Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A metal-free and recyclable synthesis of benzothiazoles using thiourea as a sulfur surrogate

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ARTICLE INFO

Article history:
Received 7 January 2015
Revised 5 February 2015
Accepted 13 February 2015
Available online xxxx

Keywords:
Benzothiazoles
Thiourea
Isothiouronium salt
TFA
ROCK inhibitors

ABSTRACT

Using odorless thiourea as the S source, benzothiazoles and asymmetric disulfides could be obtained from thioformanilides through the tandem cyclization/nucleophilic addition/hydrolysis/nucleophilic substitution reaction. Furthermore, the obtained asymmetric disulfides could readily transfer to benzothiazoles after nitro-reduction and amide formation reaction. This metal-free and recyclable synthetic methodology offered a time-efficient, less expensive, and environmentally friendly alternative to multifunctional benzothiazoles.

Introduction

The benzothiazole moiety is an important architecture due to its widespread occurrence in bioactive natural products, pharmaceuticals, organic optoelectronic materials, and ligands for phosphorescent complexes.[1] The most common method to prepare this building block involves condensations of an *ortho*-amino thiophenol with an aromatic aldehyde, carboxylic acid, acyl chloride, or nitrile under a wide set of reaction conditions (Fig. 1a).[2] However, this methodology suffered from the disadvantages in preparation of *ortho*-amino thiophenol derivatives, and the odors from thiophenols lead to bad environmental problems in work-up processes. An alternative strategy for the synthesis of benzothiazoles is ring closure of thioformanilides, which needs sulfur reagents such as P_4S_{10} or Lawesson's reagent to convert the amides to corresponding thioamides (Fig. 1b).[3] Itoh and Mase published a novel synthesis of benzothiazoles via Pd-catalyzed cross-coupling of 2-haloanilides with thiols followed by base- or TFA-promoted cyclization.[4] In this transformation the R_1 group linked to the S atom acted as the protected group to introduce sulfur to the molecule and was discarded as waste without recovery after the cyclization reaction (Fig. 1c). Recently, several copper-catalyzed approaches to benzothiazoles were reported in good yields using inorganic sulfur as sulfur sources (Fig. 1d).[5] Although much attention has been paid to the construction of the benzothiazole unit, development of new synthetic methodologies for this privileged structure is still an important and challenging task for the chemistry community.

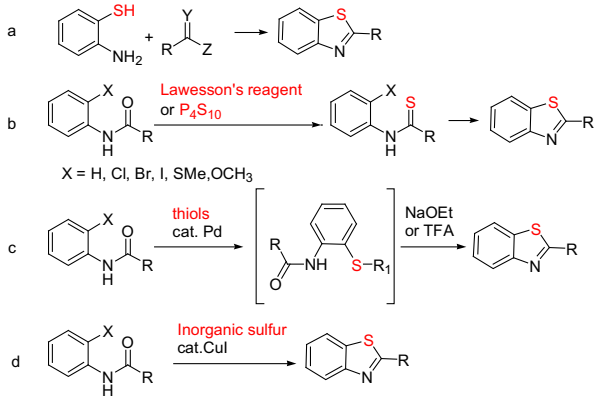

Figure 1. Synthesis of benzothiazoles.

We have previously discovered a series of benzothiazole derivatives as ROCK inhibitors with good biochemical and cellular

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http://dx.doi.org/10.1016/j.tetlet.2015.02.054
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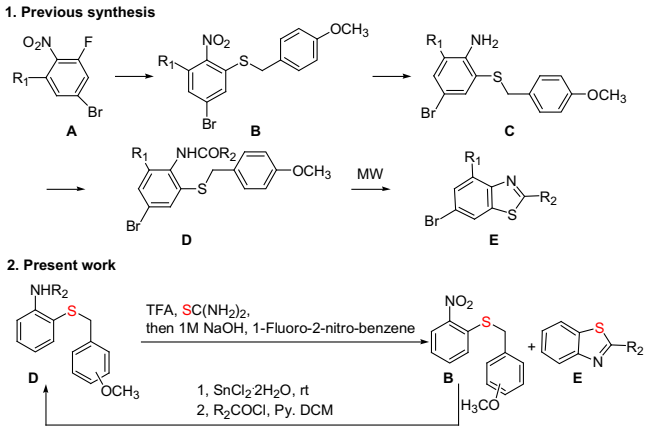


Figure 2. Synthetic route of benzothiazoles.

