Oxidative nucleophilic substitution of hydrogen in nitrobenzenes with 2-phenylpropionic esters

Mieczysław Mąkosza,* Marek Surowiec, and Maciej Paszewski

Institute of Organic Chemistry, Polish Academy of Sciences
ul. Kasprzaka 44/52, PL-01 224 Warsaw, Poland
E-mail: icho-s@icho.edu.pl

Dedicated to Professor Binne Zwanenburg on his 70th anniversary
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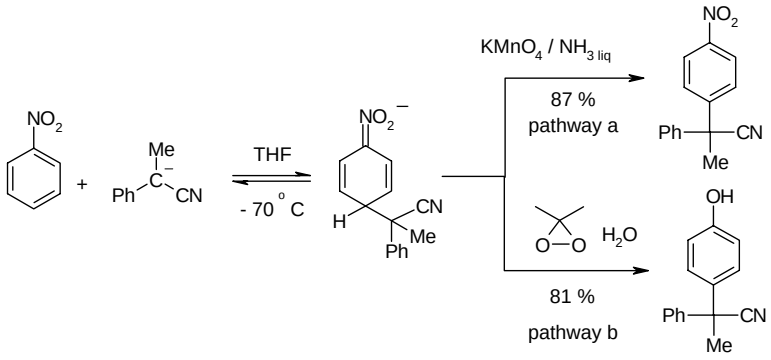
Abstract
Carbanions of alkyl 2-phenylpropionates add to nitroarenes in positions *para* to the nitro group, the produced σ^H adducts are oxidized by $KMnO_4$ to form alkyl 2-phenyl-2-(4-nitroaryl)propionates whereas oxidation with dimethyldioxirane gives esters of 2-phenyl-2-(4-hydroxyaryl)propionic acids.

Keywords: Nitroarenes, phenols, esters, nucleophilic substitution of hydrogen, oxidation

Introduction

Nucleophilic substitution of hydrogen in electron-deficient arenes proceeds *via* addition of nucleophiles to the arenes with formation of σ^H adducts, that can be subsequently converted into the final products in a variety ways.[1,2] Oxidation of the σ^H adducts giving products of oxidative nucleophilic substitution of hydrogen (ONSH) is one of the most general ways of such conversion. One of the serious obstacles in the ONSH reactions is generally the high sensitivity of C-nucleophilic agents, such as carbanions or the Grignard reagents, towards oxidation. For this reason, it appears that introduction of carbon substituents *via* ONSH can be executed provided that addition of the C-nucleophiles and the formation of σ^H adducts proceeds to completion, so amounts of the free nucleophiles in the system are negligible. In our previous papers[3, 4] we have reported that equilibrium of the addition of the 2-phenylpropionitrile carbanion to nitrobenzene and its derivatives, carried out in liquid NH_3 and THF at –70 ^oC, is shifted to the σ^H adducts almost quantitatively and that these adducts are efficiently oxidized by external oxidants such as $KMnO_4$ in liquid ammonia (pathway a in Scheme 1) and dimethyldioxirane (DMD) in THF-acetone (pathway b in Scheme 1). Oxidation with these two oxidants gave different products leading to an assumption that they interact with the σ^H adducts

at different places. Presumably permanganate anion attacks the σ^H adduct at the addition site of the nucleophile, producing substituted nitroarenes – products of oxidative nucleophilic substitution of hydrogen (ONSH),[3] whereas oxidation with DMD proceeds at the carbon bearing the nitro group giving substituted phenols in which the nitro group is replaced by hydroxy group.[4] It appears that initially cyclohexedienone derivatives are formed *via* a kind of oxidative Nef reaction subsequently rearranging to phenols.[4b] These assumptions are supported by the observation that the permanganate oxidation is hampered by bulky substituents in the vicinity of the addition site and proceeds with high kinetic isotope effect,[5] whereas such effects were not observed for the DMD oxidation.[4b]



