Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 7476–7479
Tetrahedron Letters

A novel DBU-promoted S–N-type Smiles rearrangement reaction under controlled microwave heating

Chen Ma,* Qun Zhang, Kai Ding, Liang Xin and Dongju Zhang*

School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China

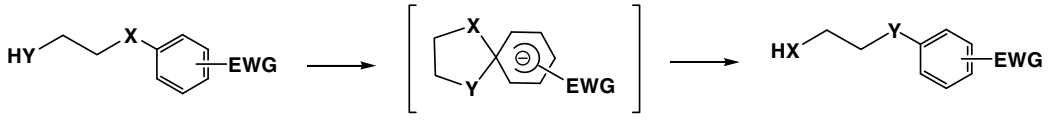
Received 3 July 2007; revised 16 August 2007; accepted 17 August 2007
Available online 22 August 2007

Abstract—A convenient process for the preparation of pyrido[1,4]thiazinone derivatives is described in the presence of DBU as base under controlled microwave heating. This process allows for efficient construction of thiazinone-fused pyridine by S–N-type Smiles rearrangement methodology.

Smiles rearrangement falls under a broad category of intramolecular aromatic nucleophilic substitution of an appropriately placed nucleophile (YH) onto aromatic rings possessing a strong electron withdrawing group and a leaving group (X) properly positioned as shown in Scheme 1.[1] This rearrangement is one of the best base-catalyzed rearrangements, which involves a Meisenheimer complex.[2,3] The nucleophilic group in this rearrangement has included alcohols, phenols, amines, amides and sulfonamides. The leaving group is often an ether, sulfide, sulfoxide, or sulfone. Despite the variety of possible substrates, Smiles rearrangement has been incorporated into only a few synthetic strategies. The modification of the pyridine nucleus is a versatile research area, which still attracts a considerable amount of interest in modern organic chemistry. Due to its presence in numerous natural products and biologically active substances,[4] the pyridine moiety is regarded as one of the most interesting heteroaromatic ring systems. Notwithstanding the fact that a multitude of different reactions on pyridine and its derivatives are known,[5] there is still a need for new approaches toward pyridine functionalization.

Smiles rearrangement on the pyridine ring is very rare.[6] S–N-type Smiles rearrangement on pyridine rings has not been reported yet. As part of our program directed toward the design and synthesis of bioactive heterocyclic compounds,[7] we became interested in sequentially combining Smiles rearrangement with annulation on the pyridine ring. Herein we report a simple and effective synthetic method for thiazinone-fused pyridines using N-substituted chloroacetamides **1** with 2-bromopyridine-3-thiol **2** (Scheme 2) or N-substituted mercaptoacetamide **5** with 3-chloro-2-nitropyridine **6** in one-pot (Scheme 3).

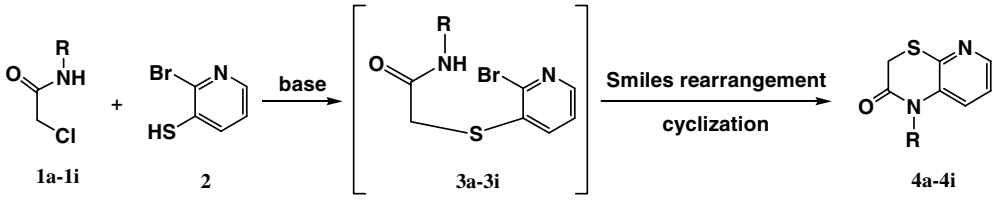
At first, N-substituted haloacetamide **1** was synthesized by the chose reaction of amine and chloroacetyl halide in high yield (Scheme 2). 2-Bromopyridine-3-thiol **2** as the other starting material was commercially available. To search for the most suitable reaction condition, the cyclization of a 2-chloro-*N*-propylacetamide **1a** and **2** was investigated. We chose a mild reaction condition for the preparation of pyrido[1,4]thiazinone using the common alkali carbonate or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) as base instead of NaOH, KOH,



Scheme 1.

