Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 567–571

New methodology for the preparation of 3-hydroxy-2-pyridinone (3,2-HOPO) chelators and extractants. Part 2: Reactions of alcohols, phenols, and thiols with an electrophilic 3,2-HOPO reagent☆

Sumathi Chittamuru, Timothy N. Lambert, Gloria Martinez, Hollie K. Jacobs and Aravamudan S. Gopalan*

Department of Chemistry and Biochemistry, MSC 3C, New Mexico State University Las Cruces, NM 88003-8001, USA

Received 3 October 2006; revised 17 November 2006; accepted 21 November 2006

Abstract—The reactions of the electrophilic iminium ester mesylate salt **1** with alcohols, phenols, and thiols have been investigated. In the presence of base, thiols, phenols, and thiophenol react with **1** to give the corresponding ether linked HOPO derivatives in good yields. However, the ring opening of salt **1** with alcohols could only be accomplished efficiently using a large excess of the alcohol in the presence of methanesulfonic acid at 80 °C. The synthetic utility of HOPO precursor, **1**, has been demonstrated by the synthesis of two polyHOPO chelators **7** and **9**.

Molecules containing the 3-hydroxy-2-pyridinone (3,2-HOPO) ligand have been of considerable interest because of their ability to form strong complexes with hard metal ions especially iron(III).[1] A number of HOPO chelators have been synthesized and examined for potential applications in the treatment of patients suffering from iron overload diseases.[2] Gadolinium HOPO chelates have been investigated for their use as relaxation agents in magnetic resonance imaging (MRI).[3] A number of HOPO derived chelators have been studied for their ability to achieve in vivo clearance of actinide ions such as Pu(IV).[4] Hydroxypyridinone ligands have been examined as potential extraction agents for Pu(IV)[5] and they have been attached to calix[4]arenes to yield useful Th(IV) extractants.[6] This ligand system has also been incorporated into polymers,[7] dendrimers,[8] and self-assembled monolayers on mesoporous silica.[9] Recently, a parallel synthesis of a library of metal ion chelators has incorporated HOPO ligands.[10]

The most common method for the preparation of 3,2-HOPO derivatives involves the coupling of an amine or amine scaffold with an activated carboxylic acid linker attached to the pyridinone ring system.[2a,11] This results in the formation of polyamide linkages reducing the organic and aqueous solubility of the final product. The direct alkylation of 2,3-dihydroxypyridine on a trimesylate under harsh conditions to yield a tris-3,2-HOPO derivative in low yields has been reported.[12] The alkylation of 1,7-dimethylcyclen with 3-benzyloxy-1-(2-chloroethyl)-1*H*-pyridin-2-one followed by hydrogenolysis has been used to prepare a diHOPO cyclen chelator.[13]

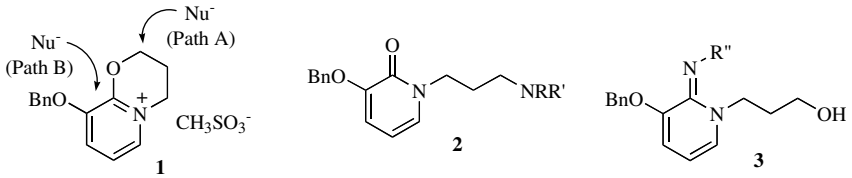
In conjunction with our program to develop selective chelators[14] for actinides and trivalent cations such as Fe(III) and Gd(III), we desired a new method that would allow the easy incorporation of the 3,2-HOPO ligand onto a variety of platforms. In particular, we desired a method that would allow the control of aqueous or organic solubility of the target chelator by proper choice of the scaffold and tethering methodology that avoids the traditional amide linkage. We recently disclosed the synthesis of a novel electrophilic 3,2-HOPO precursor **1**, and its reactions with primary and secondary amines.[15] The reactivity of **1** was found to depend on the nature of the amine (path A or B).[16] In general, secondary amines reacted with salt **1** via path A to give the corresponding amine HOPO derivatives, **2**, in high yields. Reactions of primary amines were more

☆ Portions of this work were presented at the 225th ACS National Meeting, New Orleans, LA, March 23–27, 2003; ORGN 359.

