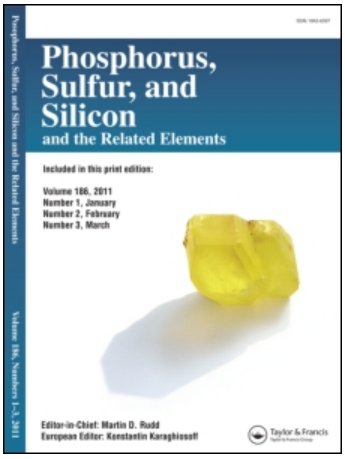

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Easy Synthetic Approach to *p*-Aminophenoxy Derivatives Bearing Phosphonic Or Carboxylic Ethyl Ester Groups

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To cite this Article Consiglio, G. A. , Failla, S. , Finocchiaro, P. , Giuffrida, C. and Recca, A.(2000) 'Easy Synthetic Approach to *p*-Aminophenoxy Derivatives Bearing Phosphonic Or Carboxylic Ethyl Ester Groups', Phosphorus, Sulfur, and Silicon and the Related Elements, 165: 1, 7 — 16
To link to this Article: DOI: 10.1080/10426500008076321
URL: http://dx.doi.org/10.1080/10426500008076321

Phosphorus, Sulfur and Silicon, 2000, Vol. 165, pp. 7-16
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EASY SYNTHETIC APPROACH TO *P*-AMINOPHENOXY DERIVATIVES BEARING PHOSPHONIC OR CARBOXYLIC ETHYL ESTER GROUPS

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(Received May 25, 2000)

Condensation of the ethyl esters of phenyl carboxylic acids or phenyl-phosphonic acids with halonitrobenzenes in anhydrous acetonitrile in presence of potassium carbonate produces 4'-nitrophenoxy-benzoic or benzo-phosphonic acid ethyl esters in good yields. This procedure, which represents a new approach for the nucleophilic condensation, is particularly useful for substrates bearing ancillary reactive groups for which the usual procedure described in literature leads to decomposition products. Reduction of the parent nitro derivatives by hydrazine in the presence of palladium catalyst yields the corresponding amines in very high yield.

Keywords: Nucleophilic substitutions – NMR and FAB characterizations – Monomers for polycondensates – Flame retardants

INTRODUCTION

Recently a convenient method, for the synthesis of methyl- and fluoro-substituted bis(4'-aminophenoxy)benzenes, was reported by Eastmond and Paprotny.[1] This method provides with good yields the parent nitrophenoxy derivatives which easily were reduced to the corresponding

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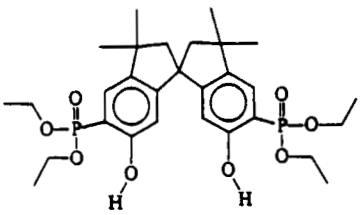
amines. The latter compounds are of considerable interest for polymer chemistry, because their incorporation into relatively stiff aromatic polymer chains may provide flexibility and thus enhances processability.

Recently, our interest on both polymer and macrocyclic chemistry, led us to report[2] on an easy access for the synthesis of new building-blocks bearing phosphonic groups, one of them is the spirobisindane bisphosphonate unit **1**. This compound is a new dissymetric molecule containing ancillary groups (the phosphonic ones) which enhances the flame-retarding properties of epoxy resins,[3] and after hydrolysis to the mono-ester opens new frontiers for the applications of such molecule as a negatively charged receptor.[4] Futhermore, monomer **1** was used by us for the synthesis a variety of medium size chiral cyclophanes.[5]

Therefore, having in mind the idea of using such monomer, both for polymer chemistry and as receptor for negatively charged guests, and taking advantage of the report of Eastmond and Paprotny[1] we decided to trasform the phenolic groups in our monomer **1** into the *p*-aminophenoxy derivative, in order to prepare the spirobisindane p-aminophenoxy unit **2**.



