A Three-Component Coupling Process Based on Vicarious Nucleophilic Substitution (VNS_{AR})−Alkylation Reactions: An Approach to Indoprofen and Derivatives

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The intermediate anion derived from the vicarious nucleophilic substitution (VNS) of hydrogen reacts with a series of alkyl halides to generate the corresponding α-alkylated conventional VNS product in a one-pot process. This one-pot VNS−alkylation reaction offers a convenient route to a range α-substituted nitrobenzyl phosphine oxides, sulfones, and esters via a three-component coupling reaction. Reactions of α-chloroethyl phenyl sulfone (**14**) and ethyl 2-chloropropionate (**16**) with nitrobenzene followed by subsequent addition of an alkylating agent give a series of sulfones and esters bearing an α-aryl quaternary center. The VNS−alkylation protocol has been applied to the synthesis of derivatives of Indoprofen from nitrobenzene using readily available inexpensive starting materials. Indoprofen itself was prepared using the conventional VNS reaction in four steps and 24% overall yield from nitrobenzene.

Introduction

In 1978 Mąkosza found that carbanions **1** possessing a nucleofugal group at the nucleophilic center react with aromatic nitro compounds replacing hydrogen atoms *ortho* or *para* to the nitro group (Scheme 1).[1] These reactions were named *vicarious nucleophilic substitution* (VNS_{AR}) of hydrogen to specify that although hydrogen in the aromatic ring is replaced by the carbanion moiety, the leaving group departing from the intermediate *σ*-adduct **2** is that originally present in the reacting carbanion. The general mechanistic pathway of the reaction has been established as a fast and reversible addition of the carbanion to the nitroarene, resulting in the formation of the *σ*-adduct **2**, from which base-induced *β*-elimination takes place to generate the anion **3a**.[2] In typical VNS reactions, nitroarenes react with carbanions that are generally prepared in situ by action of base on the corresponding CH acids.[3] Base is also consumed in the elimination step, and therefore at least 2 mol of base is required for each 1 mol of CH acid. Since the product of the reaction mixture prior to workup is a highly colored nitrobenzylic carbanion **3**, only monosubstitution takes place. The regioselectivity of the reaction is overwhelmingly controlled by steric factors. Carbanions derived from a methylene group bearing both a leaving group and electron-withdrawing group generally replace hydrogen both *ortho* and *para* to the nitro group, when these positions are available. The ratio of *para:ortho* substitution increases with the size of the leaving group. Tertiary carbanions replace hydrogen in the VNS reaction exclusively in the *para* position. The selection of base and solvent is important for the VNS reaction; it should ensure efficient deprotonation of the CH acid and fast *β*-elimination of HX from the intermediate *σ*-adduct **2**. The majority of examples of VNS of hydrogen involve the use of KOH, NaOH, *t*-BuOH, or NaH in DMSO, liquid ammonia, or DMF. Mąkosza and co-workers have elegantly shown that the VNS reaction can be applied to a large number of substituted nitrobenzenes and several five- and six-membered heterocyclic systems including nitrothiophenes,[4,5] nitrofurans,[6] nitropyrroles,[5,6] and nitropyridines.[4,7]

Subsequent transformation of the products of VNS reactions often exploits the nucleophilic reactivity of the newly created benzylic center. Several examples of the stepwise deprotonation and alkylation of VNS products, performed in two separate operations, have been reported.[8] As part of a study aimed at controlling the stereochemistry of the process, we first wished to develop a one pot VNS−alkylation process. We were hopeful also to show that the anion **3a** would embody a rich chemistry

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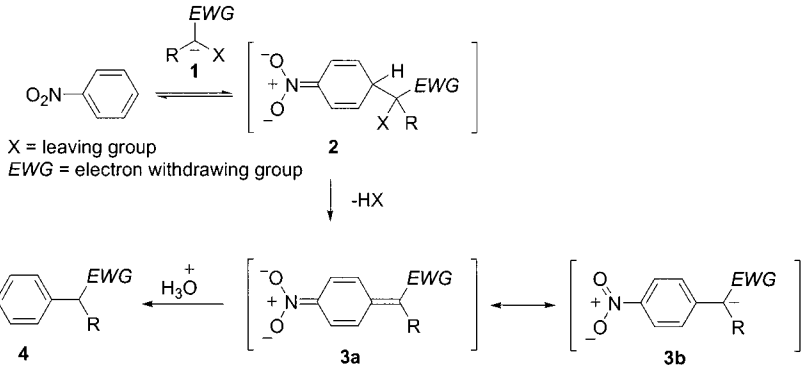
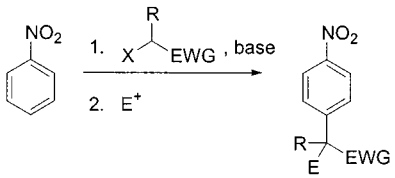
Scheme 1. General Mechanism of the VNS Reaction

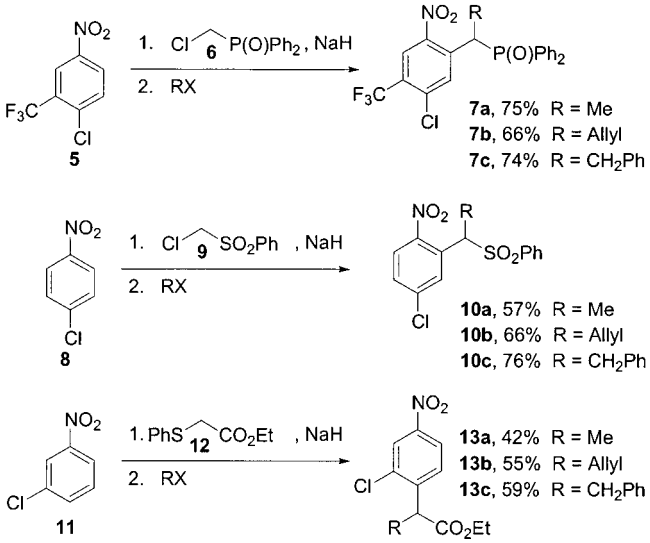


Scheme 2. Proposed Three-Component VNS−Alkylation Coupling Reaction



EWG = Electron Withdrawing Group

Scheme 3. VNS−Alkylation Eactions of Phosphine Oxides, Sulfones, and Ester Nucleophiles



similar to that of malonate anions given the similar acidities of **4** (R = H and EWG = CO_2Et)[9,10] and diethyl malonate.[11]

In a general sense, this approach is represented in Scheme 2. This represents a potentially useful and convenient method for the rapid construction of arenes bearing a quaternary center via a three-component coupling reaction. We now describe in detail that the intermediate anions **3** may indeed be alkylated directly in the VNS reaction.[12]

Results and Discussion

We have previously shown that the sodium anion of (chloromethyl)diphenylphosphine oxide[13] (**6**) reacts readily and efficiently with 4-chloro-3-(trifluoromethyl)nitrobenzene (**5**) replacing hydrogen in the 6 position.[14] The nitroarene **5** was therefore an ideal substrate with which to develop the prototypical VNS−alkylation process. The reaction was performed using sodium hydride as the base, in DMSO at room temperature, and then quenched with a variety of alkylating reagents. When the initial substitution reaction was complete (as judged by the ^{1}H NMR of an aliquot of proton-quenched reaction mixture), the appropriate alkyl halide was added and the reaction mixture left stirring for an additional 30 min. Proton NMR revealed that the products of methylation, allylation, and benzylation (**7a**−**c**) were prepared efficiently with yields similar to that of the product of protonation (74%)[14] (Scheme 3). It is noteworthy that although a slight excess of both base and the alkyl halide were used (2.5 and 1.1 mol equiv, respectively), dialkylation was not observed.[15]

The success of this one-pot VNS−alkylation reaction was not restricted to the use of phosphine oxide **6**. The phenylsulfonyl group is a well-studied electron-withdrawing group in the nucleophilic partner of the VNS reaction. Chloromethyl phenyl sulfone[16] (**9**) reacts efficiently with 4-chloronitrobenzene (**8**) with substitution of hydrogen taking place in the *ortho* position (69%).[16] Using **9**, the alkylation of the intermediate nitrobenzylic anion derived from **8** proceeded efficiently with the same three alkylating agents. In all cases dialkylation was not observed (Scheme 3).[15] The yields of the alkylated product are similar to that of the corresponding normal VNS reaction, indicating that again the alkylation reaction is efficient.

