Short Note

2-Methylsulfanylbenzo[*f*]isoquinoline

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Abstract: S-Methylation of a 4-(naphth-2-yl)-β-thiolactam gives an intermediate 4-(naphth-2-yl) substituted 1-azetine which undergoes a [2+2] ring-opening followed by electrocyclic ring closure of the resulting 2-azadiene to give a benzo[*f*]isoquinoline.

Keywords: benzoisoquinoline; 1-azetine; naphthalene

Introduction

Benzoisoquinolines (Figure 1) are relatively unexplored heterocycles which have attracted limited interest in the literature [1–8]. Benzo[*f*]isoquinolines **1** [1–4] are useful in the synthesis of aza-steroids [3] and have had their affinity for the 5-HT$_3$ receptor explored [4]. Benzo[*h*]isoquinolines **2** have also been synthesized [5–8] and some of these have been shown to be potent inhibitors of ATP-competitive Chk1 kinase [8]. The benzo[*g*]isoquinoline nucleus **3** has also been reported [8]. In this short note, we wish to report the synthesis of the previously unreported 2-methylthiobenzo[*f*]isoquinoline **4** which is obtained from an unprecedented rearrangement of 2-methylthio-4-(naphth-2-yl)-1-azetine **5**, shown in Scheme 1. Whilst benzo[*f*]isoquinolines and the isomeric 3-(naphth-1-yl)-1-azetines have been reported as common products obtained from reactions of dehydronaphthylalanines [1,2], the formation of benzoisoquinolines from 4-(naphth-2-yl)-1-azetines has not been reported. The isomeric 4-methylthiobenzo[*f*]isoquinoline **6**, obtained via an entirely different route, has been reported [3].
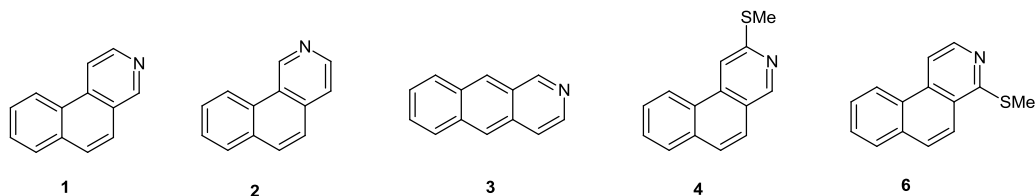
Figure 1. Benzoisoquinolines.

Discussion

2-Methylthio-4-(naphth-2-yl)-1-azetine **5** (Scheme 1) has been synthesized by us before [9,10] and used in cycloaddition reactions. Previously, the 1-azetine was obtained by alkylation of the readily available [9,10] thiolactam **7**, as shown in Scheme 1. When this reaction mixture is worked up and purified immediately, the 1-azetine is the major product, as already reported [9,10]. However, we have now found that when the crude 1-azetine reaction mixture from the reaction of thiolactam **7** with trimethyloxonium tetrafluoroborate is left overnight rather than used immediately, the 1-azetine is not the isolated product, but rearranges to give 2-methylthiobenzo[*f*]isoquinoline **4** (35% from **7**) instead. A sample of the pure 1-azetine **5** underwent quantitative rearrangement to the isoquinoline **4** after storage in CDCl$_3$ for one week, indicating that alkylation of the thiolactam **7** is the limiting step.
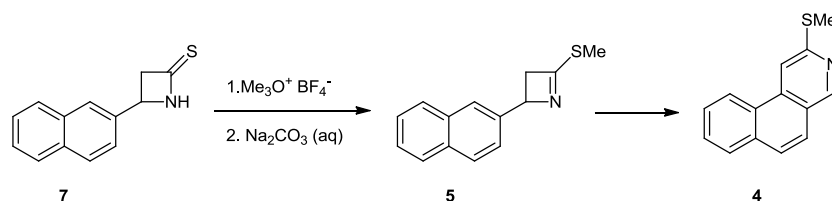
Scheme 1. Synthesis of 2-methylthiobenzo[*f*]isoquinoline **4**.