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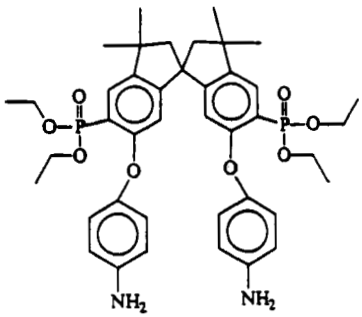
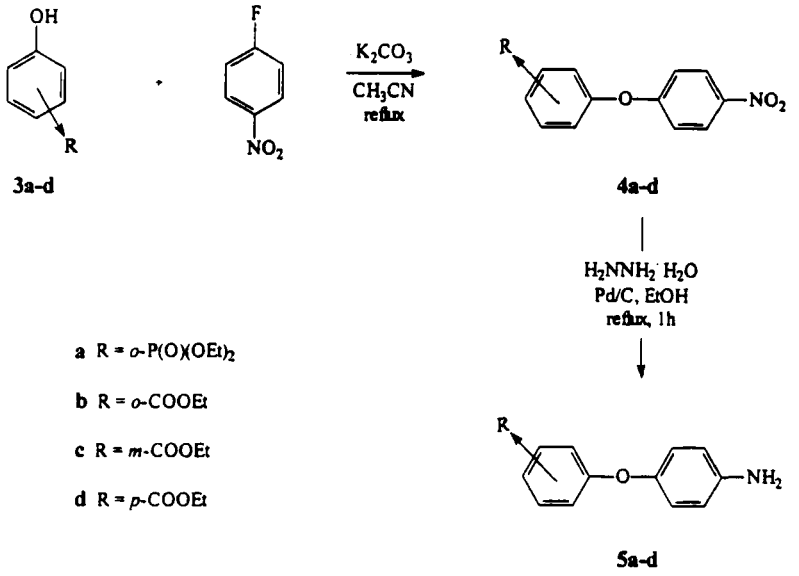


2

Thus, in this paper we shall report on a new and general easy access to the synthesis of *p*-aminophenoxy derivatives bearing phosphonic groups. Our synthetic procedure is also advantageously extended to the corresponding cognates possessing the carboxylate ethyl ester group. In fact, up to now, the ethyl- or methyl-esters of the isomeric-(4′-nitrophenoxy)-benzoic acids were prepared by complex routes using mainly Ullmann cou-



SCHEME 1

pling of 4-nitro-halobenzene derivatives with cresols,[6] hydroxybenzal aldehydes[6–8] or hydroxybenzoic acids. [9–10] In turn, the methyl or carbonyl groups where oxidized to the carboxy moiety and then esterified.

In our approach a one-pot procedure was now succesfully used for the preparation of aromatic nitroderivatives containing ancillary reactive groups such the esters **4a-d** reported on Scheme 1. Reduction of the nitro group to the amine moiety results into interesting building blocks for polymer chemistry, for the preparation of macrocycles and for conformational rigid substrates wich could mimic the "*CaaX*" motif[10–11] in *Ras* oncogene products.

RESULTS AND DISCUSSION

For the purpose of our syntheses all the above mentioned literature methods including the Eastmond and Paprotny[1] procedure, proceeded with

unsatisfactory and very low yield and gave rise always to a complex mixture due to the fact that at the high temperature employed hydrolysis of the phosphonic esters became the main reaction. On the other hand, when our ortho-substituted phenols (both phosphonic or carboxylic acid esters) where caused to react with the stoichiometric amounts of *para*-nitro fluorobenzene in anhydrous dimethylformamide in the presence of potassium carbonate at 90°C for 12 hrs, the only product isolated was N-dimethylamino-4-nitrobenzene which originates from the condensation of 1-fluoro-4-nitrobenzene with the decomposition product of DMF.

Therefore we decided to switch to acetonitrile as solvent for the fluoro-displacement reaction. The conditions leading to the desired nitroderivatives and then to the amines are depicted in Scheme 1.

In fact, using anhydrous acetonitrile as solvent in the presence of potassium carbonate and 1-fluoro-4-nitrobenzene at refluxing temperature we achieved good results for the nucleophilic aromatic substitution reaction which was the crucial step in Scheme 1. Melting points, reaction times and yields of the *p*-nitro derivatives are given in Table I. The results clearly show that yields of the nitro derivatives **4a-d** are high when *meta* or *para* functionalized phenols **3** were used, but they decrease for the *ortho* functionalized phenols, although they are still satisfactory.

TABLE I Synthesis of Functionalized (4′-nitrophenoxy)benzene Derivatives[a]

Compound	*mp (°C)*	*Reaction Time (h)*	*Yield (%)*[b]
4a	oil	12	30
		36	76
4b	28–30	12	28
		36	68
4c	oil	12	90
4d	67–68[c]	12	75
2a	196–198	36	80

[a] See general procedure for reaction conditions.
[b] Yields based on isolated products after purification.
[c] Literature,[8] 74–75°C from alcohol.

This procedure works also very well even in case of the spirobisindanol derivative **1** which possesses two phosphonic units in the molecule which

are ortho to the each hydroxy group. In fact, data reported in Table I for the dinitro-derivative **2a** indicate that the yield is very satisfactory and no appreciable side-products are formed.