* Corresponding authors. Tel./fax: +86 531 88564464 (C.M.); e-mail: chenma@sdu.edu.cn

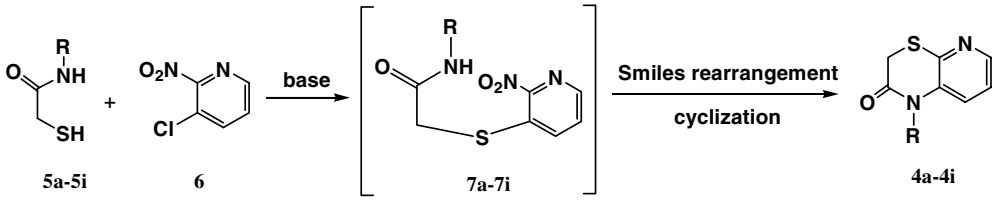
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.08.067



R a: C_3H_7- b: *c*-C_6H_{11}- c: *c*-$C_6H_{11}CH_2$- d: e: $C_6H_5CH_2$- f: $C_6H_5(CH_2)_2$-

g: (*S*)-C_6H_5-$CH(CH_3)$- h: 3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$- i: C_6H_5-

Scheme 2.



R a: C_3H_7- b: *c*-C_6H_{11}- c: *c*-$C_6H_{11}CH_2$- d: e: $C_6H_5CH_2$- f: $C_6H_5(CH_2)_2$-

g: (*S*)-C_6H_5-$CH(CH_3)$- h: 3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$- i: C_6H_5-

Scheme 3.

or NaO*t*-Bu. Although it has been reported that the latters give faster reaction, their high basicity often causes problems, which results in complex reaction mixtures consisting mostly in unidentifiable products and very low yield of the required pyrido[1,4]thiazinone **4**.[8] As can be seen from Table 1, the reactions proceeded smoothly, affording the cyclized products in good yield. Some bases such as Cs_2CO_3 and DBU showed good catalytic efficiency in refluxing acetonitrile. Some other bases such as Na_2CO_3 and K_2CO_3 also worked well, but the yields of **4a** were slightly inferior. However, Li_2CO_3 showed lower efficiency toward the synthesis of **4a**. To improve the rate and yield of the reaction, we tried to employ microwave irradiation toward the synthesis of **4a** in the presence of Cs_2CO_3 or DBU. Microwave heating has been shown to promote a variety of chemical transformations.[9] From the results showed in Table 1, enhancement of the reaction rate and yield of **4a** was obvious (yields from 70% to 83% for Cs_2CO_3as base and from 77% to 92% for DBU as base). Thus, among the five bases tested, the superior performance of DBU could be easily recognized.

Furthermore, various solvents were tested toward the synthesis of **4a** in the presence of DBU (Table 2). Polar, aprotic solvents such as *N*,*N*-dimethylformamide and acetonitrile were quite effective, whereas nonpolar solvents toluene and dichloromethane were ineffective. THF fell between the two extremes. Consequently, all following Smiles rearrangement–annulation were conducted in the presence of DBU as base and CH_3CN as solvent under controlled microwave heating.

To further demonstrate this Smiles rearrangement–annulation process, we applied a similar conversion to compound **4** by using N-substituted mercaptoacetamide **5** and 3-chloro-2-nitropyridine **6** as the substrates instead of **1** and **2** (Scheme 3). The reaction of **5** with **6** containing a nitro group ortho to the halogen atom

