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A SYNTHESIS OF SELECTED *o,o'*-DISUBSTITUTED DIARYLACETIC ESTERS AND DIARYLMETHANES

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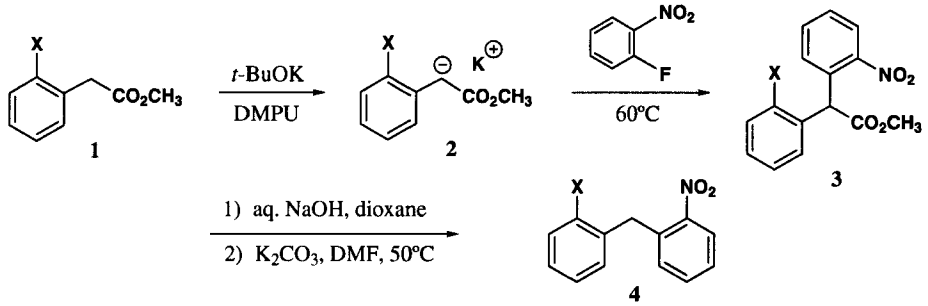
A recent project required access to 2-(2-nitrobenzyl)benzoic acid (**4a**) for a cyclization study to prepare 5,11-dihydro-6*H*-dibenz[*b.e*]azepin-6-one.[1] This compound has been previously synthesized by nitration of 2-benzylbenzoic acid,[2] but it was not purified from the accompanying C-4 nitration product. We, therefore, sought a method to prepare the C-2 nitrated compound in pure form. Our synthetic plan involved (1) nucleophilic aromatic substitution of the 2-[2-(methoxycarbonyl)phenyl]acetate anion (**2a**) to 2-fluoro-1-nitrobenzene, (2) basic hydrolysis of the two esters, and (3) selective decarboxylation of the doubly benzylic acid group.[3] Previous work in this laboratory[4] and by others[5] has shown that stabilized anions can be added to 2- and 4-halo-1-nitrobenzenes by nucleophilic aromatic substitution but, to date, additions of methyl phenylacetate derivatives bearing anion-stabilizing electron withdrawing groups at C-2 of the aromatic ring have not been described. We report here our results on the application of this strategy to the synthesis of several *o,o'*-disubstituted diarylacetic esters and diarylmethanes.

The synthesis of the target compounds is illustrated in the *Scheme*. The methyl phenylacetate derivatives **1a-d** were prepared by known methods.[6-9] The corresponding anions **2a-d** were generated using potassium *tert*-butoxide as the base; sodium hydride proved less satisfactory. As in our earlier work,[4] DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was found to be a convenient and relatively safe solvent for these reactions. Following anion formation, 0.75 equivalents of 2-fluoro-1-nitrobenzene was added dropwise and the mixture was stirred at 23°C for 1 h and at 60°C for 12-24 h. Aqueous ammonium chloride workup gave the substitution products in 60-72% yield.[10] With the exception of **3c**, all of the products were solids and easily purified by trituration with 5% petroleum ether in ether followed by filtration. Product **3c** was purified by flash chromatography to give the addition product along with *ca* 20% of recovered **1c**.



a) X = CO_2CH_3 except in **4** where X = CO_2H; b) X = CN; c) X = PhCO; d) X = NO_2

The hydrolysis-decarboxylation procedure proceeded smoothly for substrates **3a-c** to give **4a-c** in 67-92% yield. Substrate **3d**, however, underwent decomposition when treated with aqueous base in the hydrolysis step. The final product was a complex mixture containing at best only a trace of **4d**. Attempts to demethoxycarbonylate **3d** by an S_N2-type dealkylation[11] using lithium chloride in polar aprotic solvents (DMSO and DMPU) also failed and further work on this substrate was discontinued.

In summary, a procedure has been optimized for the nucleophilic aromatic substitution of several *o*-substituted phenylacetic ester anions to 2-fluoro-1-nitrobenzene. The synthesis is efficient, clean and generates products that are easily purified. The method is limited in not permitting the use of esters bearing enolizable groups at C-2, but should find use for the preparation of a modest number of *o,o'*-disubstituted diarylacetic esters and diarylmethanes.

