Tetrahedron Letters 55 (2014) 3108–3110

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An efficient ligand-free ferric chloride catalyzed synthesis of annulated 1,4-thiazine-3-one derivatives

K. C. Majumdar *, Debankan Ghosh

Department of Chemistry, University of Kalyani, Kalyani 741235, W.B., India

ARTICLE INFO

Article history:
Received 14 February 2014
Revised 31 March 2014
Accepted 1 April 2014
Available online 12 April 2014

Keywords:
C–S coupling
Ferric chloride
Sodium sulfide
1,4-Thiazine-3-one

ABSTRACT

A straight forward route for the synthesis of coumarin-, quinolone-annulated 1,4-thiazine-3-one derivatives has been achieved by using sodium sulfide as the sulfur source and ferric chloride as catalyst in a ligand-free condition. The synthetic procedure is simple, inexpensive, and affords the products in good yields. This methodology is also applicable to naphthalene and benzene systems.

Among the sulfur containing heterocyclic compounds 1,4-benzothiazine-3-one derivatives have gained much importance due to their occurrence in a large number of biologically active compounds and natural products.[1] The compounds containing 1,4-benzothiazine-3-one derivatives act as potent SGLT2 inhibitors,[2] Ca^{2+} activated potassium channel openers,[3] and show anticonvulsant,[4] antidiabetic,[5] and antiarrhythmic activities.[6]

There are a few reports in the literature regarding the synthesis of benzo[1,4]thiazine-3-one.[7] But unavailability/toxicity of the starting materials/reagents, harsh reaction conditions, or use of large amount of catalysts/bases and costly ligands are some flaws found in the available reaction conditions. Also most of the available methodologies suffer from low yields of the products. Furthermore, there is no report of construction of diversely annulated 1,4-thiazine-3-one frameworks, that is, coumarin, quinolone, and naphthalene-annulated 1,4-thiazine-3-one derivatives are yet to be synthesized. So, construction of annulated 1,4-thiazine-3-one derivatives by a simple, easy, and economical method is still demanding. Coumarin- and quinolone are very much interesting molecules as they exist in a large number of natural products and agrochemicals.[8] Moreover, a large number of compounds derived from coumarin and quinolone are also well-known for their profound bioactivity.[9]

Recently, our group reported an effective route for the formation of annulated-thiazole derivatives via iron-mediated C–S cross coupling followed by acid-promoted condensation.[10] Encouraged by the results and in our quest for the synthesis of various bioactive heterocycles,[11] we have decided to test the efficiency of this methodology that is, iron catalyzed C–S coupling using sodium sulfide as the sulfur source, for the synthesis of various annulated 1,4-thiazine-3-one derivatives. Herein we report the results of our observations.

We have initially chosen 5-bromo-1-ethyl-6-(methylamino)-quinolin-2(1*H*)-one[12] **1a** as a starting material. The compound **1a** was treated with chloroacetyl chloride (2 equiv), potassium carbonate (1.5 equiv), and TBAHS (0.1 equiv) in 2:1 (v/v) DCM: H_2O at room temperature for 5 h to access the required precursor *N*-(5-bromo-1-ethyl-2-oxo-1,2-dihydroquinolin-6-yl)-2-chloro-*N*-methylacetamide **2a**. The other precursors (**2b–l**) were also prepared by the aforesaid method from the respective starting materials (Scheme 1).

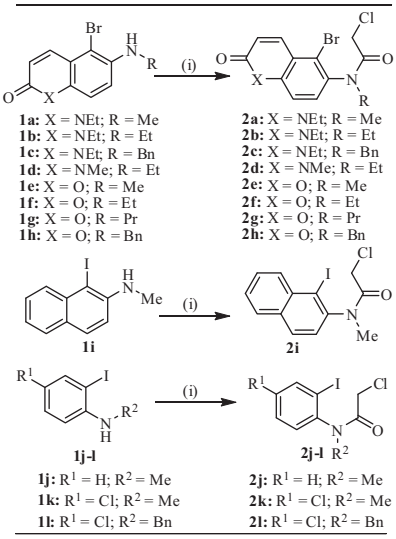
When the precursor **2a** was treated with 3 equiv of sodium sulfide and 10 mol % ferric chloride as catalyst in DMF at 120 °C for 8 h[10] full consumption of **2a** was observed with the formation of a new product (Scheme 2).