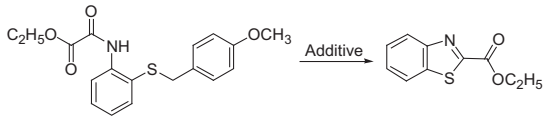
potencies and sufficient kinase selectivity.[6] The benzothiazole core was accessed in 4 steps including thionation, nitro reduction, amide coupling, and microwave-assisted cyclization. In this reported synthetic route, odorous 4-methoxyl-benzyl mercaptan was used as the sulfur source to introduce sulfur atom through thionation reaction of 2-fluoro-1-nitro-benzene derivatives (A), and the benzyl group linked to S atom acted as a leaving group and did not recover after the cyclization reaction (Fig. 2, 1).[6] A new synthetic route was recently developed in our lab. In this new route, only 3 steps were needed to build up the benzothiazole moiety (E, Fig. 2), and odorless thiourea was used as the S source. This new route is more time-efficient, less expensive, and more environmental friendly (Fig. 2, 2). Herein, the development of a metal-free and recyclable synthesis of benzothiazoles with thiourea as the sulfur source is discussed in detail, and a novel synthesis of the key intermediate of **SR6494**, an important benzothiazole-based ROCK inhibitor, is also reported.

Results and discussion

We initially screened the reaction conditions including additive, solvent, temperature, and reaction time to optimize the synthesis of benzothiazoles with *N*-[2-(4-methoxy-benzylsulfanyl)-phenyl]-oxalamic acid ethyl ester **1a** as the substrate of the model reaction (Table 1). With excess TFA (CF_3COOH), thioformanilide **1a** was transferred to benzothiazole-2-carboxylic acid ethyl ester 2 in 95% yield after 2 h at 80 °C (Table 1, entry 1). The addition of solvent such as CH_2Cl_2, $CHCl_3$, toluene, and α,α,α-trifluorotoluene to the reaction mixture slowed down the reaction and only trace amount of products was obtained after 2 h as detected by TLC analysis (Table 1, entries 2–5). If running the TFA-promoted reaction at room temperature without any solvents, the conversion of **1a** to **2** was very slow and only a small amount of **2** was observed by TLC analysis after 2 h and the conversion could not completely finish even by prolonging the reaction rime to 24 h (Table 1, entry 6). Changing the additive from TFA to formic acid (HCOOH) or acetic acid (CH_3COOH), trace or no products were obtained after heating the mixture for 2 h at 110 °C, respectively (Table 1, entries 7 and 9). By prolonging the reaction time to 18 h, a yield of 95% was obtained with formic acid as the additive (Table 1, entry 8). However, still only trace amount of products was observed using acetic acid (Table 1, entry 9). Therefore, TFA was very important for this intramolecular cyclization and will be used as the additive in further investigation.

The 4-methoxy-benyl group in **1a** was proved to be a good protecting group for this TFA-promoted cyclization. In addition, we also investigated a few other protecting groups for this conversion.

Table 1
Survey of the cyclization conditions[a]



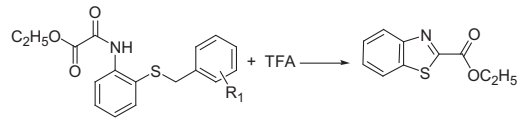
Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	CF_3COOH	—	80	2	95[b]
2[c]	CF_3COOH	CH_2Cl_2	80	2	Trace
3[c]	CF_3COOH	$CHCl_3$	80	2	Trace
4[c]	CF_3COOH	Toluene	80	2	Trace
5[c]	CF_3COOH	Trifluoromethyl-benzene	80	2	Trace
6[c]	CF_3COOH	—	rt	2	Trace
7[c]	HCOOH	—	110	2	Trace
8	HCOOH	—	110	18	95[b]
9[c]	CH_3COOH	—	110	2	N/R
10[c]	CH_3COOH	—	110	24	Trace

[a] Conditions: **1a** (0.2 mmol), additive (0.1 mL), solvent (0.2 mL).
[b] Isolated yield based on **1a**.
[c] Unconsumed **1a** was recovered.