EXPERIMENTAL SECTION

DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, Aldrich, puriss grade, absolute, over molecular sieves) was stored under nitrogen and transferred by syringe into reactions where it was used. DMF (EM Science, GR grade), from a freshly opened bottle, was dried over 4Å molecular sieves under nitrogen and transferred by syringe into reactions where it was used. Commercial anhydrous potassium carbonate was ground to a fine powder, dried under vacuum at 120°C for 24 h and stored in an oven at 120°C. Methyl 2-[2-(methoxycarbonyl)phenyl]acetate

(**1a**),[6] methyl (2-cyanophenyl)acetate (**1b**),[7] methyl (2-benzoylphenyl)acetate (**1c**)[8] and methyl (2-nitrophenyl)acetate (**1d**)[9] were prepared by literature methods. All reactions were performed under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were carried out using flash column chromatography[12] on silica gel (grade 62, 60-200 mesh) mixed with UV active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and referenced to internal TMS; coupling constants (*J*) are given in Hz. Mass spectra (EI/DP) were obtained at 70 eV.

Representative Procedure for Nucleophilic Aromatic Substitution of *o*-Substituted Methyl Phenylacetates to 2-Fluoro-1-nitrobenzene: Methyl 2-[2-(Methoxycarbonyl)phenyl]-2-(2-nitrophenyl)acetate (3a).- A 50-mL three-necked round-bottomed flask equipped with an addition funnel, a condenser and a magnetic stir bar was charged with 8 mL of DMPU and 0.57 g (5.10 mmol) of potassium *tert*-butoxide. The mixture was stirred to dissolve the potassium *tert*-butoxide and a solution of 1.04 g (5.00 mmol) of **1a** in 2 mL of DMPU was added dropwise during 5 min. The reaction became warm as the bright orange anion was formed. The mixture was stirred for 10 min and 0.53 g (3.75 mmol) of 2-fluoro-1-nitrobenzene was added. The reaction again became warm during the addition. The reaction was stirred at 23°C for 1 h and at 60°C (oil bath) for 12-24 h, then added to 10% aqueous NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with water (2x) and 5% aqueous NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil that crystallized on standing. The product was purified by trituration with 5% petroleum ether in ether to give 0.89 g (72%) of **3a** as light yellow crystals, mp 115-117°C.

IR 1738, 1716, 1527, 1351 cm^{-1}; ^{1}H NMR δ 8.05 (overlapping dd, 2 H, *J* = 7.9, 1.6), 7.54 (td, 1 H, *J* = 7.6, 1.4), 7.50 (td, 1 H, *J* = 7.6, 1.6), 7.45 (td, 1H, *J* = 7.6, 1.6), 7.40 (dd, 1 H, *J* = 7.6, 1.1), 7.23 (dd, 1 H, *J* = 7.4, 1.1), 7.05 (dd, 1 H, *J* = 7.6, 1.6), 6.56 (s, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR δ 172.4, 166.8, 148.0, 138.2, 133.8, 133.0, 132.5, 131.7, 131.0, 129.8, 129.5, 128.1, 127.9, 124.9, 52.6, 52.2, 50.7; MS *m/z* 329 (M^+).

Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.01; H, 4.56; N, 4.26. Found: C, 61.89; H, 4.52; N, 4.31

Methyl 2-(2-Cyanophenyl)-2-(2-nitrophenyl)acetate (3b): 0.75 g (68%) as tan crystals purified by trituration with 5% petroleum ether in ether, mp 109-110°C; IR 2225, 1738, 1527, 1349 cm^{-1}; ^{1}H NMR δ 8.13 (dd, 1 H, *J* = 7.6, 1.6), 7.73 (dm, 1 H, *J* = 7.6), 7.64 (td, 1 H, *J* = 7.6, 1.1), 7.57 (td, 1 H, *J* = 7.6, 1.6), 7.54-7.44 (complex, 2 H), 7.32 (d, 1 H, *J* = 7.9), 7.03 (dd, 1 H, *J* = 7.9, 1.6), 6.11 (s, 1 H), 3.80 (s, 3 H); ^{13}C NMR δ 170.7, 148.2, 140.2, 133.6, 133.5, 133.1, 131.8, 131.1, 129.3, 129.0, 128.5, 125.6, 116.9, 113.9, 53.0, 51.9; MS *m/z* 296 (M^+).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.05; N, 9.46. Found: C, 64.89; H, 4.09; N, 9.32

