Tetrahedron Letters 55 (2014) 4378–4381

Contents lists available at ScienceDirect

Tetrahedron Letters

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

I_2-catalyzed base-free cyclization of 3-homoallylquinoline-2-thiones: facile synthesis of tetracyclic, furothiopyrano[2,3-*b*]quinolines

Mrityunjaya Asthana, Neha Sharma, Ritush Kumar, Jay Bahadur Singh, Radhey M. Singh *

Department of Chemistry, Centre of Advanced Study, Banaras Hindu University, Varanasi 221005, U.P., India

ARTICLE INFO

Article history:
Received 10 May 2014
Revised 5 June 2014
Accepted 7 June 2014
Available online 16 June 2014

Keywords:
Iodine
Catalyzed
Tetracyclic, furothiopyrano[2,3-*b*]quinolines
Sulfonium
3-Homoallylquinoline-2-thiones

ABSTRACT

I_2-catalyzed base-free reactions of 3-homoallylquinoline-2-thiones have been described for the synthesis of tetracyclic quinolines, tetrahydrofuro [2′,4′:4,6]thiopyrano[2,3-*b*]quinolines in excellent yields. Similarly, I_2-catalyzed reactions could proceed to tricyclic quinolines from hydroxyl group protected 3-homoallylquinoline-2-thiones. However, deprotection of group in tricyclic quinoline with HI again transformed into tetracyclic quinoline. The sulfonium salt intermediate has been proposed to explain these reactions.

The quinoline scaffold is prevalent in various alkaloids.[1] On the other hand, its benzo/hetero-fused analogues have attracted much attention to both medicinal and synthetic chemists because of their biological, pharmaceutical, and agrochemical activities and as synthetic building blocks.[2] Thiopyran-fused quinolines have been reported to possess important biological activities.[3] For example, 3,4-dihydro-2*H*-thiopyrano[2,3-*b*]quinoline[4] and 2*H*-thiopyrano[2,3-*b*]quinolin-2-carboxylic acid,[5] have exhibited mGlu 1 receptor and antioxidant activities, respectively. Consequently, several syntheses have been reported for this class of compounds.[6] Recently, we[7] and Wang and co-workers[8] have reported the synthesis of 2*H*-thiopyrano[2,3-*b*]quinolines from 2-mercaptoquinoline-3-carbaldehydes and activated alkenes via Michael addition-cyclization and Michael–Henry reaction routes, respectively.

The electrophilic iodocyclization of alkenes with proximal nucleophilic groups has become one of the most popular routes for the syntheses of various carbocycles and heterocycles.[9] We have reported iodocyclization of homoallylquinolin-2-ones to the synthesis of tri/tetracyclic, pyrano[2,3-*b*]quinolines.[10] In contrast, iodocyclization of their 2-thiones analogues has not been studied so far. Thus, in continuation of our interest in developing new methodologies to the carbo/hetero-fused quinolines,[11] we herein describe base-free iodine-catalyzed cyclization reactions of 3-homoallylquinolin-2-thiones **3** which gives new insights into this reaction and, in turn, affords tetracyclic thiopyrano[2,3-*b*]quinolines **4**, respectively.

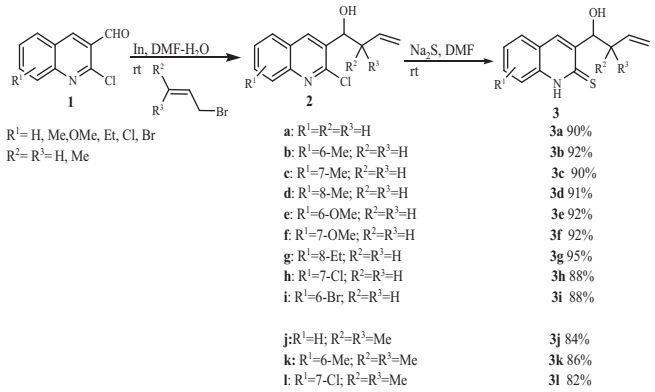
The starting substrates, 3-homoallylquinoline-2-thiones **3a**–**l**[15] were prepared from 2-chloroquinoline-3-carbaldehydes **1** in two steps via Barbier reaction[10a] followed by sodium sulfide[10b] in DMF at room temperature (82–95%) (Scheme 1).

