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Rapid synthesis of a ¹³C₆-benzothiazolium salt from ¹³C₆-aniline

Chris V. Galliford,^{*} Kimberly Voronin, David Hesk, David Koharski, and Paul McNamara

¹³C₆-labeled aniline was used as a starting material for the facile synthesis of ¹³C₆-benzothiazolium salt (1).

Keywords: benzothiazolium; carbon-13; thione

Introduction

The chemistry of benzothiazolium salts generated by alkylation of benzothiazole thiones has been studied significantly.¹ These salts have been reported to inhibit nitric oxide production and in the treatment of coronaviril infection,² and are also useful intermediates in the synthesis of bioactive 2-imino-benzothiazolines.³ The hydrolysis of these salts can be effected under a variety of conditions leading to exclusively *N*-alkyl substituted benzothiazoline structures which are useful building blocks in the synthesis of compounds containing this heterocyclic motif.⁴

The synthesis of the benzothiazolium salts is readily achieved by double alkylation of an appropriate ambidentate electrophile by benzothiazole thione (**2**).⁵ **2** is itself an important accelerator in the vulcanization of rubber among other applications.⁶ Additionally, **2** has been utilized as a convenient leaving group for the introduction of the Fmoc-protecting group (Figure 1)⁷.

 $^{13}C_6$ -labeled aniline was selected as a convenient precursor (Scheme 1), as the direct conversion of aniline to benzothiazole thione (2) has been well studied. First reported in 1923 by Sebrell and Boord,⁸ (Scheme 2) the laboratory synthesis of this compound by various strategies has been the subject of extensive study in the literature.^{1,9}

On an industrial scale, the most efficient methods to prepare **2** involve the direct reaction of near stoichiometric quantities of aniline (**3**), elemental sulfur and carbon disulfide at high temperature and pressure.¹⁰ Improved yields have been reported using Brønsted acid catalysis.¹¹ Nitrobenzene has also been used as a precursor, undergoing *in situ* reduction to generate aniline under the reaction conditions.¹² Numerous procedures for continuous recycling of unused starting materials and reprocessing of crude material have also been reported.¹³

Experimental

General methods

Pressure reactions were carried out in stainless steel screwcapped bomb reactor obtained from Parr Instruments Co. Caution: heating these reagents at high pressure requires a closed fume hood and blast shield. All other reactions were carried out under an atmosphere of argon or nitrogen in flamedried glassware with magnetic stirring. Reagents were purified prior to use unless otherwise stated. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh), or using an automated ISCO CombiFlash Rf machine. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, or phosphomolybdic acid followed by heating. ¹H NMR spectra were recorded on a Varian Mercury (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (DMSO d_6). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ¹³C-NMR spectra were recorded on a Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard $(DMSO-d_{6})$. Mass spectrometry data was acquired on a JEOL double focusing sector mass spectrometer operating in the FAB ionization mode. PEG-600 was used as the reference for the high-resolution measurements. Samples were dissolved in DMSO and 3-NBA was used as the FAB matrix. The chemical purities of 1 and 2 were determined by high-performance liquid chromatography using a Waters 2487 Dual programmable wavelength detector equipped with a Gemini NX 3 µ C18 column, $4.6 \text{ mm} \times 50 \text{ mm}$, 254 nm and 323 nm, (50:50:0.1) methanol:water:trifluoroacetic acid at 1 mL/min for 6 min followed by a gradient to 100% methanol elution.

Benzothiazole thione (2)

Aniline, sulfur and carbon disulfide were transferred and combined inside a stainless steel bomb reactor with an internal volume of 18 mL. The reaction apparatus was heated to an oil

Merck Research Laboratories, 2015 Galloping Hill Road, K-15-A4545, Kenilworth, NJ 07033, USA

^{*}Correspondence to: Chris V. Galliford, Merck Research Laboratories, 2015 Galloping Hill Road, K-15-A4545, Kenilworth, NJ 07033, USA. E-mail: chris.galliford@spcorp.com

bath temperature of 270°C (using fresh 710 CS heat-transfer fluid). The mixture was then heated for a further 12-48 h as per the entries in Table 1. The reaction vessel was removed from the heat source and allowed to cool over a 1 h period, before being brought to ambient temperature using an ice bath. The bomb reactor was carefully opened and the crude mixture purified directly by flash column chromatography using gradient elution 0-30% MTBE/hexanes (product $R_f = 0.29$, 20% MTBE/hexanes, visualized by ceric ammonium nitrate). Samples of the intermediates phenyl isothiocyanate (4), N,N-diphenyl thiourea (5) $(R_f = 0.09 \text{ and } R_f = 0.29 \text{ in } 20\% \text{ MTBE/hexanes respectively})$ were also isolated from the reaction mixture. ¹H NMR (tautomeric mixture, DMSO-d₆) δ, ppm: 8.15 s, 1H 7.6-7.48 d, 2H; 7.41–7.18 m, 1H. ¹³C NMR (DMSO-*d*₆) δ, ppm: 190.0, 141.3, 128.2, 26.9, 124.0, 121.4, 112.1. MS: M⁺ 173.99 (100%) found 174.15.