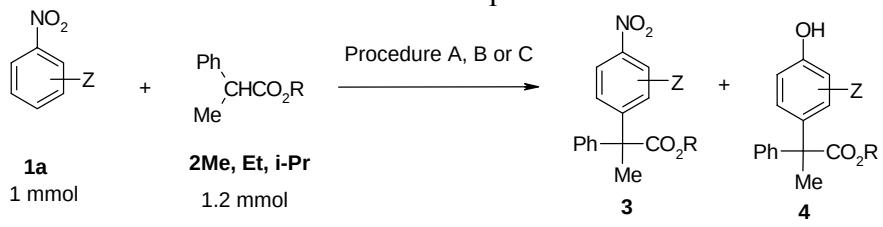
Scheme 1

Results and Discussion

Oxidation of the σ^H adducts of 2-phenylpropionitrile carbanion with permanganate is sensitive to steric hindrances of substituents in vicinity of the addition site,[3b] it was therefore of interest to learn whether the process can be extended on the σ^H adducts of much bulkier carbanions of alkyl 2-phenylpropionates. For the preliminary experiments with nitrobenzene **1a**, three esters: methyl, ethyl and *iso*-propyl 2-phenylpropionates **2Me, Et, *i*-Pr** were used. The reactions were carried out according to the standard procedures. The carbanions were generated by treatment of esters with *t*-BuOK in THF in the presence of nitrobenzene at –70 ^oC. The produced σ^H adducts were oxidized by addition of $KMnO_4$ and liquid ammonia – protocol developed by us for oxidation of the σ^H adducts of the Grignard reagents,[6] or dimethyldioxirane in acetone. Results of these experiments are given in Table, entries 1-10. Similar results of oxidative substitution *via* permanganate oxidation were obtained when the generation of carbanion and formation of the σ^H adducts were carried out in liquid ammonia with $NaNH_2$ as a base.

It should be noted that yields of the both types the oxidation products: substituted nitroarenes **3** and phenols **4** in the reactions of ethyl and *iso*-propyl esters are usually high and there is excellent balance of arenes indicating that addition to give σ^H adducts proceeds to high extent and all σ^H adducts are oxidized. Thus the bulky esters groups do not hinder the oxidation of the σ^H adducts with permanganate. Permanganate oxidation of σ^H adducts generated by addition of methyl 2-phenylpropionate carbanion gave a somewhat lower yield of the ONSH product,

obviously due to partial ammonolysis of the ester, thus in experiments with other nitroarenes ethyl and *iso*-propyl 2-phenylpropionates were used. Results of the reactions of these esters with various nitroarenes under the standard condition are presented in the Table.



Scheme 2

Table. Oxidation of σ^H adducts of 2-phenylpropionate esters to nitrobenzebne derivatives with $KMnO_4$ or dimethyldioxirane

Entry	Starting nitrocompound		Ester **2**	Procedure	Products	
	Z	**1**	R		**3**	**4**
1.	H	**1a**	Me	A	**3a Me** 66%	-
2.	H	**1a**	Me	B	**3a Me** 5%	-
3.	H	**1a**	Me	C	**3a Me** 12%	**4a Me** 78%
4.	H	**1a**	Et	A	**3a Et** 97%	-
5.	H	**1a**	Et	B	**3a Et** 90%	-
6.	H	**1a**	Et	C[a]	**3a Et** 0%	**4a Et** 67%
7.	H	**1a**	Et	C	**3a Et** 12%	**4a Et** 87%
8.	H	**1a**	*i*-Pr	A	**3a *i*-Pr** 93%	-
9.	H	**1a**	*i*-Pr	B	**3a *i*-Pr** 90%	-
10.	H	**1a**	*i*-Pr	C	**3a *i*-Pr** 10%	**4a *i*-Pr** 83%
11.	2-Cl	**1b**	**Et**	A	**3b Et** 96%	-
12.	2-Cl	**1b**	Et	C	**3b Et** 18%	**4b Et** 74%
13.	2-MeO	**1c**	**Et**	A	**3c Et** 98%	-
14.	2-MeO	**1c**	Et	C[a]	**3c Et** 18%	**4c Et** 40%
15.	2-MeO	**1c**	Et	C	**3c Et** 47%	**4c Et** 45%
16.	3-Cl	**1d**	Et	A	**3d Et** 65%	-
17.	3-Cl	**1d**	Et	C	**3d Et** 14%	**4d Et** 59%
18.	3-Cl	**1d**	*i*-Pr	B	**3d *i*-Pr** 63%	-
19.	2-CN	**1e**	*i*-Pr	B	**3e *i*-Pr** 88%	-
20.	2-CN	**1e**	*i*-Pr	C	**3e *i*-Pr** 40%	**4e *i*-Pr** 59%
21.	3-CN	**1f**	Et	A	**3f Et** 74%	-
22.	3-CN	**1f**	*i*-Pr	B	**3f *i*-Pr** 50%	-
23.	3-CN	**1f**	Et	C	**3f Et** 8%	**4f Et** 70%
24.	3-Br	**1g**	*i*-Pr	B	**3g *i*-Pr** 66%	-
25.	3-Br	**1g**	*i*-Pr	C	**3g *i*-Pr** 0%	**4g *i*-Pr** 73%

