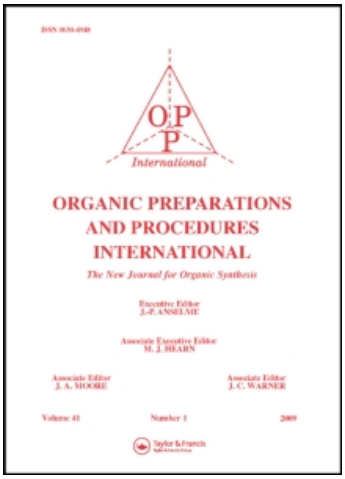

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AN IMPROVED SYNTHESIS OF 4-HYDROXY AND 4'-METHOXYBIPHENYL-2-CARBOXYLIC ACIDS

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room temperature and then acidified to pH 3 with conc. hydrochloric acid. The mixture was refluxed for 4 hrs. Upon cooling, the dione **2** precipitated and was collected. The solid was crystallized from water to give 21.8 g (95%) of colorless needles, mp. 174-176°, lit.[5] 175-176°. ^{1}H NMR ($CDCl_3$-DMSO): δ 0.89 (3H, d, J 4.9 Hz, CH_3), 1.54 (3H, s, CH_3), 1.92-1.99(3H, m), 2.29 (1H, d, J 13.5 Hz), 9.28 (1H, brs).

Anal. Calcd. for $C_8H_6O_2$: C, 68.57; H, 8.57. Found: C, 68.73; H, 8.85

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AN IMPROVED SYNTHESIS OF 4'-HYDROXY AND 4'-METHOXYBIPHENYL-2-CARBOXYLIC ACIDS

Submitted by (10/20/94)

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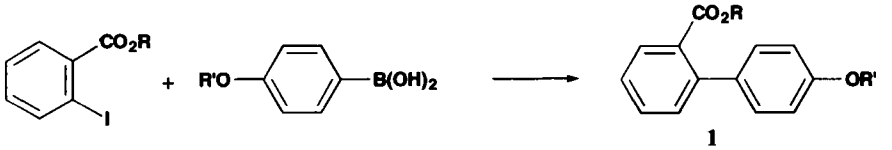
Biphenyl derivatives of type **1** were needed as part of our research on non peptidic AII antagonists.[1] Previously these compounds had been synthesized by radical coupling[2] of diazonium salts or by the Ullmann reaction.[3,4] Compound **1a** had been obtained previously in low yield (10%) by the Gomberg-Bachman reaction between *o*-anisidine and methyl benzoate;[5] this route, however, led to a mixture of products. Over the past ten years, new coupling methodologies based on the use of palladium or nickel,[6-8] have been found to be very convenient because of the mild conditions and the yields are frequently quite high. Furthermore, these techniques are often more regioselective, a valuable feature in the synthesis of unsymmetrical biphenyls. In general the syntheses are realized with palla-

dium, by coupling aryl Grignard reagents,[9] arylzinc,[9] tin chlorides[10] and more recently boronic acids[11-13] with aryl and heteroaryl halides. We now report the preparation of known compounds **1a** and **1b** and the novel structure **1c** in good yields using a boronic acid.

Coupling 4-methoxyphenylboronic acid (from *p*-bromoanisole) [14,15] with methyl *o*-iodobenzoate led to **1a** in 70% yield. The usual ether deprotection methods[16] (BBr_3/CH_2Cl_2; NaCN/DMSO) applied to **1a** were unsuccessful. With BBr_3 the starting product was recovered accompanied by traces of the corresponding fluorenone derivative while, with NaCN, reaction of the ester function also occurred. Both functions were successfully deprotected with pyridinium chloride leading to **1b** in 93% yield. Esterification with methanolic hydrochloric acid afforded the desired compound **1c** in 90% yield.



1

a) R = R' = Me b) R = R' = H c) R = Me, R' = H

EXPERIMENTAL SECTION

Reactions are carried out under nitrogen flow. All reagents and solvents were of commercial grade. Flash chromatography purification was performed on Merck Geduran SI 60 silica (0.040-0.063 mm). ^1H NMR spectra were recorded on a Bruker AC 300 P spectrometer; the chemical shifts are given in δ downfield from TMS as internal standard. IR spectra were obtained on a Perkin Elmer 782 spectrometer. Elemental analyses were carried out with a Perkin Elmer 2400 C, H, N Elemental Analyzer. Melting points were determined on a Kofler hot stage.

Methyl 4'-Methoxy-1,1'-biphenyl-2-carboxylate (1a).- To a solution of 4-methoxyphenylboronic acid (630 mg, 1.3 mmol), [14,15] methyl *o*-iodobenzoate (1 g, 3.81 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) in toluene (4 mL), was added a 2M sodium bicarbonate solution (4 mL, 7.9 mmol). This mixture was refluxed for 18 hrs. After cooling, the mixture was extracted with EtOAc. The organic layer was washed with H_2O (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was flash chromatographed (toluene) to give 0.74g (80%) of **1a** as an orange oil. Compound **1a** has been described as an oil with no other physical data.[5]

IR (neat): 1730, 1610, 1510 cm^{-1}.

