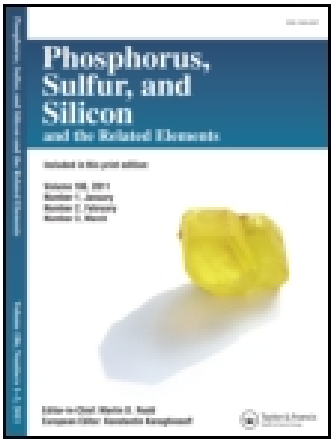

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A Study on the Phosphorylation of Indole, Imidazole, Carbazole, and Phenothiazine Derivatives

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A STUDY ON THE PHOSPHORYLATION OF INDOLE, IMIDAZOLE, CARBAZOLE, AND PHENOTHIAZINE DERIVATIVES

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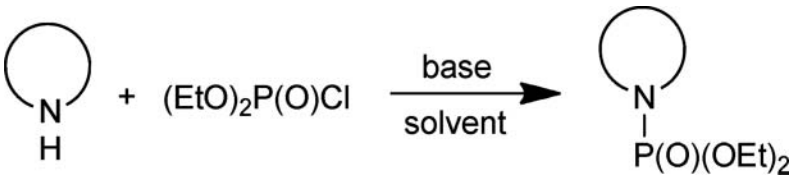
GRAPHICAL ABSTRACT



Abstract *N-Heterocycles including indolecarbaldehyde, substituted benzimidazoles, and methylimidazole could be efficiently phosphorylated by diethyl chlorophosphate at room temperature in different solvents using alkali carbonate or triethylamine as the base. However, the phosphorylation of* N*-heterocycles with a lower reactivity at the NH function, such as carbazole and phenothiazine, could not be conducted to complete conversion under the conditions applied.*

Keywords *N*-heterocycles; phosphorylation; indoles; imidazoles; carbazole; phenothiazine

INTRODUCTION

There are many substrates with bioactivity among phosphoric acid derivatives.[1–11] The diethylphosphoryl derivatives form a representative group as they may be valuable intermediates in synthetic organic chemistry,[12] or may be used as medicines or agrochemicals. The two derivatives **I** and **II** shown below serve as antitumor[13,14] and antimicrobal[15] drug, respectively.

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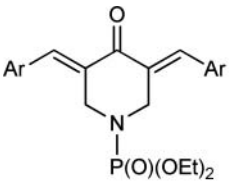
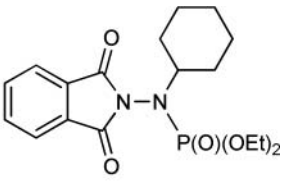


I



II

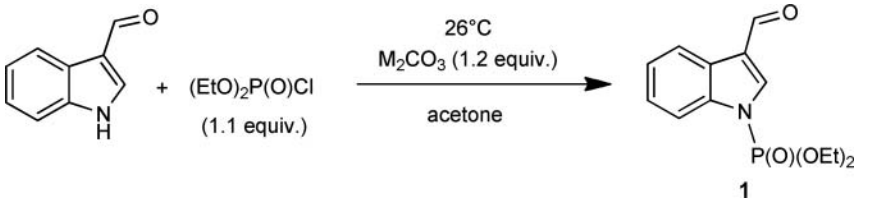
Ar = aryl, hetaryl

In our earlier study, we described the *N*-alkylation of a few *N*-heterocycles.[16] This paper gives an account on our results on the phosporylation of indole-, imidazole-, and benzimidazole derivatives, along with carbazole and phenothiazine. Obviously, a similar reactivity of the NH moiety of the *N*-heterocycles was expected in phosphorylations as compared to that in alkylations.

RESULTS AND DISCUSSION

The phosphorylation of a series of *N*-heterocycles was studied under different conditions involving the application of the phase transfer catalytic and the MW techniques. Our aim was to find the best set of conditions for the preparation of the phosphorylated species.

First, the reaction of indolecarbaldehyde with diethyl chlorophosphate was studied (Scheme 1, Table 1).



