ORGANIC LETTERS

2008
Vol. 10, No. 5
889−892

A Cascade Reaction with Iminium Ion Isomerization as the Key Step Leading to Tetrahydropyrimido[4,5-*d*]pyrimidines

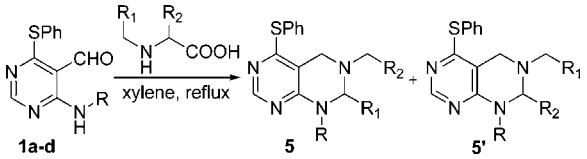
Lianyou Zheng, Fengzhi Yang, Qun Dang,* and Xu Bai*

The Center for Combinatorial Chemistry and Drug Discovery, Jilin University, 75 Haiwai Street, Changchun, Jilin 130012, People's Republic of China

xbai@jlu.edu.cn; qdang@jlu.edu.cn

Received December 19, 2007

ABSTRACT

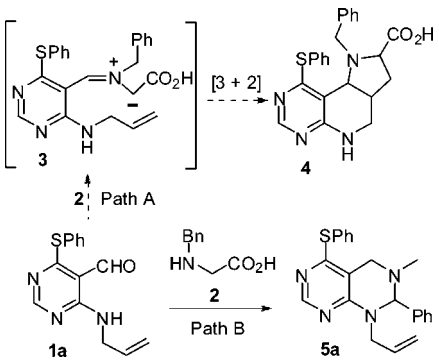


A novel cascade reaction of aminopyrimidines 1 with *N*-alkyl amino acids or analogues was investigated. The keys to this cascade are the isomerization of an iminium ion formed between the aldehyde group in pyrimidine and the secondary amine of an amino acid, and subsequent cyclization to the neighboring amino group. This sequence could be useful in the synthesis of novel tetrahydropyrimido[4,5-*d*]pyrimidine libraries.

Pyrimidine-fused compounds are of interest in medicinal chemistry and chemical biology due to their wide range of biological activities.[1] To develop new methodologies for efficient synthesis of novel pyrimidine-fused heterocycles,[2] we initially envisioned that a novel heterocyclic scaffold could be accessed via an intramolecular azomethine ylide[3] [3 + 2] cycloaddition reaction as the key step (path A, Scheme 1). However, reaction of pyrimidine aldehyde **1a** and *N*-benzylglycine **2** in refluxing xylene unexpectedly gave tetrahydropyrimido[4,5-*d*]pyrimidine **5a** (path B, Scheme 1). Investigation of this reaction led to a general synthetic methodology to access tetrahydropyrimido[4,5-*d*]pyrimidines. Herein, the preliminary results from these studies are reported.

To test our initial design of an intramolecular [3 + 2] cycloaddition reaction, the required pyrimidine **1a** was prepared from the readily accessible 4,6-dichloro-5-formylpyrimidine **6**[4] as shown in Scheme 2. Substitution of **6** with allylamine in the presence of triethylamine under well-controlled reaction conditions produced the desired mono-

Scheme 1



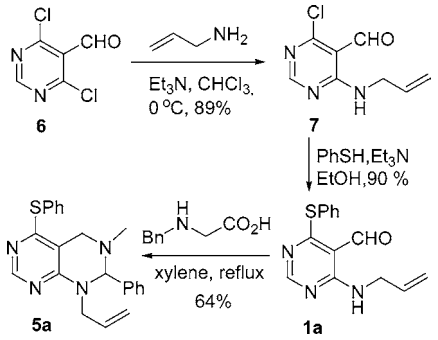
(1) For examples, see: (a)Wang, S.; Folkes, A.; Chuckowree, I.; Cockcroft, X.; Sohal, S.; Miller, W.; Milton, J.; Wren, S. P.; Vicker, N.; Depledge, P.; Scott, J.; Smith, L.; Jones, H.; Mistry, P.; Faint, R.; Thompson, D.; Cocks, S. *J. Med. Chem.* **2004**, *47*, 1329−1338. (b) Perner, R. J.; Gu, Y. G.; Lee, C. H.; Bayburt, E. K.; McKie, J.; Alexander, K. M.; Kohlhaas, K. L.; Wismer, C. T.; Mikusa, J.; Jarvis, M. F.; Kowaluk, E. A.; Bhagwat, S. S. *J. Med. Chem.* **2003**, *46*, 5249−5257. (c) McGuigan, C.; Pathirana, R. N.; Snoeck, R.; Andrei, G.; DeClercq, E.; Balzarini, J. *J. Med. Chem.* **2004**, *47*, 1847−1851. (d) Gangjee, A.; Zeng, Y.; McGuire, J. J.; Mehraein, F.; Kisliuk, R. L. *J. Med. Chem.* **2004**, *47*, 6893−6901.

