Synthesis of [1,4]Oxathiepino[5,6-*b*]quinolines via Base-Mediated Intramolecular Hydroalkoxylation

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This paper is dedicated to Prof. Issa Yavari.

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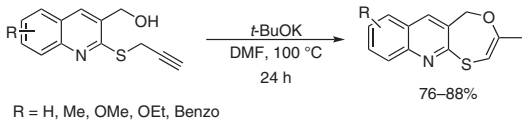

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Abstract A base-mediated intramolecular hydroalkoxylation that was used to prepare a series of seven-membered S,O-heterocycles is described. 2-Thiopropargyl-3-hydroxymethyl quinolines were prepared starting from 2-mercaptoquinoline-3-carbaldehydes, via S-propargylation and reduction of a formyl group. Interestingly, 2-mercaptopropargyl-3-hydroxymethyl quinolines were converted into the corresponding oxathiepinoquinolines in the presence of *t*-BuOK. It is proposed that the *S*-propargyl moiety, in the presence of base, is converted into its allenyl isomer; subsequent addition of a hydroxyl group to the terminal double bond yields the 3-methyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline in good to high yield. Notably, the procedure is adaptable to the conversion of *N*-propargyl indole-2-methanol into the corresponding intramolecular hydroalkoxylation product.

Key words quinoline, 2-chloroquinoline-3-carbaldehyde, intramolecular reactions, hydroalkoxylation, base-mediated cyclization, allenes

N-Heterocycles, including quinolines and isoquinolines, have attracted much attention due to their wide-ranging applications in organic synthesis[1] as precursors to polymers,[2] dyestuffs,[3] additives, pharmaceuticals, agrochemicals, veterinary products, surfactants, and corrosion inhibitors.[4,5] The possible structural variation of compounds that can be obtained by altering the type, number and location of the heteroatoms enhances enormously as the size of the ring increases. However, the chemistry of the seven-membered, or larger, heterocyclic compounds remains under-investigated, although the stability and applicability of these compounds show promise.[6] Azepines, oxepines, and thiepines and their derivatives are seven-membered-ring derivatives that have been studied most comprehensively.[7,8] Azepine and oxepine rings are constituents of a number of naturally occurring alkaloids and metabolic products of marine organisms. Furthermore, these seven-membered heterocycles and their derivatives are present in many drugs that exhibit a range of biological activities.[9,10] Importantly, the azepine derivative, caprolactam, is produced industrially as an intermediate in the manufacture of nylon-6 and in production of films and coatings.[11,12]

Oxathiepines rank among the less studied heterocycles, although groups have reported several compounds possessing (*R*,*S*)-benzo-fused, seven-membered rings with oxygen and sulfur atoms in a 1,5-relationship with interesting antiproliferative activities against the MCF-7 cancer cell line (Figure 1).[13,14]

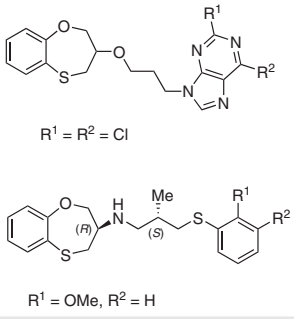
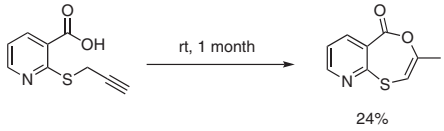


Figure 1 Examples of benzoxathiepines with anticancer properties

An atom-economical method for the synthesis of carbon–heteroatom bonds is hydrofunctionalization of unsaturated carbon–carbon bonds; for instance, intramolecular hydroalkoxylation and hydroamination of alkynyl alcohols and alkynyl amines produce cyclic vinyl ethers and imines.[15–17] In addition, a few studies have demonstrated synthetic methodologies exploiting metal complexes (e.g.,

transition metal complexes, lanthanides, and middle- to late-transition metals)[18–22] that selectively catalyse these transformations.[23] However, these methods use expensive transition-metal catalysts. Notably, Singh et al. established an efficient one-pot synthetic route to [1,4]oxathiepino[5,6-*b*]pyridin-5-one derivatives by reacting a range of α-bromo ketones with 2-mercaptonicotinic acid.[24] Furthermore, Kalita et al. found that 2-mercaptonicotinic acid propargyl thioether, on prolonged storage, forms [1,4]-oxathiepino[5,6-*b*]pyridine-5-one in 24% yield (Scheme 1).[25]