Substrates **1b**–**1e**, which contain the 2-OCH_3, 2,4,6-OCH_3, 4-H, or 4-Cl substitution on the phenyl ring, were prepared and subjected to the cyclization and the results are shown in Table 2. All substrates containing the methoxy group underwent the reaction smoothly and gave product **2** in high yields within 2 h no matter what was the substitution position on the phenyl ring (Table 2, entries 1–3). However, no cyclizations were observed when **1d** (with no substitution) and **1e** (with the electronic withdrawing group (Cl) at *para* position) were treated with TFA (Table 2, entries 4 and 5). Increasing the reaction time to 24 h led to anilines because the amide bond was unstable under acid conditions for a long time. These results suggested that the presence of methoxy groups could stabilize the benzyl cation intermediates derived from **1a** to **1c** as compared to that **1d** and **1e**.

Methoxylbenzyl cations could be seized by nucleophiles such as thiourea.[7] Thiourea was thus added to the mixture of **1** in TFA to study the tandem cyclization/nucleophilic addition. The results were just what we expected and are shown in Table 3. Cooking **1a** with TFA and thiourea for 2 h, both benzothiazole 2 and benzylisothiouronium TFA salt **3a** were obtained in 95% equal yields (Table 3, entry 1). **1b** and **1c** also underwent the tandem

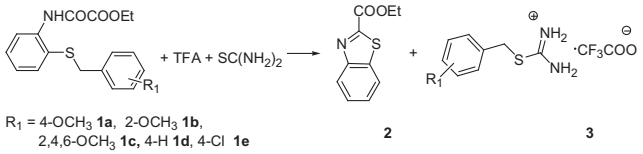
Table 2
Survey of the cyclization conditions[a]



Entry	Substrate	Time (h)	Yield of **2**[b] (%)
1	**1a**	2	95
2	**1b**	2	90
3	**1c**	2	95
4	**1d**	2	N/R[c]
5	**1e**	2	N/R[c]

[a] Conditions: **1** (0.2 mmol), TFA (0.1 mL), 80 °C.
[b] Isolated yield based on **1**.
[c] **1** was recovered.

Table 3
Tandem cyclization/nucleophilic addition[a]



Entry	Substrate	Time (h)	Yield of **2**[b] (%)	Yield of **3**[b] (%)
1	**1a**	2	95	95
2	**1b**	2	95	95
3	**1c**	2	95	95
4[c]	**1d**	2	N/R	N/R
5[c]	**1e**	2	N/R	N/R

[a] Conditions: **1** (0.2 mmol), TFA (0.1 mL), thiourea (0.2 mmol), 80 °C.
[b] Isolated yield based on **1**.
[c] **1** was recovered.

cyclization/nucleophilic addition smoothly, and good yields were obtained after 2 h (Table 3, entries 2 and 3). On the other hand, no reactions were observed when substrates **1d** and **1e**, which had no methoxy substitutions, were treated with TFA and thiourea in 2 h (Table 3, entries 4 and 5).

Hydrolysis of *S*-alkylisothiouronium salts in aqueous alkali is a simple and well established route to prepare the corresponding alkylthiols.[8] The mixture of **1a**, TFA, and thiourea was subjected to the NaOH-promoted hydrolysis to explore the tandem cyclization/nucleophilic addition/Hydrolysis reaction. After heating for 2 h, EtOAc was added to the mixture, and the upper organic phase was collected and purified through column to give **2** in 95% yield. Meanwhile, the bottom residue was treated with 1 M NaOH and 4-methoxylbenzylthiol **5** was obtained. At the same time a small amount of dimmer product **4** was obtained as a pale powder since thiol **5** was easily trapped by itself to form a disulfide (Fig. 3).

