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Bischler–Napieralski cyclocondensation in the synthesis of new 11*H*-pyrimido[4,5-*b*][1,4]benzodiazepines

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Dedicated to the memory of my ever loved wife Alma Sully Marcillo Rivera

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ABSTRACT

A synthetic strategy based on nitrosation–aminolysis–nitroso reduction and Bischler–Napieralski cyclocondensation has been developed for the synthesis of a family of 2-amino-4-methoxy-11*H*-pyrimido[4,5-*b*][1,4]benzodiazepines.

Pyrimidine-fused compounds are of general interest in medicinal chemistry and chemical biology, due to their wide range of biological activities.[1] In particular, pyrimidobenzodiazepines have attracted the attention of chemists for many years.[2] Figure 1 displays some examples of pyrimidobenzodiazepine derivatives, which have shown interesting pharmacological properties, such as antihypoxic and antipyretic (**A**);[3] analgesic (**B**);[1c] gastric secretion inhibition (**C**);[4] and immunosuppressive activity (**D**), compound **D** showed about two times higher activity than cyclosporine A when it was tested in mice.[5]

In our ongoing investigation on the preparation of pyrimidine fused to diazepine systems,[6] we have improved the method of Bai and co-workers (Scheme 1)[7] in order to afford new 11*H*-pyrimido[4,5-*b*][1,4]benzodiazepine derivatives by starting from other more versatile commercially available pyrimidines.

We have made two modifications. Firstly, we have used the commercially available 2-amino-4,6-dimethoxypyrimidine, in which there is an amino group at C2, which is used as pharmacophoric residue in this kind of compounds, and it brings an additional point of further diversification.

Secondly, we have used a methodology implemented by our group,[8] that is based on a nitrosation strategy instead of nitration,

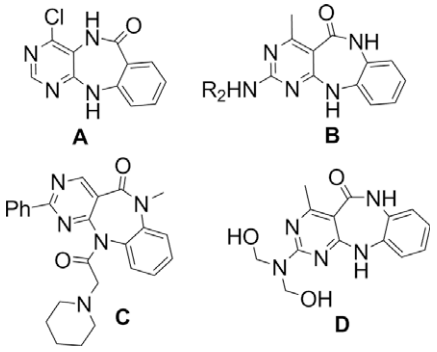
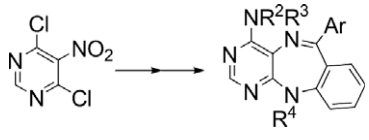


Figure 1. Examples of bioactive pyrimidobenzodiazepines.



Scheme 1. Synthesis of pyrimidobenzodiazepines from 4,6-dichloro-5-nitropyrimidine.

to activate aminolysis of methoxy groups in order to introduce an aniline residue at C4 (Scheme 2), and so affording a procedure of

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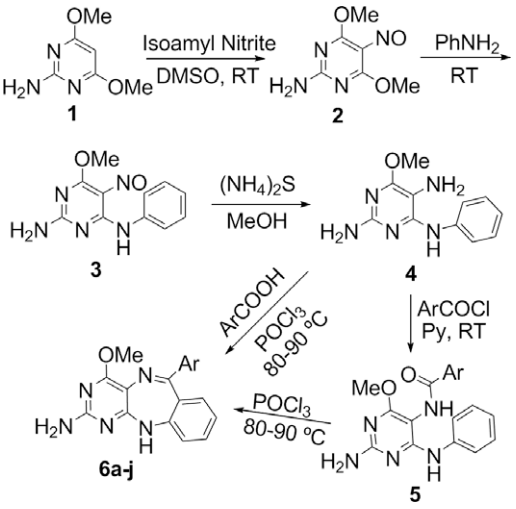

Scheme 2. Syntheses of 11*H*-pyrimido[4,5-*b*][1,4]benzodiazepines from 2-amino-4,6-dimethoxypyrimidine.

higher application than that started from the highly activated 4,6-dichloro-5-nitropyrimidine.

