JOC*Note*

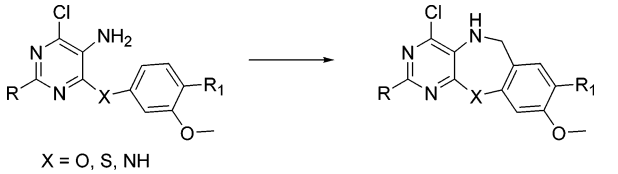
Preparation of Substituted Pyrimido[4,5-*b*]-1,4-benzoxazepines, Thiazepines, and Diazepines via a Pictet−Spengler Cyclization

Matthew A. J. Duncton,* Leon M. Smith II, Sabina Burdzovic-Wizeman, Aaron Burns, Hu Liu, Yunyu Mao, Wai C. Wong, and Alexander S. Kiselyov

Department of Chemistry, ImClone Systems, 710 Parkside Avenue, Suite 2, Brooklyn, New York 11226

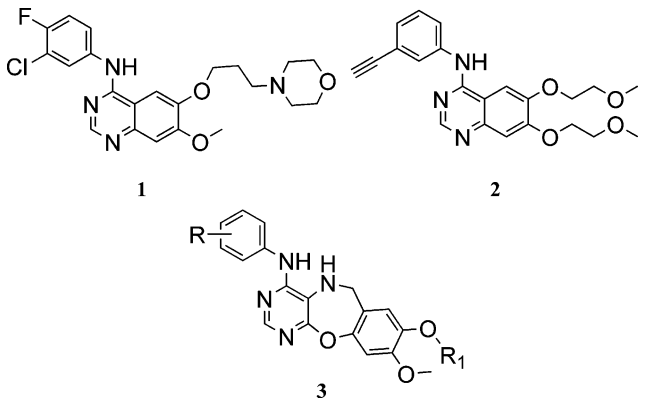
mattduncton@yahoo.com

Received July 8, 2005



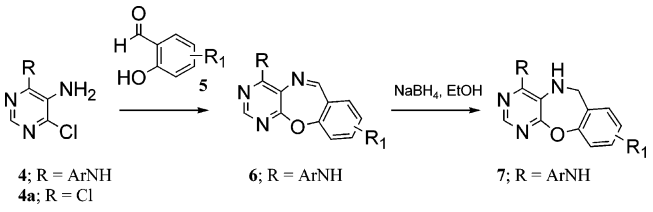
A synthesis of the title compounds, which have found use as inhibitors of certain receptor tyrosine kinases, was achieved using a Pictet−Spengler cyclization as a key step.

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that has received widespread attention as a biological target for the treatment of proliferative disorders, particularly cancer.[1] As of early 2005, the importance of inhibiting EGFR had been demonstrated in a number of oncolytic conditions. For example, cetuximab (Erbitux), an antibody inhibitor of EGFR, is an approved therapeutic agent against irinotecan-refractory colorectal cancer and under active investigation in several other tumor types.[2] Two small-molecule 4-anilinoquinazoline derivatives, gefitinib (Iressa, **1**) and erlotinib (Tarceva, **2**), which compete with adenosine triphosphate (ATP) for binding at the EGFR kinase domain, have also received approval for the treatment of some forms of lung cancer.[3,4] In an effort to seek nonquinazoline small-molecule kinase inhibitors, we recently disclosed the use of substituted pyrimido[4,5-*b*]-1,4-benzoxazepines exemplified by the generic structure **3** as inhibitors of certain receptor tyrosine kinases, particularly EGFR.[5] The interesting biological profile of this group of compounds stimulated a search for an efficient synthesis of analogues similar to **3**. In this paper, we disclose a robust approach which can be used to construct the tricyclic framework of pyrimido[4,5-*b*]-1,4-benzoxazepines in a rapid and convenient manner from readily accessible starting materials using a Pictet−Spengler cyclization as a key step. This Pictet−Spengler approach can also be extended to produce pyrimido[4,5-*b*]-1,4-benzothiazepines and pyrimido[4,5-*b*]-1,4-benzodiazepines in good to excellent yield.



