Regioselectivity in the acylation of methylhydroquinone dimethyl ether: an unprecedented case of indirect steric hindrance

Fernando Macedo Jr. [a,*], César C. Andrei [a], Danilo Campiom [a], Noemia K. Ishikawa [b]

[a] Departamento de Química, Universidade Estadual de Londrina, Rod. Celso Garcia Cid, Km 380, Londrina, PR 86051-990, Brazil
[b] Coordenação de Pesquisas em Tecnologia de Alimentos, Instituto Nacional de Pesquisas da Amazônia, Av. André de Araújo, 2936, Manaus, AM 69011-970, Brazil

ARTICLE INFO

ABSTRACT

The origin of the highly regioselective acylation of methylhydroquinone dimethyl ether was investigated using geometry minimization (ab initio and DFT) and NOE spectroscopic measurements. The theoretical and experimental results were consistent with the indirect participation of the aromatic methyl group in blocking the electrophile attack at position 3 of the aromatic ring.

© 2011 Elsevier Ltd. Open access under the Elsevier OA license.

1. Introduction

The initial step of some of the most successful synthetic routes to enokipodins[1,2] involves the acylation of 2,5-dimethoxytoluene (methylhydroquinone dimethyl ether, **1**, Scheme 1).[3]

We recently began to develop a new route to enokipodins using a similar synthetic approach. To this end, we used a previously reported protocol[4] for acylation catalyzed by $SnCl_4$ that provided good yields and regioselectivity. More precisely, the reaction gave the C4-acylated adduct (**2**) as a single isomer.

The orientation of electrophilic attack on benzene rings by previously attached substituents is well-known. The competition among substituents with different tendencies of orientation and the reinforcement of orientation to a specific position by multiple substituents are also widely discussed subjects.[5]

In view of these considerations, the selectivity for substitution at positions 3 and 4 relative to position 6 of 2,5-dimethoxytoluene could be clearly anticipated since the latter is particularly hindered by the groups at both adjacent aromatic carbons.

On the other hand, there are not obvious steric and electronic differences between positions 3 and 4 that could explain the selectivity for the latter.

Although some regioselectivity towards C4 was expected because of the synergistic orientation of the methoxyl at C5 (OMe-C5) and Methyl at C1 (Me-C1), the exclusive formation of
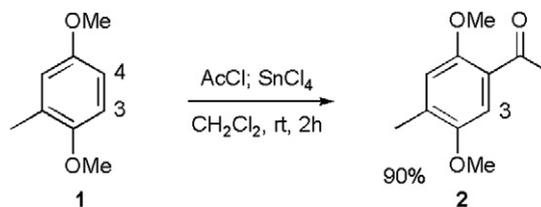
Scheme 1. Acylation of 2,5-dimethoxytoluene.

product **2** was not explainable solely by the electronic nature of the substituents.

Intrigued by the surprisingly high level of regioselectivity in the aromatic substitution at C4 of 2,5-dimethoxytoluene, we sought to determine the origin of this outcome by using ab initio calculation and spectroscopic analyses.

2. Results and discussions

The treatment of compound **1** with acetyl chloride and tin tetrachloride in dichloromethane resulted in the formation of compound **2** at high yields.[6] All physical and spectroscopic analyses for this compound agreed with those previously reported data. Carbonyl was confirmed in the IR spectra as a strong band at $1660\ cm^{-1}$. Mass spectra revealed the molecular ion (M$^+$) peak (m/z 194) and a intense peak at m/z 151 resulting from the fragmentation of M$^+$ with loss of $C(O)CH_3$. GC–MS and GC analysis of the crude product confirmed the formation of the expected regioisomers in >99:1 in favor of **2**.

* Corresponding author. Tel.: +55 43 3371 4811; fax: +55 43 3371 4286.
E-mail address: macedofc@uel.br (F. Macedo Jr).
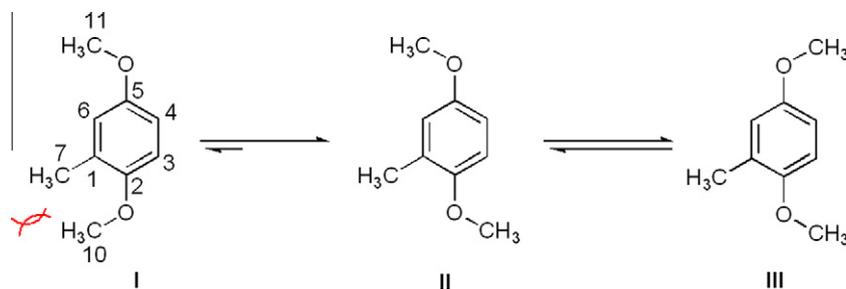
Scheme 2. Favored conformations of 2,5-dimethoxytoluene.

Table 1
Geometry minimization results to 2,5-dimethoxytoluene

Entry	Method/ basis set	Dihedral C10–O–C2–C1		Dihedral C11–O–C5–C6		Final energy (kcal/mol)
		Input	Output	Input	Output	
1	MP2/6-31G	75°	180°	0	0	−312709.97
2	MP2/6-31G	180°	180°	180°	180°	−312710.22
3	DFT/B3LYP1/ 6-31G	75°	180°	0	0	−314051.51
4	DFT/B3LYP1/ 6-31G	180°	180°	180°	180°	−314051.73
5	DFT/B3LYP1/ 6-31G(d,p)	75°	180°	0	0	−314148.39
6	DFT/B3LYP1/ 6-31G(d,p)	180°	180°	180°	180°	−314148.68

As stated above, only a subtle tendency for electrophile entrance at position 4 created by the electronic influence of the aromatic methyl group could be predicted. However, even this should be overshadowed by the methoxyl groups that have greater electron donating character.