Initially, the substrate **3a** was examined for iodocyclization reaction with and without $NaHCO_3$ under our previously reported conditions for analogous substrates,[10c] with 2.2 equiv of iodine in THF at rt under aerobic atmosphere. Both the reactions were completed in 5 min giving the same product **4a** with 82% yields (Table 1, entries 1–3). The structure of **4a** was characterized as, 2,2a,10,11-tetrahydrofuro [2′,4′:4,6] thiopyrano[2,3-*b*]quinoline, tetracyclic quinoline from its spectral and analytical data. The structure of **4a** was further confirmed unambiguously from X-ray crystallography (Fig. 1).[12]

Iodocyclization reaction of **3a** at −70 °C to isolate tricyclic, thiopyrano[2,3-*b*]quinoline **5** (Scheme 4) was also unsuccessful, although, reaction rate was slow and afforded exclusively tetracyclic **4a** with 78% yield (entry 4). The exclusive formation of **4a** in a very short period could be explained by rapid conversion of **5** into more reactive intermediate for intramolecular nucleophilic substitution reaction by the hydroxyl group. Further, it has been noticed that nucleophilic substitution of 2-halomethylthiopyrans, similar to 2-halomethylpyrrolidines,[13] would proceed through sulfonium salt intermediate. From these results, we speculated that **3a** would rapidly provide the sulfonium salt intermediate **B** from intermediate **5**

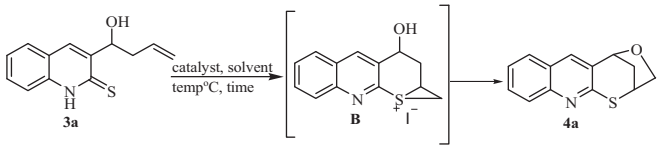
* Corresponding author. Tel.: +91 542 670 2482; fax: +91 542 2368127.
E-mail address: rmohan@bhu.ac.in (R.M. Singh).

http://dx.doi.org/10.1016/j.tetlet.2014.06.041
0040-4039/



Scheme 1. Synthesis of 3-homoallyl quinoline-2-thiones **3a–l**.

Table 1
Optimization of iodocyclization reaction conditions for the synthesis of **4a**[a]



Entry	Catalyst (equiv)	Base (equiv)	Solvent	Time (min)	Yield[b] (%)
1	I_2 (2.2)	$NaHCO_3$ (2.3)	THF	5	82
2	I_2 (2.2)	$NaHCO_3$ (1.0)	THF	5	82
3	I_2 (2.2)	—	THF	5	82
4	I_2 (2.2)	—	THF	8hr	78[c]
5	I_2 (1.0)	—	THF	5	81
6	I_2 (0.5)	—	THF	5	80
7	I_2 (0.25)	—	THF	5	83
8	**I_2 (0.1)**	—	**THF**	**20**	**85**
9	I_2 (0.1)	$NaHCO_3$ (2.3)	THF	20	85
10	I_2 (0.1)	—	THF	24 h	6+SM[d]
11	NIS (0.1)	—	THF	20	80
12	NBS (0.1)	—	THF	30	78
13	ICl (0.1)	—	THF	20	50
14	NCS (0.1)	—	THF	60	[e]
15	I_2 (0.1)	—	DCM	20	80
16	I_2 (0.1)	—	DMF	30	82
17	I_2 (0.1)	—	MeOH	30	80
18	I_2 (0.1)	—	CH_3CN	50	74
19	I_2 (0.1)	—	Benzene	90	65
20	I_2 (0.1)	—	Dioxane	90	65

Bold values signify optimized reaction condition.
[a] All reactions were performed using **3a** (1 mmol), catalyst and 4.0 ml of solvent at room temperature in air.
[b] Isolated yields.
[c] reaction was performed at −70 °C.
[d] reaction performed under inert atmosphere; S.M. = starting material.
[e] An inseparable mixture of products was obtained.

