Synthesis of Tetrasubstituted 2-Aryl-3-arylsulfonyl Pyrroles: Unexpected Regioselectivity in Directed *ortho*-Metallation Reactions

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Abstract: 3-Arylsulfonyl pyrroles can be readily obtained from 3-Br-TIPS pyrrole via halogen–metal exchange and subsequent sulfonylation. The regioselectivity of the subsequent directed *ortho*-metallation (DOM) reaction in order to functionalise the C-2 position depends on the nature of the base (LTMP, *n*- or *s*-BuLi) and the N-substituent (SEM or Boc) used. The bulk of the N-substituent also strongly influences the yield of the subsequent Suzuki coupling with 2-iodo-3-arylsulfonyl pyrrole derivatives.

Key words: phenylsulfonyl fluoride, 3-sulfonyl pyrrole, directed *ortho*-metallation, palladium, Suzuki coupling

The pyrrole core has attracted considerable synthetic interest for many years since it occurs in many alkaloids[1] and therapeutic agents,[2] including the world's best-selling drug Lipitor (**1**; Figure 1).

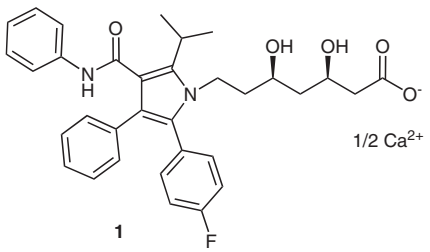

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Figure 1 Example of therapeutic agent containing a pyrrole nucleus.

Due to its electron-rich nature, the pyrrole nucleus can be easily oxidised in vitro and in vivo. One of the options to overcome this issue is to introduce electron-withdrawing substituents such as sulfonyl, carbonyl or amide moieties. Indeed, N-sulfonylation of pyrrole is straightforward but these derivatives can have stability issues, as the N–S bond can be cleaved under acidic or basic conditions. This is not the case when the sulfonyl group is carbon-linked to the pyrrole ring.

For this reason, during the course of our work, 2-aryl-3-arylsulfonyl pyrroles (Figure 2) became key intermediates capable of further functionalisation at the N-1 and C-5 positions using well-precedented reactions (alkylation, acylation, halogenation).

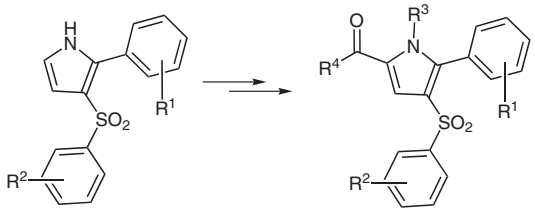
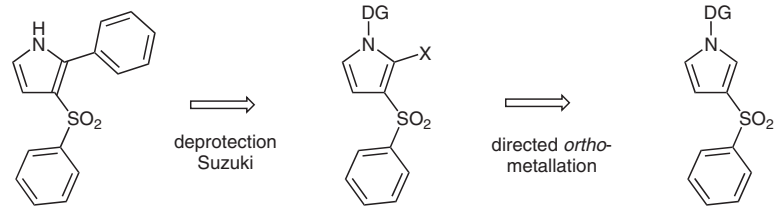


Figure 2 Disubstituted pyrroles as useful templates for further functionalisation.

The retrosynthesis envisioned for the model compound 2-phenyl-3-phenylsulfonyl pyrrole (**2**) is depicted in Scheme 1 and involves regioselective halogenation via directed *ortho*-metallation (DOM) of the appropriately protected 3-phenylsulfonyl pyrrole **3**, followed by Suzuki coupling and deprotection. DOM has already been successfully described in the case of 3-sulfonyl furans.[3]

The synthesis of 3-sulfonyl pyrroles has been described previously and can be mainly obtained via: a) rearrangement of 2-sulfinyl or 2-sulfonyl pyrroles;[4] b) [4+1]-[5]or



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Scheme 1 Retrosynthesis of 2-phenyl-3-phenylsulfonyl pyrrole. X = halogen, DG = directing group.

