Pergamon

Tetrahedron 54 (1998) 14145–14156

TETRAHEDRON

Reaction of Aromatic Diamines with Diphenylcarbonate Catalyzed by Phosphorous Acids: a New Clean Synthetic Route to Mono- and Dicarbamates

Michele Aresta*, Angela Dibenedetto and Eugenio Quaranta

Dipartimento di Chimica, Università di Bari, Campus Universitario, 70126, Bari, Italy

and

Centro CNR-MISO, Via Amendola, 173, 70126, Bari, Italy

Received 3 July 1998; revised 3 September 1998; accepted 17 September 1998

Abstract: In the presence of organophosphorus acids [$Ph_2P(O)OH$, $(PhO)_2P(O)OH$, $(BuO)_2P(O)OH$, $(BuO)P(O)(OH)_2$], aromatic diamines, such as 4,4'-methylendianiline (MDA) or 2,4-diaminotoluene (TDA), react with diphenylcarbonate (DPC) to afford in a very selective way mono- and dicarbamate phenyl esters. The carbamation process is strongly influenced by the temperature and solvent. The influence of both these factors on carbamate yield and selectivity has been investigated and we present in this study the kinetics of formation of both mono- and dicarbamate esters.

INTRODUCTION

Aromatic carbamate esters are compounds of great interest as they are intermediates in the production of agrochemicals, dyestuffs, pharmaceuticals, and, under special conditions, aromatic isocyanates.[1] In particular, dicarbamates afford di-isocyanates which are precursors of polyurethanes. The current methods of synthesis of carbamates are based on the use of phosgene.[2] Much effort is currently being used to find new alternative clean synthetic methodologies based on the use of less noxious starting materials. We have shown that both carbon dioxide[3] and carbonic acid diesters[4,5] are good substitutes for phosgene in the synthesis of carbamate esters.

Aminolysis of organic carbonates (eq. 1)[6] has become a very attractive synthetic route to carbamates[7]

$$RR'NH + R''OC(O)OR'' \longrightarrow RR'NC(O)OR'' + R''OH \qquad (R, R' = H, \text{alkyl or aryl};\ R'' = \text{alkyl or aryl}) \qquad (1)$$

since non-phosgene routes to carbonic acid diesters are now available. In fact, dimethylcarbonate (DMC) is currently produced on a large-scale by oxidative carbonylation of methanol.[8] Organic carbonates of high boiling alcohols[9] or phenols[10] can be obtained easily by trans-esterification of DMC or diethylcarbonate.

Reaction 1 usually needs a suitable catalyst to observe a good conversion rate and selectivity. Recently, we have shown that CO_2 is an effective catalyst for the synthesis of *N*-alkyl-methylcarbamates from aliphatic amines and DMC.[4] This methodology cannot be extended to the carbomethoxylation of aromatic amines, most probably because of the low reactivity of the latter towards carbon dioxide, due to its low nucleophilicity.

Carboalkoxylation of anilines, and more generally of aromatic amines, is usually achieved using metal-catalysts (Zn, Co, Sn, Al, or Ti derivatives),[11] as well as strong bases (Group 1 alkoxides) under harsh

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00873-4

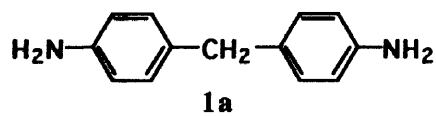
conditions.[12] 2-Hydroxypyridine[13] or metal salts[11d] have been employed as catalysts for the carbo-aryloxylation of aromatic amines with diarylcarbonates. The reaction conditions are usually severe and the side-formation of N-alkylation products and/or ureas represents a major drawback of these synthetic procedures. We have shown that aromatic mono-amines can react with DMC or diphenylcarbonate (DPC) in the presence of organophosphorus acids [$Ph_2P(O)OH$, $(PhO)_2P(O)OH$, $(BuO)_2P(O)OH$, $(BuO)P(O)(OH)_2$] to give carbamate esters with very high selectivity.[5] The catalytic role of the P-acid has been rationalized. The reaction mechanism shows intriguing analogies with the mechanism of formation, in living systems, of carbamate anion from ammonia and hydrogencarbonate catalyzed by the carbamylphosphate synthase (CPS) enzyme.[14]

We have now extended this investigation to aromatic diamines focussing our attention on 4,4'-methylendianiline (MDA, **1a**) and 2,4-diaminotoluene (TDA, **1b**), as the corresponding dicarbamates are suitable precursors to methylendiphenyldiisocyanate (MDI, **2a**) and toluenediisocyanate (TDI, **2b**), respectively. Di-isocyanates **2a** and **2b** are useful monomers for the synthesis of industrially relevant polyurethanes. In this paper we show that, in the presence of selected P-acids and under mild conditions, both MDA and TDA can react with DPC affording the corresponding dicarbamates **3a-b**, selectively and with high yields.[15] Under controlled experimental conditions, the same reaction can be used for the selective synthesis of monocarbamates **4a-b**.

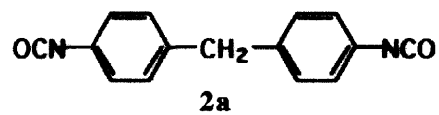
RESULTS AND DISCUSSION

Reactivity of MDA towards DPC in the presence of "P-acids"

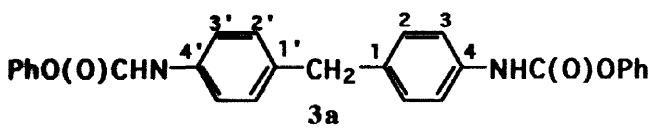
When a THF solution of **1a** (0.85 mmol) and DPC (1.75 mmol) is stirred at 363 K, under dinitrogen, for 24 hours, in the absence of any catalyst, no reaction is observed. Noteworthy, when $Ph_2P(O)OH$ is added to the system, mono-carbamate **4a** is immediately formed in very good yield followed by dicarbamate **3a**. In order to find out the correct conditions for the synthesis of both **3a** and **4a**, we have performed an extended kinetic work.



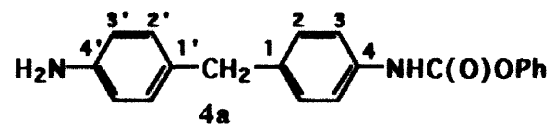
1a



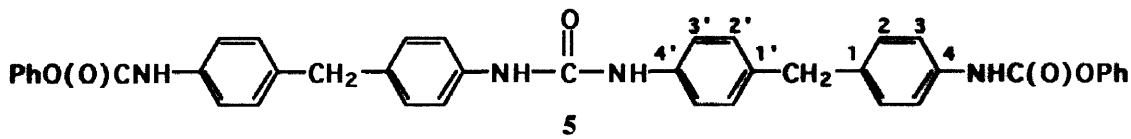
2a



3a



4a



5

The kinetics of formation of **3a** and **4a** from DPC and MDA, in the presence of $Ph_2P(O)OH$ as catalyst and THF as solvent, at the temperature of 393, 363 and 323 K, respectively, are reported in Figures 1-3 . The inspection of the kinetic curves shows that, depending on the reaction time and working temperature, is possible to address the reaction towards the preferential formation of either mono- **4a** or dicarbamate **3a**. The shorter the reaction time and the lower the reaction temperature, the higher the selectivity toward the mono-carbamate **4a**. For instance, after 8h at 323 K, a THF (10 mL) solution of **1a** (2.67 mmol) and DPC (5.30 mmol) containing also $Ph_2P(O)OH$ (0.27 mmol) gives **4a** selectively (100 %), although in a yield of ca. 20 % (Figure 3). A general