Scheme 1 Intramolecular conversion of 2-mercaptonicotinic acid propargyl thioether

In continuation of our studies on quinoline chemistry,[26] herein we wish to describe a novel synthetic approach using intramolecular hydroalkoxylation based on base-mediated reactions.

The first step in the synthetic sequence was the preparation of 2-thiopropargyl-3-hydroxymethyl quinolines, which started from the corresponding acetanilides. The latter, in the presence of $POCl_3$/DMF, gave 2-chloroquinoline-3-carbaldehydes.[27] Thiolation of these 2-chloroquinoline-3-carbaldehydes with NaSH, followed by S-propargylation and reduction of the formyl group resulted in 2-thiopropargyl-3-hydroxymethyl quinolines **1**.[28] Interestingly, **1a**, in the presence of *t*-BuOK at room temperature in DMF, was converted into the 3-methyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (**2a**) but in a low yield (Table 1, entry 1). However, on increasing the temperature to 100 °C the reaction was complete after 1 h and **2a** was isolated in 87% yield (entry 2).

With the preparation of **2a** as a model study, the reaction was examined at 100 °C with a variety of bases in DMF such as TEA, pyridine, DABCO, KOH, Cs_2CO_3, and K_2CO_3 (Table 1, entries 3–8), and it was found that *t*-BuOK was the best base, giving the highest yield (87%) of the desired product **2a** (entry 2). After establishing the optimum base, the reaction was carried out in different solvents including CH_2Cl_2, MeOH and MeCN (entries 9–11), but no improvement was observed.

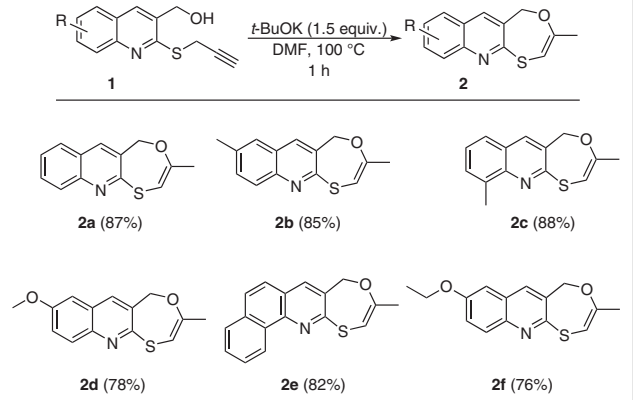
After identifying the optimal reaction conditions, the scope and generality of the reaction was examined using various hydroxymethyl quinolines to afford the desired products in good to excellent yields (76–88%; Scheme 2).

The procedure could also be used for the conversion of *N*-propargyl indole-2-methanol **3** into the corresponding intramolecular hydroalkoxylation product (Scheme 3). It is notable that Vandavasi et al. previously studied the synthesis of indole/pyrrole-fused 1,4-oxazines.[29] All structures of the newly synthesized compounds were confirmed by ^1H and ^{13}C NMR spectroscopic and elemental analysis.

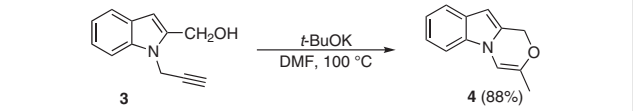
Table 1 Optimization of the Reaction Conditions for the Synthesis of Oxathiepino Quinoline **2a**[a]

Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	*t*-BuOK	DMF	r.t.	23
2	*t*-BuOK	DMF	100[c]	87
3	TEA	DMF	100	N.R
4	pyridine	DMF	100	N.R
5	DABCO	DMF	100	N.R
6	KOH	DMF	100	complex
7	Cs_2CO_3	DMF	100	complex
8	K_2CO_3	DMF	100	12
9	*t*-BuOK	CH_2Cl_2	reflux	11
10	*t*-BuOK	MeOH	reflux	complex
11	*t*-BuOK	MeCN	reflux	51

[a] Reaction conditions: **1a** (1 mmol), base (1.5 equiv), solvent (5 mL), 24 h.
[b] Isolated yield.
[c] 1 h.