Therefore, following the mentioned strategy and after reducing the C5-nitroso group we were able to obtain triaminopyrimidine **4** in an excellent yield (96%).[9] This compound was then used to provide new pyrimidobenzodiazepines by reaction with acid derivatives. Our first attempt was the preparation of three different amide derivatives **5a–c** by reaction of **4** with corresponding benzoyl chlorides,[10] which then underwent a cyclization reaction under *Bischler–Napieralski* conditions ($POCl_3$) to yield the new desired 11*H*-pyrimido[4,5-*b*][1,4]benzodiazepines **6a–c** (Scheme 2), with no presence of by-product purine derivatives (see Fig. 2).[11]

We then decided to explore the one-step cyclocondensation to obtain directly compounds **6** from compound **4**, so we carried out the reaction of **4** with the corresponding acid derivatives under the cyclization conditions ($POCl_3$) yielding the expected compounds **6a–c**[12] (Table 1).

By comparing both procedures, the yields to get **6a–c** from **4** are found to be nearly identical. Other acidic compounds were used to produce pyrimidobenzodiazepines **6d–j** in acceptable to good yields by direct cyclocondensation from derivative **4**.

It is important to note that formation of the intermediate amide derivatives **5** prior to cyclization to form the desired compounds **6** appears to be an unnecessary step, but this step can be very useful in cases where the 4,5-diamino analogs of **4** are not stable and cannot be isolated. Formation of amide **5** helps to stabilize these analogs and hence increases the final yield.

It is worthy of notice that the use of polyphosphoric acid (PPA) for cyclization is not working unlike Bai's methodology (PPA/$POCl_3$); under these conditions they reported the formation of purines like **7** if there is a secondary amino group at C4.[7c] In fact, we have also noted that the presence of a Brønsted acid favors the formation of purine **7** as the major product (see Fig. 2).

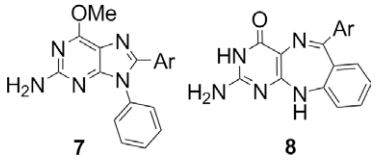

Figure 2. By-products in the preparation of 2-amino-4-methoxy-11*H*-pyrimido-[4,5-*b*][1,4]benzodiazepines.

Table 1
Reaction yields in the direct cyclocondensation of **4** to 11*H*-pyrimido[4,5-*b*][1,4]-benzodiazepines **6** and *via* precursors **5**

Entry	Ar	Yields		
		4→6[12]	**4→5**[10]	**5→6**[11]
a	C_6H_5	52	73	76
b	4-Cl–C_6H_4	60	82	80
c	4-NO_2–C_6H_4	74	92	80
d	4-CF_3–C_6H_4	84	–	
e	3-NO_2–C_6H_4	50	–	
f	4-Br–C_6H_4	62	–	
g	4-Me–C_6H_4	87	–	
h	4-MeO–C_6H_4	71	–	
i	2-F–C_6H_4	64	–	
j	4-F–C_6H_4	50	–	

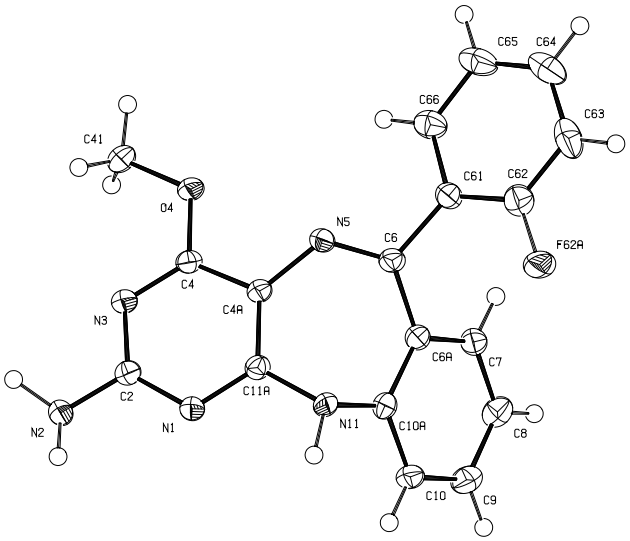

Figure 3. Ortep drawing of structure for compound **6i**.[13]

In a general view, this strategy can be of a broader application starting from substituted 4-alkoxy or 4-chloropyrimidines, and reported derivatives **6** incorporate two new points of diversity on the pyrimidobenzodiazepine framework (at C2–NH_2 and N(11)–H positions), which afford the opportunity of introducing new substituents. This, in principle, widens the range of compounds which may be synthesized and tested in biological studies. On the other hand, the methoxy at C4 can be readily hydrolyzed, and, in fact, if after processing the cyclization reaction with water and base, the mixture is left for one day and pyrimidobenzodiazepin-4-one **8** is isolated (Fig. 2).