We next applied the VNS−alkylation process to the synthesis of a range of structurally similar esters, which arguably are synthetically more useful. In the VNS reactions of acetate esters, a thiophenoxy leaving group

(9) The *p*-nitro-substituted aryl group renders the hydrogen adjacent to the electron-withdrawing group particularly acidic and stabilizes the anion **3b**: ethyl (*p*-nitrophenyl)acetate, pK_a (DMSO) = 15.1;[10a] ethyl phenylacetate, pK_a (DMSO) = 22.7.[10b]

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(15) The amount of dialkylation is estimated as being <5%. No material corresponding to dialkylated product was seen in the ^{1}H NMR spectrum of the crude reaction mixture.

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Scheme 4. Synthesis of Quaternary Centers via the VNS−Alkylation Reaction

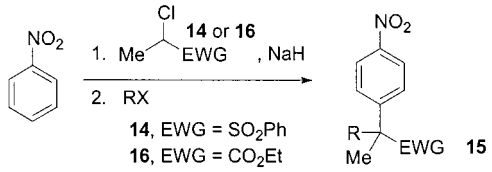

Table 1. Synthesis of Quaternary Centers via the VNS−Alkylation Reaction

15	EWG	R	RX	yield (%)
a	SO_2Ph	Me	MeI	74
b	SO_2Ph	allyl	allyl Br	80
c	SO_2Ph	$PhCH_2$	$PhCH_2Br$	72
d	CO_2Et	Me	MeI	60
e	CO_2Et	allyl	allyl Br	67
f	CO_2Et	$PhCH_2$	$PhCH_2Br$	63
g	CO_2Et	CH_2CO_2Et	$BrCH_2CO_2Et$	80
h	CO_2Et	Et	EtBr	54
i	CO_2Et	$(CH_2)_3Me$	$Me(CH_2)_3Br$	59
j	CO_2Et	$PhCOCH_2$	$PhCOCH_2Br$	65
k	CO_2Et	$(CH_2)_2CO_2Me$	$H_2C{=}CHCO_2Me$	56
l	CO_2Et	CH_2CN	$ClCH_2CN$	56

is normally used since the enolate of ethyl α-chloroacetate undergoes facile self-condensation.[17] The analogous thiophenoxyacetate **12** was prepared from commercially available ethyl chloroacetate via displacement of chloride with thiophenol.[18] The enolate of ethyl thiophenoxyacetate was found to react exclusively in the *para* position when treated with 3-chloronitrobenzene (**11**). The regioselectivity is the same as that reported in the reaction of *tert*-butyl thiophenoxyacetate with 3-chloronitrobenzene (**11**).[17] The reaction was quenched with the same series of alkyl halides to give the α-alkylated esters **13a**−**c** in moderate yield (Scheme 3). The alkylation with methyl iodide gave the expected product **13a** (R = Me) accompanied by a small amount of the dimethylated product (10%). Dialkylation was not observed when the electrophiles allyl bromide and benzyl bromide were used. We realized that the one-pot VNS−methylation process incorporating ester nucleophiles represents a useful route to a number of the medicinally important α-phenylpropionic acids.[19] The route to one member of this class of compounds is disclosed at the end of this discussion.

The one-pot VNS−alkylation reaction may be used in the synthesis of α-aryl quaternary centers. This is illustrated by the reaction of the anion of α-chloroethyl phenyl sulfone[20] (**14**) and the enolate of ethyl 2-chloropropionate (**16**) with nitrobenzene using the same range of electrophiles (Scheme 4 and Table 1). As expected the tertiary anion of **14** replaces the *para* hydrogen of nitrobenzene exclusively.[20] The subsequent alkylation, using the standard alkylating agents, proceeded in good yields to give the corresponding sulfones **15a**−**c** possessing a nitroaryl group bearing a quaternary center at the *para* position.

Similarly, the sodium enolate of ethyl 2-chloropropionate (**16**) reacted efficiently in the *para* position of nitrobenzene using DMF as solvent. In this reaction a thiophenoxy-substituted ester is not required since the base-catalyzed self-condensation of the α-chloroester **16** is slow compared to the rate of the VNS reaction, presumably for steric reasons. This particular VNS reaction was found to be highly exothermic, and hence, the addition of **16** and nitrobenzene to the sodium hydride is carried out at 0 °C. The reaction was quenched with the usual three electrophiles to generate the esters **15d**−**f** bearing the quaternary center in moderate yield. Other electrophiles were also used. The α-aryl succinate derivative **15g** was produced from the use of ethyl bromoacetate. We have also shown that the less reactive electrophiles *n*-butyl bromide and ethyl bromide behave well in the VNS reaction of ethyl 2-chloropropionate. Clearly in these cases (**15h,i**), alkylation is more favorable than elimination. The use of an α-haloketone as the electrophile gives rise to the efficient synthesis of the corresponding 1,4-keto ester bearing a quaternary center, such as **15j**. Our hope that the (nitrophenyl)acetate anion would react like a malonate enolate was well met by the reaction with methyl acrylate. In a process that is similar to the true Michael reaction, conjugate addition produces the mixed glutaric acid diester **15k**. For this reaction, it was necessary to cool the reaction mixture to −68 °C after the VNS reaction and prior to and during the addition of the methyl acrylate. If both processes were performed at 0 °C very little diester **15k** was formed; the enolate formed from the Michael reaction presumably reacts with more acrylate. Chloroacetonitrile reacts well (when added to the reaction at −68 °C) in the reaction to generate a potentially useful cyanopropionate derivative **15l**. It is noteworthy that in all these VNS−alkylation processes the product of type **15** is not directly accessible via a single VNS reaction from a nucleophile already bearing two alkyl groups. The one-pot VNS−alkylation reaction this methodology in principle also offers a convenient way to regioselectively alkylate nitrobenzenes. Decarboxylation of the α-ester group in **15d**−**l** using the procedure developed by Bull et al.[21] will produce α-branched alkylnitroarenes.

Other electrophiles react with the anion **3**. We have shown that the VNS reaction of (chloromethyl)diphenylphosphine oxide[13] (**6**) and several nitrobenzenes may be quenched with substituted benzaldehydes to generate the corresponding *E*-stilbene.[14] However, the anion **3** derived from ester nucleophiles does not react efficiently with substituted benzaldehydes. This is probably because the reaction is reversible and favors the stabilized anion **3**. Indeed when addressing this problem, we serendipitously found that the VNS reactions of ethyl 2-chloropropionate and various nitrobenzenes may be quenched with benzaldehyde, in the presence of air, to give α-aryl-α-hydroxy esters.[22]

We have sought to illustrate the potential of the one pot VNS−alkylation protocol by the synthesis of some biologically active molecules. We have already reported the full details of a synthesis of the anticancer drug (±)-aminoglutethimide.[23] We now report the synthesis of a second drug. This time we used the VNS−alkylation protocol to make Indoprofen (**21**), a member of the

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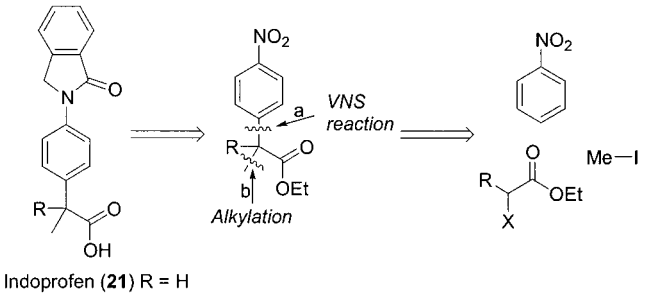
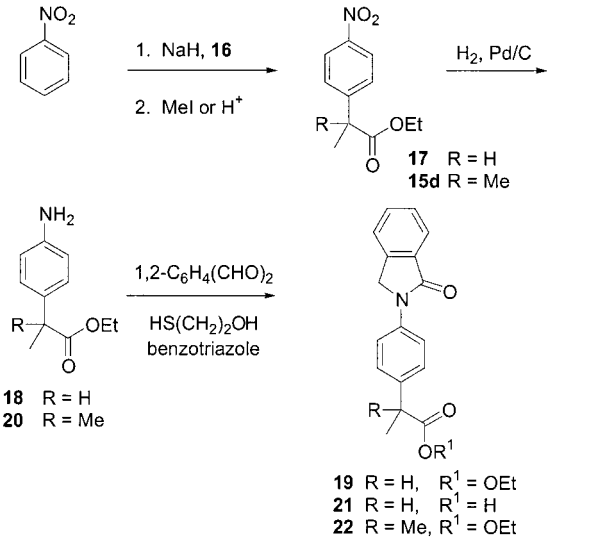
Scheme 5. Retrosynthetic Route to Indoprofen (21)



Scheme 6. VNS Synthesis of Indoprofen and Derivatives



arylpropionic acid nonsteroidal antiinflammatory drugs.[24] Indoprofen is amenable to synthesis via our methodology since the *para*-amino functionality can be derived from a nitro group.

