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A Cascade Reaction Consisting of Pictet–Spengler-Type Cyclization and Smiles Rearrangement: Application to the Synthesis of Novel Pyrrole-Fused Dihydropteridines

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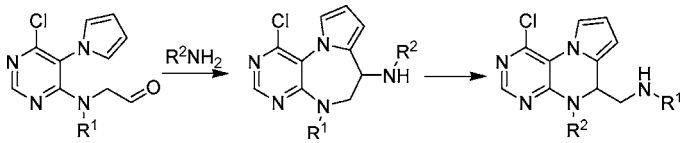
ABSTRACT



Tandem Pictet–Spengler-type cyclization and Smiles rearrangement have been discovered in the synthesis of pyrimidine-fused heterocycles. The reaction of 4-chloro-5-pyrrol-1-ylpyrimidine amino aldehyde with an amine under an acidic condition yielded the Pictet–Spengler-type cyclization product diazepine, which readily underwent Smiles rearrangement to give a novel pyrrolo[1,2-*f*]pteridine derivative.

Pyrimidine moiety, as a structural component of several key biomolecules, has been widely employed in the design of biologically active agents. Its fused bicyclic analogues, pteridines, have also been reported to exhibit a variety of biological activities and constitute the backbones of several marketed drugs. For example, methotrexate (MTX) is used as an antitumor agent and triamterene as a diuretic. In addition, some pteridine derivatives exhibit potent inhibitory activity against biological targets such as dihydrofolate reductase,[1] adenosine kinase,[2] neuronal nitric oxide synthase,[3] cAMP-specific phosphodiesterase,[4] mycobacterial FtsZ,[5] and hepatitis C virus NS5B RNA-dependent RNA polymerase.[6] Although there are a few examples of pteridine scaffolds, few reports exist describing the synthesis of pyrrolo[1,2-*f*]-pteridines.[7]

As a part of our ongoing interest in novel pyrimidine-fused heterocycles,[7b,8] we sought efficient methodologies to construct novel fused heterocyles. Tandem reactions are efficient strategies in organic synthesis, since they enable

(1) (a) Taylor, E. C.; Berrier, J. V.; Cocuzza, A. J.; Kobylecki, R.; McCormack, J. J. *J. Med. Chem.* **1977**, *20*, 1215. (b) Rosowsky, A.; Cody, V.; Galitsky, N.; Fu, H.; Papoulis, A. T.; Queener, S. F. *J. Med. Chem.* **1999**, *42*, 4853.

(2) Gomtsyan, A.; Didomenico, S.; Lee, C. H.; Stewart, A. O.; Bhagwat, S. S.; Kowaluk, E. A.; Jarvis, M. F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4165.

(3) (a) Fröhlich, L. G.; Kotsonis, P.; Traub, H.; Taghavi-Moghadam, S.; Al-Masoudi, N.; Hofmann, H.; Strobel, H.; Matter, H.; Pfleiderer, W.; Schmidt, H. H. H. W. *J. Med. Chem.* **1999**, *42*, 4108. (b) Matter, H.; Kotsonis, P.; Klingler, O.; Strobel, H.; Fröhlich, L. G.; Frey, A.; Pfleiderer, W.; Schmidt, H. H. H. W. *J. Med. Chem.* **2002**, *45*, 2923.

(4) Merz, K. H.; Marko, D.; Regiert, T.; Reiss, G.; Frank, W.; Eisenbrand, G. *J. Med. Chem.* **1998**, *41*, 4733.

(5) Reynolds, R. C.; Srivastava, S.; Ross, L. J.; Suling, W. J.; White, E. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3161.

(6) Ding, Y.; Girardet, J.; Smith, K. L.; Larson, G.; Prigaro, B.; Lai, V. C. H.; Zhong, W.; Wu, J. Z. *Bioorg. Med. Chem Lett.* **2005**, *15*, 675.