Existing synthetic routes to the pyrimido[4,5-*b*]-1,4-benzoxazepine class of compounds use a displacement/condensation approach by reacting a chloropyrimidine **4** with a salicyaldehyde derivative **5**. Reduction of the imine product **6** with a separate reaction step yields the desired benzoxazepine (Scheme 1).[6] During our investigation on the use of substituted pyrimido[4,5-*b*]-1,4-benzoxazepines as inhibitors of receptor tyrosine kinases it was found that the methodology described in Scheme 1 failed to yield any cyclized imine product when performed on the dichloro starting material **4a**, thus hampering our ability to synthesize analogues in a rapid manner using a short synthetic sequence. We therefore sought an alternative synthetic approach and became attracted to the Pictet−Spengler reaction (Figure 1) due to its widespread utility in preparing tetrahydroisoquinolines and β-carbolines,[7]

SCHEME 1. Synthesis of Pyrimido[4,5-*b*]-1,4-benzoxazepines by Displacement/Condensation Chemistry[6]



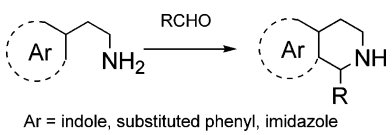


FIGURE 1. Pictet−Spengler reaction.

(1) (a) Arteaga C. *Semin. Oncol.* **2003**, *30* (Suppl. 1), 3−11. (b) Khalil, M. Y.; Grandis, J. R.; Shin D. M. *Expert Rev. Anticancer Ther.* **2003**, *3*, 367−380.

(2) Ciardiello, F.; De Vita, F.; Orditura, M. Comunale, D.; Galizia, G. *Future Oncology* **2005**, *1*, 173−181.

(3) Tamura, K.; Fukuoka, M. *Expert Opin. Pharmacother.* **2005**, *6*, 985−993.

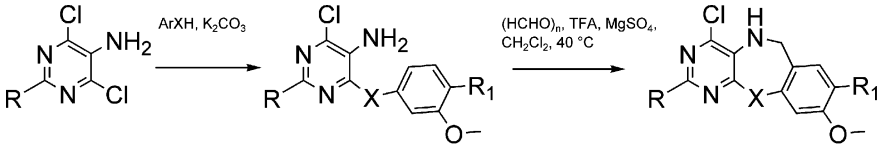
(4) Blackhall, F. H.; Rehman, S.; Thatcher, N. *Expert Opin. Pharmacother.* **2005**, *6*, 995−1002.

(5) Hadari, Y.; Smith, L. M., II. Patent WO 2005009384, 2005; *Chem. Abstr.* **2005**, *142*, 172179.

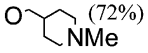
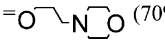
(6) Levkovskaya, L. G.; Sazonov, N. V.; Grineva, N. A.; Mamaeva, I. E.; Serochkina, N. A.; Safonova, T. S. *Khim. Geterotsikl. Soedin.* **1985**, 122−125.

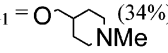
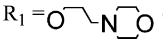
10.1021/jo051419g CCC: $30.25
Published on Web 10/14/2005

SCHEME 2. Synthesis via a Pictet–Spengler Reaction

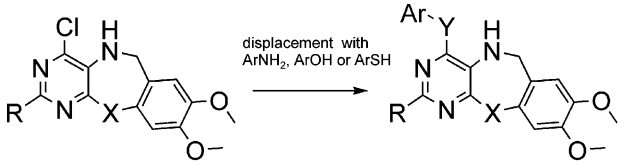


4a; R= H
4b; R = Me

8a; X = O, R = H, R_1 = OMe (94%)
8b; X = S, R = H, R_1 = OMe (64 %)
8c; X = S, R = Me, R_1 = OMe (76%)
8d; X = NH, R = H, R_1 = OMe (45 %)
8e; X = NH, R = H, R_1 = H (68%)
8f; X = NH, R = H, R_1 =  (72%)
8g; X = NH, R = H, R_1 =  (70%)

9a; X = O, R = H, R_1 = OMe (62%)
9b; X = S, R = H, R_1 = OMe (76 %)
9c; X = S, R = Me, R_1 = OMe (43%)
9d; X = NH, R = H, R_1 = OMe (73 %)
9e; X = NH, R = H, R_1 = H (34%)
9f; X = NH, R = H, R_1 =  (34%)
9g; X = NH, R = H, R_1 =  (83%)

