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Stereoselective tribromomethylation of *N*-(*tert*-butanesulfinyl)imines with bromoform: practical synthesis of α-tribromomethyl amines

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ABSTRACT

The unprecedented nucleophilic tribromomethylation of *N*-(*tert*-butanesulfinyl)imines with bromoform has been shown to be a highly stereoselective and practical method for the synthesis of enantiomerically pure α-tribromomethyl amines. THF has proven to be the best solvent in this addition reaction. By changing the reaction solvent from THF to DMF, 2,2-dibromoaziridines can also be synthesized directly from bromoform and *N*-(*tert*-butanesulfinyl)imines under similar reaction conditions.

Introduction

Considered bizarre and rare only about 50 years ago, more than 2100 brominated natural products of both marine and terrestrial origin have been discovered to date. These compounds exhibit a wide range of biological activity, including antitumor, antibiotic or cytotoxic and analgesic activity.[1] Even though the concentration of bromide is only 0.3% of that for chloride in sea water, organobromine compounds are more prevalent in marine organisms than organochlorine derivatives, which can be attributed to the easier oxidation of bromide to the equivalent of bromonium ion (Br^+) by peroxidase.[2] As our understanding of the function and toxicity of natural organobromines continues to unfold and novel natural organobromine compounds are discovered and evaluated for their biological activity, it holds promise that new brominated antibiotics, anticancer and antifungal agents and medicinal drugs will be discovered.[3]

The tribromomethyl group existed in a lot of bioactive compounds, and it was found to be the key component for potent activity in some cases.[4] For example, 1-tribromomethyl-1,2,3,4-tetrahydro-β-carboline (TaBro) has been shown to be the most potent toxin in vitro and in vivo, compared with its 1-trifluromethyl- and 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline counterparts.[4a] Moreover, the tribromomethyl group is synthetically very useful, which can undergo many synthetically useful transformations such as substitution and elimination.[5] While brominated natural products are attracting increasing attention as targets for chemical synthesis, the development of methods for the stereoselective introduction of the tribromomethyl group or bromine atom(s) into organic compounds significantly lags behind.[6] To the best of our knowledge, we are not aware of any reports of stereoselective tribromomethylation. The lack of sophistication in this area, coupled with the broad range of important brominated natural and non-natural products, drives our laboratory to develop new methods for the stereoselective introduction of the tribromomethyl group into organic scaffolds. Herein, we wish to disclose the highly stereoselective and practical tribromomethylation reaction using bromoform and Ellman's *N*-(*tert*-butanesulfinyl)imines which has enabled us to efficiently synthesize enantiomerically pure α-tribromomethyl amines.

Results and discussion

Very recently, our group has successfully developed a highly efficient and practical method for the asymmetric synthesis of α-trichloromethyl amines based on nucleophilic trichloromethylation of *N*-(*tert*-butylsulfinyl)imines with chloroform.[7] The trichloromethyl anion generated in situ from chloroform and sodium bis(trimethylsilyl)amide (NaHMDS) in THF solvent at a low reaction temperature showed reasonable thermal stability and very good nucleophilicity. This remarkable trichloromethylation reaction inspired us to investigate whether bromoform could act as the tribromomethyl anion source in a similar manner to afford

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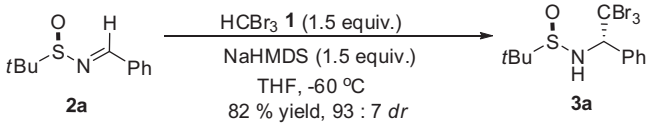
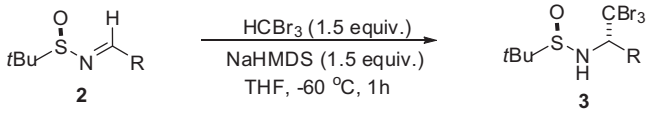


Scheme 1. Tribromomethylation of **2a** using $HCBr_3$.