Attempts to improve the yield of aromatic nucleophilic substitution by changing the reagents (potassium salts of phenols **3a**) or the reaction solvents (tetrahydrofuran, dimethylacetamide) or the temperature (70–90°C) resulted only in small changes in the reaction times, but not in the yields of the final products.

All of the *p*-nitro derivative compounds prepared were then readily reduced by hydrazine in the presence of palladium catalyst; according to the published procedure;[1] the yields of the corresponding amines were greater than 80%. The full characterization of these new compounds are given in the experimental section.

In conclusion, a general and convenient synthesis of functionalized amines via nucleophilic fluoro displacement reaction and subsequent reduction has been developed. The yields of the two reaction steps were good and the work-up procedure was very easy.

Further studies aimed to the use of bisamine **2** for synthesizing receptors for anionic guests are in progress.

Experimental Section

All reactions were performed under an inert nitrogen atmosphere, and the solvents were refluxed and freshly distilled before use. ^{1}H-, ^{13}C-, ^{31}P-NMR spectra were recorded on a Varian-Inova 500 MHz instrument operating at 500 MHz, 125 MHz and 200 MHz respectively, using $SiMe_4$ as internal reference and 85% H_3PO_4 as external reference. Mass spectra were obtained using a double-focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system using 3-nitro-benzylalcohol as matrix. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

Acetonitrile was dried by distillation from calcium hydride under nitrogen. Compound **1** and phenol **3a** were prepared according to published procedure.[2, 12] Unless otherwise stated, commercial chemicals were used as supplied.

General Synthetic Procedure of Functionalized *p*-Nitrophenoxy Derivatives

In a three-necked round flask equipped with condenser, magnetic stirring bar, nitrogen inlet and a dropping funnel, were placed anhydrous K_2CO_3 (6.9 g, 50 mmol), a functionalized phenol (**1, 3a-d**, 10 meq) and freshly distilled anhydrous CH_3CN (100 mL). The reaction mixture was heated to refluxing temperature and to this stirred suspension was added over a period of 0.5 h from a dropping funnel a solution of 1-fluoro-4-nitrobenzene (11 meq) in freshly distilled CH_3CN (25 mL). After the addition was completed, the reaction mixture was refluxed and stirred overnight, filtered, and the solvent was evaporated to give a powder, which was collected with hexane by filtration and washed several times with water. The product was purified by crystallization from hexane/ethylacetate to give **2b, 4b** and **4d** as pale yellow crystals. Compounds **4a** and **4c** which were oil were purified by column chromatography (SiO_2; cyclohexane:ethylacetate 7:3).

General Synthetic Procedure of Functionalized p-Aminophenoxy Derivatives

To a solution (EtOH 30 mL) of *p*-nitrophenoxy derivative **4** (5 meq) synthesized as described above was added 10% Pd/C (0.1 g) and heated to refluxing temperature, then hydrazine monohydrate (1 mL, 20 meq) was added over a period of 0.5 h. Refluxing was continued for a period of 1 h after which the catalyst was filtered off and the solvent evaporated at reduced pressure. The oily residue was crystallized from a mixture of hexane/ethylacetate, to give the corresponding amine as white crystals. Compounds **5b-c** which were oil were purified by column chromatography (SiO_2; cyclohexane:ethylacetate 5:5).

Bis-(5,5′-diethyloxyphosphonyl)-6,6′-bis-(p-nitrophenoxy)-3,3,3′,3′-tetramethyl-1,1′-spirobisindane (2a)

6.5 g, 80%. Pale yellow crystals, mp 196–198°C (cyclohexane). FAB-MS: *m/z* 823.8 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 8.15 (d, 4H, $J_{HH} = 9$ Hz, ArH), 7.76 (d, 2H, $^3J_{HP} = 14.5$ Hz, ArH), 6.90 (d, 4H, $J_{HH} = 9$ Hz, ArH), 6.45 (d, 2H, $^4J_{HP} = 5.5$ Hz), 4.11–3.99 (m, 8H, $PO\underline{CH_2}CH_3$), 2.45 (d, 2H, $J_{HH} = 13.5$ Hz, spiroCH_2), 2.19 (d, 2H,

J_{HH} = 13.5 Hz, spiroCH_2), 1.40 (s, 6H, spiroCH_3), 1.38 (s, 6H, spiroCH_3), 1.15 (t, 6H, POCH$_2$C$\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz), 1.14 (t, 6H, POCH$_2$C$\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz).

