Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2121–2123

TETRAHEDRON LETTERS

Fast and highly efficient one-pot synthesis of 9-deazaxanthines

Angela Stefanachi,† Francesco Leonetti,† Anna Cappa and Angelo Carotti*

Dipartimento Farmaco-chimico, University of Bari, via Orabona 4, I-70125 Bari, Italy

Received 6 December 2002; revised 16 January 2003; accepted 16 January 2003

Abstract—$SnCl_2$ enables a direct, high-yield conversion of 5-nitro-1,3-dialkyl-6-styryl(furyl-, thienyl-vinyl)-uracils to 8-substituted-9-deazaxanthines under very mild experimental conditions. The method has a general applicability and it is compatible with the reactivity of the most common organic functional groups. In slightly experimental different conditions, it allows a high-yield and fast (<5 min) preparation of pure 7-*N*-hydroxy-9-deazaxanthines.

Recent studies indicate that adenosine receptor ligands acting selectively on one of the four distinct receptor subtypes (A_1, A_{2A}, A_{2B} and A_3), may be attractive therapeutics in many pathophysiological conditions.[1–4]

A huge number of adenosine receptor agonists and antagonists have been synthesized and some of them proved to be highly potent and subtype selective ligands.[5–9] Along with tricyclic condensed heterocycles,[5–7] the most studied compounds are by far xanthine derivatives, whereas 9-deazaxanthines[10] and their 7 and 8-substituted derivatives,[11,12] have received much less attention.

Despite their potential biological interest, the published syntheses of these compounds are unsatisfactory in terms of yields, reaction time, experimental conditions and work up.

Several approaches have been proposed so far for the preparation of substituted 9-deazaxanthines.[11,13–20] The most widely used have been reported by Taylor[17] and Nishigaki.[18] In Taylor's scheme the cyclization of the key 5-nitro-1,3-dialkyl-6-styryl-uracil intermediate is obtained with neat triethyl phosphite[17,19] at high temperature, whereas in Nishigaki's approach formic acid and sodium dithionite[18] have been used to accomplish the same reaction. Both schemes showed two main drawbacks: the yields of the cyclization reaction are low (11–65%) and the experimental conditions used are very harsh and often incompatible with the chemical stability of many organic functional groups. Hirota and co-workers[20] reported an alternative synthetic protocol to prepare 9-deazaxathines. Starting from 1,3,6-trimethyl-5-nitro uracil, the final 9-deazaxanthines have been obtained through an additional chemical step, compared to the above cited methods. Moreover, such a protocol, requiring the use of refluxing ethanolic solution of 0.1 M KOH, presents a limited applicability and it is unsuited for the preparation of chemical libraries based on solid phase synthetic methodologies.

Herein, we report a new, straightforward and high yield synthesis of 9-deazaxanthines that overcomes most of the drawbacks exhibited by previous procedures.

The target compounds were prepared in two simple steps starting from a suitable 1,3-dialkyl-6-methyl-5-nitrouracil[11,12,17–19] that was condensed with appropriate aldehydes in refluxing EtOH in the presence of piperidine, according to previously reported methods.[10,17]

Looking for a valuable procedure for the reductive cyclization of uracil intermediates **I** (Scheme 1) to 9-deazaxanthines, we planned to reduce first the nitro group of the uracil moiety operating in mild conditions and to perform then the subsequent cyclization reaction. Since previous literature procedures reported that the use of Pd/C, besides the reduction of the nitro group afforded the undesired hydrogenation of the styryl double bond,[19] we decided to use a reducing Lewis acid to carry out smoothly the reduction of the nitro group. $ZnCl_2$ gave no reduction of nitrouracils **I** at room temperature. In contrast, $SnCl_2$ in DMF not only gave the reduction of the nitro group but efficiently catalysed the subsequent cyclization affording the corresponding 7-*N*-hydroxy-9-deazaxanthine derivatives **1**–**13** (Scheme 1).[21]

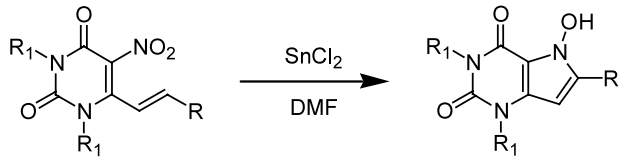
* Corresponding author. Tel.: ++39-080-5442782; fax: ++39-080-5442230; e-mail: carotti@farmchim.uniba.it

† These authors contributed equally to this work.

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00173-4

Two main goals were reached in this way. First the yield of the reaction was very high (from 95 to 99%) and the compounds purity, as detected by NMR analyses, was also very high. Second, the workup of the reaction was very easy: the product was simply recovered by filtering the solid obtained upon addition of water to the reaction mixture.