We envisaged that the ester **17** would serve as a convenient precursor (Scheme 5). The method of Takahashi and co-workers[25] provides a useful way to construct a phthalimidine derivative from a substituted aniline by 1,2,3-1*H*-benzotriazole- and 2-mercaptoethanol-mediated condensation with *o*-phthalaldehyde. In our general strategy to Indoprofen and analogues, the carbon−carbon bond positioned *para* to the nitro group can be constructed by VNS of the *para* hydrogen atom of nitrobenzene (disconnection a). The second carbon−carbon bond can be made by the alkylation of the VNS intermediate anion via disconnection b, using a substituted acetate derivative in the usual way.

We first showed that the product **17** previously prepared by the VNS reaction of ethyl 2-chloropropionate (**16**) with nitrobenzene could be efficiently converted to the ethyl ester of Indoprofen (**21**) (Scheme 6). Reduction of the nitroarene **17**, via catalytic hydrogenation, produced the corresponding aniline **18** in reasonable yield. The Takahashi protocol for phthalimidine synthesis produced the ethyl Indoprofen (**19**) without problems. Saponification of the ester **19** gave Indoprofen in an overall 24% yield from nitrobenzene. The same approach was applied to the α-methyl Indoprofen derivative **22**, as a representative analogue accessible by our VNS−alkylation procedure. The VNS reaction of ethyl 2-chloropropionate (**16**) with nitrobenzene followed by reaction with iodomethane gave the ester **15d** (60%). The aniline **20** was obtained by treatment of **15d** with Pd/C and hydrogen (63%). The oxoisoindole **22** was prepared in the same fashion from **20** (65%). Since we have prepared a variety of adducts **15d**−**l** from ethyl 2-chloropropionate (**16**) and nitrobenzene followed by an electrophilic quench, a similar number of Indoprofen analogues in principle could be derived in the same manner.

In summary, we have demonstrated that VNS reactions may be quenched with a series of alkyl halides and this approach may be used to construct α-aryl quaternary centers. This one-pot VNS−alkylation reaction offers a convenient route to a range α-substituted nitrobenzyl phosphine oxides, sulfones, and esters. This type of process may form a variety of products from a single VNS nucleophile, possibly allowing the introduction of functionality that would not be compatible with the basic conditions of the initial VNS reaction. We have also developed a route to Indoprofen in four steps and 24% overall yield from nitrobenzene using readily available inexpensive starting materials, in a way that will allow the rapid construction of many analogues. This clearly illustrates the potential of the one-pot VNS−alkylation reaction.

Experimental Section

General Information. The 200 MHz ^{1}H NMR spectra were recorded using a Bruker AC 200 NMR spectrometer while all 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were recorded using a Bruker AC 300 spectrometer. ^{13}C NMR spectra were recorded using distortionless enhancement by polarization transfer. Both ^{1}H and ^{13}C spectra were recorded using $CHCl_3$ as internal standard. Chemical ionization (CI) mass spectra were recorded using a Kratos MS25 mass spectrometer; fast atom bombardment (FAB) mass spectra were recorded with a Kratos MS50 with a *meta*-nitrobenzyl alcohol matrix. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Elemental analyses were performed using a Carlo-Erba 1106 elemental analyzer. Infrared spectra were recorded using a Perkin-Elmer 783 spectrometer equipped with a PE 600 data station. Melting points were determined using an electrothermal melting point apparatus and were uncorrected. Column chromatography was conducted using silica gel 60 230−400 mesh (Merck & Co.). Silica TLC was conducted on precoated aluminum sheets (60 F_{254}) with a 0.2 mm thickness (Aldrich Chemical Co.). DMSO was distilled from calcium hydride and stored under nitrogen prior to use. Anhydrous methanol and DMF were obtained from Aldrich Chemical Co. and used as supplied.

Diphenyl-1-{1-[3′-chloro-6′-nitro-4′-(trifluoromethyl)-phenyl]ethyl}phosphine Oxide (7a). Sodium hydride (60% dispersion in oil, 400 mg, 10.00 mmol) was added to anhydrous DMSO (5 mL) and the mixture flushed with nitrogen. (Chloromethyl)diphenylphosphine oxide[13] (**6**) (1.0 g, 3.99 mmol) and 4-chloro-3-(trifluoromethyl)nitrobenzene (**5**) (1.0 g, 4.43 mmol) were dissolved in anhydrous DMSO (5 mL) and added dropwise to the sodium hydride slurry. The mixture was stirred at ambient temperature for 6 h before methyl iodide (3.0 mL, 48.17 mmol) was added and the resulting mixture stirred for a further 30 min. The reaction was quenched with distilled

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water, acidified with hydrochloric acid (1 M solution), and extracted with chloroform (3 × 20 mL). The combined extracts were washed with distilled water (3 × 20 mL), dried (magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to yield the phosphine oxide (**7a**) (1.36 g, 75%) as a yellow colored solid, mp 127−128 °C after chromatography (silica, 9:1, chloroform−ethyl acetate). Anal. Found: C, 55.9; H, 3.5; N, 3.2; Cl, 7.8; F, 12.3; P, 6.7. Calcd for $C_{21}H_{16}ClF_3NO_3P$: C, 55.6; H, 3.6; N, 3.1; Cl, 7.8; F, 12.6; P, 6.8. R_f = 0.62 (silica, 9:1, chloroform−ethyl acetate). ν_{max} (KBr disk)/cm^{-1}: 1620, 1530, 1440. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.61 (3H, dd, J = 7.1 and 15.2 Hz), 4.73 (1H, quin, J = 7 Hz), 7.25−7.31 (2H, m), 7.37−7.49 (3H, m), 7.55−7.65 (3H, m), 7.91−8.00 (3H, m), 8.28 (1H, d, J = 1.1 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.50 (d, J_{PC} = 3 Hz), 34.63 (d, J_{PC} = 64 Hz), 121.44 (q, J_{FC} = 274 Hz), 123.9, 124.0, 128.4, 128.6, 128.9, 129.0, 129.4, 130.0, 130.2, 130.4, 130.7, 131.0, 131.1, 131.4, 132.0, 132.0, 132.3, 132.4, 134.2, 134.3, 137.1, 139.4, 139.5, 146.6, 146.6. MS (*m*/*z*) (CI using ammonia): 454 [(M + H)$^+$, 100].

Diphenyl-1-{1-[3′-chloro-6′-nitro-4′-(trifluoromethyl)-phenyl]but-3-enyl}phosphine Oxide (7b). 7b was prepared from (chloromethyl)diphenylphosphine oxide[13] (**6**) (1.0 g, 3.99 mmol), 4-chloro-3-(trifluoromethyl)nitrobenzene (**5**) (1.0 g, 4.43 mmol), and allyl bromide (0.5 mL, 5.78 mmol) in a way to similar to that for **7a**. The phosphine oxide **7b** (1.27 g, 66%) was obtained as a white solid, mp 116−118 °C after chromatography (silica, 9:1, chloroform−ethyl acetate) and recrystallization from ethyl acetate−hexane. Anal. Found: C, 57.3; H, 3.6; N, 3.0; Cl, 7.4; F, 12.1; P, 6.1. Calcd for $C_{23}H_{18}ClF_3NO_3P$: C, 57.6; H, 3.8; N, 2.9; Cl, 7.4; F, 11. 9; P, 6.5. R_f = 0.58 (silica, 9:1, chloroform−ethyl acetate). ν_{max} (KBr disk)/cm^{-1}: 1530, 1440, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.68−2.90 (2H, m), 4.85−4.93 (3H, m), 5.47−5.61 (1H, m), 7.24−7.62 (8H, m), 7.92−8.01 (3H, m), 8.27 (1H, s). ^{13}C NMR (75 MHz; $CDCl_3$): δ 34.5, 40.10 (d, J_{PC} = 63 Hz), 118.60, 121.40 (q, J_{FC} = 274 Hz), 124.0, 124.0, 128.4, 128.6, 129.0, 129.1, 129.4, 129.9, 130.2, 130.3, 130.7, 131.0, 131.1, 131.3, 132.0, 132.0, 132.4, 132.5, 133.1, 133.3, 134.2, 134.3, 137.0, 137.5, 137.6, 147.4, 147.5. MS (*m*/*z*) (FAB): 480 [(M + H)$^+$, 95], 201 (100).