(7) (a) Nishimura, N.; Hasegawa, Y.; Mizuno, S.; Yuasa, M.; Maeba, I. *Heterocycles* **1998**, *48*, 2339. (b) Zheng, L.; Dang, Q.; Guo, S.; Xiang, J.; Bai, X. *Chem. J. Chinese Univ.* **2006**, *27*, 1869.

(8) (a) Yang, J.; Dang, Q.; Liu, J.; Wei, Z.; Wu, J.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 474. (b) Liu, J.; Dang, Q.; Wei, Z.; Zhang, H.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 627. (c) Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Bai, X. *Org. Lett.* **2005**, *7*, 1541. (d) Fu, R.; Xu, X.; Dang, Q.; Bai, X. *J. Org. Chem.* **2005**, *70*, 10810. (e) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Tetrahedron* **2006**, *62*, 2563. (f) Zheng, L.; Xiang, J.; Dang, Q.; Guo, S.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 813. (g) Zheng, L.; Xiang, J.; Dang, Q.; Guo, S.; Bai, X. *J. Comb. Chem.* **2006**, *8*, 381. (h) Liu, J.; Dang, Q.; Wei, Z.; Shi, F.; Bai, X. *J. Comb. Chem.* **2006**, *8*, 410. (i) Fu, R.; Xu, X.; Dang, Q.; Chen, F.; Bai, X. *Org. Lett.* **2007**, *9*, 571−574.

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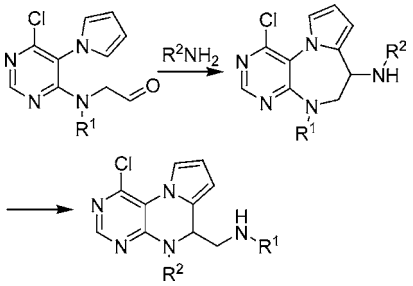
multiple transformations via a series of cascade reactions.[9] Consequently, they have found wide application in the preparation of complex molecules. For example, several interesting nitrogen-containing natural products have been synthesized using tandem reactions.[9b,10] The success of tandem reactions provides the impetus to new synthetic strategies that combine existing reactions into a single operation—new tandem reactions. Pictet−Spengler cyclization reactions[8e−g,11] have been widely used for C−C bond formation to build various nitrogen ring systems. Another important reaction often reported in the synthesis of condensed heterocyclic systems is the Smiles rearrangement.[12]

We envisioned that a tandem Pictet−Spengler-type cyclization and Smiles rearrangment may be feasible with potential application to the synthesis of pyrrolo[1,2-*f*] peridine derivatives outlined in Scheme 1. Reaction of 4-chloro-5-

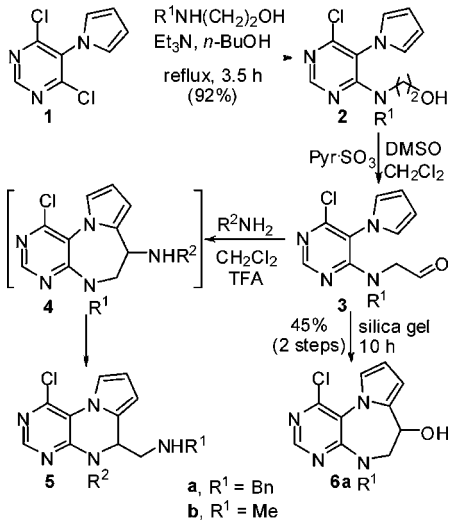
Scheme 1. Design of a Tandem Pictet−Spengler Cyclization/Smiles Rearrangement



pyrrol-1-ylpyrimidine amino aldehyde and an amine via a Pictet−Spengler-type cyclization reaction provides a diazepine intermediate which then readily undergoes a Smiles rearrangement to give the six-membered ring dihydropteridine analogue.