Table 1
Tribromomethylation of *N*-(*tert*-butylsulfinyl) aldimines **2** using $HCBr_3$



Entry	Sulfinylimine **2**	Product **3**	Yield[a] (%)	dr[b]
1	**2a**	**3a**	82	93:7
2	**2b**	**3b**	85	97:3
3	**2c**	**3c**	81	99:1
4	**2d**	**3d**	79	98:2
5	**2e**	**3e**	70	96:4
6	**2f**	**3f**	78	90:10
7	**2g**	**3g**	84	93:7
8	**2h**	**3h**	80	91:9
9	**2i**	**3i**	81	89:11
10	**2j**	**3j**	83	93:7
11	**2k**	**3k**	72	90:10
12	**2l**	**3l**	51	90:10
13	**2m**	**3m**	62	N[c]

[a] Yields of isolated pure material.
[b] Diastereomeric ratios were determined by ^1H NMR spectroscopy and HPLC–MS analysis on the crude reaction mixture. For more details, see the Supplementary data.
[c] Not determined.

the corresponding α-tribromomethyl amines. It should be pointed out that, currently, the few known methods for the synthesis of α-tribromomethyl amines are mainly based on the use of 2,2,2-tribromoethanimine derivatives as precursors or a tribromomethyl anion equivalent such as tribromoacetic acid.[8] With this in mind, compound **2a** was used as a model compound and its tribromomethylation reaction was carried out under similar reaction conditions for the above mentioned trichloromethylation reaction. As expected, this addition reaction proceeded smoothly and the corresponding product **3a** could be obtained in 82% yield with diastereoselectivity up to 93:7 (Scheme 1). Further optimization using different bases such as lithium bis(trimethylsilyl)amide (LiHMDS) and potassium bis(trimethylsilyl)amide (KHMDS) did not get better results. The yield for this addition reaction was lower as compared to its trichloromethylation analogue, which can be associated with the relatively weak nucleophilicity of this bulky anion and the facile decomposition of the tribromomethyl anion to dibromocarben at room temperature and even below.

Next, we used the reaction conditions shown in Scheme 1 as the standard condition, and studied the scope of the reaction between bromoform and a variety of structurally diverse imines.[9] The results are shown in Table 1. In most cases, the tribromomethylated products **3** were obtained in very good isolated yields with high diastereoselectivities (except **3l** and **3m**). A remarkable feature of this reaction is that it works pretty well for non-enolizable imines (entries 1–11). For enolizable imines (**2l** and **2m**), this reaction proceeded to give expected product in moderate to good yields, which is in contrast to our reported chloroform chemistry: trichloromethylation of enolizable imines (such as **2l** and **2m**) usually delivered the addition products in very good yields.[7b] Also, the electronic donating/withdrawing nature of the substituents (including methoxy, methyl, chloro and extremely electron-withdrawing nitro group) on the aromatic ring had little effect on both the yield and diastereoselectivity. The configuration of the addition product was assigned to be (Rs, S), based on our recent research on trichloromethylation that a similar non-chelation controlled transition state was proposed in which the tribromomethyl anion attack the Re face of the imine leading to the Cram products (Fig. 1).[7] The sulfinyl oxygen in s-*cis* arrangement with respect to the C=N bond is supposed to be the most stable conformation mainly due to the contribution of intramolecular hydrogen bonding of the oxygen with the iminic hydrogen, based on recent computational studies.[7a,10]

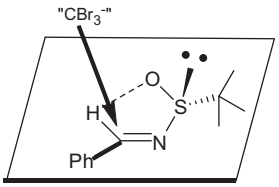
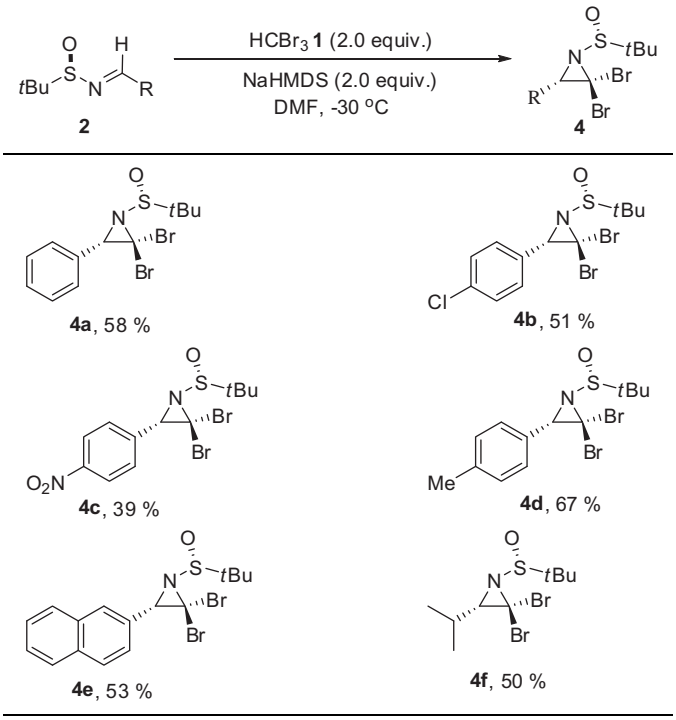


Figure 1. Depiction of its stereoselective formation of compound **3a**.