* Corresponding author. Tel.: +1 505 646 2589; fax: +1 505 646 2649; e-mail: agopalan@nmsu.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.128

complex and often proceeded via path B to yield amidine products, **3**. In this letter, we report the reactivity of salt **1** with alcohols, phenols and their sulfur analogs in order to access a variety of HOPO compounds. This reaction offers a direct method for the attachment of 3,2-HOPO ligands onto a variety of platforms via oxygen and sulfur linkages.



1 **2** **3**

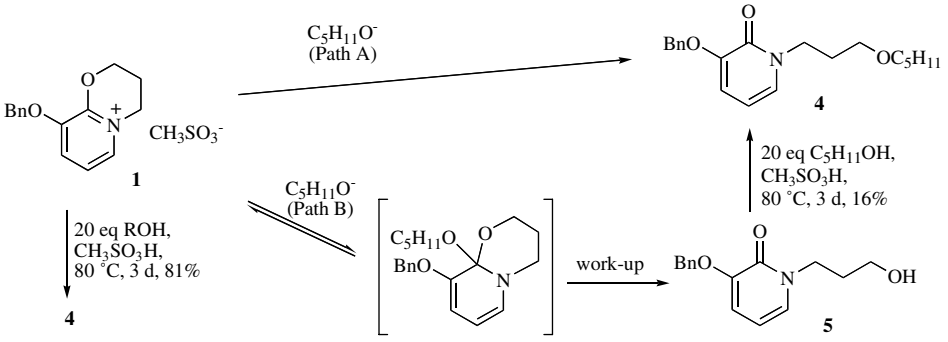
The preparation of mesylate salt **1** from commercially available 2,3-dihydroxypyridine in four steps has been disclosed.[15] We began our investigation by exploring the ring opening reactions of **1** with alcohols. To our surprise, salt **1** was recovered unchanged even after refluxing in dry ethanol. We then examined the reaction of **1** with alcohols under basic conditions. When 1-pentanol was treated with sodium hydride in THF followed by the addition of **1** in acetonitrile, only 10–15% of the desired product **4** was obtained (path A). The major product (40–50%) from this reaction was HOPO alcohol, **5**, which likely arises from the attack of the alkoxide at the iminium carbon of **1** (Path B) to give an adduct which hydrolyzes upon work-up (Scheme 1).[16] Numerous attempts to achieve the desired ring opening under basic conditions gave only low yields of the desired product.

The acid catalyzed ring opening of salt **1** with alcohols was then examined. Stoichiometric attempts to open the salt with alcohols in the presence of methanesulfonic acid with heating were unsuccessful. However, when salt **1** was dissolved in 1-pentanol (20 equiv) in the presence of MsOH (one drop) and the reaction heated to 80 °C for 3 days, the desired product was obtained in 81% yield after purification (Table 1, entry 1).[17] Reaction of 3-pentanol with **1** was slower (Table 1, entry 2) and only gave moderate yields of the desired product under the same reaction conditions. Our attempts to enhance the rate of this reaction by increasing the reaction temperature resulted in the acid catalyzed cleavage of the benzyl protecting group from the desired product (Table 1, entry 3). Using the standard conditions, it was also possible to monoalkylate diols (Table 1, entries 3 and 4) to give HOPO derivatives that can be further elaborated.

We are unable to postulate a definitive mechanism for the acid catalyzed ring opening of salt **1** with alcohols at this time. However, it is pertinent to mention that when alcohol **5** was treated with pentanol (20 equiv) in the presence of methanesulfonic acid at 80 °C for 3 days, we could isolate about 16% of ether **4** along with significant amounts of the unreacted alcohol **5** after chromatographic purification (Scheme 1).

In contrast to the alcohols, nucleophilic ring opening reactions of salt **1** with thiols could be readily effected under basic conditions (NaH in THF/acetonitrile at rt) in moderate yields to give the desired products. The preparation of the fluorinated thio HOPO ligand (Table 2, entry 1) was of interest in order to demonstrate the use of this methodology to access ligands that are potentially useful in supercritical carbon dioxide metal ion extractions, an area of much recent interest.[18] Further, it was possible to dialkylate propanedithiol to obtain the corresponding diHOPO compound (Table 2, entry 2).

