

Short Note

Bis(2-hydroxyethyl) 2-phenylsuccinate

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Abstract: Succinic acid esters are important compounds that find many applications in various industrial fields. One of the most promising and easy ways of producing these molecules is represented by the bis-alkoxycarbonylation reaction of olefins. In particular, a recently developed catalytic system, consisting of an aryl α -diimine/palladium(II) catalyst and *p*-benzoquinone as an oxidant, has allowed succinates to be obtained in high yields. A similar methodology was applied here for the unprecedented synthesis of the bis(2-hydroxyethyl) 2-phenylsuccinate in 78% isolated yield, starting from the cheap and commercially available compounds styrene and ethylene glycol. To our knowledge, no other examples of bis-alkoxycarbonylations of olefins involving diols have been reported thus far. The obtained product was fully characterized by NMR and ESI-MS analyses.

Keywords: homogeneous catalysis; aryl α -diimine ligand; palladium; bis-alkoxycarbonylation; carbonylation; succinic acid ester; succinates



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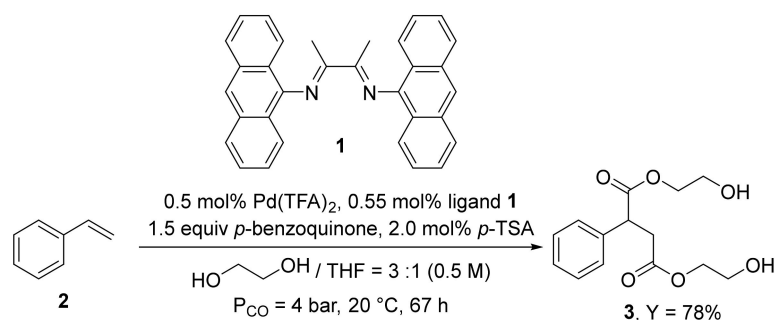
1. Introduction

As is known, 1,4-dicarbonyl compounds are useful reagents, especially as precursors for the synthesis of diverse bioactive molecules and (hetero)cyclic compounds. Among these, succinic acid and its derivatives are very attractive products for their wide range of uses [1,2]. In particular, succinic esters find applications in various industrial fields. For example, they are widely used as components of creams and perfumes in cosmetics [3], are used as a green plasticizer to replace phthalates [4–6], can be found in the main structure of polymers [7,8] and dendrimers [9], and are also employed in agrochemistry and in the food industry [2]. Even if it is possible to obtain succinic acid by fermentation [10], and the respective succinate by subsequent esterification reaction, with this methodology, only minor modifications can be made on the structure, unless long synthetic routes are employed. A very efficient way for achieving one-pot variously substituted succinic acid esters consists in the bis-alkoxycarbonylation of olefins [11,12], in which a cheap functionalized alkene can be easily converted into the desired product in the presence of CO and an alcohol. This kind of reaction is usually metal-catalyzed and requires an oxidizing agent in order to regenerate the active species. Over the past years, we have developed an efficient method for the bis-alkoxycarbonylation of terminal, internal, and electron-deficient olefins and allyl compounds, which utilized aryl α -diimine/palladium(II) complexes as a catalyst and *p*-benzoquinone as an oxidant [13–16]. By applying an analogous methodology, we have realized the synthesis of the bis(2-hydroxyethyl) 2-phenylsuccinate **3**, bearing a phenyl group on the succinic scaffold and two terminal hydroxyl groups on the ester chain, potentially useful for successive post-functionalization reactions.

2. Results and Discussion

A successful bis-alkoxycarbonylation of styrene derivatives was previously developed [13,14] utilizing palladium trifluoroacetate and the ligand **1** (*N*²,*N*³-di(anthracen-9-yl)butane-2,3-diimine), in the presence of 1.5 equiv of *p*-benzoquinone as an oxidant and a

catalytic amount of *p*-toluenesulfonic acid. The reaction proceeded under mild conditions, such as room temperature and only 4 bar of CO pressure, and a mixture of alcohol and THF in a 7:1 ratio was used as the solvent. Unfortunately, when applying these conditions to the bis-alkoxycarbonylation of styrene with ethylene glycol as an alcohol, the high amount of the glycol with respect to the olefin and its high boiling point made the purification of the product difficult and resulted in a low yield eventually being obtained. Therefore, we reduced the amount of glycol, using an ethylene glycol/THF ratio of 3:1, as reported in Scheme 1. The reaction was followed through ¹H-NMR, monitoring the disappearance of the signals of the olefinic double bond of the styrene. The pure product **3** was isolated in 78% yield by column chromatography. To the best of our knowledge, this represents the first example of bis-alkoxycarbonylation of olefins utilizing a diol as an alcohol. A proposed catalytic cycle is reported in Scheme S1 of the Supporting Information.