The experimental ^{13}C NMR chemical shifts for C3 (δ_C 111.2) and C4 (δ_C 110.9) are in agreement with the similarity of the electronic densities for these carbon atoms (these attributions were unequivocally confirmed by HSQC allied to NOE experiments).

We therefore envisaged differential steric hindrance at positions 4 and 3 by the methoxyl groups at C5 and C2, respectively. We suggest there is intensified hindrance at position 3 by OMe-C2 that, because of a van der Waals repulsive interaction with the methyl group at C1 (conformation I, Scheme 2), tends to adopt a conformation in which OMe-C2 is orientated towards position 3 (conformations II and III). This would result in an indirect steric effect of the aromatic methyl group on C3. Consequently, access of the electrophile to position 4 would be favored in conformation
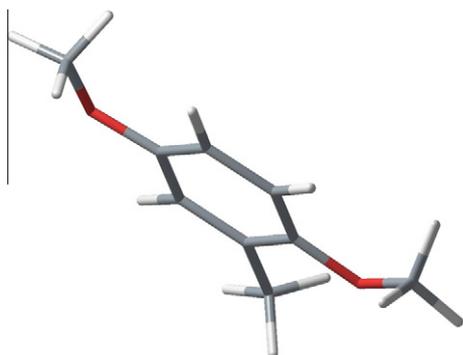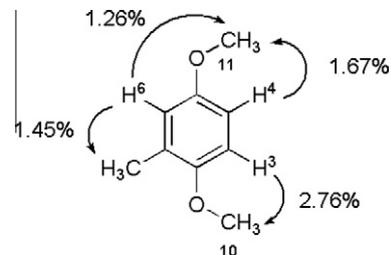

Figure 2. Observed NOE differences for 2,5-dimethoxytoluene.

II while attack at position 3 would be precluded in both of the conformations (II and III).

To investigate this proposal, we used geometry minimization with ab initio computational calculations (MP2) and DFT (B3LYP1) at the levels of 6-31G and 6-31G(d,p) basis set. As predicted, calculations based on inputs with a dihedral angle of 75° converged to a conformation in which OMe-C2 was orientated towards position 3 with an angle of 180° (Table 1, entries 1, 3 and 5).[7]

In addition, there was a slight preference for the C11–O–C5–C6 dihedral value of 180° (Fig. 1). An energy difference of only of 0.3 kcal/mol between the conformations with C11–O–C5–C6 at 180° and C11–O–C5–C6 at 0° was calculated (Table 1, entries 5 and 6).

These theoretical results were spectroscopically supported by NMR using quantitative NOE experiments (Fig. 2). Selective excitation of H-3 revealed its closer proximity to hydrogens of Me-10 compared with the mean distance between H-4 and hydrogens at Me-11. The former showed a signal enhancement of 2.8% whereas the signal of the latter was increased only by 1.7%.

Besides, selective excitation of H-4 results in lower signal enhancement for hydrogens of the OMe group at C-5, but comparable with those for H-6 (1.3%). These experimental data also agreed well with the slight preference for the periplanar conformation with C11–O–C5–C6 at 180° suggested theoretical calculations.

In conclusion, the results describe here indicate the contribution of a steric factor to regioselectivity in the acylation of 2,5-dimethoxytoluene. The theoretical (MP2 and DFT) and NOE experimental measurements were consistent with the indirect participation of the aromatic methyl group in blocking electrophilic attack at position 3 of the aromatic ring. To the best of our knowledge, this is the first description of an indirect, remote steric hindrance strong enough to influence the regiochemical outcome of aromatic electrophilic substitution.

Acknowledgments

Figure 1. Minimized geometry (6-31G) for 2,5-dimethoxytoluene.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.130.

References and notes

1. Ishikawa, N. K.; Yamaji, K.; Tahara, S.; Fukushi, Y.; Takahashi, K. *Phytochemistry* **2000**, *54*, 777.
2. Ishikawa, N. K.; Fukushi, Y.; Yamaji, K.; Tahara, S.; Takahashi, K. *J. Nat. Prod.* **2001**, *64*, 932.
3. Srikrishna, A.; Rao, M. S. *Synlett* **2004**, 374.
4. Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758.
5. Smith, M. B.; March, J. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley Interscience: New York, 2007; pp 665–674. and references therein.
6. *Acylation protocol*: 2,5-Dimethoxytoluene (0.40 g; 2.6 mmol) was dissolved in CH_2Cl_2 (5 mL) in a round bottom flask and was treated with AcCl (0.23 mL, 3.2 mmol) followed by the dropwise addition of $SnCl_4$ (0.31 mL, 2.6 mmol). The resulting solution was stirred at room temperature for 2 h and then was poured in ice–water. The mixture was extracted with diethyl ether (2 × 20 mL) and the organic phase was washed successively with 5% aq $NaHCO_3$ (2 × 15 mL) and brine (15 mL). The solvents were removed under reduced pressure furnishing 0.46 g (90%) of a brownish solid. Crystallization of the latter from hexane afforded the product as colorless needles. Physical data for an analytical sample purified by crystallization from hot hexane (p.f. 75–77 °C); v_{max} (cm^{-1}): 2996, 2917, 2831, 1660, 1609, 1501, 1397, 1213, 1042, 886, 801. EM (*m/z*): 194, 179 (100%), 164, 151, 136, 121, 91, 77.
7. Curiously, minimizations using 3-21G/MP2 or STO-3G/HF suggested a local minimum with the C–O bonds almost orthogonal (102°) with respect to the ring.