Methyl 2-(2-Benzoylphenyl)-2-(2-nitrophenyl)acetate (3c): 0.84 g (60%) as a light yellow oil, purified by flash column chromatography using increasing concentrations of ether in hexane

(0.20 g of the starting keto ester was recovered); IR 1738, 1657, 1527, 1349 cm^{-1}; ^1H NMR δ 7.99 (dd, 1 H, *J* = 8.2, 1.4), 7.73 (dd, 2 H, *J* = 8.2, 1.4), 7.56-7.48 (complex, 3 H), 7.46- 7.37 (complex, 5 H), 7.28 (dd, 1 H, *J* = 7.9, 0.5), 7.22 (dd, 1 H, *J* = 7.9, 1.4), 6.04 (s, 1 H), 3.73 (s, 3 H); ^{13}C NMR δ 197.5, 171.9, 148.6, 138.4, 137.3, 136.5, 133.6, 133.1 (2), 131.5, 131.0, 130.3, 130.2, 129.8, 128.3 (2), 127.0, 125.2, 52.8, 50.5; MS *m/z* 375 (M^+).

Anal. Calcd for $C_{22}H_{17}NO_5$: C, 70.40; H, 4.53; N, 3.73. Found: C, 70.17; H, 4.49; N, 3.81

Methyl 2,2-*bis*(2-Nitrophenyl)acetate (3d): 0.78 g (66%) as tan crystals purified by trituration with 5% petroleum ether in ether, mp 101-102°C; IR 1742, 1528, 1349 cm^{-1}; ^1H NMR δ 8.11 (dd, 2 H, *J* = 8.2, 1.4), 7.61 (td, 2 H, *J* = 7.6, 1.6), 7.54 (td, 2 H *J* = 7.9, 1.6), 7.19 (dd, 2 H, *J* = 7.6, 1.4), 6.34 (s, 1 H), 3.77 (s, 3 H); ^{13}C NMR δ 171.0, 148.8, 133.5, 132.0, 130.9, 128.9, 125.6, 52.9, 50.1; MS *m/z* 316 (M^+).

Anal. Calcd for $C_{15}H_{12}N_2O_6$: C, 59.96; H, 3.80; N, 8.86. Found: C, 59.69; H, 3.85; N, 8.98

Representative Procedure for Hydrolysis-Decarboxylation: 2-[(2-Nitrophenyl)methyl]-benzoic Acid (4a).- The procedure of Bull and co-workers was modified.[3] Step 1: A solution of 1.15 g (3.50 mmol) of **3a** in 15 mL of dioxane was treated with 4.2 mL of aqueous 2.0 M NaOH (8.40 mmol) and stirred for 6 h at room temperature. The dioxane was removed under vacuum, the aqueous product was acidified to pH 2 with 1.0 M HCl and extracted with ether (3x). The combined ether extracts were washed with water (2x) and 5% aqueous NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The crude product contained a mixture of the dicarboxylic acid and the monodecarboxylated product, which was carried on without further purification.

Step 2: The above mixture was dissolved in 15 mL of anhydrous DMF, 1.00 g (7.25 mmol) of anhydrous K_2CO_3 was added and the mixture was stirred at 50°C (oil bath) for 1-2 h. The reaction mixture was cautiously added to 1.0 M HCl and extracted with ether (3x). The combined ether extracts were washed with water (2x) and 5% aqueous NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by trituration from 5% petroleum ether in ether to give 0.60 g (67%) of **4a** as light yellow crystals. An analytical sample was obtained by recrystallization from benzene, mp 143-144°C.