Diphenyl-1-{1-[3′-chloro-6′-nitro-4′-(trifluoromethyl)-phenyl]-2-phenylethyl}phosphine Oxide (7c). 7c was prepared from (chloromethyl)diphenylphosphine oxide[13] (**6**) (1.0 g, 3.99 mmol), 4-chloro-3-(trifluoromethyl)nitrobenzene (**5**) (1.0 g, 4.43 mmol), and benzyl bromide (0.71 mL, 5.97 mmol) in a way similar to that for **7a**. The phosphine oxide **7c** (1.20 g, 79%) was obtained as a cream solid, mp 144−145 °C after chromatography (silica, 19:1, chloroform−ethyl acetate) and recrystallization from ethyl acetate−hexane. Anal. Found: C, 61.3; H, 3.6; N, 2.8; Cl, 6.8; F, 10.7; P, 5.7. Calcd for $C_{27}H_{20}ClF_3NO_3P$: C, 61.2; H, 3.8; N, 2.6; Cl, 6.7; F, 10.8; P, 5.9. R_f = 0.49 (silica, 19:1, chloroform−ethyl acetate). ν_{max} (KBr disk)/cm^{-1}: 1530, 1440. ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.20−3.39 (2H, m), 5.18−5.25 (1H, m), 6.82−6.85 (2H, m), 7.08−7.11 (3H, m), 7.25−7.30 (2H, m), 7.35−7.40 (1H, m), 7.56−7.64 (5H, m), 7.84 (1H, s), 8.01−8.08 (2H, m), 8.45 (1H, s). ^{13}C NMR (75 MHz; $CDCl_3$): δ 36.3, 41.5 (d, J_{PC} = 62 Hz), 121.2 (q, J_{FC} = 274 Hz), 123.9, 124.0, 124.0, 124.1, 126.9, 128.3, 128.4, 128.6, 129.0, 129.2, 129.8, 130.2, 130.3, 130.4, 130.9, 131.0, 131.2, 131.5, 132.0, 132.0, 132.4, 132.4, 134.2, 134.2, 136.7, 136.8, 137.1, 137.9, 137.9, 147.2, 147.3. MS (*m*/*z*) (FAB): 530 [(M + H)$^+$, 100].

1-[1-(3′-Chloro-6′-nitrophenyl)ethyl] Phenyl Sulfone (10a). Sodium hydride (60% dispersion in oil, 470 mg, 11.75 mmol) was added to anhydrous DMSO (5 mL) and the flask flushed with nitrogen. Chloromethyl phenyl sulfone[16] (**9**) (1.0 g, 5.25 mmol) and 4-chloronitrobenzene (**8**) (910 mg, 5.78 mmol) were dissolved in anhydrous DMSO (5 mL) and added dropwise to the sodium hydride slurry. The mixture was stirred at ambient temperature for 2 h before methyl iodide (0.4 mL, 6.42 mmol) was added and the resulting mixture stirred for a further 30 min. The reaction was quenched with distilled water, acidified with hydrochloric acid (1 M solution), and extracted with chloroform (3 × 20 mL). The combined extracts were washed with distilled water (3 × 20 mL), dried (magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to yield **10a** (0.97 g, 57%) as a white solid, mp 110−112 °C (lit.[8a] mp 114 °C) after chromatography (silica, 7:3, chloroform−hexane) and recrystallization from ethyl acetate. Anal. Found: C, 51.7; H, 3.8; N, 4.2; Cl, 10.8; S, 9.5. Calcd for $C_{14}H_{12}ClNO_4S$: C, 51.6; H, 3.7; N, 4.3; Cl, 10.9; S, 9.8. R_f = 0.41 (silica, 7:3, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1535, 1360. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.77 (3H, d, J = 7.0 Hz), 5.47 (1H, q, J = 7.0 Hz), 7.44−7.52 (3H, m), 7.62−7.69 (3H, m), 7.75 (1H, d, J = 2.2 Hz), 7.79 (1H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.4, 58.1, 126.5, 129.0, 129.3, 129.8, 130.3, 130.4, 134.3, 136.7, 139.7, 148.3. MS (*m*/*z*) (FAB): 348 [(M + Na)$^+$, 27%], 326 [(M + H)$^+$, 67], 184 (100).

1-[1-(3′-Chloro-6′-nitrophenyl)but-3-enyl] Phenyl Sulfone (10b). 10b was prepared from chloromethyl phenyl sulfone[16] (**9**) (1.0 g, 5.25 mmol), 4-chloronitrobenzene (**8**) (910 mg, 5.78 mmol), and allyl bromide (0.50 mL, 5.78 mmol) in a way similar to that for **10a**. The sulfone **10b** (1.21 g, 66%) was obtained as yellow crystals, mp 103−104 °C after column chromatography (silica, 7:3, chloroform−hexane) and recrystallization from ethanol. Anal. Found: C, 54.3; H, 4.3; N, 4.3; Cl, 10.1; S, 9.0. Calcd for $C_{16}H_{14}ClNO_4S$: C, 54.6; H, 4.0; N, 4.0; Cl, 10.1; S, 9.1. R_f = 0.46 (silica, 7:3, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1530, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.85−2.96 (1H, m), 3.11−3.19 (1H, m), 5.01 (1H, d, J = 10.8 Hz), 5.06 (1H, d, J = 18.2 Hz), 5.48 (1H, dd, J = 4.2 Hz, 11.3 Hz), 5.53−5.61 (1H, m), 7.42−7.50 (3H, m), 7.61−7.66 (3H, m), 7.72−7.76 (2H, m). ^{13}C NMR (75 MHz; $CDCl_3$): δ 32.3, 62.1, 119.5, 126.3, 128.7, 128.8, 129.2, 129.6, 130.4, 131.4, 134.2, 136.8, 139.5, 148.8. MS (*m*/*z*) (FAB): 352 [(M + H)$^+$, 100].

1-[1-(3′-Chloro-6′-nitrophenyl)-2-phenylethyl] Phenyl Sulfone (10c). 10c was prepared from chloromethyl phenyl sulfone[16] (**9**) (1.0 g, 5.25 mmol), 4-chloronitrobenzene (**8**) (910 mg, 5.78 mmol), and benzyl bromide (0.70 mL, 5.89 mmol) in a way similar to that for **10a**. The sulfone **10c** (1.40 g, 66%) was obtained as pale yellow needles, mp 137−139 °C after column chromatography (silica, 3:2, dichloromethane−hexane) and recrystallization from ethanol. Anal. Found: C, 59.5; H, 4.0; N, 3.5; Cl, 8.9; S, 8.0. Calcd for $C_{20}H_{16}ClNO_4S$: C, 59.8; H, 4.0; N, 3.5; Cl, 8.8; S, 8.0. R_f = 0.46 (silica, 7:3, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1530, 1355, 1310, 1150. ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.37 (1H, dd, J = 11.5 and 14.2 Hz), 3.78 (1H, dd, J = 4.2 and 14.2 Hz), 5.82 (1H, dd, J = 4.2 and 11.5 Hz), 7.00 (2H, d, J = 7.6 Hz), 7.04−7.18 (3H, m), 7.35 (1H, dd, J = 2.2 and 8.7 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.59−7.64 (2H, m), 7.70 (2H, d, J = 7.6 Hz), 7.93 (1H, d, J = 2.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 34.3, 63.6, 126.3, 127.0, 128.6, 128.8, 129.1, 129.5, 130.3, 134.2, 134.8, 136.9, 139.4, 148.5; *m*/*z* (FAB) 402 [(M + H)$^+$, 100].