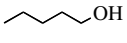
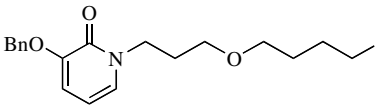
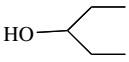
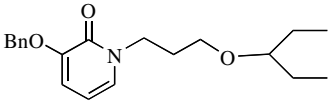
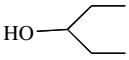
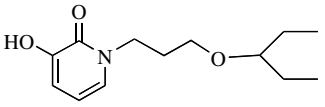
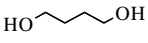
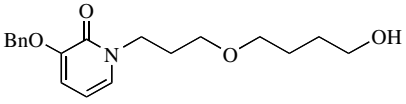
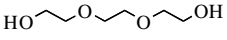
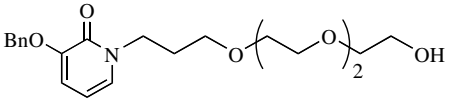
The reactions of phenols and thiophenol with salt **1** were then examined using a variety of bases (NaH, Et_3N, K_2CO_3). For phenols, it was found that the best yields were obtained using sodium hydride for deprotonation. For example, treatment of phenol (1.1 equiv) with sodium hydride (1 equiv) in dry THF followed by addition of a solution of mesylate salt, **1** (1 equiv) in dry acetonitrile gave the corresponding HOPO derivative in 63% yield after purification (Table 2, entry 3). Other phenols could be alkylated using these conditions (Table 2, entries 4 and 5). In the case of thiophenol, better yields



1 **4** **5**

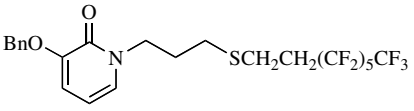
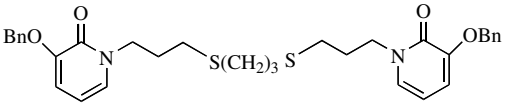
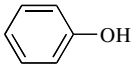
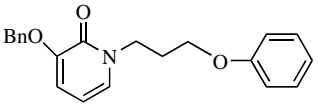
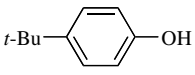
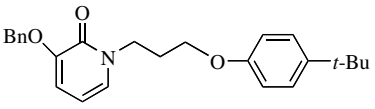
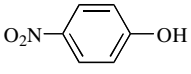
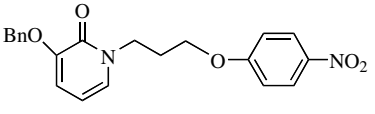
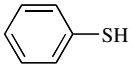
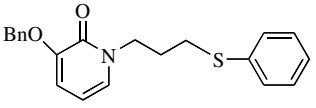
Scheme 1.

Table 1. Reaction of alcohols with mesylate salt **1**

Entry	Reactant	Product	Yield[a] (%)
1			81
2			50
3			45[b]
4			82
5			46

[a] Conditions: alcohol (20 equiv), salt **1** (1 equiv), methanesulfonic acid one drop, 80 °C, 3 days.
[b] Conditions: alcohol (20 equiv), salt **1** (1 equiv), methanesulfonic acid one drop, 100 °C, 3 days.

Table 2. Reaction of thiols, phenols, and thiophenol with mesylate salt **1**

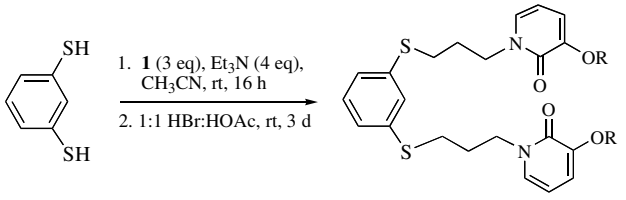
Entry	Reactant	Product	Yield[a] (%)
1	$CF_3(CF_2)_5CH_2CH_2SH$		49
2	$HSCH_2CH_2CH_2SH$		48[b]
3			63
4			79
5			52
6			63 75[c]

[a] ROH or RSH (1.1 equiv), NaH (1 equiv), **1** (1 equiv), 20%THF/CH_3CN, 0 °C to rt.
[b] 1,3-Propanedithiol (1 equiv), NaH (3 equiv), **1** (3 equiv), 20%THF/CH_3CN, 0 °C to rt.
[c] PhSH (1 equiv), Et_3N (1.5 equiv), **1** (1 equiv), CH_3CN, rt.

