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The facile synthesis of α-aryl-α-hydroxy esters *via* one-pot vicarious nucleophilic substitution and oxidation

Nicholas J. Lawrence,* Olivier Lamarche† and Nabil Thurrab‡

Department of Chemistry, UMIST, PO Box 88, Manchester, UK M60 1QD. E-mail: n.lawrence@umist.ac.uk

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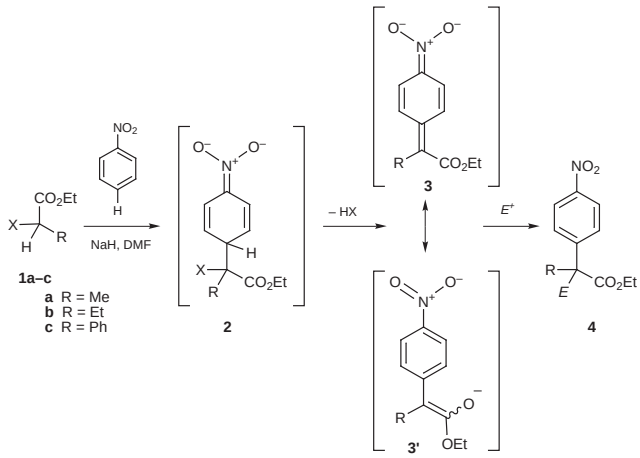
The anion produced by the vicarious nucleophilic substitution reaction of nitroarenes and α-chloro esters is hydroxylated by the action of air and benzaldehyde, thereby producing α-hydroxy esters.

The recently developed process of vicarious nucleophilic substitution (VNS), pioneered by Makosza and co-workers,[1,2] offers a selective mild method for the controlled substitution of hydrogen atoms of aromatic systems. As part of our contribution to the study of the VNS reaction we have developed[3] a one-pot coupling reaction of three components (a nitroarene, a stabilised carbanion derived from **1** and an electrophilic species E^+) for the construction of nitroarenes **4** bearing an adjacent quaternary chiral centre, as illustrated in Scheme 1.[4,5] This process first involves a VNS reaction between the nitroarene and the carbanion to give the intermediate anion **3** *via* loss of HX from the σ-adduct **2**. This post-VNS anion is sufficiently nucleophilic to be quenched *in situ* with a variety of electrophiles E^+ to give the *para*-functionalised nitroarene **4**.

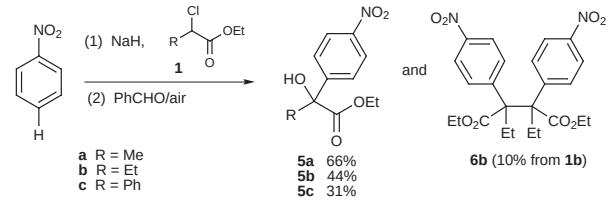
During the study of the reaction of the post-VNS anion **3** with aldehydes, we serendipitously discovered a process for the synthesis of α-aryl-α-hydroxy esters. When the anion **3a** (R = Me), derived from ethyl 2-chloropropionate **1a**, was reacted with benzaldehyde we did not observe the formation of an aldol product. However on one occasion, when air was inadvertently introduced into the reaction flask, we obtained the hydroxy ester **5a** in approximately 50% yield. A careful study of the reaction revealed that the yield could be increased to 66% when 3 equiv. of the ester is used with respect to nitrobenzene (Scheme 2).§ In most of these reactions a small amount (5–10%) of *p*-nitroacetophenone was also produced. It was clear that both benzaldehyde and air were required in the reaction. In the absence of air, the only product obtained upon work up (**4**, R = Me, *E* = H) arose from protonation of the anion **3**. The reaction of the post-VNS anion **3a** with air in the absence of benzaldehyde gave a mixture of α-hydroxy ester **5a** and ketone *p*-nitroacetophenone in near equal proportions. We then applied this intriguing one-pot VNS–hydroxylation process to the reaction of ethyl 2-chlorobutanoate **1b** with nitrobenzene and obtained the ester **5b**. This ester was also obtained in 40% yield when the post-VNS anion was prepared *via* direct deprotonation (NaH, DMF) of ethyl 2-(*p*-nitrophenyl)butanoate followed by oxidation with air and benzaldehyde. In this case the ester was accompanied by 2-(*p*-nitrophenyl)propiophenone (8%) and the diester **6b** (10% as 1 : 1 mixture of *racemic* : *meso* stereoisomers). As confirmation of its structure, the diester **6b** was obtained in 89% yield (*racemic* : *meso* 1 : 1) by treatment of the post-VNS anion **3b** with iodine (Scheme 2).[6] Since such an oxidative coupling is thought to occur *via* a mechanism involving single electron transfer,[5] this reaction also sheds light on the mechanism of the hydroxylation reaction (*vide supra*). Reaction of ethyl α-chlorophenylacetate with nitrobenzene gave ethyl benzoylformate in 35% yield when the VNS reaction was performed at 0 °C for 1 h and 25 °C for 1.5 h; the product presumably arising from direct oxidation of the anion of **1c**. The hydroxy ester **5c** was obtained, albeit in low yield, when nitrobenzene was used in excess (1.5 equiv.) and a longer period of time was used for the VNS reaction (0 °C for 1 h and 25 °C for 3 h). It seems that the enolate derived from **1c** is insufficiently nucleophilic to react efficiently with nitrobenzene. We then applied the hydroxylation reaction to other nitroarenes (Table 1).

