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THE REACTIONS OF HALOGENATED PHENYLNITROMETHANES WITH TRIETHYL PHOSPHITE

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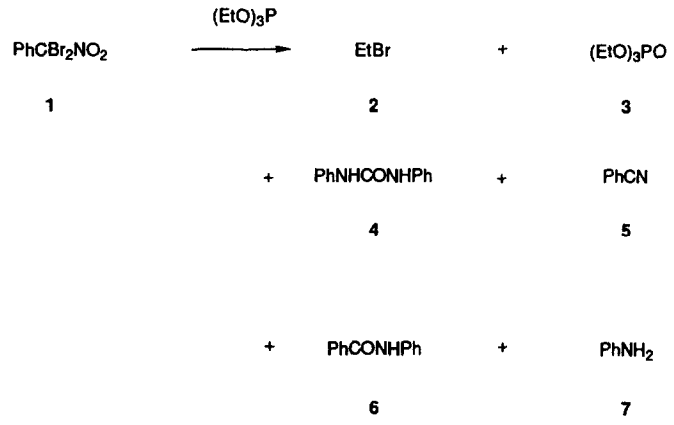
Abstract - Dibromo and dichloro phenylnitromethanes reacted with triethyl phosphite to yield mainly benzonitrile, ethyl halide, and triethyl phosphate. In addition, the products of molecular rearrangement, N,N-diphenylurea, N-phenylbenzamide, and aniline, were isolated. It is proposed that they arise from the rearrangement of an intermediate, benzonitrile oxide, to phenyl isocyanate. A seventh type of product, chlorobenzalimino diethyl phosphate (9), was obtained from dichlorophenylnitromethane. No rearranged product was isolated from the reaction of triethyl phosphite with the monohalogenated phenylnitromethanes which gave the same main products as their dihalogenated analogues.

Introduction

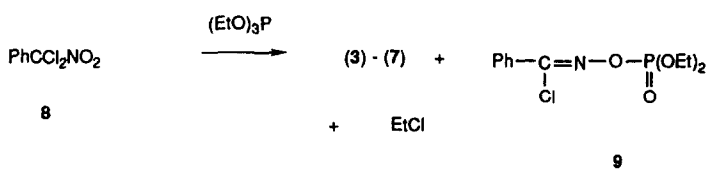
In 1947, Arbuzov and co-workers,[1] continuing the study of the Michaelis-Arbuzov and related reactions,[2] reported that dibromophenylnitromethane (**1**) reacted exothermically with slightly more than two molar equivalents of triethyl phosphite at 4 °C with elimination of ethyl bromide. They increased the temperature of the reaction mixture to 180 °C before distilling the product. This gave triethyl phosphate and an oil, bp 78-81 °C/4 mm Hg which, on standing, deposited crystals of an unidentified product, mp 237-9 °C and molecular formula $C_{14}H_{12}N_2O$. While studying the substitution of fluorine for halogen in dihalogenophenylnitromethanes, the opportunity was availed of to repeat this reaction.

Results

The loss of ethyl bromide and the formation of triethyl phosphate (3) were readily confirmed by ^1H NMR spectroscopy and the expected white solid, mp 235-6 °C, crystallised out of the distillate. Its mass spectrum, however, showed a molecular ion at m/z 212, suggesting a molecular formula (supported by elemental analysis) of $C_{13}H_{12}N_2O$ not $C_{14}H_{12}N_2O$. It was identified as *N,N*-diphenylurea (4). Two additional products were isolated, benzonitrile (5), the major product of the reaction, and *N*-phenylbenzamide (6). The formation of the urea 4 and the amide 6 was of particular interest because of the molecular rearrangement involved.

