aryl-2,3-dibromo-*N*-methylpyrroles, 2,5-diaryl-3-bromo-*N*-methylpyrroles and 2,3,5-triaryl-*N*-methylpyrrole.

2,3,5-Tribromo-*N*-methyl-pyrrole **2** was prepared, following a known procedure,[12] by reaction of *N*-methylpyrrole (**1**) with NBS (3.1 equiv) in THF (Scheme 1).

The S–M reaction of **2** with 1.1 equiv of various arylboronic acids afforded 5-aryl-2,3-dibromo-*N*-methylpyrroles **3a–g** in 43–82% yields (Scheme 2, Table 1).[13] The reactions proceeded with

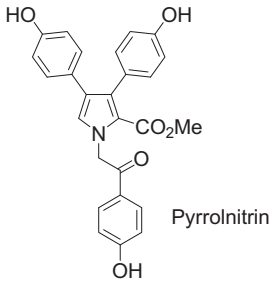

Chart 1. Structure of pyrrolnitrin.

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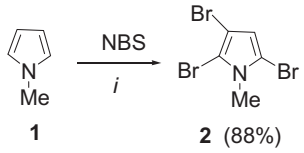
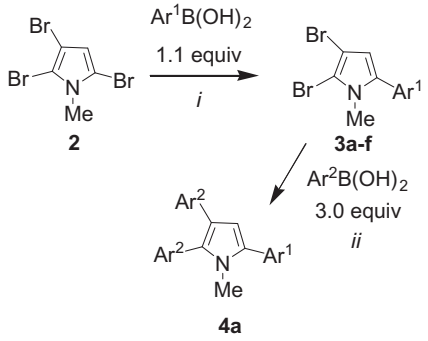


Scheme 1. Synthesis of **2**. Reagents and Conditions: **1** (1.0 equiv), NBS (3.1 equiv), THF, −78→ 20 °C, 12 h.



Scheme 2. Synthesis of **3a–g** and **4a**. Reagents and Conditions: (i) **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (4.0 equiv), 1,4-dioxane/toluene = 1:1, 100 °C, 8 h; (ii) **3d** (1.0 equiv), $Ar^2B(OH)_2$ (3 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4(4.0 equiv), toluene, 110 °C, 36 h.

very good site-selectivity in favour of position 5. The relatively low yield of **3a** can be explained by the steric hindrance of 2,6-di(methoxy)phenylboronic acid. Good yields were obtained for nearly all products when $Pd(PPh_3)_4$ (5 mol %) and K_3PO_4 (4.0 equiv) were employed as the catalyst and as the base, respectively, when 1.1 equiv of the boronic acid was used and when the reaction was carried out at 100 °C (8 h). The temperature should not be too high and the reaction time not too long to avoid multiple coupling. Employment of a solvent mixture dioxane/toluene proved to be important, due to reasons of solubility of the boronic acids. Analysis of the crude product mixture (GC–MS, ^1H NMR) shows that small amounts of products derived from double-coupling are present which could, however, be removed by chromatography. The structure of **3a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[14]

The S–M reaction of **3d** with 4-methoxyphenylboronic acid afforded the 2,3,5-triaryl-*N*-methylpyrrole **4a** in 74% yield (Scheme 2, Table 2). The best yield of this compound was obtained when an excess of the boronic acid was employed (3.0 equiv) and when the reaction time was extended to 36 h and the temperature elevated to 110 °C. The yield of the one-pot synthesis of **4a** from **2** (sequential addition of the boronic acids) was less than the yield of the stepwise process. Therefore, the one-pot synthesis was not further studied.

Table 1
Synthesis of 5-aryl-2,3-dibromo-*N*-methylpyrroles **3a–g**

3	Ar^1	*T* [°C]	*t* [h]	(%) (3)[a]
a	$2,6\text{-}(MeO)_2C_6H_3$	90	8	43
b	$4\text{-}MeC_6H_4$	100	8	82
c	$4\text{-}EtC_6H_4$	100	6	73
d	$4\text{-}tBuC_6H_4$	90	8	64
e	$2\text{-}(MeO)C_6H_4$	90	8	61
f	$3,5\text{-}Me_2C_6H_3$	110	6	58
g	$3\text{-}FC_6H_4$	90	8	51

[a] Yields of isolated products.

