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Synthesis of Xenbucin using Suzuki reaction catalyzed by Pd/C in water

Short Communication

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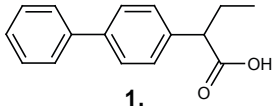
Abstract: Xenbucin **1**, an analgesic drug, was synthesized in 4 steps using two different routes. The biaryl fragment could successfully be produced via a Pd/C catalysed Suzuki coupling in water using sodium tetraphenylborate as a phenylation reagent. Overall yields of the routes were 36% and 59%, respectively.

Keywords: *Xenbucin • Suzuki coupling • Pd/C • Sodium tetraphenylborate • NSAID*

1. Introduction

Xenbucin (**1, Scheme 1**) is a non-steroidal antihypercholesterolemic and analgesic drug possessing anti-inflammatory properties as the *trans*-4-phenylcyclohexylamine salt (Flectar) [1]. The first synthesis of **1** was reported in 1943 by Bilke *et al.* using Friedel-Crafts acylation followed by a Grignard reaction [2]. Cavallini *et al.*, on the other hand, reported the preparation from commercially available 4-biphenylylactonitrile [3]. Recently, **1** was also prepared using a zwitterionic technique, where the biaryl moiety was prepared using a Suzuki reaction [4]. Total yields in these reactions were low overall (20 - 35%).



1.

Scheme 1. Xenbucin.

Recently, we developed a Pd/C catalyzed, ligandless Suzuki reaction, involving tetra-arylborates in water. Advantages of our chemistry are low catalyst loading (0.05% - 0.5%) and use of a non-toxic phenylation reagent. Pd/C catalyzed Suzuki coupling was utilized in the preparation of different biphenyl carboxylic acids in excellent yields [5]. We also synthesized three non-steroidal anti-inflammatory drugs Fenbufen, Flurbiprofen and Felbinac (**3, Scheme 2**) using this method [5-6]. The Pd/C catalyzed reaction not involving tetra-arylborates has been published previously [5,7-9].

In this communication we would like to present two new synthesis-routes for the drug Xenbucin. The biaryl-moiety was successfully obtained using the Suzuki reaction in water in excellent yield and high purity.

The synthesis of **1** was performed by two different routes **A** and **B** (**Scheme 2**). In route **A**, the Suzuki reaction between 4-bromophenylacetic acid **2** and sodium tetraphenylborate gave Felbinac (**3**) in excellent yield (95%). Compound **3** was then esterified to give **4**, which was alkylated to yield **5**. After hydrolysis we obtained Xenbucin (**1**) in 36% overall yield. Route **B** started with the esterification of 4-bromophenylacetic acid (**2**), followed by alkylation and hydrolysis to produce 2-(4-bromophenyl)butanoic acid **8**, which was subsequently reacted with sodium tetraphenylborate to produce **1** in good yield (85%). The overall yield of route B was 59%.

In conclusion, we found that route **B** was more efficient than route **A** for the synthesis of **1**; it runs with

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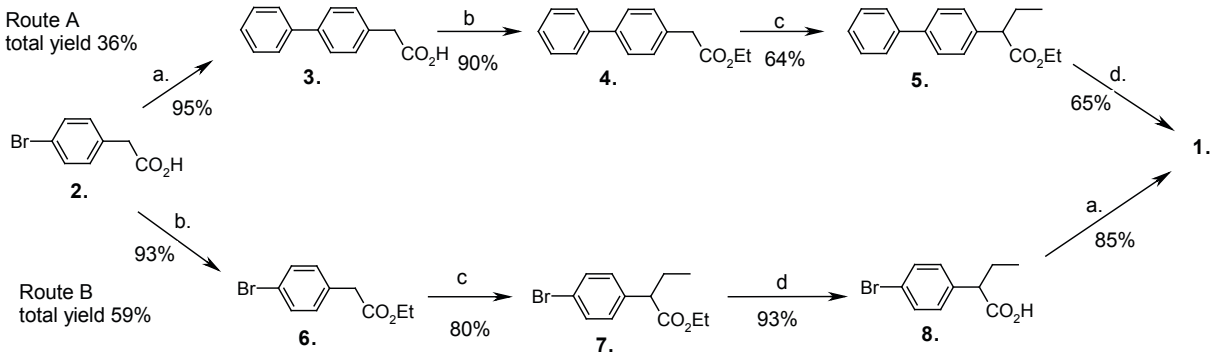

Scheme 2. Synthesis of Xenbucin **1**. a. Ph_4BNa, Na_2CO_3, 0.5 mol% Pd/C(5%), H_2O, reflux in air; b. cat. H_2SO_4, EtOH; c. NaH, EtI, DMF, 0°C → rt; d. NaOH, MeOH/THF.

shorter reaction times and gives a better overall yield. However, the Suzuki reaction in route **A** gave higher yields and better purity compared to performing the reaction as the final step in route **B**.