Procedures: A – *t*-BuOK/THF, then $KMnO_4$ / $NH_{3\ liq}$; B – $NaNH_2/NH_{3\ liq}$, then $KMnO_4$; C - *t*-BuOK/THF, than DMD / acetone. Oxidants were added 15 min after the carbanion and nitrobenzene were mixed. [a] DMD was added after 5 min.; 32% of nitrobenzene or 33% of 4-nitroanisole were recovered.

The results show that permanganate oxidation of the σ^H adducts to *meta* substituted nitrobenzenes gave somewhat lower yields of the ONSH products, perhaps these substituents, together with bulky ester group of the carbanions, hinder oxidation of the σ^H adducts. Such effect was not observed in the analogous reactions of 2-phenylpropionitrile.[3]

It appears that addition of carbanions of esters to nitroarenes proceeds slower than that of 2-phenylpropionitrile, thus it needs longer time for completion. Because of that, relatively slow process of so called spontaneous oxidation competing with DMD oxidation become noticeable (see entries 6, 7 and 14, 15). This process does not affect results of the permanganate oxidation since both of these reactions gave the same product. On the other hand it is responsible for formation of significant amounts of the substituted nitroarenes **3a**, **c**, **e** on the expenses of phenols **4a**, **c**, **e** in the DMD oxidation.

Additionally we have attempted to oxidize some σ^H adducts of the esters to nitroarenes with 2,3-dichloro-5,6-dicyanobenzoquinone, DDQ, oxidant widely used for aromatization of σ^H adducts to arenes.[7] In our hands oxidation of the σ^H adducts with DDQ gave expected substituted nitroarenes, the ONSH products, although in somewhat lower yields than with $KMnO_4$ oxidant.

The results presented in this paper indicate that oxidation of σ^H adducts of carbanions of alkyl 2-phenylpropionates with $KMnO_4$ or DDQ gave alkyl 2-phenyl-2-nitroarylpropionates – products of the ONSH reactions, whereas oxidation with DMD leads to alkyl 2-phenyl-2-(4-hydroxyaryl)propionates. Both of these reactions offer attractive possibilities in organic synthesis.

Experimental Section

General Procedures. Melting points were uncorrected. ^{1}H NMR spectra were recorded with a Varian Gemini 200 (200 MHz) or Mercury-400BB (400 MHz) instruments. Mass spectra were measured on AMD 604 Inectra GmbH spectrometer using EI. For analytical TLC Merck alufolien sheets Kieselgel 60 F_{254} were used. For column chromatography silica gel 230-400 mesh, Merck was used. DMF was distilled over calcium hydride and stored over molecular sieves, tetrahydrofuran was distilled over potassium benzophenone ketyl. Potassium *tert*-butoxide was reagent grade purchased from Fluka and was handled in a drybox under argon. Acetone solution of DMD was prepared according to the procedure described by Adam.[8] All reactions were performed under argon atmosphere.