(2) (a) Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Gao, S.; Bai, X. *Org. Lett.* **2005**, *7*, 1541−1543. (b) Fu, R.; Xu, X.; Dang, Q.; Bai, X. *J. Org. Chem.* **2005**, *70*, 10810−10816. (c) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Tetrahedron* **2006**, *62*, 2563−2568. (d) Xiang, J.; Zheng, L.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765−767.

(3) (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765−2809. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484−4517.

10.1021/ol703049j CCC: $40.75
Published on Web 02/09/2008

Scheme 2



substituted pyrimidine **7** in 89% yield.[5] A second nucleophilic displacement of the remaining chloro group in **7** by thiophenol led to the desired precursor **1a** in 90% yield.

It is interesting to note that the reaction of pyrimidine **1a** with *N*- benzylglycine in refluxing xylene did not give the anticipated intramolecular cycloaddition product **4**, but instead gave a new pyrimidine derivative that was assigned the structure of **5a** based on proton NMR and MS data (Scheme 2). The structure of compound **5a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

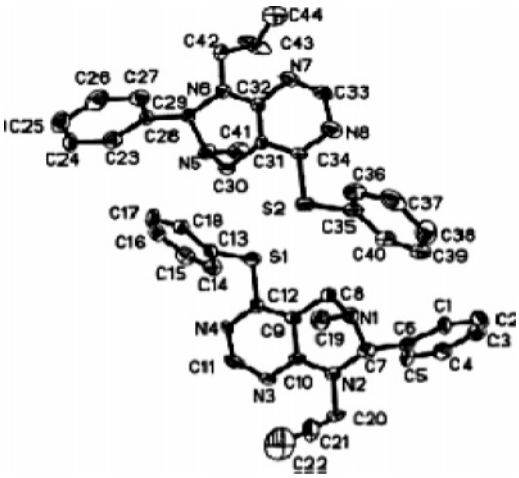
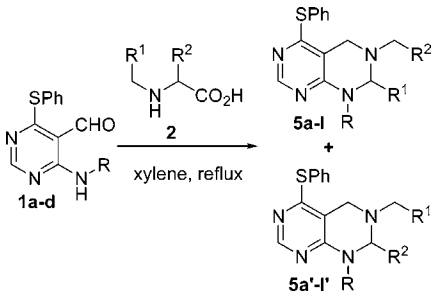


Figure 1. X-ray structure of compound **5a**.

We were intrigued by this new reaction since it may be developed into a new synthetic route to tetrahydropyrimido-[4,5-*d*]pyrimidines. Pyrimidopyrimidines exhibit a variety of pharmacological activities, such as antitumor,[6] antiviral,[7] dihydrofolate reductase inhibition,[8] and hepatoprotective activities.[9] It is therefore logical to explore this type of heterocyclic scaffold for various drug discovery programs. Although numerous reports exist for the synthesis of various keto derivatives of pyridopyrimidines[10] and pyrimido[4,5-*d*]pyrimidines,[11] few were directed to the synthesis of tetrahydropyrimido[4,5-*d*]pyrimidines.[12] Thus, we set out to optimize this new reaction and to explore its scope.

Screening of various acids (e.g., TFA and CSA) including Lewis acids (e.g., CuBr, LiBr, $MgCl_2$, $TiCl_4$, and $CoCl_2$) as well as base (e.g., Et_3N) did not lead to any improvement in the yield of **5a**, while using DMF as the solvent only produced a trace amount of **5a**. Therefore, the refluxing xylene conditions were used to explore reactions between various *N*-alkyl-substituted amino acids and aldehydes **1a**−**d** (R = allyl, H, Me, Ph). As evidenced in Table 1, most reactions (except with *N*-methylglycine, entry 3) gave products **5a**−***l*** and/or **5a′**−***l′*** in moderate to good yields. The cyclic amino acids, such as proline and homoproline, yielded a single isomer of the product as expected (entries 6−9, 12,

Table 1. Synthesis of 1,2,3,4-Tetrahydropyrimido[4,5-*d*]pyrimidines[a]



entry	R^1	R^2	R	time (h)	product **5**	yield (%)[b]
1	Ph	H	allyl	5	**5a**	64
2	*p*-MeO-Ph	H	allyl	12.5	**5b**	48
3	H	H	allyl	5		NR[c]
4	Ph	CH_3	allyl	6	**5c/5c′** (1:1.57)[d]	60
5	Ph	Bn	allyl	30	**5d/5d′** (1:1.36)[e]	73
6	$-(CH_2)_2-$		allyl	4	**5e**	76
7	$-(CH_2)_3-$		allyl	6	**5f**	65
8	$-(CH_2)_2-$		H	4	**5g**	76
9	$-(CH_2)_2-$		CH_3	6.5	**5h**	70
10	Ph	H	CH_3	3	**5i**	69
11	Ph	CH_3	CH_3	10	**5j/5j′** (1:2.3)[d]	70
12	$-(CH_2)_2-$		Ph	4	**5k**	67
13	$-CH_2)_3-$		Ph	4.5	***5l***	10