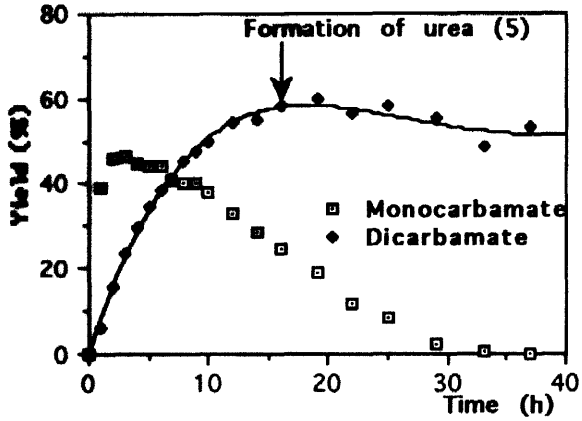


Fig.1. Kinetics of formation of **4a** and **3a** from **1a** (0.535 g, 2.70 mmol) and DPC (1.159 g, 5.41 mmol) in the presence of $Ph_2P(O)OH$ (0.058 g, 0.26 mmol), in THF (10 mL), at 393 K. Internal standard: biphenyl (0.193 g, 1.25 mmol).

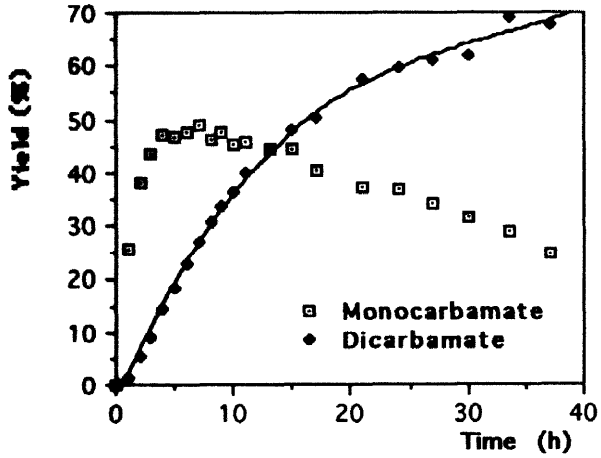


Fig. 2. Kinetics of formation of **4a** and **3a** from **1a** (0.511 g, 2.58 mmol) and DPC (1.101 g, 5.14 mmol) in the presence of $Ph_2P(O)OH$ (0.057 g, 0.26 mmol), in THF (10 mL), at 363 K. Internal standard: biphenyl (0.206 g, 1.34 mmol).

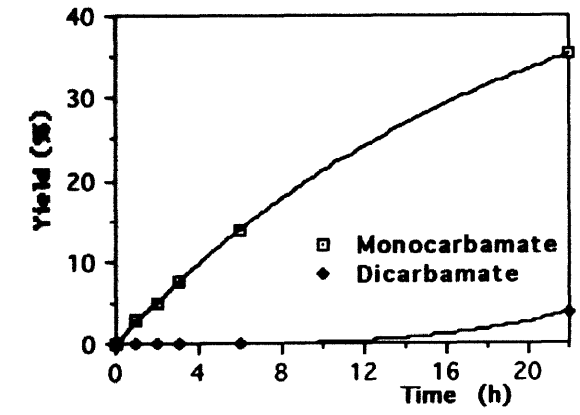


Fig. 3. Kinetics of formation of **4a** and **3a** from **1a** (0.530 g, 2.68 mmol) and DPC (1.151 g, 5.37 mmol) in the presence of $Ph_2P(O)OH$ (0.059 g, 0.27 mmol), in THF (10 mL), at 323 K. Internal standard: biphenyl (0.205 g, 1.33 mmol).

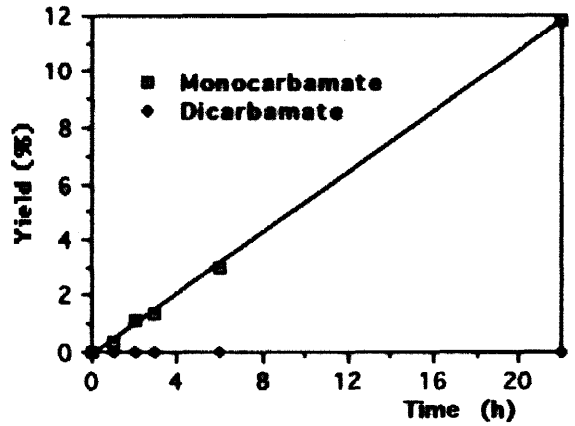


Fig. 4. Kinetics of formation of **4a** and **3a** from **1a** (0.508 g, 2.57 mmol) and DPC (1.100 g, 5.14 mmol) in the presence of $Ph_2P(O)OH$ (0.0566 g, 0.26 mmol), in Et_2O (10 mL), at 323 K. Internal standard: biphenyl (0.212 g, 1.37 mmol).

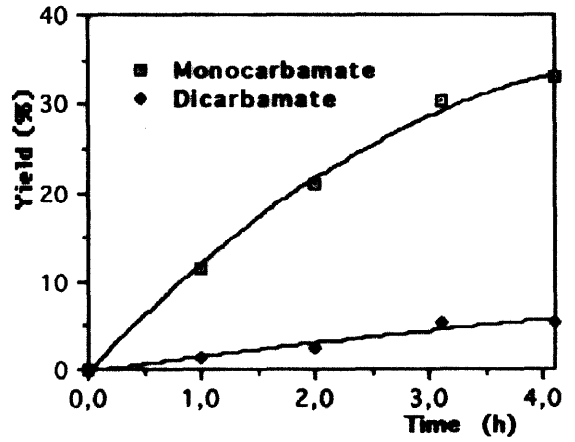


Fig. 5. Kinetics of formation of **4a** and **3a** from **1a** (0.252 g, 1.27 mmol) and DPC (0.545 g, 2.55 mmol) in the presence of $Ph_2P(O)OH$ (0.028 g, 0.13 mmol), in PhOH (5.061 g), at 363 K. Internal standard: biphenyl (0.099 g, 0.639 mmol).

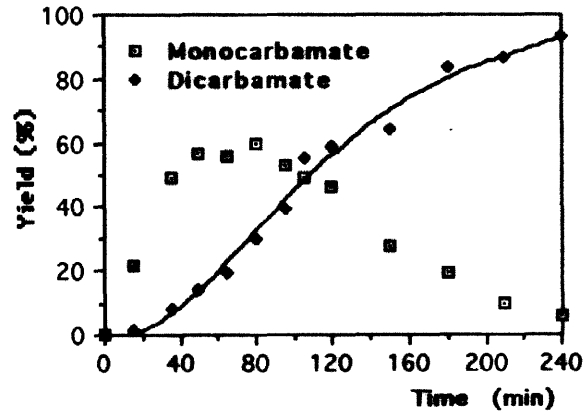


Fig. 6. Kinetics of formation of **4a** and **3a** from **1a** (0.267 g, 1.35 mmol) and DPC (5.586 g, 26.1 mmol) in the presence of $Ph_2P(O)OH$ (0.0299 g, 0.135 mmol), at 363 K. Internal standard: biphenyl (0.121 g, 0.785 mmol).

trend is that the concentration of **4a** reaches a maximum (Figures 1 and 2), and then decreases with time due to the conversion of **4a** into **3a**.

