Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 2161–2164

Novel route to the synthesis of 4-quinolyl isothiocyanates

Boyu Zhong,* Rima S. Al-Awar, Chuan Shih, John H. Grimes, Jr., Michal Vieth and Chafiq Hamdouchi

Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285, USA

Received 8 December 2005; accepted 23 January 2006

Abstract—4-Quinolyl isothiocyanates were synthesized in a regiospecific fashion from the corresponding 4-chloroquinolines and silver thiocyanate in refluxing toluene. The products were isolated in quantitative yield and high purity (>95%) by simple filtration and concentration. Reactivity and mechanism of the reaction are discussed. The new approach would provide a new mean which had been lacking for the synthesis of functionalized 4-quinolinyl isothiocyanate.

Isothiocyanate is a very useful building block in synthetic chemistry, especially for constructing heterocycles such as thiodiazole, triazole, thiouracil, thioquinazolone, thiopyrimidine, etc.[1] It has been proven to be a key reagent in Edman peptide sequencing and other biological assays of DNA and protein.[2] Due to their synthetic and biological importance,[3] several methods for the preparation of isothiocyanate have been reported.[4,5] Although these methods were shown to be highly effective in alkyl and homocyclic systems, they suffered from the limited scope such as their applicability to heterocyclic systems. In fact, the synthesis of *N*-heterocyclic isothiocyanates has been a very challenging topic,[5,6] as they are prone to oligomerize by autocatalysis. As a result, they are generally generated in situ and trapped with amines or other reagents. Recently, 2-methyl-4-quinolyl isothiocyanate was synthesized.[7] Although the overall yield was as high as 80%, it required a two-step process including the isolation of a thiuronium salt intermediate, treatment with aqueous sodium hydroxide solution, and recrystallization in a nucleophilic solvent of aqueous alcohol. Nevertheless, it is the only 4-quinolyl isothiocyanate ever reported.

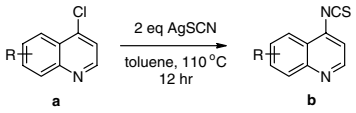
Our ongoing medicinal chemistry effort prompted us to undertake the synthesis of a variety of 4-quinolinyl isothiocyanates as key building blocks in the search for compounds with pharmacological importance. Our efforts using reported transformations starting from 4-aminoquinoline had led to failure. We turned to the direct replacement of the chlorine atom in 4-chloroquinolines with inorganic thiocyanates, inspired by the previous work of Kristian.[8] Our use of silver thiocyanate turned out to be successful. In a typical reaction, a mixture of 4-chloroquinoline and silver thiocyanate in anhydrous toluene was rapidly stirred at 110 °C for 12 h.[9] The reaction mixture was filtered and the filtrate was concentrated under vacuum to provide 4-quinolyl isothiocyanate as an off-white solid in quantitative yield.[10] Attempts to purify the isothiocyanate on silica gel or recrystallization resulted in its decomposition. However, the crude product was sufficiently pure (>95%) for routine synthetic uses.

Representative examples of 4-quinolyl isothiocyanates that were successfully prepared using our new approach are listed in Tables 1 and 2. The data illustrate the broad scope of the reaction. The reaction was compatible with a variety of functional groups. Interestingly, the electronic nature of the substitution did not significantly affect the reaction. For instance, the substrates with electron withdrawing groups, such as phenyl, fluorine, bromine, chlorine, trifluoromethyl, and carboxylic ester groups gave the products in similar yields and purities to those with electron-donating groups such as methyl, methoxy, and methylthio. The 4-chlorine is specifically activated during the reaction with no apparent effect on the other positions. The availability of these haloquinolyl isothiocyanates was found to be valuable for further chemical transformations. The quantitative

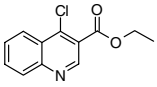
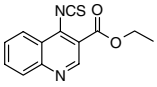
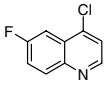
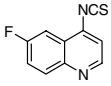
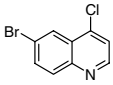
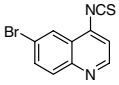
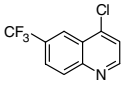
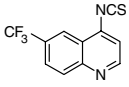
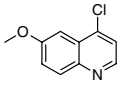
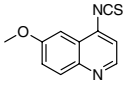
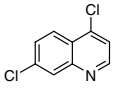
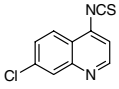
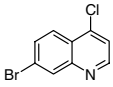
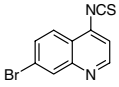
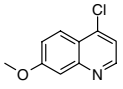
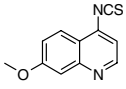
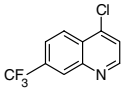
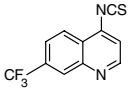
Keywords: 4-Quinolyl isothiocyanate; Thiocyanate; Silver thiocyanate.
* Corresponding author. Tel.: +1 317 277 6024; fax: +1 317 277 3652; e-mail: zhong_boyu@lilly.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.119