1

Scheme 1

Carrying out the reaction using 1.1 equiv. of $(EtO)_2P(O)Cl$ in the presence of 1.2 equiv. of K_2CO_3 in acetone at 26 °C, the phosphorylation was complete after a 1 day stirring (Table 1, Entry 1). The presence of tetrabutylammonium bromide (TBAB) was harmful (Table 1, Entry 2). Applying Cs_2CO_3 instead of K_2CO_3, the phosphorylation was complete already after 50 min stirring (Table 1, Entry 3). In the latter case, the isolated

Table 1 The phosphorylation of indolecarbaldehyde

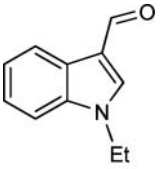
Base	Catalyst	Time	Conversion to **1** (%)[a]	Yield of **1** (%)	Entry
K_2CO_3	—	24 h	97	not determined	1
K_2CO_3	TBAB (10%)	24 h	55	not determined	2
Cs_2CO_3	—	50 min	100	93	3

[a]Determined by LC-MS.

yield of the phosphorylated indole derivative **1** was 93%. Compound **1** has been previously characterized only by melting point and ^{1}H NMR data.[17] We observed an 11–12 °C higher melting point and characterized the product also by ^{31}P and ^{13}C NMR spectroscopy. The different melting points may be the consequence of the different media (hexane–diisopropyl ether vs. ethyl acetate[17]) used for recrystallization.

Our method is simpler than that described in the literature applying potassium *tert*-butylate as the base and THF as solvent.[17]

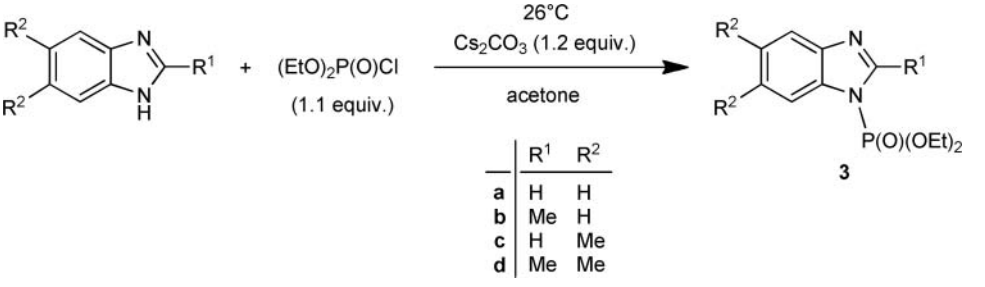
It is noteworthy that after refluxing the components in acetone for 5 h, 1-ethyl-indole-3-carbaldehyde **2** also appeared in the reaction mixture in a relative quantity of 10%.



2

Heterocycle **2** has been described in the literature.[18] This minor component was not isolated in pure form, however, its elemental composition was confirmed by HRMS ($(M+H)^+_{found} = 174.0916$, $C_{11}H_{12}NO$ requires 174.0919). The ethylating ability of diethyl chlorophosphate and analogous thio derivatives is well-known.[19,20]

Benzimidazole underwent quantitative phosphorylation with diethyl chlorophosphate in the presence of Cs_2CO_3 in acetone after stirring at 26 °C for 20 min. The diethoxyphosphoryl benzimidazole **3a** was isolated with a yield of 91%. According to a literature method, the benzimidazole is first converted to the sodium salt by reaction with sodium methylate, then the salt is phosphorylated to provide the product (**3a**) in a yield of 42%.[21] One can see that our method is simpler and more efficient. The phosphorylation was extended to methyl-, dimethyl-, and trimethylbenzimidazole, to afford products **3b–d** in 90–95% yield (Scheme 2). Benzimidazole derivatives **3b–d** are new. Compound **3a** was described,[21] but no NMR characterization was provided.



	R^1	R^2
a	H	H
b	Me	H
c	H	Me
d	Me	Me

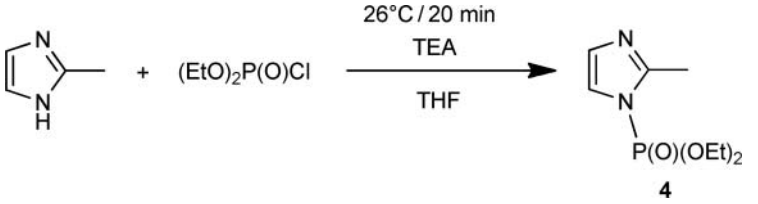
3

Scheme 2

The use of alkali carbonates as a base is a better alternative than applying trialkylamines. The use of the alkali carbonate/acetone system is "greener" than that of the trialkylamine/aromatics or THF mixture.