^{13}C-NMR ($CDCl_3$, ppm) δ: 163.32, 156.55, 155.50, 149.68 (d, J_{CP} = 14 Hz), 142.63, 129.37 (d, J_{CP} = 2.8 Hz), 125.76, 121.48 (d, $^1J_{CP}$ = 188.8 Hz), 117.25 (d, J_{CP} = 7.4 Hz), 116.55, 62.30 (d, J_{CP} = 6 Hz), 59.09, 58.02, 43.69, 31.46, 30.03, 16.18 (d, J_{CP} = 6.6 Hz). ^{31}P-{H}-NMR ($CDCl_3$): 15.34 ppm. Anal. calcd. for $C_{41}H_{48}N_2O_{12}P_2$ (822.78): C 59.85, H 5.88, N 3.40; found C 59.79, H 5.93, N 3.35.

Bis-(5,5'-diethyloxyphosphonyl)-6,6'-bis-(p-aminophenoxy)-3,3,3',3'-tetramethyl-1,1'-spirobisindane (2)

3.4 g, 90%. White crystals, mp 173–175°C (EtOH/H_2O). FAB-MS: *m/z* 763.8 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 7.63 (d, 2H, $^3J_{HP}$ = 14.5 Hz, ArH), 6.72 (d, 4H, J_{HH} = 9 Hz, ArH), 6.59 (d, 4H, J_{HH} = 9 Hz, ArH), 6.21 (d, 2H, $^4J_{HP}$ = 5.5 Hz), 4.20–4.08 (m, 8H, PO$\underline{CH}_2CH_3$), 2.4 (brs., 4H, NH_2), 2.28 (d, 2H, J_{HH} = 13.5 Hz, spiroCH_2), 2.05 (d, 2H, J_{HH} = 13.5 Hz, spiroCH_2), 1.28 (m, 24H, spiroCH_3 + POCH$_2$C$\underline{H}_3$).

^{13}C-NMR ($CDCl_3$, ppm) δ: 159.59, 156.09, 148.97, 142.33, 128.76 (d, J_{CP} = 7.6 Hz), 125.78 (d, J_{CP} = 12 Hz), 119.86, 118,06 (d, $^1J_{CP}$ = 187.5 Hz), 116.19, 113.06 (d, J_{CP} = 11.4 Hz), 62.20 (d, J_{CP} = 6 Hz), 59.09, 58.13, 43.09, 31.48, 30.20, 16.33 (d, J_{CP} = 6.6 Hz). ^{31}P-{H}-NMR ($CDCl_3$): 17.47 ppm. Anal. calcd. for $C_{41}H_{52}N_2O_8P_2$ (762.82): C 64.56, H 6.87, N 3.67; found C 64.67, H 6.80, N 3.75.

Diethoxy[2- [4'-nitrophenoxy)phenyl]phosphonate (4a)

2.6 g, 75%. Pale yellow oil. FAB-MS: *m/z* 352.3 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 8.17 (d, 2H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.95 (dd, 1H, $^3J_{HP}$ = 14.5 Hz, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.57 (t, 1H, $^3J_{HH}$ = 8 Hz, ArH), 7.31 (tt, 1H, $^3J_{HH}$ = 8 Hz, $^4J_{HP}$ = 4 Hz, ArH), 7.03 (t, 1H, $^3J_{HH}$ = 8 Hz, ArH), 6.98 (d, 2H, $^3J_{HH}$ = 7.5 Hz, ArH), 4.05 (m, 4H, PO$\underline{CH}_2CH_3$), 1.64 (t, 6H, POCH$_2$C$\underline{H}_3$, $^3J_{HH}$ = 7.0 Hz).

Diethoxy[2- (4'-aminophenoxy)phenyl]phosphonate (5a)

1.3 g, 80%. White crystals, mp 114–115°C (EtOH/H_2O). FAB-MS: *m/z* 322.4 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 7.88 (dd, 1H,

$^3J_{HP}$ = 14.5 Hz, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.38 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.06 (tt, 1H, $^3J_{HH}$= 7.5 Hz, $^4J_{HP}$ = 3.5 Hz, ArH), 6.86 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 6.76 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 6.68 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 4.16 (m, 4H, PO$\underline{CH_2}CH_3$), 3.35 (brs, 2H, NH_2), 1.31 (t, 6H, POCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, ppm) δ: 160.72, 148.01, 142.98, 135.01 (d, J_{CP} = 7.13 Hz), 133.92 (d, J_{CP} = 1.9 Hz), 121.69 (d, J_{CP} = 14.5 Hz), 121.37, 118.08 (d, $^1J_{CP}$ = 187 Hz), 116.41 (d, J_{CP} = 9.13 Hz), 116.27, 62.24 (d, J_{CP} = 5.8 Hz), 16.35 (d, J_{CP} = 6.5 Hz).). ^{31}P-{H}-NMR ($CDCl_3$): 16.72 ppm. Anal. calcd. for $C_{16}H_{20}NO_4P$ (321.31): C 59.81, H 6.27, N 4.36; found C 59.73, H 6.15, N 4.30.

