Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *80* (10) 1273–1278 (2015) UDC 547.451.63'454+66.095.253:547.415.1
JSCS–4795 *Original scientific paper*

Alkylating ability of carbohydrate oxetanes: Practical synthesis of bolaform skeleton derivatives

PAVLE A. HADŽIĆ[1]*#, MIRJANA M. POPSAVIN[2#] and SUNČICA Z. BOROZAN[3#]

[1]*Goša Institute, Milana Rakića 35, 11000 Belgrade, Serbia,* [2]*Faculty of Sciences, Department of Chemistry, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia and* [3]*Faculty of Veterinary Medicine, University of Belgrade, Bulevar oslobođenja 18, 11000 Belgrade, Serbia*

(Received 24 February, revised 30 March, accepted 16 April 2015)

Abstract: The alkylating ability of the oxetane ring in the carbohydrate structure was investigated and a flexible method for the construction of a bolaform amphiplile skeleton with xylose as the polar head is proposed. The method is based on oxetane ring opening in the easily accessible 3,5-anhydro-1,2-*O*-cyclohexylidenexylofuranose (**1**). One-step nitrogen alkylation in terminal diamines with **1** gave the basic cationic bolaform skeleton with xylose as potential polar head and a deliberately chosen length of the non-polar spacer. Under similar experimental conditions, but with an appropriate mole ratio of the alkylating agent, the alkylation reaction provide for selective monoalkylation of the diamines. Successful alkylation in the xanthine series (theophylline) was also achieved with **1**, giving a new 5-deoxy-5-(1,2,3,6-tetrahydro-1,3-dimethyl--2,6-dioxo-7*H*-purin-7-yl)-*α*-D-xylofuranose derivative.

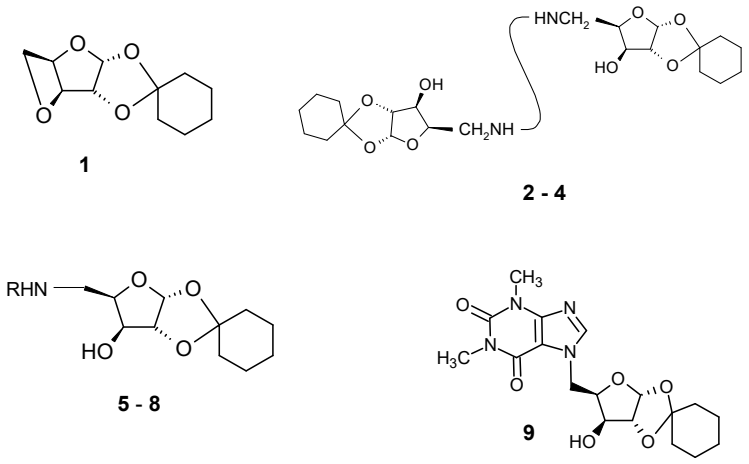
Keywords: bolaform skeleton; oxetane ring; alkylation; ring opening.

INTRODUCTION

Oxiranes and oxetanes, as highly strained heterocycles, are archetypical alkylating agents. Oxetanes are widely used in organic syntheses and are considered to be less carcinogenic and lack genotoxic capacity compared to epoxides and *β*-lactones.[1] The alkylating potential of the oxetane ring is a consequence of its ring strain, which was determined to be 106 kJ mol^{-1}, a value close to that of oxirane (112 kJ mol^{-1}).[2] However, the ring-opening reactions of oxetanes usually require powerful acid catalysts, or other specific catalysts providing for particular synthetic features.[3] The oxetane ring is for steric reasons rarely encountered in carbohydrates. When present, it frequently possesses interesting pharmaceutical properties and offers numerous possibilities for chemical transformations.[4] In

* Corresponding author. E-mail: pavle.hadzic@institutgosa.rs
# Serbian Chemical Society member.
doi: 10.2298/JSC150224033H

this report, the high alkylation potential of the oxetane ring in the easily accessible 3,5-anhydro-1,2-*O*-cyclohexylidene-*α*-D-xylofuranose[5] (**1**) toward the nitrogen in aliphatic diamines and in xanthine series (Scheme 1) is presented.