Table 1. Synthesis of 4-quinolyl isothiocyanates



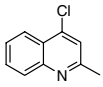
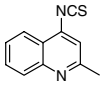
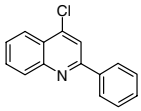
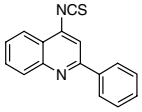
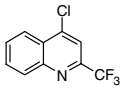
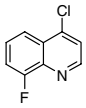
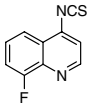
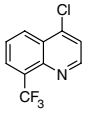
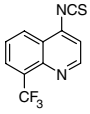
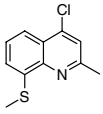
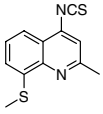
Yield: 100%
Purity: 100% (HPLC-CLND)
>95% (^{1}H NMR)

Entry	Chloride *a*	Isothiocyanate *b*
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

nature and regiospecificity of this reaction coupled with the minimal purification requirements make it an efficient synthesis.

During the course of this study, we noticed an important effect of the size of the substituents at both positions 2 and 8 on the outcome of the reaction. As shown in Table 2, with a substituent at 2-position the reaction is much slower (18 h for methyl and 60 h for phenyl). When a trifluoromethyl group, an isostere of an *i*-propyl or *t*-alkyl groups,[11] was present at 2-position (entry 13), the chloride failed to react. The steric effect of groups at 8-position was not as pronounced as that at position 2. For instance, 4-chloro-8-trifluoromethyl quinoline (entry 15), a counterpart of entry 13, was converted into isothiocyanate in 60 h. These results suggested that the ring nitrogen may interact with a silver cation to promote the aromatic substitution. Interestingly, 8-methylthio group (entry 16) accelerated the reaction as compared

Table 2. Synthesis of 2- and 8-substituted 4-quinolyl isothiocyanates (reaction, yield, and purity as in Table 1)

Entry	Chloride *a*	Isothicyanate *b*	Reaction time (h)
11			18
12			60
13		Not detected	60
14			12
15			60
16			12

to entry 11. The high affinity between sulfur atom and silver cation further suggested participation of silver. Finally, we noted that silver salt is critical to the reaction. When the silver salt was replaced with either potassium thiocyanate or copper(I) thiocyanate, very little or no product was obtained. Besides the driving force of the formation of silver chloride, it is worth to note the possible catalytic role of the silver cation.

Reactions of silver thiocyanate with 4-chloroquinoline (entry 1) and 2-methyl-4-chloroquinoline (entry 11) were monitored by HPLC-CLND. The kinetics of both reactions seemed to be similar with the exception that the latter was much slower. The outcome of the reaction is outlined in Figure 1 for entry 11 and a typical stepwise process. In the first five hours, 52% of the starting material was converted exclusively into an intermediate, which was isolated and found to be 2-methyl-4-quinolyl thiocyanate (**17**). When submitted to the same reaction conditions, intermediate **17** rearranged to isothiocyanate **11b** quantitatively. Figure 1 also showed a noticeable induction period (about two hours) followed by a chain-like kinetics. When one equimole (to silver thiocyanate) of TEMPO was initially added, the reaction failed to proceed. This observation strongly suggested the involvement of radical intermediates in the process. It was not clear however if the silver cation acted as an electron-transferring agent in this radical reaction. The details of the reaction mechanism and the role of the silver cation are currently under investigation and the results will be published in due course.