Starting nitroarenes were commercial products. Methyl, ethyl and *iso*-propyl 2-phenylpropionates **2Me, 2Et** and **2*i*-Pr** were prepared from phenylpropionic acid.[9]

***iso*-Propyl 2-phenylpropionates 2*i*-Pr.** Colourless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28-7.34 (m, 4H), 7.22-7.26 (m, 1H), 4.94 - 5.02 (m, 1H), 3.66 (q, 1H, J = 7.15), 1.48 (d, 3H, J = 7.15), 1.21(d, 3H, J = 6.2), 1.13 (d, 3H, J = 6.2). ^{13}C-NMR ($CDCl_3$): δ = 174.0, 140.8, 128.5, 127.4, 126.9, 67.9, 45.7, 21.5, 18.2.

Procedures for the oxidative substitution of hydrogen with 2-phenylpropionic esters in nitroarenes

Procedure A. To a solution of *t*-BuOK (135 mg, 1.2 mmol) in THF (5 ml) at –70°C, a solution of a nitroarene 1 (1 mmol) and an ester 2 (1.2 mmol) in THF (2 ml) was added during 1 minut and the mixture was stirred at -70°C 15 minutes. To this solution powdered $KMnO_4$ (190 mg, 1.2 mmol) and then liquid ammonia (5 ml) were added at –70°C. The reaction mixture was stirred at this temperature for 15 minutes, treated with powdered NH_4Cl (106 mg, 2 mmol) and the cooling bath was removed. Upon evaporation of the ammonia the residue was treated with a solution of oxalic acid in 10% hydrochloric acid (20 ml) and the products were extracted with methylene chloride (4 x 10 ml). The solvent was evaporated and products were purified by column chromatography and recrystalized from appropriate solvents.

Procedure B. To a suspension of sodium amide prepared from sodium (30 mg, 1.2 mmol) in liquid ammonia (ca 15 ml), an ester **2** (1.2 mmol) was added at –70°C, after 3 minutes followed by addition of nitroarene **1** (1 mmol) in THF (1.5 ml). The mixture was stirred for 15 minutes and powdered potassium permanganate (170 mg, 1.2 mmol) was added. Further treatment as in procedure A .

Procedure C. As procedure A but instead of $KMnO_4$ and liquid ammonia water (18 μl, 1 mmol) and acetone solution of DMD (ca. 1.2 mmol, 20 mL of 0.06 – 0.09 M) was added to the mixture. After 5 minutes aqueous NH_4Cl (0.1 mL) was added and cooling bath removed. the solution was dried with $MgSO_4$ the solvent evaporated and the residue was purified by column chromatography.

Oxidation of the σ^H adducts with DDQ. As in procedure A but DDQ (273 mg, 1.2 mmol) dissolved in DMF (2 ml) before it was added. Further treatment as usual.

Physical characteristic and analysis of products

Methyl 2-phenyl-2-(4-nitrophenyl)propionate (3a Me). Procedure A. Yield 189 mg, 66%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 – 8.30 (m, 2H), 8.43 – 8.35 (m, 2H), 7.40 – 7.21 (m, 5H), 3.78 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.7, 152.3, 146.9, 143.0, 129.4, 128.8, 127.9, 127.8, 123.4, 56.9, 53.1, 27.0. Anal. calcd. for $C_{16}H_{15}NO_4$ (M = 285.30): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.07; H, 5.22; N, 5.10.

Methyl 2-phenyl-2-(4-hydroxyphenyl)propionate (4a Me). Procedure C. Yield 200 mg, 78%, colourless crystals mp. 83 – 84°C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.18 (m, 5H), 7.15 – 7.07 (m, 2H), 6.84 – 6.75 (m, 2H), 6.68 (s broad, 1H), 3.75 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 155.2, 145.2, 135.9, 129.5, 128.3, 128.1, 127.0, 115.2, 56.1,

52.8, 27.4. MS EI m/z: 257 (1.3), 256 (7.2), 198 (15.5), 197 (100.0). HRMS (EI): Calcd. for $C_{16}H_{16}O_3$ M = 256.1099; Found M = 256.1080.

Ethyl 2-phenyl-2-(4-nitrophenyl)propionate (3a Et). Procedure A. Yield 290 mg, 97%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 – 8.11 (m, 2H), 7.41 – 7.36 (m, 2H), 7.36 – 7.28 (m, 4H), 7.24 – 7.20 (m, 1H), 4.23 (q, 2H, J = 7.1), 1.96 (s, 3H), 1.22 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 152.2, 146.6, 142.9, 129.2, 128.4, 127.7, 127.4, 123.1, 61.7, 56.6, 26.8, 13.9. Anal. calcd. for $C_{17}H_{17}NO_4$ (M = 299.33): C, 68.22; H, 5.72; N, 4.68. Found: C, 68.44; H, 5.72; N, 4.55.

