Pergamon

Tetrahedron Letters 41 (2000) 9741–9745

TETRAHEDRON LETTERS

Synthesis of pyrrolo[2,3-*d*]pyrimidines via cyclocondensation of β-alkoxy- and β-amino-α-bromoaldehydes

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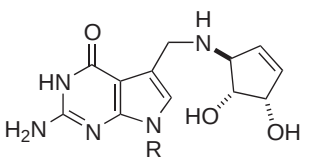
Received 21 August 2000; revised 2 October 2000; accepted 3 October 2000

Abstract

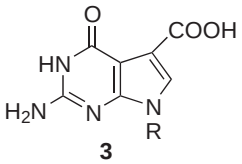
A series of β-alkoxy- and β-amino-α-bromoaldehydes was synthesized. The cyclocondensation of these intermediates with 2,4-diamino-6-hydroxypyrimidine yielded a series of pyrrolo[2,3-*d*]pyrimidines containing heteroatoms in the side chain. Choice of protecting group proved critical to the success of the bromination and cyclocondensation reactions. A number of oxygen and nitrogen protecting groups were examined and the results are described herein. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: pyrrolo[2,3-*d*]pyrimidines; α-bromoaldehydes; cyclocondensation.

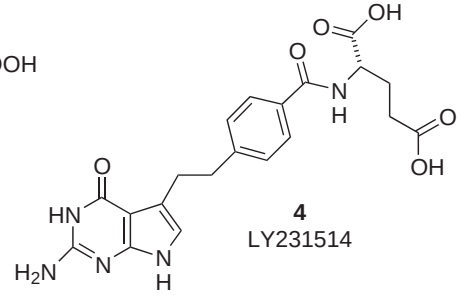
The pyrrolo[2,3-*d*]pyrimidine ring system is a common motif in several natural products and biologically active molecules, including Q base (**1**), Nucleoside Q (**2**), and cadeguomycin (**3**).[1] Multitargeted antifolate LY231514 (**4**), of particular interest as a potential pharmaceutical, also features the pyrrolo[2,3-*d*]pyrimidine ring system.



1 Q base (R = H)
2 Nucleoside Q (R = ribose)



3
Cadeguomycin
R = ribose



4
LY231514

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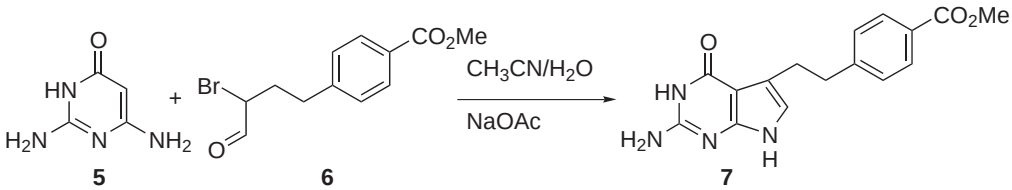
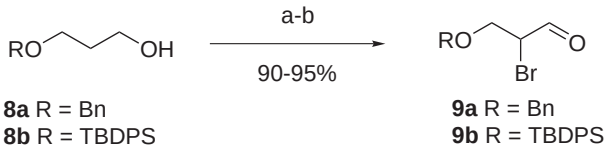
PII: S0040-4039(00)01768-8

We recently published a practical synthesis of **4** in which the key step was the cyclocondensation of 2,4-diamino-6-hydroxypyrimidine (**5**) with bromoaldehyde **6** (Scheme 1) to give pyrrolopyrimidine **7**.[2] In the case of **7**, an all carbon chain links the pyrrolopyrimidine to the pendant aryl group. While condensations of this sort have been reported previously in the literature,[3] to our knowledge condensations of β-alkoxy- and β-amino-α-bromoaldehydes to form pyrrolopyrimidines containing heteroatoms in the functionality found at the 5-position in natural products **1**, **2**, and **3** have not previously been reported. We sought to expand the scope of this cyclization to include syntheses of molecules containing heteroatom linkers, envisioning that such a strategy would provide a new entry into this class of compounds. Determination of oxygen and nitrogen protecting groups that would allow for the synthesis of the β-amino- and β-alkoxy-α-bromoaldehydes needed for the cyclization reaction was necessary to achieve this goal. Stability of these bromoaldehyde intermediates once obtained also proved important to the success of the cyclization reaction. Here we report our results thus far.



Scheme 1.