Table 1. Effect of base for Smiles rearrangement

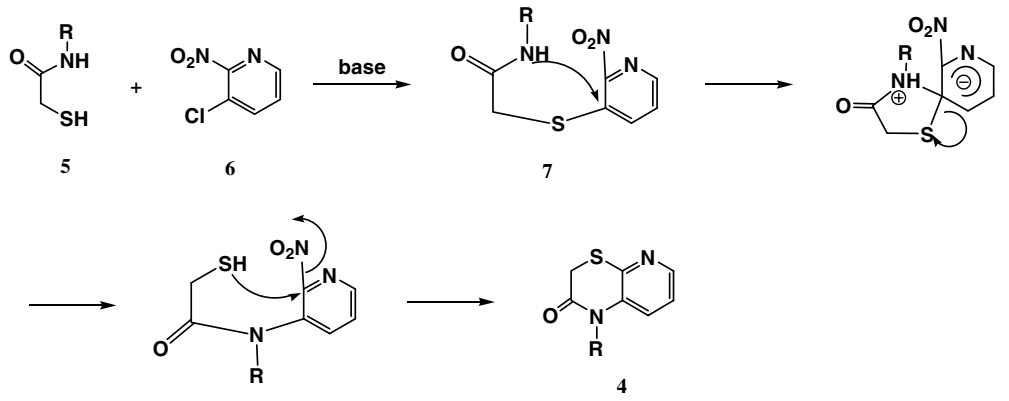
Base	Solvent	*T*/*t* (°C/h)	Product	Yield[a] (%)
Li_2CO_3	CH_3CN	Reflux/4	**4a**	16
Na_2CO_3	CH_3CN	Reflux/4	**4a**	51
K_2CO_3	CH_3CN	Reflux/4	**4a**	54
Cs_2CO_3	CH_3CN	Reflux/4	**4a**	70
DBU	CH_3CN	Reflux/4	**4a**	77
Cs_2CO_3	CH_3CN	80/10 min[b]	**4a**	83
DBU	CH_3CN	80/10 min[b]	**4a**	92

[a] Isolated yield.
[b] Microwave heating was used.

Table 2. Effect of solvent for Smiles rearrangement

Base	Solvent	*T*/*t* (°C/h)	Product	Yield[a] (%)
DBU	CH_3CN	Reflux/4	**4a**	77
DBU	DMF	100/4	**4a**	65
DBU	Toluene	Reflux/4	**4a**	12
DBU	THF	Reflux/4	**4a**	36
DBU	CH_2Cl_2	Reflux/4	**4a**	8
DBU	CH_3CN	80/10 min[b]	**4a**	92

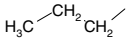
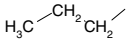
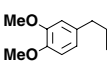
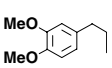
[a] Isolated yield.
[b] Microwave heating was used.



Scheme 4.

yielded compound **7**. In the presence of base, imido nitrogen donates its lone pair of electrons with its intramolecular nucleophilic attack on the carbonium ion (carbon carrying the halogen atom). As a result, sulfur loses its electron pair and the positively charged nitrogen provides the proton, which attaches to S^-, yielding 2-mercapto-*N*-(2-nitropyridin-3-yl)acetamide. The latter undergoes cyclization with the loss of nitrous acid yielding cyclized product **4** (Scheme 4).

Table 3. One-pot synthesis of pyrido[1,4]thiazinone **4**

Amides		Pyridines	Product[a]	Yield[b] (%)
1a	R = 	**2**	**4a**	92
5a	R = 	**6**	**4a**	86
1b	R = 	**2**	**4b**	83
5b	R = 	**6**	**4b**	71
1c	R = 	**2**	**4c**	89
5c	R = 	**6**	**4c**	77
1d	R = 	**2**	**4d**	86
5d	R = 	**6**	**4d**	83
1e	R = 	**2**	**4e**	91
5e	R = 	**6**	**4e**	76
1f	R = 	**2**	**4f**	87
5f	R = 	**6**	**4f**	81
1g	R = 	**2**	**4g**	80
5g	R = 	**6**	**4g**	75
1h	R = 	**2**	**4h**	89
5h	R = 	**6**	**4h**	83
1i	R = 	**2**	**4i**	57
5i	R = 	**6**	**4i**	42

[a] Reaction condition: DBU as base and CH_3CN as solvent under 80 °C microwave heating for 10 min.
[b] Isolated yield.

