Pergamon

Tetrahedron Letters 41 (2000) 755–758

TETRAHEDRON LETTERS

Synthesis of 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide, a 2-sulfone analogue of pentalongin

Bart Kesteleyn and Norbert De Kimpe *

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

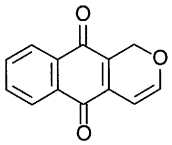
Received 19 April 1999; accepted 17 November 1999

Abstract

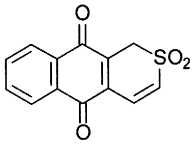
The synthesis of 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**), a 2-sulfone derivative of the natural pyranonaphthoquinone pentalongin (**1**), was accomplished using the acid-catalysed cyclisation of the naphthoquinone sulfone acetal **6** as a key step in the synthesis.

1. Introduction

Naturally occurring 1*H*-naphtho[2,3-*c*]pyranoquinones have always attracted considerable attention in synthetic organic chemistry since these compounds exhibit interesting physiological properties.[1] The pyranonaphthoquinone pentalongin (**1**), a major constituent from the roots of *Pentas longiflora* Oliv. (Rubiaceae), was found to exhibit antifungal and antiprotozoan activity.[2] Pentalongin (**1**) is a representative member of a growing family of 3,4-dehydropyranonaphthoquinones which are characterised by the presence of a double bond between C(3) and C(4) in the pyran ring, and which were found to possess interesting antimicrobial properties. As a result, many papers have described new valuable strategies for the synthesis of 3,4-dehydropyranonaphthoquinones, including pentalongin (**1**).[3]



1 (pentalongin)



2

This paper reports on the synthesis of a 2-thiapyranonaphthoquinone **2**, a 2-sulfone analogue of pentalongin (**1**). The *Chemical Abstracts* name of **2** is 1*H*-2-naphtho[2,3-*c*]thiopyran-5,10-dione-2,2-dioxide, which refers to the old thio-nomenclature for sulfur-containing heterocyclic ring systems. However, in

* Corresponding author.

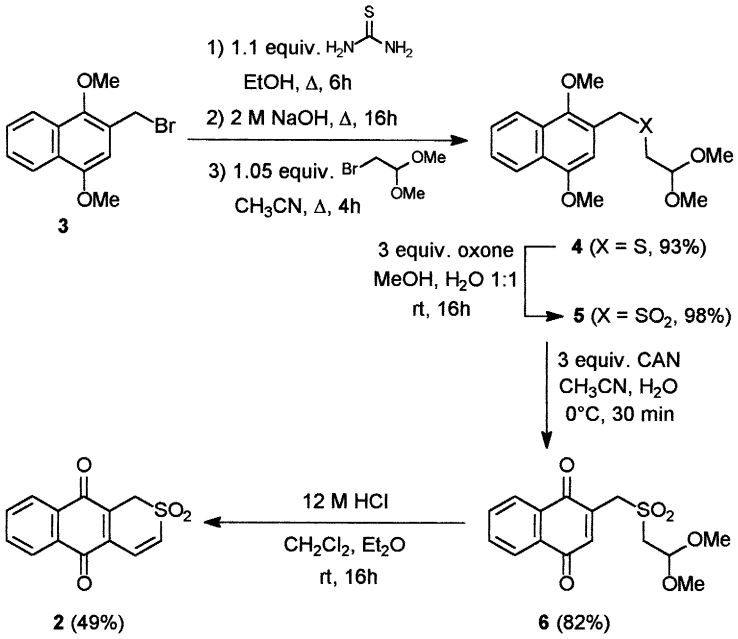
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02146-2

this article, the use of the prefix 'thia' is preferred as prescribed by IUPAC. The synthesis of 1*H*-2-naphtho[2,3-*c*]thiapyranoquinones has thus far been largely unexplored. A series of 3-alkoxycarbonyl- and 3-carbamoyl-substituted 2-thiapyranonaphthoquinones have recently been claimed to possess anti-tumour activity.[4] These compounds have been obtained in moderate yields using a one-pot double alkylation process of 2,3-bis(bromomethyl)-1,4-dimethoxybenzene with α-mercaptocarbonyl compounds in the presence of sodium alkoxides, followed by oxidative demethylation with cerium(IV) ammonium nitrate (CAN) and subsequent cycloaddition of the intermediate isothiachromanquinones with 1-acetoxy-1,3-butadiene.[4] In this paper, a Friedel–Crafts approach is introduced as a new and facile route for the synthesis of 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**). To our knowledge, this is the first report on the synthesis of the 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide heterocyclic system.