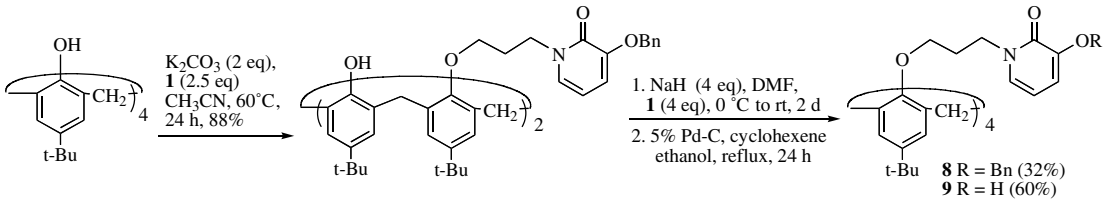
were obtained using triethylamine as the base (Table 2, entry 6).

It is not surprising that the softer and less basic thiolate and phenolate anions (compared to the alkoxides) give predominantly the products of alkylation (path A). In these cases, nucleophilic addition to the iminium carbon of **1** (path B) is readily reversible ultimately leading to the formation of the desired alkylation product.[16]

Finally, the utility of this methodology has been demonstrated by the synthesis of two new polyhydroxypyridinone chelators. The diHOPO chelator, **7**, was readily prepared in two steps from benzenedithiol in good yield (Eq. 1).[19] The synthesis of calix tetraHOPO chelator **9**, targeted for actinide(IV) extraction, was accomplished using a two-step alkylation procedure followed by transfer hydrogenolysis (Eq. 2). Some tetraHOPO calixarenes have been shown to effectively extract Th(IV) and Fe(III) from aqueous solutions, even below pH 2, into chloroform.[6]



(1)



(2)

In conclusion, the facile alkylation of HOPO salt **1** with a variety of nucleophiles makes it an extremely useful reagent for the introduction of the HOPO group onto a variety of structural platforms including calixarenes. The fact that a large excess of alcohol must be used to achieve an efficient ring opening of salt **1** does pose a synthetic limitation. However, the reaction is quite efficient with phenols, thiols, and thiophenols and can be used to prepare polyHOPO derivatives. The new classes of ligands described in this letter are not accessible by existing methods. This methodology is particularly valuable in developing novel extractants for actinides that must have the requisite organic solubility for separations. Further, the methodology allows access to new chelators for biomedically relevant cations such as iron and gadolinium, which may have potential diagnostic and therapeutic applications.

Acknowledgements

This work was supported by grants from the National Institutes of Health under PHS Grant no. S06 GM08136 and the Waste-Management Education and Research Consortium of New Mexico. We also thank NIH-RISE (GM61222) for a fellowship to G.M.