Ethyl 2-phenyl-2-(4-hydroxyphenyl)propionate (4a Et). Procedure C. Yield 235 mg, 87 %, colourless crystals mp. 106 – 107°C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.17 (m, 5H), 7.12 – 7.07 (m, 2H), 6.78 – 6.72 (m, 2H), 5.42 (s, 1H), 4.20 (q, 2H, J = 7.1), 1.88 (s, 3H), 1.21 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 154.4, 145.0, 136.2, 129.3, 128.0, 127.8, 126.6, 114.8, 61.4, 55.8, 27.1, 14.0 Anal. calcd. for $C_{17}H_{18}O_3$ (M = 270.33): C, 75.53; H, 6.71. Found: C, 75.45; H, 6.64.

***iso*-Propyl 2-phenyl-2-(4-nitrophenyl)propionate (3a *i*-Pr). Procedure A.** Yield 292 mg, 93%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 – 8.11 (m, 2H), 7.42 – 7.37 (m, 2H), 7.37 – 7.22 (m, 5H), 5.15 – 5.05 (m, 1H, J = 6.2), 1.95 (s, 3H), 1.21 (d, 3H, J = 6.2), 1.18 (d, 3H, J = 6.2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 152.2, 146.5, 142.9, 129.1, 128.3, 127.6, 127.2, 122.9, 69.2, 56.5, 26.6, 21.3, 21.2. MS (EI): m/z (%) = 313 (M^+, 2), 226 (100), 180 (13), 165 (12), 43 (14). Anal. calcd. for $C_{18}H_{19}NO_4$ (M = 313.35): C, 68.99; H, 6.11; N, 4.47. Found: C, 69.01; H, 6.17; N, 4.24.

***iso*-Propyl 2-phenyl-2-(4-hydroxyphenyl)propionate (4a *i*-Pr). Procedure C.** Yield 237 mg, 83%, colourless crystals mp. 95 – 96°C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.19 (m, 5H), 7.13 – 7.08 (m, 2H), 6.76 – 6.71 (m, 2H), 5.13 – 5.03 (m, 1H, J = 6.2), 1.88 (s, 3H), 1.19 (d, 3H, J = 6.2), 1.20 (d, 3H, J = 6.2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 154.8, 145.1, 135.6, 129.2, 127.9, 127.8, 126.5, 114.7, 68.8, 55.7, 27.1, 25.5, 21.4. Anal. calcd. for $C_{18}H_{20}O_3$ (M = 284.36): C, 76.03; H, 7.09. Found: C, 75.72; H, 6.82.

Ethyl 2-phenyl-2-(3-chloro-4-nitrophenyl)propionate (3b Et). Procedure A. Yield 320 mg, 96%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, 1H, J = 8.6), 7.40 (d, 1H, J = 2.0), 7.39 – 7.30 (m, 3H), 7.24 (dd, 1H, J = 8.6, J = 2.0), 7.23 – 7.19 (m, 2H), 4.24 (q, 2H, J = 7.1), 1.94 (s, 3H), 1.24 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 151.1, 146.1, 142.3, 131.6, 128.6, 127.7, 127.6, 127.5, 126.7, 125.1, 61.9, 56.3, 26.6, 13.9. Anal. calcd. for $C_{17}H_{16}NO_4Cl$ (M = 333.77): C, 61.18; H, 4.83; N, 4.20. Found: C, 60.94; H, 4.88; N, 4.50.

Ethyl 2-phenyl-2-(3-chloro-4-hydroxyphenyl)propionate (4b Et). Procedure C. Yield 225 mg, 74%, colourless crystals mp. 80 – 81°C ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.23 (m, 5H), 7.21 (d, 1H, J = 2.2), 7.22 – 7.15 (m, 2H), 5.59 (s, 1H), 4.21 (q, 2H, J = 7.1), 1.87 (s, 3H), 1.22 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7, 150.1, 144.4, 137.6, 128.7, 128.4, 128.1, 127.6, 126.9, 119.4, 115.6, 61.4, 55.7, 27.1, 14.0 Anal. calcd. for $C_{17}H_{17}ClO_3$ (M = 304.77): C, 67.00; H, 5.62. Found: C, 66.99; H, 5.67.