As shown in Scheme 2, we propose that the 1-azetine **5** undergoes ring-opening to the 2-azadiene **8**, a thermal ring-opening process known in 1-azetines [11–13]. Electrocyclic ring closure then occurs onto the more reactive and favored naphthyl 1-position [14–16] as opposed to the alternative, less reactive, dis-favored 3-position. Loss of hydrogen and aromatization then gives the benzo[*f*]isoquinoline **4**.
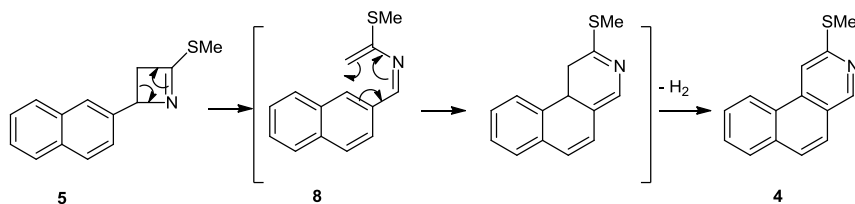
Scheme 2. Proposed mechanism.

Experimental

To 4-naphthylazetidin-2-thione **7** [9,10] (300 mg, 1.42 mmol) in dry dichloromethane (10 mL) in a 50 mL round-bottomed flask was added Meerwein's salt (312 mg, 2.11 mmol) under an atmosphere of

dry nitrogen. The mixture was stirred at room temperature for 1 h and then at reflux for 1 h. The solution was cooled to room temperature and added drop-wise to a 50% aqueous solution of potassium carbonate (10 mL) at −10 °C and left to warm to room temperature overnight. The resulting mixture was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 10 mL), and the combined organic extracts were dried (MgSO$_4$). After filtration the solvent was removed under reduced pressure using a rotary evaporator to give a dark orange oil which was purified by silica column chromatography (hexane/EtOAc; 3:1) to give the product as a light yellow oil (112 mg, 35%), R_f = 0.48. The reaction was monitored by TLC, which was carried out on 0.20 mm Macherey-Nagel Alugram® Sil G/UV$_{254}$ silica gel-60 F$_{254}$ precoated aluminium plates (Fisher Scientific UK Ltd, Loughborough, UK) and visualisation was achieved using UV light. Column chromatography was performed on silica gel (0.063–0.200 mm, 60 Å) from the same supplier.

Spectroscopic Data

IR υ_{max} (neat, cm^{-1}): 3043 (w), 2955 (m), 1587 (m), 1556 (m), 1493 (m), 1441 (m), 1391 (m), 1144 (m), 1124 (s), 1073 (m), 835 (m), 748 (s).

^{1}H-NMR: δ (400 MHz, CDCl$_3$): 9.19 (1H, dd, *J* = 7.8, 1.6 Hz, ArH), 7.83 (1H, d, *J* = 8.4 Hz, ArH), 7.80 (1H, dd, *J* = 7.3, 1.8 Hz, ArH), 7.64–7.56 (3H, m, ArH), 7.53 (1H, d, *J* = 8.7 Hz, ArH), 7.29 (1H, d, *J* = 8.4 Hz, ArH), 2.77 (3H, s, Me).

^{13}C-NMR δ (100 MHz, CDCl$_3$): 158.51 (C), 146.18 (C), 134.63 (CH), 133.21 (C), 130.21 (C), 127.34 (CH), 127.04 (CH), 125.99 (CH), 125.41 (CH), 124.50 (CH), 123.72 (CH), 122.53 (C), 120.19 (CH), 13.26 (CH$_3$).

HRMS (ESI+, *m/z*) [M + H]$^+$ for C$_{14}$H$_{12}$NS calculated 226.0685, measured 226.0692.

Acknowledgments

Author Contributions

Hemming designed the project and is the principal and corresponding author and wrote the text. Khan and Jamshaid conducted the practical work associated with this project and contributed equally.

Conflicts of Interest

The authors declare no conflict of interest.

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