Reaction of ethyl 2-chlorobutanoate **1b** with *o*- and *m*-chloronitrobenzenes (entries 1 and 2) and two nitro-substituted pyridines (entries 3 and 4) gave the hydroxy ester products in which the VNS nucleophile has added *para* to the nitro group, as determined from their ^{1}H NMR spectra.¶ The product from 2-nitrothiophene with ethyl 2-chloropropionate **1a** (entry 5) is the 5-substituted hydroxy ester **5e**, as determined from its ^{1}H nmr spectrum.¶ A pair of doublets were observed at δ 7.05 and 7.80 with a coupling constant of 4.3 Hz corresponding to signals from H-3 and H-4 (expected coupling constants:[7] $J_{3,4}$ 3.45–4.35 Hz and $J_{4,5}$ 4.90–5.80 Hz). At low temperature (−33 °C, NH_3, KOH), 2-nitrothiophene is attacked by a variety VNS nucleophiles predominantly at the 3-position.[8] However, as the nucleophile **1a** provides a tertiary anion, it is not surprising that at room temperature the 5-substituted isomer is the exclusive product. It should be noted that oxidation of nitrobenzylic carbanions (made by deprotonation of products of VNS reaction) to aldehydes and ketones has been reported.[9]

The oxidation of enolates by oxygen is, of course, not without precedent. For example, Wasserman and Lipshutz have shown



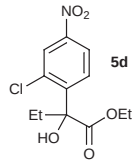
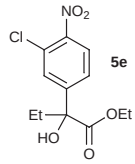
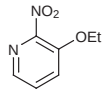
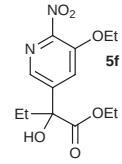
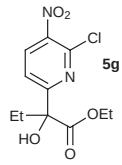
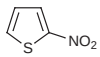
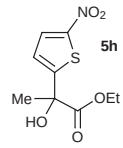
Scheme 1



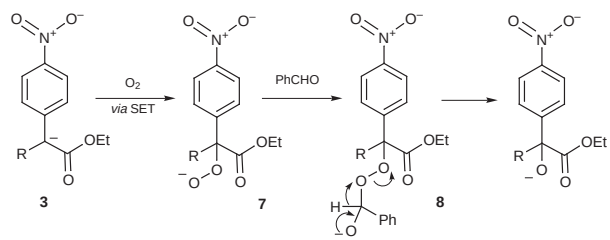
Scheme 2

† Undergraduate research assistant from the Ecole Nationale Supérieure de Synthèses, de Procédés, et d'Ingénierie Chimiques d'Aix-Marseille.
‡ MSc candidate from the University of Al Azhar, Gaza, Palastine.