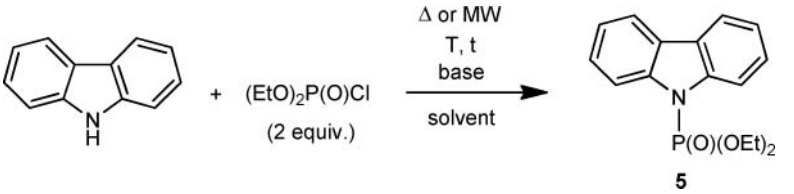
Imidazole could also be phosphorylated under similar conditions, but during the work-up procedure the phosphorylated imidazole decomposed. This decomposition is known

from the literature.[22–24] The unstable phosphorylated imidazole **3a** could only be isolated by Michalski et al. by distillation in high vacuum.[25] Methylimidazole could also be phosphorylated, but in this instance, product **4** was more stable and could be identified by spectral methods. The best method giving the phosphorylated imidazole **4** in a quantitative yield involved the phosphorylation in THF in the presence of triethylamine at 26 °C (Scheme 3). Product **4** is new.



Scheme 3

The next model to be studied was the phosphorylation of carbazole. Due to the decreased reactivity of the NH moiety of carbazole, this reaction was investigated in a more detailed way (Scheme 4, Table 2).



Scheme 4

The use of 2 equiv. of $(EtO)_2P(O)Cl$ and 2 equiv. of sodium hydride at 110 °C (24 h) in toluene resulted in a conversion of 26%, that could be increased to 53% by applying DMF as the solvent at the same temperature allowing a shorter reaction time (3.5 h) (Table 2, Entries 1 and 2). Conducting the reaction in the presence of 2 equiv. of Cs_2CO_3 in acetone at 26 °C or boiling acetonitrile the conversions were around 30% (Table 2, Entries 3 and 4). The presence of a phase transfer catalyst, TBAB, did not have a positive impact on the course of the reaction (Table 2, Entry 5). Under MW conditions in the presence of Cs_2CO_3

Table 2 Phosphorylation of carbazole under different conditions

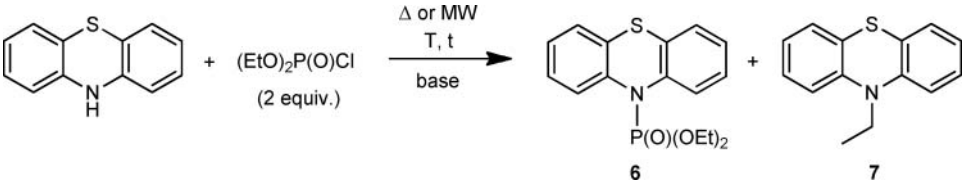
Base	Catalyst	Solvent	Mode of heating	T (°C)	t (h)	Conversion to **5** (%)[a]	Entry
NaH (2 equiv.)	—	PhMe	Δ	110	26	26	1
NaH (2 equiv.)	—	DMF	Δ	110	3.5	53	2
Cs_2CO_3 (2 equiv.)	—	Me_2CO	—	RT	24	32	3
Cs_2CO_3 (2 equiv.)	—	MeCN	Δ	82	24	29	4
Cs_2CO_3 (2 equiv.)	TBAB 10%	MeCN	Δ	82	24	28	5
Cs_2CO_3 (2 equiv.)	—	MeCN	MW	100	1	21	6
Cs_2CO_3 (2 equiv.)	TBAB 10%	MeCN	MW	100	1	5	7

[a]Determined by LC-MS.

in acetonitrile at 110 °C even lower conversions were observed, especially in the presence of TBAB (Table 2, Entries 6 and 7). It was impossible to obtain the phosphorylated carbazole **5** in pure form due to its high instability. Our attempts of separation by chromatography failed. Hence, product **5** was identified from the mixture of the best experiment (Table 2, Entry 2). It may not be without reason that the phosphorylated carbazole **5** was described without characterization.[26] Here, we provide for the first time NMR spectroscopic characterization for the phosphorylated carbazole **5**.

Preparation of the phosphorylated carbazole **5** was reported via the corresponding potassium salt in acetonitrile. A yield of 97% was claimed, but no characterization of the product was provided.[26] We could not reproduce the results reported by the authors.

The last model was the phosphorylation of the not too reactive phenothiazine (Scheme 5, Table 3).