The structure of pyrimidobenzodiazepines **6** was unambiguously confirmed by single crystal X-ray diffraction analysis of derivative **6i** (Fig. 3).

In conclusion, we have developed a synthetic route with two alternatives having as key steps, the selective monosubstitution of methoxy group in 5-nitrosopyrimidines and Bischler–Napieralski cyclocondensation with acid derivatives for obtaining new pyrimidobenzodiazepine derivatives in acceptable yields. These new compounds may be useful in the field of medicinal chemistry since they belong to the so-called bicyclic privileged structures,[6,14] which have several points of diversification.

Acknowledgments

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Supplementary data

Full experimental details and characterization data (^{1}H and ^{13}C NMR, MS, and HRMS spectra) for all new compounds are supplied. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.026.

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9. *2,4,5-Triamino-6-methoxy-N^4-phenylpyrimidine* (**4**). After preparation of 2,4-diamine-6-methoxy-5-nitroso-*N*^{4}-phenylpyrimidine (**3**) starting from 2-amino-4,6-dimethoxypyrimidine by nitrosation and aminolysis with aniline, that we have previously reported.[7] Then, an aqueous ammonium sulfide solution was added (15 mL, 20% w/w) to a solution of (**3**) (0.500 g, 2.04 mmol) in methanol (15 mL). This mixture was stirred at room temperature for 4 h, the volume was reduced under reduced pressure and cooled in a refrigerator for several hours. Compound **4** precipitated as a white solid, which was filtered off and dried. Yield 98% (0.46 g), mp: 139–141 °C. ^{1}H NMR (DMSO-d_6) δ. 3.47 (s, 2H), 3.78 (s, 3H), 5.57 (s, 2H), 6.87 (t, 1H, 8 Hz), 7.21 (t, 2H, 8 Hz), 7.69 (d, 2H, 8 Hz), 7.86 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 159.06, 155.41, 151.75, 141.09, 128.34, 120.76, 118.97, 101.26, 52.89. MS *m*/*z* (assignation, abundance %): 231 (M^+, 100), 230 (14) 216 (M−15, 7), 215 (M−16, 7), 119 (12), 104 (29), 93 (4), 86 (21), 77 ($C_6H_5^+$, 32), 43 ($CHNO^+$, 30); HRMS calcd for $C_{11}H_{13}N_5O$: 231.1120, found 231.1150.
10. *General procedure for the synthesis of N-(2-amino-4-methoxy-6-phenylaminopyrimidin-5-yl)benzamides* (**5a–c**). To a solution of compound **4** (0.217 g, 0.938 mmol) in pyridine (9 mL), the appropriate benzoyl chloride derivative (1.22 mmol) was added and the mixture stirred for 1 h. An ice-water mixture was added on the reaction mixture and the precipitated solid was filtered off and dried to afford compounds **5**. Data for *N-(2-amino-4-methoxy-6-phenylaminopyrimidin-5-yl)benzamide* **5a**. White solid. Yield 73%, mp: 187–189 °C. ^{1}H NMR (DMSO-d_6) δ: 3.73 (s, 3H), 6.27 (s, 2H), 6.92 (m, 1H), 7.22 (m, 2H), 7.40–7.70 (m, 5H), 7.95–8.05 (m, 2H), 8.13 (s, 1H), 9.06 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 53.0, 91.4, 120.6, 121.6, 128.0, 128.05, 128.1, 131.2, 134.34, 140.5, 158.5, 160.4, 165.2, 166.2. MS *m*/*z* (assignation, abundance %): 230 ($[M-PhCO]^+$, 4), 105 ($PhCO^+$, 100), 77 ($C_6H_5^+$ 38), 57 ($C_2H_3NO^+$, 84).
