Tetrahedron Letters 49 (2008) 4633–4635

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 8-substituted xanthines via 5,6-diaminouracils: an efficient route to A_{2A} adenosine receptor antagonists

Ma Dong [a], Mikhail Sitkovsky [b], Amy E. Kallmerten [a], Graham B. Jones [a,*]

[a] Bioorganic and Medicinal Chemistry Laboratories, Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115, United States
[b] New England Inflammation and Tissue Protection Institute, Northeastern University, Boston, MA 02115, United States

ARTICLE INFO

Article history:
Received 16 April 2008
Revised 12 May 2008
Accepted 14 May 2008
Available online 20 May 2008

Keywords:
Xanthine
(Bromodimethyl)sulfonium bromide
Adenosine antagonist
Diaminouracils

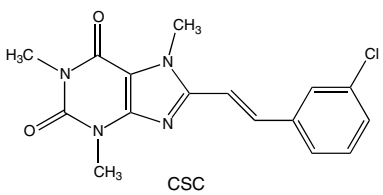
ABSTRACT

A one-pot route to 8-substituted xanthines has been developed from 5,6-diaminouracils and carboxaldehydes. The process, promoted by (bromodimethyl)sulfonium bromide, is mild and efficient and eliminates the need for external oxidants. Yields are good and the process is applicable to a range of substrates including a family of A_{2A} adenosine receptor antagonists. Preparation of a new analog of the antagonist KW-6002 is presented, and in situ bromination of aryl substituted products demonstrated.

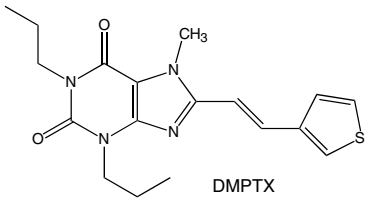
1. Introduction

A_{2A} Adenosine receptor antagonists have become major targets in CNS drug discovery due to pathway interactions between A_{2A} and D_2 dopamine receptors.[1] A number of lead compounds have emerged based on the xanthine skeleton, including the chlorostyryl caffeine CSC,[2] the thienylated xanthine DMPTX,[3] and the dimethoxystyryl xanthine KW-6002.[4] The latter, now referred to as istradefylline, is a clinical candidate for Parkinson's disease based on promising results obtained with co-administration of levodopa.[5] A variety of annulation strategies have been applied to the construction of the xanthine nucleus **1**, most commonly via disconnection to the corresponding amino-acylaminouracil **2**,[6] or closure of the 6-amino-5-iminouracils **3**, typically utilizing oxidative methods (Scheme 1).[7]

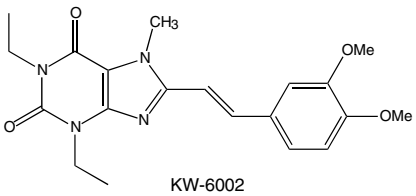
We became interested in the prospect of developing a one-pot route to xanthines through direct coupling of the readily available 5,6 diaminouracils **4** and corresponding carboxaldehydes, and began to investigate coupling parameters. A direct route has been reported, but involves forcing conditions.[8] A variety of reagents



CSC



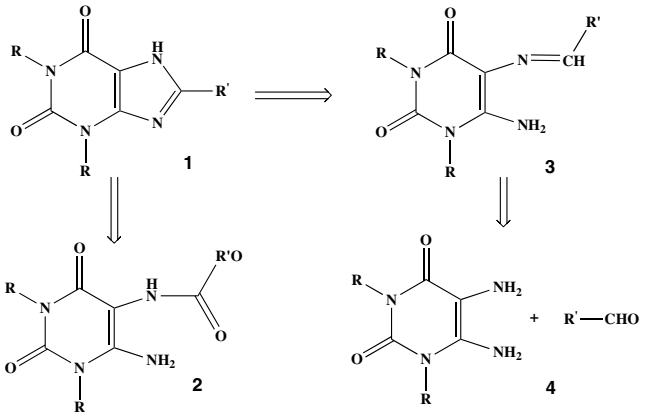
DMPTX



KW-6002

* Corresponding author. Tel.: +1 617 373 8619; fax: +1 617 373 8795.
E-mail addresses: gr.jones@neu.edu, grjones@lynx.neu.edu (G. B. Jones).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.05.071