Scheme 5

Carrying out the phosphorylation in the presence of 2 equiv. of the acylating agent and 2.5 equiv. of NaH in boiling toluene as the solvent, the conversion was only 20% after 24 h. The phosphorylated phenothiazine **6** (15%) and a by-product (5%) were present in the reaction mixture beside the szarting phenothiazine (80%) (Table 3, Entry 1). The change in the solvent was again helpful. Reaction in DMF at 110 °C for 24 h resulted in a conversion of 66%. In the reaction mixture, the proportion of the desired product was 52% along with 14% of the by-product mentioned above (Table 3, Entry 2). Using boiling acetonitrile, the conversion was 45% when Cs_2CO_3 was added as the base and the degree of transformation was 60% when K_2CO_3 was applied with 10% of TEBAC. In these cases no diethoxyphosphoryl-phenothiazine **6** was present in the reaction mixture. Instead, the above mentioned by-product predominated (Table 3, Entries 3 and 4). After isolation and spectroscopic identification, the by-product was found to be the ethylated phenothiazine **7**.

Table 3 Phosphorylation of phenothiazine under different conditions

Base	Catalyst	Solvent	Mode of heating	*T* (°C)	*t* (h)	Composition (%)[a]			Entry
						Phenothiazine	**6**	**7**	
NaH	—	PhMe	Δ	110	24	80	15	5	1
NaH	—	DMF	Δ	110	24	34	52	14	2
Cs_2CO_3	—	MeCN	Δ	82	24	55	—	45	3
K_2CO_3	TEBAC 10%	MeCN	Δ	82	24	40	—	60	4
NaOH	—	PhMe	Δ	110	24	80	—	20	5
Cs_2CO_3	—	MeCN	MW	100	1	69	—	31	6
Cs_2CO_3	—	no solvent	MW	100	1	53	—	47	7
K_2CO_3	—	no solvent	MW	100	1	20	—	80	8

[a]Determined by LC-MS.

The use of NaOH as base resulted again in the formation of the by-product **7** (Table 3, Entry 5). A similar outcome was experienced when the phosphorylation was attempted under MW conditions (Table 3, Entries 6–8). The phosphorylated phenothiazine **6** decomposed on our attempts to separate it from the other components. For this reason product **6** was identified from the best experiment (Table 3, Entry 2). No data can be found on the preparation and characterization of diethoxyphosphoryl-phenothiazine **6** in the literature. Here, we provide for the first time at least a partial characterization of the phosphorylated phenothiazine **6**.

It is noteworthy that the *N*-heterocycles studied revealed the same trend regarding the reactivity of the NH unit in both phosphorylation and alkylation.[16]

In summary, indolecarbaldehyde, four benzimidazole derivatives, and methylimidazole were efficiently phosphorylated at room temperature in different solvents using alkali carbonate or triethylamine as the base. Six phosphorylated *N*-heterocycles have been synthesized and characterized; four of them are new and the remaining two were characterized by NMR spectroscopy for the first time. However, the phosphorylation of *N*-heterocycles with a lower reactivity at the NH function, such as carbazole and phenothiazine, could not be accomplished quantitatively under the conditions applied. Due to the high degree of instability, the phosphorylated carbazole and phenothiazine were characterized from the reaction mixtures, thus, providing NMR spectroscopic data for these unstable species, for the first time.

EXPERIMENTAL

Melting points were determined on a Kofler Boëtius micro-apparatus and were not corrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with a Varian Unity Inova 500 MHz spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded with a Bruker Avance III spectrometer (400, 100, and 162 MHz, respectively) or a Varian Mercury Plus 200 spectrometer (200, 50, and 80 MHz, respectively). $CDCl_3$ was used as solvent. Tetramethylsilane (TMS) and 85% H_3PO_4 were used as internal (^{1}H, ^{13}C) and external (^{31}P) standards, respectively. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively.

The MW-assisted reactions were carried out in a CEM Discover microwave reactor equipped with a pressure controller using ca. 30 W irradiation power.

