Tetrahedron Letters 53 (2012) 1905-1907

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of novel 2,2-disubstituted naphthodioxoles via an unprecedented reaction

Satish Kumar^a, Pallvi^a, Shally Chadha^a, Sumita Dham^b, Tanya Hundal^c, Kamal K. Kapoor^{a,*}

^a Department of Chemistry, University of Jammu, Jammu 180 006, India

^b Government College for women, Parade, Jammu 180 001, India

^c Department of Chemistry, University of Delhi, Delhi 110 007, India

ARTICLE INFO

Article history: Received 29 November 2011 Revised 28 January 2012 Accepted 30 January 2012 Available online 8 February 2012

Keywords: Naphthodioxoles Unprecedented reaction Dihydroxynaphthalene

ABSTRACT

A reaction of 2,3-dihydroxynaphthalene with ethyl-2,3-dibromo-3-phenyl-propionate or 1,3-diaryl-2,3dibromo ketone under basic conditions led to the formation of novel 2,2-disubstituted naphthodioxoles. © 2012 Elsevier Ltd. All rights reserved.

The 1,4-benzodioxines are potent biologically active molecules, reported to possess anti-cancer activity¹ and most of them are curative against the remotely sited Lewis Lung carcinoma.² They are known to have an affinity for adrenergic receptor sites and the strongly basic or quartenary side chains seem to be a prerequisite for adrenergic neurone blockade.³ 2,2-disubstituted benzodioxoles are widely used as pesticides or pesticide intermediates,⁴ herbicides,⁵ anti-oxidants,⁶ and inhibitors of mono-oxygenase⁷ enzymes. A series of benzodioxoles is reported as cannabinoid-1 receptor inverse agonists for the treatment of obesity and the (+)-[(R)-2-(2,4-dichloride-phenyl)-6-fluoro-2-(4-fluorophenyl)-benzo[1,3]dioxol-

5-yl]-morpholin-4-yl-methanone) **1** has shown promising results.⁸ The 2,2-disubstituted-5-hydroxy-1,3-benzodioxoles **2** are shown to have greater anti-oxidant effects than the parent sesamol (5-hydroxybenzo[1,3]dioxole) due to the introduction of lipophilic side chain at position 2 on the dioxole ring.⁹



5

EtOOC

COOEt



Ŕr

K₂CO₃

acetone, reflux

Scheme 1. Synthesis of ethyl-2-(2-phenylnaphtho[2,3-*d*][1,3]dioxol-2-yl)-acetate.

* Corresponding author. E-mail address: k2kapoor@yahoo.com (K.K. Kapoor).







Figure 1. Showing an ORTEP view of the molecule at 50% probability and its labeling scheme.

In view of the rich biological activities associated with benzodioxines, we wished to prepare novel naphthodioxines to study their biological activity.

2,3-Dihydroxynaphthlene was treated¹⁰ with ethyl-2,3-dibromo-3-phenylpropionate in the presence of anhydrous potassium carbonate and to our chagrin, the formation of the desired product naphtho(2,3-*b*)[1,4]-dioxine **5** did not occur as revealed by the NMR (¹H and ¹³C) data. Analysis of spectroscopic data (vide experimental), spoke in favor of the formation of ethyl-2-(2-phenylnaphtho[2,3-*d*][1,3]dioxol-2-yl)-acetate **6**¹¹ (Scheme 1).

The most diagnostic signal in the ¹H NMR spectrum being the singlet at δ 3.35 for 2-protons in the aliphatic region. Further corroboration to the proposed structure **6** came from the X-ray crystallographic data.¹² Figure 1 shows the ORTEP diagram of **6**. All the bond lengths and bond angles are normal. A least square plane may be passed through the naphthodioxole moiety with the ester and the phenyl groups lying almost perpendicular on each side of this plane as shown below in Figure 2 forming a T-shaped structure.