The product was isolated in 70% yield and was characterized as 7-ethyl-4-methyl-2*H*-[1,4]thiazino[2,3-*f*]quinoline-3,8(4*H*,7*H*)-dione **3a** from its elemental and spectral data. The reaction condition was then optimized to obtain better yield of the desired product (Table 1).

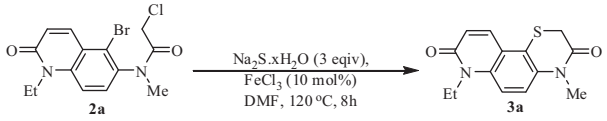
From the optimization of the reaction condition it was evident that the decrease in the concentration of Na_2S in the reaction from 3 equiv to 2 equiv increases the yield of **3a** (entry 2), but further reduction of Na_2S to 1 equiv lowers the yield (entry 5). Furthermore, when the reaction time is reduced to 6 h, the yield

* Corresponding author. Tel.: +91 33 25828750; fax: +91 33 25828282.
E-mail address: kcmklyuniv@gmail.com (K.C. Majumdar).

http://dx.doi.org/10.1016/j.tetlet.2014.04.005
0040-4039/

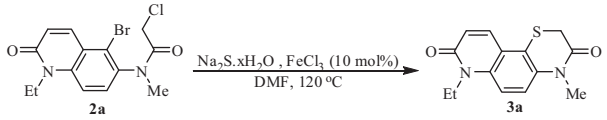


Scheme 1. Synthesis of the precursors. Reaction condition: (i) chloroacetyl chloride (2 equiv), TBAHS (0.1 equiv), K_2CO_3 (1.5 equiv) in DCM/H_2O (2:1); room temperature, 4–6 h.



Scheme 2. Synthetic route for the formation of product **3a** from precursor **2a**.

Table 1
Optimization of the reaction condition



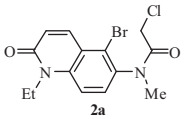
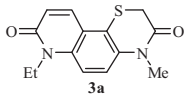
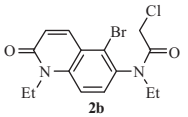
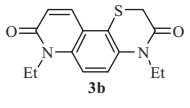
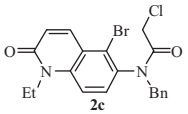
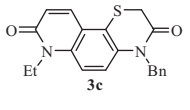
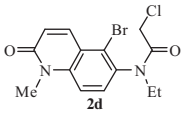
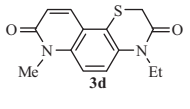
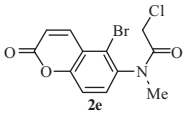
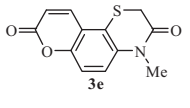
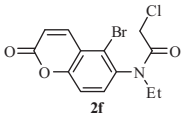
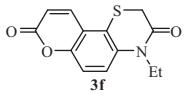
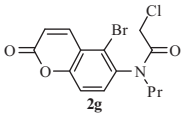
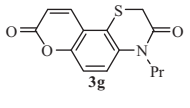
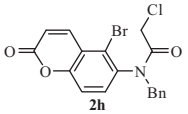
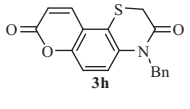
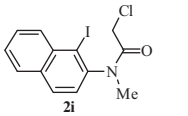
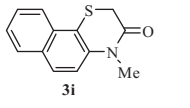
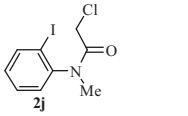
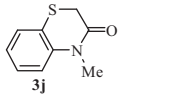
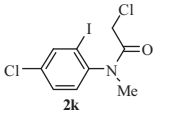
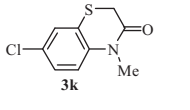
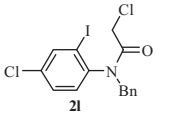
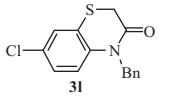
Entry	Catalyst (mol %)	Equiv of Na_2S	Time (in hour)	Yield[a]
1	$FeCl_3$ (10)	3	8	70
2	$FeCl_3$ (10)	2	8	78
3[b]	**$FeCl_3$ (10)**	**2**	**6**	**87**
4	$FeCl_3$ (10)	2	4	52
5	$FeCl_3$ (10)	1	6	47
6	$FeCl_3$ (05)	2	6	64
7	$FeCl_3$ (20)	2	6	86
8[c]	$FeCl_3$ (10)	2	6	30
9[d]	$FeCl_3$ (10)	2	6	72