After 1 M NaOH solvent was proved to be the effective aqueous alkali in generating the thiolate anion by decomposing isothiouronium TFA salts, we further invested the coupling between the thiolate anion and electrophiles to yield asymmetric dialky sulfides. We tried the tandem cyclization/nucleophilic addition/hydrolysis/nucleophilic substitution reaction with organohalogens as the electrophiles,[9] and the results are shown in Table 4. 1-Bromo-butane, 1-bromo-heptane, allylic bromide, and chlorinated alkene were transferred to asymmetric thioesters **6** in medium yields after 6 h at 50 °C, and disulfide **4** was also separated in 6–11% yields. Thiol **5** was not detected after the transformation (entries 1–4). To our surprise, when an aryl fluoride such as 1-fluoro-2-nitro-benzene was subjected to the transformation, the phenyl benzyl thioester was obtained in 80% yield after 6 h at 50 °C and only trace amount of disulfide 4 was observed (entry 5). When 4-bromo-2-fluoro-1-nitro-benzene was subjected the reaction to compare the reaction selectivity between fluoride and bromide, only fluoride was substituted by thiol **5** to give 4-bromo-2-(4-methoxy-benzylsulfanyl)-1-nitro-benzene in 78% yield, and again trace disulfide **4** was detected (entry 6).

SR6494, a promising ROCK inhibitor for the treatment of glaucoma, exhibited excellent biochemical and cellular potencies (IC_{50} = 0.4 nM and 6 nM, respectively) and over 100-fold ROCK/PKA selectivity.[6] A large amount of **SR6494** was needed for further

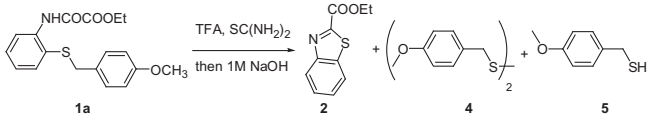
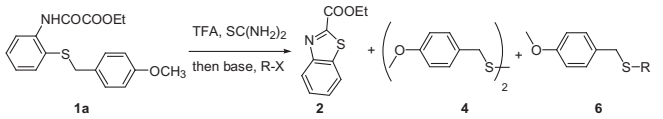
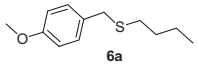
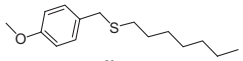
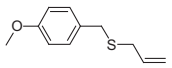
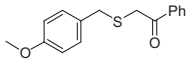
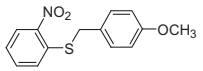
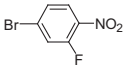
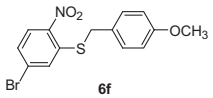


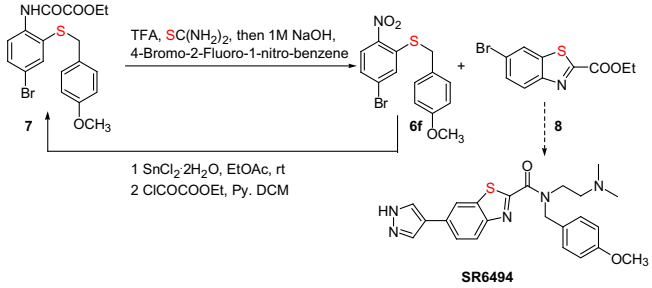
Figure 3. Tandem cyclization/nucleophilic addition/hydrolysis.

