Tetrahedron Letters 50 (2009) 3897–3900

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Novel $ZnCl_2$-catalyzed one-pot multicomponent synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

Madabhushi Sridhar *, Beeram C. Ramanaiah, Chinthala Narsaiah, Bellam Mahesh, Mudam Kumaraswamy, Kishore K. R. Mallu, Vishnu M. Ankathi, Pamulaparty Shanthan Rao

Fluoroorganics Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 14 March 2009
Revised 13 April 2009
Accepted 15 April 2009
Available online 18 April 2009

Keywords:
2-Amino-3,5-dicarbonitrile-6-thio-pyridines
Multicomponent reaction
Lewis acid catalysis
$ZnCl_2$
Microwave reaction

ABSTRACT

$ZnCl_2$-catalyzed one-pot multicomponent synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines under microwave heating and conventional heating is described.

Multicomponent reactions (MCRs) have drawn high efforts in recent years owing to exceptional synthetic efficiency, intrinsic atom economy, high selectivity, and procedural simplicity.[1] These reactions constitute a valuable approach for creation of large libraries of structurally related, drug-like compounds, thereby enabling lead identification and lead optimization in drug discovery.[2] In a true sense, these represent environmentally friendly processes by reducing the number of steps, energy consumption, and waste production.

Compounds with 2-amino-3,5-dicarbonitrile-6-thio-pyridines ring system exhibit diverse pharmacological activities and are useful as *anti*-prion,[3] *anti*-hepatitis B virus,[4] *anti*-bacterial,[5] and *anti*-cancer[6] agents and as potassium channel openers for treatment of urinary incontinence.[7] In addition, several of these compounds were discovered to be highly selective ligands for adenosine receptors,[8] which were recently recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, and cancer.[9]

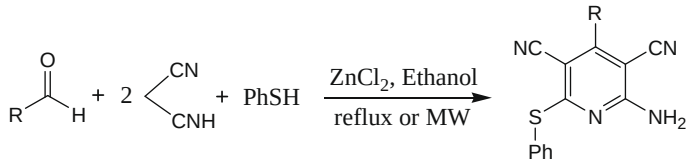
In most of the existing studies[10] on 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives, these compounds were synthesized by multistep methods.[8a,b,10] Recently, Evodkimov et al.[11] have developed a simple protocol for preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines by a multicomponent reaction of an aldehyde, malononitrile, and a thiol in one pot in the presence of a base catalyst such as DABCO or triethylamine. As the yields of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives obtained by this method are poor (20–48%), a modification to this method was reported recently by Ranu et al.[12] using the basic ionic liquid 1-methyl-3-butylimidazolium hydroxide or [bmIm]OH, which could serve as a base as well as a reaction medium. In all the reported methods for preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines, reactions were conducted essentially under base catalysis. Conversely, we discovered that Lewis acids are also effective catalysts and we report here the first observation of one-pot multicomponent reaction of a variety of aldehydes **1a–i** with malononitrile **2** and thiophenol **3** under $ZnCl_2$ catalysis producing 2-amino-3,5-dicarbonitrile-6-thio-pyridines **4a–i** in moderate to good yields (Scheme 1).

In our preliminary studies, we have investigated the multicomponent reaction of tolualdehyde **1a** with malononitrile **2** and thiophenol **3**, using a variety of Lewis acids such as $ZnCl_2$, $AlCl_3$, $FeCl_3$, I_2, $Cu(OTf)_3$, $InCl_3$, and $BF_3{\cdot}Et_2O$ as catalysts, to obtain the corresponding pyridine derivative **4a** under conventional and microwave heating conditions using ethanol as a solvent (Table 1).

In this study, $ZnCl_2$ was observed to be highly efficient producing **4a** in 73 and 77% yields under conventional and microwave heating conditions, respectively. We have also synthesized a variety of pyridine derivatives **4** using $ZnCl_2$ as catalyst under the same conditions using aliphatic, aryl, and heteroaryl aldehydes. The representative results[13] are given in Table 2.