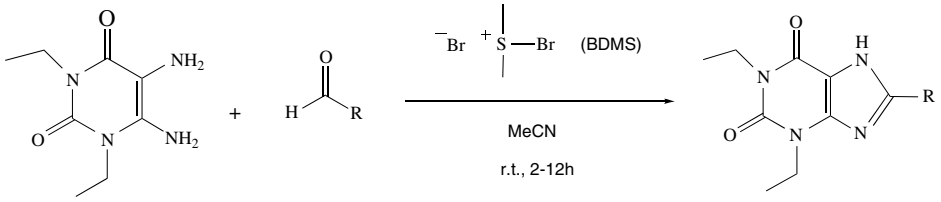


Scheme 1. Retrosynthetic approaches to 5,6-xanthines.

have been successfully used to effect dehydrative elimination from intermediate iminium ions, among them (bromodimethyl)sulfonium bromide (BDMS) is particularly effective.[9] Routine treatment of **4** (R = Et) with benzaldehyde and 0.5 equiv BDMS gave appreciable conversion to product **1** (Scheme 2 and Table 1). The process proved amenable to a wide variety of medicinally relevant substrates (Table 1), and in all cases yields are good to excellent and purification of products is trivial.[10]

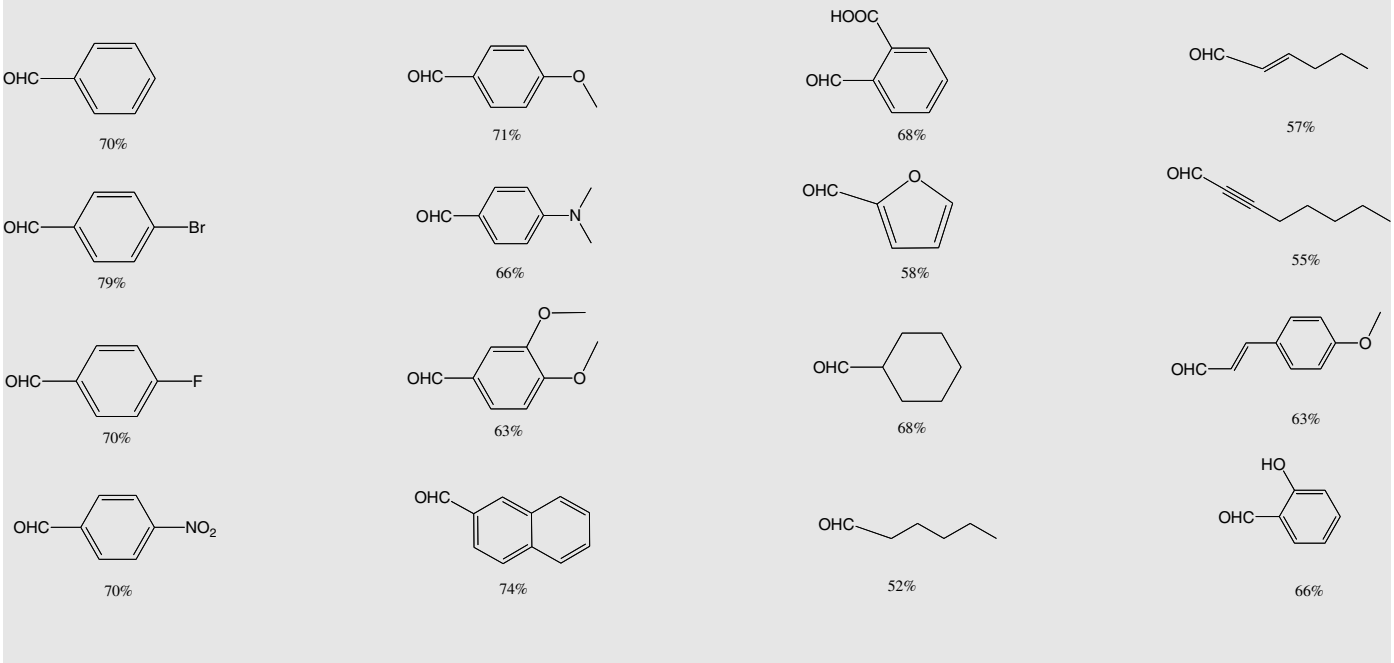
In order to demonstrate the effectiveness of our approach, we conducted comparative synthesis of the KW-6002 analog **9** (Scheme 3). This agent is a lead compound in our studies of the A_{2A} pathway, and it is available routinely from precursor **6**. As can be easily seen the direct route is superior, and now opens the prospect of targeted library design for this class.[11] In an effort to extend the synthetic versatility of the process, we have also investigated the potential to effect in situ bromination of the aryl xanthine substituent. Mild bromination is observed on extended exposure of products for example, **9** to BDMS. Using 1.6 equiv of the reagent (0.5 equiv for 4 h then additional 1.1 equiv for 10 h) in situ bromination was effected, in the case of **6** and *p*-methoxybenzaldehyde, giving bromoarene **11** in good yield, and in the case of *o*-salicaldehyde, bromophenol **10** together with traces of the *o*-product (Scheme 4). Finally, preliminary experiments have been initiated to expedite this (mild) process using microwave heating. In an initial example, 4-bromobenzaldehyde reacts with **6** (MeCN) under microwave irradiation (CEM Discover, 150W, 110 °C, 100 psi) to produce the corresponding xanthine in 72% yield *within 30 min*. This result bodes well for the application of the method for the rapid production of libraries of xanthine derivatives under automated conditions.