References and notes

1. (a) Thompson, K. H.; Barta, C. A.; Orvig, C. *Chem. Soc. Rev.* **2006**, *35*, 545–556; (b) Xu, J.; Whisenhunt, D. W. Jr.; Veeck, A. C.; Uhlir, L. C.; Raymond, K. N. *Inorg. Chem.* **2003**, *42*, 2665–2674; (c) Gorden, A. E. V.; Xu, J.; Raymond, K. N. *Chem. Rev.* **2003**, *103*, 4207–4282; (d) Santos, M. A. *Coord. Chem. Rev.* **2002**, *228*, 187–203; (e) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1992**, *196*, 185–194.
2. (a) Hider, R. C.; Liu, Z. D. *Curr. Med. Chem.* **2003**, *10*, 1051–1064; (b) Liu, Z. D.; Hider, R. C. *Coord. Chem. Rev.* **2002**, *232*, 151–171; (c) Liu, Z. D.; Hider, R. C. In *Medicinal Research Reviews*. In *Design of Clinically Useful Iron(III)-Selective Chelators*; John Wiley, 2001; pp 26–64; (d) Yokel, R. A.; Fredenburg, A. M.; Durbin, P. W.; Xu, J. D.; Rayens, M. K.; Raymond, K. N. *J. Pharm. Sci.* **2000**, *89*, 545–555; (e) Cohen, S. M.; O'Sullivan, B.; Raymond, K. N. *Inorg. Chem.* **2000**, *39*, 4339–4346; (f) Martell, A. E.; Motekaitis, R. J.; Sun, Y.; Ma, R.; Welch, M. J.; Pajeau, T. *Inorg. Chim. Acta* **1999**, *291*, 238–246.
3. (a) Pierre, V. C.; Botta, M.; Aime, S.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 5344–5345; (b) Raymond, K. N.; Pierre, V. C. *Bioconjugate Chem.* **2005**, *16*, 3–8; (c) O'Sullivan, B.; Doble, D. M. J.; Thompson, M. K.; Siering, C.; Xu, J.; Botta, M.; Aime, S.; Raymond, K. N. *Inorg. Chem.* **2003**, *42*, 2577–2583.
4. (a) Durbin, P. W.; Kullgren, B.; Xu, J.; Raymond, K. N.; Hengé-Napoli, M.-H.; Bailly, T.; Burgada, R. *Radiat. Prot. Dosim.* **2003**, *105*, 503–508; (b) Xu, J.; Durbin, P. W.; Kullgren, B.; Ebbe, S. N.; Uhlir, L. C.; Raymond, K. N. *J. Med. Chem.* **2002**, *45*, 3963–3971; (c) Xu, J.; Radkov, W.; Ziegler, M.; Raymond, K. N. *Inorg. Chem.* **2000**, *39*, 4156–4164; (d) Bailly, T.; Burgada, R. *C.R. Acad. Sci. Paris.* **1998**, *t.1 Serie II*, 241–245.
5. Veeck, A. C.; White, D. J.; Whisenhunt, D. W., Jr.; Xu, J.; Gorden, A. E. V.; Romanovski, V.; Hoffman, D. C.; Raymond, K. N. *Solv. Extr. Ion Exc.* **2004**, *22*, 1037–1068.
6. Lambert, T. N.; Dasaradhi, L.; Huber, V. J.; Gopalan, A. S. *J. Org. Chem.* **1999**, *64*, 6097–6101.
7. (a) Zhao, P.; Romanovski, V. V.; Whisenhunt, D. W., Jr.; Hoffman, D. C.; Mohs, T. R.; Xu, J.; Raymond, K. N. *Solvent Extr. Ion Exc.* **1999**, *17*, 1327–1353; (b) Feng, M.; van der Does, L.; Bantjes, A. *J. Appl. Polym. Sci.* **1995**, *56*, 1231–1237; (c) Koshti, N. M.; Parab, B.; Naik, S. *J. Indian Chem. Soc.* **2005**, *82*, 68–70.