^1H NMR ($CDCl_3$): δ 3.67 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3), 6.83 (d, 2H, J = 8.4 Hz, $H_{3',5'}$), 7.19 (d, 2H, J = 8.4 Hz, $H_{2',6'}$), 7.37 (pt, 1H, J = 7.5 Hz, H_4), 7.38 (dd, 1H, J_1= 7.5 Hz, J_2 = 1.2 Hz, H_6), 7.51 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.4Hz, H_5), 7.79 (dd,1H, J_1 = 7.2 Hz, J_2 = 1.6 Hz, H_3).

4'-Hydroxy-1,1'-biphenyl-2-carboxylic Acid (1b).- An intimate mixture of **1a** (1.2 g, 5 mmol) and pyridinium chloride (4 g, 35 mmol) was heated at 200° for 4 hrs. After cooling and acidification with 1N hydrochloric acid, the mixture was extracted with EtOAc (2 x 50 mL). The organic layers were combined and washed with brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* under reduced

pressure. The residue was triturated with petroleum ether to give 1g (80%) of **1b** as a brown grey solid, mp 206°, lit. [17] 207-208°.

IR (KBr): 3400-3200, 2700, 1690, 1630, 1600, 1530 cm^{-1}.

^1H NMR (DMSO-d_6): δ 6.79 (d, 2H, J = 8.3 Hz, $H_{3',5'}$), 7.15 (d, 2H, J = 8.3 Hz, $H_{2',6'}$), 7.33 (d, 1H, J = 7.3 Hz, H_6), 7.37 (t, 1H, J = 7.3 Hz, H_4), 7.51 (pt, 1H, J = 7.3 Hz, H_5), 7.64 (d, 1H, J = 7.3 Hz, H_3), 9.51 (s, 1H, OH), 12.71 (s, 1H, CO_2H).

Methyl 4'-Hydroxy-1,1'-biphenyl-2-carboxylate (1c).- A solution of **1b** (3.5g, 16.3 mmol) in MeOH (30 mL) was saturated with HCL gas at 0°. The mixture was kept for 4 days at RT. After evaporation of the solvent, water was added (20 mL) to the residue and the solution was extracted with EtOAc (2 x 50 mL). After drying ($MgSO_4$) and evaporation of the organic layer *in vacuo*, the residue was chromatographed (toluene-EtOAc) to give 3.2g (90%) of **1c** a grey powder, mp 105°.

Anal . Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.47; H, 5.36.

IR (KBr): 3400, 1740-1720, 1620, 1600, 1525 cm^{-1}

^1H NMR ($CDCl_3$): δ 3.71 (s, 3H, CO_2CH_3), 5.62 (s, 1H, OH), 6.80 (d, 2H, J = 8.5 Hz, $H_{3',5'}$) 7.17 (d, 2H, J = 8.5 Hz, $H_{2',6'}$), 7.36 (pt, 1H, J = 7.6 Hz, H_4), 7.39 (dd, 1H, J_1 = 7.45 Hz, J_2 = 1.30 Hz, H_6), 7.50 (t d, 1H, J_1 = 7.45 Hz, J_2 = 1.3 Hz, H_5), 7.78 (d, 1H, J = 7.9 Hz, H_3).

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1-(BENZENESULFONYL)PYRROLE-3-CARBOXALDEHYDE

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The value of 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde as a synthon in heterocyclic chemistry, especially for the preparation of highly functionalized indoles,[1] has impelled the search for methods of preparation based on direct formylation.[2] However, although 1-(benzenesulfonyl)pyrrole displays an unusual proclivity toward β-substitution in aluminum chloride mediated Friedel-Crafts acylations,[3] all previous attempts to introduce one carbon units at the β-position by this process have failed. Thus, even in the presence of aluminum chloride, one carbon "acylations" using oxalyl chloride or 1,1-dichloromethyl methyl ether proceed exclusively at the α-position, as does cyanation with cyanogen bromide.[3a,c,d]

Recently, Natsume[4] devised a method for converting readily available 3-acetyl-1-(benzenesulfonyl)pyrrole[3] to the corresponding 3-formyl derivative. In this approach, 3-acetyl-1-(benzenesulfonyl)pyrrole (**1**) was oxidized by selenium dioxide to a vicinal ketoaldehyde which was reduced *in situ* with sodium borohydride to afford the vicinal diol **2**. This diol was then cleaved with sodium metaperiodate[5] to afford 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde (**3**) in 85% overall yield. Despite the efficacy of this three-step procedure, the major drawback of this method is that a four fold excess of selenium dioxide is required.