Pergamon

Tetrahedron Letters 41 (2000) 2207–2210

TETRAHEDRON LETTERS

# A new route towards the synthesis of substituted naphthalenes via Friedel–Crafts acylation

Chai-Lin Kao, Shu Y. Yen and Ji-Wang Chern *

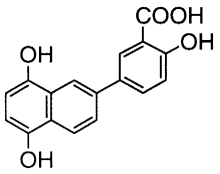
*School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei (100), Taiwan, Republic of China*

Received 15 September 1999; accepted 18 January 2000

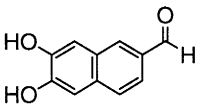
**Abstract**

A novel approach towards the synthesis of substituted naphthalene derivatives is achieved by a treatment of the 4-aryl-4-hydroxy-3-*p*-toluenesulfonylbutanal ethylene acetals (**6a**–**e**) with a catalytic amount of *p*-toluene sulfonic acid. 

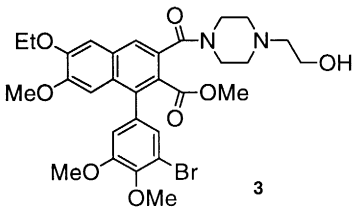
Substituted naphthalene derivatives constitute a class of biologically important substances and have recently attracted attention.[1] Compound **1** was found to be a potent protein tyrosine kinase inhibitor.[2] Compound **2**[3] was reported to be an HIV integrase inhibitor and compound **3**[4] is a phosphodiesterase type V inhibitor. Hydroxylated naphthalene derivatives are of special interest since they have demonstrated potential biological activity in several aspects, and an efficient and versatile approach for their synthesis is needed.




1




2



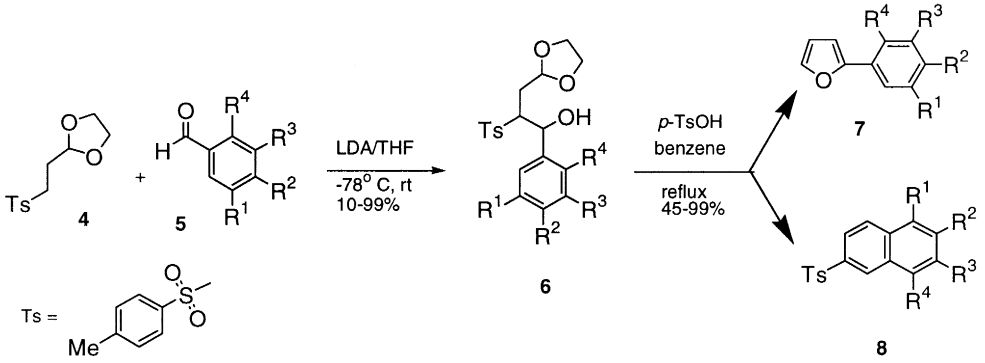

3

A perusal of the literature has revealed that there are several approaches towards the synthesis of substituted naphthalenes.[5] Herein, we report an alternative approach for polyhydroxylated naphthalene derivatives by treatment of 4-aryl-4-hydroxy-3-*p*-toluenesulfonylbutanal ethylene acetals (**6**) with acid. This was reported by Kotake et al.[6] that a series of 4-substituted 4-hydroxy-3-*p*-toluenesulfonylbutanal ethylene acetals have been utilized in synthesizing 2-substituted furans via a transacetalization mechanism. Most examples involved treatment of 4-alkyl-substituted materials with a catalytic amount of *p*-toluenesulfonic acid to provide the 2-alkylfuran. There was only one example with a 4-phenyl group.

* Corresponding author. Tel: 886-2-2393-9462; fax: 886-2-2393-4221; e-mail: chern@jwc.mc.ntu.edu.tw (J.-W. Chern)

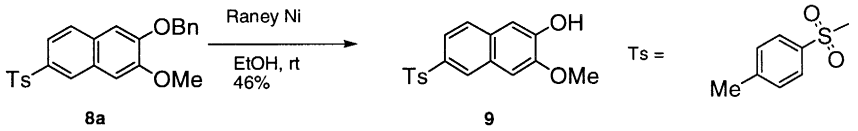
0040-4039/00/$ - see front matter 
*PII:* S0040-4039(00)00145-3

However, it afforded only 2-phenylfuran (**7b**) in 58% yield without any other product.[7] We reasoned that compounds **6** might react by an alternative pathway, a Friedel–Crafts acylation followed by aromatization and elimination of one molecule of water and ethylene glycol to provide the substituted naphthalene **8**. Competitive ring closure of **6**, either through the intramolecular Friedel–Crafts reaction to form the naphthalene skeleton **8**, or through intramolecular transacetalization to form the furan ring **7**, is possible. For the preparation of polyhydroxynaphthalene derivatives, we assumed that an electron-donating group on the 4-aryl ring of **6** would favor the formation of the naphthalene derivatives **8** (Scheme 1).