There are weak C–H···O type H-bonding interactions found in the crystal structure (Fig. 3). Each molecule is H-bonded to its centrosymmetric counterpart through the aryl carbon C3 and dioxole oxygen O2 $(C3-H3\cdots O2^i)$ forming a self assembled dimer, down the *a* axis. These dimers are further strengthened by C3–H3···O4ⁱ and C5–H5···O4ⁱ H-bonding interactions Figure 3a. These Hbonded dimers are further attached to each other through H-bonding interactions of phenylene carbon C18 with carbonyl oxygen O3 $(C18-H18\cdots O3^{ii})$ and dioxole oxygen O1 $(C18-H18\cdots O1^{ii})$ forming a linear chain running along the *b* axis. These chains are also supported by C–H··· π interactions between methyl carbon C15 and the naphthalene moiety with a C–H··· π (centroid) distance of 3.024(5) Å (shown as H1···C10 interaction in Fig. 3b). These centrosymmetric chains form a 3D network due to $\pi \cdots \pi$ interactions between symmetry related phenylene and naphthalene rings.

To explore the scope of reaction, a variety of α,β -dibromochalcones (Scheme 2) were used and the results are depicted in (Table 1). Naphthodioxoles have been prepared from 2,3-dihydroxynaphthalene by treatment with diazodiphenylmethane and dichlorodicyanoquinone,¹³ thiophosgene,¹⁴ bromochloromethane,¹⁵ 1-ethynesulfonyl-4methylbenzene,¹⁶ dimethylacetylene-dicarboxylate (DMADC).¹⁷



Figure 2. Showing a T-shaped structure of the molecule with the naphthalenedioxide ring in a plane.



Figure 3. Showing the self assembled dimer (a) and a linear tape (b) running along the b axis. C (green), O (red), H(grey).



Scheme 2. Synthesis of 2,2-disubstituted napthodioxoles from 1,3-diaryl-2,3-dibromoketone.

 Table 1

 Synthesis of 2,2-disubstituted napthodioxoles from 1,3-diaryl-2,3-dibromoketone

S. No.	\mathbb{R}^1	R ²	Yield (%)	mp (°C) ^a
a	Н	C ₆ H ₅	65	172-174
b	Н	4-ClC ₆ H ₄	70	215-216
с	Н	4-MeC ₆ H ₄	68	202-203
d	Н	4-BrC ₆ H ₄	65	227-229
e	4-Cl	C ₆ H ₅	75	218-219
f	4-Me	C ₆ H ₅	70	205-206
g	4-Br	C ₆ H ₅	65	235-236

^a Melting points are uncorrected.

In summary the reaction provides an easy and mild method for the formation of 2,2-disubstituted naphthodioxoles from easily and cheaply available starting materials.

Acknowledgments

The authors wish to thank the Department of Chemistry, University of Jammu for providing laboratory facilities, IIIM Jammu for recording the analytics and DST, GOI (Project No. SR/S1/OC-38/2010) for funding.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.126.

References and notes

- Barron, D. I.; Bavin, P. M. G.; Durant, G. J.; Natoff, I. L.; Spickett, R. G. W.; Vallence, D. K. J. Med. Chem. **1963**, 6, 705.
- Lee, H. H.; Palmer, B. D.; Boyd, M.; Baguley, B. C.; Denny, W. A. J. Med. Chem. 1992, 35, 258.