Table 2
Synthesis of 2,2-dibromoaziridines **4** from imines **2** and bromoform



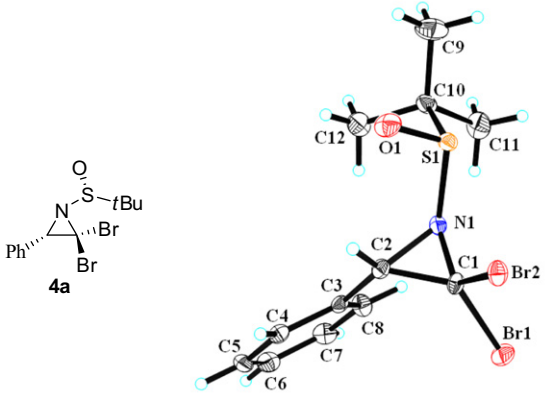


Figure 2. The X-ray crystal structure of compound **4a**.

The chemical outcome of the reaction between bromoform and imine is highly solvent-dependent. When DMF was used as the reaction solvent, compound **4a** was the sole isolable new compound (58% yield) and the tribromomethylated product **3a** could not be detected even by NMR spectroscopy on the crude reaction mixture. Table 2 shows the scope of the reaction.[11] As indicated, this reaction can be applied to both non-enolizable and enolizable imines. Generally, moderate to good yields can usually be obtained for imines with electron-donating or moderate electron-withdrawing substituents on the aromatic ring.

The reaction of imine **2e** containing a strong electron-withdrawing nitro group also gave the expected product **4c**, albeit in lower yield (39%). To our knowledge, this is the first case for asymmetric synthesis of 2,2-dibromoaziridines.[12] The structure and configuration of the cyclization product were determined by single-crystal X-ray analysis (Fig. 2).[13]

Next we went on to explore whether iodoform could undergo similar reactions. However, the addition reaction between iodoform and imine **2a** cannot proceed at all, which may be due to the ready decomposition of the triiodomethyl anion generated under the specified reaction conditions as indicated by the dark brown solution once the base was added to the reaction mixture.

In conclusion, we have developed a highly practical and stereoselective synthesis of α-tribromomethyl amines and 2,2-dibromoaziridines from bromoform. Nucleophilic tribromomethylation of *N*-(*tert*-butanesulfinyl)imines with bromoform in THF solvent affords α-tribromomethyl amines in very good yields with high diastereoselectivities. By simply changing the reaction solvent to DMF, 2,2-dibromoaziridines can be synthesized directly from bromoform and *N*-(*tert*-butanesulfinyl)imines under similar reaction conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.100.

References and notes

1. (a) Gribble, G. W. *Naturally Occurring Organohalogen Compounds—A Comprehensive Update*; SpringerWienNewYork: Germany, 2010; (b) Gribble, G. W. *J. Chem. Educ.* **2004**, *81*, 1441–1449; (c) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141–152; (d) Neidleman, S. L.; Geigert, J. *Biohalogenation: Principles, Basic Roles and Applications*; J. Wiley & Sons: New York, 1986.
2. (a) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364–3378; (b) Carter-Franklin, J. N.; Butler, A. *J. Am. Chem. Soc.* **2004**, *126*, 15060–15066; (c) Wagner, C.; El Omari, M.; König, G. M. *J. Nat. Prod.* **2009**, *72*, 540–553.
3. Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335–346.
4. (a) Bringmann, G.; Feineis, D.; Brückner, R.; Blank, M.; Peters, K.; Peters, E.-M.; Reichmann, H.; Janetzky, B.; Grote, C.; Clementd, H.-W.; Wesemann, W. *Bioorg. Med. Chem.* **2000**, *8*, 1467–1478; (b) Bringmann, G.; Feineis, D.; God, R.; Maksimenka, K.; Muhlbacher, J.; Messer, K.; Munchbach, M.; Gulden, K.-P.; Peters, E.-M.; Peters, K. *Tetrahedron* **2004**, *60*, 8143–8151; (c) Gurjar, M. K.; Deshmukh, M. N.; Arora, S. K.; Mehta, A.; Ashok, R. WO 2006/040614, 2006.
5. (a) Sahu, B.; Gururaja, G. N.; Mobin, S. M.; Namboothiri, I. N. N. *J. Org. Chem.* **2009**, *74*, 2601–2604; (b) Liu, H.; Kondo, S.-I.; Takeda, N.; Unno, M. *Eur. J. Inorg. Chem.* **2009**, 1317–1319; (c) Gururaja, G. N.; Mobin, S. M.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2011**, 2048–2052; (d) Hasegawa, E.; Tamura, Y.; Suzuki, K.; Yoneoka, A.; Suzuki, T. *J. Org. Chem.* **1999**, *64*, 8780–8785; (e) Jean-Gérard, L.; Pauvert, M.; Collet, S.; Guinganta, A.; Evain, M. *Tetrahedron* **2007**, *63*, 11250–11259; (f) Ranu, B. C.; Samanta, S.; Das, A. *Tetrahedron Lett.* **2002**, *43*, 5993–5995; (g) Pauvert, M.; Collet, S.; Guingant, A. *Tetrahedron Lett.* **2003**, *44*, 4203–4206.
6. (a) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821–4823; For several important