Ethyl 2-(4'-nitrophenoxy)benzoate (4b)

1.8 g, 65%. Pale yellow crystals, mp 28–30°C (EtOEt/hexane). FAB-MS: *m/z* 288.1 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 8.19 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 8.03 (d, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.61 (t, 1H, $^3J_{HH}$ = 7.5, $^4J_{HH}$= 1.5 Hz, ArH), 7.37 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.14 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 6.92 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 4.20 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}CH_3$), 1.48 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz). Anal. calcd. for $C_{15}H_{13}NO_5$ (287.27): C 62.72, H 4.56, N 4.88; found C 62.60, H 4.64, N 4.94.

Ethyl 2-(4'-aminophenoxy)benzoate (5b)

1.8 g, 65%. Pale yellow oil. FAB-MS: *m/z* 258.2 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 7.84 (d, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.36 (t, 1H, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz, ArH), 7.07 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 6.86 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 6.82 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 6.64 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 4.32 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}CH_3$), 3.47 (brs, 2H, NH_2), 1.31 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, ppm) δ: 166.03, 157.65, 149.04, 142.52, 133.04, 131.36, 122.46, 122.09, 120.33, 118.68, 116.12, 60.91, 14.15.

Ethyl 3-(4'-nitrophenoxy)benzoate (4c)

2.6 g, 90%. Yellow oil. FAB-MS: *m/z* 288.3 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 8.22 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 7.94 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.75 (s, 1H, ArH), 7.51 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH),

7.28 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.03 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 4.39 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}$CH$_3$), 1.39 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz).

Ethyl 3-(4'-aminophenoxy)benzoate (5c)

1.0 g, 80%. Pale yellow oil. FAB-MS: *m/z* 258.4 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 7.70 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.59 (s, 1H, ArH), 7.33 (t, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 7.10 (d, 1H, $^3J_{HH}$ = 7.5 Hz, ArH), 6.87 (d, 2H, $^3J_{HH}$ = 9.0 Hz, ArH), 6.68 (d, 2H, $^3J_{HH}$ = 9.0 Hz, ArH), 4.35 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}$CH$_3$), 3.6 (brs, 2H, NH$_2$), 1.36 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, ppm) δ: 166.14, 158.89, 148.01, 143.01, 131.97, 129.38, 123.12, 121.56, 121.04, 117.95, 116.23, 60.99, 14.21.

Ethyl 4-(4'-nitrophenoxy)benzoate (4d)

2.15 g, 75%. Pale yellow crystals, mp 67–68 (EtOAc/hexane). FAB-MS: *m/z* 288.3 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 8.24 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 8.11 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 7.11 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 7.08 (d, 2H, $^3J_{HH}$ = 9.5 Hz, ArH), 4.40 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}$CH$_3$), 1.40 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz).

Ethyl 4-(4'-aminophenoxy)benzoate (5d)

1.1 g 83%, oil. FAB-MS: *m/z* 258.2 (100) $[M + H]^+$. ^{1}H-NMR ($CDCl_3$, ppm) δ: 7.96 (d, 2H, $^3J_{HH}$ = 9.0 Hz, ArH), 6.91 (d, 2H, $^3J_{HH}$ = 9.0 Hz, ArH), 6.88 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 6.70 (d, 2H, $^3J_{HH}$ = 8.5 Hz, ArH), 4.34 (q, 2H, $^3J_{HH}$ = 7.0 Hz, O$\underline{CH_2}$CH$_3$), 3.5 (brs, 2H, NH$_2$), 1.37 (t, 3H, OCH$_2\underline{CH_3}$, $^3J_{HH}$ = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, ppm) δ: 166.21, 162.97, 147.14, 143.45, 131.46, 123.91, 121.65, 116.22, 116.04, 60.67, 14.32.

Acknowledgements

We thank C.N.R. and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) for financial support.

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