[a] **1a**, R = allyl; **1b**, R = H; **1c**, R = Me; **1d**, R = Ph. [b] Isolated yields. [c] NR = no reaction. [d] Ratio based on isolated products. [e] The structure of **5d′** was based on LC-MS and ^{1}H NMR of the crude product, and the ratio was estimated since pure **5d′** could not be obtained due to an unknown contaminant.

(4) Gomtsyan, A.; Didomenico, S.; Lee, C. H.; Matulenko, M. A.; Kim, K.; Kowaluk, E. A.; Wismer, C. T.; Mikusa, J.; Yu, H.; Kohlhaas, K.; Jarvis, M. F.; Bhagwat, S. S. *J. Med. Chem.* **2002**, *45*, 3639−3648.

(5) Clark, J.; Parvizi, B.; Southon, I. W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 125−130.

(6) Curtin, N. J.; Barlow, H. C.; Bowman, K. J.; Calvert, A. H.; Davison, R.; Golding, B. T.; Huang, B.; Loughlin, P. J.; Newell, D. R.; Smith, P. G.; Griffin, R. J. *J. Med. Chem.* **2004**, *47*, 4905−4922.

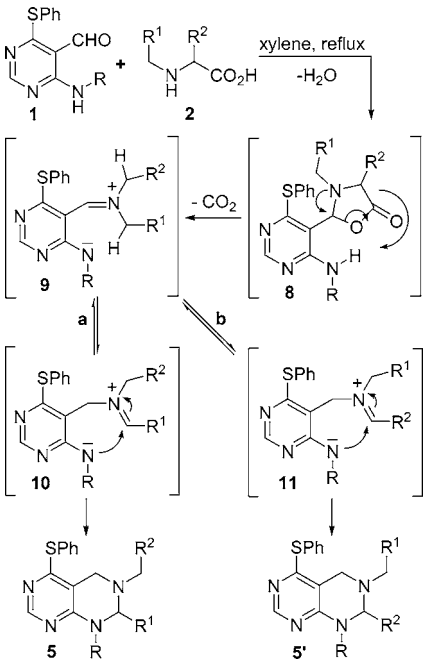
(7) Sanghvi, Y. S.; Larson, S. B.; Matsumoto, S. S.; Nord, L. D.; Smee, D. F.; Willis, R. C.; Avery, T. H.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1989**, *32*, 629−637.

(8) Gebauer, M. G.; McKinlay, C.; Gready, J. E. *Eur. J. Med. Chem.* **2003**, *38*, 719−728.

and 13). In the reaction with *N*-benzylglycine, the cyclization occurred regioselectively to produce only one product (entries 1, 2, and 10), while other *N*-benzyl-substituted amino acids, such as alanine, led to two isomers without significant selectivity (entries 4, 5, and 11). The ratios of the two isomeric products **5** and **5′** were calculated based on their corresponding ^{1}H NMR spectrum. It is also noteworthy that the reaction of homoproline with *N*-phenylaminopyrimidine aldehyde **1d** gave a much lower yield compared to the one with proline (entry 13 vs 12).

To rationalize the above results, a possible cascade reaction mechanism was envisioned as depicted in Scheme 3.

Scheme 3

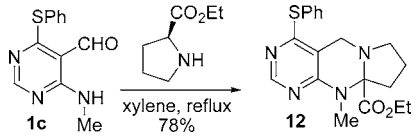


Condensation of amino acid **2** with aldehyde **1** gives oxazolidinone **8**, which undergoes a decarboxylation reaction with loss of carbon dioxide to lead to a zwitterionic species **9**. The iminium ion **9** may undergo isomerization to iminium ions **10** or **11** (via path a or b, respectively). And subsequent intramolecular cyclization onto the neighboring amino group forms the desired products **5** or **5′**.

It is logical that when R^1 and R^2 are the same (entries 6−9, 12, and 13, Table 1), only one isomer was obtained as expected. When R^1 is a carbon substituent and R^2 is a proton only isomer **5** is obtained presumably due to the formation of the more stable rearranged benzylic iminium **10** (entries 1, 2, and 10, Table 1). However, when both R^1 and R^2 are carbon substituents the competition of iminium ions **10** and **11** leads to a mixture of isomer **5** and **5′** (entries 4, 5, and 11, Table 1). In these cases, **5′** is the major isomer probably due to the kinetic preference for trapping of **11** by the intramolecular cyclization. Otherwise, the trapping of the thermodynamically more stable benzylic iminium **10** would have led to product isomer **5** as the major one.