Scheme 1.

To examine this hypothesis, compound **6a**, prepared by treating 3-*p*-toluenesulfonylpropanal ethylene acetal (**4**)[6] with 4-benzyloxy-3-methoxybenzaldehyde (**5a**) in the presence of LDA in THF at −78°C, was refluxed in benzene with a catalytic amount of *p*-toluene sulfonic acid. As expected, the naphthalene derivative (**8a**) was isolated as the sole product instead of **7a**. Confirmation of the structure of **8a** was achieved by X-ray crystallographic analysis of **9**,[7] which was obtained in 46% yield by treatment of **8a** with Raney nickel (Scheme 2). Encouraged by this exciting result, we re-examined the ring closure reaction of **6b** under Kotake's conditions.[8] Surprisingly, 2-phenylfuran (**7b**) was isolated in only 22% yield. In addition, **8b** was obtained in 57% yield as the major product. This lends support to our assumption that there is competition between the formation of the 2-substituted furan and substituted hydroxylated naphthalene, and that an electron-donating group on the 4-phenyl substituent of **6** facilitates formation of substituted polyhydroxynaphthalene derivatives.




Scheme 2.

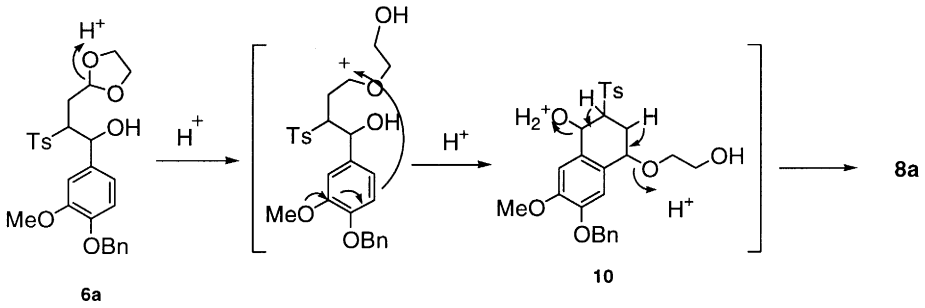
To study the positional effect of the alkoxy groups on the ring closure, compounds **6c**–**e**, obtained by treatment of **4** with a variety of alkoxy-substituted benzaldehydes, were subjected to ring closure in the same manner.[9] The results are summarized in Table 1 and demonstrate that compounds **6** with an alkoxy group at the *meta*-position of the 4-phenyl group, provide moderate to excellent yields of **8** (entries 1, 3–5).

Attempts to perform this ring closure with compounds **6** having an electron-withdrawing group, such as trifluoromethyl and nitro, at either the *para*- or *meta*-position, failed. These reactions gave complex mixtures and difficult to separate products. To our surprise, no obvious transacetalization products, 2-substituted furans **7**, were observed in these reactions. This is probably due to the instability of these compounds under the reaction conditions. These results confirm our assumption that an electron-donating

Table 1
Ring closure of compound **6**

| entry | | | | | | Yield (%) | |
|---|---|---|---|---|---|---|---|
| | **6** | | | | | **7** | **8** |
| | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | |
| 1 | **a** | H | OBn | OMe | H | 0 | 45 |
| 2 | **b** | H | H | H | H | 22 | 57 |
| 3 | **c** | H | OMe | OBn | H | 0 | 52 |
| 4 | **d** | OBn | H | OBn | H | 0 | 58 |
| 5 | **e** | H | H | OBn | OMe | 0 | >99 |

group on the benzene ring, especially at the *meta*-position of **6**, plays an important role in promoting the Friedel–Crafts cyclization. Thus, the ring closure of **6a** is facilitated by participation of the lone pair electrons of the oxygen atom of the *meta*-methoxy group, consistent with common electrophilic substitution reactions, via the oxocarbenium ion generated by protonation-ring opening of the acetal (Scheme 3).