2. Results and discussion

The starting point for the synthesis of 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**) was the bromomethylation of 1,4-dimethoxynaphthalene with paraformaldehyde and hydrobromic acid giving the readily available 2-bromomethyl-1,4-dimethoxynaphthalene (**3**).[5]

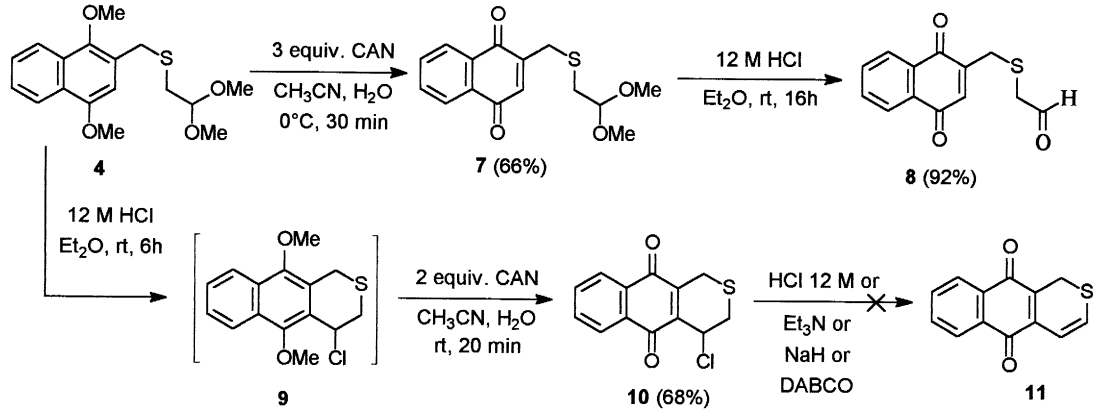
A one-pot double alkylation of **3** with thiourea and bromoacetaldehyde dimethyl acetal afforded the sulfide acetal **4** in 93% yield. The chemoselective oxidation of this sulfide **4** using oxone[6] in aqueous methanol gave the sulfone acetal **5** in 98% yield, while subsequent oxidative demethylation using cerium(IV) ammonium nitrate (CAN) resulted in the naphthoquinone sulfone acetal **6** in a yield of 82%. Upon treatment with concentrated hydrochloric acid in a biphasic system with ether, compound **6** afforded, via hydrolysis of the acetal, intramolecular cyclisation of the intermediate aldehyde and elimination of hydrogen chloride, 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**)[7] in 49% yield (Scheme 1).



Scheme 1.

In order to obtain also the 2-thia analogue **11** of pentalongin (**1**), the naphthoquinone sulfide acetal **7**, obtained by oxidative demethylation of **4** with CAN, was treated with 12 M HCl, using the same

conditions as those used for the synthesis of the 2-sulfone analogue **2**. However, in this case, only the hydrolysis of the acetal functionality of **7** to the corresponding aldehyde **8** was observed, but no cyclisation occurred (Scheme 2). The cyclisation could, however, be accomplished in the reduced state by reaction of the dimethoxynaphthalene sulfide acetal **4** with concentrated hydrochloric acid in a biphasic system with diethyl ether, giving the 4-chloro-thiapyranonaphthalene **9** which was immediately oxidised to the 4-chloro-thiapyranonaphthoquinone **10**.[8] Again, neither acid (HCl 12 M) nor basic (Et_3N, NaH, DABCO) reagents could induce the elimination of hydrogen chloride from **10** to afford the 2-thia derivative **11**. Probably, the tendency for elimination is determined by the acidity of the proton at C(3) which depends upon the oxidation state of the sulfur atom.



Scheme 2.

In conclusion, the synthesis of the 1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**), an unnatural 2-sulfone derivative of pentalongin (**1**) was developed in good yield from 2-bromomethyl-1,4-dimethoxynaphthalene **3** using the acid catalysed cyclisation of the naphthoquinone sulfone acetal **6** as a key step in the synthesis.