LC-MS experiments were carried out on an Agilent 1200 liquid chromatography system connected with a 6120 MSD (Agilent Technologies). Analysis was performed at 40 °C on an Kinetex C_{18} column (5 cm × 2.1 mm, 2.6 μm) (Phenomenex) with a mobile phase flow rate of 0.9 mL/min. Composition of eluent A was 0.1% (v/v) trifluoroacetic acid in water (pH 1.9), eluent B was a 95:5 (v/v) mixture of acetonitrile, and water with 0.1% (v/v) trifluoroacetic acid. A fast linear gradient of 0–100% B was applied at a range of 0–4 min, then 100% B kept for 3 min. The injection volume was set at 1 μL and the sample concentration was uniformly 1.0 mg/mL (DMSO). The chromatographic profile was registered at 240 nm. The MSD operating parameters were as follows: positive ionization mode, scan spectra from *m/z* 100 to 800, drying gas temperature 350 °C, nitrogen flow rate 12 L/min, nebulizer pressure 60 psi, quadrupole temperature 100 °C, capillary voltage 3000 V, fragmentor voltage 50 V.

Carefully dried solvents and reactants were used in the experiments. The alkali carbonates were calcinated at 280 °C before use.

O,O-Diethyl (3-Formyl-1*H*-indol-1-yl)phosphonate (1)[17]

To a stirred slurry of 1*H*-indole-3-carbaldehyde (0.26 g, 1.8 mmol) and 0.70 g cesium carbonate (2.16 mmol) in 10 mL of acetone was added 0.29 mL of diethyl chlorophosphate (0.34 g, 1.98 mmol) in one portion. The solution was stirred at 26 °C until the starting material disappeared (50 min). The reaction mixture was filtered, evaporated in vacuo, and the residue was dissolved in dichloromethane. The solution was extracted with 10 mL of water and the water phase was washed with dichloromethane (10 mL). The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo, and the residual yellow oil was recrystallized from hexane–diisopopyl ether. Yield: 0.47 g (93%); mp 68–69 °C [lit.[17] 57 °C (ethyl acetate)]. ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = -4.6$; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta =$ 185.4 (d, $J = 1.0$ Hz, CHO), 140.3 (d, $J = 7.3$ Hz, C=), 137.8 (C=), 126.8 (CH=), 125.5 (CH=), 124.3 (C=), 122.4 (CH=), 113.6 (CH=), 64.7 (d, $J = 5.4$ Hz, CH_2), 15.8 (d, $J = 6.8$ Hz, CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 10.10$ (s, 1H, CHO), 8.32 (d, $J = 7.3$ Hz, 1H, arom-H), 8.14 (d, $J = 3.1$ Hz, 1H, arom-H), 7.73 (t, $J = 9.0$ Hz, 1H, arom-H), 7.40–7.38 (m, 2H, arom-H), 4.31–4.25 (m, 2H, CH_2), 4.13–4.08 (m, 2H, CH_2), 1.32 (t, $J =$ 7.1 Hz, 6H, CH_3) [lit.[17] ^{1}H NMR ($CDCl_3$): $\delta = 9.95$ (s, CHO), 7.0–8.2 (m, indolyl-H), 3.7–4.4 (m, CH_2), 1.23 (t, $J = 7$ Hz, CH_3)]; LC-MS: *m/z* 282 $(M+H)^+$; $(M+H)^+_{found} =$ 282.0899, $C_{13}H_{17}NO_4P$ requires 282.0895.

O,O-Diethyl (1*H*-Benzo[*d*]imidazol-1-yl)phosphonate (3a)[21]

To a stirred slurry of benzo[*d*]imidazole (0.21 g, 1.80 mmol) and 0.70 g of cesium carbonate (2.16 mmol) in 10 mL of acetone was added 0.29 mL of diethyl chlorophosphate (0.34 g, 1.98 mmol) in one portion. The solution was stirred at 26 °C until the starting material disappeared (40 min). The reaction mixture was filtered, evaporated in vacuo, and the residue was dissolved in dichloromethane. The solution was extracted with 10 mL of water and the water phase was washed with dichloromethane (10 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. Yield: 0.41 g (91%), colorless oil. ^{31}P NMR ($CDCl_3$, 80 MHz): $\delta = -6.1$; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 144.9$ (d, $J = 12.6$ Hz, CH=), 144.4 (d, $J = 7.2$ Hz, C=), 133.0 (C=), 124.7 (CH=), 123.9 (CH=), 120.6 (CH=), 112.8 (CH=), 64.7 (d, $J = 5.0$ Hz, CH_2), 15.8 (d, $J = 6.9$ Hz, CH_3); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 8.27$ (s, 1H, CH=N), 7.85–7.82 (m, 1H, arom-H), 7.73–7.68 (m, 1H, arom-H), 7.40–7.35 (m, 2H, arom-H), 4.35–4.05 (m, 4H, CH_2), 1.32 (t, $J = 7.0$ Hz, 6H, CH_3); LC-MS: *m/z* 255 (M+H); $(M+H)^+_{found} = 255.0900$, $C_{11}H_{16}N_2O_3P$ requires 255.0899.