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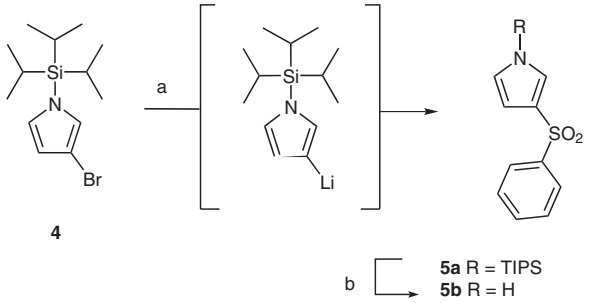
[3+2]-annulation[6] followed by oxidation of the intermediate 3-pyrroline; c) cycloaddition involving sydnone or *N*-acyl pyrroles and alkynyl sulfones.[7,8] In our case, because of the wide range of arylsulfonyl chlorides commercially available, we chose to synthesise this derivative via functionalisation of the 3-lithio-TIPS pyrrole derivative, easily obtained from commercially available 3-bromo-TIPS pyrrole **4** (Scheme 2).[9]

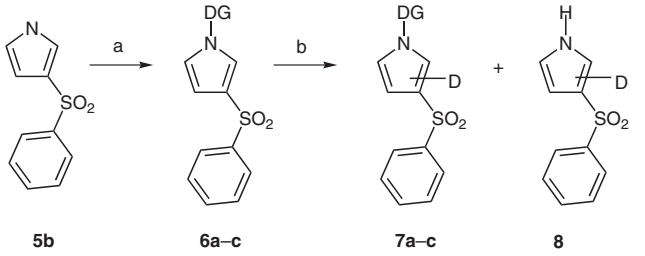


Scheme 2 *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C, 10 min then $PhSO_2F$, –78 °C; (b) TBAF, THF, 0 °C, 63% (2 steps).

Following halogen–metal exchange the intermediate could be quenched with phenylsulfonyl fluoride, easily available from the corresponding sulfonyl chloride,[10] in order to avoid formation of the 3-chloro derivative.[11]

As F^- is a byproduct of the reaction, **5a** was often accompanied by small amounts (ca. 15%) of the deprotected pyrrole **5b**. As the pyrrole nitrogen needed to be appropriately substituted for the following DOM step, it proved easier to operate the functionalisation at C-3 and deprotection in one pot and **5b** was obtained from 3-bromo-TIPS pyrrole **4** in 63% overall yield.

The first attempt of regioselective DOM was performed following the procedure described by Fowler and Levy,[12] using the Boc-protected pyrrole **6a** (DG = Boc, Scheme 3) and LTMP as a base. Deuterated methanol was used as trapping agent.



Scheme 3 *Reagents and conditions*: (a) Boc_2O, DMAP, MeCN, 25 °C, **6a** (98%) or NaH, DMF, 0 °C then SEMCl, **6b** (81%), or NaH, DMF, 0 °C then $PhSO_2Cl$, **6c** (84%); (b) base, THF, –78 °C then CD_3OD; **6a**,**7a**: DG = Boc; **6b**,**7b**: DG = SEM; **6c**,**7c**: DG = $PhSO_2$.

To our surprise, incorporation of deuterium occurred at both C-2 and C-5 positions (Table 1, entry 1).[13] One explanation for this lack of selectivity is the combined bulk of the Boc and sulfonyl groups, which prevents access to the C-2 proton for the large LTMP. This ratio was unaffected by increasing the temperature before adding the trapping reagent, but this rise in temperature was limited to –45 °C due to the instability of the lithiated intermediate. A complete selectivity in favour of the C-2 position could be obtained when *n*-BuLi or *s*-BuLi were used (entries 2 and 3), but significant amounts of partially deuterated pyrrole **8** were obtained in each case. Moreover, we were more interested in using non-nucleophilic bases as we wanted to transfer this methodology to functionalised arylsulfonyl derivatives.