Scheme 1. Alkylation ability of 3,5-anhydro-1,2-*O*-cyclohexylidene-*α*-D-xylofuranose (**1**). Its use for basic bolaform skeleton synthesis (**2**–**4**, the graphical curve represent the hydrophobic spacer), selective monoalkylation of diamines (**5**–**8**), and alkylation in the xanthine series **9**.

From the practical standpoint, the alkylation of aliphatic diamines leads to one-step construction of basic cationic bolaform detergent skeleton, while in the xanthine series, a new type of 7-xylose substituted theophylline derivative was obtained under mild and operationally simple reaction conditions. All alkylations were performed under solvent-free reaction conditions, additionally illustrating alkylation potential of the carbohydrate oxetane ring.

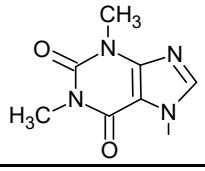
EXPERIMENTAL

Thermal solid-state alkylation reactions are classical examples among solvent-free reactions, and not a new concept. In particular, the *N*-alkylation of phthalimides and heterocyclic systems, such as carbazole with alkyl halides, are known examples.[6] Unexpectedly, the high inclination of the oxetane structure in **1** toward nitrogen alkylation in this investigation enabled the realization of solvent-free reactions, giving benefits in product isolation procedures.

General reaction conditions. **1** and a diamine (1,2-diaminoethane, 1,4-diaminobutane, piperazine, *N*-methylpiperazine or theophylline from commercial suppliers and without further purification) were mixed in the appropriate mole ratio for alkylation of both nitrogen atoms, or selective alkylation of a single nitrogen in diamine compounds, with addition of water as catalyst. The reaction mixture was held in a hermetically sealed stainless steel reaction flask at temperature 110–130 °C for 12 h with occasional mixing. The products were isolated either as free bases, hydrochloride or oxalate salts (Table I).

Detailed experimental synthetic procedures and analytical data confirming the structures of the newly synthesized compounds are given in Supplementary material to this paper.

TABLE I. Products of alkylation of diamines and alkylation in xanthine series with a carbohydrate oxetane ring

Cmpd.	Alkylation position	Compound name
2	–HNCH$_2$CH$_2$NH–	5,5′-(1,2-Ethanediyldiimino)bis[1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose]
3	–HNCH$_2$(CH$_2$)$_2$CH$_2$NH–	5,5′-(1,4-Butnediyldiimino)bis[1,2-*O*-cyclohexylidene-5-deoxy-*α*-D-xylofuranose]
4	–N(CH$_2$CH$_2$)$_2$N–	5,5′-(1,4-Piperazinediyl)bis[1,2-*O*-cyclohexylidene--5-deoxy-*α*-D-xylofuranose]
5	H$_2$NCH$_2$CH$_2$NH–	5-((2-Aminoethyl)amino)-1,2-*O*-cyclohexylidene-5--deoxy-*α*-D-xylofuranose dioxalate
6	H$_2$NCH$_2$(CH$_2$)$_2$CH$_2$NH–	5-((4-Aminobutyl)amino)-1,2-*O*-cyclohexylidene--5-deoxy-*α*-D-xylofuranose dioxalate
7	HN(CH$_2$CH$_2$)$_2$N–	1,2-*O*-Cyclohexylidene-5-deoxy-5-(1-piperazinyl)--*α*-D-xylofuranose
8	CH$_3$N(CH$_2$CH$_2$)$_2$N–	1,2-*O*-Cyclohexylidene-5-deoxy-5-(4-methyl-piperazin-1-yl)-*α*-D-xylofuranose
9		1,2-*O*-Cyclohexylidene-5-deoxy-5-(1,2,3,6-tetra-hydro-1,3-dimethyl-2,6-dioxo-7*H*-purin-7-yl)--*α*-D-xylofuranose