Scheme 1.

$$NH_2$$
 + S + CS₂ conditions NH_2 + S + CS₂ NH_2 + S + CS₂ NH_2

Scheme 2.

$^{13}C_6$ -Benzothiazole thione ($^{13}C_6$ -2)

 ${}^{13}C_6$ -Aniline, sulfur and carbon disulfide were transferred and combined inside a stainless steel bomb reactor with an internal volume of 18 mL. The reaction apparatus was heated to an oil bath temperature of 270°C (using fresh 710 CS heat-transfer fluid). The mixture was then heated for a further 12 h. The reaction vessel was removed from the heat source and allowed to cool over a 1 h period, before being brought to ambient temperature using an ice bath. The bomb reactor was carefully opened and the crude mixture purified directly by flash column chromatography using gradient elution 0–30% MTBE/hexanes (product R_f =0.29, 20% MTBE/hexanes, visualized by ceric ammonium nitrate). After SiO₂ chromatography, 5.89 g of ${}^{13}C_6$ -**2** (86% yield) was isolated with spectral and chromatographic analyses consistent with the data above.

2,3-dihydrothiazolo[2,3-b] benzothiazolium bromide (1)

To a mixture of 2-benzothiazoline thione (250 mg, 1.44 mmol) in DMF (1.5 mL), was added NaOH pellets (60 mg, 1.51 mmol). The resulting solution was stirred at room temperature until a homogenous solution was observed. This solution was then added dropwise into a solution of ethylene dibromide (1.24 ml, 14.43 mmol) in DMF (1 mL) at 75°C over 10 min via syringe pump. A white solid precipitated at the end of the addition and the reaction mixture was stirred at 75°C for 30 min, and then at room temperature overnight. The white solid was then filtered and washed with CH_2Cl_2 (2 × 10 mL), followed by drying in a vacuum overnight to give the product as a white crystalline solid (185 mg, 46% yield), and an oily residue containing the remaining product that was not further manipulated. 1: ¹H NMR $(DMSO-d_6)$ δ , ppm: 8.31–8.29 (d; J=7.5 Hz; 1H), 7.99–7.96 d; J = 7.5 Hz; 1H), 7.80–7.74 t; J = 7.5 Hz; 1H), 7.61–7.66 t; J = 7.5 Hz; 1H), 5.00–4.95 t; J=7.9 Hz; 2H), 4.27–4.22 t; J=7.9 Hz; 2H). ¹³C NMR (DMSO-*d*₆) δ, ppm: 182.0, 137.4, 133.9, 128.6, 126.6, 124.7, 115.6, 51.3, 37.1. HR MS: M⁺ 194.0098 (100%) found 194.0097. ¹³**C₆-1**: ¹H NMR (DMSO- d_6) δ, ppm: 8.31–8.29 (m; 1H), 7.99-7.96 m; 1H), 7.80-7.74 m; 1H). 7.61-7.66 m; 1H), 5.00-4.95

Table 1.	Table of optimization			
Entry	PhNH ₂ :S:CS ₂	Reaction conditions (h) ^a	Scale ^b	Yield % ^c
1	1:1.05:1.1	12	32	79
2	1:1.05:1.1	12	16	70
3	1:1.05:1.1	16	8	44
4	1:1.05:1.1	48	8	48
5	1:1.05:1.1	12	39.6	86 ^d
6	1:1.5:1.5	20	8	39
7	0.8:1.05:1.5	20	8	27
8	1.2:1.05:1.1	20	8	22 ^e
9	1:1.05:1.1	20	4	25
10	1:1.05:1.5	20	4	6
11	11:1.05:1.1	20	4	0 ^f

^aAll reactions were performed in a sealed Parr stainless steel bomb reactor heated by an oil bath containing 710 CS heat transfer fluid at an oil bath temperature of 260–270°C for the indicated duration.

^bBased on mmol PhNH₂.

