Tetrahedron Letters 51 (2010) 6687–6689

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

2-Benzyliden-2*H*-thieto[3,2-*b*]quinoline: a new heterocycle and its rearrangement to 2-phenylthieno[3,2-*b*]quinoline

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ARTICLE INFO

Article history:
Received 14 September 2010
Accepted 6 October 2010
Available online 8 November 2010

Keywords:
Friedländer reaction
Thieto[3,2-*b*]quinoline
Base-mediated rearrangement
Thieno[3,2-*b*]quinoline

ABSTRACT

Synthesis of the strained 2*H*-thieto[3,2-*b*]quinoline ring system is reported for the first time. Treatment of (*Z*)-2-benzyliden-2*H*-thieto[3,2-*b*]quinoline derivatives of this heterocycle with base, at reflux in ethanol, causes a novel rearrangement to 2-phenylthieno[3,2-*b*]quinolines. Indeed, the one-pot reaction of 2-aminobenzaldehydes and (*Z*)-2-benzylidenethietan-3-one in refluxing basic ethanol leads directly to 2-phenylthieno[3,2-*b*]quinolines in good yields.

Cyclobuta[*b*]naphthalene was first synthesized by Cava in 1960.[1] On the other hand, heteroatoms in this tricyclic ring are rare in the literature. For example, 1,2-dihydrocyclobuta[*b*] quinolines **1a**,**b**, 1,2-dihydrocyclobuta[*b*]quinoxaline (**2a**), 6,7-dihydrocyclobuta[*g*]quinoxaline (**2b**), and naphthothietes **3a**,**b**,**c** have been reported as stable isolable compounds.[2–4] However, naphthooxetes **4a**,**b** were assumed to be precursors of the corresponding highly reactive *o*-quinonemethides[5] (Fig. 1).

To the best of our knowledge, no cyclobutanaphthalene ring systems with two different heteroatoms are known. We wish to report, for the first time, the synthesis of the new heterocycle 2-benzyliden-2*H*-thieto[3,2-*b*]quinoline and some of its derivatives which contain sulfur and nitrogen as the heteroatoms.

A Friedländer reaction between 2-aminobenzaldehyde (**5a**) and thietanone **6** in 10% KOH in ethanol at room temperature gave the desired (*Z*)-2-benzyliden-2*H*-thieto[3,2-*b*]quinoline (**7a**) as an off-white solid in 75% yield (Fig. 2). The structure of **7a** was established by ^{1}H NMR, ^{13}C NMR, and mass spectrometry and this was confirmed by X-ray crystallography (Fig. 3a; see experimental details for all new compounds[6]).

When the Friedländer reaction of **5a** with **6** was conducted under the same basic conditions, but at reflux temperature, the product was shown to be 2-phenylthieno[3,2-*b*]quinoline (**8a**). This novel rearrangement product was also obtained in 94% when

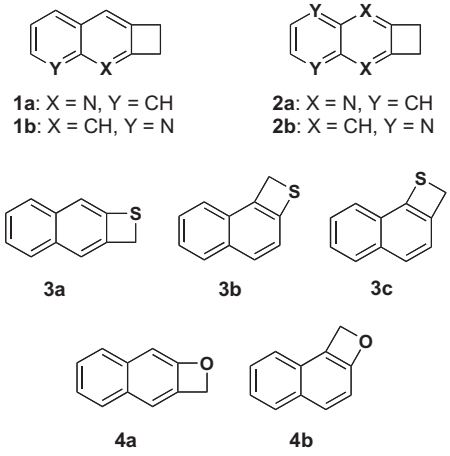

Figure 1. Reported cyclobutanaphthalene heteroanalogs.

Friedländer product **7a** was heated at reflux in 10% KOH/ethanol. The structure of **8a** was established by ^{1}H NMR, ^{13}C NMR, and mass spectrometry and confirmed by X-ray crystallography (Fig. 3b).