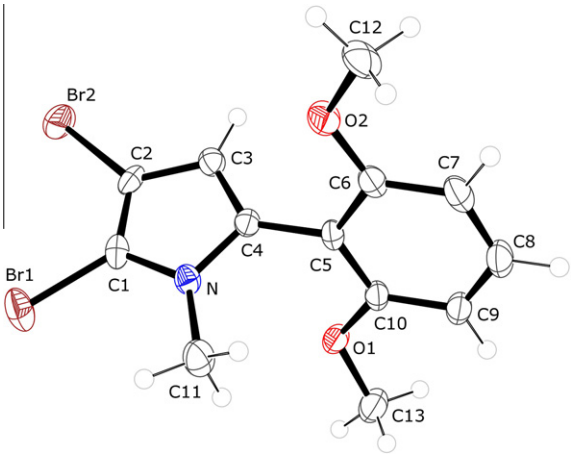
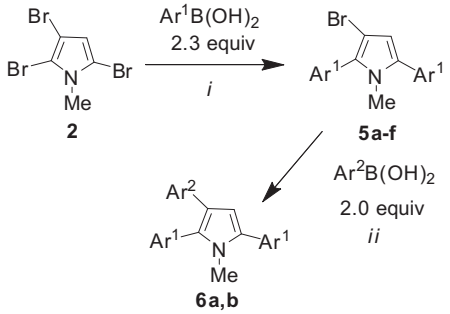


Figure 1. Ortep plot of **3a.**

Table 2
Synthesis of 2,3,5-triaryl-*N*-methylpyrrole **4a**

4	Ar^1	Ar^2	(%) (4)[a]
a	$4\text{-}tBuC_6H_4$	$4\text{-}(MeO)C_6H_4$	74

[a] Yields of isolated products.



Scheme 3. Synthesis of **5a–d** and **6a,b.** Reagents and Conditions: (i) **2** (1.0 equiv), $Ar^1B(OH)_2$ (2.3 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (4.0 equiv), 1,4-dioxane/toluene = 1:1, 100 °C, 12 h; (ii) **5d,f** (1.0 equiv), $Ar^2B(OH)_2$ (2.0 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (4.0 equiv), toluene, 110 °C, 36 h.

Table 3
Synthesis of 2,5-diaryl-3-bromo-*N*-methylpyrroles **5a–f**

5	Ar^1	(%) (5)[a]
a	$3\text{-}(MeO)C_6H_4$	53
b	$3,5\text{-}Me_2C_6H_3$	42
c	$2\text{-}(EtO)C_6H_4$	45
d	$4\text{-}(MeO)C_6H_4$	58
e	$2,6\text{-}(MeO)_2C_6H_3$	40
f	$4\text{-}tBuC_6H_4$	37

[a] Yields of isolated products.

Table 4
Synthesis of 2,3,5-triaryl-*N*-methylpyrroles **6a,b**

6	Ar^1	Ar^2	(%) (6)[a]
a	$4\text{-}(MeO)C_6H_4$	$4\text{-}ClC_6H_4$	72
b	$4\text{-}tBuC_6H_4$	$2\text{-}(EtO)C_6H_4$	83

[a] Yields of isolated products.

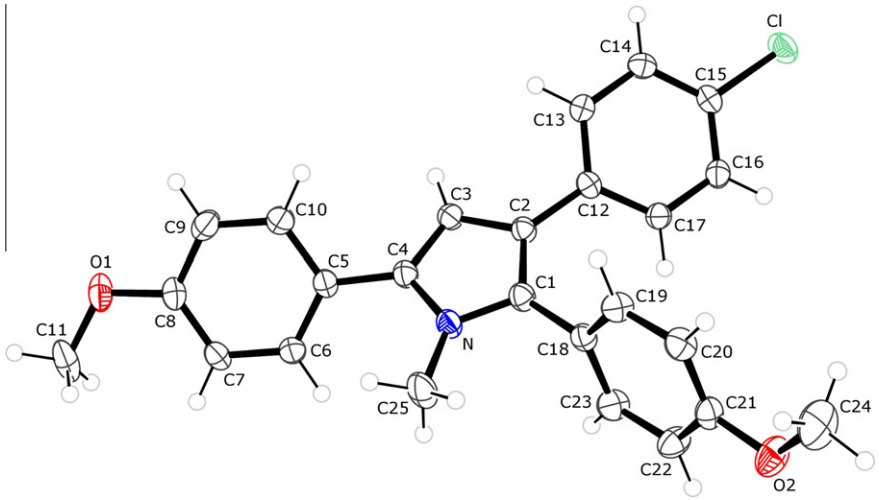
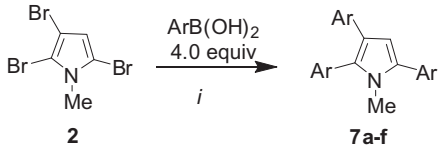
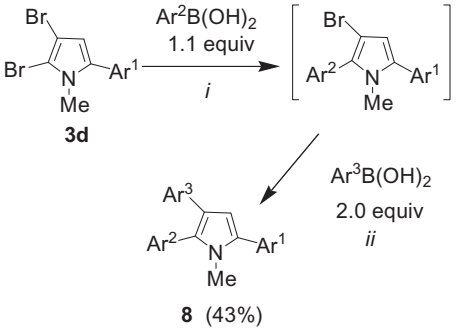