RESULTS AND DISCUSSION

Amphiphiles with two polar heads connected by a hydrophobic spacer (bola-amphiphiles) have attracted ever-increasing attention since similar structures were found in some archaebacteria cell membranes that sustain harsh environments, high salt concentrations and elevated ambient temperatures.[7] A range of bolaamphiphiles have been synthesized so far, either to imitate components of a natural cell structure, or to investigate their lipophilic–hydrophilic properties.[8] In attempts to realize specific properties, a variety of bolaform surfactants with a carbohydrate as the hydrophilic moiety have also been considered. Carbohydrate-based detergents are recognized, and convenient syntheses of compounds with variable lipophilic–hydrophilic balance based on xylose, in particular, as the polar head, or from other carbohydrate but with preserved *xylo*-configuration, are known.[9] Specifically, syntheses of bolaamphiphiles based on xylose are also described.[10] The authors affirmed earlier findings[11] on the significant impact of the length of the hydrophobic linkage (spacer) on the aggregation properties of bolaamphiphiles with sugar heads. Consequently, a simple synthetic method for the construction of the basic bolaform skeleton with xylose-based hydrophilic heads and deliberately preferred hydrophobic spacer length is intriguing. Herein, the alkylation ability of the oxetane ring in **1** toward terminal diamino compounds as a simple, practical and flexible method for the construction of the

cationic bolaform skeleton, or selective monoalkylation of aliphatic diamines and natural products are reported.

The opening of oxetane ring in 3,5-anhydro-derivatives of suitably protected[12] xylofuranose derivatives with aqueous ammonia[13] and amines[14] was investigated earlier. The reaction leads to one-step nitrogen alkylation. Under simple reaction conditions, the one-step dialkylation of *α*,*ω*-diamines of the general formula $H_2N–(CH_2)_n–NH_2$, or cyclic diamines (piperazine) with **1** lead smoothly to the basic bolaform skeleton **2**–**4**.

For further demonstration of akylating ability of carbohydrate oxetane **1**, the alkylation of diamines accomplished under essentially the same experimental conditions but with a different mole ratio of **1** toward the diamines resulted in selective monoalkylation of diamines **5**–**8**.

Frequently, prior activation of oxirane and oxetane rings is a necessary step in alkylation reactions and different catalysts are used for this purpose. Protonation of oxygen in oxetane ring significantly eases nucleophillic attack of nucleophillic species present and hence, the ring opening is facilitated by acids. As demonstrated earlier, water could also play the role of the catalyst,[15] and the present experiments afforded further experimental evidence on the subject. Particularly, water was found to be an appropriate catalyst for the alkylation tendency of **1**, owing to the expected significant strain energy release in the system of three condensed small rings in **1**.

Our previous investigations of the reactivity of the 3,5-anhydro ring in **1** towards selected nucleophiles demonstrated pronounced regioselectivity of the oxetane ring-opening process.[16] Again, it was found to be the case in the reaction of **1** with diamines. The only isolable products originated from the regioselective nucleophillic attack of nitrogen on the terminal carbon atom of xylofuranose (C-5). No detectable products of inversion at the C-3 carbon of starting **1** were found because of the hypothetic nucleophilic attack at C-3, *i.e.*, the *xylo*- configuration was preserved throughout.

To prove further the alkylating ability of the oxetane ring in the carbohydrate structure **1**, the alkylation of some natural products was considered. Many nitrogen-containing heterocycles demonstrate pronounced pharmaceutical activity. Among them, xanthine and substituted xanthine derivatives are an important class of compounds with a well-known spectrum of activity.[17] In particular, theophylline pentosides are the subject of intensive synthetic interest because of their structural resemblance to nucleosides. Theophylline-7-riboside was evaluated as a partial agonist for ubiquitous adenosine receptors[18] with the conclusion that it has characteristics between full agonists and full antagonists (xanthines). Following thee findings, further attempts were made to synthesize different 7-substituted xanthine derivatives with a modified ribose rest.[19] To the best of our knowledge, among other theophylline 7-pentofuranosides, arabinoside and xyloside are also known.[20]

In further experiments, it was found that alkylating potential of the oxetane ring in **1** could be used for the facile synthesis of a 7-xylose substituted theophylline derivative, however with a new pentose substitution pattern. Namely, all previously synthesized pentose derivatives were connected to theophylline through C1 xylose carbon.