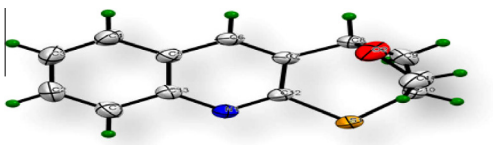


Figure 1. ORTEP diagram of **4a**.

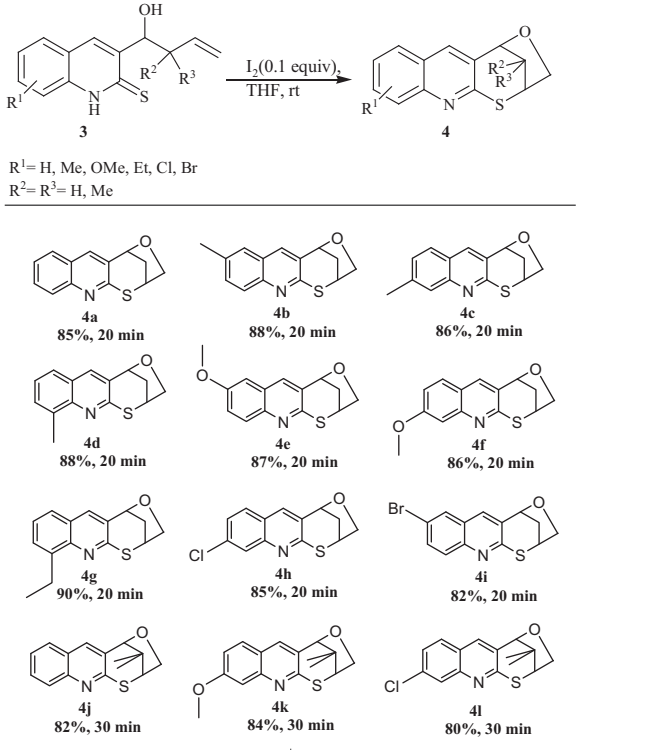
which in turn, affords the tetracyclic **4a** via intramolecular nucleophilic substitution reaction (Scheme 5).

Next, we carried out a series of experiments for standardization of iodocyclization reaction conditions by varying iodine loadings, catalysts, and different solvents. Decreasing the amount of iodine ranging from 2.2 equiv to 0.1 equiv, the reactions proceeded smoothly and afforded the cyclized product **4a** in 80% to 85% yields (entries 5–8, Table 1). Further, using base with catalytic iodine, the reaction again completed in 20 min showing ineffectiveness of base (entry 9). Further, the cyclization reaction under inert atmosphere afforded only trace amount of **4a** even after 24 h demonstrating no regeneration of I_2 (entry 10). Other catalysts such as NIS, NBS, ICl, and NCS and solvents such as DCM, MeOH, benzene, and dioxane were also examined for the reactions but none of them led to any enhancement in the yield (Table 1, entries 11–20). Thus, the optimal conditions for iodocyclization reaction were found to be a combination of 1 equiv of **3a** and 0.1 equiv of I_2 in THF at room temperature providing the best yield of **4a** (entry 8).

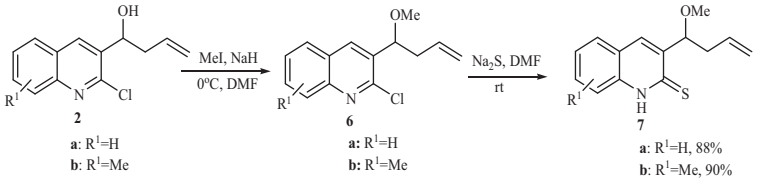
Having established the optimal conditions for cyclization, we next examined a series of substituted 3-(1-hydroxy-but-3-enyl)-quinolin-2-thiones (**3b–i**) and 3-(1-hydroxy-2,2-dimethyl-but-3-enyl)-quinolin-2-thiones (**3j–l**) which afforded the tetracyclic quinolines **4b–l**[16] in good to excellent yields, respectively. The results are summarized in Table 2.