Figure 2. Ortep plot of **6a**.



Scheme 4. Synthesis of **7a–f.** Reagents and Conditions: (i) 2 (1.0 equiv), $ArB(OH)_2$ (4.0 equiv), $Pd(OAc)_2$ (5 mol %)/$P(Cy)_3$ (10 mol %), K_3PO_4 (4.0 equiv), toluene, 110 °C, 36 h.



Scheme 5. Synthesis of **8.** Reagents and Conditions: (i) **3d** (1.0 equiv), $Ar^2B(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (4.0 equiv), 1,4-dioxane/toluene = 1:1, 100 °C, 6 h; (ii) $Ar^3B(OH)_2$ (2.0 equiv), K_3PO_4 (2.0 equiv), 110 °C, 24 h.

Table 5
Synthesis of 2,3,5-triaryl-*N*-methylpyrroles **7a–f**

7	Ar^1	(%) (7)[a]
a	4-MeC_6H_4	68
b	4-$(MeO)C_6H_4$	89
c	3-$(MeO)C_6H_4$	76
d	4-*t*BuC_6H_4	72
e	2,3,4-$(MeO)_3C_6H_2$	92
f	3-FC_6H_4	62

[a] Yields of isolated products; Cy = cyclohexyl.

Table 6
Synthesis of 2,3,5-triaryl-*N*-methylpyrrole **8a**

	Ar^1	Ar^2	Ar^3	(%) (8)
8%	4-*t*BuC_6H_4	2-$(MeO)C_6H_4$	4-Et C_6H_4	43

[a]Yields of isolated products.

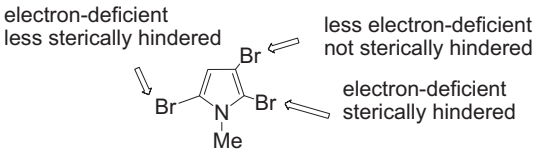


Figure 3. Possible explanation for the site-selectivity of the reactions of **2.**

The S–M reaction of **2** with 2.3 equiv of arylboronic acids gave 2,5-diaryl-3-bromo-*N*-methylpyrroles **5a–f** in 40–53% yields (Scheme 3, Table 3).[15] The reactions were carried out at 100 °C (12 h). The S–M reactions of **5d,f** with 2.0 equiv of arylboronic acids afforded the 2,3,5-triaryl-*N*-methylpyrroles **6a,b** (Scheme 3, Table 4). Similar to the synthesis of **4a**, the yield of the one-pot synthesis of **6a** was lower compared to the stepwise synthesis. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[14]

The moderate yields of compounds **5a–f** can be explained by the need to separate small amounts of trisubstituted compounds and of starting material by chromatography. Due to close R_f values, the separations were difficult and resulted in a decrease of the yield.

The S–M reaction of **2** with 4.0 equiv of arylboronic acids resulted in the formation of the 2,3,5-triarylpyrroles **7a–f** in 68–92% yields (Scheme 4, Table 4).[16] The reactions were carried using $Pd(OAc)_2/P(Cy)_3$ (Cy = cyclohexyl) which gave better yields than $Pd(PPh_3)_4$.