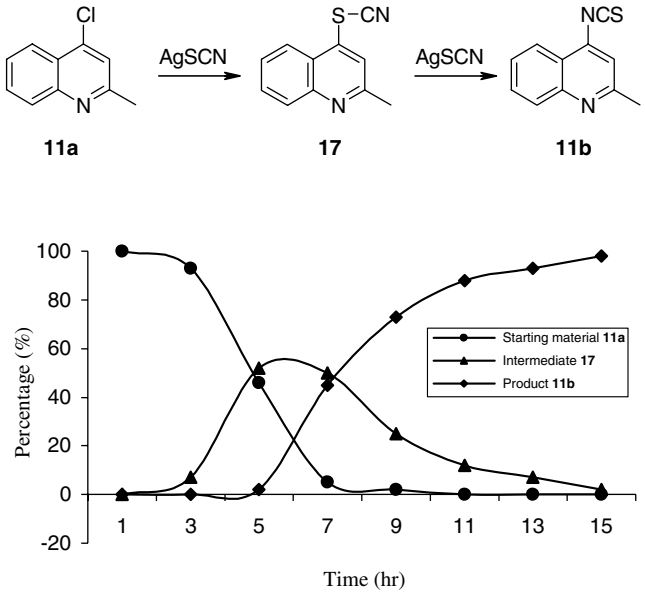


Figure 1. Reaction of 2-methyl-4-chloroquinoline with AgSCN.

In summary, we have described a novel and practical approach to the construction of 4-quinolyl isothiocyanates by reacting 4-chloroquinolines and silver thiocyanate in refluxing toluene. A stepwise kinetics was illustrated. The protocol provides a simple and efficient access to 4-quinolyl isothiocyanates in quantitative yield and excellent purity.

Acknowledgements

The authors gratefully thank Mr. James M. Gilliam for the collection of HRMS data, Mr. Darrell S. Coleman for the gift of compound **16a**, Ms. Kathryn Lawrence and Mr. Thomas J. Mitchell for the assistance in FTIR experiments, and Dr. Robert C. Anderson for many useful discussions.

Supplementary data

General experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS, FTIR, and melting point) for all products and intermediate **17** are available. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2006.01.119.