Ethyl 2-phenyl-2-(3-methoxy-4-nitrophenyl)propionate (3c Et). Procedure A. Yield 323 mg, 98%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, 1H, J = 8.6), 7.38 – 7.28 (m, 3H), 7.25 – 7.20 (m, 2H), 6.94 (d, 1H, J = 1.8), 6.90 (dd, 1H, J = 8.6, J = 1.8), 4.23 (q, 2H, J = 7.1), 3.83 (s, 3H), 1.95 (s, 3H), 1.23 (t, 3H, J = 7.1).^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 152.5, 151.8, 142.9, 137.9, 134.2, 128.3, 127.7, 127.3, 125.2, 120.1, 113.8, 61.7, 56.7, 26.7, 13.9. HR MS (EI): Calcd. for $C_{18}H_{19}O_5N$ M = 329.1263; Found M = 329.1269.

Ethyl 2-phenyl-2-(3-methoxy-4-hydroxyphenyl)propionate (4c Et). Procedure C. Yield 135 mg, 45%, light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.19 (m, 5H), 6.86 (dd, 1H, J = 7.8, J = 0.9), 6.81 – 6.76 (m, 2H), 5.60 (s, 1H), 4.26 – 4.16 (m, 2H), 3.78 (s, 3H), 1.88 (s, 3H), 1.22 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 145.9, 145.2, 144.5, 135.8, 127.9, 127.8, 126.6, 120.8, 113.6, 111.2, 61.2, 56.1, 27.2, 14.0. Anal. calcd. for $C_{18}H_{20}O_4$ (M = 300.36): C, 71.98; H, 6.71. Found: C, 71.73; H, 6.56. MS EI m/z (%): 301 (2.9), 300 (14.8), 228 (16.2), 227 (100.0). HRMS (EI): Calcd. for $C_{18}H_{20}O_4$ M = 300.1362; Found M = 300.1365.

Ethyl 2-phenyl-2-(2-chloro-4-nitrophenyl)propionate (3d Et). Procedure A. Yield 214 mg, 65%, light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.29 (d, 1H, J = 2.4), 7.96 (dd, 1H, J = 8.7, J = 2.4), 7.58 – 7.40 (m, 5H), 7.02 (d, 1H, J = 8.7), 4.35 - 4.08 (m, 2H), 2.06 (s, 3H), 1.30 – 1.20 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 173.1, 150.9, 140.1, 135.1, 130.9, 129.7, 128.9, 128.4, 126.7, 126.0, 121.6, 62.1, 56.3, 23.5, 14.1. MS EI m/z (%): 333 (1.6), 298 (20.8), 262 (33.2), 260 (100.0), 179 (17.7), 178 (28.6), 149 (29.7). HR MS (EI): Calcd. for $C_{17}H_{16}O_4{}^{35}Cl$ M = 333.0768; Found M = 333.0752.

Ethyl 2-phenyl-2-(2-chloro-4-hydroxyphenyl)propionate (4d Et). Procedure C. Yield 180 mg, 59%, colourless crystals mp. 103 – 104°C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.48 (m, 2H), 7.42 – 7.30 (m, 3H), 7.1 (s broad, 1H), 6.86 (d, 1H, J = 2.4), 6.61 (d, 1H, J = 8.7), 6.52 (dd, 1H, J = 8.7, J = 2.4), 4.38 – 4.17 (m, 2H), 2.00 (s, 3H), 1.24 (t, 3H, J = 7.1). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 155.9, 141.5, 134.9, 134.3, 130.7, 128.6, 128.5, 127.7, 118.1, 113.9, 62.1, 55.5, 24.4, 14.1. MS EI m/z (%): 306 (1.4), 304 (4.1), 270 (3.5), 269 (18.1), 233 (31.2), 231 (100.0). HRMS (EI): Calcd. for $C_{17}H_{17}O_3{}^{35}Cl$ M = 304.0866; Found M = 304.0852.