Acknowledgements

We are indebted to the Janssen Research Foundation (Beerse, Belgium) for financial support.

References

1. Naruta, Y.; Maruyama, K. In *The Chemistry of Quinonoid Compounds*; Patai, S.; Rappoport, Z., Eds. Recent Advances in the Synthesis of Quinonoid Compounds. John Wiley: New York, 1988; Vol. II., p. 241.
2. (a) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991**, *30*, 1726–1727. (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erlekens, C.; Verpoorte, R. *Mag. Reson. Chem*. **1993**, *31*, 329–330.
3. (a) Naito, T.; Makita, Y.; Yazaki, S.; Kaneko, C. *Chem. Pharm. Bull*. **1986**, *34*, 1505–1516. (b) Aldersley, M. F.; Dean, F. M.; Hamzah, A. S. *Tetrahedron Lett*. **1986**, *27*, 255–258. (c) Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2163–2174. (d) Kobayashi, K.; Uchida, M.; Uneda, T.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett*. **1998**, *39*, 7725–7728. (e) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1579–1584. (f) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem*. **1999**, *64*, 1173–1179. (g) Giles, R. G. F.; Green, I. R.; Taylor, C. P. *Tetrahedron Lett*. **1999**, *40*, 4871–4872.
4. (a) Xu, Y. C.; Lebeau, E.; Attardo, G.; Breining, T. *Synthesis* **1994**, 363. (b) Attardo, G.; Xu, Y. C.; Lavallee, J. F.; Rej, R.; Belleau, B. PCT Int. Appl. WO 91 19752 1991; *Chem. Abstr*. **1991**, *116*, 153134. (c) Attardo, G.; Wang, W.; Breining, T.; Li, T.; St.-Denis, Y.; Kraus, J.-L. PCT Int. Appl. WO 95 12588 1995; *Chem. Abstr*. **1995**, *123*, 1186. (d) Wang, W.; Breining, T.; Li, T.; Milburn, R.; Attardo, G. *Tetrahedron Lett*. **1998**, *39*, 2459–2462.

5. Gates, M. *J. Org. Chem*. **1982**, *47*, 578–582.
6. Trost, B. M.; Curran, D. P. *Tetrahedron Lett*. **1981**, *22*, 1287–1290.
7. 1*H*-2-Naphtho[2,3-*c*]thiapyran-5,10-dione-2,2-dioxide (**2**) occurred as an orange powder, mp 200°C (dec.). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.48 (2H, s, CH_2), 7.07 (1H, d, *J*=10.9 Hz, H-4), 7.68 (1H, d, *J*=10.9 Hz, H-3), 7.80–7.86 (2H, m, H-7 and H-8), 8.13–8.21 (2H, m, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 46.94, 127.10, 127.29, 129.27, 130.91, 131.70, 133.65, 134.59, 134.82, 134.88, 136.78, 180.59, 181.34. IR (KBr): ν_{max} 1651 (C=O), 1610 (C=O), 1584 (C=C), 1549 (C=C) cm^{-1}. MS *m/z* (%): 260 (M^+, 2), 212 (5), 200 (2), 184 (4), 84 (59), 49 (100). Anal. calcd for $C_{13}H_8O_4S$: C 59.99%, H 3.10%. Found: C 59.37%, H 2.80%.
8. Spectral data of 4-chloro-3,4-dihydro-1*H*-2-naphtho[2,3-*c*]thiapyran-5,10-dione (**10**): ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.97 (1H, dd, *J*=11.2, 2.6 Hz, C*H*$_a$H$_b$-3), 4.14–4.23 (2H, m, C*H*$_a$H$_b$-1 and CH$_a$*H*$_b$-3), 4.36 (1H, dd, *J*=17.8, 5.6 Hz, CH$_a$*H*$_b$-1), 5.18–5.23 (1H, m, H-4), 7.73–7.79 (2H, m, H-7 and H-8), 8.08–8.14 (2H, m, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 37.03, 49.47, 56.23, 126.56, 126.66, 133.55, 133.94, 134.14 (2C), 145.98, 150.04, 182.48, 182.82. IR (KBr): ν_{max} 1661 (C=O), 1633 (C=O), 1592 (C=C) cm^{-1}. MS *m/z* (%): 264/6 (M^+, 8), 228 (12), 215 (100).