References and notes

1. A comprehensive review on NCS chemistry: Drobnica, L.; Kristian, P.; Augustin, J. In *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; Vol. 2, pp 1003–1221; Recent reviews on isothiocyanates as synthetic intermediates: (a) Sharma, S. *Sulfur Rep.* **1989**, *8*, 327; (b) Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1; (c) Avalos, M.; Bablano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Heterocycles* **1992**, *33*, 973; (d) Nedolya, N. A.; Trofimov, B. A.; Senning, A. *Sulfur Rep.* **1996**, *17*, 183; (e) Trofimov, B. A. *J. Heterocycl. Chem.* **1999**, *36*, 1469; (f) Brandsma, L.; Nedolya, N. A.; Tarasova, O. A.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2000**, *36*, 1241; (g) Sommen, G. *Synlett* **2004**, *7*, 1323–1324.
2. (a) Edman, P. *Arch. Biochem.* **1949**, *22*, 475; (b) Cabantchik, Z. I.; Rothstein, A. *J. Membr. Biol.* **1974**, *15*, 227; (c) Podhradsky, D.; Oravec, P.; Antalik, M.; Kristian, P. *Collect. Czech. Chem. Commun.* **1994**, *59*, 213.
3. Recent reviews on chemoprevention of cancers by isothiocyanates: (a) Hecht, S. S. *Adv. Exp. Med. Biol.* **1996**, *401*, 1; (b) Hecht, S. S. *J. Nutr.* **1999**, *129*, 768S; (c) Hecht, S. S. *Drug Metab. Rev.* **2000**, *32*, 395; (d) Chung, F.-L. *Exp. Lung Res.* **2001**, *27*, 319; (e) Smith, T. J. *Expert Opin. Invest. Drugs* **2001**, *10*, 2167; (f) Conaway, C. C.; Yang, Y.-M.; Chung, F.-L. *Curr. Drug Metab.* **2002**, *3*, 233; (g) Thornalley, P. J. *Anti-Cancer Drugs* **2002**, *13*, 331; (h) Watanabe, M.; Ohata, M.; Hayakawa, S.; Isemura, M.; Kumazawa, S.; Nakayama, T.; Furugori, M.; Kinae, N. *Phytochemistry* **2003**, *62*, 733–739; (i) Solowiej, E.; Kasprzycka-Guttman, T.; Fiedor, P.; Rowinski, W. *Acta Pol. Pharm.* **2003**, *60*, 97–100; (j) Visanji, J. M.; Duthie, S. J.; Pirie, L.; Thompson, D. G.; Padfield, P. J. *J. Nutr.* **2004**, *134*, 3121–3126.
4. (a) Drobnica, L.; Kristian, P.; Augustin, J. In *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; Vol. 2, pp 1013–1062; (b) Molina, P.; Arques, A. A. *Synthesis* **1982**, 596; (c) Mazagova, D.; Sabolova, D.; Kristian, P.; Imrich, J.; Antalik, M.; Podhradsky, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 203; (d) Adam, W.; Bargon, R. M.; Bosio, S. G.; Schenk, W. A.; Stalke, D. *J. Org. Chem.* **2002**, *67*, 7037; (e) Le Count, D. J.; Dewsbury, D. J.; Grundy, W. *Synthesis* **1977**, 582; (f) Hansen, E. T.; Petersen, H. J. *Synth. Commun.* **1984**, *14*, 537.
5. L'abbe, G. *Synthesis* **1987**, 525.
6. Knott, E. B. *J. Chem. Soc.* **1956**, 1644.
7. Avetisyan, A. A.; Aleksanyan, I. L.; Ambartsumyan, L. P. *Russ. J. Org. Chem. (Translation of Zhurnal Organicheskoi Khimii)* **2004**, *40*, 407–408.
8. (a) Kristian, P. *Chem. Zvesti* **1961**, *15*, 164; (b) Kristian, P. *Chem. Zvesti* **1969**, *23*, 371; (c) De Leenheer, A.; Sinsheimer, J. E.; Burckhalter, J. H. *J. Pharm. Sci.* **1972**, *61*, 273; (d) Vlassa, M.; Kezdi, M. *J. Prakt. Chem.* **1985**, *327*, 1010.
9. The rapid stirring was crucial for the success of the reaction; otherwise, the reaction either progressed very slowly or completely ceased. A mixture of 4-chloroquinoline and silver thiocyanate in anhydrous toluene was stirred at 110 °C for 12 h. The hot reaction mixture was filtered and washed three times with chloroform. The filtrate was concentrated under vacuum to afford the 4-quinolinyl isothiocyanate as an off-white solid. We thank a reviewer for the suggestion of using regular toluene. Reactions 1, 5, 7 and 11 were carried out in anhydrous toluene and regular toluene side by side. No obvious differences were noted in yields and proton NMR spectra between the two sets of reactions.
10. The structure of the product was confirmed by a strong and broad infrared band in the range of 2000–2130 cm^{-1} and a peak around 138–143 ppm (-NCS) on the ^{13}C NMR spectrum.[12,13] The purity of the product was determined using ^{1}H NMR spectroscopy and an HPLC coupled with a Chemiluminescent Nitrogen Detector (CLND) that linearly responds to the nitrogen content in the sample.[14] In the ^{1}H NMR spectrum of the crude product, only trace amount of impurities (<5%) was observed. In the HPLC-CLND chromatography, the desired isothiocyanate was

the only peak (sample concentration 1 mg/1 mL). The absence of any other peaks on CLND detector indicated that the impurities on the NMR spectrum did not contain the quinoline moiety or that they were below the detection limit of CLND (<25 picomole/5 μL).[14]

11. (a) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618; (b) Hanzawa, Y.; Kawagoe, K.-i.; Ito, M.; Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1633.
12. (a) Ham, N. S.; Willis, J. B. *Spectrochim. Acta* **1960**, *16*, 393; (b) Bellamy, L. J. *Advances in Infrared Group Frequencies*; Methuen & Co. Ltd., 1968; pp 57–61.
13. (a) Janovec, L.; Suchar, G.; Imrich, J.; Kristian, P.; Sasinkova, V.; Alfoldi, J.; Sedlak, E. *Collect. Czech. Chem. Commun.* **2002**, *67*, 665; (b) Kalinowski, H. D.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 90; (c) Maciel, G. E.; Beatty, D. A. *J. Phys. Chem.* **1965**, *69*, 3920; (d) Danihel, I.; Imrich, J.; Kristian, P.; Liptaj, T.; Mazagova, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1833.
14. (a) Fujinari, E. M.; Courthaudon, L. O. *J. Chromatogr. A* **1992**, *592*, 209; (b) Taylor, E. W.; Qian, M. G.; Dollinger, G. D. *Anal. Chem.* **1998**, *70*, 3339.