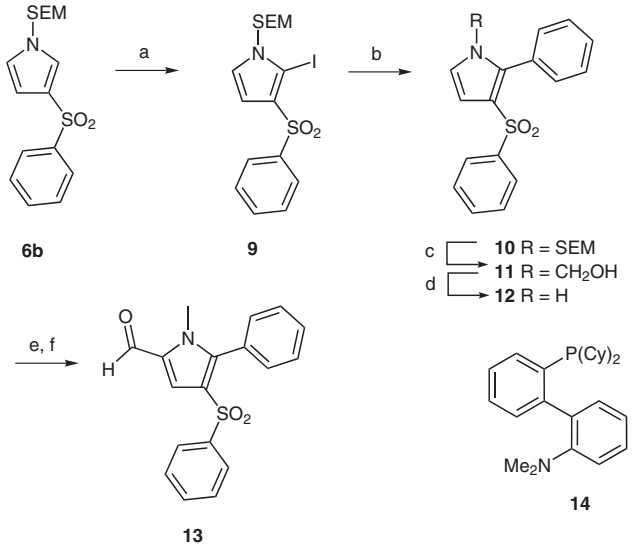
Hence, we decided to use SEM as a less hindered N-substituent as it has been shown to be as efficient as the Boc group in DOM reactions albeit at higher temperatures.[14] In this case, pyrrole **6b** was *ortho*-metallated with complete regioselectivity at C-2 using LTMP as a base (entry 4). It is interesting to note that using phenyl sulfone as a directing group led again to poor selectivity, confirming the major role of steric hindrance in this reaction (entry 6). DOM reactions using SEM as the directing group could be performed at low temperature and the proton-exchange was rapid (<10 min, see entry 5).

Table 1 Regioselectivity of Deuteration of 3-Phenylsulfonyl pyrrole **6a–c** following Directed *ortho*-Metallation

Entry	DG	Base[a]	**7**/**8**[b]	%D incorporated in **7**[b]				%D incorporated in **8**[b]			
				C-2	C-4	C-5	Total	C-2	C-4	C-5	Total
1	Boc	LTMP	>95:5	23	5	60	88				
2	Boc	*n*-BuLi	67:33	82	0	0	82	59	0	0	59
3	Boc	s-BuLi	67:25	50	0	0	50	38	0	2	40
4	SEM	LTMP	>95:5	90	0	0	90[c]				
5	SEM	LTMP	>95:5	90	0	0	90[d]				
6	SO_2Ph	LTMP	>95:5	45	0	50	95				

[a] Reaction conditions: base, THF, –78 °C, 50 min then CD_3OD, –78 °C, 5 min.
[b] Determined using ^1H NMR of the crude reaction. No evidence of any deuteration of the phenyl ring attached to SO_2 was observed in all cases.
[c] Isolated yield: 89%.
[d] Reaction time of 10 min prior to addition of CD_3OD.

Using iodine as a trapping agent under the same conditions gave pyrrole **9** (Scheme 4), which could now be reacted in Suzuki couplings. However, the conditions of the Suzuki reaction had to be optimised, again probably due to the steric hindrance around the iodine.[15] Standard conditions [$PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene–EtOH (1:1), reflux] gave a complex mixture in which both **10** and the reduced adduct **6b** were present in small quantities (<20%). Synthetically useful yields were obtained only when conditions reported by Buchwald[16] were used [$Pd(OAc)_2$, K_3PO_4, $PhB(OH)_2$, **14**, toluene]. However, the temperature needed to be lowered from 100 °C to 50 °C in order to avoid reduction of the intermediate and formation of **6b**.[17] Overall, the C-2 phenyl adduct could be obtained in 85% yield.



Scheme 4 *Reagents and conditions*: (a) LTMP, THF, –78 °C then I_2, 96%; (b) $PhB(OH)_2$, $Pd(OAc)_2$, K_3PO_4, **14**, toluene, 50 °C, 85%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C; (d) Triton B, MeCN, reflux, 73% (2 steps); (e) NaH, DMF, 0 °C then MeI, 86%; (f) $MeOCHCl_2$, $AlCl_3$, $(CH_2Cl)_2$, –30 °C to 0 °C, 77%.

Deprotection of the pyrrole **10** was performed using the method described by Muchowski et al.[14b,18] to afford the pyrrole **12** in good yields via the formation of **11**. Further reactions of pyrrole **12** proceeded as expected in good yields and with complete regioselectivity towards formylation or alkylation to give compounds such as **13**.[19,20]

Overall, we have described an efficient synthesis of 2-phenyl-3-phenylsulfonyl pyrrole thanks to a precise choice of directing group during the DOM step and conditions of reaction for the Suzuki coupling. This derivative is a useful building block for further functionalisation, allowing the regioselective synthesis of tetrasubstituted pyrroles. The full scope of this methodology will be reported in due course.