examples of asymmetric introduction of bromine atom into organic compounds, see: (b) Kano, T.; Shirozu, F.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 7590–7592; (c) Gustafson, J. L.; Lim, D.; Barrett, K. T.; Miller, S. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5125–5129; (d) Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133–2137; (e) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; (f) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 259–260; (g) Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 1482–1483; (h) Gu, Z.; Herrmann, A. T.; Zakarian, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7136–7139; (i) Gu, Z.; Zakarian, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9702–9705; (j) Ilardi, E. A.; Zakarian, A. *Chem. Asian J.* **2011**, *6*, 2260–2263; (k) Miltz, W.; Steglich, W. *Synthesis* **1990**, *9*, 750–751; (m) Zajac, M.; Peters, R. *Org. Lett.* **2007**, *9*, 2007–2010; Mitani, M.; Sakata, H.; Tabei, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1807–1814; (n) Sugimoto, J.; Miura, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1991**, 1319–1322.

7. (a) Li, Y.; Cao, Y.; Gu, J.; Wang, W.; Wang, H.; Zheng, T.; Sun, Z. *Eur. J. Org. Chem.* **2011**, 676–679; (b) Li, Y.; Zheng, T.; Wang, W.; Xu, W.; Ma, Y.; Zhang, S.; Wang, H.; Sun, Z. *Adv. Synth. Catal.* **2012**, 308–312.
8. (a) Bal'on, Y. G.; Smirnov, V. A. *Russ. J. Org. Chem.* **1989**, *25*, 2507–2513; (b) Lukasiewicz, A. *Tetrahedron* **1964**, *20*, 1–20; (c) Lukasiewicz, A.; Lesinska, J. *Tetrahedron* **1965**, *21*, 3247–3252.
9. General procedure for tribromomethylation of imines using bromoform **1**: NaHMDS (1.5 equiv, 1.5 mmol, 1.0 mol/L in THF) was added to a mixture of the imine **2a** (1.0 mmol) and bromoform (1.5 equiv, 1.5 mmol) in THF (3.0 mL) at −60 °C. When the reaction was finished, half-saturated NH_4Cl–H_2O solution (2.0 mL) was added at a lower temperature and the quenched reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product, which was subject to flash chromatography to give the corresponding α-tribromomethyl amine **3a** (378 mg, 82%).
10. (a) Arroyo, Y.; Meana, A.; Rodriguez, J. F.; Sanz-Tejedor, M. A.; Aloson, I.; Garcia Ruano, J. L. *J. Org. Chem.* **2009**, *74*, 4217–4224; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.
11. Procedure for direct synthesis of 2,2-dibromoaziridine **4a** from bromoform **1** and imine **2a**: NaHMDS (2.0 equiv, 2.0 mmol, 1.0 mol/L in THF) was added to a mixture of the imine **2a** (1.0 mmol) and bromoform (2.0 equiv, 2.0 mmol) in DMF (3.0 mL) at −30 °C. Reaction mixtures were stirred over 0.5 h. Then water (10 mL) was added at lower temperature and the quenched reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product, which was subject to flash chromatography to give pure 2,2-dibromoaziridine **4a** (220 mg, 58%).
12. Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135.
13. CCDC-870907 (for compound **4a**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.