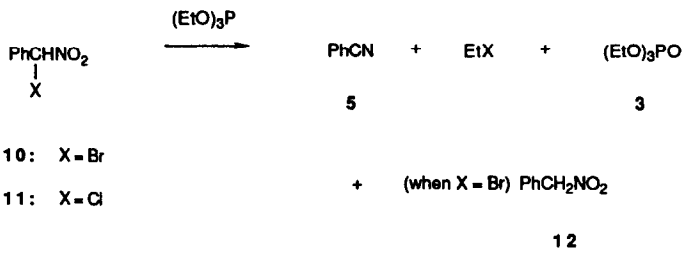


It was found more practical to carry out the reaction at 0 °C and then to allow it to go to completion at ambient temperature over five hours. The requirement of two molar equivalents of triethyl phosphite was confirmed. The use of three molar equivalents gave the same products in approximately the same ratios; the use of one molar equivalent resulted in the recovery of almost half of the nitromethane reactant 1. Dichlorophenylnitromethane (8) did not react with triethyl phosphite at 0 °C but reproducible results were obtained by slow, dropwise addition of the phosphite to the chloronitromethane 8 at 10-15 °C. Except that ethyl chloride replaced ethyl bromide, the same products 3-6 were obtained as from dibromophenylnitromethane (1) but, in addition, a new compound, chlorobenzalimino diethyl phosphate (9), was isolated.



The results of a study, by liquid chromatography, of the reaction of dibromophenylnitromethane (1) with two molar equivalents of triethyl phosphite, for various lengths of time and mainly at ambient temperature, are given in Table I. This study led to the observation of a sixth product from this reaction - aniline. It can be seen that the dibromonitromethane 1 is entirely consumed after thirty minutes. This is in contrast with the results, given in Table II, of a similar study of dichlorophenylnitromethane (8) which shows the presence of this reactant even after sixteen hours. This reaction also differs from that of its dibromo analogue 1 in that lower yields of

benzonitrile, *N,N*-diphenylurea, aniline, and *N*-phenylbenzamide were obtained as well as by the formation of the above-mentioned new compound, chlorobenzalimino diethyl phosphate **9**.

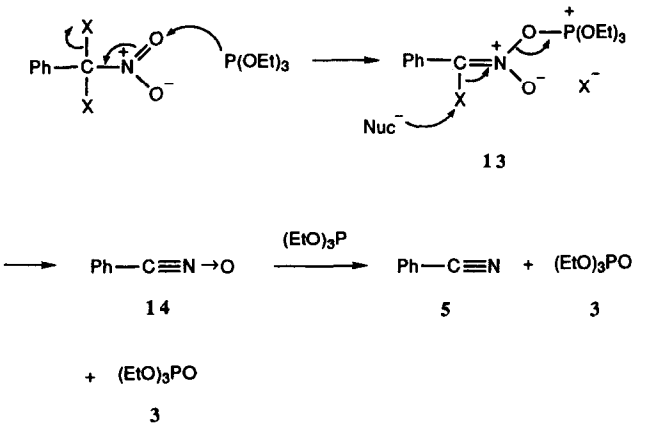


Monobromophenylnitromethane (**10**) reacted with two molar equivalents of triethyl phosphite at 0 °C and afforded benzonitrile (**5**) as the major product, together with phenylnitromethane (**12**), ethyl bromide, and triethyl phosphate. Monochlorophenylnitromethane (**11**) did not react at low temperatures and had to be heated at 70 °C; benzonitrile (**5**), ethyl chloride, and triethyl phosphate (**3**), but not phenylnitromethane (**12**), were isolated.