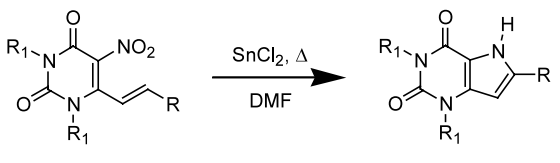
The reaction was carried out also in different solvents to study their influence in the reduction and cyclization processes. In DMSO the product was obtained in yields and times comparable with DMF, while in dioxane no detectable trace of the desired product was found.



I **1-13**

Cpd	R_1	R
1	$CH_2CH_2CH_3$	*p*-$CH_3C_6H_4$
2	CH_3	*p*-$CH_3C_6H_4$
3	$CH_2CH_2CH_3$	C_6H_5
4	”	*o*-$CH_3C_6H_4$
5	”	*p*-$N(CH_3)_2C_6H_4$
6	”	*p*-$OCH_3C_6H_4$
7	”	*p*-$(NHCOCH_3)C_6H_4$
8	”	*o*-BrC_6H_4
9	”	*o*-FC_6H_4
10	”	*p*-$CH(CH_3)_2C_6H_4$
11	”	2-Thienyl
12	”	2-Furyl
13	”	*p*-$COCH_3C_6H_4$

Scheme 1. Conversion of nitrouracil intermediates **I** into the corresponding 7-*N*-hydroxy-9-deazaxanthines **1–13**



I **14-26**

Scheme 2. One-pot synthesis of 9-deazaxanthines **14–26**. R_1 and R as in the corresponding sequence of 7-*N*-hydroxy derivatives **1–13→14–26**.

7-*N*-Hydroxy-9-deazaxanthines present, in comparison with classical xanthines, an interesting chemical structure showing some peculiar pharmacophoric elements for a good affinity (and possibly selectivity) towards adenosine receptors. In addition, compared to simple 9-deazaxanthines they should posses more favorable pharmacokinetic profile in terms of water solubility, lipophilicity and bioavailability. To the best of our knowledge no systematic work has been published on the structure-affinity relationships of 7-*N*-hydroxy-9-deazaxanthines towards the four main classes of adenosine receptor subtypes. We are presently working on this subject.

Starting from our encouraging results achieved in the synthesis of 7-*N*-hydroxy-9-deazaxanthines, we decided to evaluate the possibility to obtain easily also 9-deazaxanthines in a way chemically amenable to the preparation of chemical libraries of biological interest. As suggested by Hirota,[20] we tried to deoxygenate *N*-hydroxy-9-deazaxanthines **1–13** by heating in DMF. Unfortunately, we failed to obtain the desired compounds in good yields and purity as claimed in that previous work.[20]

We tried next to accomplish the synthesis of these compounds in a one-pot way starting from 1,3-dialkyl-5-nitro-uracils. Satisfactorily indeed, by reacting uracil intermediates **I** with $SnCl_2$ in refluxing DMF for 2 h, the corresponding 9-deazaxanthines **14–26** were obtained in high yields (from 95 to 99%) and purity (Scheme 2).[22]

In summary the methods described allow the synthesis of 8-substituted-9-deazaxanthines and of the corresponding 7-*N*-hydroxy derivatives in high yields and in mild experimental conditions. As for the latter, the reaction time (<5 min) and easily available reagents used in the synthesis represent two important advantages of our protocol compared with other published ones. Furthermore, the approach proved to be of general applicability, allowing us to accomplish the synthesis of a large variety of 7-*N*-hydroxy-8-substituted-9-deazaxantines starting from aryl and heteroaryl aldehydes. Notably, good yields were obtained with benzaldehydes bearing substituents with quite different stereoelectronic properties. As for the synthesis of 8-substituted-9-deazaxanthines, it must be stressed that it can be carried out by a one-pot procedure and in almost quantitative yields.

Finally, preliminary data indicates that our methods are fully compatible with a synthesis on solid phase, and this may allow the preparation of 7-*N*-hydroxy-8-substituted-9-deazaxanthine and 8-substituted-9-deazaxanthine libraries of biological interest, expanding the scope and the utility of our synthetic procedures. Full details of the preparation of both 7-*N*-hydroxy-9-deazaxanthines and 9-deazaxanthines libraries will be published in a forthcoming paper.

Acknowledgements

The authors gratefully acknowledge the financial support of the University of Bari (Italy), the Italian Ministry for Education, Universities and Research (MIUR, Rome, Italy). A.S. thanks the European Community for partially granting her Ph.D. fellowship.