The temperature strongly affects the selectivity of the carbamation process: high temperature (above 373 K) favours the formation of urea **5** (generated by reaction of **4a** with **3a**). At 393 K (Figure 1), this species is formed and, being poorly soluble in THF, separates from the reaction mixture and can be isolated easily. It is worth noting that after **5** appears, the concentration of **3a** remains practically constant despite the fact that the concentration of **4a** decreases to analytically negligible values. This fact may suggest that **4a** converts into **5** by reaction with **3a** at a reaction rate comparable with that of the formation of **4a** from **1a** and DPC. The formation of **5** is not observed at temperatures below 363 K.

THF was a particularly suitable solvent in these reactions. We have also investigated diethyl ether at 323 K (Figure 4), and phenol at 393 K (Figure 5).

The utilization of diethyl ether was suggested by the fact that **3a** is poorly soluble in ether. It would, thus, separate from the reaction medium as it forms, making the isolation procedure easier. In fact, we have found that the concentration of **3a** in solution is practically constant and very low all through the reaction time. However, comparison with the results obtained in THF at the same temperature (323 K) clearly demonstrates that, despite this positive aspect, diethyl ether is not a good solvent as the process is much slower than in THF. Under the working conditions $Ph_2P(O)OH$ is converted by reaction with the excess of **1a** into $(H_2MDA)(O_2PPh_2)_2$, which is supposed to be the catalytically active species.[16] At 293 K the phosphinate salt is poorly soluble both in THF and in ether, and immediately separates from the reaction medium after mixing the reagents. Warming the reaction mixture to 323 K causes complete dissolution of the salt if THF is used as solvent, but the reaction system still remains heterogeneous in the case of diethyl ether. Therefore, the different activity of $Ph_2P(O)OH$ in diethyl ether and THF, at 323 K, can be related to the different solubility of the phosphinate salt, $(H_2MDA)(O_2PPh_2)_2$, in each of the two solvents at the working temperature.

The use of phenol as solvent is very attractive as this species is a reaction co-product. Figure 5 reports the results obtained at 363 K. The presence of a strong excess of phenol has an inhibitory effect on the formation of both **3a** and **4a**, that seems to be more prominent in the case of the dicarbamate **3a**. A much stronger inhibitory effect can be observed with alcoholic solvents, i.e. methanol. As a matter of fact, no formation of carbamate **3a** or **4a** is observed when a methanol solution of **1a** (2.51 mmol), DPC (5.06 mmol) and $Ph_2P(O)OH$ (0.025 mmol) is heated at 343 K for 9 h. The GC-MS analysis of the reaction mixture shows the formation of both PhOH and methylphenylcarbonate, MeOC(O)OPh, obtained by transesterification of DPC by methanol.

Conversely, very interesting results are obtained using DPC itself as solvent. Figure 6 illustrates the kinetics of formation of **3a** and **4a** from MDA (1.35 mmol) and DPC (26.1 mmol), used as reagent and solvent, in the presence of $Ph_2P(O)OH$ (0.135 mmol), at 363 K. Under these conditions, the carbamation process is very selective (100 %), and the conversion of MDA into **3a** is practically quantitative within 4 hours.[17] The kinetic of formation of **3a** reveals a short induction time during which a fast increase of the concentration of the mono-carbamate **4a** can be observed. This feature ensures that by stopping the reaction after 30 minutes, the mono-carbamate **4a** can be synthesized with good yield (50 %) and selectivity (> 90 %).

Other organophosphorous acids, such as $(PhO)_2P(O)OH$ or a commercial equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ have also been tested as catalysts. Under experimental conditions analogous to those reported above, $(PhO)_2P(O)OH$ (Figure 7) seems to show a markedly lower catalytic activity than $Ph_2P(O)OH$, while the equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ shows a catalytic activity

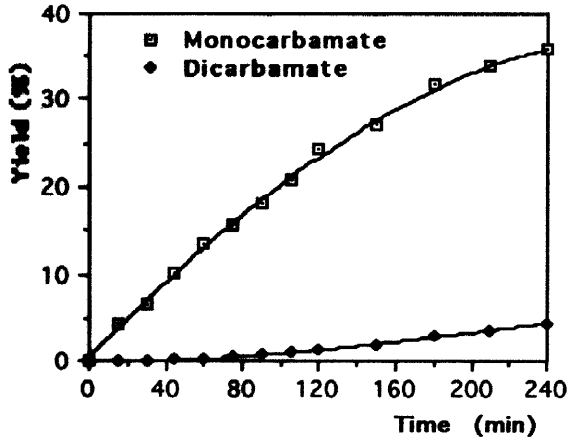


Fig. 7. Kinetics of formation of **4a** and **3a** from **1a** (0.246 g, 1.24 mmol) and DPC (5.665 g, 26.4 mmol) in the presence of $(PhO)_2P(O)OH$ (0.032 g, 0.128 mmol), at 363 K. Internal standard: biphenyl (0.094 g, 0.61 mmol).

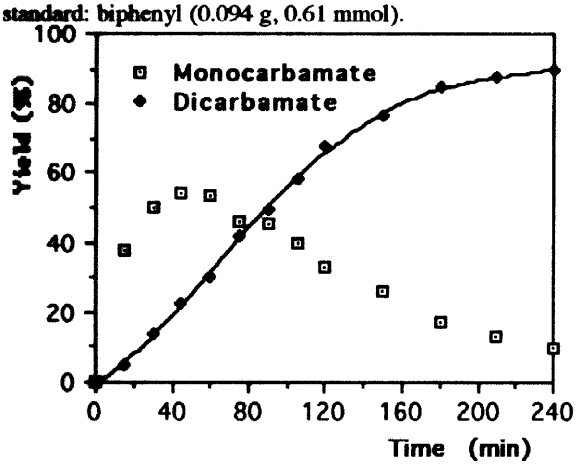


Fig. 8. Kinetics of formation of **4a** and **3a** from **1a** (0.275 g, 1.38 mmol) and DPC (5.501 g, 25.7 mmol) in the presence of a equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ (0.031 g, 0.170 mmol), at 363 K. Internal standard: biphenyl (0.133 g, 0.86 mmol).

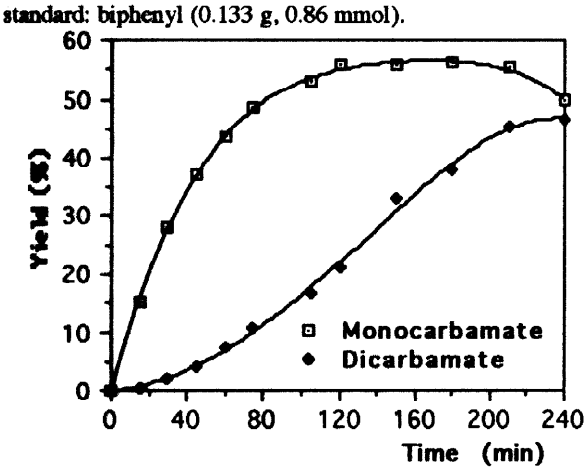


Fig. 9. Kinetics of formation of **4a** and **3a** from **1a** (0.252 g, 1.27 mmol) and DPC (5.686 g, 26.5 mmol) in the presence of a equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ (0.00300 g, 0.016 mmol), at 363 K. Internal standard: biphenyl (0.102 g, 0.66 mmol).