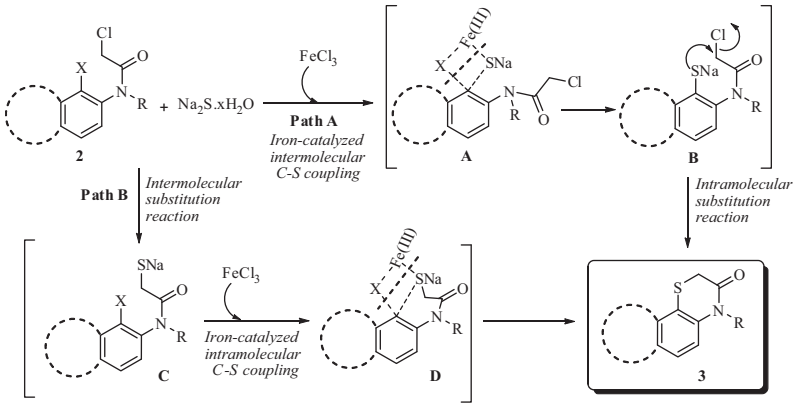
[a] Isolated yield.
[b] Optimized reaction condition.
[c] Reaction was carried out at 100 °C.
[d] Reaction was carried out at 140 °C.

of **3a** increases to 87% (entry 3). However further decrease in the reaction time lowers the yield of **3a**, probably due to the incomplete conversion of **2a** to **3a** (entry 4). Decrease in the amount of catalyst decreases the yield whereas increasing the amount of catalyst does not show any change in the yield of **3a** (entry 6, 7, respectively). Decrease of reaction temperature (100 °C) dramatically reduces the yield to 30% whereas increase in reaction temperature (140 °C) leads to the reduced yield (72%) perhaps due to decomposition of the product. So from the above table we observe that 2 equiv of sodium sulfide, 10 mol % ferric chloride as catalyst in DMF at 120 °C for 6 h afforded the optimum yield of **3a** (87%). Encouraged by the result, the other precursors **2b–l** were also treated similarly to give the desired annulated 1,4-thiazine-3-one derivatives **3b–l** in good to excellent yields (75–90%). The synthesized substrates **2a–l** and the products **3a–l** are listed in Table 2.

The formation of the products **3** can be explained as shown in Scheme 3. The precursors **2** may participate in the reaction in two possible ways. In path-A, precursor **2** in the presence of

Table 2
Synthesized products

Entry	Precursors	Products	Yield
1			87
2			88
3			80
4			82
5			77
6			89
7			80
8			85
9			75
10			82
11			86
12			90



Scheme 3. Plausible mechanistic route.

sodium sulfide as the sulfur source and iron(III) chloride as the catalyst, may undergo iron-mediated intermolecular C–S coupling similar to Cu-catalyzed σ-bond metathesis[13] reaction to form the intermediate **B** via transition state **A**, which in turn may undergo intramolecular cyclization to produce the cyclized product **3**. We have earlier demonstrated the possibility of formation of **B** type intermediate in the iron-catalyzed C–S coupling step by the intermediate trapping method.[10] However, the occurrence of other pathway (path-B) cannot be ruled out. In path-B intermolecular substitution reaction may take place in between sodium sulfide and the terminal chlorine atom present in the precursors **2** to give intermediate **C**, which may undergo iron-mediated intramolecular C–S coupling[14,15] to give the cyclized products **3** via transition state **D**. Here both the pathways can afford the same products **3**. However, further work is necessary to establish the mechanism of the reaction.

In summary, we have developed a versatile, easy, clean, and economical route for the formation of diversely annulated 1,4-thiazine-3-one derivatives. A number of substituted 2-chloro-*N*-methylacetamide derivatives **2a–h** were successfully reacted to generate quinolone and coumarin-annulated 1,4-thiazine-3-one derivatives **3a–h** in 75–90% yields. Moreover, this methodology is also applicable to naphthalene and benzene systems. The precursor **2i** under the same reaction condition leads to the formation of the corresponding naphthalene-annulated 1,4-thiazine-3-one derivative **3i** and the precursors **2j–l** afford 1,4-benzothiazine-3-one derivatives **3j–l** in good yields. This demonstrates the versatility of the methodology. This method utilizes inexpensive and easy to handle sodium sulfide as the sulfur source instead of the use of expensive and toxic organo-sulfur reagents. Furthermore, no ligands are required in this method which makes this method more attractive to the synthetic organic chemists.