Ethyl 2-(2′-Chloro-4′-nitrophenyl)propionate (13a). Sodium hydride (60% dispersion in oil, 430 mg, 10.75 mmol) was added to anhydrous DMSO (5 mL) and the mixture flushed with nitrogen. Ethyl thiophenoxyacetate[26] (**12**) (1.0 g, 5.10 mmol) and 3-chloronitrobenzene (**11**) (880 mg, 5.59 mmol) were dissolved in anhydrous DMSO (5 mL) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at ambient temperature for 2 h before methyl iodide (0.32 mL, 5.14 mmol) was added and the resulting mixture stirred for a further 30 min. The reaction was then poured into distilled water (100 mL), acidified with hydrochloric acid (1 M solution), and extracted with chloroform (3 × 20 mL). The combined extracts were washed with distilled water (3 × 50 mL) and saturated aqueous sodium bicarbonate solution (3 × 50 mL), dried (magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to yield **13a** as a yellow oil (550 mg, 42%) after chromatography (silica, 3:2, hexane−chloroform): R_f = 0.16 (silica, 3:2, hexane−chloroform); ν_{max} (liquid film on CsI plates)/cm^{-1} 1740, 1530, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz), 1.54 (3H, d, J = 7.2 Hz), 4.12−4.20 (2H, m), 4.25 (1H, q, J = 7.2 Hz), 7.53 (1H, d, J = 8.6 Hz), 8.11 (1H, dd, J = 2.4 and 8.6 Hz), 8.26 (1H, d, J

(26) Dressler, H.; Graham, J. E. *J. Org. Chem.* **1967**, *32*, 985.

= 2.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 13.9, 17.2, 42.3, 61.3, 121.9, 124.6, 129.1, 134.6, 145.6, 147.0, 172.5; found (CI) (M + H)$^+$ *m/z* 258.0533, calcd for $C_{11}H_{13}ClNO_4$ (M + H)$^+$ *m/z* 258.0533; *m/z* (FAB) 258 [(M + H)$^+$, 100].

Ethyl 2-(2′-Chloro-4′-nitrophenyl)pent-4-enoate (13b). This was prepared from ethyl thiophenoxyacetate[26] (**12**) (1.0 g, 5.10 mmol), 3-chloronitrobenzene (**11**) (880 mg, 5.59 mmol), and allyl bromide (0.5 mL, 5.78 mmol) in a way similar to that for **13a**. The ester **13b (**800 mg, 55%) was obtained as a yellow oil after chromatography (silica, 1:1, chloroform−hexane): R_f = 0.36 (silica, 1:1, chloroform−hexane); ν_{max} (liquid film on CsI plates)/cm^{-1} 1740, 1430; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.22 (3H, t, *J* = 7 Hz), 2.51−2.61 (1H, m), 2.80−2.85 (1H, m), 4.11−4.23 (2H, m), 4.30 (1H, t, *J* = 7.5 Hz), 5.01−5.09 (2H, m), 5.65−5.79 (1H, m), 7.59 (1H, d, *J* = 8.6 Hz), 8.11 (1H, dd, *J* = 2.3 and 8.6 Hz), 8.27 (1H, d, *J* = 2.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.1, 36.6, 47.4, 61.4, 118.0, 121.9, 124.7, 129.8, 133.8, 135.0, 143.7, 147.1, 171.5; found (CI) (M + H)$^+$ *m/z* 284.0696, calcd for $C_{13}H_{15}ClNO_4$ (M + H)$^+$ *m/z* 284.0690; *m/z* (FAB) 284 [(M + H)$^+$, 80%], 129 (100).

Ethyl 2-(2′-Chloro-4′-nitrophenyl)-3-phenylpropionate (13c). This was prepared from ethyl thiophenoxyacetate[26] (**12**)-(1.0 g, 5.10 mmol), 3-chloronitrobenzene (**11**) (880 mg, 5.59 mmol), and benzyl bromide (0.7 mL, 5.89 mmol) in a way similar to that for **13a**. The ester **13c** (1.0 g, 59%) was obtained as a cream colored solid, mp 57−59 °C after chromatography (silica, 3:2, hexane−chloroform) and recrystallization from hexane. Anal. Found: C, 60.9; H, 5.0; N, 4.5; Cl, 10.7. Calcd for $C_{17}H_{16}ClNO_4$: C, 61.2; H, 4.8; N, 4.2; Cl, 10.6. R_f = 0.37 (silica, 1:1, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1740, 1530, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.15 (3H, t, *J* = 7.1 Hz), 3.07 (1H, dd, *J* = 7.8 and 13.8 Hz), 3.40 (1H, dd, *J* = 7.8 and 13.8 Hz), 4.04−4.17 (2H, m), 4.50 (1H, t, *J* = 7.8 Hz), 7.12−7.27 (5H, m), 7.62 (1H, d, *J* = 8.7 Hz), 8.08 (1H, dd, *J* = 2.3 and 8.7 Hz), 8.24 (1H, d, *J* = 2.3 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.1, 38.8, 49.8, 61.5, 121.9, 124.9, 126.9, 128.6, 129.0, 129.9, 135.0, 137.7, 143.8, 147.3, 171.7. MS (*m/z*) (FAB): 334 [(M + H)$^+$, 65%], 91 (100).

2-[2-(4′-Nitrophenyl)propyl] Phenyl Sulfone (15a). Sodium hydride (60% dispersion in oil, 490 mg, 12.25 mmol) was added to anhydrous DMSO (5 mL) and the flask flushed with nitrogen. 1-(1-Chloroethyl)phenyl sulfone[20] (**14**) (1.0 g, 4.89 mmol) and nitrobenzene (660 mg, 5.37 mmol) were dissolved in anhydrous DMSO (5 mL) and added dropwise to the sodium hydride slurry. The mixture was stirred at ambient temperature for 2 h before methyl iodide (0.4 mL, 6.42 mmol) was added and the resulting mixture stirred for a further 30 min. The reaction was quenched with distilled water, acidified with hydrochloric acid (1 M solution), and extracted with chloroform (3 × 20 mL). The combined extracts were washed with distilled water (3 × 20 mL), dried (magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to yield **15a** (1.10 g, 74%) as orange colored crystals, mp 129−130 °C (lit.[27] mp 130−131 °C) after chromatography (silica, chloroform) and recrystallization from ethanol. Anal. Found: C, 59.3; H, 5.1; N, 4.7; S, 10.4. Calcd for $C_{15}H_{15}NO_4S$: C, 59.0; H, 5.0; N, 4.6; S, 10.5%. R_f = 0.40 (silica, chloroform). ν_{max} (KBr disk)/cm^{-1}: 1520, 1360. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.85 (6H, s), 7.37−7.44 (4H, m), 7.54−7.62 (3H, m), 8.12 (2H, d, *J* = 9.0 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 22.7, 65.6, 122.9, 128.6, 129.7, 130.3, 134.0, 134.4, 144.5, 147.6. MS (*m/z*) (FAB): 306 [(M + H)$^+$, 47], 288 (100).

2-[2-(4′-Nitrophenyl)pent-4-enyl] Phenyl Sulfone (15b). 15b was prepared from 1-(1-chloroethyl)phenyl sulfone[20] (**14**) (1.0 g, 4.89 mmol), nitrobenzene (660 mg, 5.37 mmol), and allyl bromide (0.5 mL, 5.78 mmol) in a way similar to that for **15a**. The sulfone **15b** (1.30 g, 80%) was obtained as an orange solid, mp 122−124 °C after column chromatography (silica, 4:1, chloroform−hexane) and recrystallization from ethanol. Anal. Found: C, 61.3; H, 5.5; N, 4.3; S, 9.3. Calcd for $C_{17}H_{17}NO_4S$: C, 61.6; H, 5.2; N, 4.2; S, 9.7. R_f = 0.49 (silica, 4:1, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1540, 1515, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.76 (3H, s), 2.89 (1H, dd, *J* = 7.9 and 14.1), 3.42 (1H, dd, *J* = 5.7 and 14.1 Hz), 5.07 (1H, d, *J* = 9.7 Hz), 5.17 (1H, d, *J* = 16.9 Hz), 5.27−5.40 (1H, m), 7.36−7.42 (4H, m), 7.53 (2H, d, *J* = 9.0 Hz), 7.54−7.62 (1H, m), 8.13 (2H, d, *J* = 9.0 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 19.6, 38.3, 68.7, 120.8, 122.8, 128.5, 130.2, 133.9, 134.3, 142.3 147.5. MS (*m/z*) (FAB): 332 [(M + H)$^+$, 32], 314 (100).