SCHEME 3. Displacement of Chloride with N, O, and S Nucleophiles



9a; X = O, R = H
9b; X = S, R = H
9c; X = S, R = Me
9d; X = NH, R = H

10a; X = O, R = H, Y = NH, Ar = β-naphthyl (73%)
10b; X = S, R = H, Y = NH, Ar = 3-Br-C_6H_4 (77%)
10c; X = S, R = H, Y = NMe, Ar = 3-Br-C_6H_4 (55%)
10d; X = S, R = H, Y = NMe, Ar = 3-Cl-C_6H_4 (57%)
10e; X = S, R = Me, Y = NH, Ar = 3-Br-C_6H_4 (72%)
10f; X = S, R = Me, Y = NH, Ar = 3-Cl,4-F-C_6H_3 (61%)
10g; X = S, R = Me, Y = NH, Ar = 3-Cl,2-F-C_6H_3 (53%)
10h; X = S, R = Me, Y = NH, Ar = 3-Br,4-Me-C_6H_3 (43%)
10i; X = S, R = Me, Y = NH, Ar = 4-Cl,3-Me-C_6H_3 (49%)
10j; X = NH, R = H, Y = NH, Ar = 3-Br-C_6H_4 (8%)
10k; X = O, R = H, Y = O, Ar = 3-Br-C_6H_4 (29%)
10l; X = O, R = H, Y = O, Ar = 3-Cl,4-F-C_6H_3 (59%)
10m; X = S, R = H, Y = O, Ar = 3-Cl,2-F-C_6H_3 (25%)
10n; X = S, R = H, Y = O, Ar = 3-Br-C_6H_4 (29%)
10o; X = O, R = H, Y = S, Ar = 3-Br-C_6H_4 (30%)
10p; X = O, R = H, Y = S, Ar = 3-Cl-C_6H_4 (74%)
10q; X = S, R = H, Y = S, Ar = 3-Br-C_6H_4 (10%)
10r; X = S, R = H, Y = S, Ar = 3-Cl-C_6H_4 (26%)

although it was noted that the use of this reaction to prepare seven-membered rings was not as well documented.[8]

Our synthesis of substituted pyrimido[4,5-*b*]-1,4-benzoxazepines began by displacing 5-amino-4,6-dichloropyrimidine **4a** with 3,4-dimethoxyphenol to afford the monodisplaced ether product **8a** in good yield (Scheme 2). The ether **8a** was then smoothly cyclized to the desired pyrimido[4,5-*b*]-1,4-benzoxazepine **9a** using paraformaldehyde in dichloromethane under acidic and dehydrating conditions (trifluoroacetic acid and magnesium sulfate).[9] This Pictet–Spengler reaction proceeded in a good yield (62%) upon heating at 40 °C in a sealed tube[10] and furnished the pure benzoxazepine product **9a** after workup and purification by column chromatography upon silica gel. Interestingly, attempted cyclization of the ether **8a** using formaldehyde (excess) in water and methanol as reaction solvent failed to give any of the desired benzoxazepine **9a**, even under refluxing conditions. As expected, the synthesis of pyrimido[4,5-*b*]-1,4-benzoxazepines outlined above could also be expanded to prepare analogous pyrimido[4,5-*b*]-1,4-benzothiazepine and benzodiazepine derivatives (Scheme 2).[11] Thus, compounds **8b**–**g** were subjected to the standard conditions of paraformaldehyde, TFA, and $MgSO_4$ under mild heating in dichloromethane to furnish the desired tricycles **9b**–**g** in good to excellent yield. In two instances, the synthesis of **9e** and **9f**, a minor byproduct was also

(7) For reviews, see: (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045–1070. (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.

(8) For some examples of the Pictet–Spengler reaction being used to prepare seven-membered rings, see: (a) Kundu, B.; Sawant, D.; Partani, P.; Kesarwani, A. P. *J. Org. Chem.* **2005**, *70*, 4889–4892. (b) Dancso, A.; Kajtar-Peredy, M.; Szantay, C. *J. Heterocycl. Chem.* **1989**, *26*, 1867–1868. (c) Orazi, O. O.; Corral, R. A.; Giaccio, H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1977–1982.