We further envisioned that the iodocyclization reaction of the hydroxyl group protected thione **7** under the optimal reaction condition could afford tricyclic quinoline **5**. The starting thiones **7a–b** were prepared in 88–90% yields in two steps according to Scheme 2. Thus, the cyclization reaction of **7a** was initially examined under the optimal reaction conditions for 5 min, 40 min, and every 4 h intervals, reactions were not completed at all and

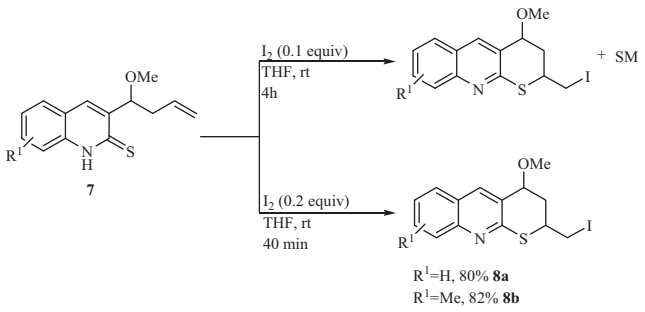
Table 2
Iodocyclization of 3-homoallyl quinolin-2-thiones **3**[a] for the synthesis of tetracyclic thiopyrano[2,3-*b*]quinolines **4**[b]



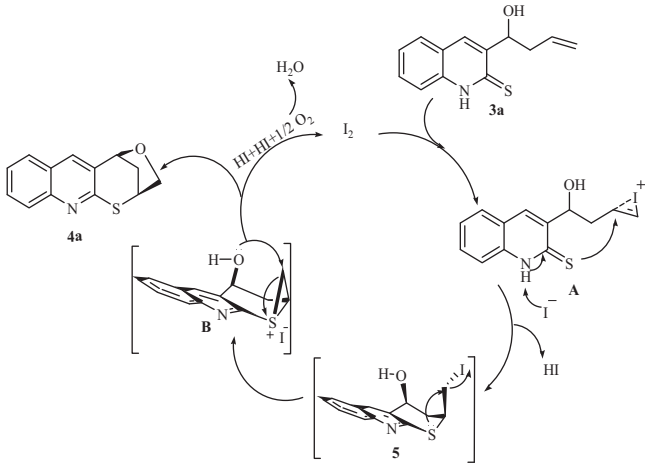
[a] All reactions were performed using **3** (0.5 mmol) and I_2 (0.1 equiv) in 4.0 ml of THF at room temperature in air.
[b] Isolated yields.



Scheme 2. Synthesis of starting material **7**.



Scheme 3. Synthesis of tricyclic thiopyrans **8**.



Scheme 5. Plausible mechanism for the formation of **4a**.

afforded the tricyclic quinoline **8a** in 30%, 75%, and 80% yields along with starting material (SM) **7a**. Further, using 0.2 and 2.2 equiv of I_2, the reactions were completed in 40 min and 5 min with 80% yield (**8a**), respectively (Scheme 3), demonstrating I_2-catalyzed synthesis of tricyclic quinoline. Similarly, **8b** was prepared in 82% yield.

Next, the methyl group of **8a** was deprotected to synthesize tricyclic compound **5**. However, the deprotection reaction of **8a** with HI in DMF afforded tetracyclic quinoline **4a**, not tricyclic **5** which again supports that the nucleophilic substitution reaction proceeds through sulfonium salt intermediate to afford **4a** (Scheme 4).