2-[2-(4′-Nitrophenyl)-1-phenylpropyl] Phenyl Sulfone (15c). 15c was prepared from 1-(1-chloroethyl)phenyl sulfone[20] (**14**) (1.0 g, 4.89 mmol), nitrobenzene (660 mg, 5.37 mmol), and benzyl bromide (0.6 mL, 5.05 mmol) in a way similar to that for **15a**. The sulfone **15c** (1.35 g, 72%) was obtained as a cream solid, mp 141−142 °C after column chromatography (silica, 4:1, chloroform−hexane) and recrystallization from ethanol. Anal. Found: C, 66.4; H, 5.3; N, 3.7; S, 8.1. Calcd for $C_{21}H_{19}NO_4S$: C, 66.1; H, 5.0; N, 3.7; S, 8.4. R_f = 0.49 (silica, 4:1, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1520, 1350, 1305, 1290, 1140. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.63 (3H, s), 3.53 (1H, d, *J* = 13.6 Hz), 4.03 (1H, d, *J* = 13.6 Hz), 6.82 (2H, dd, *J* = 2.2 and 7.2 Hz), 7.07−7.17 (3H, m), 7.34−7.44 (4H, m), 7.54−7.59 (1H, m), 7.67 (2H, d, *J* = 8.8 Hz), 8.14 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 19.4, 39.3, 69.9, 122.9, 127.2, 128.6, 130.3, 130.4, 130.5, 134.0, 134.1, 134.7, 142.7, 147.6. MS (*m/z*) (FAB): 382 [(M + H)$^+$, 56], 240 (100).

Ethyl 2-Methyl-2-(4′-nitrophenyl)propionate (15d). Sodium hydride (60% dispersion in oil, 730 mg, 18.25 mmol) was added to anhydrous DMF (5 mL) and the mixture flushed with nitrogen and cooled to 0 °C. Ethyl 2-chloropropionate (**16**) (1.0 g, 7.33 mmol) and nitrobenzene (0.83 mL, 0.99 g, 8.07 mmol) were dissolved in anhydrous DMF (5 mL) and added dropwise to the sodium hydride slurry. The reaction mixture was stirred at 0 °C for 30 min. and then allowed to warm to rt (room temperature). Methyl iodide (0.32 mL, 5.14 mmol) was then added and the resulting mixture stirred for a further 30 min. The reaction mixture was poured onto ice/hydrochloric acid (1 M solution) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed well with distilled water (5 × 50 mL), saturated aqueous sodium bicarbonate solution (3 × 50 mL), and dried (magnesium sulfate), and the solvent was removed under reduced pressure to give **15d** (1.05 g, 60%) as a yellow colored oil after chromatography (silica, 3:2, chloroform−hexane): R_f = 0.26 (silica, 1:1, chloroform−hexane); ν_{max} (liquid film on CsI plates)/cm^{-1} 1730, 1525, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.18 (3H, t, *J* = 7.1 Hz), 1.65 (6H, s), 4.13 (2H, q, *J* = 7.1 Hz), 7.50 (2H, d, *J* = 9.0 Hz), 8.18 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 13.8, 26.2, 46.7, 61.1, 123.4, 126.7, 146.5, 152.0, 175.3; found (CI) (M + H)$^+$ *m/z* 238.1081, calcd for $C_{12}H_{16}NO_4$ (M + H)$^+$ *m/z* 238.1079; *m/z* (FAB) 238 [(M + H)$^+$, 100].

Ethyl 2-Methyl-2-(4′-nitrophenyl)pent-4-enoate (15e). 15e was prepared from ethyl 2-chloropropionate (**16**) (1.0 g, 7.33 mmol), nitrobenzene (0.83 mL, 8.07 mmol), and allyl bromide (0.7 mL, 8.10 mmol) in a way similar to that for **15e**. The ester **15e** (1.30 g, 67%) was obtained as a yellow oil after chromatography (silica, 1:1, chloroform−hexane): R_f = 0.32 (silica, 1:1, chloroform−hexane); ν_{max} (liquid film on CsI plates)/cm^{-1} 1730, 1525, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.17 (3H, t, *J* = 7.1 Hz), 1.55 (3H, s), 2.66 (1H, dd, *J* = 7.1 and 13.8 Hz), 2.81 (1H, dd, *J* = 7.4 and 13.8 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 5.01−5.07 (2H, m) 5.48−5.62 (1H, m), 7.46 (2H, d, *J* = 8.9 Hz), 8.15 (2H, d, *J* = 8.9 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 13.8, 22.4, 43.4, 50.2, 61.1, 119.1, 123.3, 127.1, 132.8, 146.5, 150.6, 174.4; found (CI) (M + H)$^+$ *m/z* 264.1232, calcd for $C_{14}H_{18}NO_4$ (M + H)$^+$ *m/z* 264.1236; *m/z* (FAB) 264 [(M + H)$^+$, 100].

Ethyl 2-Methyl-2-(4′-nitrophenyl)-3-phenylpropionate (15f). 15f was prepared from ethyl 2-chloropropionate (**16**) (1.0 g, 7.33 mmol), nitrobenzene (0.83 mL, 8.07 mmol), and benzyl bromide (0.95 mL, 7.99 mmol) in a way similar to that for **15d**. The ester **15f** (1.45 g, 63%) was obtained as a yellow oil after chromatography (silica, 1:1, chloroform−hexane): R_f = 0.32 (silica, 1:1, chloroform−hexane); ν_{max} (liquid film on CsI plates)/cm^{-1} 1730, 1530, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.20 (3H, t, *J* = 7.1 Hz), 1.54 (3H, s), 3.22 (1H, d, *J* = 13.4 Hz), 3.40 (1H, d, *J* = 13.4 Hz), 4.10−4.22 (2H, m), 6.83−6.86 (2H, m),

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7.15−7.19 (3H, m), 7.42 (2H, d, J = 9.0 Hz), 8.17 (2H, d, J = 9.0 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 13.82, 21.8, 45.1, 51.4, 61.2, 123.2, 126.6, 127.4, 127.8, 130.2, 136.1, 146.5, 150.5, 174.5; found (CI) $(M + H)^+$ m/z 314.1388, calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$ m/z 314.1392; m/z (FAB) 314 [$(M + H)^+$, 97], 91 (100).

Diethyl 1-Methyl-1-(4′-nitrophenyl)succinate (15g). 15g was prepared from ethyl 2-chloropropionate (**16**) (2.2 g, 16.12 mmol), nitrobenzene (1.0 g, 8.13 mmol), and ethyl bromoacetate (1.00 mL, 9.02 mmol) in a way similar to that for **15d**. The ester **15g** (2.0 g, 80%) was obtained as a yellow oil after chromatography (silica, 7:3, chloroform−hexane). Anal. Found: C, 58.0; H, 6.4; N, 4.6. Calcd for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.2; N, 4.5. R_f = 0.22 (silica, 7:3, chloroform−hexane). ν_{max} (KBr disk)/cm^{-1}: 1740, 1530, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.20 (6H, t, J = 7.1 Hz), 1.74 (3H, s), 2.90 (1H, d, J = 16.2 Hz), 3.21 (1H, d, J = 16.2 Hz), 4.09 (2H, q, J = 7.1 Hz), 4.18 (2H, q, J = 7.1 Hz), 7.53 (2H, d, J = 9.0 Hz), 8.19 (2H, d, J = 9.0 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 13.7, 13.9, 23.2, 43.1, 48.4, 60.5, 61.4, 123.4, 126.9, 146.7, 149.7, 170.1, 173.5. MS (m/z) (FAB): 310 [$(M + H)^+$, 95], 264 (100).

Ethyl 2-Methyl-2-(4′-nitrophenyl)butyrate (15h). 15h was prepared from ethyl 2-chloropropionate (**16**) (1.0 g, 7.33 mmol), nitrobenzene (0.83 mL, 8.07 mmol), and ethyl bromide (0.60 mL, 8.04 mmol) in a way similar to that for **15d**. The ester **15h** (1.10 g, 54%) was obtained as a yellow oil after chromatography (silica, 1:1, chloroform−hexane): R_f = 0.48 (silica, 1:1, chloroform−hexane); ν_{max} (liquid film on CsI plates)/cm^{-1} 1730, 1525, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.83 (3H, t, J = 7.4 Hz), 1.19 (3H, t, J = 7.1 Hz), 1.56 (3H, s), 1.92−2.16 (2H, m), 4.14 (2H, q, J = 7.1 Hz), 7.47 (2H, d, J = 9.0 Hz), 8.18 (2H, d, J = 9.0 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 8.8, 13.9, 22.0, 31.7, 50.9, 61.0, 123.3, 127.1, 146.5, 151.2, 174.9; found (CI) $(M + H)^+$ m/z 252.1236, calcd for $C_{13}H_{18}NO_4$ $(M + H)^+$ m/z 252.1236; m/z (FAB) 252 [$(M + H)^+$, 80].