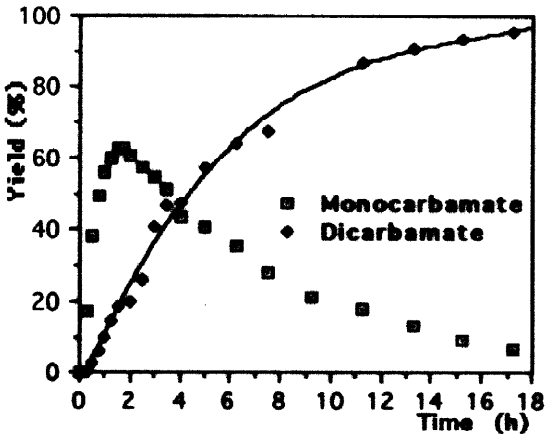


Fig. 10. Kinetics of formation of **4b** and **3b** from **1b** (0.221 g, 1.81 mmol) and DPC (5.851 g, 27.3 mmol) in the presence of $Ph_2P(O)OH$ (0.041 g, 0.19 mmol), at 363 K. Internal standard: naphtalene (0.130 g, 1.01 mmol).

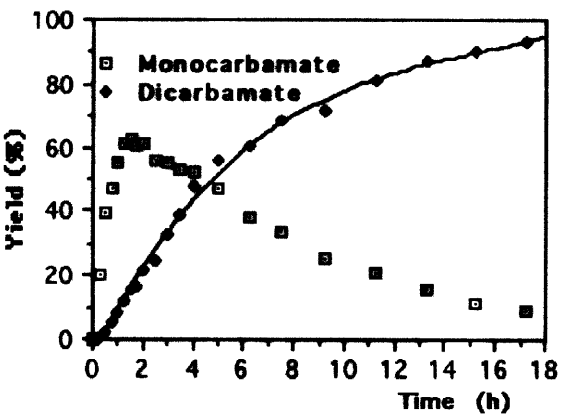
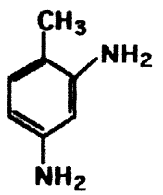


Fig. 11. Kinetics of formation of **4b** and **3b** from **1b** (0.186 g, 1.53 mmol) and DPC (5.686 g, 26.3 mmol) in the presence of an equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ (0.029 g, 0.16 mmol), at 363 K. Internal standard: naphtalene (0.106 g, 0.827 mmol).

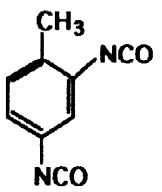
analogous (Figure 8) to that reported for diphenylphosphinic acid. The order of catalytic activity is similar to that described for aromatic mono-amines.[5] Very interestingly, the mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ shows a good catalytic activity even when the concentration in the reaction mixture is about 1 mol% with respect to MDA (Figure 9).

Reactivity of TDA towards DPC in the presence of "P" acids

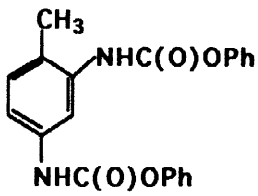
$Ph_2P(O)OH$ or the equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ have also been investigated as catalysts in the case of the carbamation of TDA with DPC. The acids were found to promote the formation of **3b** with a very interesting yield and selectivity.



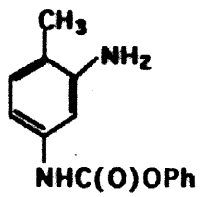
1b



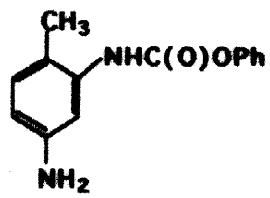
2b



3b



4b



4b'

The formation of **3b** from TDA and DPC requires the carbamation of two non-equivalent amino groups of the aromatic diamine and raises the question about which is functionalized first. In principle, two mono-carbamates, **4b** and **4b'**, can be obtained. In order to answer this question, we have synthesized pure samples of and **4b'**. We have demonstrated that the amino group in the *para* position is carbamated more rapidly than that in *ortho*. HPLC analysis has allowed us to conclude that **4b'** is formed in a very low yield and does not accumulate as it reacts very fast with DPC to give **3b**. The steric hindrance of the methyl group can induce the faster reactivity of the amino group in the para-position.

Figures 10 and 11 report the kinetics of formation of **3b** and **4b** from TDA and DPC used as reagent and solvent, at 363 K, in the presence of $Ph_2P(O)OH$ or an equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$, respectively.[18] Under these conditions the carbamation process is very selective (100 %), and no formation of ureas was observed.[19] Inspection of the kinetic curves shows that both catalysts have a similar activity. However, comparison of Figures 10 and 11 with Figures 4 and 8, respectively, clearly demonstrates that the conversion of TDA is slower than that of MDA.

Synthetic and mechanistic aspects. Fate of the catalyst

The kinetic study has been of great help for setting the most suitable experimental conditions for the synthesis of carbamates **3a-b** and **4a-b** with satisfactory yield and good selectivity. The full set of details is reported in the experimental section.

The mono- and dicarbamates of both TDA and MDA can be prepared in good yield by heating for a convenient time at 363 K a mixture of the amine and DPC, used as solvent and reagent, in the presence of $Ph_2P(O)OH$. All the products have been isolated and characterized by NMR spectroscopy and elemental analysis. The monocarbamates can be obtained in quite good yield if the reaction is stopped after 40-50 min. Only in the case of **4a** have we found some difficulties in isolating the mono-carbamate in an analytically pure form - this species, the unreacted amine **1a**, and **3a** have similar solubility in many solvents. It is worth noting that isolated carbamates are not contaminated by phosphorus derivatives.

Interestingly, the catalyst is still active at the end of the run as fresh amine added to the reaction mixture is converted into the dicarbamate with a similar rate as during the first run. In part, however, the catalyst converts

into $Ph_2P(O)OPh$, which has been detected by GC-MS in the reaction mixture. We have ascertained that this species can also act as a catalyst for the carbamation process, but its catalytic activity is lower than that exhibited by $Ph_2P(O)OH$ or the $(BuO)_2P(O)OH/(BuO)P(O)(OH)_2$ mixture.[20] A specific study allowed us to rule out that the phenyl ester is formed by reaction of $Ph_2P(O)OH$ with DPC.[21] The formation of $Ph_2P(O)OPh$ can be rationalized in terms of the mechanism previously proposed for the carbamation of aromatic mono-amines[5] and involving the intermediacy of a phosphocarbonate species $Ph_2P(O)OC(O)OPh$ formed according to reactions (2) and (3). $Ph_2P(O)OC(O)OPh$ can react with the aromatic diamine to give the carbamate (eq. 4) or also decarboxylate (eq. 5)[5] to give the ester $Ph_2P(O)OPh$.