Discussion

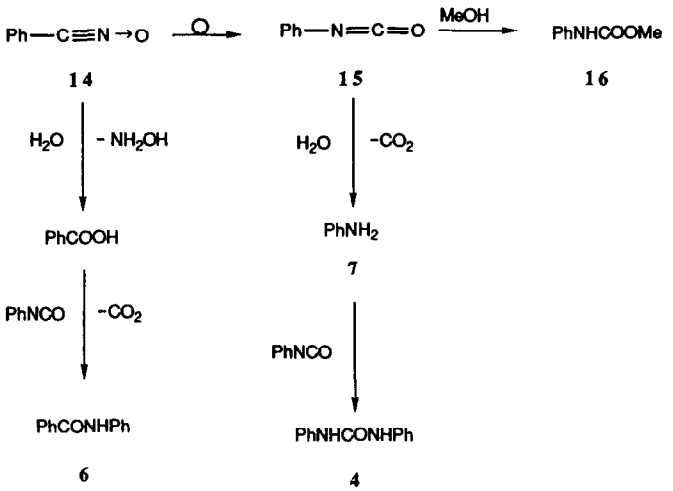
The results of the reactions of triethyl phosphite with dibromophenylnitromethane (**1**) and dichlorophenylnitromethane (**8**) are sufficiently similar to warrant the suggestion that, in the main, the reactions proceed *via* the same pathway. The greater reactivity of the bromo compound is to be expected. The failure to observe the bromo analogue of cholorobenzalimino diethyl phosphate (**9**) was probably due to the greater reactivity of its precursor (**17**, X=Br) , the chloro compound **9** was not sufficiently stable to obtain a completely satisfactory elemental analysis.

Based on a study by Fishwick, Rowles, and Stirling [3] of bromonitromethane, it is likely that the major product, benzonitrile (**5**), is formed from the *di*halogenophenylnitromethanes (Scheme 1) by indirect displacement of halide by triethyl phosphite to give a salt **13** which is attacked at the remaining halogen by some nucleophile, not necessarily halide, to eliminate triethyl phosphate (**3**) and form benzonitrile oxide (**14**); this oxide is then reduced [4a] by the second molar equivalent of triethyl phosphite to benzonitrile (**5**). The intermediacy of nitrile oxides has been advanced, [3,5] though not detected, in the reactions of *mono*halogenonitromethanes with trivalent phosphorus reagents.



Scheme 1

It is proposed that the urea **4**, amide **6**, and amine **7** are the result (Scheme 2) of the long known, [4b] if little understood, molecular rearrangement of nitrile oxides to isocyanates. Phenyl isocyanate (**15**), formed by rearrangement of benzonitrile oxide (**14**) is unstable in the presence of moisture [6] and readily forms these three products. Indirectly, therefore, these by-products point to the formation of a nitrile oxide intermediate **14**. Evidence for the formation of phenyl isocyanate (**15**) was obtained by adding methanol to the reaction mixture when methyl *N*-phenylcarbamate (**16**) was isolated; this is a characteristic reaction [6] of phenyl isocyanate. It was also observed that, when a molar equivalent of water was added to the reaction mixture of the dibromonitromethane **1**, aniline hydrobromide eventually precipitated; when an excess of water was added, aniline (**7**) itself was isolated.



