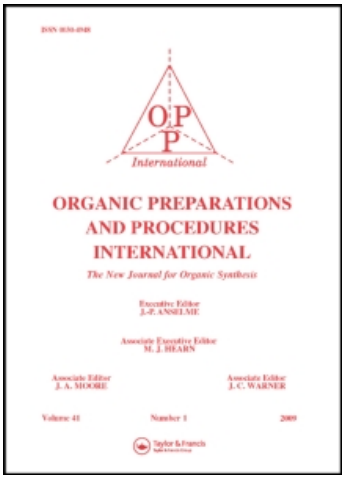

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REDUCTIVE THIOLATION APPROACH TO PURE CYCLOBUTYL PHENYL SULFIDE

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8. Beilstein, **6**, 667.

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REDUCTIVE THIOLATION APPROACH TO PURE CYCLOBUTYL PHENYL SULFIDE

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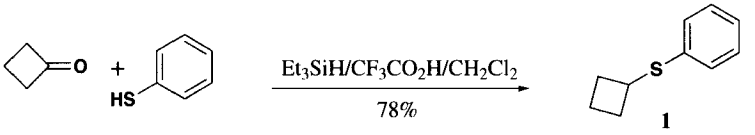
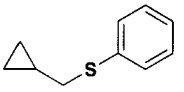
Cyclobutyl phenyl sulfide (**1**) is a precursor of cyclobutyl phenyl sulfoxide, a reagent extremely useful for the synthesis of spirocyclic cyclopentanones.[1a] In our laboratories, we required a method for the large scale production of **1**, a compound necessary for the construction of a range of potent glucokinase activators (GKAs)[2] that could form the basis of a treatment for type 2 diabetes. Here, we discuss how the difficulties associated with previous syntheses[1] of **1** were overcome by the development of a novel synthetic route that relies upon a modified reductive thiolation[3] protocol.



1

Two approaches have previously been employed for the synthesis of **1**, *viz.*, the radical addition of thiophenol to bicyclo[1.1.0]butane[1b] and the alkylation of sodium thiophenolate with cyclobutyl bromide.[1a] The first of these approaches was not attempted because of the difficulties associated with procuring large quantities of bicyclo[1.1.0]butane.[4] Moreover, the second of these approaches, involving the reaction of thiophenolate with cyclobutyl bromide, did not proceed as planned. In this instance, an 85% yield of a mixture, comprising the desired thioether **1** (89%) and cyclopropylmethyl phenyl sulfide (**2**, 11%), was obtained. The starting cyclobutyl bromide, purchased from Aldrich (Catalogue no.: 22,699-8), contained 6% cyclopropylmethyl

bromide.[5] Thus, the relative amount of cyclopropylmethyl compound had nearly doubled during the reaction, indicating that a cyclobutyl-cyclopropylmethyl rearrangement[6] was occurring. Separation of **1** and **2** by column chromatography was not possible, as the two compounds have identical R_F values. Moreover, these two thioethers could not be purified by distillation since their boiling points are very similar.[7] The difficulties associated with the isolation of pure **1** from a **1**·**2** mixture had implications for the synthesis of GKAs. Accordingly, we sought a route to **1** where no **2** was produced at all.



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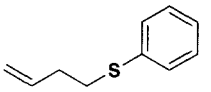
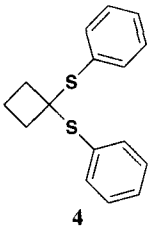


3

Our initial studies utilized pure cyclobutyl tosylate[9] which was not contaminated with the corresponding cyclopropylmethyl analogue. However, condensation of this compound with thiophenol, in the presence of potassium carbonate and sodium iodide in *N*,*N*-dimethylacetamide at 130°C, produced even less of the desired thioether than the equivalent reaction with cyclobutyl bromide. In this instance, a 66% yield of a mixture of **1** (56%), **2** (18%), and 3-butenyl phenyl sulfide (**3**, 26%) was isolated.