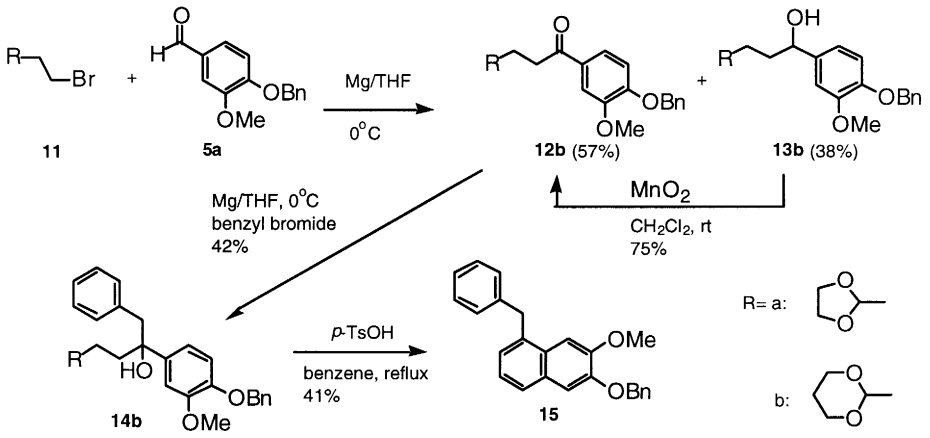

Scheme 3.

To explore the generality of this reaction, it was reasoned that treatment of **14** with a catalytic amount of *p*-toluenesulfonic acid should provide **15**. The reaction of compound **11a** with **5a** in the presence of magnesium in THF failed to give compound **13a**, presumably because the ethylene acetal is not stable enough to survive these conditions.[10] Interestingly, when compound **11b** was used, **12b** and **13b** were formed in 57 and 38% yields, respectively. Compound **12b** was probably formed by air oxidation of **13b**. Compound **12b** was obtained in 75% yield by direct oxidation of **13b** with $MnO_2$. Compound **12b** was treated with benzyl bromide in the presence of magnesium in THF to provide **14b**, which was subsequently subjected to ring closure under acidic conditions to afford **15** in 41% yield (Scheme 4).

In summary, this investigation provides a new approach for the synthesis of various substituted polyhydroxynaphthalene derivatives starting from 4-substituted phenyl-4-hydroxybutanal ethylene acetals in acidic conditions. Compounds with an electron-donating group at the *meta*-position of the 4-phenyl ring of **6** facilitate this reaction.

## Acknowledgements

This investigation was supported by a research grant from the National Science Council (NSC 88-2314-B-002-009) of the Republic of China on Taiwan. S.-Y. Yen is a summer student from the College of Chemical Engineering, The University of Michigan, Ann Arbor, Michigan, USA.




Scheme 4.

## References


1. (a) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 86. (b) Ward, R. S. *Natural Product Report* **1995**, *12*, 183.
2. (a) Smyth, M. S.; Stefanova, I.; Horak, I. D.; Burke Jr., T. R. *J. Med. Chem*. **1993**, *36*, 3015. (b) Thakkar, K.; Geahlen, R. L.; Cushman, M. *J. Med. Chem*. **1993**, *36*, 2950.
3. Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y.; Burke Jr., T. R. *J. Med. Chem*. **1997**, *40*, 1186.
4. Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Takahashi, M.; Kotera, J.; Ikeo, T. *J. Med. Chem.* **1999**, *42*, 1293.
5. (a) De Koning, C. B.; Michael, J. P.; Rousseau, A. L. *Tetrahedron Lett.* **1997**, 893. (b) Kobayashi, K.; Uneda, T.; Takada, K.; Tanaka, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Org. Chem.* **1997**, *62*, 664. (c) Seong, W. R.; Song, H. N.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 7101.
6. (a) Inomata, K.; Suhara, H.; Kinoshita, K.; Kotake, H. *Chem. Lett.* **1988**, 813. (b) Kinoshita, H.; Tanaka, S.; Inomata, K. *Chem. Lett.* **1989**, 1107. (c) Inomata, K.; Sumita, M.; Kotake, H. *Chem. Lett.* **1979**, 709. (d) Kotake, H.; Inomata, K.; Sumita, M. *Chem. Lett.* **1978**, 717. (e) Inomata, K.; Aoyama, S.-I.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 930.
7. The X-ray structural analysis of **10** was performed by Dr. Shuenn-Shing Chern at the Academia Sinica, Taipei, Taiwan.
8. Inomata, K.; Nakayama, Y.; Kotake, H. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 565.
9. (a) Chung, S.-K. *J. Org. Chem*. **1981**, *46*, 5457. (b) Camps, F.; Coll, J.; Guerrero, A.; Guitart, J.; Riba, M. *Chem. Lett.* **1982**, 715. (c) Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737.
10. Stowell, J. C.; Keith, D. R.; King, B. T. *Org. Synth*. **1984**, *62*, 140.