The plausible mechanism for the tetracyclic thiopyranoquinoline is illustrated in Scheme 5. The electrophilic addition of I_2 to olefinic bond of substrate **3a** results in the formation of iodonium ion **A**. Intramolecular attack by sulfide anion, generated by I^- from thioamide, on **A** gave tricyclic intermediate **5**, which rapidly converts into sulfonium salt intermediate **B** by neighboring group participation of sulfur atom on 2-iodomethyl carbon atom. Lastly, sulfonium salt ring open by the hydroxyl group, via exo-dig, to afford tetracylic **4a**. The aerobic oxidation of HI regenerates I_2[14] to complete the reactions.

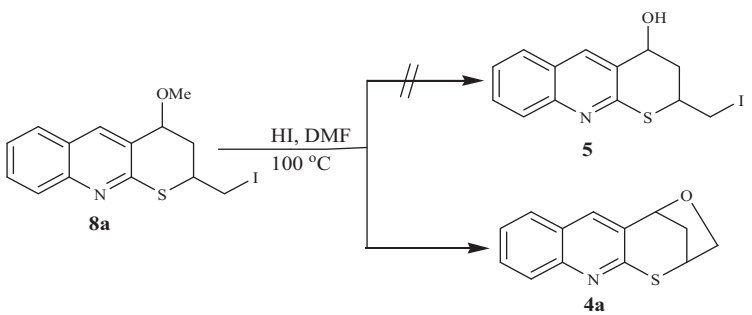
In conclusion, we have described I_2-catalyzed and base-free facile synthesis of tetracyclic quinolines 4 in excellent yields. The catalyzed reaction could be extended to the synthesis of tricyclic quinoline 8 by protecting the hydroxyl group. The sulfonium salt intermediate has been proposed to explain these reactions. All reactions were completed in very short time under aerobic conditions.

Acknowledgments

M.A. and J.B. thank CSIR, New Delhi for their Senior and Junior research fellowships, respectively, and N.S. to UGC, New Delhi for senior research fellowship. We are thankful to Dr. G. Pandey, Director, CBMR, India for spectral help. The authors acknowledge Vikram Singh and Virendra Kumar for help in solving the crystal data.

Supplementary data

Supplementary data (spectroscopic data of selected entries from Scheme 1 and Table 2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.041.



Scheme 4. Synthesis of tetracyclic **4a** using HI.