(9) Adams, D. R.; Bentley, J. M.; Davidson, J. E.; Duncton, M. A. J.; Porter, R. H. P. Patent WO 200044753, 2000; *Chem Abstr.* **2000**, *133*, 150579.

(10) A sealed tube was used to minimize any loss of dichloromethane during the reaction. The cyclizations were not examined using reaction conditions other than those detailed in this manuscript.

(11) For a Friedel–Crafts approach to the synthesis of pyrimido-[4,5-*b*]-1,4-benzodiazepines, see: Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Gao, S.; Bai, X. *Org. Lett.* **2005**, *7*, 1541–1543.

isolated in less than 10% yield (see the Supporting Information for the identity of each of these byproducts).

The chloro group in compounds **9a**−**d** could be displaced with substituted anilines, phenols, or thiophenols to afford a range of 4-aminoaryl, 4-oxyaryl, or 4-thioaryl products (Scheme 3).[12] For example, the chlorobenzoxazepine derivative **9a** was reacted with β-naphthylamine in the presence of catalytic hydrochloric acid in 2-propanol at 120 °C to afford the displaced product **10a**. These general conditions were also successful in displacing the chloro group from the benzothiazepines **9b** and **9c** to give a range of derivatives **10b**−**i**. The corresponding diazepine **9d** required the use of microwave irradiation under alternative reaction conditions (HCl, DMF, 150 °C) to facilitate displacement with an aniline. The efficiency of this displacement reaction was also low, as evidenced by the 8% yield obtained for example **10j**. Displacement of the chloro group in compounds **9a**−**c** with an oxygen or sulfur nucleophile was accomplished by reaction with an appropriately substituted phenol, or thiophenol, in the presence of K_2CO_3 in DMF with heating (80 °C for phenols and 65 °C for thiophenols). Again, a range of examples **10k**−**r** was produced.

In conclusion, we have developed a rapid and efficient synthesis of pyrimido[4,5-*b*]-1,4-benzoxazepine, benzothiazepine, and benzodiazepine heterocyles using a Pictet−Spengler reaction as the key step. The products from this synthesis were reacted further to give compounds useful for inhibiting receptor tyrosine kinases such as EGFR.[5] Since our approach accesses a chloro intermediate, which in turn can be displaced with multiple anilines, phenols, or thiophenols, it is envisaged that a large set of diverse final compounds, based around the pyrimido[4,5-*b*]-1,4-benzoxazepine, thiazepine, and diazepine cores, could be synthesized this way. Products from such an exercise could be envisaged to inhibit other kinase targets.[13]

Experimental Section

4-Chloro-6-(3,4-dimethoxyphenoxy)pyrimidin-5-ylamine 8a. 5-Amino-4,6-dichloropyrimidine **4a** (0.27 g, 2.0 mmol), 3,4-dimethoxyphenol (0.37 g, 2.4 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) were suspended in DMF (6 mL) and stirred overnight at 60 °C under argon. After being cooled to rt, the mixture was poured in to EtOAc (50 mL) and H_2O (50 mL). The aqueous and organic layers were partitioned, and the aqueous layer was extracted with EtOAc (1 × 25 mL). The combined organic extracts were washed with brine (1 × 25 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo to leave a crude oil. The oil was purified by column chromatography on silica gel (EtOAc/hexane 1:3) to give the desired product **8a** (0.53 g, 94%) as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (d, 1H), 6.99 (dd, 1H), 6.83 (s, 1H), 6.76 (dd, 1H), 5.73 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H); MS *m/z* 282 (M + 1 for ^{35}Cl).