IR 3515-2109, 1688, 1524, 1348 cm^{-1}; ^1H NMR δ 11.7 (br s, 1 H), 8.13 (dd, 1 H, *J* = 7.9, 1.4), 7.94 (dd, 1 H, J = 7.9, 1.3), 7.50 (td, 1 H, *J* = 7.4, 1.6), 7.44 (td, 1 H, *J* = 7.6, 1.4), 7.35 (m, 2 H), 7.13 (dd, 1 H, *J* = 7.6, 0.5), 7.04 (dd, 1 H, *J* = 7.9, 1.1), 4.71 (s, 2 H); ^{13}C NMR δ 172.4, 149.6, 141.5, 135.8, 133.4, 132.8, 132.2, 131.6, 131.5, 128.2, 127.1, 127.0, 124.5, 37.0; MS *m/z* 257 (M^+).

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.28; N, 5.45. Found: C, 65.42; H, 4.31; N, 5.39

2-[(2-Nitrophenyl)methyl]benzonitrile (4b): run on a 1.70 mmol scale; step 1 used 2.0 mL of 2.0 M NaOH (4.00 mmol) in 8 mL of dioxane; step 2 used 0.23 g (1.70 mmol) of K_2CO_3 in 8 mL of DMF; 0.37 g (92%) of **4b** was isolated as a light yellow powder purified by trituration with 2% ether in petroleum ether, mp 107-108°C; IR 2218, 1521, 1344 cm^{-1}; ^1H NMR δ 8.03 (dd, 1 H, *J* = 8.2, 1.4), 7.68 (dd, 1 H, *J* = 7.6, 1.4), 7.58 (td, 1 H, *J* = 7.6, 1.4), 7.47 (m, 2 H), 7.34 (tm, 1 H, *J* = 7.6), 7.28 (ddd, 1 H, *J* = 7.6, 1.4, 0.5), 7.09 (dm, 1 H, *J* = 7.9), 4.58 (s, 2 H); ^{13}C NMR δ

149.2, 142.5, 133.4, 133.1 (2), 133.0, 132.5, 129.5, 128.2, 127.3, 125.2, 117.7, 113.0. 37.0; MS *m/z* 238 (M^+).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.59; H, 4.20; N, 11.76. Found: C, 70.46; H, 4.14; N, 11.91

2-[(2-Nitrophenyl)methyl]benzophenone (4c): run on a 1.88 mmol scale; step 1 used 2.2 mL of 2.0 M NaOH (4.40 mmol) in 8 mL of dioxane; step 2 used 0.26 g (1.88 mmol) of K_2CO_3 in 8 mL of DMF; 0.54 g (91%) of **4c** was isolated as a tan oil purified by flash column chromatography; IR 1660, 1524, 1349 cm^{-1}; ^1H NMR δ 7.87 (dd, 1 H, *J* = 8.2, 1.4), 7.74 (dm, 2 H, *J* = 8.4), 7.56 (tt, 1 H, *J* = 7.4, 1.4), 7.46-7.40 (complex, 4 H), 7.38-7.26 (complex, 3 H), 7.23 (dm, 1 H, *J* = 8.7), 7.13 (dm, 1 H, *J* = 7.9), 4.42 (s, 2 H); ^{13}C NMR δ 198.2, 149.5, 138.6, 138.1, 137.4, 135.3, 133.2, 133.0, 132.9, 130.6, 130.4, 130.2, 129.1, 128.3, 127.4, 126.0, 124.7, 36.2; MS *m/z* 317 (M^+).

Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.73; N, 4.42. Found: C, 75.50; H, 4.68; N, 4.29

1-Nitro-2-[(2-nitrophenyl)methyl]benzene (4d): Compound **3d** decomposed under the basic hydrolysis conditions to give a complex mixture of products. The trace amount of **4d** produced could not be isolated.

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A CONVENIENT SYNTHESIS OF 3-ETHOXYCARBONYLAMINO-2-HYDROXY-4-PHENYLBUTYRIC ACID

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3-Amino-2-hydroxy-4-phenylbutyric acid (AHPBA) and its derivatives[1] are useful starting materials for the preparation of HIV-1 protease inhibitors such as saquinavir[2] and amprenavir.[3] Various synthetic routes for the preparation of this type of compounds have been published.[4-6] We previously reported a novel and facile synthetic route to AHPBA and its derivatives (4*S*,5*S*)-4-benzyl-5-hydroxymethyl oxazolidin-2-one as part of our study of the synthesis of HIV-1 protease inhibitors.[7] In this paper, *N*-phthaloyl protected *L*-phenylalanine was treated with