References and notes

1. (a) Elderfield, R. C. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley: New York, NY, London, 1960; Vol. 4,. Chapter 1 (b) Sekar, M.; Rajendra Prasad, K. J. *J. Nat. Prod.* **1998**, *61*, 294; (c) Wright, C. W.; Kyereme, J. A.; Breen, G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Gokcek, Y.; Kendrick, H.; Phillips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187; (d) Sahu, N. S.; Pal, C.; Mandal, N. B.; Nanerjee, S.; Raha, M.; Kundu, A. P.; Basu, A.; Ghosh, M.; Roy, K.; Bandyopadhyay, S. *Bioorg. Med. Chem.* **2002**, *10*, 1687; (e) Bringman, G.; Reichert, Y.; Kane, V. *Tetrahedron* **2004**, *60*, 3539; (f) Kournetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141.
2. (a) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, NY, 1984; Vol. 2,. Chapter 2.09 (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood: Amsterdam, 1998; (c) Kalita, P. K.; Baruah, B.; Bhuyan, P. J. *Tetrahedron Lett.* **2007**, *47*, 777; (d) Zhong, W.; Lin, F.; Chen, R.; Su, W. *Synthesis* **2009**, 2333.
3. (a) Jasinski, P.; Welsh, B.; Galvez, J.; Land, D.; Zwolak, P.; Ghandi, L.; Terai, K.; Dudek, A. Z. *Invest. New Drugs* **2008**, *26*, 223; (b) Geies, A. A.; Bakhite, E. A.; El-Kashef, H. S. *Pharmazie* **1998**, *53*, 686; (c) Wagner, G.; Vieweg, H.; Leistner, S. *Pharmazie* **1993**, *48*, 576; (d) Shiraki, H.; Kozar, M. P.; Mlelndez, V.; Hudson, T. H.; Ohrt, C.; Magill, A. J.; Lin, A. J. *J. Med. Chem.* **2011**, *54*, 131; (e) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Org. Chem.* **2010**, *45*, 3245; (f) Harrison, E. A., Jr.; Rice, K. C. *J. Heterocycl. Chem.* **1977**, *14*, 909.
4. Lesage, A. S. J.; Bischoff, F. P.; Janssen, C. G. M.; Lavreysen, H. Patent WO 2003082350, 2003.
5. Naik, H. R. P.; Naik, H. S. B.; Naik, T. R. R.; Bindu, P. J.; Naika, H. R.; Aravinda, T.; Lamani, D. S. *Med. Chem.* **2009**, *5*, 148.
6. (a) Prabhuswamy, B.; Ambekar, S. Y. *Synth. Commun.* **1999**, *29*, 3477; (b) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966; (c) Wang, X.-S.; Li, Q.; Wu, J.-R.; Tu, S.-J. *J. Comb. Chem.* **2009**, *11*, 433; (d) Nandeshwarappa, B. P.; Kumar, D. B. A.; Kumaraswamy, M. N.; Kumar, Y. S. R.; Naik, H. S. B.; Mahadevan, K. M. *Phosphorus Sulfur Silicon* **2006**, *181*, 1545; (e) Ramesh, E.; Vidhya, T. K. S.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 2810; (f) Zhong, W.; Ma, W.; Liu, Y. *Tetrahedron* **2011**, *67*, 3509.
7. Singh, B.; Chandra, A.; Asthana, M.; Singh, R. M. *Tetrahedron Lett.* **2012**, *53*, 3242.
8. Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Adv. Synth. Catal.* **2013**, *355*, 1053.
9. (a) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354; (b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem. Eur. J.* **2012**, *18*, 5460; (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321; (d) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33; (e) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814; (f) Bedford, S. B.; Bell, K. E.; Bennett, F.; Hayes, C. J.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2143; (g) Bedford, S. B.; Bell, K. E.; Fenton, G.; Hayes, C. J.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6511.
10. (a) Chandra, A.; Singh, M. K.; Singh, R. M. *Synth. Commun.* **2007**, *37*, 1689; (b) Srivastava, A.; Singh, R. M. *Ind. J. Chem.* **2005**, *44B*, 1868; (c) Singh, M. K.; Chandra, A.; Singh, B.; Singh, R. M. *Tetrahedron Lett.* **2007**, *48*, 5987.