The reaction of 5-aryl-3,4-dibromopyrazoles **4** with arylboronic acids **3a**,**b**,**d**,**g**,**o** afforded the 3,4,5-triarylpyrazoles **7a–i** in 74–92% yield (Scheme 5, Table 5).

One-pot reaction of **3d** with two different arylboronic acids, which were sequentially added, gave 2,3,5-triaryl-*N*-methylpyrrole **8** containg three different aryl groups in 43% yield (Scheme 5, Table 6).

The site-selectivites can be explained by electronic and steric parameters.[6,17] Position 5 is the most reactive because it is more electron deficient than position 3 and less sterically hindered than position 2 (Fig. 3). From the electronic viewpoint, positions 2 and 5 are similar.

In conclusion, we have reported the first Suzuki–Miyaura reactions of 2,3,5-tribromo-*N*-methylpyrrole. The reactions provide a convenient and site-selective approach to various arylated pyrroles which are not readily available by other methods.

Acknowledgments

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13. *Synthesis of 5-aryl-2,3-dibromo-N-methylpyrroles* **3a–f**: To a mixture of **2** (0.159 g, 0.5 mmol), aryl boronic acid (0.55 mmol), and $Pd(PPh_3)_4$ (5 mol %) was added a mixture of 1,4-dioxane and toluene (1:1; 5 mL) and K_3PO_4 (4.0 equiv, 424 mg) under an argon atmosphere. The reaction mixture was stirred at 100 °C for 8 h and was subsequently allowed to cool to 20 °C. The solution was poured into H_2O and EtOAc (25 mL each) and the organic and the aqueous layers were separated. The latter was extracted with EtOAc (3 × 25 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (flash silica gel, eluent: *n*-heptane). *Synthesis of 2,3-dibromo-5-(3,5-dimethylphenyl)-1-methyl-1H-pyrrole* **(3f).** Starting with **2** (0.159 g, 0.5 mmol) and 3,5-dimethylphenylboronic acid (0.082 g, 0.55 mmol), **3f** was isolated (0.099 g, 58%) as a colourless oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.21 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.50 (s, 3H, NCH_3), 6.16 (s, 1H, $CH_{pyrrole}$), 6.92 (s, 3H, Ar). ^{13}C NMR (75 MHz, acetone-d_6): δ = 21.3 ($2CH_3$), 35.4 (NCH_3), 98.4, 105.5 (CBr), 111.3 (CH), 127.4 (2CH), 130.3 (CH), 132.9, 137.7 (C), 138.9 (2C). IR (KBr, cm^{-1}): ν = 3120, 2947, 2915, 2855 (w), 1600, 1466, 1450, 1372, 1322, 1302, 1273 (m), 1205, 1181 (w), 1086, 1036, 950 (m), 899 (w), 851, 840, 775, 695 (s), 663, 602 (m). GC/MS (EI, 70 eV): m/z (%) = 343 (100) [M$^+$ (^{81}Br, ^{79}Br)], 183 (10), 168 (13). HRMS (EI, 70 eV): *m/z* [M$^+$ (^{81}Br, ^{79}Br)] calcd for $C_{13}H_{13}NBr_2$: 342.93888; found: 342.939847.
14. CCDC-824509 (**3a**) and CCDC-824510 (**6a**) contain 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)1223-336-033; or deposit@ccdc.cam.ac.uk.
15. *Synthesis of 2,5-diaryl-3-bromo-N-methylpyrroles* **5a–f.