Thus, the alkylation of theophylline with **1** smoothly gave 5-deoxy-5--(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purin-7-yl)-*α*-D-xylofuranose derivative **9**. However, theophylline did not react under the standard procedure (heating a mixture of diamine, oxetane **1** and water as catalyst), but further activation of the 7′-theophylline position was necessary, and hence the potassium salt of theophylline was prepared.[21]

CONCLUSIONS

The use of protected 3,5-anhydroxylofuranose as alkylating agent represent a new practical and adaptive method to reach the basic cationic bolaform skeleton with xylose-based polar heads and variable lengths of non polar spacer. The described one-step synthetic procedure give products that could be easily converted into carbohydrate polar heads with retained *xylo*-configuration, with deliberately chosen hydrophobic spacer length and in acceptable isolated yields. In the xanthine series, the alkylation provide for new 7-xylose substituted theophylline with the substitution pattern reversed to that previously described.

SUPPLEMENTARY MATERIAL

Description of specific synthesis methods and the analytical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

И З В О Д

АЛКИЛУЈУЋИ ПОТЕНЦИЈАЛ УГЉЕНОХИДРАТНИХ ОКСЕТАНА: ПРАКТИЧНА СИНТЕЗА ДЕРИВАТА БОЛАФОРМНОГ СКЕЛЕТА

ПАВЛЕ А. ХАЦИЋ[1], МИРЈАНА М. ПОПСАВИН[2] и СУНЧИЦА З. БОРОЗАН[3]

[1]Институт Гоша, Милана Ракића 35, 11000 Београд, [2]Природно–математички факултет, Департман за хемију, Универзитет у Новом Саду, Трг Д. Обрадовића 3, 21000 Нови Сад и [3]Факултет ветеринарске медицине, Универзитет у Београду, Булевар ослобођења 18, 11000 Београд

Истражена је алкилујућа способност оксетанског прстена у структури угљених хидрата и предложена је флексибилна метода за синтезу скелета болаформних амфифила са ксилозом као поларном главом. Метода је заснована на реакцији отварања оксетанског прстена код лако достуне 3,5-анхидро-1,2-*O*-циклохексилиден ксилофуранозе (**1**). Алкиловање на атому азота код терминалних диамина са **1** даје основни болаформни скелет са заштићеном ксилозом као потенцијалном хидрофилном главом и по вољи изабраном дужином хидрофобног тела. У сличним реакционим условима, али са другачијим одговарајућим молским односом алкилујућег агенса, остварено је селективно моноалкиловање диамина. Такође, остварено је успешно алкиловање у структури ксантина, при чему је добијен раније неописани дериват ксантина 1,2-*O*-циклохекси-

лиден-5-деокси-5-(1,2,3,6-тетрахидро-1,3-диметил-2,6-диоксо-7*H*-пурин-7-ил)-*α*-D-ксилофураноза.

(Примљено 24. фебруара, ревидирано 30. марта, прихваћено 16. априла 2015)