To test the feasibility of the above design, compound **2a** was prepared and reacted with *p*-toluidine as depicted in Scheme 2 (R^1 = Bn, R^2 = *p*-Me-Ph). Clauson−Kaas reaction[13] of 4,6-dichloro-5-aminopyrimidine and 2,5-dimethoxytetrahydrofuran gave 4,6-dichloro-5-pyrrol-1-ylpyrimidine **1** in good yield. Nucleophilic substitution of pyrimidine **1** by *N*-benzylglycinol afforded **2a** in excellent yield. Amino alcohol **2a** was then oxidized under conditions of the Parikh−Doering oxidation[14] to give the corresponding aldehyde **3a**, which readily cyclized to give hydroxydiazepine **6a** during purification on a silica gel column. However, when crude aldehyde **3a** was treated with *p*-toluidine under Pictet−Spengler cyclization reaction conditions, the desired diaze-

Scheme 2. Tandem Pictet−Spengler-Type Cyclization/Smiles Rearrangement



pine **4.10a** was formed. Diazepine **4.10a** was not stable and quickly underwent Smiles rearrangement to produce the expected pteridine derivative **5.10a** at ambient temperature. The initial Pictet−Spengler-type product could be intercepted if the reaction time was kept short. Thus, after 12 min of reaction between aldehyde **3a** and *p*-toluidine, a careful isolation afforded 26% of diazepine **4.10a**, whereas the same reaction but with prolonged reaction time to ensure complete conversion of diazepine **4.10a** gave the desired pteridine **5.10a** in 58% yield. To unambiguously identify the structures of these products, X-ray structures of both products **4.10a** and **5.10a** (Figure 1) were obtained. These experiments

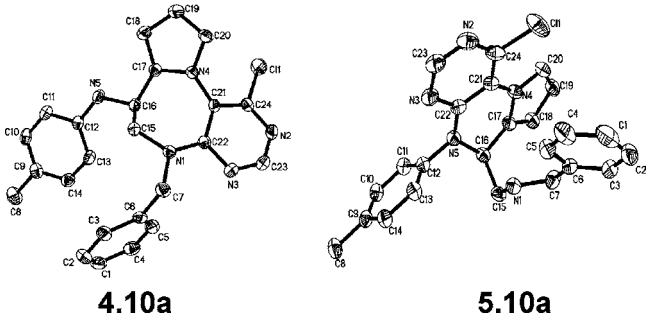


Figure 1. X-ray structures of compounds **4.10a** and **5.10a**.

exemplified the feasibility of the proposed novel sequence of Pictet−Spengler-type cyclization/Smiles rearrangement and its utility in the synthesis of novel heterocycles.

The scope of this new cascade reaction was investigated with pyrimidines **3** (**a**, R^1 = Bn or **b**, R^1 = Me) and various amines, and the results are summarized in Table 1.

As evidenced in Table 1, moderate to good yields (21−62%) of the desired product **5** could be obtained considering

(9) (a) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(10) Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 620.

(11) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Dinsmore, C. J.; Zartman, C. B.; Baginsky, W. F.; O'Neill, T. J.; Koblan, K. S.; Chen, I.-W.; McLoughlin, D. A.; Olah, T. V.; Huff, J. R. *Org. Lett.* **2000**, *2*, 3473. (c) Kundu, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem.* **2005**, *7*, 317.

Table 1. Synthesis of 5,6-Dihydropyrrolo[1,2-*f*]pteridines[a]