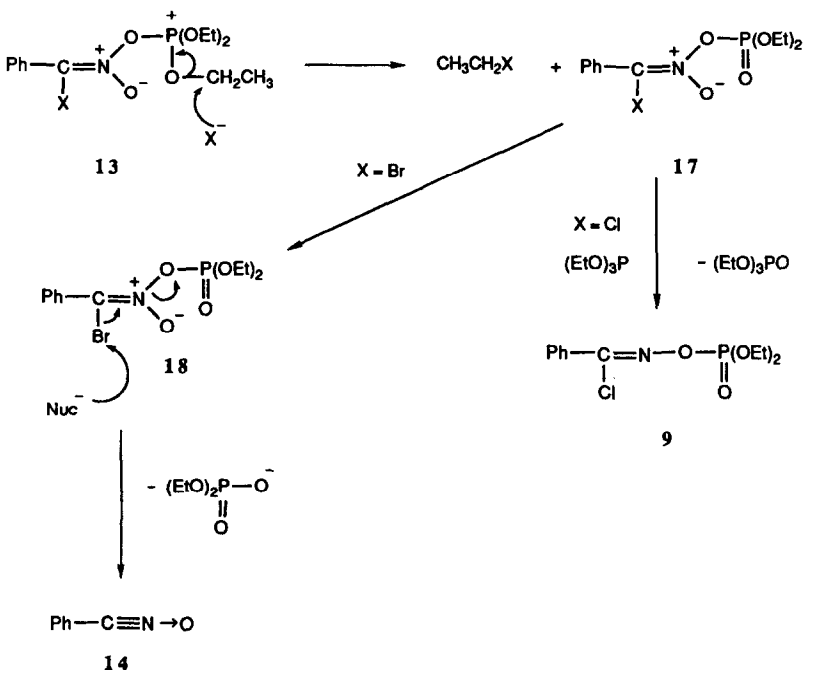
Scheme 2

It is presumed that ethyl halide arises by the action of halide on the initially formed salt **13** (Scheme 3) in a reaction characteristic of the second stage of the Michaelis-Arbuzov reaction [2] and that, when the halogen of the resulting phosphate **17** is chlorine, the ester **17** is reduced by triethyl phosphite to chlorobenzalimino diethyl

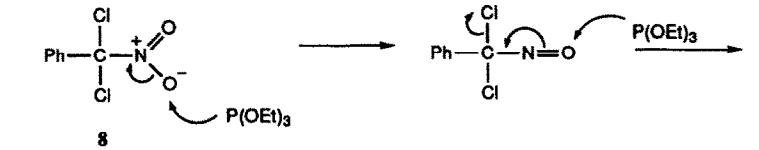
phosphate (**9**). However, when the halogen of the resulting ester **18** is bromine, an alternative reaction apparently takes place, presumably leading to the formation of benzonitrile oxide (**14**) by nucleophilic attack on the bromine. It is conceivable that the phosphate **9** is formed (Scheme 4) by way of a nitroso intermediate [7]. However, it had been reported [1] that the aliphatic nitro group is not reduced by triethyl phosphite.

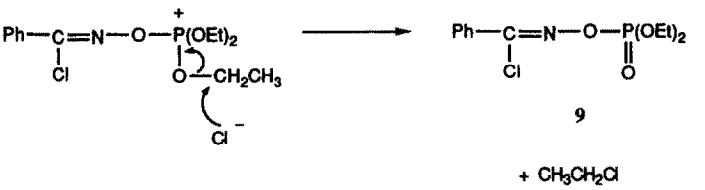
While neither the reaction of the monobrominated phenylnitromethane **10** nor that of its monochlorinated analogue **11**, with triethyl phosphite, has been investigated, the reaction of the former **10** with triphenyl phosphine had been studied by Tripett and Walker [5]. They isolated benzonitrile in good yield and considered the reaction to proceed *via* a nitrile oxide (Scheme 5) although their attempts to trap this intermediate failed. On the other hand, Speziale and Smith [8] believe that the initial phosphine attack (Scheme 6) is on halogen, not oxygen.

That we did not observe the formation of any of the typical hydrolysis products **4**, **6**, **7** of phenyl isocyanate from the reaction of either monohalogenated phenylnitromethane **10**, **11** with triethyl phosphite, suggests that neither this isocyanate nor its precursor, benzonitrile oxide, is formed to any significant extent. It is possible that the first step of this reaction (Scheme 7), forming the salt **19**, is similar to that of the reaction (Scheme 1) of the dihalogenated phenylnitromethanes but, lacking a second halogen to be attacked by triethyl phosphite or some other nucleophile, this salt **19** is , instead, reduced by the phosphite to eventually give benzonitrile with triethyl phosphate or ethyl halide. The isolation of phenylnitromethane (**20**) from the reaction of bromophenylnitromethane (**10**) may be the result (Scheme 8) of initial phosphite attack on bromine.