2. Experimental Procedures

Solvents and reagents were purchased from Sigma-Aldrich or Merck and were used without purification. TLC was performed on precoated (silicagel 60 F_{254}) aluminium plates and detected by UV-light. Silica gel 100, particle size 0,063 – 0,2 mm were used for column chromatography. ^{1}H and ^{13}C NMR spectra were measured with Varian Mercury 300 MHz Spectrometer using $CDCl_3$ or DMSO-*d6* as solvents. Chemical shifts are reported in δ values (ppm) relative to tetramethylsilane. Melting points were determined with a Stuard 110 meltingpoint apparatus. ESI-MS spectra were recorded by ESI-TOF Waters LCT Premier XE.

2.1. Synthesis route A

2.1.1. 4-Biphenyl acetic acid (Felbinac, 3)

4-Biphenylacetic acid was synthesized as reported by Xu *et al.* [5]. 4-Bromophenylacetic acid (**2**, 2.03 g, 9.4 mmol), sodium tetraphenylborate (0.87 g, 2.5 mmol), 5% Pd/C (water wet 50 %, 200 mg, 0.5 mol%), Na_2CO_3 (2.0 g, 18.9 mmol) and water (100 mL) were placed in flask and refluxed for 1 h. Reaction mixture was quenched with 3 M HCl. The precipitate was filtered and washed with water. Precipitate was then dissolved in THF to remove Pd/C by filtration. Product was dried over $MgSO_4$ and concentrated to give white crystals of **3** (1.90 g). Yield: 95%. M.p: 162 - 164°C (lit. 163 – 164°C). ^{1}H NMR (DMSO-d6) 7.62 – 7.59 (m, Ar, 4H), 7.46 (t, Ar, 2H), 7.34 – 7.39 (m, Ar, 3H), 3.62 (s, CH_2, 2H); ^{13}C NMR (DMSO-d6) 172.1, 140.9, 139.7, 134.5, 130.2, 129.1, 127.5, 127.1, 127.0, 40.3; ESI-MS: 211.06 (58) $[M-H]^-$, 423.13 (100) $[2M-H]^-$ ($C_{14}H_{12}O_2$: 212.08).

2.1.2. 4-Biphenyl acetic acid ethyl ester (4)

4-Biphenyl acetic acid (**3**, 1.00 g, 4.7 mmol) was diluted with ethanol (20 mL) and few drops of conc. H_2SO_4 was added. The reaction mixture was refluxed for 2h (followed by TLC, eluent Hex/EtOAc 7:1). Water (50 mL) was added and product was extracted with diethyl ether (2 x 20 mL). The organic layers were washed with water (20 mL), sat. $NaHCO_3$ (20 mL), water (2 x 20 mL) and brine (20 mL) and dried over $MgSO_4$. Solvent was removed in vacuum to obtain **4** as an oil (1.02 g, 90%) ^{1}H NMR ($CDCl_3$) 7.60 – 7.56 (m, Ar, 4H), 7.44 – 7.34 (m, Ar, 5H), 3.61 (s, CH_2, 2H), 4.14 (q, OCH_2, 2H), 1.23 (t, CH_3, 3H) ^{13}C NMR (DMSO-d6) 171.5, 140.8, 140.0, 133.2, 129.6, 128.7, 127.3 (2C), 127.1, 60.9, 41.0, 14.2, ESI-MS: 241.10 (8) $[M+H]^+$, 263.08 (99) $[M+Na]^+$, ($C_{16}H_{16}O_2$: 240.12).

2.1.3. 2-(4-Biphenylyl)butanoic acid ethyl ester (5)

Glassware was dried in an oven, and DMF was dried over 4Å molecular sieves before use. The reaction was performed under argon. 4-Biphenylacetic acid ethyl ester (**4**, 288 mg, 1.20 mmol) was dissolved in DMF (3 mL) and cooled at 0°C. NaH (60% dispersion in mineral oil) (58 mg, 1.44 mmol) was added in one portion and stirred at 0°C for 45 min. Iodoethane (116 µL, 1.44 mmol) was added dropwise to reaction mixture, which was stirred at 0°C for 15 min and warmed to rt. The reaction was followed by TLC (Hex/EtOAc 7:1). When the reaction was completed, sat. NH_4Cl was added. The reaction mixture was poured in water and extracted with ether (3 x 20 mL). The combined ether fractions were washed with water (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, and solvents were removed under reduced pressure. The product was purified with column chromatography (Hex/EtOAc7:1). Oil **5** (205.8 mg) was obtained in 64% yield. ^{1}H NMR ($CDCl_3$) 7.52 – 7.59 (m, Ar, 4H), 7.45 – 7.30 (m, Ar, 5H), 4.20 – 4.01 (m, OCH_2, 2H), 3.48 (t, CH; 1H), 2.09 (m, CH_2, 1H), 1.80 (m, CH_2, 1H), 1.20 (t, CH_3, 3H),

0.90 (t, CH_3, 3H) ^{13}C NMR ($CDCl_3$) 174.5, 140.8, 140.1, 138.4, 128.8, 128.4, 127.3 (2C), 127.1, 60.8, 53.3, 26.9, 14.3, 12.3, ESI-MS: 269.14 (100) $[M+H]^+$, 291.19 (12) $[M+Na]^+$, ($C_{18}H_{20}O_2$: 268.14).