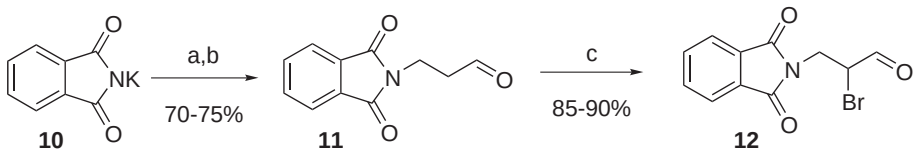
In the β-alkoxy protected series, two protecting groups examined, benzyl and TBDPS, proved effective. β-Alkoxybromoaldehydes **9a** and **9b** were synthesized in two steps in 90–95% overall yield from monoprotected 1,3-propanediols **8a** and **8b** (Scheme 2).[4] Oxidation of the alcohols[5] proceeded smoothly, followed by treatment with dibromobarbituric acid (DBBA) in acetonitrile[6] to give bromoaldehydes **9a** or **9b** in 90–95% overall yield.



Scheme 2. Reagents: (a) TEMPO, KBr, NaOCl, H_2O/CH_2Cl_2; (b) DBBA, CH_3CN

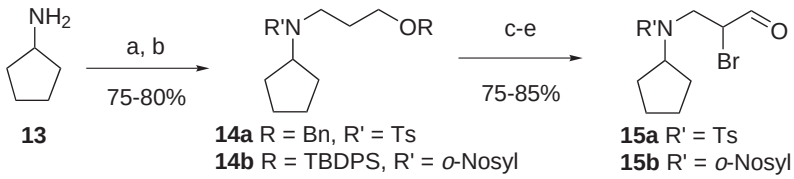
Several other oxygen protecting groups examined were not effective. Oxidation of mono-TBDMS, -TIPS, -benzoyl, and -trityl protected 1,3-propanediols, for example, proceeded smoothly but attempts to brominate the resulting aldehydes led only to decomposition of starting material with no significant amount of bromoaldehyde formation as determined by ^1H NMR.

We next turned our attention to the protected β-aminoaldehyde series. Bromoaldehyde **11** was synthesized in three steps from potassium phthalimide **10** (Scheme 3). Alkylation of **10** with 3-bromopropionaldehyde dimethyl acetal was followed by treatment with acid, which gave the known aldehyde **11**.[7] Bromination with DBBA in CH_3CN gave bromoaldehyde **12** in 60–65% overall unoptimized yield.



Scheme 3. Reagents: (a) 3-bromopropionaldehyde dimethyl acetal, DMF; (b) THF, HCl; (c) DBBA, CH_3CN

A series of nitrogen protected cyclopentylamines was synthesized as a model for the synthesis of Q Base (**1**) (Scheme 4). Several protecting group strategies were examined in order to determine which might permit high yielding bromination of aldehydes. Tosyl and *o*-nosyl groups gave the best results. Cyclopentylamine derivatives **15a** and **15b** were synthesized in five steps, beginning with reductive amination[8] of cyclopentylamine (**13**) and an appropriately functionalized three carbon aldehyde. Installation of the protecting group on nitrogen (Ts or Ns) provided intermediates **14a** and **14b** in 75–85% yield. Further elaboration of **14a** and **14b** was accomplished by removal of the oxygen protecting group, oxidation to the aldehyde, and bromination using DBBA to give bromoaldehydes **15a** and **15b** in 75–85% yield.



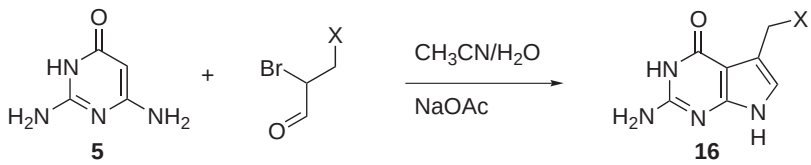
Scheme 4. Reagents: (a) $ROCH_2CH_2CHO$, MeOH, $NaBH_4$; (b) R′Cl, Et_3N, CH_2Cl_2; (c) remove R; (d) TEMPO, KBr, NaOCl, H_2O/CH_2Cl_2; (e) DBBA, CH_3CN

Use of a sulfonamide protecting group on nitrogen was essential for successful bromination of the aldehyde.[9] Other nitrogen protecting groups examined included the BOC, acetyl, and benzoyl groups. β-Aminoalcohols containing these protecting groups could be cleanly oxidized to the corresponding aldehydes. However, upon treatment of the aldehyde with DBBA only decomposition of the starting aldehyde was observed. In each case no appreciable amount of the desired β-amino-α-bromoaldehydes was observed by ^1H NMR.

With the determination of most suitable protecting groups and synthesis of a series of bromoaldehydes achieved, the cyclocondensation of these substrates was examined (Table 1). We were gratified to achieve in moderate to good yields the synthesis of a series of pyrrolo[2,3-*d*]pyrimidines **16** via cyclocondensation of these bromoaldehyde substrates (**9a**–**b**, **12**, **15a**–**b**). Conditions examined were the same as those reported in the synthesis of **4**.[2] A mixture of bromoaldehyde, 2,4-diamino-6-hydroxypyrimidine, and NaOAc were warmed in $MeCN/H_2O$ for 2–3 h, after which the precipitated product was filtered.[10] Yields shown in Table 1 represent isolated yields and are unoptimized. The generality of this reaction has thus been greatly enhanced from that previously reported.