Table 1 Reaction of nitroarenes to give hydroxy esters

Entry	Nitroarene	Ester	Product	Yield (%)
1		**1b**	 **5d**	53
2		**1b**	 **5e**	62
3		**1b**	 **5f**	52
4		**1b**	 **5g**	50
5		**1a**	 **5h**	44

that lithium enolates of esters react with molecular oxygen to give α-hydroxy esters (after reduction of the first formed peroxide with sodium sulfite).[10] A similar procedure lacking the reductive work-up gives the α-hydroperoxy acids from carboxylic acids.[11] The post-VNS hydroxylation we observe is possibly occurring *via* initial oxidation of the anion **3**, *via* single electron transfer, to a radical which combines with an oxygen radical anion to give peroxide **7** which is trapped by benzaldehyde to give species **8** (Scheme 3). Finally a 1,3-hydride shift gives the alkoxide **8**.[12] Clearly the formation of products such as **6** indicate a mechanism involving radicals. We found that the enolate of **1c**, generated by reaction of sodium hydride, in the absence of nitrobenzene, does not react with oxygen. This suggests that the nitro group also plays a role in the oxidation process, in addition to activating the arene to attack by the VNS nucleophile and stabilising the anion **3**. This is in agreement with the finding of Russel and Bemis[13] that nitrobenzene acts as a single eletron transfer catalyst in the oxidation of stabilised



Scheme 3

benzylic anions to peroxides. In summary, we have developed an intriguing one-pot VNS–hydroxylation reaction using inexpensive reagents that lead to novel α-aryl-α-hydroxy esters.

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Notes and references

§ To a stirred slurry of NaH (0.74 g of a 60% dispersion in oil, 18.5 mmol) in dry DMF (10 cm^3) at 0 °C was added dropwise solution of ethyl 2-chloropropionate **1a** (1.68 g, 12.33 mmol) and nitrobenzene (0.76 g, 6.16 mmol) in dry DMF (10 cm^3). The deep blue–purple reaction mixture was stirred at 0 °C for 60 min and room temperature for 2 h. Benzaldehyde (0.98 g, 9.25 mmol) was added and the reaction mixture stirred at room temperature under an atmosphere of dry air for 24 h. The resulting brown mixture was poured onto a slurry of ice and hydrochloric acid (1 M, 20 cm^3) and extracted with $CHCl_3$ (3 × 20 cm^3). The solvent (DMF and $CHCl_3$) was removed from the combined extracts *in vacuo*. $CHCl_3$ (75 cm^3) was added to the residue. This solution was washed with water (5 × 75 cm^3) and aq. $NaHCO_3$ (5 × 75 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography to give the hydroxy ester **5a**.

¶ *Selected data* for **5d**: δ_H(300 MHz, $CDCl_3$) δ_H 1.25 (3H, t, *J* 7.15, OCH_2CH_3), 1.85 (3H, s, CH_3), 3.75 (1H, s, OH), 4.25 (2H, q, *J* 7.15, OCH_2CH_3), 7.84 (1H, d, *J* 8.7, H-6′), 8.15, (1H, dd, *J* 8.7 and 2.3, H-5′) and 8.23 (1H, d, *J* 2.3, H-3′). For **5e**: δ_H 0.90 (3H, t, *J* 7.4, CH_2CH_3), 1.30 (3H, t, *J* 7.2, OCH_2CH_3), 1.98 (1H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 2.20 (1H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 3.95 (1H, s, OH), 4.19–4.38 (2H, m, OCH_2CH_3), 7.67 (1H, d, *J* 8.6 and 1.9, H-6′), 7.85 (1H, d, *J* 8.6, H-5′) and 7.87 (1H, d, *J* 1.9, H-2′). For **5f**: δ_H 0.92 (3H, t, *J* 7.4, CH_2CH_3), 1.32 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.45 (3H, *J* 6.9, OCH_2CH_3), 2.01 (1H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 2.23 (1H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 3.97 (1H, s, OH), 4.18–4.40 (4H, m, 2 × OCH_2CH_3), 7.85 (1H, d, *J* 1.8, H-4′) and 8.30 (1H, d, *J* 1.8, H-6′). For **5g**: δ_H 0.95 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 2.02 (1 H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 2.37 (1H, dq, *J* 14.7 and 7.4, $CH_aH_bCH_3$), 4.20–4.32 (2H, m, OCH_2CH_3), 4.35 (1H, s, OH), 7.78 (1H, d, *J* 8.3, H-5′) and 8.25 (1H, d, *J* 8.3, H-4′). For **5h**: δ_H 1.35 (3H, t, *J* 7.15, OCH_2CH_3), 1.80 (3H, s, CH_3), 4.24 (1H, s, OH), 4.26–4.40 (2H, m, CH_2CH_3), 7.05 (1H, d, *J* 4.3, 3′-H) and 7.80 (1H, *J* 4.3, 4′-H).

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