A variety of pyrido[1,4]thiazinone **4** were synthesized with two routes (Schemes 1 and 2). The experimental results are summarized in Table 3.[10] Noteworthy is the fact that the ring opening compounds **3** and **7** in every reaction was first formed and cyclized product **4** increased as reaction time went on. In all cases, the ring opening compounds **3** and **7** could be isolated. For example, we studied the Smiles rearrangement–annulation process of 2-chloro-*N*-(3,4-dimethoxyphenethyl)acetamide **1h** with 2-bromopyridine-3-thiol **2** in the presence of DBU as base under controlled microwave heating. When the mixture was heated for 3 min at 80 °C in the microwave reactor, the reaction furnished a mixture consisting of the ring opening compound **3h** with 39% isolated yield[11] and cyclized product **4h** with 53% isolated yield. When the mixture was heated for 10 min under the same conditions, the reaction furnished cyclized product **4h** with 89% isolated yield, and the ring opening compound **3h** was not found. All products were characterized by ^1H NMR, ^{13}C NMR, IR, and elemental analyses, and had satisfactory microanalysis.

In conclusion, we have developed an operationally simple and efficient synthesis of pyrido[1,4]thiazinones based on the S–N-type Smiles rearrangement–annulation process. DBU has been demonstrated to promote this process efficiently. The reaction rates can be further accelerated by utilizing microwave heating (physical acceleration). Further studies on its application in the synthesis of natural compounds are currently in progress.

Acknowledgment

The authors thank the Natural Science Foundation of Shandong Province (Z2006B03) for financial assistance.