Acknowledgment

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References and Notes

(1) (a) Pinder, A. R. In *The Alkaloids*, Vol. 12; Grundon, M. F., Ed.; Chemical Society: London, **1982**. (b) Massiot, G.; Delaude, C. In *The Alkaloids*, Vol. 27; Manske, R. H. F., Ed.; Academic Press: New York, **1986**, Chap. 3.
(2) A search for the pyrrole core in WDI database retrieved more than 160 hits.
(3) Hartman, D. G.; Halczenko, W. *Tetrahedron Lett.* **1987**, *28*, 3241.
(4) (a) DeSales, J.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 3668. (b) Ortiz, C.; Greenhouse, R. *Tetrahedron Lett.* **1985**, *26*, 2831.
(5) (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041. (b) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801.
(6) (a) Burley, I.; Hewson, A. T. *Synthesis* **1995**, 1151. (b) For a related approach using 2-substituted vinamidinium salts, see: Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *J. Org. Chem.* **1990**, *55*, 4735.
(7) (a) Dalla Croce, P.; Gariboldi, P.; La Rosa, C. *J. Heterocycl. Chem.* **1987**, *24*, 1793. (b) Castro, J.; Coteron, J. M.; Fraile, M. T.; Garcia-Ochoa, S.; Gomez de las Heras, F.; Martin-Cuesta, A. *Tetrahedron Lett.* **2002**, *43*, 1851. (c) Chen, Z.; Trudell, M. L. *Tetrahedron Lett.* **1994**, *35*, 9649.
(8) This list is not exhaustive. See for examples: (a) Moranta, C.; Molins-Pujol, A. M.; Pujol, M. D.; Bonal, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3285. (b) Barnes, K. D.; Ward, R. *J. Heterocycl. Chem.* **1995**, *32*, 871.
(9) For the synthesis from TIPS pyrrole, see: Kozikowski, A. P.; Cheng, X.-M. *J. Org. Chem.* **1984**, *49*, 3239.
(10) Ichihara, J.; Matsuo, T.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* **1986**, 793.
(11) For difference of reactivity of sulfonyl chloride and fluoride on α-functionalisation of enolate, see: (a) Hirsch, E.; Hünig, S.; Reißig, H.-U. *Chem. Ber.* **1982**, *115*, 399. (b) Kende, A. S.; Mendoza, J. S. *J. Org. Chem.* **1990**, *55*, 1125. (c) Sandanayaka, V. P.; Zask, A.; Venkatesan, A. M.; Baker, J. *Tetrahedron Lett.* **2001**, *42*, 4605. (d) For application to sulfonylation of aryl metal, see: Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *J. Org. Chem.* **1992**, *57*, 697. (e) In our case, use of phenylsulfonyl chloride gave almost quantitatively the corresponding 3-Cl pyrrole.
(12) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
(13) The cooperative effects of *meta*-related directed metallation groups usually give excellent selectivity. See Table 3, p. 885 in: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(14) (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630. (b) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503. (d) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.
(15) In a previous attempt using 2-Br-3-$PhSO_2$ pyrrole, no Suzuki coupling was effective, possibly due to the acidity of the N-1 hydrogen; results to be published.
(16) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(17) At 100 °C, the ratio of **10** and **6b** was 1.85:1 according to the ^1H NMR of the crude reaction. This ratio was at least 95:5 at 50 °C. Lower temperatures were not considered.
(18) For deprotection under acidic conditions, see: (a) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Heterocycl. Chem.* **1987**, *24*, 689. (b) See also ref. 14d.
(19) Regioselectivity of every reaction leading to **13** was confirmed unambiguously by NOE experiments. Compound

13 (pale yellow solid) has the following characteristics: mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 7.14 (d, *J* = 6.8 Hz, 2 H), 7.28 (d, *J* = 7.2 Hz, 2 H), 7.42–7.48 (m, 5 H), 7.51–7.55 (m, 1 H), 7.55 (s, 1 H), 9.65 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.4, 124.1, 125.1, 127.2, 127.3, 128.4, 128.6, 130.1, 130.6, 130.8, 132.7, 142.0, 143.1, 180.0. MS (ESI): *m*/*z* = 326.0 $[M + H]^+$.