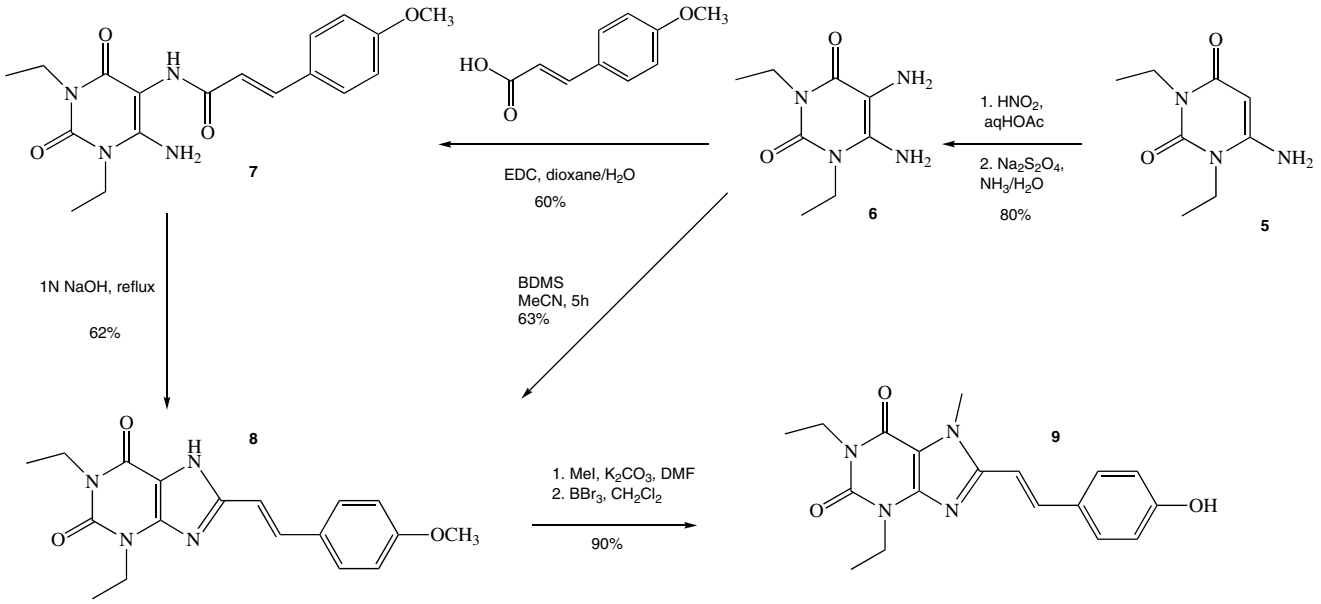
In summary, a direct route to the xanthine class of adenosine receptor antagonists has been developed. The process is efficient, scalable, and can be applied to versatile and diverse library construction. In the case of aryl aldehyde substrates tandem in situ



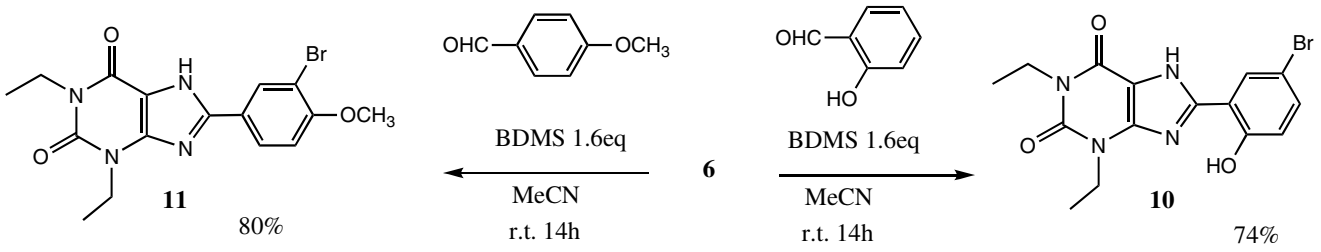
Scheme 2. (Bromodimethyl)sulfonium bromide route to xanthines.

Table 1
Carboxaldehyde substrates for in situ xanthine synthesis using 5,6-diaminopurines





Scheme 3. Synthesis of KW-6002 antagonist.