Acknowledgements

K.C.M. is thankful to UGC (New Delhi) for UGC Emeritus Fellowship and D.G. is grateful to CSIR (New Delhi) for a senior research fellowship. We also thank DST (New Delhi) for providing Bruker NMR spectrometer (400 MHz) and Perkin–Elmer CHN analyzer, UV–VIS spectrometer, and Perkin–Elmer FT-IR under FIST program.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.005.

References and notes

1. (a) Zhang, L. L.; Yan, Y.; Liu, Z.; Abliz, Z.; Liu, Z. *J. Med. Chem.* **2009**, *52*, 4419; (b) Borate, H. B.; Maujan, S. R.; Sawargave, S. P.; Chandavarkar, M. A.; Vaiude, S. R.; Kelkar, R. G.; Chavan, S. P.; Kunte, S. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 722; (c) Gowda, J.; Khader, A.; Shree, P.; Shabaraya, A. B.; Kalluraya, B. *Eur. J. Med. Chem.* **2011**, *46*, 4100.
2. Li, A.-R.; Zhang, J.; Greenberg, J.; Lee, T.; Liu, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2472.
3. Calderone, V.; Spogli, R.; Martelli, A.; Manfroni, G.; Testai, L.; Sabatini, S.; Tabarrini, O.; Cecchetti, V. *J. Med. Chem.* **2008**, *51*, 5085.
4. Zhang, L.-Q.; Guan, L.-P.; Wei, C.-X.; Deng, X.-Q.; Quan, Z.-S. *Chem. Pharm. Bull.* **2010**, *58*, 326.
5. Kawashima, Y.; Ota, A.; Mibu, H. WO Patent 9405647, 1993.
6. Fujita, M.; Ito, S.; Ota, A.; Kato, N.; Yamamoto, K.; Kawashima, Y.; Yamauchi, H.; Iwao, J. *Eur. J. Med. Chem.* **1990**, *33*, 1898.
7. (a) Huang, W.-S.; Xu, R.; Dodd, R.; Shakespeare, W. C. *Tetrahedron Lett.* **2013**, *54*, 5214; (b) Krapcho, J.; Szabo, A.; Williams, J. *J. Med. Chem.* **1963**, *6*, 214; (c) Chen, D.; Wang, Z.-J.; Bao, W. *J. Org. Chem.* **2010**, *75*, 5768; (d) Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G.; Terni, P. *J. Med. Chem.* **1987**, *30*, 465; (e) Zuo, H.; Li, Z.-B.; Ren, F.-K.; Falck, J. R.; Meng, L.; Ahn, C.; Shin, D.-S. *Tetrahedron* **2008**, *64*, 9669; (f) Zhao, Y.; Wu, Y.; Jia, J.; Zhang, D.; Ma, C. *J. Org. Chem.* **2012**, *77*, 8501; (g) Xu, X.-B.; Liu, J.; Zhang, J.-J.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550.
8. Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642.
9. (a) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3397; (b) Lee, Y. R.; Kim, B. S.; Kweon, H. I. *Tetrahedron* **2000**, *56*, 3867; (c) Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71; (d) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642; (e) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719.
10. Majumdar, K. C.; Ghosh, D. *Tetrahedron Lett.* **2013**, *54*, 4422.
11. For some of our recent synthesis of heterocycles, see: (a) Majumdar, K. C.; Mondal, S.; Ghosh, D. *Synthesis* **2010**, *7*, 1176; (b) Majumdar, K. C.; Mondal, S.; Ghosh, D.; Chattopadhyay, B. *Synthesis* **2010**, *8*, 1315; (c) Majumdar, K. C.; Ponra, S.; Ghosh, D.; Taher, A. *Synlett* **2011**, 104; (d) Majumdar, K. C.; Mondal, S.; Ghosh, D. *Tetrahedron Lett.* **2009**, *50*, 4781; (e) Majumdar, K. C.; Ghosh, D.; Mondal, S. *Synthesis* **2011**, *4*, 599; (f) Majumdar, K. C.; Ghosh, D.; Ponra, S. *Synthesis* **2013**, *45*, 2983; (g) Majumdar, K. C.; Nandi, R. K.; Ponra, S. *Synlett* **2012**, 113; (h) Majumdar, K. C.; Ganai, S.; Nandi, R. K.; Ray, K. *Tetrahedron Lett.* **2012**, *53*, 1553.
12. Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2008**, *49*, 2418.
13. Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338.
14. Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880.
15. Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450.