To gain further insights into the reaction mechanism, the reaction of **1c** with L-proline ethyl ester was tested under the current reaction conditions, and the expected tetrahydropyrimido[4,5-*d*]pyrimidine was still formed in good yield (Scheme 4), suggesting that neither the formation of an

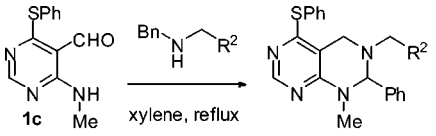
Scheme 4



oxazolidinone nor the decarboxylation reaction is essential for the production of tetrahydropyrimido[4,5-*d*]pyrimidine. Moreover, the use of an amino acid ester allowed the formation of a quarternary center and the ester group can be used as a handle for further diversification.

Another question to address is whether the current reaction system is only limited to an amino acid or its esters. Thus, two *N*-benzyl amines were tested with compound **1c** under the current reaction conditions, and the desired tetrahydropyrimido[4,5-*d*]pyrimidines **5i** and **13** were generated in good yields (Scheme 5), indicating that the scope of the current

Scheme 5



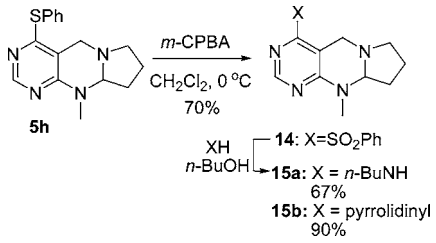
reaction is beyond amino acids and amino acid esters. On the other hand, an iminium ion stabilizing group such as a phenyl group is required since the simple *N*,*N*-diethylamine did not produce a detectable amount of tetrahydropyrimido-[4,5-*d*]pyrimidine under the current reaction conditions (not listed).

The 4-phenylthio group in a pyrimidine ring has been shown to function as a transition point to introduce other

(9) Ram, V. J.; Goel, A.; Sarkhel, S.; Maulik, P. R. *Bioorg. Med. Chem.* **2002**, *10*, 1275−1280.
(10) (a) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2007**, *63*, 1770−1774. (b) Prajapati, D.; Gohain, M.; Thakur, A. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3537−3540. (c) Sharma, P.; Kumar, A.; Rane, N.; Gurram. V. *Tetrahedron* **2005**, *61*, 4237−4248. (d) Prajapati, D.; Thakur, A. J. *Tetrahedron Lett.* **2005**, *46*, 1433−1436. (e) Sharma, P.; Rane, N.; Gurram, V. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4185−4190. (f) Devi, I.; Borah, H. N.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 2405−2408. (g) Gebauer, M. G.; McKinlay, C.; Gready, J. E. *Eur. J. Med. Chem.* **2003**, *38*, 719−728. (h) Srivastava, S. K.; Haq, W.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 965−966. (i) Graveleau, N.; Masquelin, T. *Synthesis* **2003**, *11*, 1739−1743.
(11) (a) Wang, Z. J.; Neidlein, R. *Tetrahedron* **1998**, *54*, 9903−9910. (b) Burch, H. A.; Benjamin, L. E. *J. Med. Chem.* **1974**, *17*, 451−453.
(12) Harmon, R. A.; Parsons, J. L.; Gupta, S. K. *J. Org. Chem.* **1969**, *34*, 2760−2762.

substituents such as an amino, alkoxy, and alkylthio.[2b] To test the applicability of this strategy, tetrahydropyrimdo[4,5-*d*]pyrimidine **5h** was readily oxidized to its sulfone **14**, which was substituted by an amine[13] to yield the desired compounds **15a**,**b** (Scheme 6). This sequence of transformations confirmed the feasibility of the phenylthio group as a suitable diversification point in the molecular system.

Scheme 6



(13) Liu, J.; Dang, Q.; Wei, Z.; Zhang, H.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 627−636.

In conclusion, a novel methodology to prepare tetrahydropyrimido[4,5-*d*]pyrimidine via a cascade reaction of an 6-amino-5-formylpyrimidine with a suitable secondary amine (including amino acids and amino acid esters) has been developed. The key step of this cascade reaction is the iminium ion isomerization during the reaction sequence. This method provides a convenient access to diversified 1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidines. Further transformations of the phenylthio group in these 1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidines were demonstrated by an oxidation and subsequent nucleophilc substitution sequence.

Acknowledgment. This work was supported by grants from the China Natural Science Foundation (20572032 and 90713008) and Changchun Discovery Sciences, Ltd.

Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR and LC-MS-ELSD spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL703049J