In view of the complications associated with obtaining pure compound through the alkylation of thiophenolate with cyclobutyl bromide or tosylate, we decided to employ a reductive thiolation protocol[3] for the synthesis of **1**. We chose to utilize the reductive thiolation protocol of Olah, Prakash, and coworkers[3b] for the preparation of cyclohexyl phenyl sulfide by triethylsilane (TESH) reduction of the hemithioacetal formed *via* the condensation of cyclohexanone with thiophenol in the presence of boron trifluoride monohydrate. As boron trifluoride monohydrate is not commercially available and is thermally unstable,[10] we opted to evaluate alternative acidic components for the reaction. The use of boron trifluoride diethyl etherate in place of the monohydrate in the reductive thiolation reaction of cyclobutanone with thiophenol gave the desired compound **1** in low yield (20%), together with a substantial quantity of the thioacetal **4** (40%).[11] The ratio of **1** to **4** was similar when the reaction was carried out in the presence of commercially available boron trifluoride dihydrate. Finally, the reaction was performed in the presence of trifluoroacetic acid (TFA), a commercially available reagent, commonly employed in TESH reduction reactions,[12] recently utilized for macrocycle synthesis *via* reductive thiolation.[3f] Gratifyingly, in this instance, **1** was formed in good yield with no contamination by **2**, **3**, or **4**. This procedure was easily carried out on a large scale to yield multigram quantities of pure **1**. We surmise that **2** and **3** are not generated during the reductive thiolation reaction since the intermediate hemithioacetal **5** undergoes ionic hydrogenation by TESH[3b] before any rearrangement processes can occur.



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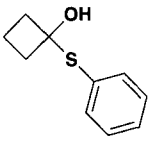

5

In summary, we have developed a new approach to the synthesis of large quantities of pure cyclobutyl phenyl sulfide (**1**), free of the corresponding cyclopropylmethyl- (**2**) and 3-butenyl (**3**) analogues; the availability of pure **1** allowed the preparation of a wide range of potent GKAs.[2] This new route relied on a modified reductive thiolation procedure involving the condensation of cyclobutanone with thiophenol in the presence of TESH-TFA.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich, with the exception of cyclobutanone, which was obtained from Alfa Aesar. TLC was performed on aluminum sheets coated with silica gel $60F_{254}$ (Merck). Flash chromatography was carried out using silica (40–63 mesh). ^1H NMR spectra were recorded on a Varian Mercury 400 spectrometer; chemical shifts are reported relative to TMS ($\delta = 0.00$).

Cyclobutyl Phenyl Sulfide (1).- TFA (200 mL) was added slowly to a stirred solution of cyclobutanone (25.0 g, 350 mmol) and thiophenol (30.5 mL, 297 mmol) in anhydrous CH_2Cl_2 (200 mL), under argon over 10 min, while keeping the internal temperature below 10°C. TESH (80.0 mL, 501 mmol) was then added to the reaction mixture over 5 min, again ensuring that the internal temperature stayed below 10°C. The mixture was stirred at 20°C for 6 h, after which TLC (isohexane) indicated the disappearance of both thiophenol and **4**. The reaction mixture was partitioned between CH_2Cl_2 (250 mL) and H_2O (200 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 x 250 mL), then the combined organic extracts were washed with H_2O (2 x 250 mL), saturated aqueous Na_2CO_3 (3 x 250 mL), and H_2O (250 mL), before being dried ($MgSO_4$). Filtration, solvent removal, and flash chromatography (isohexane) furnished the title compound (38.3 g, 78%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz, 27°C): δ 1.95-2.20 (m, 4H), 2.47-2.55 (m, 2H), 3.89-3.98 (m, 1H), 7.16-7.22 (m, 1H), 7.29-7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz, 27°C): δ 18.8, 30.7, 40.3, 125.7, 128.8, 129.0, 137.0.

Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36; S, 19.52; Found: C, 73.34; H, 7.08; S, 19.50

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