References

1. Hess, S. *Expert Opin. Ther. Pat.* **2001**, *11*, 1–29.
2. Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Meringhi, S.; Verani, K.; Borea, P. A.; Spalluto, G. *Med. Res. Rev.* **2000**, *20*, 103–128.
3. Baraldi, P. G.; Borea, P. A. *Trends Pharmacol. Sci.* **2000**, *21*, 456–459.
4. Müller, C. E. *Drugs of the Future* **2000**, *25*, 1043–1052.
5. Baraldi, P. G.; Cacciari, B.; Moro, S.; Spalluto, G.; Pastorin, G.; Da Ros, T.; Klotz, K. N.; Varani, K.; Gessi, S.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 770–780.
6. Maconi, A.; Pastorin, G.; Da Ros, T.; Spalluto, G.; Gao, Z. G.; Jacobson, K. A.; Baraldi, P. G.; Varani, K.; Moro, S.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 3579–3582.
7. Ongini, E.; Monopoli, A.; Cacciari, B.; Baraldi, P. G. *Farmaco* **2001**, *56*, 87–90.
8. Jacobson, K. A.; Al Ijzerman, P.; Linden, J. *Drug Dev. Res.* **1999**, *47*, 45–53.
9. Müller, C. E. *Farmaco* **2001**, *56*, 77–80.
10. Senda, S.; Hirota, K. *Chem. Pharm. Bull.* **1974**, *22*, 2593–2598.
11. Grahner, B.; Winiwarter, S.; Lanzner, W.; Müller, C. E. *J. Med. Chem.* **1994**, *37*, 1526–1534.
12. Hayallah, A. M.; Sandoval-Ramirez, J.; Reith, U.; Schobert, U.; Preiss, B.; Schumacher, B.; Daly, J. W.; Müller, C. E. *J. Med. Chem.* **2002**, *45*, 1500–1510.
13. Pfleider, W.; Mosthaf, H. *Chem. Ber.* **1957**, *90*, 738–745.
14. Kawahara, N.; Nakajima, T.; Itoh, T.; Ogura, H. *Chem. Pharm. Bull.* **1985**, *33*, 4740–4748.
15. Modnikova, G. A.; Titkova, R. M.; Glushkov, R. G.; Sokolova, A. S.; Silin, V. A.; Chernov, V. A. *Khim. Farm. Zh.* **1988**, *22*, 185–191.
16. Tsupak, E. B.; Tkachenko, Y. N.; Pozharsky, A. F. *Khim. Geter. Soedin.* **1994**, 1242–1248.
17. Taylor, E. C.; Garcia, E. E. *J. Org. Chem.* **1965**, *30*, 655–657.
18. Nishigaki, S.; Kanamori, Y.; Senga, K. *Chem. Pharm. Bull.* **1980**, *28*, 1636–1641.
19. Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.* **1979**, *44*, 3830–3834.
20. Hirota, K.; Sugiyama, T.; Kitade, Y.; Senda, S.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 583–588.
21. *5-Hydroxy-1,3-dipropyl-6-p-tolyl-1,5-dihydro-pyrrolo-[3,2-d] pyrimidine-2,4-dione* **1**. To a solution of 0.50 g (1.5 mmol) of 1,3-dipropyl-5-nitro-(2-*p*-tolyl-vinyl)-1*H*-pyrimidine-2,4-dione in 6 ml of DMF, 2.93 g (15 mmol) of $SnCl_2$ were added portion wise under magnetic stirring. After 5 min, 6 ml of water were added to the reaction mixture to yield a white solid that was filtered and washed with water affording 0.45 g of the desired product **1** (99% yield) mp 233–234°C dec., IR cm^{-1}: 3413, 2963, 1689, 1623, 756; ^1H NMR (DMSO-d_6), δ (ppm), J=Hz: δ: 11.77 (s, 1H, exch. D_2O); 7.68 (d, 2H, J=7.8); 7.27 (d, 2H, J=7.8); 6.37 (s, 1H); 3.90–3.80 (m, 4H); 2.33 (s, 3H); 1.68–1.51 (m, 4H); 0.91–0.78 (m, 6H). MS (ESI), m/z calcd for $C_{19}H_{23}N_3O_3$: 341.2. Found: 340.2 $[M-H]^-$. Anal. calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.52; H, 6.98; N, 12.54.
22. *1,3-Dipropyl-6-p-tolyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione* **14**. To a solution of 0.50 g (1.5 mmol) of 1,3-dipropyl-5-nitro-(2-*p*-tolyl-vinyl)-1*H*-pyrimidine-2,4-dione in 6 ml of DMF, 2.93 g (15 mmol) of $SnCl_2$ were added portion wise under magnetic stirring. The mixture was refluxed for 2 h. After cooling to room temperature, an aqueous solution of HCl 2N (6 ml) was added to the DMF solution. The white precipitate was collected, washed with water and dried under vacuum, to afford 0.43 g of pure **14**. (95% yield) mp >250°C; IR cm^{-1}: 3258 (s), 2964, 1687. ^1H NMR (DMSO-d_6), δ: 12.26 (s, 1H, exch. D_2O); 7.80 (d, 2H, J=8.2); 7.22 (d, 2H, J=8.2); 6.67 (s, 1H); 3.87–3.82 (m, 4H); 2.30 (s, 3H); 1.70–1.51 (m, 4H); 0.92–0.83 (m, 6H). MS (ESI), m/z calcd for $C_{19}H_{23}N_30_2$: 325.2. Found: 324.2 $[M-H]^-$. Anal. calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 69.82; H, 7.48; N, 12.63.