entry	R^2	product	time[b] (h)	yield[c] (%)
1	Me[d]	**5.1a**	48	30 (12)[e]
2	*n*-Bu	**5.2a**	20	32
3	Bn	**5.3a**	30	34
4	cyclohexyl	**5.4a**	42[f]	35 (5)[e]
5	*i*-Pr	**5.5a**	48[f]	42
6	*o*-MeO-Ph	**5.6a**	96	61
7	*p*-MeO-Ph	**5.7a**	16	40
8	*o*-Me-Ph	**4.8a**	18	86
9	*m*-Me-Ph	**5.9a**	18	31
10	*p*-Me-Ph	**5.10a**	16	58
11	Ph	**5.11a**	18	55
12	*o*-Cl-Ph	**4.12a**	20	64
13	*m*-Cl-Ph	**5.13a**	20	38
14	*p*-Cl-Ph	**5.14a**	20	62
15	*p*-F-Ph	**5.15a**	22	50
16	*o*-NO_2-Ph	**4.16a**	14[f]	32
17	*p*-NO_2-Ph	**5.17a**	24[f]	43
18	BnO[g]	**5.18a**	72	21
19	*p*-Me-Ph	**5.10b**	20	51
20	*p*-Cl-Ph	**5.14b**	96	36

[a] Reactions were conducted at room temperature unless otherwise specified. [b] Reaction time from **3** to **5** or **4**. [c] Overall yield (three steps) from alcohol **2** and isolated via flash chromatography. [d] Methylamine alcohol solution (27−32%) was used. [e] The numder in parentheses represents the isolated yield of hydroxydiazepine **6**. [f] Refluxed. [g] *O*-Benzylhydroxylamine hydrochloride was used in absence of TFA.

that these yields represent overall yields for three reactions. Both aromatic and aliphatic amines can be employed for this tandem reaction. The yields were higher with an aromatic amine (entries 6, 7, 9−11, 13−15, 17, 19, and 20) compared to the ones with an aliphatic or benzyloxy amine. On the other hand, a substituent at the meta position of the aromatic amine led to lower yields of the final product **5** (entries 9 and 13) compared to its corresponding para-substituted analogue (entries 10 and 14). Substitution at the ortho position of the aniline (entries 8, 12, and 16) only led to the Pictet−Spengler-type cyclization product, while an *o*-MeO substitution did generate the desired product **5.6a** (entry 6). These results suggest that the Smiles rearrangement stage of this tandem reaction is sensitive to electronic effects at the ortho position. This reaction appears to tolerate various functional groups in the aromatic amine, such as electron-donating groups (*m*- and *p*-methyl or -methoxy) and electron-withdrawing groups (*m*- and *p*-halo or -nitro).

In conclusion, a novel methodology involving tandem Pictet−Spengler-type cyclization and Smiles rearrangement was reported. The utility of this reaction sequence has been demonstrated by the synthesis of novel pyrrolo[1,2-*f*]pteridine derivatives. This new method complements existing pteridine chemistry, thus allowing access of additional new pteridine analogues. Exploration of this new strategy in the synthesis of other interesting molecules is currently underway.

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Supporting Information Available: Experimental details, ^1H 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.

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(12) (a) Selvakumar, N.; Srinivas, D.; Azhagan, A. M. *Synthesis* **2002**, *16*, 2421. (b) Soukri, M.; Lazar, S.; Akssira, M.; Guillaumet, G. *Org. Lett.* **2000**, *2*, 1557. (c) 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. (d) Proudfoot, J. R.; Patel, U. R.; Campbell, S. J. *J. Org. Chem.* **1993**, *58*, 6996. (e) Shawali, A. S.; Abdallah, M. A.; Mosselhi, M. A. N.; Farghaly, T. A. *Heteroatom Chem.* **2002**, *13*, 136. (f) Rotas, G.; Kimbaris, A.; Varvounis, G. *Tetrahedron* **2004**, *60*, 10825. (g) Wang, H.-Y.; Liao, Y.-X.; Guo, Y-L.; Tang, Q-H.; Lu, L. *Synlett* **2005**, *8*, 1239. (h) Cho, S-D.; Park, Y.-D.; Kim, J.-J.; Joo, W.-H.; Shiro, M.; Esser, L.; Falck, J. R.; Ahn, C.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron* **2004**, *60*, 3763. (i) Kaim, L. E.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019. (j) Kaim, L. E.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7961.

(13) Clauson-Kaas, N.; Tyle, Z. *Acta. Chem. Scand.* **1952**, *6*, 667.

(14) Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.