$$Ph_2P(O)OH + H_2NArNH_2 \rightleftharpoons Ph_2P(O)O^- {}^+H_3NArNH_2 \quad (H_2NArNH_2 = MDA, TDA) \quad (2a)$$

$$Ph_2P(O)O^- {}^+H_3NArNH_2 + Ph_2P(O)OH \rightleftharpoons (H_3NArNH_3)(O_2PPh_2)_2 \quad (H_2NArNH_2 = MDA) \quad (2b)$$

$$Ph_2P(O)O^- {}^+H_3NArNH_2 + (PhO)_2C{=}O \longrightarrow Ph_2P(O)OC(O)OPh + PhOH + H_2NArNH_2 \quad (3a)$$

$$(H_3NArNH_3)(O_2PPh_2)_2 + (PhO)_2C{=}O \longrightarrow Ph_2P(O)OC(O)OPh + PhOH + Ph_2P(O)O^- {}^+H_3NArNH_2 \quad (3b)$$

$$Ph_2P(O)OC(O)OPh + H_2NArNH_2 \longrightarrow H_2NArNHC(O)OPh + Ph_2P(O)OH \quad (4)$$

$$Ph_2P(O)OC(O)OPh \longrightarrow Ph_2P(O)OPh + CO_2 \quad (5)$$

The inhibitory effect of PhOH or aliphatic alcohols (methanol, for instance) as solvent has been explained. In fact, these nucleophilic species can compete with the diamine for the phosphocarbonate, to give, respectively, DPC or methylphenylcarbonate (eq. 6). However, the stronger inhibitory effect of MeOH with respect to PhOH can be explained taking into account the higher nucleophilicity of aliphatic alcohols with respect to the aromatic.

$$Ph_2P(O)OC(O)OPh + ROH \longrightarrow PhOC(O)OR + Ph_2P(O)OH \quad (R = alkyl, aryl) \quad (6)$$

CONCLUSIONS

In this paper we report the first example of the synthesis of carbamate esters from diamines and carbonates promoted by non-metal catalysts. We have investigated in detail the aminolysis of DPC by MDA or TDA and shown that the synthesis of mono- and dicarbamates of both amines is promoted by organophosphorus Broensted acids such as $Ph_2P(O)OH$, $(PhO)_2P(O)OH$ or an equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$. Both $Ph_2P(O)OH$ and the equimolar mixture of $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ show a similar, quite good catalytic activity. Other Broensted acids, such as HCl, CF_3SO_3H, $CF_3C(O)OH$, $CH_3CH_2C(O)OH$, are less effective than the P-acids investigated here. The best temperature range is around 363 K. At temperatures higher than 363 K the selectivity of the carbamation process is reduced as the formation of ureas takes place. In all cases, the utilization of DPC as reagent and reaction solvent is recommended.

EXPERIMENTAL SECTION

All reactions and manipulations were carried out under a dinitrogen atmosphere with rigorous exclusion of both air and atmospheric moisture using vacuum line techniques. All solvents were dried as described in the literature[22] and stored under dinitrogen. Amines **1a-b** and DPC were a gift from EniChem Synthesis and were

used as received. $Ph_2P(O)Cl$, $Ph_2P(O)OH$ and $(PhO)_2P(O)OH$ were Aldrich products, $(BuO)_2P(O)OH/(BuO)P(O)(OH)_2$ (1:1 mol/mol) was from Strem Chemicals.

IR spectra were obtained with a Perkin Elmer 883 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 500 spectrometer. Proton and carbon chemical shifts are in ppm *vs* TMS and have been referenced to the solvent peak. GC-MS analyses were carried out with a HP 5890 gas-chromatograph linked to a HP 5970 selective mass detector (capillary column: 30 m SE-30, 0.25 μm film thickness). GC analyses were made with a DANI HR 3800 gas-chromatograph equipped with a SE-30 packed column. HPLC analyses were performed with a Perkin Elmer Series 4 LC connected with a LC 290 UV/Vis spectrophotometer detector.

Kinetic measurements

The reaction vessel was a 25 mL tube sealed with a two-way valve that allowed the solution to be withdrawn using a chromatography syringe out of contact with air. The reaction mixture containing the reactants (DPC and **1a** or **1b**), the acid catalyst (if used) and the internal standard was heated up to the working temperature (±1 K). At fixed times the reaction mixture was cooled to room temperature (293 K) and the liquid phase analyzed by HPLC. The following HPLC analysis conditions were used.

- Reactions involving DPC and **1a**: biphenyl (internal standard); Supelcosil LC8, 5 μm, 250 x 4.6 mm (column); acetonitrile/water 50:50 v/v (mobile phase); 2 mL/min (flow).
- Reactions involving DPC and **1b**: naphthalene (internal standard); Supelcosil LC-DP, 5 μm, 250 x 4.6 mm (column); acetonitrile/water 47.5:52.5 v/v (mobile phase); 2 mL/min (flow).

Reaction of MDA with DPC in the presence of $Ph_2P(O)OH$. *Synthesis and isolation of MDA di-carbamate* **3a**

A mixture of DPC (1.16925 g, 5.46 mmol), MDA (0.56760 g, 2.87 mmol) and $Ph_2P(O)OH$ (0.06265 g, 0.286 mmol) was stirred at 363 K for 7 h. The melted mixture was cooled to room temperature (293 K) and extracted with diethyl ether (1 x 10 mL and 1 x 5 mL). The white residue, poorly soluble in diethyl ether, was pure dicarbamate **3a**. Yield: 1.14030 g, 91 %. Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.99; H, 4.99; N, 6.36. M.p.: 442-445 K. IR (Nujol, KBr disks, cm^{-1}): 3337 (s, br, ν_{NH}), 3062 (w), 3040 (w), 1719 (s, ν_{CO}), 1610 (m), 1589 (m-s), 1526 (s), 1491 (s), 1410 (m-s), 1312 (m-s), 1231 (s), 1206 (s), 1180 (m), 1160 (m-w), 1107 (m-w), 1070 (m-w), 1028 (m), 1018 (m), 995 (w), 910 (m-w), 893 (m-w), 849 (m), 808 (m), 786 (m-s), 755 (m-s), 722 (m-s), 710 (w), 687 (m-s), 647 (m-s, br), 630 (m), 610 (m), 550 (m-w), 507 (m), 495 (m). ^1H NMR (THF-d_8, 500.138 MHz, 293 K): δ 3.87 (s, 2 H, CH_2), 7.10 (d, 4 H, ^3J = 8.41 Hz, MDA moiety aromatic protons), 7.14 (m, 2 H, $H_{para,OPh}$), 7.16 (m, 4 H, $H_{ortho,OPh}$), 7.32 (m, 4 H, $H_{meta,OPh}$), 7.44 (d, 4 H, ^3J = 8.41 Hz, MDA moiety aromatic protons), 9.16 (s, br, 2 H, NH). ^{13}C NMR (THF-d_8, 125.760 MHz, 293 K): δ 150.98 ($C_{ipso,OPh}$), 150.86 (slightly broad, *C*(O)O), 136.74 and 135.61 (C1 and C1', C4 and C4', MDA moiety), 128.61 and 128.46 ($C_{meta,OPh}$ and C2 and C2' of MDA moiety), 124.31 ($C_{para,OPh}$), 121.08 ($C_{ortho,OPh}$), 117.84 (br, C3 and C3', MDA moiety), 39.92 (CH_2). The above assignment was supported by a DEPT experiment.