Scheme 1. Pd-catalyzed bis-alkoxycarbonylation of styrene using 1,2-ethanediol.

As expected, the diester **3** displaces two different C=O signals (173.4 ppm and 172.1 ppm) on the ¹³C-NMR spectrum. Other analyses, which confirm the structure, such as ¹H-NMR, COSY, HMBC, HSQC, and the ESI-MS spectrum, can be found in the Supporting Information.

The DFT-calculated free Gibbs energy associated with the process was −43.8 kcal/mol, indicating that the whole process is highly exergonic (see Supporting Information).

3. Materials and Methods

Chemicals and instruments. The reaction was carried out in a nitrogen atmosphere with dry solvent under anhydrous conditions, in a stainless steel autoclave, by using the Schlenk technique. The reaction was monitored by ¹H-NMR, taking a direct sample of the crude mixture. ¹H-NMR and ¹³C-NMR were recorded on a Bruker Avance 400 spectrometer (¹H: 400 MHz, ¹³C: 101 MHz), using CDCl₃ as a solvent. Chemical shifts are reported in the δ scale relative to residual CHCl₃ (7.26 ppm) for ¹H-NMR and to the central line of CDCl₃ (77.16 ppm) for ¹³C-NMR. ¹³C-NMR was recorded with ¹H broadband decoupling. The following abbreviations have been used for the multiplicities: s = singlet, br = broad, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet. Coupling constants (J) are reported in Hertz (Hz). An ESI-MS spectrum was recorded on Waters Micromass ZQ 4000, using electrospray ionization techniques, with the sample dissolved in MeOH. Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide (carbon monoxide is a toxic gas with potentially lethal action, so adequate precautions must be observed). The *p*-benzoquinone was purchased by Alfa Aesar and was filtered off a plug of silica gel washing with CH₂Cl₂, obtaining a yellow solid after drying the solution under vacuum. The pure compound **3** was isolated through flash column chromatography on silica gel 60 (40–60 μm, 230–400 mesh). Styrene **2** was purchased from Merck Sigma-Aldrich and, before use, was filtered off a plug of neutral Al₂O₃ without further purification. Anhydrous THF was distilled from sodium-benzophenone. Ethyl glycol was dried over molecular sieves (Alfa Aesar, 4 Å, 1–2 mm, beads). Pd(TFA)₂ was purchased by Flurochem; all the other chemicals were purchased from Merck Sigma-Aldrich and used without

further purification. The ligand **1** was synthesized according to the literature [17]. All solid reagents were weighted in an analytical balance without excluding moisture and air.

Computational Details. All DFT calculations have been performed using the ORCA 4.2.1 suite of quantum chemistry programs [18,19]. Geometries were optimized in vacuum using the Becke–Perdew (BP) functional [20,21] and the def2-TZVP basis [22]. Vibrational frequencies were calculated at the optimized geometries to check the stability of the stationary points and to evaluate the vibrational contribution to free energies at 298 K. Final single-point energy calculations at the optimized geometries were performed with the large def2-QZVPP basis [22] and the M06 functional [23], with the inclusion of solvation effects (with THF as a solvent) through the SMD model [24] and of dispersion interactions [25]. The final free energy of each structure, used to evaluate the reaction free energy, was built by summing the difference between the def2-TZVP electronic and free energies to the def2-QZVPP single-point electronic energy.