* Corresponding author. Tel.: +91 40 2719 1772; fax: +91 40 27160387.
E-mail address: smiict@gmail.com (M. Sridhar).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.051



1a-i **2** **3** **4a-i**

R = alkyl, aryl

45-73% (Conventional heating)
46-77% (Microwave heating)

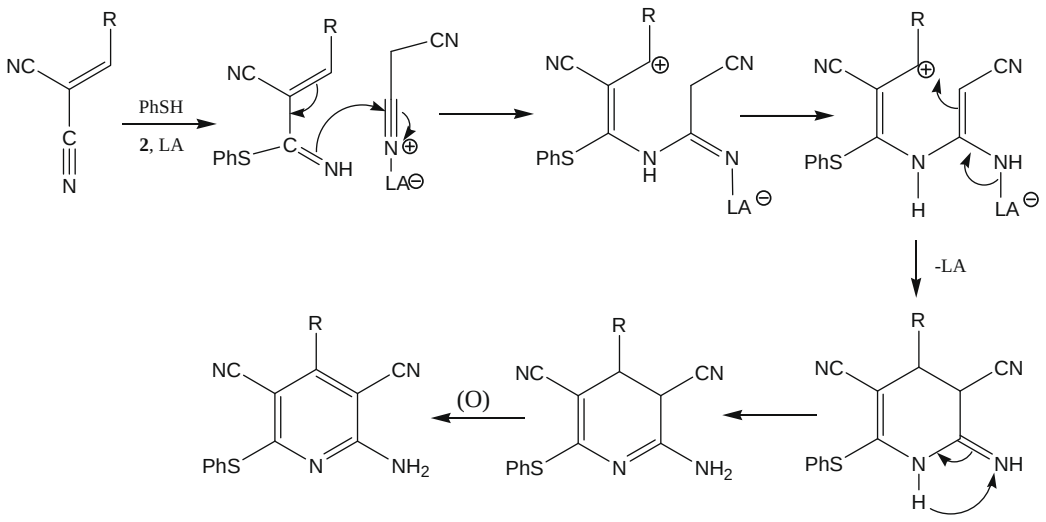
Scheme 1.

Table 1
Lewis acid-catalyzed multicomponent reaction of tolualdehyde, thiophenol, and malononitrile

S. No.	Catalyst	Microwave heating		Conventional heating	
		Time (min)	Yield (%)	Time (h)	Yield (%)
1	$ZnCl_2$	2	77	2	73
2	$AlCl_3$	5	20	12	7
3	$FeCl_3$	5	17	12	–
4	I_2	5	15	12	–
5	$Cu(OTf)_3$	5	30	12	15
6	$InCl_3$	5	–	12	–
7	$BF_3{\cdot}Et_2O$	5	–	12	–
8	K10 clay	5	–	12	–

Evodkimov et al.[11] have reported formation of side products such as 1,4-dihyropyridine derivatives and enaminonitrile in their base-catalyzed multicomponent reaction. However, under Lewis acid catalysis, formation of these products has not been observed. The plausible mechanism for the formation of pyridines under Lewis acid catalysis is shown in Scheme 2.

In conclusion, the present work describes an efficient one-pot multicomponent synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines under microwave and conventional heating conditions using $ZnCl_2$ as catalyst. This work is the first application of Lewis acid as catalyst in the preparation of these compounds.



Scheme 2.