Ethyl 2-Methyl-2-(4′-nitrophenyl)hexanoate (15i). 15i was prepared from ethyl 2-chloropropionate (**16**) (1.0 g, 7.33 mmol), nitrobenzene (0.83 mL, 8.07 mmol), and bromobutane (0.80 mL, 7.42 mmol) in a way similar to that for **15d**. The ester **15i** (1.20 g, 59%) was obtained as a yellow oil after chromatography (silica, 1:1, chloroform−hexane). Anal. Found: C, 64.8; H, 7.3; N, 5.1. Calcd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0. R_f = 0.40 (silica, 1:1, chloroform−hexane). ν_{max} (liquid film on CsI plates)/cm^{-1}: 2960, 1730, 1530, 1350. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.87 (3H, t, J = 7.1 Hz), 1.07−1.20 (5H, m), 1.30 (2H, quin, J = 7 Hz), 1.57 (3H, s), 1.87−2.10 (2H, m), 4.13 (2H, q, J = 7.1 Hz), 7.47 (2H, d, J = 8.9 Hz), 8.17 (2H, d, J = 8.9 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 13.8, 13.9, 22.7, 23.0, 26.7, 38.7, 50.6, 61.1, 123.4, 127.1, 146.5, 151.6, 175.0. MS (m/z) (FAB): 280 [$(M + H)^+$, 100].

Ethyl 2-Methyl-2-(4-nitrophenyl)-4-oxo-4-phenylbutyrate (15j). 15j was prepared from ethyl 2-chloropropionate (**16**) (1.20 g, 8.8 mmol), nitrobenzene (0.99 g, 8.0 mmol), and α-bromoacetophenone (1.60 g, 8.0 mmol) in a way similar to that for **15d**. The ester **15j** (1.78 g, 65%) was obtained as colorless crystals, mp 105−106 °C, after chromatography (silica, 5:4:1, hexane−chloroform−ether, v/v). Anal. Found: C, 67.0; H, 5.8; N, 4.2. Calcd for $C_{19}H_{19}NO_5$: C, 66.9; H, 5.6; N, 4.1. R_f = 0.57 (5:4:1, hexane−chloroform−ether, v/v). ν_{max} (KBr disk)/cm^{-1}: 3000−2800 (m), 1750 (s), 1690 (s), 1600 (s), 1350 (s), 1100 (s). ^{1}H (200 MHz, $CDCl_3$): δ 1.20 (3H, t, J = 7.1 Hz), 1.80 (3H, s), 3.65 (1H, d, J = 17.8 Hz), 3.90 (1H, d, J = 17.8 Hz), 4.20 (2H, q, J = 7.1 Hz), 7.43−7.60 (3H, m), 7.63 (2H, d, J = 8.9 Hz), 7.94−7.99 (2H, m), 8.21 (2H, d, J = 8.9 Hz). ^{13}C (75 MHz, $CDCl_3$): 14.0, 23.6, 47.7, 48.4, 61.5, 123.6, 127.8, 127.9, 128.7, 133.5, 136.7, 146.8, 150.7, 174.6, 196.3. MS (m/z) (FAB): 342 ([M + H]$^+$, 70), 296 (54), 256 (7), 137 (11), 105 (100), 89 (13).

1-Ethyl 5-Methyl 2-methyl-2-(4-nitrophenyl)pentanedioate (15k). A mixture of ethyl 2-chloropropionate (**16**) (1.2 g, 8.8 mmol) and nitrobenzene (0.99 g, 8.0 mmol) in dry DMF (20 mL) was added to a slurry of sodium hydride (80% dispersion in oil, 0.6 g, 20 mmol) in dry DMF (20 mL). The resulting deep purple colored mixture was stirred for 1 h at 0 °C and 2 h at ambient temperature. The mixture was cooled to −68 °C using a methanol/CO_2 cooling bath. Methyl acrylate (0.9 g, 8.0 mmol) was added to the mixture that was allowed to slowly warm to room temperature. After being stirred for 1 h at rt, the reaction was worked up in the same way as used in the preparation of **15d**. The diester **15k** (1.4 g, 56%) was obtained as a yellow oil after chromatography (silica, $CHCl_3$). Anal. Found: C, 58.4; H, 6.4; N, 4.4. Calcd for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.2; N, 4.5%. R_f = 0.37 (chloroform). ν_{max} (liquid film on NaCl plates)/cm^{-1}: 2960 (m), 1720 (s), 1600 (s), 1350 (s), 1010 (s), 900 (s), 750 (m), 700 (m). ^{1}H (300 MHz, $CDCl_3$): δ 1.19 (3H, m), 1.60 (3 H, s), 2.14−2.40 (4H, m), 3.60 (3H, s), 4.02−4.18 (2H, m), 7.46 (2H, d, J = 7.7 Hz), 8.16 (2H, d, J = 7.7 Hz). ^{13}C (75 MHz, $CDCl_3$): 14.0, 22.7, 29.7, 34.0, 50.1, 51.7, 61.5, 123.6, 127.2, 146.7, 150.2, 173.2, 174.3. MS (m/z) (FAB): 310 ([M + H]$^+$, 88), 278 (59), 264 (29), 250 (92), 236 (68), 204 (31), 137 (39), 130 (100), 107 (48), 95 (36), 91 (68), 85 (27).

Ethyl 3-Cyano-2-methyl-2-(4′-nitrophenyl)propionate (15l). 15l was prepared from ethyl 2-chloropropionate (**16**) (1.81 g, 13.2 mmol), nitrobenzene (1.48 g, 12 mmol), and chloroacetonitrile (0.9 g, 12 mmol) in a way similar to that for **15k**. The cyanoester **15l** (1.75 g, 56%) was obtained as a yellow colored oil after chromatography (silica, 5:3:2, hexane−chloroform−ether). Anal. Found: C, 59.9; H, 5.6; N, 10.8. Calcd for $C_{13}H_{14}N_2$: C, 59.6; H, 5.4; N, 10.7. R_f = 0.27 (silica, 5:3:2, hexane−chloroform−ether). ν_{max} (liquid film on NaCl plates)/cm^{-1}: 3000−2800, 2250, 1750, 1600, 1350, 990. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.22 (3H, t, J = 7.1 Hz), 1.83 (3H, s), 2.98 (1H, d, J = 17.0 Hz), 3.07 (1H, d, J = 17.0 Hz), 4.20 (2H, q, J = 7.1 Hz), 7.52 (2H, d, J = 8.9 Hz), 8.15 (2H, d, J = 8.9 Hz). ^{13}C NMR (75 MHz; $CDCl_3$): δ 13.9, 22.5, 28.9, 48.7, 66.0, 123.4, 116.8, 124.1, 127.1, 146.9, 147.5, 172.5. MS (m/z) (FAB): 263 [$(M + H)^+$, 100], 246 (40), 235 (50), 189 (18), 154 (15), 136 (20), 91 (12).

Ethyl 2-(4′-Nitrophenyl)propionate (17). Sodium hydride (60% dispersion in oil, 2.69 g, 67 mmol) was added to anhydrous DMF (30 mL) at 0 °C and the flask flushed with nitrogen. Ethyl 2-chloropropionate (**16**) (2.86 mL, 22 mmol) and nitrobenzene (2.29 mL, 22 mmol) were dissolved in anhydrous DMF (15 mL) and added dropwise to the sodium hydride slurry. The mixture was stirred at 0 °C for a further 0.5 h before warming to room temperature over 2 h. The mixture was poured onto an HCl (1 M)/ice slurry and extracted with chloroform (3 × 50 mL). The combined extracts were washed well with distilled water (5 × 100 mL) and dried (magnesium sulfate), and the solvent was removed under reduced pressure to give the nitrobenzyl ester[28] **17** (3.21 g, 72%) as a yellow oil after chromatography (silica, 2:3, hexane−chloroform): R_f = 0.3 (silica, 1:1, hexane−chloroform); ν_{max} (liquid film on NaCl plates)/cm^{-1} 3000−2800, 1750, 1600, 1350; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.19 (3H, t, J = 7.1 Hz), 1.52 (3H, d, J = 6.6 Hz), 3.82 (1H, q, J = 6.6 Hz), 4.08−4.19 (2H, m), 7.49 (2H, d, J = 8.4 Hz) 8.17 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.1, 16.4, 45.5, 61.3 123.9, 28.5, 147.1, 147.9, 173.2; found (CI) [M + H]$^+$ m/z 224.0919, calcd for $C_{11}H_{13}NO_4$ m/z 224.0917; m/z (FAB) 224 ([M + H]$^+$, 40), 95 (100).