The other benzimidazole derivatives were prepared analogously, except using 1.3 equivalent of Cs_2CO_3 and $(EtO_2P(O)Cl$.

O,O-Diethyl (2-Methyl-1*H*-benzo[*d*]imidazol-1-yl)phosphonate (3b)

Yield: 0.43 g (90%); colorless oil. ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -5.4$; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 154.2$ (d, $J = 6.6$ Hz, CH=), 143.4 (C=), 135.6 (d, $J = 7.2$ Hz, C=), 125.5 (CH=), 123.7 (d, $J = 7.3$ Hz, CH=), 119.1 (CH=), 113.6 (CH=), 65.2 (d, $J = 6.4$ Hz, CH_2), 64.4 (d, $J = 5.1$ Hz, CH_2), 16.7 (CH_3), 15.9 (d, $J = 6.7$ Hz, CH_3); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.81–7.80$ (m, 1H, arom-H), 7.69–7.67 (m, 1H, arom-H), 7.30–7.27 (m, 2H, arom-H), 4.28–4.24 (m, 2H, CH_2), 4.14–4.10 (m, 2H, CH_2), 2.79 (s, 3H,

CH_3), 1.34 (t, $J = 7.0$ Hz, 6H, CH_3); LC-MS: *m/z* 269 (M+H); $(M+H)^+_{found} = 269.1056$, $C_{12}H_{18}N_2O_3P$ requires 269.1055.

O,O-Diethyl (5,6-Dimethyl-1*H*-benzo[*d*]imidazol-1-yl)phosphonate (3c)

Yield: 0.48 g (95%); colorless oil. ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -5.8$; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 143.6$ (d, $J = 7.3$ Hz, CH=), 143.3 (d, $J = 13.2$ Hz, C=), 134.0 (C=), 133.0 (CH=), 131.5 (d, $J = 5.3$ Hz, CH=), 120.6 (CH=), 113.0 (CH=), 65.2 (d, $J = 5.8$ Hz, CH_2), 64.5 (d, $J = 5.1$ Hz, CH_2), 20.5 (CH_3), 20.1 (CH_3), 15.9 (d, $J = 6.8$ Hz, CH_3); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.14$ (s, 1H, CH=N), 7.58 (s, 1H, arom-H), 7.46 (s, 1H, arom-H), 4.30–4.23 (m, 2H, CH_2), 4.13–4.08 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.38 (t, $J = 7.1$ Hz, 3H, CH_3), 1.33 (t, $J = 7.0$ Hz, 3H, CH_3); LC-MS: *m/z* 283 (M+H); $(M+H)^+_{found} = 283.1211$, $C_{13}H_{20}N_2O_3P$ requires 283.1212.

O,O-Diethyl (2,5,6-Trimethyl-1*H*-benzo[*d*]imidazol-1-yl)phosphonate (3d)

Yield: 0.51 g (95%); colorless oil. ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -5.1$; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 141.8$ (d, $J = 13.7$ Hz, C=), 134.1 (C=), 132.8 (CH=), 132.4 (CH=), 123.2 (C=), 119.3 (C=), 113.9 (C=), 65.2 (d, $J = 5.9$ Hz, CH_2) 64.2 (d, $J = 5.1$ Hz, CH_2), 20.4 (CH_3), 20.0 (CH_3), 16.6 (CH_3), 16.0 (d, $J = 6.6$ Hz, CH_3); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.59$ (s, 1H, arom-H), 7.42 (s, 1H, arom-H), 4.29–4.22 (m, 2H, CH_2), 4.12–4.08 (m, 2H, CH_2), 2.74 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 1.38 (t, $J = 7.0$ Hz, 3H, CH_3), 1.33 (t, $J = 7.0$ Hz, 3H, CH_3); LC-MS: *m/z* 297 (M+H); $(M+H)^+_{found} = 297.1372$, $C_{14}H_{22}N_2O_3P$ requires 297.1368.