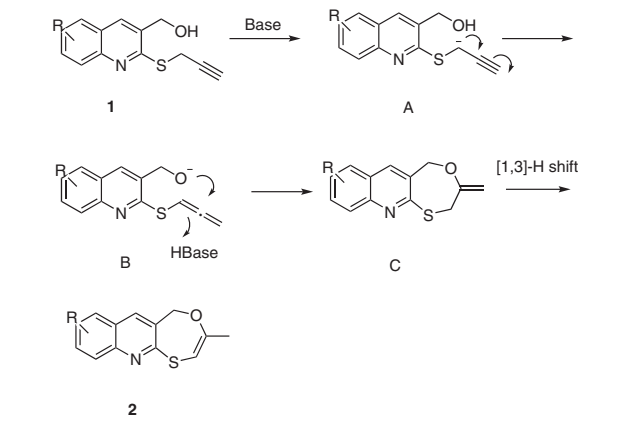


Scheme 2 Extension of the cyclization reaction to derivatives



Scheme 3 Synthesis of 3-methyl-1*H*-[1,4]oxazino[4,3-*a*]indole

A possible mechanism for this reaction is shown in Scheme 4. In the proposed mechanism, abstraction of the proton neighboring the sulfur by base results in generation of anion **A**, and isomerization to allene **B**. Subsequent intramolecular cyclization and protonation of the alkoxide provides ring-closed product **C**. Finally, a [1,3]-H shift gives oxathiepine **2**.



Scheme 4 Proposed mechanism for the intramolecular hydroalkoxylation pathway

In conclusion, we have developed a practical and transition-metal-free intramolecular hydroalkoxylation reaction for the synthesis of [1,4]oxathiepino[5,6-*b*]quinolines in good to excellent yields using *t*-BuOK as the optimal base.

All purchased solvents and chemicals were of analytical grade and used without further purification. 2-Chloroquinoline-3-carbaldehydes[27] were prepared by reported procedures. Melting points were measured with an Electrothermal 9100 apparatus. NMR spectra were acquired with a Bruker Avance spectrometer at 400 or 300 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR analysis. A Leco CHNS 932 instrument was used for elemental analysis.

Preparation of 2a–f and 4; General Procedure

Compound **1** or **3** (1.0 mmol) and *t*-BuOK (1.5 mmol) were dissolved in DMF (5 mL) and the resulting mixture was stirred at 100 °C for 1 h. The reaction was monitored by TLC analysis. On completion, the mixture was cooled to r.t. and then water (20 mL) was added. The resulting solution was extracted with CH_2Cl_2 (20 mL), the organic phase was washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated to give a crude residue that was purified by flash chromatography on a silica gel column (hexane/EtOAc, 8:2) to obtain pure product **2** or **4**.

3-Methyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (2a)

Yield: 0.201 g (87%); white solid; mp 190–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 4.80 (s, 1 H), 5.41 (s, 2 H), 7.52–7.57 (m, 1 H), 7.72–7.82 (m, 2 H), 7.97 (t, *J* = 12 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 70.2, 85.9, 126.6, 126.7, 127.6, 128.6, 130.6, 132.9, 136.6, 147.4, 154.9.

Anal. calcd for $C_{13}H_{11}NOS$: C, 68.10; H, 4.84; N, 6.11; S, 13.98. Found: C, 68.19; H, 4.87; N, 6.02; S, 13.84.

3,8-Dimethyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (2b)

Yield: 0.206 g (85%); white solid; mp 180–182 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (s, 3 H), 2.80 (s, 3 H), 4.80 (s, 1 H), 5.40 (s, 2 H), 7.43 (t, *J* = 12 Hz, 1 H,), 7.57–7.65 (m, 2 H), 7.97 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 23.1, 70.2, 77.1, 86.2, 125.6, 126.5, 126.6, 130.7, 132.6, 136.7, 136.9, 146.5, 154.8, 161.5.