2.1.4. 2-(4-Biphenylyl)butanoic acid (Xenbucin, 1)

2-(4-Biphenyl)butanoic acid ethyl ester **5** (150 mg, 0.56 mmol) was dissolved in MeOH (4 mL) and 2 M NaOH(aq) (3.5 mL) was added. THF was added until reaction mixture was clear. Reaction mixture was stirred at RT and followed by TLC (Hex/EtOAc 7:1). After reaction was completed, the mixture was acidified using 3 M HCl. Product was extracted with ethylacetate and the combined EtOAc fractions were washed with brine and dried over $MgSO_4$. Solvent was removed and 87.3 mg of white crystals of **1** was obtained. Yield 65%. M.p: 114 – 116°C ^1H NMR (DMSO-*d6*) 7.66 – 7.59 (m, Ar, 4H), 7.47 – 7.32 (m, Ar, 5H), 3.46 (t, CH; 1H), 2.00 (m, CH_2, 1H), 1.69 (m, CH_2, 1H), 0.85 (t, CH_3, 3H) ^{13}C NMR (DMSO-*d6*) 172.2, 140.0, 139.3, 138.7, 128.9, 128.4, 127.3, 126.6 126.7, 52.6, 26.3, 12.9, ESI-MS: 239.09 (36) $[M-H]^-$, 479.10 (32) $[2M-H]^-$, ($C_{16}H_{16}O_2$: 240.12).

2.2. Synthesis route B

2.2.1. 4-Bromophenyl acetic acid ethyl ester (6)

Esterification was performed using the same procedure as for 4-biphenylacetic acid ethyl ester (see 2.1.2) Colorless crystals of **6** could be obtained in 93% yield. M.p: 30 - 32°C (lit. 31 – 34°C), ^1H NMR ($CDCl_3$): 7.45 (dd, Ar, 2H), 7.15 (dd, Ar, 2H), 4.15 (q, OCH_2, 2H), 3.55 (s, CH_2, 2H), 1.24 (t, CH_3, 3H); ^{13}C NMR ($CDCl_3$) 171.2, 133.3, 131.9, 131.3, 121.3, 61.2, 41.0, 14.4, ESI-MS: 243.05 (6) $[M+H]^+$, 264.97 (100) $[M+Na]^+$, ($C_{10}H_{11}BrO_2$: 241.99).

2.2.2. 2-(4-Bromophenyl)butanoic acid ethyl ester (7)

The alkylation was performed by the same procedure as for 2-(4-biphenyl)butanoic acid ethyl ester (see 2.1.3). A pale yellow oil **7** could be obtained in 80% yield. ^1H NMR ($CDCl_3$) 7.41 (dd, Ar, 2H), 7.20 (dd, Ar, 2H), 4.16 – 4.06 (m, OCH_2, 2H), 3.40 (t, CH, 1H), 2.05 (m, CH_2, 1H), 1.76 (m, CH_2, 1H), 1.19 (t, CH_3, 3H), 0.90 (t, CH_3, 3H); ^{13}C NMR ($CDCl_3$) 173.8, 138.4, 131.7, 129.8, 121.2, 61.0, 53.1, 26.9, 14.3, 12.8, ESI-MS: 273.01 (52) $[M+H]^+$, 294.98 (100) $[M+Na]^+$, ($C_{12}H_{15}BrO_2$: 270.03).

2.2.3. 2-(4-Bromophenyl)butanoic acid (8)

The hydrolysis was performed as for 2-(4-biphenyl) butanoic acid (see 2.1.4). Pale yellow crystals of **8** was obtained in 93% yield. M.p: 66 - 69°C; ^1H NMR ($CDCl_3$) 7.50 (dd, Ar, 2H), 7.25 (dd, Ar, 2H), 3.43 (t, CH, 1H), 1.96 (m, CH_2, 1H), 1.64 (m, CH_2, 1H), 0.81 (t, CH_3, 3H); ^{13}C NMR ($CDCl_3$) 174.5, 139.1, 131.3, 130.1, 120.0, 52.0, 26.1, 11.9, ESI-MS: 240.97 (57) $[M-H]^-$, 484.93 (100) $[2M-H]^-$, ($C_{10}H_{11}BrO_2$: 241.99).

2.2.4. 2-(4-Biphenyl)butanoic acid (Xenbucin) (1)

The Suzuki reaction was performed using the same procedure as for 4-biphenylacetic acid (see 2.1.1). The reaction time was 24 h. Light yellow crystals of Xenbucin **1** could be obtained. Yield 85%.

Acknowledgements

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