General Procedure for the Pictet−Spengler Reaction: Preparation of 1-Chloro-7,8-dimethoxy-10,11-dihydro-5-oxa-2,4,11-triazadibenzo[*a*,*d*]cycloheptene 9a. TFA (100 μL) was added in one portion to a suspension of paraformaldehyde (65 mg, 2.2 mmol), 4-chloro-6-(3,4-dimethoxyphenoxy)pyrimidin-5-ylamine **8a** (0.42 g, 1.5 mmol), $MgSO_4$ (0.35 g), and CH_2Cl_2 (6 mL) in a sealed tube. The suspension was stirred at 40 °C overnight. After being cooled to rt, the mixture was filtered and the filter cake washed with CH_2Cl_2. The filtrate was concentrated in vacuo and then purified by column chromatography on silica gel (EtOAc/hexane 1:9−2:3) to give the desired compound **9a** (0.27 g, 62%) as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (s, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 6.34 (t, 1H), 4.45 (d, 2H), 3.70 (s, 6H); MS *m/z* 294 (M + 1 for ^{35}Cl).

General Procedure for Displacement of the Chloro Group in 9a−d with Anilines: Preparation of (7,8-Dimethoxy-10,11-dihydro-5-oxa-2,4,11-triazadibenzo[*a*,*d*]cyclohepten-1-yl)-naphthalen-2-ylamine 10a. 1-Chloro-7,8-dimethoxy-10,11-dihydro-5-oxa-2,4,11-triazadibenzo[*a*,*d*]cycloheptene **9a** (100 mg, 0.34 mmol) and naphthalen-2-ylamine (146 mg, 1.02 mmol) were suspended in ^{i}PrOH (4.00 mL), and concd aq HCl (3 drops) was added. The mixture was stirred in a sealed tube under an argon atmosphere at 120 °C for 18 h. The solid that formed overnight was collected by filtration, washed with ^{i}PrOH and Et_2O, respectively, and then sonicated with MeOH for 30 min. The mixture was filtered, and the filter cake was washed with Et_2O and dried overnight in a vacuum oven at 60 °C to give the title compound **10a** (100 mg, 73%) as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.13 (s, 1H), 7.87 (s, 1H), 7.72−7.54 (m, 4H), 7.34−7.26 (m, 2H), 6.92 (s, 1H), 6.74 (s, 1H), 4.41−4.31 (m, 5H, broad peak), 3.56 (s, 6H); MS *m/z* 401 (M + 1).

Free base of 10a: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.26 (s, 1H), 7.71 (s, 1H), 7.61−7.46 (m, 4H), 7.23−7.10 (m, 2H), 6.83 (s, 1H), 6.78 (s, 1H), 5.25 (t, 1H), 4.18 (d, 2H), 3.53 (s, 6H); MS *m/z* 401 (M + 1).

General Procedure for Displacement of the Chloro Group in Compounds 9a−d with Phenols or Thiophenols: Preparation of 1-(3-Bromophenoxy)-7,8-dimethoxy-10,11-dihydro-5-oxa-2,4,11-triazadibenzo[*a*,*d*]cycloheptene 10k. 1-Chloro-7,8-dimethoxy-10,11-dihydro-5-oxa-2,4,11-triazadibenzo[*a*,*d*]cycloheptene **9a** (155 mg, 0.5 mmol), 3-bromophenol (121 mg, 0.7 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in DMF (7 mL) were heated to 80 °C and stirred overnight. After the mixture was cooled to rt, EtOAc was added, the mixture was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (using EtOAc/hexane 4:6 as eluent) to give the desired product **10k** (65 mg, 29%) as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.48−7.60 (m, 3H), 7.33−7.38 (m, 1H), 7.05 (s, 1H), 7.00 (s, 1H), 6.24 (br. s, 1H), 4.52 (s, 2H), 3.89 (2 × s, 6H); MS *m/z* 430 (M + 1 for ^{79}Br).

The same reaction conditions were employed for displacements using thiophenols, except a reaction temperature of 65 °C was used.

Supporting Information Available: General procedures and copies of ^{1}H NMR, mass spectra, and HPLC traces for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051419G

(12) The chloro group in compounds **9e**−**g** could also be displaced with nitrogen, oxygen, and sulfur nucleophiles, but no examples are detailed in this paper.

(13) This strategy has been well documented for kinase inhibitors containing a quinazoline or quinoline nitrile heterocyclic core. For example, see: Boschelli, D. H. *Med. Chem. Rev. − Online* **2004**, *1*, 457−463.