REFERENCES

1. a) R. Gómez-Bombarelli, B. B. Palma, C. Martins, M. Kranendonk, A. S. Rodrigues, E. Calle, J. Rueff, J. Casado, *Chem. Res. Toxicol.* **23** (2010) 1275; b) R. G. Bombarelli, *PhD Thesis*, Universidad de Salamanca, Spain, 2011
2. a) B. Rigner, S. Sunner, H. Watanabe, *Acta Chem. Scand*. **25** (1971) 141; b) S. W. Benson, C. R. Vickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, R. Walsh, *Chem. Rev.* **69** (1969) 279
3. a) Z. Wang, Z. Chen, J. Sun, *Org. Biomol. Chem.***12** (2014) 6028; b) A. Harrane, N. Naar, M. Belbachir, *Mater. Lett*. **61** (2007) 3555; c) B. Guo, J. T. Njardarson, *Chem. Commun*. **49** (2013) 10802; d) R. N. Loy, E. N. Jacobsen, *J. Am. Chem. Soc.* **131** (2009) 2786
4. F. Ç. Telli, K. Ay, G. Murat, G. Kök, Y. Salman, *Med. Chem. Res*. **22** (2013) 2253
5. M. Kawana, H. Kuzuhara, S. Emoto, *Bull. Chem. Soc. Jpn*. **54** (1981) 1492
6. a) D. Bogdal, J. Pielichowsky, A. Boron, *Synlett*. (1996) 873; b) D. Bogdal, J. Pielichowsky, K. Jascot, *Synth. Commun*. **45** (1997) 715
7. a) G. H. Escamilla, G. R. Newkome, *Angew. Chem. Int. Ed. Engl.* **33** (1994) 1937; b) T. Benvegnu, M. Brard, D. Plusquellec, *Curr. Opin. Colloid Interface Sci*. **8** (2004) 469
8. a) J. H. Fuhrhop, T. Y. Wang, *Chem. Rev.* **104** (2004) 2901; b) A. Meister, A. Blume, *Curr. Opin. Colloid Interface Sci.* **12** (2007) 138
9. a) S. R. Borkar, B. N. Manjunath, B. Sivaraman, I. S. Aidhen, *Carbohydr. Res.* **358** (2012) 23; b) P. Hadzic, M. Popsavin, *Carbohydr. Res*. **345** (2010) 543
10. a) C. Damez, S. Bouquillon, D. Harakat, F. Hénin, J. Muzart, I. Pezron, L. Komunjer, *Carbohyd. Res*. **342** (2007) 154; b) M. Deleu, C. Damez, S. Gatard, K. Nott, M. Paquot, S. Bouquillon, *New J. Chem*. **35** (2011) 2258; c) M. Deleu, S. Gatard, E. Payen, L. Lins, K. Nott, C. Flore, R. Thomas, M. Paquot, S. Bouquillon, *C. R. Chim.* **15** (2012) 68
11. F. Brisset, R. Garelli-Calvet, J. Azema, C. Chebli, I. Rico-Lattes, A. Lattes, *New J. Chem*. **20** (1996) 595
12. Z. S. Kovačević, R. L. Jevrić, O. S. Podunavac-Kuzmanović, D. N. Kalajdžija, S. E. Lončar, *Acta Chim. Slov*. **60** (2013) 420
13. B. Helferich, M. Burgdorf, *Tetrahedron* **3** (1958) 274
14. P. Hadžić, N. Vukojević, *Carbohydr. Res*. **338** (2003) 1243
15. H. Reiff, D. Dieterich, R. Braden, H. Ziemann, *Liebigs Ann. Chem*. (1973) 365
16. P. Hadžić, N. Vukojević, M. Popsavin, J. Čanadi, *J. Serb. Chem. Soc*. **66** (2001) 1
17. a) R. V. Kalla, E. Elzein, T. Perry, X. Li, V. Palle, V. Varkhedkar, A. Gimbel, T. Maa, D. Zeng, J. Zablocki, *J. Med. Chem*. **49** (2006) 3682; b) R.-Y. Lin, B.-N. Wu, Y.-C. Lo, L.-M. An, Z.-K. Dai, Y.-T. Lin, C.-S. Tang, I.-J. Chen, *Pharmacol. Exp. Ther*. **316** (2006) 709; c) K. Ito, S. Lim, G. Caramori, B. Cosio, K. F. Chung, I. M. Adcock, P. J. Barnes, *Proc. Natl. Acad. Sci. USA. A* **99** (2002) 8921
18. A. P. Ijzerman, E. M. van der Venden, J. K. von Frijtag Drabbe Kűnzel, R. A. A. Mathôt, M. Danhof, P. A. Boreal, K. Varani, *Arch. Pharmacol*. **350** (1994) 638
19. a) R. V. Kalla, E. Elzein, T. Perry, X. Li, V. Palle, M. A. N. Mosselhi, *Nucleosides Nucleotides* **12** (1993) 432; b) Z. Wang, Z. Chen, J. Sun, *Org. Biomol. Chem.* **12** (2014) 6028
20. a) P. A. Levene, H. Sobotka, *J. Biol. Chem*. **65** (1925) 463; b) J. Pryde, T. R. Williams, *J. Chem. Soc*. (1933) 640
21. D. B. Ishay, *J. Chem. Soc.* (1956) 3975.