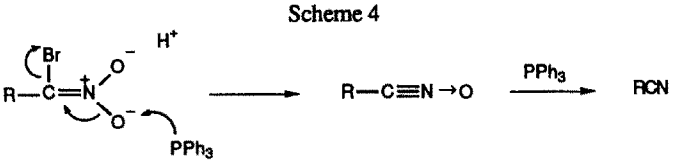


Scheme 3

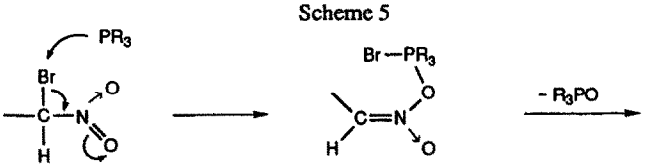


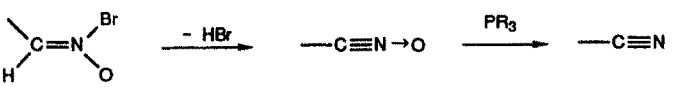


Scheme 4



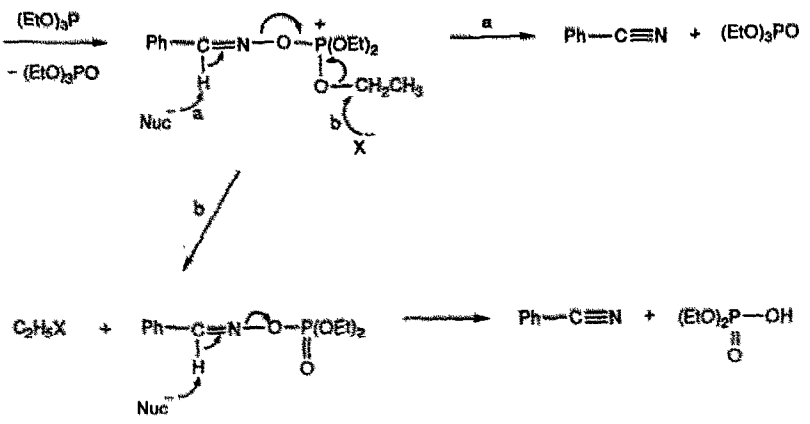
Scheme 5



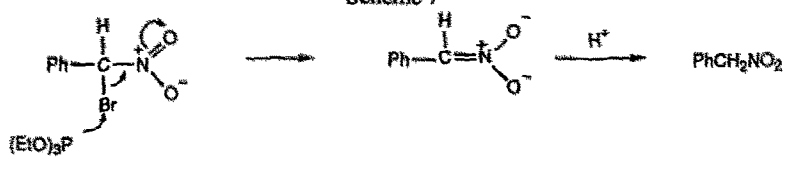


Scheme 6

10, 11 19



Scheme 7



10 20

Scheme 8

Table I. Reaction (ambient temp.): $PhCBr_2NO_2 + 2\ (EtO)_3P$. Percentage yields by LC [a]

Time / Products	0.5 h	2 h	3 h	16 h	1 week	Heated [b]
PhCN	58	68	60	64	61	62
$PhNH_2$	15	14	18	17	12	12
PhNHCONHPh	7	9	9	8	8	12
PhNHCOPh	0.4	0.4	0.6	0.5	0.5	1
$PhCBr_2NO_2$	0	0	0	0	0	0

[a] Mobile phase, MeOH:H_2O 60:40; flow rate, 1.5 ml/min. [b] 60 °C for 2 h.

Table II. Reaction (ambient temp.): $PhCCl_2NO_2 + 2\ (EtO)_3P$. Percentage yields by LC [a]

Time / Products	0.5 h	1.5 h	3 h	5.5 h	16 h	Heated [b]
PhCN (**5**)	23	26	28	31	32	33
$PhCClNOP(O)(OEt)_2$ (**9**)	14	21	23	29	29	33
PhNHCONHPh (**4**)	1.5	1.9	2.0	2.4	2.3	2.6
$PhNH_2$ (**7**)	0.5	0.7	1.0	0.9	1.1	0.8
PhNHCOPh (**6**)	0.001	0.001	0.003	0.005	0.009	0.011
$PhCCl_2NO_2$ (**8**)	65	32	12	9	6.2	0.0