(20) **Typical Procedures**:

Compound **5b**: To a solution of 3-bromo-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (12.8 g, 42.4 mmol, 1 equiv) in THF (200 mL) at –78 °C under nitrogen was slowly added *n*-BuLi (2.5 M in hexanes, 17.8 mL, 44.5 mmol, 1.05 equiv) over 3 min and the resulting mixture was stirred for 15 min at this temperature. Phenylsulfonyl fluoride (7.5 g, 46.6 mmol, 1.1 equiv) in THF (20 mL) was added via syringe over 5 min and the resulting mixture was stirred for 45 min at this temperature, then partitioned between EtOAc (200 mL) and brine (100 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in THF (200 mL) and TBAF (1 M in THF, 42 mL, 1 equiv) was added and the resulting mixture was stirred for 30 min and then dissolved with EtOAc (200 mL). The organic phase was washed with a sat. aq $NaHCO_3$ solution (3 × 30 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (isohexane–EtOAc, 3:1 → 1:1) gave 3-(phenylsulfonyl)-1*H*-pyrrole (**5b**; 5.53 g, 63%) as a white solid; mp 145–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.48 (m, 1 H), 6.78 (m, 1 H), 7.38 (m, 1 H), 7.45–7.55 (m, 3 H), 7.92 (m, 2 H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 108.4, 120.4, 122.4, 124.6, 127.2, 129.0, 132.6, 143.3. MS (ESI): *m*/*z* = 208.1 $[M + H]^+$.

Compound **9**: To a solution 3-(phenylsulfonyl)-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-pyrrole (1.3 g, 3.86 mmol, 1 equiv) in THF (30 mL) at –78 °C under nitrogen was added LTMP (0.5 N in THF, 8.9 mL, 4.45 mmol, 1.15 equiv) over 1 min and the resulting mixture was stirred at this temperature for 50 min. Iodine (1.22 g, 4.82 mmol, 1.25 equiv) in THF (7 mL) was slowly added via syringe over 1 min. After 2 min, the mixture was partitioned between EtOAc (100 mL) and a 10% aq $Na_2S_2O_3$ solution (100 mL). The two layers were vigorously stirred for 5 min. Brine (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (isohexane–EtOAc, 95:5 → 4:1) gave 2-iodo-3-(phenylsulfonyl)-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-pyrrole (**9**; 1.71 g, 96%) as a white solid; mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 9 H), 0.94 (t, *J* = 8.8 Hz, 2 H), 3.54 (t, *J* = 8.8 Hz, 2 H), 5.29 (s, 2 H), 6.94 (d, *J* = 3.2 Hz, 1 H), 7.13 (d, *J* = 3.2 Hz, 1 H), 7.52–7.63 (m, 3 H), 8.06 (d, *J* = 6.4 Hz, 2 H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.0, 19.1, 68.0, 76.9, 81.1, 114.4, 127.5, 128.8, 130.3, 131.1, 134.2, 143.8. MS (ESI): *m*/*z* = no molecular ion.

Compound **10**: A flask was charged under nitrogen with 2-iodo-3-(phenylsulfonyl)-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-pyrrole (**9**; 1.04 g, 2.25 mmol, 1 equiv), $Pd(OAc)_2$ (50 mg, 0.22 mmol, 0.1 equiv), K_3PO_4 (952 mg, 4.49 mmol, 2 equiv), 2′-(dicyclohexylphosphanyl)-*N*,*N*-dimethyl-2-biphenylamine (176 mg, 0.45 mmol, 0.2 equiv) and $PhB(OH)_2$ (411 mg, 3.37 mmol, 1.5 equiv), then toluene (20 mL) was added and the resulting mixture was stirred at 50 °C for 4 h and then cooled to r.t. The mixture was dissolved with EtOAc (50 mL) and the organic phase was washed with a sat. $NaHCO_3$ solution, then with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (isohexane–EtOAc: 9:1 → 3:1) gave **10** (790 mg, 85%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.0 (s, 9 H), 0.83 (t, *J* = 8.4 Hz, 2 H), 3.36 (t, *J* = 8.4 Hz, 2 H), 5.01 (s, 2 H), 6.87 (d, *J* = 2.8 Hz, 1 H), 6.92 (d, *J* = 2.8 Hz, 1 H). 7.26–7.56 (m, 10 H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.0, 67.7, 77.4, 111.6, 124.8, 128.4, 129.4, 129.9, 130.1, 130.7, 132.9, 133.6, 137.7, 144.7. MS (ES): *m*/*z* = 413.9 $[M + H]^+$.