Table 2
$ZnCl_2$-catalyzed multicomponent synthesis of pyridines

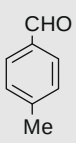
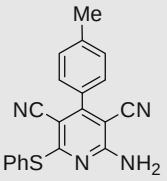
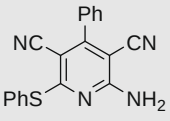
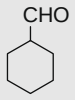
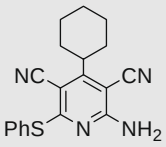
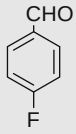
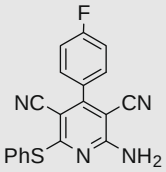
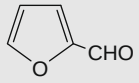
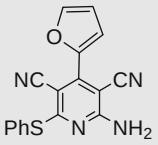
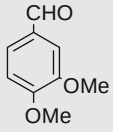
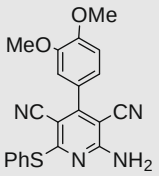
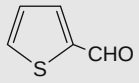
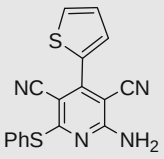
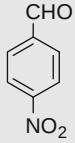
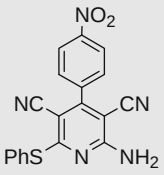
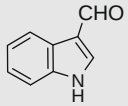
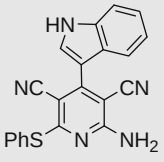
Entry	R-CHO **1**	Product **4**	Conventional heating % Yield[a] (reaction time)	Microwave heating % Yield[a] (reaction time)	Melting point (°C)
a			73 (2 h)	77 (2 min)	208–211[11b]
b	PhCHO		65 (2 h)	65 (2 min)	216–218[11b]

Table 2 (*continued*)

Entry	R-CHO **1**	Product **4**	Conventional heating % Yield[a] (reaction time)	Microwave heating % Yield[a] (reaction time)	Melting point (°C)
c			45 (2.5 h)	46 (3 min)	219–220
d			62 (2 h)	67 (2 min)	221–223
e			60 (2.5 h)	62 (3 min)	174–175
f			52 (2 h)	50 (2 min)	226–228
g			60 (2.5 h)	60 (3 min)	208–210[3b]
h			50 (2 h)	52 (2 min)	287–289[11b]
i			50 (2 h)	50 (3 min)	220–222

[a] Isolated yields. All products were characterized by NMR, IR, and mass spectral data.

Acknowledgments

B.C.R., C.N., M.K.K.R., and V.M.A. are thankful to the Director, IICT for financial assistance in the form of Project JRF. B.M., and M.K. are thankful to CSIR, New Delhi for financial support in the form of CSIR-JRF.

References and notes

1. (a)*Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; Reviews: (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634; (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980; (e) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; (f) Bienaymé, H.; Hulme, C.; Oddon,