[a] Mobile phase for the products **4-7**, MeOH:H_2O 60:40; flow rate, 1.5 ml/min. Mobile phase for the products **8** & **9**, MeOH:H_2O 80:20; flow rate, 0.5 ml/min. [b] 60 °C for 2 h.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer 337 and Perkin-Elmer 1710 I.R. Fourier Transform spectrometers. ^1H NMR spectra were recorded at 60 MHz on a Perkin-Elmer R12 and JEOL JNM-PMX60 spectrometers in $CDCl_3$ solutions containing Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNX-GX F.T. NMR spectrometer. The spectral data for all previously known products were comparable with those of authentic samples. Melting points were obtained on a Reichert Thermovar hot-plate apparatus and are uncorrected. Mass spectra were recorded on a VG Micromass 7070H spectrometer. Merck Silica $PF_{254+366}$ was used for preparative thin layer chromatography (PLC); PLC plates were repeatedly developed using increasingly more polar solvent mixtures. Merck Kieselgel 60 F_{254} was employed for thin layer chromatography (TLC). For liquid chromatography (LC), a Waters Associates H.P.L.C., fitted with a μ-Bondapak (100mm x 8mm) C_{18} reverse phase cartridge and connected to a LDC/Milton Roy C1-108 integrator and a fixed wavelength (214 nm) detector was employed using an external standard.

Reaction of Dibromophenylnitromethane (1) with Triethyl Phosphite. $(EtO)_3P$ (6.64 g, 40 mmol) was added dropwise to **1** (5.0 g, 17 mmol) at 0 °C and stirred at room temperature for 30 min. A

sample of the evolved ethyl bromide was passed into $CDCl_3$. Distillation of the reaction mixture gave a colourless oil, bp 68-72 °C/2 mm Hg which was fractionated by PLC giving **5** (0.728 g, 42% yield), **6** (0.044 g, 3% yield), mp 162-3 °C, **4** (0.162 g, 9% yield), mp 235-6 °C, and **3** (3.882 g, 63% yield). **5**: ^{1}H NMR δ 7.20-7.92 (m); ^{13}C NMR δ 112.35 (s), 118.87 (s), 129.15 (d), 132.13 (d), 132.84 (d); IR (KBr) 2229 cm^{-1} (C≡N); MS m/z 103 (M^+). **6**: ^{1}H NMR δ 4.00 (s, OH), 7.36-7.74 (m, 8 H), 8.05-8.26 (m, 2 H); MS m/z 197 (M^+); Found C, 73.79; H, 5.71; N, 13.47. $C_{13}H_{12}N_2O$ requires C, 73.57; H, 5.70; N, 13.20%. **4**: ^{1}H NMR (DMSO-d_6) δ 6.94-6.99 (m, 2 H), 7.22-7.28 (m, 4 H), 7.43-7.59 (m, 4 H), 8.32 (bs, NH x 2, exchangeable in D_2O); ^{13}C NMR (DMSO-d_6) δ 118.60 (d), 122.10 (d), 128.71 (d), 139.50 (s), 153.10 (s); IR (KBr) 3326 cm^{-1} (NH), 1651 cm^{-1} (C=O); MS m/z 212 (M^+). **3**: ^{1}H NMR δ 1.37 (t, J = 7 Hz, CH_3), 4.16 (q, J = 7 Hz, CH_2). **2**: ^{1}H NMR δ 1.69 (t , J = 7 Hz), 3.50 (q, J = 7 Hz, CH_2).