** To a mixture of **2** (0.159 g, 0.5 mmol), aryl boronic acid (1.15 mmol), and $Pd(PPh_3)_4$ (5 mol %) was added a mixture of 1,4-dioxane and toluene (1:1; 5 mL) and K_3PO_4 (4.0 equiv, 424 mg) under an argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h and was subsequently allowed to cool to 20 °C. The solution was poured into H_2O and EtOAc (25 mL each) and the organic and the aqueous layers were separated. The latter was extracted with EtOAc (3 × 25 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (flash silica gel, eluent: heptanes/EtOAc). *Synthesis of 3-bromo-2,5-bis(3,5-dimethylphenyl)-1-methyl-1H-pyrrole* (***5b***). Starting with **2** (0.159 g, 0.5 mmol) and 3,5-dimethylphenylboronic acid (0.172 g, 1.15 mmol), **5b** was isolated (0.077 g, 42%) as a colourless oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.34 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.48 (s, 3H, NCH_3), 6.26 (s, 1H, $CH_{pyrrole}$), 7.00 (s, 1H, Ar), 7.04 (s, 1H, Ar), 7.10 (s, 4H, Ar). ^{13}C NMR (75 MHz, acetone-d_6): δ = 21.3 ($2CH_3$), 21.4 ($2CH_3$), 35.0 (NCH_3), 95.9 (CBr), 111.4 (CH), 127.4 (2CH), 129.1 (2CH), 129.8, 130.2 (CH), 132.2, 133.3, 134.1, 136.9 (C), 138.6 (2C), 138.8 (2C). IR (KBr, cm^{-1}): ν= 3005, 2918, 2856, 1711, 1679, 1663 (w), 1600, 1462 (m), 1376, 1330, 1270, 1191, 1038, 900 (w), 854, 841 (m), 780, 696, 659 (w). GC/MS (EI, 70 eV): m/z (%) = 367 (99) [M$^+$ (^{79}Br)], 272 (10). HRMS (EI, 70 eV): *m/z* [M$^+$ (^{79}Br)] calcd for $C_{21}H_{22}NBr$: 367.09301; found: 367.09300.
16. *Synthesis of 2,3,5-triaryl-N-methylpyrroles* **7a–f**: In a pressure tube (glass bomb) a suspension of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 5 mol %) and TCHP (28.04 mg, 0.10 mmol, 10 mol %) in Toluene (5 mL) was purged with Ar and stirred at 20 °C to give a brownish solution. To the stirred solution were added **2** (0.159 g, 0.5 mmol), arylboronic acid (2.0 mmol), and K_2PO_4 (4.0 equiv, 424 mg) under argon atmosphere. The reaction mixture was stirred at 110 °C for 36 h and was subsequently allowed to cool to 20 °C. The solution was poured into H_2O and EtOAc (25 mL each) and the organic and the aqueous layer were separated. The latter was extracted with EtOAc (3 × 25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (flash silica gel, eluent: heptanes/EtOAc). *Synthesis of 2,3,5-tris(4-methoxyphenyl)-1-methyl-1H-pyrrole* (***7b***). Starting with **2** (0.159 g, 0.5 mmol) and 4-methoxyphenylboronic acid (0.304 g, 2.0 mmol), **7b** was isolated (0.177 g, 89%) as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ = 3.30 (s, 3H, NCH_3), 3.59 (s, 3H, OCH_3), 3.71 (s, 6H, $2OCH_3$), 6.19 (s, 1H, $CH_{Pyrrole}$), 6.60 (dd, *J* = 2.1, 6.7 Hz, 2H, Ar), 6.84 (dd, *J* = 2.1, 6.7 Hz, 2H, Ar), 6.88 (dd, *J* = 2.2, 6.8 Hz, 2H, Ar), 6.98 (dd, *J* = 2.1, 6.7 Hz, 2H, Ar), 7.12 (dd, *J* = 2.1, 6.7 Hz, 2H, Ar), 7.31 (dd, *J* = 2.1, 6.7 Hz, 2H, Ar). ^{13}C NMR (62 MHz, acetone-d_6): δ = 33.7 (NCH_3), 55.4, 55.5, 55.5 (OCH_3), 108.5 (CH), 114.3 (2CH), 114.7 (2CH), 114.8 (2CH), 122.7, 126.7, 127.1 (C), 129.3 (2CH), 130.4 (C), 130.7 (2CH), 131.8 (C), 133.1 (2CH), 135.5, 158.4, 159.8, 160.1 (C). IR (KBr, cm^{-1}): ν = 3004, 2952, 2930, 2833, 1608, 1600, 1574, 1562 (w), 1517, 1497, 1461, 1440 (m), 1373, 1343, 1304 (w), 1285 (m), 1239, 1170 (s), 1108 (m), 1026, 832 (s), 806, 790 (m), 752, 650 (w), 585, 534 (m). GC/MS (EI, 70 eV): m/z (%) = 399 (100) [M$^+$], 384 (35). HRMS (EI, 70 eV): *m/z* [M$^+$] calcd for $C_{26}H_{25}O_3N$: 399.18290; found: 399.18262.
17. For a simple guide to predict the regioselectivity based on ^{1}H NMR chemical shifts of the non-halogenated parent compound, see: Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.