References and notes

1. (a) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1971**, *18*, 99; (b) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
2. (a) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 956; (b) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 1327; (c) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1931**, 2207; Review: (d) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99.
3. For Smiles rearrangement, see: (a) Weidner, J. J.; Weintraub, P. M. *J. Heterocycl. Chem.* **1997**, *34*, 1857; (b) Huber, V. J.; Bartsch, R. A. *Tetrahedron* **1998**, *54*, 9281; (c) Anelli, P. L.; Brocchetta, M.; Calabi, L.; Secchi, C.; Uggeri, F.; Verona, S. *Tetrahedron* **1997**, *53*, 11919; (d) Weidner, J. J.; Weintraub, P. M.; Schnettler, R. A.; Peet, N. P. *Tetrahedron* **1997**, *53*, 6303; (e) Proudfoot, J. R.; Patel, U. R.; Campbell, S. J. *J. Org. Chem.* **1993**, *58*, 6996.
4. (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491; (b) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581; (c) Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
5. (a) Katritzky, A. R.; Tymoshenko, D. O.; Monteux, D.; Vvedensky, V.; Nikonov, G.; Cooper, C. B.; Deshpande, M. *J. Org. Chem.* **2000**, *65*, 8059; (b) Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. *Tetrahedron* **2000**, *56*, 1349; (c) Queguiner, G. *J. Heterocycl. Chem.* **2000**, *37*, 615.
6. (a) Soukri, M.; Lazar, S.; Pujol, M. D.; Akssira, M.; Leger, J. M.; Jarry, C.; Guillaumet, G. *Tetrahedron* **2003**, *59*, 3665–3672; (b) Lazar, S.; Soukri, M.; El Haddad, M.; Akssira, M.; Leger, J. M.; Jarry, C.; Morin, Ph.; Guillaumet, G. *Chirality* **2005**, *17*, 30–36; (c) Morak, B.; Pluta, K.; Suwinska, K.; Grymel, M.; Besnard, C.; Schiltz, M.; Kloc, C.; Siegrist, T. *Heterocycles* **2005**, *65*, 2619–2634.
7. (a) Ma, C.; Liu, S.-J.; Xin, L.; Falck, J. R.; Shin, D.-S. *Tetrahedron* **2006**, *62*, 9002–9009; (b) Ma, C.; Liu, S.-J.; Xin, L.; Zhang, Q.; Ding, K.; Falck, J. R.; Shin, D.-S. *Chem. Lett.* **2006**, *35*, 1010–1011; (c) Ma, C.; Cho, S.-D.; Falck, J. R.; Shin, D.-S. *Heterocycles* **2004**, *63*, 75–85; (d) Ma, C.; Cho, S.-D.; Falck, J. R.; Shin, D.-S. *Synth. Commun.* **2004**, *34*, 1399–1405; (e) Cho, S.-D.; Park, Y.-D.; Kim, J.-J.; Lee, S.-G.; Ma, C.; Song, S.-Y.; Joo, W.-H.; Falck, J. R.; Shiro, M.; Shin, D.-S.; Yoon, Y.-J. *J. Org. Chem.* **2003**, *68*, 7918.
8. (a) Ding, D.; Li, X.; Wang, X.; Du, Y.; Shen, J. *Tetrahedron Lett.* **2006**, *47*, 6997; (b) Cave, G. W. V.; Raston, C. L. *Tetrahedron Lett.* **2005**, *46*, 2361; (c) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413; (d) Guillena, G.; Najera, C. *J. Org. Chem.* **2000**, *65*, 7310.
9. (a) Kingston, H. M.; Haswell, S. J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*; American Chemical Society: Washington, DC, 1997, Chapter 8; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213; (c) Varma, R. S. *Green Chem.* **1999**, 43; (d) Krstenansky, J. L.; Cotterill, I. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 454.
10. *Typical procedure for one-pot synthesis of pyrido[1,4]thiazinone* (**4**): A 10 mL process vial was charged with a mixture of 2-chloro-*N*-(3,4-dimethoxyphenethyl)acetamide **1h** (0.5 mmol), 2-bromopyridine-3-thiol **2** (1.0 equiv), and DBU (2.2 equiv) in distilled CH_3CN (2 mL) and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated in the fixed mode. The solvent was removed under reduced pressure and CH_2Cl_2/H_2O was added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude products were purified by flash column chromatography using $EtOAc/CH_2Cl_2$ as eluent to afford the cyclized product 1-(3,4-dimethoxyphenethyl)-1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one (**4h**) with 89% yield. IR (KBr) 3056, 2967, 2932, 2847, 1689, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, $J = 4.8$, 1.5 Hz, 1H), 7.17 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.04 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.68–6.79 (m, 3H), 4.82 (s, 2H), 4.08–4.15 (t, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.85–2.93 (t, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 42.5, 54.1, 58.2, 68.6, 113.3, 115.0, 119.7, 121.1, 124.5, 130.2, 135.7, 142.6, 148.9, 155.2, 163.9, 176.8; Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.87; H, 5.53; N, 8.45.
11. 2-(2-Bromopyridin-3-ylthio)-*N*-(3,4-dimethoxyphenethyl)-acetamide (**3h**). IR (KBr) 3406, 3061, 2976, 2928, 2831, 1673, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, $J = 3.0$, 1.5 Hz, 1H), 7.25 (dd, $J = 4.8$, 7.8 Hz, 1H), 7.05 (dd, $J = 6.9$, 4.5 Hz, 1H), 6.82–6.86 (m, 1H), 6.72–6.78 (m, 3H), 4.55 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.64 (q, $J = 6.6$ Hz, 2H), 2.83 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 40.4, 53.2, 55.9, 67.5, 113.9, 116.0, 120.2, 120.8, 123.1, 130.4, 143.1, 148.3, 149.2, 151.2, 165.6, 180.6; Anal. Calcd for $C_{17}H_{19}BrN_2O_3S$: C, 49.64; H, 4.66; N, 6.81. Found: C, 49.72; H, 4.69; N, 6.75.