***iso*-Propyl 2-phenyl-2-(2-chloro-4-nitrophenyl)propionate (3d *i*-Pr). Procedure B.** Yield 219 mg, 63%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, 1H, J = 2.5), 7.94 (dd, 1H, J = 2.5, J = 8.8), 7.3-7.42 (m, 5H), 7.02 (d, 1H, J = 8.8), 5.05-5.11 (m, 1H), 2.03 (s, 3H), 1.20 (d, 3H, J = 6.3), 1.19 (d, 3H, J = 6.3), ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 150.6, 146.8, 140.0, 134.9, 130.6, 128.6, 128.1, 128.0, 125.7, 121.3, 69.5, 56.1, 23.2, 21.3, 21.3. MS (EI): m/z (%) = 260 (M^+ - 87, 100.0), 244 (8.0), 43 (66.0). Anal. calcd. for $C_{18}H_{18}ClNO_4$: C, 62.16; H, 5.22; Cl, 10.19; N, 4.03. Found: C, 62.23; H, 5.11; Cl, 10.15; N, 3.99.

***iso*-Propyl 2-phenyl-2-(3-cyano-4-nitrophenyl)propionate (3e *i*-Pr). Procedure B.** Yield 295 mg, 88%, colourless crystals mp. 108 – 109°C (hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, 1H, J = 8.8), 7.71 (d, 1H, J = 2.2), 7.63 (dd, 1H, J = 2.2, J = 8.8), 7.32-7.42 (m, 3H), 7.2 (m, 2H), 5.1 (m, 1H), 1.96 (s, 3H), 1.24 (d, 3H, J = 6.2), 1.18 (d, 3H, J = 6.2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 152.8, 146.7, 141.6, 135.5, 133.6, 128.9, 127.9, 127.3,

124.9, 115.1, 107.5, 67.0, 56.4, 26.4, 21.5, 21.3. MS (EI): m/z (%) = 251 (M^+-87, 100), 235 (20), 205 (18), 190 (26), 178 (17), 165 (15), 43 (98). Anal. calcd. for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.07; H, 5.63; N, 7.91.

***iso*-Propyl 2-phenyl-2-(3-cyano-4-hydroxyphenyl)propionate (4e *i*-Pr). Procedure C.** Yield 183 mg, 59%, orange oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.85 (dd, 1H, J = 8.4, J = 2.2), 7.42 – 7.20 (m, 5H), 7.18 (d, 1H, J = 2.2), 6.86 (d, 1H, J = 8.4), 5.24 – 4.95 (m, 1H), 2.56 (s, 1H), 1.86 s, 3H), 1.29 – 1.15 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 174.4, 157.4, 144.1, 135.8, 134.6, 133.0, 128.5, 127.8, 126.8, 125.8, 120.7, 116.6, 68.0, 55.8, 27.0, 21.7, 21.5. MS (EI): m/z (%) = 309 (6), 281 (4), 249 (7), 236 (100), 222 (82), 206 (12). HRMS (EI): Calcd. for $C_{19}H_{19}NO_3$ M = 309.1365; Found M = 309.1381.

Ethyl 2-phenyl-2-(2-cyano-4-nitrophenyl)propionate (3f Et). Procedure A. Yield 238 mg, 74%, light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.56 (d, 1H, J = 2.5), 8.24 (dd, 1H, J = 8.9, J = 2.5), 7.48 – 7.42 (m, 5H), 7.10 (d, 1H, J = 8.9), 4.42 – 4.20 (m, 2H, J = 7.1), 2.13 (s, 3H), 1.29 (t, 3H, J = 7.1). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 172.6, 156.2, 146.9, 139.7, 130.6, 129.3, 128.7, 128.5, 128.0, 127.1, 125.4, 114.6, 62.7, 56.9, 24.9, 14.1. MS EI m/z (%): 324 (2.0), 280 (11.8), 253 (10.5), 252 (67.1), 251 (100.0), 205 (73.5), 204 (40.7), 193 (8.7), 190 (9.1). HRMS (EI): Calcd. for $C_{18}H_{16}O_4N_2$ M = 324.1110; Found M = 324.1124.