Scheme 4. In situ ring closure-tandem bromination sequence.

bromination of the products is an effective adaptation of the process, and promises to extend the versatility in the form of heavily substituted xanthine derivatives.[12]

Experimental procedure: 8-(4-Bromo-phenyl)-1,3-diethyl-3,4,5,7-tetrahydro-purine-2,6-dione.

Conventional thermolysis: (Bromodimethyl) sulfonium bromide (0.055 g, 0.25 mmol) was added to a mixture of 4-bromobenzaldehyde (0.092 g, 0.5 mmol), 1,3-diethyl-5,6-aminouracil (0.1 g, 0.5 mmol), and anhydrous acetonitrile (5 ml) and the mixture was stirred at room temperature. After 12 h the resulting precipitate was filtered, washed with ethyl acetate (10 ml), methanol (5 ml), and then recrystallized (EtOAc) to yield the title compound (0.143 g, 79%) as a yellow solid mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13 (t, J = 7 Hz, 3H), 1.26 (t, J = 7 Hz, 3H), 3.94 (q, J = 7 Hz, 2H), 4.08 (q, J = 7 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H, ArH), 8.05 (d, J = 8.5 Hz, 2H, ArH); HRMS (ESI), m/z (M+H)$^+$: calcd 363.0433, obs. 363.0441.

Microwave thermolysis: (Bromodimethyl) sulfonium bromide (0.010 g, 0.045 mmol) was added to a mixture of 4-bromobenzaldehyde (0.0466 g, 0.25 mmol), 1,3-diethyl-5,6-aminouracil (0.4955 g, 0.25 mmol), and anhydrous acetonitrile (500 μl) in a 14 × 86 mm (o.d.) glass microwave tube. The tube was capped with a CEM Corp. PL cap, the atmosphere was flushed with argon gas, and then the tube was placed in the cavity of a CEM Discover® Lab Mate reactor. The solution was subjected to microwave irradiation while stirring, the temperature was brought to 110 °C over 15 min. and then held for 10 min (150 W, 100 psi). The resulting precipitate was filtered, washed with ethyl acetate (5 ml) and methanol (2.5 ml), and then recrystallized (EtOAc) to yield the title compound (0.065 g, 72%) as a yellow solid spectroscopically identical to an authentic sample.

References and notes

1. Cacciari, B.; Pastorin, G.; Spalluto, G. *Curr. Top. Med. Chem.* **2003**, *3*, 403.
2. Jacobson, K. A.; Gallo-Rodriguez, C.; Melman, N.; Fischer, B.; Maillard, M.; van Bergen, A.; van Galen, P. J. M.; Karton, Y. J. *J. Med. Chem.* **1993**, *36*, 1333.
3. Del Giudice, M. R.; Borioni, A.; Mustazza, C.; Gatta, F.; Dionisotti, S.; Zocchi, C.; Ongini, E. *Eur. J. Med. Chem.* **1996**, *31*, 59.
4. Knutsen, L. J.; Weiss, S. M. *Curr. Opin. Invest. Drugs* **2001**, *2*, 668.
5. Bara-Jimenez, W.; Sherzai, A.; Dimitrova, T.; Favit, A.; Bibbiani, F.; Gillespie, M.; Morris, M. J.; Mouradian, M. M.; Chase, T. N. *Neurology* **2003**, *61*, 293; Koga, K.; Kurokawa, M.; Ochi, M.; Nakamura, J.; Kuwana, Y. *Eur. J. Pharmacol.* **2000**, *408*, 249.
6. Perumattam *J. Synth. Commun.* **1989**, *19*, 3367.
7. de Araujo, A. D.; Bacher, E.; Joachim Demnitz, F. W.; Santos, D. A. *Heterocycles* **1999**, *51*, 29.
8. Jerchel, D.; Kracht, M.; Krucker, K. *Liebigs Ann. Chem.* **1954**, *590*, 232.
9. Das, B.; Holla, H.; Srinivas, Y. *Tetrahedron Lett.* **2007**, *48*, 61; Choudhury, L. H. *Synlett* **2006**, 1619; Khan, A. T.; Ashif, M.; Goswami, P.; Choudhury, L. H. *J. Org. Chem.* **2006**, *71*, 8961; Das, B.; Ramu, R.; Ravikanth, B.; Reddy, K. R. *Synthesis* **2006**, 1419.
10. All new compounds were fully characterized by appropriate spectroscopic and analytical techniques.
11. Ma, D.; Sitkovsky, M.; Jones, G. B., in preparation.

12. We acknowledge financial support for this work from the PRF (33920-AC1) and NIH (RO1GM57123).