Anal. calcd for $C_{14}H_{13}NOS$: C, 68.11; H, 5.39; N, 5.76; S, 13.18. Found: C, 68.02; H, 5.44; N, 5.69; S, 13.13.

3,10-Dimethyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (2c)

Yield: 0.215 g (88%); white solid; mp 187–189 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H), 2.52 (s, 3 H), 4.76 (s, 1 H), 5.36 (s, 2 H), 7.54 (t, *J* = 4 Hz, 2 H), 7.90 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 23.1, 70.2, 86.0, 126.5, 126.7, 128.3, 132.8, 132.8, 136.1, 136.7, 154.8, 161.6.

Anal. calcd for $C_{14}H_{13}NOS$: C, 68.11; H, 5.39; N, 5.76; S, 13.18. Found: C, 68.17; H, 5.31; N, 5.71; S, 13.24.

8-Methoxy-3-methyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (2d)

Yield: 0.203 g (78%); white solid; mp 195–197 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H), 3.92 (s, 3 H), 4.77 (s, 1 H), 5.36 (s, 2 H), 7.03 (d, *J* = Hz, 1 H), 7.34–7.37 (m, 1 H), 7.9 (t, *J* = 8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 55.6, 70.2, 86.0, 105.3, 123.1, 127.8, 130.1, 133.2, 135.5, 143.4, 154.7, 158.0, 159.5.

Anal. calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.72; H, 5.14; N, 5.50, 12.31.

10-Methyl-8*H*-benzo[*h*][1,4]oxathiepino[5,6-*b*]quinoline (2e)

Yield: 0.230 g (82%); white solid; mp 172–174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (s, 3 H), 4.73 (s, 1 H), 5.32 (s, 2 H), 7.53 (d, *J* = 12 Hz, 1 H), 7.63 (m, 2 H), 7.70 (d, *J* = 14.8 Hz, 1 H), 7.81 (t, *J* = 9.2 Hz, 1 H), 7.90 (s, 1 H), 9.16 (d, *J* = 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 70.2, 86.4, 124.6, 124.7, 124.9, 127.2, 127.8, 127.9, 128.6, 130.6, 133.5, 134.1, 136.6, 145.7, 155.1, 161.4.

Anal. calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01; S, 11.48. Found: C, 73.12; H, 4.61; N, 5.05; S, 11.44.

8-Ethoxy-3-methyl-5*H*-[1,4]oxathiepino[5,6-*b*]quinoline (2f)

Yield: 0.208 g (76%); white solid; mp 211–213 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (t, *J* = 9 Hz, 3 H), 1.85 (s, 3 H), 4.13–4.20 (m, 2 H), 4.80 (s, 1 H), 5.39 (s, 2 H), 7.03 (d, *J* = 3 Hz, 1 H),7.30–7.39 (m, 1 H), 7.92 (t, *J* = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 23.1, 63.8, 70.1, 86.0, 105.9, 123.3, 127.8, 130.0, 133.0, 135.5, 143.3, 154.6, 157.3, 159.3.

Anal. calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73. Found: C, 65.98; H, 5.47; N, 5.07; S, 11.81.

3-Methyl-1*H*-[1,4]oxazino[4,3-*a*]indole (4)

Yield: 0.163 g (88%); white solid; mp 115–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 5.26 (s, 2 H), 6.34 (s, 1 H), 6.60 (s, 1 H), 7.17 (t, *J* = 10.4 Hz, 1 H), 7.27 (t, *J* = 9.2 Hz, 1 H), 7.38 (d, *J* = 10.8 Hz, 1 H,), 7.66 (d, *J* = 10 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.32, 63.71, 96.89, 101.41, 108.42, 120.12, 120.94, 121.90, 128.30, 128.36, 133.00, 140.18.

Anal. calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.73; H, 5.78; N, 7.63.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719868.

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