Ethyl 2-(4′-Aminophenyl)propionate (18). A solution of the nitrobenzyl ester **17** (3.0 g, 13.4 mmol) in anhydrous methanol (15 mL) ws added to a stirred slurry of palladium on charcoal (10% Pd/C, 1.0 g) in anhydrous methanol (15 mL) under an atmosphere of hydrogen. The resulting mixture was stirred at room temperature until reduction was complete (by TLC). The reaction mixture was filtered over a bed of Celite and the solvent removed under reduced pressure to yield the aminobenzyl ester[25b] **18** (1.68 g, 65%), as a brown oil after chromatography (silica, chloroform): R_f = 0.4 (silica, chloroform); ν_{max} (liquid film on NaCl plates)/cm^{-1} 3500, 3400, 3000−2800, 1750, 1600; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.18 (3H, t, J = 7.1 Hz), 1.43 (3H, d, J = 7.6 Hz), 3.56 (1H, q, J = 7.6 Hz) overlapping 3.50−3.60 (2H, s), 4.04−4.18 (2H, m), 6.69 (2H, d, J = 8.4 Hz), 7.10 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.2, 18.7, 44.7, 60.6, 115.3, 128.4, 130.8, 145.4, 175.1; found (CI) [M + H]$^+$ m/z 194.1184, calcd for $C_{11}H_{15}NO_2$ m/z 194.1186; m/z (FAB) 194 ([M + H]$^+$, 80), 120 (100).

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Ethyl 2-(4′-(1-Oxo-2-isoindolinyl)phenyl)propionate (19). To a stirred solution of *ortho*-benzyldicarboxaldehyde (0.35 g, 2.6 mmol) in acetonitrile (10 mL) was added successively 2-mercaptoethanol (1.16 mL, 22.36 mmol), a solution of the amino ester **18** (0.5 g, 2.6 mmol) in acetonitrile (2.6 mL), benzo-1,2,3-1*H*-triazole, (0.31 g, 2.6 mmol), and pH 9.6 buffer solution (0.05 M, H_3BO_3−KCl−NaOH, 1.3 mL), over 1 min each. The resulting homogeneous brown solution was stirred for a further 13 h, evaporated in vacuo, triturated with diethyl ether, and filtered, and the solvent was removed under reduced pressure to give the phthalimidine[25b] **19** (0.55 g, 68%) as needles, mp 102−106 °C, after chromatography (silica, dichloromethane) and recrystallization from dioxane: R_f = 0.1 (silica, 2:3, chloroform−hexane); ν_{max} (KBr disk) 3500, 2970, 1750, 1600, 1650; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.21 (3H, t, J = 7.1 Hz), 1.50 (3H, d, J = 7.1 Hz), 3.71 (1H, q, J = 7.1 Hz), 4.06−4.18 (2H, m), 4.83 (2H, s), 7.37 (2H, d, J = 8.7 Hz), 7.50 (1H, d, J = 8.7 Hz), 7.56 (1H, d, J = 7.3 Hz), 7.81 (2H, d, J = 8.7 Hz), 7.90 (1H, d, J = 7.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.0, 18.4, 44.8, 50.5, 60.6, 119.4, 122.5, 123.9, 128.1, 128.2, 131.9, 132.9, 136.6, 138.2, 139.9, 167.3, 174.3; found (CI) $[M + H]^+$ m/z 310.1436, calcd for $C_{19}H_{19}NO_3$ m/z 310.1435; m/z (FAB) 310 $[M + H]^+$, 100).

2-(4′-(1-Oxo-2-isoindolinyl)phenyl)propionic Acid (21). To a stirred solution of 10% sodium hydroxide (10 mL) in ethanol (10 mL) was added the ester **19** (0.5 g, 1.62 mmol), and the resulting mixture was refluxed for 2.5 h. The resulting colorless solution was cooled to room temperature, extracted with diethyl ether, dried (magnesium sulfate), and filtered, and the solvent was removed under reduced pressure to give Indoprofen (**21**) (0.34 g, 75%) as needles, mp 213−214 °C (lit.[29] mp 213−214 °C) after recrystallization from hexane: ν_{max} (KBr disk)/cm^{-1} 3500, 2800, 1740, 1420; ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.38 (3H, d, J = 7.0 Hz), 3.69 (1H, q, J = 7.0 Hz), 5.01 (2H, s), 7.35 (2H, d, J = 8.7 Hz), 7.51−7.57 (1H, m), 7.67−7.69 (1H, m), 7.78 (2H, d, J = 7.6 Hz), 7.85 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz; DMSO-d_6) δ 22.4, 48.0, 54.4, 123.4, 127.1, 127.2, 131.9, 132.1, 136.1, 136.3, 140.9, 142.0, 144.9, 170.5, 179.3; found (CI) $[M + H]^+$ m/z 282.1122, calcd for $C_{17}H_{15}NO_3$ m/z 282.1130; m/z (FAB), 307 (40), 282 ($[M + H]^+$, 100).

Ethyl 2-Methyl-2-(4′-aminophenyl)propionate (20). 20 was prepared from the nitrophenyl ester **15d** in a way similar to that for the aniline **18.** The aniline[30] **20** (1.38 g, 63%) was obtained as a brown oil: R_f = 0.4 (silica, chloroform); ν_{max} (liquid film on NaCl plates)/cm^{-1} 3500, 3400, 3000−2800, 1750, 1600, 1200; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.18 (3H, t, J = 7.1 Hz), 1.52 (6H, s), 3.41−3.52 (2H, m), 4.10 (2H, q, J = 7.1 Hz), 6.65 (2H, d, J = 8.4 Hz), 7.14 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.2, 26.6, 45.6, 60.7, 115.1, 126.7, 135.0, 144.8, 177.2; found (CI) $[M + H]^+$ m/z 208.1340, calcd for $C_{12}H_{17}NO_2$ m/z 208.1337; m/z (FAB), 208 ($[M + H]^+$, 100).

Ethyl 2-Methyl-2-(4′-(1-Oxo-2-isoindolinyl)phenyl)propionate (22). 22 was prepared from the aniline **20** (0.54 g, 2.6 mmol), *ortho*-benzyldicarboxaldehyde (0.35 g, 2.6 mmol), 2-mercaptoethanol (1.16 mL, 22.36 mmol), benzo-1,2,3-1*H*-triazole, (0.31 g, 2.6 mmol), and pH 9.6 buffer solution (0.05 M, H_3BO_3−KCl−NaOH, 1.3 mL) in a way similar to that for **19**. The ester **26** (0.5 g, 65%) was obtained as needles, mp 119−120 °C, after chromatography (silica, 3:1, chloroform−hexane) and recrystallization from dioxane: R_f = 0.15 (silica, 3:1, chloroform−hexane); ν_{max} (KBr disk)/cm^{-1} 3400, 2970, 1750, 1600, 1580, 1500; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.20 (3H, t, J = 7.2 Hz), 1.59 (6H, s), 4.13 (2H, q, J = 7.2 Hz), 7.41 (2H, d, J = 8.8 Hz), 7.49−7.53 (1H, m), 7.59 (1H, t, J = 7.0 Hz), 7.82 (2H, d, J = 8.8 Hz), 7.73 (1H, d, J = 7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 14.2, 26.6, 46.2, 50.8, 61.0, 119.4, 122.7, 124.3, 126.6, 128.5, 132.2, 138.1, 140.2, 141.0, 155.0, 176.7, 182.8; found (CI) $[M + H]^+$ m/z 324.1595, calcd for $C_{20}H_{21}NO_3$ m/z 324.1600; m/z (FAB), 324 ($[M + H]^+$, 80).

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Supporting Information Available: Figures showing NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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