Similarly, Friedländer reactions of **6** with aminobenzaldehydes **5b** and **5c** delivered thieno[3,2-*b*]quinolines **7b** and **7c** in 69% and 35% yields, respectively (Fig. 4). Attempts to prepare thieno[3,2-*b*]quinoline **7d** (~10% crude yield) were foiled by the instability of 2-amino-4,5-dimethoxybenzaldehyde (**5d**) and the difficulty in isolating **7d** from the multicomponent, intractable mixture. The direct, one-pot Friedländer reaction/base-mediate rearrangement of **5b** + **6**

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doi:10.1016/j.tetlet.2010.10.039

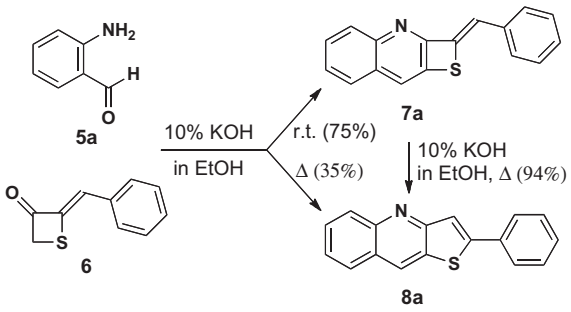

Figure 2. Friedländer reaction to give (*Z*)-2-benzyliden-2*H*-thieto[3,2-*b*]quinoline (**7a**) and its subsequent base-mediated rearrangement to 2-phenylthieno[3,2-*b*]quinoline (**8a**).

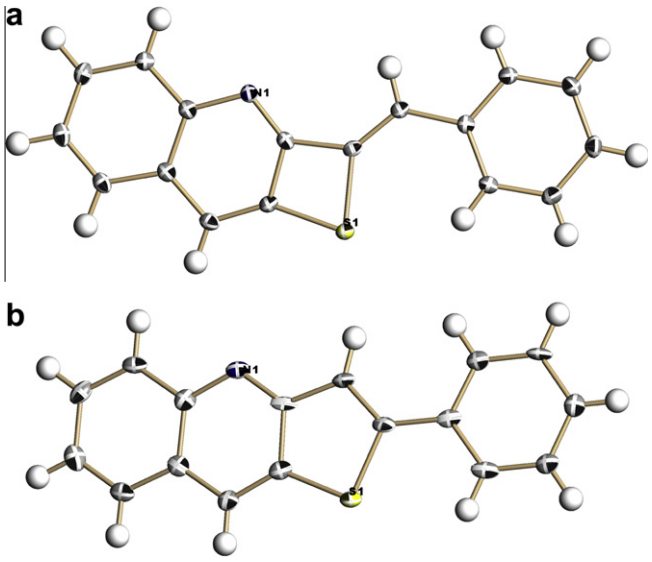

Figure 3. (a) X-ray crystallographic structure of **7a** (see Supplementary data). (b) X-ray crystallographic structure of **8a** (see Supplementary data).

and **5c** + **6** gave **8b** and **8c** in 74% and 70% yields, respectively. The easily effected procedures reported herein constitute an effective and novel method for the synthesis of thieno[3,2-*b*]quinolines; indeed, the literature cites only a few cases of this heterocycle prepared by flash-vacuum pyrolysis (54% yield),[9a] or nitrene insertion reaction which gives very low yields (5%).[9b,c]

We propose the following mechanism (Fig. 5) to explain the rearrangement of **7a**–**8a**. The driving force for this rearrangement lies in the fact that **7a** has properties of both a potential Michael acceptor and the inherent strain of a four-membered ring.

In conclusion, we have synthesized the first examples of thieto[3,2-*b*]quinoline heterocycles as their 2-benzylidene derivatives which we show to rearrange readily to interesting and rare thieno[3,2-*b*]quinolines.

Acknowledgments

We wish to thank Mr. Tharallah Shoker for the spectroscopic data and the National Science Foundation (CHE-0910870) for generous financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.039.