Table 4
Tandem cyclization/nucleophilic addition/hydrolysis/nucleophilic substitution reaction[a]



Entry	R–X	Structure of **6**[b]	Yield of **6**[b]	Yield of **4**[b]
1	*n*-BuBr	 **6a**	60	11
2	1-Bromo-heptane	 **6b**	61	10
3		 **6c**	63	9
4	$PhCOCH_2Cl$	 **6d**	67	6
5		 **6e**	80	Trace
6		 **6f**	78	Trace

[a] Conditions: **1a** (0.2 mmol), TFA (0.1 mL), thiourea (0.2 mmol), 80 °C; then 1 M NaOH, R–X (0.2 mmol), 50 °C, 6 h.
[b] Isolated yield based on **1a**.



Scheme 1. Access to the key intermediate of **SR6494**.

biological evaluation in our lab. Based on the synthesis of **6f**, we tested a new synthetic methodology to prepare 6-bromo-benzothiazole-2-carboxylic acid ethyl ester **8** (Scheme 1), which is the key intermediate of **SR6494**. **8** was obtained[10] through a tandem cyclization/nucleophilic addition/hydrolysis/nucleophilic substitution reaction started from thioformanilides **7**, which could be obtained via two steps including nitro reduction and amide formation. Continuous preparation of **8** in a gram scale was preliminarily investigated and the results suggested that the benzyl group linked to S atom was recyclable (Supporting information for detail).

Conclusion

We developed a metal-free and recyclable procedure for benzothiazoles. In this new synthetic methodology, odor-free and cheap thiourea was used as a sulfur surrogate. Two types of valuable chemicals including benzothiazoles and asymmetric disulfides

could be obtained in one reaction through the tandem cyclization/nucleophilic addition/hydrolysis/nucleophilic substitution reaction starting from thioformanilides. Meanwhile, asymmetric disulfides could further transform to benzothiazoles through nitro reduction and amide formation. In the preparation of the key intermediate of **SR6494**, this synthetic route fully displayed its time saving, cost efficient, and environmental friendly advantages. Preparation of newly designed benzothiazole-based ROCK inhibitors by this novel method is underway in our lab and will be published in due course.

Acknowledgments

The work was supported by Science and Technology Commission of Shanghai Municipality (Grant no. 12ZR1431100) and National Natural Science Foundation of China (No. 21172148). Support from Prof. Gang Zhao and Prof. Guanjun Wang was also greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.054.