Reaction of Dichlorophenylnitromethane (8) with Triethyl Phosphite. $(EtO)_3P$ (3.70 g, 22 mmol) was added dropwise to **8** (2.0 g, 10 mmol) at 10-15 °C and stirred at room temperature overnight. A sample of the evolved ethyl chloride was passed into $CDCl_3$. The reaction mixture was fractionated by PLC giving **5** (0.251 g, 25% yield), **9** (0.826 g, 29% yield) , **4** (0.068 g, 7% yield), mp 235-6 °C, **6** (0.002 g, 0.2% yield), mp 160-1 °C, and **3** (1.48 g, 42% yield). **9**: ^{1}H NMR δ 1.41 (t, J = 7 Hz, CH_3 x 2), 4.32 (m, CH_2 x 2), 7.40-7.51 (m, 3 H), 7.89 7.93 (m, 2 H); ^{13}C NMR δ 16.12, 16.20 (CH_3), 65.26, 65.36 (CH_2), 127.94 (CH), 128.66 (CH), 131.05 (C), 132.06 (CH), 148.26, 148.50 (C=N); ^{31}P NMR δ 1.61 (quintet); MS m/z 291 (M^+); Found C, 45.09; H, 5.67; Cl, 13.10; N, 4.51; P 10.59. $C_{11}H_{15}ClNO_4P$ requires C, 45.30; H, 5.18; Cl, 12.16; N, 4.80; P, 10.62%. Ethyl chloride: ^{1}H NMR δ 1.52 (t, J = 7 Hz, CH_3), 3.68 (q, J = 7 Hz, CH_2).

Reaction of Dibromophenylnitromethane (1) with Triethyl Phosphite and (i) Methanol, and (ii) Water. (i) $(EtO)_3P$ (1.30 g, 8 mmol) was added dropwise to **1** (1.0 g, 3 mmol) at 0 °C. A sample of the evolved **2** was passed into $CDCl_3$. The mixture was stirred at 0 °C for 30 min. MeOH (0.11 g, 3 mmol) was added and the mixture was stirred at room temperature for 1h. It was fractionated by PLC giving **5** (0.132 g, 38% yield), **6** (0.030 g, 9% yield), mp 161-2 °C, **4** (0.127 g, 35% yield), mp 234-5 °C, **16** (0.029 g, 6% yield), mp 72-3 °C, and **3** (1.052 g, 85% yield). **16**: ^{1}H NMR δ 3.86 (s, OCH_3), 6.91-7.61 (m, 6 H). IR (KBr) 1704 cm^{-1} (C=O).

(ii) This reaction was carried out as above using $(EtO)_3P$ (6.64 g, 40 mmol), **1** (5.0 g, 17 mmol), and H_2O (0.31 g, 17 mmol). $CHCl_3$ (10 ml) was added to the reaction mixture after it had been stirred overnight. White crystals of aniline hydrobromide (0.512 g, 17% yield) precipitated. The mother liquor was fractionated by PLC giving **5** (0.618 g, 35% yield), **6** (0.052 g, 2% yield), mp 160-1 °C, **4** (0.602 g, 17% yield), mp 234-5 °C, and **3** (4.680 g, 76% yield). Aniline hydrobromide ^{1}H NMR (CD_3OD) δ 5.34 (bs, NH_3, exchangeable in D_2O), 7.52 (s, 5 H); MS m/z 93 (M^+- HBr); Found C, 41.33; H, 4.54; Br, 46.10; N, 7.93. C_6H_8BrN requires C, 41.41; H, 4.63; Br, 45.91; N, 8.05%.

Reaction of Bromophenylnitromethane (10) with Triethyl Phosphite. $(EtO)_3P$ (3.54 g, 21 mmol) was added to **10** (2.0 g, 9 mmol) at 0 °C with stirring. A sample of the evolved **2** was passed into $CDCl_3$. The mixture was stirred for 30 min and then fractionated by PLC, giving **5** (0.426 g, 45% yield), **12** (0.219 g, 17% yield), and **3** (1.92 g, 57% yield). **12**: ^{1}H NMR δ 5.43 (s, CH_2), 7.54 (s, 5 H).

Reaction of Chlorophenylnitromethane (11) with Triethyl Phosphite. $(EtO)_3P$ (1.58 g, 10 mmol) was added to **11** (1.0 g, 6 mmol) at 10 °C. The mixture was heated to 70 °C when EtCl was evolved. This reaction temperature was maintained for 2 h. The mixture was then fractionated by PLC, giving **5** (0.326 g, 54% yield) and **3** (0.86 g, 41% yield).

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