Reaction of MDA with DPC in the presence of $Ph_2P(O)OH$.*Synthesis and isolation of MDA mono-carbamate* **4a**

A mixture of DPC (2.38185 g, 11.1 mmol), MDA (0.99020 g, 4.99 mmol) and $Ph_2P(O)OH$ (0.106 g, 0.486 mmol) was stirred at 363 K for 35 min. The melted mixture was cooled to room temperature (293 K) and extracted several times with hexane in order to remove phenol and DPC. The residue was washed with

diethylether until a solid residue was obtained that did not show any absorption due to C=O groups in the infrared spectrum. The etheral solution was concentrated *in vacuo*. By cooling to 253 K and filtering the precipitate, a solid was obtained in which the major component was **4a** as established by HPLC. Other fractions, containing **4a** contaminated by **1a** and **3a**, could be isolated from the mother solution by addition of hexane and cooling to 253 K. All the fractions containing **4a** were collected together and, by recrystallization from THF/hexane, 0.242 g (15 %) of **4a**, slightly impure mainly for **3a**, were isolated. Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.79. Found: C, 75.24; H, 5.86; N, 8.40. IR (Nujol, KBr disks, cm^{-1}): 3396 (m), 3324 (m), 3221 (m, br), 3170 (m-w, br), 3104 (m-w, br), 1710 (s, ν_{CO}), 1602 (m-s), 1590 (m), 1540 (s), 1511 (m-s), 1491 (m-s), 1412 (m-s), 1314 (m), 1303 (m), 1260 (m), 1228 (s), 1204 (s), 1160 (m), 1126 (w), 1110 (w), 1084 (w), 1068 (w), 1025 (m), 1013 (m-s), 994 (m), 907 (m), 853 (m), 812 (s), 794 (m-s), 755 (m-s), 722 (m-s), 707 (m-s), 690 (m-s), 560 (m), 510 (m), 500 (m-s). ^{1}H NMR (THF-d_8, 500.138 MHz, 293 K): δ 3.77 (s, 2 H, CH_2), 6.50 (d, 2 H, ^3J = 8.43 Hz, H2' or H3', MDA moiety), 6.86 (d, 2 H, ^3J = 8.43 Hz, H2' or H3', MDA moiety), 7.09 (d, 2 H, ^3J = 8.40 Hz, H2 or H3, MDA moiety), 7.16 (m, 3 H, $H_{ortho,OPh}$ and $H_{para,OPh}$), 7.33 (m, 2 H, $H_{meta,OPh}$), 7.43 (d, 2 H, ^3J = 8.40 Hz, H2 or H3, MDA moiety), 9.16 (s, br, 1 H, NH). The NH_2 protons give a very broad signal around 4 ppm. ^{13}C NMR (THF-d_8, 125.760 MHz, 293 K): δ 150.98 (broad) and 150.93 (*C*(O)O and $C_{ipso,OPh}$), 146.07 (C4'), 136.62 and 136.37 (C1 and C4, MDA moiety), 128.75, 128.72 and 128.46 ($C_{meta,OPh}$ and C2, C1' and C2' of MDA moiety), 124.30 ($C_{para,OPh}$), 121.09 ($C_{ortho,OPh}$), 117.68 (C3, MDA moiety), 113.76 (C3', MDA moiety), 39.74 (*C*H_2).

Isolation and characterization of urea **5**

The formation of urea **5** has been observed when a THF solution of **1a** and DPC was heated at temperatures higher than 373 K in the presence of Ph2P(O)OH. Urea **5** can be easily isolated by filtration as it is not soluble in THF. The yield depends on the temperature and reaction time. **5** has been characterized by elemental analysis, IR and NMR spectroscopy. M.p.: > 503 K. Anal. Calcd for $C_{41}H_{34}N_4O_5$: C, 74.31; H, 5.17; N, 8.45. Found: C, 74.26; H, 5.01; N, 8.24. IR (Nujol, KBr disks, cm^{-1}): 3335 and 3316 (s, br, ν_{NH}), 1718 (vs, carbamic ν_{CO}), 1631 (s, ureidic ν_{CO}), 1609 (m), 1589 (m-s), 1534 (s), 1510 (m), 1491 (m-s), 1410 (s), 1314 (m), 1302 (m), 1237 (s), 1218 (m-s), 1203 (s), 1182 (m), 1160 (m-w), 1108 (m-w), 1072 (m-w), 1027 (m), 1017 (m-w), 995 (w), 959 (w), 907 (w), 847 (m), 816 (m), 787 (m-s), 753 (m-s), 726 (m-s), 688 (m-s), 647 (m, br), 626 (m), 610 (m), 530 (m-w), 507 (m), 492 (m). ^{1}H NMR (DMSO-d_6, 500.138 MHz, 293 K): δ 3.34 (s, 4 H, CH_2), 7.09 (d, 4 H, ^3J = 8.54 Hz, MDA moiety aromatic protons), 7.15 (d, 4 H, ^3J = 8.55 Hz, MDA moiety aromatic protons), 7.19 (m, 4 H, $H_{ortho,OPh}$), 7.24 (m, 2 H, $H_{para,OPh}$), 7.33 (d, 4 H, ^3J = 8.55 Hz, MDA moiety aromatic protons), 7.41 (m, 8 H, $H_{meta,OPh}$ and MDA moiety aromatic protons), 9.54 (s, br, 2 H, NH), 10.15 (s, br, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125.760 MHz, 293 K): δ 152.57, 151.72, 150.65 and 150.56 (ureidic and carbamic *C*(O) and $C_{ipso,OPh}$), 137.69 and 137.64, 136.51 and 135.25, 134.90 and 134.78 (C1,C1', C4 and C4', MDA moiety), 129.52, 129.39, 129.02 and 128.90 ($C_{meta,OPh}$ and C2 and C2' of MDA moiety), 126.36 and 125.36 ($C_{para,OPh}$), 121.93 and 121.18 ($C_{ortho,OPh}$), 118.65 (br) and 118.35 (C3 and C3', MDA moiety). The resonance of methylene carbon atoms is obscured by the signals of the solvent at 39.50 ppm. The fact that the resonance of some carbon atoms (those of the phenoxy group, for instance) presents two close signals may be interpreted considering the presence of two different rotamers.[5]

The mother solution obtained after the isolation of the urea can be further worked up to isolate pure dicarbamate **3a**. In fact, after evaporation *in vacuo* of the solvent (THF), the residue was extracted several times

with diethyl ether in order to remove PhOH and unreacted DPC. The residual solid insoluble in ether, after drying *in vacuo*, analysed as pure **3a**.