11. *General procedure for the synthesis of 2-amino-4-methoxy-6-aryl-11H-pyrimido[4,5-b][1,4]benzodiazepines 6 from compounds* **5**. A mixture of **5a–c** (0.396 mmol) and $POCl_3$ (5 mL) was heated between 80 and 90 °C for the appropriate time: 1.5 h for **5a**; 2.0 h for **5b**, and 2.5 h for **5c** (TLC monitoring). The mixture was cooled down, then a mixture of ice-water was added and neutralized with solid K_2CO_3. A solid precipitated when the pH was basic (ca. 9), the solid was filtered off and washed several times with water, that after drying and recrystallization from methanol afforded compounds **6**. Data for *2-amino-4-methoxy-6-phenyl-11H-pyrimido[4,5-b][1,4]benzodiazepine* **6a**.Yellow solid. Yield 76%, mp >300 °C. ^{1}H NMR (DMSO-d_6) δ: 3.87 (s, 3H), 6.27 (s, 2H), 6.81 (dd, 1H, 7.8 Hz, 1.3 Hz), 6.91 (ddd, 1H, 7.8 Hz, 7.5 Hz, 0.8 Hz), 6.98 (d, 1H, 7.5 Hz), 7.30 (ddd, 1H, 7.8 Hz, 7.5 Hz, 1.6 Hz). 7.38–7.43 (m, 3H), 7.50–7.56 (m, 3H). ^{13}C NMR (DMSO-d_6) δ: 53.2, 108,6, 120.9, 121.9, 127.0, 127.7, 128.4, 128.9, 130.6, 131.4, 140.76, 150.5, 160.3, 160.5, 163.8, 165.6. MS *m*/*z* (assignation, abundance %): 318 (M+1, 20) 317 (M, 100), 316 (M–1, 56), 301 (M–16, 7), 77 ($C_6H_5^+$, 17), 57 (C_2H_3NO+, 7), 43 (CHNO+, 22). HRMS calcd for $C_{18}H_{15}N_5O$: 317.1277; found: 317.1262.
12. *General procedure for the synthesis compounds* **6** *from compound* **4**. A mixture of **4** (0.200 g; 0.864 mmol), the corresponding benzoic acid derivative (1.73 mmol) and $POCl_3$ (5 mL) was heated between 80 and 90 °C for 1.5–3 h. The mixture was cooled down, then a mixture of ice-water was added and neutralized with solid K_2CO_3. A solid precipitated when the pH was basic (ca. 9), the solid was filtered off and washed several times with water, that after drying and recrystallization from methanol afforded compounds **6**. Data for *2-amino-6-(2-fluorophenyl)-4-methoxy-11H-pyrimido[4,5-b][1,4]benzodiazepine* **6i**. Reaction time 1.5 h. Reddish solid. Yield 64%, mp >300 °C. ^{1}H NMR (DMSO-d_6) δ: 3.81 (s, 3H), 6.47 (s, 2H), 6.61 (d, 1H, 8 Hz), 6.81 (t, 1H, 8 Hz), 6.89 (d, 1H, 8 Hz), 7.16–7.24 (m, 2H), 7.28 (t, 1 H, 8 Hz), 7.45–7.54 (m, 2H), 7.67 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 53.5, 108,2, 115.7, 120.6, 122.6, 124.4, 128.4, 129.6, 130.8, 131.4, 131.9, 148.7, 159.7, 160.8, 161.0, 166.1. MS *m*/*z* (assignation, abundance %): 336 (M+1, 23), 335 (M^+, 100), 334 (M−1, 23), 305 (M−30, 18), 240 ($[M-C_6H_4F]^+$, 4), 95 ($[C_6H_4F]^+$, 13), 76 ($C_6H_4^+$, 9), 57 ($C_2H_3NO^+$, 33); 43 ($CHNO^+$, 67), 42 ($CH_2N_2^+$, 27). HRMS calcd for $C_{18}H_{14}FN_5O$: 335.1182, found: 335.1195. Crystallographic data for **6i** were collected at 120 K on a Bruker Nonius Kappa CCD area diffractometer using Mo Kα X-ray radiation (λ = 0.71073 Å) and deposited at Cambridge Crystallographic data Center (CCDC reference: 686626).
13. Displacement ellipsoids are drawn at the 50% probability level and H are represented as small spheres at arbitrary radii. The 2-fluorophenyl substituent is disordered in two positions with occupancies of 0.75 for fluoride at C62 (represented in Fig. 3), and 0.25 for fluoride at C66.
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