^cIsolated yields after SiO₂ chromatography.

^dScale used for production of ${}^{13}C_6$ -**2**.

^eIn addition to **5**, an unidentified impurity, close in R_f to the product was isolated from this crude reaction mixture. ^fAniline hydrochloride used in place of aniline.

t; J = 7.9 Hz; 2H), 4.27–4.22 t; J = 7.9 Hz; 2H). ¹³C NMR (DMSO- d_6) δ , ppm: 182.0, 137.4, 133.9, 128.6, 126.6, 124.7, 115.6, 51.3, 37.1. MS: M⁺ 200.0229 (100%) found 200.0303.

$^{13}\text{C}_6\mbox{-2,3-dihydrothiazolo[2,3-b]}$ benzothiazolium bromide ($^{13}\text{C}_6\mbox{-1})$

To a mixture of 2-benzothiazoline thione (250 mg, 1.44 mmol) in DMF (1.5 mL), was added NaOH pellets (60 mg, 1.51 mmol). The resulting solution was stirred at room temperature until a homogenous solution was observed. This solution was then added dropwise into a solution of ethylene dibromide (1.24 ml, 14.43 mmol) in DMF (1 mL) at 75 °C over 10 min via syringe pump. A white solid precipitated at the end of the addition and the reaction mixture was stirred at 75 °C for 30 min, and then at room temperature overnight. The white solid was then carefully filtered and washed with CH₂Cl₂ (2 × 10 mL), followed by drying in a vacuum overnight to give the product as a white crystalline solid (300 mg, 74% yield). The isolated product provided spectral and chromatographic analyses consistent with the data above.

Results and discussion

Unfortunately, our initial attempts to replicate this process using either screw-capped pressure reaction vials or microwave vials either failed completely or gave only trace quantities of product. Either insufficient heat was provided to start the reaction, or in the case where $> 170^{\circ}$ C was used as the reaction temperature, the resultant high pressures generated as the reaction proceeded caused the seal of the vial to fail.

Successfully down-sizing this industrial process to a laboratory scale was eventually achieved by utilizing a stainless steel bomb reactor with an 18 mL internal capacity reaction chamber. This removed the hazards associated with sealed tube reactions in glass vessels and also allowed for sufficiently high pressures of hydrogen disulfide to be generated to allow the reaction to proceed to completion.¹⁰ Our initial run under these conditions furnished an isolated yield of **2** in 44% yield after column chromatography (Table 1, entry 3). Gratifyingly, by using the same apparatus and conditions, we were able to investigate the effect of internal pressure by simply increasing the scale of reaction within the same bomb reactor. In this way the optimal scale on which to perform our reaction was identified (Table 1).

We were able to observe conversion of aniline to the intermediates phenyl isothiocyanate (**4**) and N,N'-diphenyl thiourea (**5**) by LC-MS of the reaction mixtures, and by isolation of these compounds as side products (Figure 2). In most cases the mass balance was completely accounted for by the formation of these side products.

As predicted, manipulation of the internal pressure of the reaction in the fixed volume of the bomb reactor led to efficient conversion to final product. A clear trend quickly emerged during this optimization: increased scale led to more efficient conversion to **2**, with varying quantities of the intermediates **4** and **5** observed as side products (Table 1, entries 1–3).

Prolonged heating of the reaction mixture failed to significantly improve conversion to product (Entry 4). The lower limit of the reaction conditions was discovered when the reaction was performed on a 4 mmol scale (based on aniline), where the isolated yield of **2** dropped to only 25% (Entry 9). Attempts to manipulate the stoichiometry in order to increase the yield failed when the reaction was performed with less than 10 mmol



Figure 2. Isolated side products.



Scheme 3.

of each reactant (Entries 6–8 and 10). This deleterious effect upon lowering the reaction scale is most likely due to decreased pressure in the reaction chamber.

With optimized conditions for the synthesis of **2** in hand, we were able to prepare 5.89 g (86% isolated yield) of ${}^{13}C_6$ -**2** (Table 1, entry 5). Completion of the synthesis was achieved by treatment of ${}^{13}C_6$ -**2** with an excess dibromoethane in dimethyl-formamide to yield in ${}^{13}C_6$ -**1** 74% yield (Scheme 3).

Conclusion

A convenient and rapid synthesis of the ${}^{13}C_6$ -2,3-dihydrothiazolo[2,3-b] benzothiazolium salt (1) was accomplished. A highyielding preparation of benzothiazole thione (2) in ${}^{13}C_6$ -labeled form was also developed.

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