Synthesis of bis(2-hydroxyethyl) 2-phenylsuccinate. In a nitrogen-flushed Schlenk tube, equipped with a magnetic stirring bar, styrene **2** (2 mmol), ethylene glycol (3 mL), and THF (0.5 mL) were added in sequence. The mixture was left under stirring for 10 min. In another nitrogen-flushed Schlenk tube, equipped with a magnetic stirring bar, the Pd(TFA)₂ (3.3 mg, 0.01 mmol) and THF (0.5 mL) were added in sequence. After the mixture came to show a red/brown color (20 min), ligand **1** (4.8 mg, 0.011 mmol) was added. The mixture was left under stirring for 15 min, turning to a dark orange-brown color with a precipitate. The olefin solution and the formed catalyst were injected in sequence in a nitrogen-flushed autoclave, equipped with a magnetic stirring bar, containing *p*-benzoquinone (325 mg, 3 mmol) and *p*-TSA·H₂O (7.6 mg, 0.04 mmol). After 5 min of stirring, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at room temperature (20 °C) for 67 h. The autoclave was vented off and flushed with nitrogen, and the crude was dried under reduced pressure and filtered off a plug of silica gel, washing with CH₂Cl₂/Et₂O = 2:3. The solution was dried up in a vacuum and H₂O (30 mL) was added. The solution was extracted with EtOAc (4 × 30 mL). The organic layers were combined, dried over Na₂SO₄, and evaporated under reduced pressure. Product **3** was eventually obtained after column chromatography on silica gel (EtOAc/CH₂Cl₂ = 40:60). Yield: 78% (440 mg), pale yellow oil.

R_f = 0.14 (EtOAc/CH₂Cl₂ = 40:60). ¹H-NMR (400 MHz, CDCl₃) δ 7.35–7.24 (m, 5H, CH_{Ar}), 4.31 (ddd, *J* = 11.8, 5.8, 3.7 Hz, 1H, COOCH₂), 4.23 (ddd, *J* = 11.8, 5.2, 4.1 Hz, 1H, COOCH₂), 4.18 (ddd, *J* = 11.8, 5.1, 4.2 Hz, 1H, COOCH₂), 4.12 (dd, *J* = 11.0, 4.7 Hz, 1H, CH-CO), 4.10 (ddd, *J* = 11.9, 5.2, 3.6 Hz, 1H, COOCH₂), 3.81–3.75 (m, 2H, CH₂OH), 3.75–3.69 (m, 2H, CH₂OH), 3.26 (dd, *J* = 16.9, 11.0 Hz, 1H, CH₂-CO), 2.77 (br s, 2H, OH), 2.71 (dd, *J* = 16.9, 4.7 Hz, 1H, CH₂-CO). ¹³C-NMR (101 MHz, CDCl₃) δ 173.4 (C=O), 172.1 (C=O), 137.3 (C_{q,Ar}), 129.1 (C_{ortho,Ar}), 128.0 (C_{para,Ar}), 127.8 (C_{meta,Ar}), 66.8 (COOCH₂), 66.5 (COOCH₂), 60.82 (CH₂OH), 60.80 (CH₂OH), 47.4 (CH-CO), 38.1 (CH₂-CO). ESI-MS: *m/z* = 283 [M + H]⁺; *m/z* = 300 [M + NH₄]⁺; *m/z* = 305 [M + Na]⁺.

4. Conclusions

Starting from cheap and commercially available compounds, the one-pot synthesis of the new succinic acid ester bis(2-hydroxyethyl) 2-phenylsuccinate, bearing hydroxy groups on the ester moieties, has been obtained in high yield through a bis-alkoxycarbonylation reaction. A low catalyst loading (i.e., 0.5 mol%) of the aryl α -diimine/palladium(II) catalyst and mild reaction conditions (i.e., 4 bar of CO at 20 °C) can be utilized. Moreover, to the best of our knowledge, this is the first time that a bis-alkoxycarbonylation reaction has been applied to diols. The final compound has been characterized by NMR and ESI-MS, and Δ_rG of the reaction has been calculated by DFT calculations.

Supplementary Materials: Scheme S1: Proposed catalytic cycle; Figure S1: ¹H-NMR spectrum; Figure S2: Zoom of the ¹H-NMR spectrum (from 5.0 ppm to 2.2 ppm); Figure S3: ¹³C-NMR spectrum; Figure S4: DEPT 135 (CH and CH₃ positive, CH₂ negative); Figure S5: COSY spectrum; Figure S6:

Zoom of the COSY spectrum (from 5.0 ppm to 2.2 ppm); Figure S7: HSQC spectrum; Figure S8: HMBC spectrum; Figure S9: ESI-MS (ESI+) spectrum of compound **3**.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds **3** are available from the authors.

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