- (a) McLean, R. A.; Geus, R. J.; Mohrbacher, R. J.; Mattis, P. A.; Ullyot, G. E. J. Pharmacol. Exp. Ther. **1960**, 129, 11; (b) Exley, K. A. Brit. J. Pharmacol. **1957**, 12, 297.
- (a) Anderson, M., Brinnard, A. G., Woodall, R. E. Eur. Patent 235642, 1992.; (b) Tozzi, A. Eur. Patent 11874, 1993.; (c) Anderson, M., Brinnard, A. G., Woodall, R. E. Eur. Patent, 95537, 1993.
- 5. Arndt, F.; Franke, H. Ger. Patent 1976, 2624822.
- 6. Minh, T. H.; Cole, E. R.; Crank, G. Aust. patent 1980, 533866.
- 7. Cole, E. R.; Crank, G.; Minh, H. T. Aust. J. Chem. 1980, 33, 675
- Alig, L.; Alsenz, J.; Andjelkovic, M.; Bendels, S.; Benardeau, A.; Bleicher, K.; Bourson, A.; Pierson, P. D.; Guba, W.; Idbrand, S. H.; Plancher, J. M. J. Med. Chem. 2008, 51, 2115–2127.
- 9. Cole, E. R.; Crank, G.; Minh, H. J. Agric. Food Chem. 1982, 30, 719-724.
- Quaglia, W.; Pigini, M.; Tayebati, S. K.; Piergentili, A.; Giannella, M.; Marucci, G.; Melchiorre, C. J. Med. Chem 1993, 36, 1520–1528.
- 11. Procedure for preparation of ethyl-2-(2-phenylnaphtho[2,3-d][1,3]dioxol-2-yl)-acetate, **6**: A mixture of 2,3-dihydroxynaphthalene (0.8 g, 5 mmol) and ethyl-2,3-dibromo-3-phenyl propionate (1.7 g, 5 mmol) in 30 ml of dry acetone was refluxed with stirring in presence of 1 g of anhydrous K₂CO₃ for 6–7 h. After the completion of reaction (TLC), the reaction mixture was filtered to separate K₂CO₃ and acetone was distilled off. The residue after dilution with ethylacetate (50 mL) was washed with water (15 mL), dil NaOH (5 mL), brine (5 mL) and dried (Na₂SO₄). The solution was concentrated and the residue obtained was column chromatographed using gradient of pet ether and ethyl acetate mixture to yield the desired product **6** (1.1 g, 65%). MP: 82 °C, ¹H NMR (CDCl₃, 300 MHz): δ 7.65–7.14 (m, 11H), 4.02 (q, 2H, *J* = 7.1 Hz), 3.35 (s, 2H), 1.03 (t, 3H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 167.34 (C, OC=O), 147.28, 139.35, 130.46, 129.84, 129.31, 128.40, 126.96, 125.18, 124.24, 115.08, 103.96, 60.92 (CH₂, OCH₂CH₃), 45.26, 13.84 (CH₃, OCH₂CH₃); MS(ESI) *m/z*: 334.93 [M+1]*. Anal. calcd for C₂₁H₁₈O₄: C, 75.51; H, 5.38%. Found: C, 75.46; H, 5.43.
- 12. Crystal data: C_{21} H₁₈ O₄, Mol. Wt. 334.35, $\lambda = 0.71069$ Å, monoclinic, P_{21}/n , a = 13.410(5) Å, b = 8.307(4) Å, c = 15.572(5) Å, $\beta = 92.890(5)$ Å, V = 1732.5(12) Å³, Z = 4, $R_1 = 0.0704$, $wR_2 = 0.1312$ (for observed data), $R_1 = 0.1899$, $wR_2 = 0.1780$ for all data. CCDC No. 831678. The relevant crystallographic and refinement parameters, important bond lengths and angles and H-bonds are given in Supplementary data.
- 13. Oshima, T.; Nishioka, R.; Nagai, T. Tetrahedron Lett. 1980, 21, 3919-3922.
- 14. Gleiter, R.; Uschmann, J. J. Org. Chem. 1986, 51, 370-380.
- 15. Zelle, R. E.; McClellan, N. J. Tetrahedron Lett. 1991, 32, 2461-2464.
- 16. Llubes, M.; Mazzega, P. Synthesis 1996, 12, 1481-1484.
- Fan, M. J.; Li, G. Q.; Li, L. H.; Yang, S. D.; Liang, Y. M. Synthesis 2006, 14, 2286– 2292.