8. Cohen, S. M.; Petoud, S.; Raymond, K. N. *Chem. Eur. J.* **2001**, *7*, 272–279.
9. Lin, Y.; Fiskum, S. K.; Yantasee, W.; Wu, H.; Mattigod, S. V.; Vorpagel, E.; Fryxell, G. E. *Environ. Sci. Technol.* **2005**, *38*, 1332–1337.
10. Meunier, S.; Siaugue, J.-M.; Sawicki, M.; Calbour, F.; Dézard, S.; Taran, F.; Mioskowski, C. *J. Comb. Chem.* **2003**, *5*, 201–204.
11. For some recent synthesis of hydroxypyridinone ligands including some mixed ligand systems, see: (a) Jurchen, K. M. C.; Raymond, K. M. *Inorg. Chem.* **2006**, *45*, 1078–1090; (b) Abergel, R. J.; Raymond, K. M. *Inorg. Chem.* **2006**, *45*, 3622–3631; (c) Ambrosi, G.; Formica, M.; Fusi, V.; Giorgi, L.; Guerri, A.; Lucarini, S.; Micheloni, M.; Paoli, P.; Rossi, P.; Zappia, G. *Inorg. Chem.* **2005**, *44*, 3249–3260; (d) Jurchen, K. M. C.; Raymond, K. M. *J. Coord. Chem.* **2005**, *58*, 55–80; (e) Bailly, T.; Burgada, R.; Prangé, T.; Lecouvey, M. *Tetrahedron Lett.* **2003**, *44*, 189–192.
12. Sun, Y.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chim. Acta* **1998**, *281*, 60–63.
13. Ambrosi, G.; Dapporto, P.; Formica, M.; Fusi, V.; Giorgi, L.; Guerri, A.; Lucarini, S.; Micheloni, M.; Paoli, P.; Pontellini, R.; Rossi, P.; Zappia, G. *New J. Chem.* **2004**, *28*, 1359–1367.
14. (a) Gopalan, A.; Huber, V.; Koshti, N.; Jacobs, H.; Zincircioglu, O.; Jarvinen, G.; Smith, P. Synthesis and Evaluation of Polyhydroxamate Chelators for the Selective Actinide Ion Sequestration. In *Separations of f Elements*; Nash, K. L., Choppin, G. R., Eds.; Plenum: New York, 1995; pp 77–98; (b) Koshti, N.; Huber, V.; Smith, P.; Gopalan, A. S. *Tetrahedron* **1994**, *50*, 2657–2664; (c) Koshti, N. M.; Jacobs, H. K.; Martin, P. A.; Smith, P. H.; Gopalan, A. S. *Tetrahedron Lett.* **1994**, *35*, 5157–5160.
15. Lambert, T. N.; Chittamuru, S.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett.* **2002**, *43/41*, 7379–7383.
16. For a discussion of the nucleophilic ring opening of iminium ethers, see: Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10–11, and references cited therein.
17. Spectroscopic and elemental analyses of all compounds are in agreement with the assigned structures.
18. *Supercritical Carbon Dioxide-Separations and Processes*; Gopalan, A. S., Wai, C. M., Jacobs, H. K., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 2003; Vol. 860.
19. A solution of mesylate salt **1** (0.5 g, 1.48 mmol) in dry acetonitrile (1.5 mL) was added to a solution of 1,3-benzenedithiol (0.070 g, 0.493 mmol) and triethylamine (0.199 g, 1.97 mmol) in dry acetonitrile (3.5 mL) at rt under nitrogen. After stirring for 16 h, the reaction mixture was diluted with dichloromethane (75 mL) and washed with saturated $NaHCO_3$ (2×30 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by radial chromatography to give **6** (0.225 g, 70%). IR (neat) 3033, 2943, 1652 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.44–7.12 (m, 14H), 6.88 (d, $J = 7$ Hz, 2H), 5.98 (t, $J = 7.1$ Hz, 2H), 5.07 (s, 4H), 4.06 (t, $J = 6.8$ Hz, 4H), 2.90 (t, $J = 7$ Hz, 4H), 2.11–2.00 (m, 2H); ^{13}C (50 MHz, $CDCl_3$): δ 158.21, 149.05, 136.96, 136.36, 129.54, 129.22, 128.61, 128.05, 127.42, 127.11, 115.63, 104.80, 70.83, 48.54, 30.67, 28.16. Anal. Calcd for $C_{36}H_{36}N_2O_4S_2 \cdot H_2O$: C, 67.26; H, 5.96; N, 4.36. Found: C, 67.36; H, 5.53; N, 4.26. A solution of concentrated HBr/glacial AcOH (1:1, 2 mL) was added to **6** (0.080 g, 0.129 mmol) and stirred at rt for 3 days. The solvents were removed under reduced pressure and the residue was washed with ethyl acetate and chloroform and dried in vacuo to give diHOPO **7** (0.040 g, 70%); IR (KBr) 3048, 1647 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.2 (d, $J = 6.2$ Hz, 2H), 7.06–6.92 (m, 6H), 6.41 (t, $J = 7.1$ Hz, 2H), 4.09 (t, $J = 7$ Hz, 4H), 2.78 (t, $J = 7$ Hz, 4H), 1.92–1.80 (m, 4H); ^{13}C (50 MHz, CD_3OD): δ 158.85, 147.82, 138.35, 130.57, 129.84, 128.22, 119.3, 110.57, 50.73, 31.15, 29.53. Anal. Calcd for $C_{22}H_{26}Br_2N_2O_4S_2$: C, 43.58; H, 4.32; N, 4.62. Found: C, 43.94; H, 4.11; N, 4.58.