11. (a) Singh, R. M.; Kumar, R.; Sharma, N.; Asthana, M. *Tetrahedron* **2013**, *69*, 9443; (b) Sharma, N.; Asthana, M.; Nandini, D.; Singh, R. P.; Singh, R. M. *Tetrahedron* **2013**, *69*, 1822; (c) Singh, R. M.; Sharma, N.; Kumar, R.; Asthana, M.; Upadhyay, S. *Tetrahedron* **2012**, *68*, 10318; (d) Singh, R. M.; Chandra, A.; Sharma, N.; Singh, B.; Kumar, R. *Tetrahedron* **2012**, *68*, 9206; (e) Chandra, A.; Upadhyay, S.; Singh, B.; Sharma, N.; Singh, R. M. *Tetrahedron* **2011**, *67*, 9219; (f) Singh, B.; Chandra, A.; Singh, R. M. *Tetrahedron* **2011**, *67*, 244; (g) Chandra, A.; Singh, B.; Singh, R. M. *J. Org. Chem.* **2009**, *74*, 5664; (h) Chandra, A.; Singh, B.; Upadhyay, S.; Singh, R. M. *Tetrahedron* **2008**, *64*, 11680; (i) Singh, B.; Chandra, A.; Upadhyay, S.; Puerta, M. C.; Valerga, P.; Singh, R. M. *Tetrahedron Lett.* **2008**, *49*, 6423.
12. Crystal data for **4a**: empirical formula, $C_{13}H_{11}NOS$; formula weight 229.30; crystal colour: colourless, block; crystal system, orthorhombic; lattice parameters, $a = 8.7137(8)$, $b = 11.5146(13)$, $c = 21.820(3)$, $\alpha = \beta = \gamma = 90$, space group P b c a; $Z = 8$; $D_{calcd} = 1.391$ g/cm^3; R(reflections) = 0.0469 (1951); wR^2 (reflections) = 0.1256 (2518); refinement method full-matrix least-squares on F^2; Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC **951596**. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk.
13. Diaba, F.; Ricou, E.; Bonjoch, J. *Org. Lett.* **2007**, *9*, 2633.
14. Gabriele, B.; Veltri, L.; Maltese, V.; Spina, R.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2011**, 5626.
15. *General procedure for the synthesis of 3-homoallylquinoline-2-thiones* ***3****:* Indium metal (2.5 mmol) and allyl bromide (3 mmol) were added to a solution of aldehydes **1** (1 mmol) in DMF (8 ml) and stirred for 8–12 h. After completion of the reaction, the reaction mixture was quenched with a few drops of 2N HCl, diluted with water, and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuum. The products 2-chloro-3-homoallylquinolines **2** were recrystallized from ethyl acetate-hexane. The 2-chloro-3-homoallylquinolines **2** were dissolved in DMF and Na_2S (1.5 equiv) was added to it. After completion of the reaction, acetic acid was added into the reaction mixture and the corresponding 2-thiones **3** precipitated out which was filtered out. The solid products were pure enough for further use.
*3-(1-Hydroxy-but-3-enyl)-1H-quinoline-2-thione (****3a****).* Yield: 207.90 mg (90%), yellow solid; mp 149–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.57–2.64$ (m, 1H), 2.95–2.98 (m, 1H), 3.57 (s, 1H), 5.15–5.24 (m,3H), 5.89-5.97 (m, 1H), 7.34–7.43 (m, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.87 (s, 1H), 11.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 39.5$, 70.7, 116.0, 117.4, 122.6, 124.2, 127.6, 130.6, 132.1, 134.9, 138.2, 141.6, 179.6; HRMS calcd for $C_{13}H_{13}NOS$ $[M+Na]^+$ 254.0616, found 254.0610.
16. *General procedure for the synthesis of tetracyclic derivatives* ***4a–l****:* To a solution of **3a–l** (0.5 mmol) in THF (4 ml) was added I_2 (0.1 equiv). The reaction mixture was continuously stirred at room temperature. After completion of reaction mixture (as monitored by TLC), the reaction mixture was quenched with saturated solution of aqueous sodium thiosulfate. The resulting solution was extracted with EtOAc, washed with water, saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on basic alumina using hexane/ethyl acetate (97:3) as eluent to afford corresponding tetracyclic derivatives 4a–l.
*2,2a,10,11-Tetrahydrofuro[2′,4′:4,6]thiopyrano[2,3-b]quinoline (****4a****).* Yield 97.32 mg (85%), white solid, mp 124–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.47$ (d, $J = 12.3$ Hz, 1H), 2.62 (ddd, $J = 12.3$ Hz, 6.0 Hz, 1H), 3.73–3.76 (m, 1H), 4.32 (dd, $J = 8.4$ Hz, 4.2 Hz, 1H), 4.54 (d, $J = 8.4$ Hz, 1H), 5.16 (d, $J = 6.0$ Hz, 1H), 7.40 (t, $J = 7.8$ Hz, 1H), 7.62–7.68 (m, 3H), 7.86 (d, $J = 8.4$ Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) $\delta = 33.9$, 41.6, 76.2, 80.1, 125.3, 125.5, 127.4, 127.6, 129.9, 131.9, 133.5, 148.0, 157.8; HRMS calcd for $C_{13}H_{11}NOS$; $[M+H]^+$ 230.0640; Found: 230.0615.