Reaction of TDA with DPC in the presence of $Ph_2P(O)OH$. *Synthesis and isolation of TDA di-carbamate* **3b**

A mixture of DPC (11.63150 g, 54.30 mmol), TDA (0.54755 g, 4.49 mmol) and $Ph_2P(O)OH$ (0.09790 g, 0.449 mmol) was stirred at 363 K for 15 h. The reaction was monitored by HPLC: after about 10 h the starting amine had completely reacted converting into a mixture of the mono- and di-carbamate. The melted mixture was cooled to room temperature (293 K) and extracted with CCl_4 until complete solubilization of the DPC excess. The white residue, poorly soluble in CCl_4, was pure dicarbamate **3b**. Yield: 0.97140 g, 60 %. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.72. Found: C, 69.53; H, 4.93; N, 7.68. M.p.: 422-424 K. IR (Nujol, KBr disks, cm^{-1}): 3366 and 3308 (s, br, ν_{NH}), 3208 (w), 3146 (w), 3070 (w), 3040 (w), 1746 and 1696 (vs, ν_{CO}), 1624 (m), 1607 (m-s), 1589 (m), 1540 (vs), 1481 (s), 1443 (s), 1411 (m-s), 1326 (m-s), 1293 (m-w), 1247 (s), 1220 (s), 1200 (vs), 1188 (vs), 1158 (m-s), 1121 (m), 1066 (m-w), 1042 (m-w), 1025 (m-s), 1015 (m), 1002 (m-s), 950 (m-s), 904 (m-w), 876 (m-w), 864 (m), 834 (w), 814 (m), 790 (m), 755 (m), 728 (m), 721 (m), 706 (w), 688 (m), 645 (w), 623 (w), 606 (m), 500 (m), 495 (m). ^1H NMR (acetone-d_6, 500.138 MHz, 293 K): δ 2.33 (s, 3 H, CH_3), 7.21 (m, 7 H), 7.39 (m, 5 H), 7.91 (s, 1 H, H3), 8.44 (s, br, 1 H, NH), 9.18 (s, br, 1 H, NH). ^{13}C NMR (acetone-d_6, 125.760 MHz, 293 K): δ 153.13 and 153.06 (both slightly broad), 152.53 and 152.46 (both slightly broad), 152.39, 151.96 and 151.95 (*C*(O)O) and $C_{ipso,OPh}$), 137.98 and 137.89 (C2 or C4), 137.30 and 137.20 (C2 or C4), 131.49 (C6), 130.02 ($C_{meta,OPh}$), 126.04 and 126.00 ($C_{para,OPh}$), 122.71 (C1), 122.66 and 122.58 ($C_{ortho,OPh}$), 116.13 and 114.64 (both very broad, C3 and C5), 17.43 (CH_3). The above assignement was supported by a DEPT experiment. The doubling of the resonances of a few carbon atoms may suggest the presence of two different conformers.[5] More di-carbamate **3b** (overall yield: 84 %) was obtained by further processing the CCl_4 solution. This solution was evaporated *in vacuo* and the residue extracted with diethyl ether (2 x 5 mL). The ethereal phase was evaporated and the solid obtained washed with hexane (6 x 30 mL). The residue insoluble in hexane (0.390 g, 24 %) was mainly **3b** slightly impure for **4b** and $Ph_2P(O)OPh$. No attempt to optimize the purification of this fraction was further undertaken.

Reaction of TDA with DPC in the presence of $Ph_2P(O)OH$. *Synthesis and isolation of TDA mono-carbamate* **4b**

A mixture of DPC (5.263 g, 24.6 mmol), TDA (1.024 g, 8.38 mmol) and $Ph_2P(O)OH$ (0.192 g, 0.880 mmol) was stirred at 363 K for 50 min. The melted mixture was cooled to room temperature (293 K), extracted with hexane until complete solubilization of both phenol and DPC excess, and, then, with diethyl ether. The ether solution was evaporated *in vacuo*, and the residue dissolved in dichloromethane (30 mL). The CH_2Cl_2 solution was extracted with distilled water in order to eliminate the unreacted amine, dried over $MgSO_4$, filtered out and, then, concentrated *in vacuo*. By cooling to 253 K, pure carbamate **4b** precipitated that was isolated by filtration, washed with hexane and dried *in vacuo*. Yield: 0.853 g, 42 %. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.55. Found: C, 69.50; H, 5.88; N, 11.60. IR (Nujol, CsI disks, cm^{-1}): 3409 (m), 3318 (m-s), 3249 (m-s, br), 3204 (m), 3130 (m, br), 3070 (m), 3031 (m), 1738 and 1725 (vs, ν_{CO}), 1625 (m-s), 1611 (s), 1592 (m), 1554 (vs), 1511 (m), 1490 (m-s), 1452 (m-s), 1427 (m), 1338 (m-w), 1292 (m-s), 1249 (vs), 1220 (s), 1207 (vs), 1194 (s), 1161 (m), 1151 (m), 1091 (m), 1069 (m), 1021 (m-s), 989 (m-s), 976 (m-w), 962 (w), 923 (w), 910 (w), 877 (s), 855 (m-w), 834 (w), 810 (m-s), 785 (s), 762 (m), 740 (s), 721 (m-s), 706 (m-s), 686 (s), 619 (m-s), 561 (w), 511 (m), 492 (m-s), 456 (m), 434 (m), 405 (w), 344 (m-w), 330 (m-w). ^1H NMR (acetone-d_6,

500.138 MHz, 293 K): δ 2.08 (s, 3 H, CH_3), 4.43 (s, br, 2 H, NH_2), 6.76 (dd, 1 H, ^3J = 8.04 Hz, ^4J = 2.03 Hz, H5), 6.89 (d, 1 H, ^3J = 8.04 Hz, H6), 7.01 (d, unresolved, 1 H, H3), 7.19 (m, 3 H, $H_{para,OPh}$ and $H_{ortho,OPh}$), 7.39 (m, 2 H, $H_{meta,OPh}$), 8.80 (s, br, 1 H, NH). ^{13}C NMR (acetone-d_6, 125.760 MHz, 293 K): δ 152.09 (*C*(O)O), 151.79 ($C_{ipso,OPh}$), 147.06 (C2), 137.92 (C4), 130.67 (C6), 129.65 ($C_{meta,OPh}$), 125.56 ($C_{para,OPh}$), 122.32 ($C_{ortho,OPh}$), 117.19 (C1), 108.16 (C5), 105.31 (C3), 16.62 (CH_3).

Synthesis of $Ph_2P(O)OPh$

A THF (2 mL) solution of $Ph_2P(O)Cl$ (0.46 mL, 2.41 mmol) was added dropwise to a solution of PhONa (0.28415 g, 2.45 mmol) in THF (10 mL). The reaction mixture was stirred at 293 K for 3 h and, then, filtered out. The mother solution was concentrated *in vacuo*. By adding *n*-pentane (40 mL) and cooling to 253 K, a white solid separated, that was isolated by filtration, washed with more pentane (2 x10 mL), dried *in vacuo* and identified as pure $Ph_2P(O)OPh$. Yield: 0.630 g, 89 %. Anal. Calcd for $C_{18}H_{15}PO_2$: C, 73.46; H, 5.14. Found: C, 72.91; H, 5.01. IR (Nujol, KBr disks, cm^{-1}): 3090 (w), 3070 (w), 3050 (w), 1585 (m), 1483 (m), 1438 (s), 1315 (w), 1220 (s), 1195 (m-s), 1185 (m-s), 1165 (m), 1125 (m), 1110 (m), 1070 (m-w), 1023 (m-w), 995 (w), 920 (s), 900 (m), 763 (m-s), 755 (m-s), 745 (m-s), 738 (m-s), 732 (s), 698 (s), 692 (m-s), 683 (m), 610 (m-w), 582 (m-s), 535 (s), 513 (m-s), 493 (w), 455 (w), 435 (w). ^{1}H NMR (CD_2Cl_2, 500.138 MHz, 293 K): δ 7.10 (m, 1 H, $H_{para,OPh}$), 7.21 (m, 2 H, $H_{ortho,OPh}$), 7.26 (m, 2 H, $H_{meta,OPh}$), 7.49 (m, 4 H, H_{PPh}), 7.56 (m, 2 H, $H_{para,PPh}$), 7.89 (m, 4 H, H_{PPh}). ^{13}C NMR (CD_2Cl_2, 125.760 MHz, 293 K): δ 150.74 (d, J_{CP} = 7.62 Hz, $C_{ipso,OPh}$), 132.10 (d, J_{CP} = 2.86 Hz, $C_{para,PPh}$), 131.39 (d, J_{CP} = 10.25 Hz, $C_{ortho,PPh}$), 130.96 (d, J_{CP} = 138.34 Hz, $C_{ipso,PPh}$), 129.28 (s, $C_{meta,OPh}$), 128.29 (d, J_{CP} = 13.35 Hz, $C_{meta,PPh}$), 124.24 (s, $C_{para,OPh}$), 120.36 (d, J_{CP} = 4.76 Hz, $C_{ortho,OPh}$).