Ethyl 2-phenyl-2-(2-cyano-4-hydroxyphenyl)propionate (4f Et). Procedure C. Yield 207 mg, 70%, colourless crystals mp. 128 – 129°C ($CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.48 – 7.26 (m, 6H), 7.15 (d, 1H, J = 2.6), 6.86 (dd, 1H, J = 8.8, J = 2.6), 6.72 (d, 1H, J = 8.8), 4.44 – 4.12 (m, 2H), 2.06 (s, 3H), 1.27 (t, 3H, J = 7.1). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 174.9, 155.3, 141.3, 140.8, 130.5, 128.8, 128.1, 126.5, 121.4, 120.1, 118.3, 112.9, 62.5, 56.1, 25.7, 14.1. Anal. calcd. for $C_{18}H_{17}NO_3$ (M = 295.34): C, 73.20; H, 5.80; N, 4.74. Found: C, 72.91; H, 5.66; N, 4.91.

***iso*-Propyl 2-phenyl-2-(2-cyano-4-nitrophenyl)propionate (3f *i*-Pr). Procedure B.** Yield 170 mg, 50%, colourless crystals mp. 116 - 117°C (hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (d, 1H, J = 2.4), 8.22 (dd, 1H, J = 2.4, J = 8.8), 7.36-7.48 (m, 5H), 7.08 (d, 1H, J = 8.8), 5.17 (m, 1H), 2.1 (s, 3H), 1.28 (d, 3H, J = 6.2), 1.19 (d, 3H, J = 6.2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7, 156.0, 146.1, 139.6, 130.3, 129.2, 128.9, 128.4, 127.7, 126.7, 116.3, 114.4, 70.3, 56.7, 24.6, 21.5, 21.3. MS (EI): m/z (%) = 308 (4), 251 (M^+-87, 53), 221 (100), 205 (55), 190 (24), 43 (97). Anal. calcd. for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.57; H, 5.45; N, 8.30.

***iso*-Propyl 2-phenyl-2-(2-bromo-4-nitrophenyl)propionate (3g *i*-Pr). Procedure B.** Yield 220 mg, 66%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, 1H, J = 2.5), 7.98 (dd, 1H, J = 2.5, J = 8.8), 7.49 - 7.54 (m, 2H), 7.32 – 7.43 (m, 3H), 7.03 (d, 1H, J = 8.8), 5.07 (m, 1H), 1.92 (s, 3H), 1.23 – 1.15 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 151.9, 146.6, 140.2, 130.8, 129.3, 128.5, 128.1, 127.9, 124.2, 121.8, 69.6, 57.4, 23.7, 21.4, 21.3. MS (EI): m/z (%) = 304 (100, M^+-87), 260 (66), 225 (27), 178 (38), 43 (44). Anal. calcd. for $C_{18}H_{18}NO_4Br$: C, 54.98; H, 4.87; N, 3.56. Found: C, 55.03; H, 5.00; N, 3.72.

***iso*-Propyl 2-phenyl-2-(2-bromo-4-hydroxyphenyl)propionate (4g *i*-Pr). Procedure C.** Yield 265 mg, 73%, orange oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.58 – 7.48 (m, 2H), 7.44 – 7.26 (m,

5H), 7.07 (d, 1H, J = 2.2), 6.64 (s, 1H), 5.23 - 4.98 (m, 1H), 2.03 (s, 3H), 1.24 (d, 6H, J = 6.2). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 174.7, 155.3, 141.8, 136.5, 131.0, 128.6, 128.4, 127.6, 124.2, 121.7, 114.3, 69.5, 56.9, 24.7, 21.7, 21.6. MS EI m/z (%): 364 (5.6), 362 (5.4), 304 (11.0), 302 (10.8), 283 (30.0), 277 (90.1), 276 (22.4), 275 (100.0), 241 (31.5), 196 (58.8), 195 (24.6), 181 (36.0). HRMS (EI): Calcd. for $C_{18}H_{19}O_3{}^{79}Br$ M = 362.0518; Found M = 362.0531.

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