In conclusion, we have successfully synthesized a series of pyrrolo[2,3-*d*]pyrimidines from β-amino- and β-alkoxy-α-bromoaldehydes. The key condensation step as well as the bromination of the aldehydes was sensitive to the protecting group employed. Utility of this new methodology is currently being demonstrated by the total synthesis of Q Base (**1**). Details of this work will be reported elsewhere.

Table 1



α-Bromoaldehyde	Product	Yield (%)
9a, X = OBn	**16a**	80
9b, X = OTBDPS	**16b**	50
12, X = N-phth	**16c**	75
15a, X = N(cyclopentyl)Ts	**16d**	45
15b, X = N(cyclopentyl)Ns	**16e**	68

Acknowledgements

The authors would like to thank Michael E. Kobierski for valuable discussions and suggestions concerning the cyclocondensation reactions.

References

1. Some selected references: Kondo, T.; Oghi, T.; Goto, T. *Chem. Lett*. **1983**, 419–422. Kondo, T.; Okamoto, K.; Oghi, T.; Goto, T. *Tetrahedron* **1986**, *42*, 207–213. Kondo, T.; Okamoto, K.; Yamamoto, M.; Goto, T. *Tetrahedron* **1986**, *42*, 199–206. Ramasamy, K.; Joshi, R. V.; Robins, R.; Revankar, G. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2375–2384.
2. Barnett, C. J.; Wilson, T, M.; Kobierski, M. E. *Org. Process Res. Dev*. **1999**, *3*, 184–188. Alimta™, the disodium salt of **1**, is currently in Phase III clinical trials for treatment of mesothelioma.
3. (a) Secrist, J. A.; Liu, P. S. *J. Org. Chem*. **1978**, *43*, 3937–3941. (b) Noell, C. W.; Robins, R. K. *J. Heterocyclic Chem*. **1964**, *1*, 34–41.
4. All new compounds were characterized by ^{1}H and ^{13}C NMR, IR and HRMS where possible. Bromoaldehydes, however, were unstable and used as obtained from the bromination reactions after analysis by ^{1}H NMR.
5. Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth*. **1990**, *69*, 212–219.
6. Grundke, G.; Keese, K.; Rimpler, M. *Chem. Ber*. **1985**, *118*, 4288–4291.
7. Baxter, A. D.; Montana, J.; Owen, D. A. PCT Int. Appl. 9635714, 1996; *Chem. Abstr*. **1997**, *126*, 60363.
8. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem*. **1996**, *61*, 3849–3862.
9. Triflyl and trifluoroacetyl protected β-aminoaldehydes also gave the desired α-bromoaldehydes. However, cyclization reactions performed with these substrates gave only trace amounts of the desired pyrrolopyrimidine. The reason for this result is not immediately clear but could be related to the stability of the β-amino-α-bromoaldehydes under the cyclization conditions, with decomposition of the bromide occurring before significant product formation was achieved.
10. A representative procedure is as follows: Bromide **9a** (22.7 mmol), 2,4-diamino-6-hydroxyprimidine (22.8 mmol), and sodium acetate (47.1 mmol) were combined in 100 mL of 1:1 acetonitrile/water. The mixture was warmed to 40°C, dissolving all solids within 5–10 min. After heating for 1–2 h the product (**16a**) precipitated from the reaction mixture. After continued stirring for 1–2 h to ensure complete reaction, the mixture was cooled to room temperature and the product isolated by filtration. The filtrate was concentrated to approximately one-half volume and filtration yielded a second batch of product for a total of 5.50 g (20.3 mmol) **16a**. Spectroscopic data

for **16a**: ^{1}H NMR (DMSO-d_6) δ 4.51(s, 2 H), 4.57 (s, 2 H), 6.07 (s, 2 H), 6.60 (s, 1 H), 7.23–7.33 (m, 5 H), 10.29 (s, 1 H), 10.90 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 64.6, 70.9, 98.5, 115.0, 115.7, 127.1, 127.4, 128.0, 138.9, 151.2, 152.3, 159.0. IR (cm^{-1}) (KBr) 3324, 3158, 2860, 1632, 1350. HRMS calculated for $C_{14}H_{14}N_4O_2$+Na 293.1014, found 293.1013. In the case of **16b** separation of the reaction solution into two phases was observed but little solid precipitated. Isolation of the product was accomplished by repeated extraction of the reaction mixture with CH_2Cl_2 or $CHCl_3$, drying with $MgSO_4$, and concentration to give the product as a pink solid.