Acknowledgements.

This work was supported by the MURST through the "Piano Nazionale della Chimica" and, in part, by the 40% and 60 % Programmes. We thank ENICHEM Synthesis for a loan of DPC and DMC.

REFERENCES AND NOTES

1. (a) Barthelemy, J. *Lyon Pharm.* **1986**, *37(6)*, 297. (b) Tai-Teh Wu; Huang, J.; Arrington, N.D.; Dill, G.M. *J. Agric. Food Chem.* **1987**, *35*, 817. (c) Kato, T.; Suzuki, K.; Takahashi, J.; Kamoshita, K. *J. Pesticide Sci.* **1984**, *9*, 489. (d) Picardi, P. *La Chimica e l'Industria* **1986**, *68 (11)*, 108. (e) Rivetti, F.; Romano, U.; Sasselli, M. *U.S. Pat.* 4514339, 1985.
2. Babad, H.; Zeiler, A.G. *Chem. Rev.* **1973**, *73*, 75.
3. (a) Aresta, M.; Quaranta, E. *ChemTech*, **1997**, *27(3)*, 32. (b) Aresta, M.; Quaranta, E. *J. Org. Chem.* **1988**, *53*, 4153. (c) Aresta, M.; Quaranta, E. *Ital. Pat.* 1198206, 1988. (d) Aresta, M.; Quaranta, E. *J. Chem. Soc., Dalton Trans.* **1992**, 1893. (e) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515. (f) Aresta, M.; Quaranta, E. *Ital. Pat.* 1237208, 1993.
4. (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489. (b) Aresta, M.; Quaranta, E. *Ital. Pat.* 1237207, 1993.
5. Aresta, M.; Berloco, C.; Quaranta, E. *Tetrahedron* **1995**, *51*, 8073.

6. (a) Cahours, A. *Ann.* **1845**, *56*, 266. (b) Bortnick, N.; Luskin, L. S.; Hurwitz, M.D.; Rytina, A.W. *J. Am. Chem. Soc.* **1956**, *78*, 4358. (c) Hagemann, C. Kohlensaure derivate. In *Methoden der Organischen Chemie*; Houben-Weil, Eds.; G. Thieme Verlag: Stuttgart, 1983, 4th ed.; Band E4, p. 159.
7. Adams,P.; Baron F.A. *Chem. Rev.* **1965**, *65*, 567.
8. Massi Mauri, M.; Romano, U.; Rivetti, F. *Ing. Chim. Ital.* **1985**, *21*, 6 and references therein.
9. Kock, P.; Romano, U. *Ital. Pat. Appl.* 20264 A/82.
10. Romano, U.; Tesei, R. *US Pat.* 4045464, 1977.
11. (a) Frulla, F.F.; Stuber, A.F.; Whitman, J.P. *U.S. Pat.* 4550188, 1985; *Chem. Abstr.* **1986**, *104*, 224725u. (b) Giurgiolo, A.E. *U.S. Pat.* 4268684, 1981; *Chem. Abstr.* **1981**, *96*, 97407k. (c) Giurgiolo, A.E. *U.S. Pat.* 4268683, 1981; *Chem. Abstr.* **1981**, *95*, 168832h. (d) Romano, U.; Tesei, R. *Ger. Offen.* 2716540, 1977; *Chem. Abstr.* **1978**, *88*, 37459. (e) Onoda, T.; Tano, K.; Hara, Y. *Jap. Pat. Appl.* 04316, 1980. (f) Buysch, H.J.; Krimm, H.; Richter, W. *Eur. Pat. Appl.* 48371, 1982. (g) Romano, U.; Fornasari, G.; Sgambato, U. *Ital. Pat. Appl.* 22967 A/82.
12. (a) Anon., *Res. Discl.* **1987**, *275*, 162; *Chem. Abstr.* **1988**, *108*, 167429g. (b) Romano, U.; Fornasari, G.; Di Gioacchino, S. *Ger. Offen.* DE 3202690, 1982; *Chem. Abstr.* **1982**, *97*, 144607d. (c) Mukai, T.; Suenobu, K.; Masago, M. *Japan Kokai* 77 14745, 1977; *Chem. Abstr.* **1977**, *87*, 52961e.
13. Yamazaki, N.; Higashi, F. *Int. Prog. Urethanes* **1980**, *2*, 61.
14. (a) Knight W.B. Carboxyphosphate: Predicted Chemical Properties, Synthesis and Role as an Intermediate in Enzymic Reactions. In *Enzymatic and Model Carboxylation and Reduction Reactions for Carbon Dioxide Utilization*; Aresta, M.; Schloss, J.V. Eds.; Kluwer Academic Publishers: Dordrecht, 1990; NATO-ASI Series C, Vol. 314, p. 239. (b) Rubio, V. *Biochem. Soc. Trans.* **1993**, *21*, 198.
15. Aresta, M.; Bosetti, A.; Quaranta, E. *Ital. Pat. Appl.* 002202, 1996.
16. Aresta, M.; Dibenedetto, A.; Quaranta, E. forthcoming paper
17. A mixture of **1a** (0.585 mmol) and DPC (12.2 mmol), heated at 363 K for 4 h in the absence of any catalyst, produced only traces of **3a**, while **4a** was obtained with a yield of 10 %.
18. When **1b** (0.655 mmol) was heated in DPC (11.2 mmol) at 363 K for 10 h, in the absence of any catalyst, only traces of **3b** were obtained. **4b** yield was not higher than 20 % (by HPLC).
19. The formation of ureas was observed when a THF (7 mL) solution of TDA (4.09 mmol) and DPC (8.18 mmol) was reacted in the presence of $Ph_2P(O)OH$ (0.409 mmol) at 393 K for 72 hours.
20. Carbamates **3a** and **4a** were obtained in 10 and 47 % yield (HPLC), respectively, when MDA (0.526 mmol), DPC (11.0 mmol) and $Ph_2P(O)OPh$ (0.053 mmol) were reacted at 363 K for 4 h. Analogously, a mixture of TDA (0.776 mmol), DPC (12.0 mmol) and $Ph_2P(O)OPh$ (0.083 mmol) heated at 363 K for 10 h afforded **3b** and **4b** with yield of 20 and 80 % (HPLC), respectively.
21. No reaction was observed when a mixture of DPC (3.0 mmol) and $Ph_2P(O)OH$ (0.30 mmol) was heated at 363 K for 5h hours. Analogously, $Ph_2P(O)OPh$ was not found when a MeOH solution of the acid and DPC was stirred at 343 K for several hours. In this case, the GC-MS analysis of the reaction mixture revealed the formation of traces of PhOH and methylphenylcarbonate.
22. Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, England, 1986.