G.; Schmitt, P. *Chem.-Eur. J.* **2000**, *6*, 3321–3329; (g) Ulaczyk-Lesanko, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266–276.
2. (a) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085–2093; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80.
3. (a) Perrier, V.; Wallace, A. C.; Kaneko, K.; Safar, J.; Prusiner, S. B.; Cohen, F. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6073–6078; (b) Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *46*, 607–615; (c) May, B. C. H.; Zorn, J. A.; Witkop, J.; Sherrill, J.; Wallace, A. C.; Legname, G.; Prusiner, S. B.; Cohen, F. E. *J. Med. Chem.* **2007**, *50*, 65–73.
4. Chen, H.; Zhang, W.; Tam, R.; Raney, A. K. PCT Int. Appl. WO 2005058315 A1 20050630, 2005.
5. Levy, S. B.; Alekshun, M. N.; Podlogar, B. L.; Ohemeng, K.; Verma, A. K.; Warchol, T.; Bhatia, B.; Bowser, T.; Grier, M. U.S. Patent Appl., 2005124678 A1 20050609, 2005.
6. (a) Cocco, M. T.; Congiu, C.; Lilliu, V.; Onnis, V. *Eur. J. Med. Chem.* **2005**, *40*, 1365; (b) Anderson, D. R.; Stehle, N. W.; Kolodziej, S. A.; Reinhard, E. J. PCT Int. Appl. WO 2004055015 A1 20040701, 2004.
7. Harada, H.; Watanuki, S.; Takuwa, T.; Kawaguchi, K.; Okazaki, T.; Hirano, Y.; Saitoh, C. PCT Int. Appl. WO 2002006237 A1 20020124, 2002.
8. (a) Beukers, M. W.; Chang, L. C. W.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2004**, *47*, 3707–3709; (b) Chang, L. C. W.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Roerink, S. F.; van den Hout, G.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 2045–2053;; (c) Rosentreter, U.; Kraemer, T.; Shimada, M.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Henninger, K.; Stasch, J. -P. DE 10238113 A1 20030618, 2003.; (d) Rosentreter, U.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Dembowsky, K.; Stasch, J. -P.; Shimada, M. WO 2002079195 A1 20021010, 2002.; (e) Rosentreter, U.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Dembowsky, K.; Stasch, J.-P. WO 2002070520 A1 20020912, 2002.; (f) Rosentreter, U.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Dembowsky, K.; Stasch, J.-P. WO 2002070485 A1 20020912, 2002.; (g) Rosentreter, U.; Henning, R.; Bauser, M.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Dembowsky, K.; Salcher-Schraufstaetter, O.; Stasch, J.-P.; Krahn, T.; Perzborn, E. WO 2001025210 A2 2001041 *2*, 2001.
9. Fredholm, B. B.; Ijzerman, A. P.; Jacobson, K. A.; Klotz, K.-N.; Linden, J. *Pharmacol. Rev.* **2001**, *53*, 527–552.
10. (a) Tu, S.; Jiang, B.; Jiang, H.; Zhang, Y.; Jia, R.; Zhang, J.; Shao, Q.; Li, C.; Zhou, D.; Cao, L. *Tetrahedron* **2007**, *63*, 5406–5414; (b) Rosentreter, U.; Kramer, T.; Shimada, M.; Bubsch, W.; Diedrichs, N.; Krahn, T.; Henninger, K.; Stasch, J. -P.; U.S. 7,045,631, 2006.; (c) Attia, A. M. E.; Ismail, A. E.-H. A. A. *Tetrahedron* **2003**, *59*, 1749–1752.
11. (a) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443–3453; (b) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Konienko, A. *Org. Lett.* **2006**, *8*, 899–902.
12. Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152–3154.
13. *Typical experimental procedure for $ZnCl_2$-catalyzed multicomponent synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines under microwave heating: p*-fluoro benzaldehyde (0.5 g, 4.0 mmol), malononitrile (0.53 g, 8.0 mmol), thiophenol (0.45 g, 4.0 mmol), zinc chloride (0.1 g, 20 mol %), and ethanol (1 ml) were taken in a 10-ml pressure tube and were subjected to microwave heating (CEM Discover, 180 W, 250 psi, 100 °C) for 2 min. The mixture was extracted with ethyl acetate (3 × 10 ml) and the combined extract was washed with water (1 × 5 ml) and brine (1 × 5 ml) and was dried over anhyd. $MgSO_4$. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography(silica gel 100–200 mesh, ethyl acetate/hexane = 1:7) to afford the corresponding pyridine derivative **4d** as a yellow solid 0.92 g, 67%, mp 221–223 °C). The product gave satisfactory spectral data.*Procedure for reaction under conventional heating:* The reactants were taken as described above into a 25-ml round-bottomed flask provided with a condenser and the mixture was refluxed with 15 ml of ethanol for 2 h. The reaction was kept open to air during reflux and the progress of the reaction was monitored with TLC. After completion of the reaction, ethanol was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 × 10 ml). The combined extract was washed with water (1 × 5 ml) and brine (1 × 5 ml) and was dried over anhyd. $MgSO_4$. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel 100–200 mesh, ethyl acetate/hexane = 1:7) to obtain **4d** (0.86 g, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5 (s, 2H), 7.3–7.4 (m, 2H), 7.4–7.7 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 90.0, 91.5, 127.0, 128.5, 129.0, 129.5, 130.0, 136.0, 141.3, 159.2, 160.0, 169.5; IR (KBr, cm^{-1}): ν 34951, 3341, 2904, 2884, 2206, 1616, 1540, 1459, 1259, 1018, 755, 682; ESI MS (*m*/*z*, %): 346 (M^+, 55), 345 (60), 327 (10), 251 (15), 237 (20), 183 (25), 146 (20), 109 (80), 77 (65), 65 (100), 51 (98); exact mass observed for $C_{19}H_{11}FN_4S$: 346.069 (calcd: 346.063).