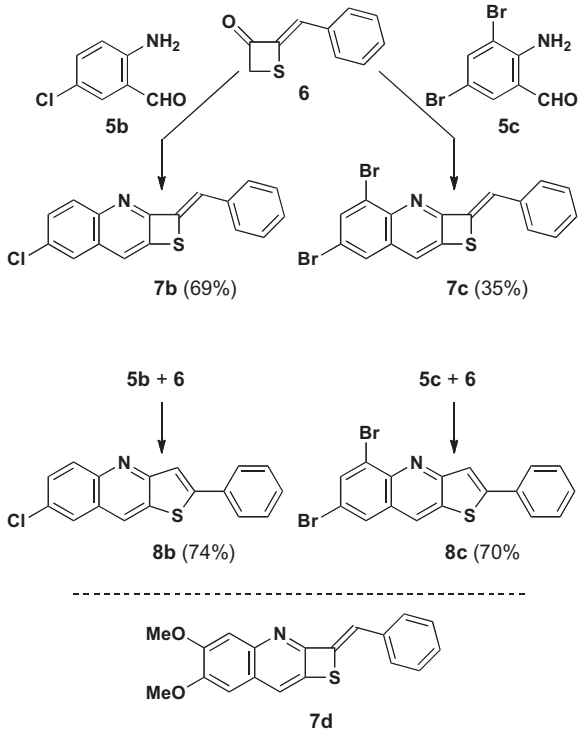

Figure 4. Friedländer reaction to give (*Z*)-2-benzyliden-2*H*-thieto[3,2-*b*]quinoline (**7a**).

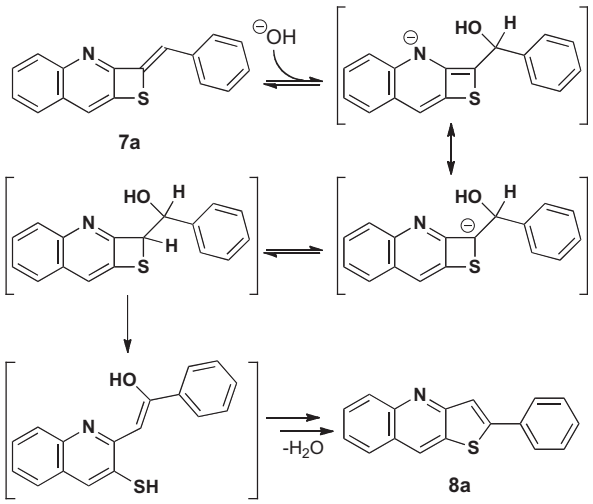

Figure 5. Base-mediated 2*H*-thieto[3,2-*b*]quinoline→thieno[3,2-*b*]quinoline rearrangement.

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6. (a) General procedure for the synthesis of (*Z*)-2-benzyliden-2*H*-thieto[2,3-*b*]quinolines (**7a/b/c**). Equivalent amounts of thietanone[7] **6** (1.07 mmol) and 2-aminobenzaldehyde[8] (**5a**; 1.07 mmol) or its derivatives (**5b** or **5c**) were

dissolved in 10% KOH/ethanol (10 mL) and the solution was stirred at room temperature until completion of the reaction (5 h by TLC). The resulting precipitate was collected by suction filtration and washed with water and dried leading to the corresponding (*Z*)-2*H*-thieto[2,3-*b*]quinoline. All ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ at 300 MHz and 75 MHz, respectively. 2-Aminobenzaldehydes were prepared according to the literature method.[8] In the cases of **5b/c/d**, the reaction mixtures were not steam-distilled as it is for **5a**, but extracted with CH_2Cl_2 and the extracted residues were purified by silica gel column chromatography.

(Z)-2-Benzyliden-2H-thieto[3,2-b]quinoline (**7a**). Cream colored solid, (75% yield). ^{1}H NMR: δ 8.02 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.72–7.65 (m, overlapped doublet with a singlet, 3H), 7.60 (dt, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.52–7.65 (m, 6H). ^{13}C NMR: δ 159.0, 146.7, 137.8, 137.6, 134.4, 130.7, 129.5, 129.1, 129.05, 128.8, 128.2, 127.3, 126.6, 124.5, 122.0. GC–MS Calcd = 261.3. Found M+1 = 262.0.