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9. Typical procedure: The mixture of **1a** (0.2 mmol), TFA (0.1 mL), and $SC(NH_2)_2$ (0.2 mmol) was heated at 80 °C. After the reaction was complete (detected by TLC), the mixture was cooled to room temperature and EtOAc (2 mL × 2) was added. The upper organic phase was evaporated and purified through column to give **2** in 95% yield. Meanwhile, the bottom residue was stirred with 1 M NaOH (1 mL) and R–X (0.2 mmol) at 50 °C for 6 h. After the reaction was complete (detected by LC–MS), the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. The residue was purified through column to give asymmetric disulfide **6**. *Benzothiazole-2-carboxylic acid ethyl ester (**2**)*: white solid; mp 58–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20–8.18 (m, 1H), 7.92–7.90 (m, 1H), 7.54–7.47 (m, 2H), 4.49 (q, *J* = 6.8 Hz, 2H), 1.43 (t, *J* = 6.8 Hz, 3H); IR (KBr, cm^{-1}): 2926, 2853, 1741, 1716, 1498, 1293, 1095, 763, 730. *Butylsulfanylmethy-4-methoxy-benzene (**6a**)*: white solid; mp 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) = 7.25 (d, *J* = 8.5 HZ, 2H), 6.87 (d, *J* = 8.5 HZ, 2H), 3.82 (s, 2H), 2.43 (t, *J* = 7.5 HZ, 2H), 1.56 (m, 2H), 1.39 (m,2H), 0.91(t, *J* = 7.5 HZ, 3H); IR (KBr, cm^{-1}): 2955, 2930, 2833, 1610, 1511, 1464, 1301, 1249, 1174, 1106, 1035, 830, 742, 545. *1-Heptyl sulfanylmethyl-4-methoxy-benzene (**6b**)*: white solid; mp 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.5 HZ, 2H) 6.87 (d, *J* = 8.5 HZ, 2H), 3.82 (s, 3H), 3.68 (s, 2H), 2.42 (t, *J* = 7.5 HZ, 2H), 1.58 (m, 2H), 1.37–1.28 (m, 8H), 0.90 (t, *J* = 6.5HZ, 3H); IR (KBr, cm^{-1}): 3000, 2954, 2925, 2853, 1610, 1511, 1464, 1377, 1249, 1174, 1106, 1036, 828, 735, 670, 546. *4-Bromo-2-(4-methoxy-benzylsulfanyl)-1-nitro-benzene (**6c**)*: colorless oil ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 6.0 HZ, 2H) 6.93 (d, *J* = 6.0 HZ, 2H) 5.98–5.89 (m, 1H) 5.50–5.36 (m, 2H) 3.99–3.93 (m, 2H) 3.83 (s, 3H), 3.45–3.41 (m, 1H) 3.30–3.26 (m, 1H); IR (KBr, cm^{-1}): 3002, 2907, 2833, 1609, 1511, 1301, 1248, 1174, 1106, 1035, 990, 917, 833, 740, 674, 545. *2-(4-Methoxy-benzylsulfanyl)-1-phenyl-ethanone (**6d**)*: white solid; mp 52–53 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.5 HZ, 2H), 7.61–7.58 (m, 1H) 7.48 (d, *J* = 7.5 HZ, 2H), 7.28 (d, *J* = 8.5 HZ, 2H), 6.87 (d, *J* = 8.5 HZ, 2H), 3.82 (s, 3H), 3.74 (s, 2H), 3.69 (s, 2H); IR (KBr, cm^{-1}): 2927, 1672, 1511, 1447, 1277, 1249, 1175, 1032, 833, 688. *1-Benzylsulfanyl-2-nitro-benzene (**6e**)*: yellow solid; mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22–8.20 (m, 1H), 7.54–7.52 (m, 1H), 7.50–7.45 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28–7.23 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.16 (s, 2H), 3.80 (s, 3H); IR (KBr, cm^{-1}): 3086, 2830, 1506, 1334, 1304, 1248, 1176, 1028, 736, 654, 541; ^{13}C NMR (100 MHz, $CDCl_3$) 159.18, 155.52, 138.07, 133.55, 130.28, 126.89, 126.84, 126.07, 124.62, 114.23, 55.39, 37.00; LC/MS ($M+H^+$) (*m*/*z*) 276; HRMS (ESI-Orbitrap) calcd for $C_{14}H_{14}NO_3S$ [$M+H^+$]: 276.0694, found 276.0706. *4-Bromo-2-(4-methoxy-benzylsulfanyl)-1-nitro-benzene (**6f**)*: yellow solid; mp 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12–8.10 (m, 1H) 7.63–7.62 (m, 1H) 7.40–7.38 (m, 1H) 7.35 (d, *J* = 6.4 Hz, 2H) 6.91 (d, *J* = 6.4 Hz, 2H) 4.17 (s, 2H) 3.83 (s, 3H); IR (KBr, cm^{-1}): 3107, 2966, 2919, 2359, 1581, 1503, 1327, 1250, 1110, 1030, 750, 672, 527.
10. *6-Bromo-benzothiazole-2-carboxylic acid ethyl ester (**8**)*. white solid; mp 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13–8.09 (m, 2H), 7.88–7.60 (m, 1H), 4.56 (q, *J* = 6.0 Hz, 2H) 1.50 (t, *J* = 6.0 Hz, 3H); IR (KBr, cm^{-1}): 3089, 2981, 1741, 1715, 1497, 1316, 1102, 814, 759, 744, 522; ^{13}C NMR (100 MHz, DMSO) 160.32, 158.99, 151.96, 138.26, 130.84, 126.56, 124.66, 121.78, 63.33, 14.26; LC/MS ($M+H^+$) (*m*/*s*): 286; HRMS (ESI-Orbitrap) calcd for $C_{10}H_9BrNO_2S$ [$M+H^+$]: 285.9537, found 285.9556.