(Z)-6-Chloro-2-benzyliden-2H-thieto[3,2-b]quinoline (**7b**). Cream colored solid (69% yield). ^{1}H NMR: δ 8.07 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.54–7.36 (m, 5H). ^{13}C NMR: δ 157.7, 138.3, 133.9, 133.0, 131.0, 130.9, 130.4, 129.8, 129.6, 129.2, 129.1, 129.0, 126.2, 125.7, 125.0. GC–MS Calcd = 295/297. Found: M+1 = 296/298.

(Z)-6,8-Dibromo-2-benzyliden-2H-thieto[3,2-b]quinoline (**7c**). Cream colored solid (35% yield). ^{1}H NMR: δ 7.98 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.47 (s, 1H), 7.44–7.29 (m, 6H). ^{13}C NMR: δ 195.9, 142.8, 139.7, 136.8, 134.5, 134.0, 132.4, 130.2, 129.5, 129.2, 128.8, 125.6, 124.1, 123.5, 119.8. GC–MS Calcd = 417/419/421. Found: M+1 = 418/420/422.

(b) Rearrangement of **7a**–**8a.**

2-Phenylthieno[3,2-b]quinoline (**8a**). Intermediate **7a** (50 mg, 0.19 mmol) was dissolved in 10% KOH/ethanol (10 mL) and the mixture was heated at reflux temperature for 4 h. Upon cooling, **8a** precipitated as a white solid which was collected by suction filtration and washed with water to give a pure product (47 mg, 94% yield). ^{1}H NMR: δ 8.63 (s, 1H), 8.18 (dd, J_1 = 8.6 Hz, J_2 = 0.8 Hz, 1H), 7.91 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H), 7.85–7.79 (m, 2H), 7.75 (dt, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.59–7.41 (m, 4H). ^{13}C NMR: δ 158.4, 151.8, 147.2, 133.6, 131.6, 129.7, 129.2, 129.18, 129.1, 129.0, 127.4, 126.7, 125.6, 125.3, 119.8. GC–MS Calcd = 261. Found: M+1 = 262.1.

General procedure for the direct synthesis of 2-phenythieno[3,2-*b*]quinolines (**8a,b,c**). The above general procedure was followed except that the reaction mixture was heated at reflux temperature until the reaction was complete (4 h by TLC). Upon cooling, the product precipitated as a white solid.

2-Phenylthieno[3,2-b]quinoline (**8a**). 35% yield. See above for spectroscopic and mass spectrometric data.

6-Chloro-2-phenylthieno[3.2-b]quinoline (**8b**). 74% yield). ^{1}H NMR: δ 8.73 (s, 1H), 8.41 (d, J = 9.3 Hz, 1H), 8.10 (s, 1H), 7.75–7.70 (m, 2H), 7.58–7.47 (m, 4H). ^{13}C NMR: δ 157.7, 138.3, 135.0, 133.8, 132.9, 131.0, 130.8, 130.4, 129.7, 129.5, 129.2, 129.1, 129.0, 126.2, 124.9. GC–MS Calcd = 295/297. Found: M+1 = 296/298.

6,8-Dibromo-2-phenylthieno[2,3-b]quinoline (**8c**). 70% yield). ^{1}H NMR: δ 8.48 (s, 1H), 8.12 (d, J = 1.5 Hz, 1H), 8.05 (s, 1H), 7.98 (apparent d, J = 1.8 Hz, 1H), 7.76 (d, J = 6.0 Hz, 2H), 7.56–7.38 (m, 3H). ^{13}C NMR: δ 158.2, 141.6, 136.3, 133.7, 132.8, 130.6, 130.0, 129.4, 129.3, 129.2, 129.0, 127.0, 126.5, 119.4, 118.7. GC–MS Calcd = 417/419/421. Found: M+1 = 418/420/422.

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