O,O-Diethyl (2-Methyl-1*H*-imidazol-1-yl)phosphonate (4)

2-Methyl-1*H*-imidazole (0.15 g, 1.8 mmol) and 0.25 mL of triethyamine (0.18 g, 1.8 mmol) were dissolved in 10 mL of anhydrous THF and 0.26 mL (1.8 mmol, 0.31 g) of diethyl chlorophosphate was added. After 20 min of stirring at 26 °C the precipitate was removed by filtration and the filtrate was concentrated. Yield: 0.39 g (99%); ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -5.2$; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 148.2$ (d, $J = 5.0$ Hz, C=), 128.6 (d, $J = 14.0$ Hz, C=), 121.1 (d, $J = 8.1$ Hz, C=), 65.1 (d, $J = 6.1$ Hz, CH_2), 64.5 (d, $J = 5.2$ Hz, CH_2), 15.9 (d, $J = 7.0$ Hz, CH_3), 15.1 (CH_3); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.29$ (s, 1H, arom-H), 6.99 (s, 1H, arom-H), 4.29–4.18 (m, 2H, CH_2), 4.14–4.00 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 1.37 (t, $J = 7.0$ Hz, 6H, CH_3); LC-MS: *m/z* 219 (M+H); $(M+H)^+_{found} = 219.0895$, $C_8H_{16}N_2O_3P$ requires 219.0899.

O,O-Diethyl (9*H*-Carbazole-9-yl)phosphonate (5) (Table 2, Entry 2)

To 0.24 g (1.4 mmol) of carbazole in 10 mL of dimethylformamide was added 0.14 g (3.5 mmol) of sodium hydride under N_2 atmosphere. The mixture was heated to 110 °C, and 0.42 mL (2.9 mmol) of diethyl chlorophosphate in 2 mL of dimethylformamide was added dropwise. The content of the flask was stirred at this temperature for 3.5 h. After filtration, the filtrate was concentrated to afford a mixture containing 53% of the carbazolephosphate **5** and 47% of the starting carbazole. ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -2.8$; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 128.1$ (C=), 122.2 (CH=), 120.1 (CH=),

119.8 (CH=), 116.2 (C=), 110.6 (CH=), 63.6 (d, $J = 4.5$ Hz, CH_2), 15.9 (d, $J = 7.1$ Hz, CH_3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8,08–8.05 (m, 2H, arom-H), 8.03–8.00 (m, 2H, arom-H), 7.42–7.39 (m, 2H, arom-H), 7.23–7.19 (m, 2H, arom-H), 4.07–3.95 (m, 4H, CH_2), 1.26 (t, $J = 7.1$ Hz, 6H, CH_3); LC-MS: *m*/*z* 304 (M+H); $(M+H)^+_{found} = 304.1110$, $C_{16}H_{19}NO_3P$ requires 304.1103.

O,O-Diethyl (10*H*-Phenothiazine-10-yl)phosphonate (6) (Table 3, Entry 2)

To 0.36 g (1.8 mmol) of phenothiazine in 10 mL of dimethylformamide was added 0.18 g (4.5 mmol) of sodium hydride under N_2 atmosphere. The mixture was heated to 110 °C and 0.52 mL (3.6 mmol) of diethyl chlorophosphate was added dropwise. The mixture was stirred at this temperature for 1 day. Filtration and concentration of the filtrate yielded a mixture containing 52% of product **6,** 34% of the starting material, and 14% of by-product **7**. ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = 0.1$; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 141.7 (C=), 127.2 (CH=), 126.7 (CH=), 122.2 (CH=), 118.1 (C=), 116.8 (CH=), 62.0 (d, $J = 5.9$ Hz, CH_2), 16.1 (d, $J = 6.8$ Hz, CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.97–6.94 (m, 4H, arom-H), 6.81–6.78 (m, 2H, arom-H), 6.56–6.54 (m, 2H, arom-H), 4.08–3.98 (m, 4H, CH_2), 1.31 (t, $J = 7.1$ Hz, 6H, CH_3); LC-MS: *m*/*z* 336 (M+H).

10-Ethyl-10*H*-phenothiazine (7)[24] (Table 3, Entry 8)

To a mixture of 0.36 g (1.8 mmol) of phenothiazine and 0.50 g (3.6 mmol) of potassium carbonate 0.52 mL (3.6 mmol) of diethyl chlorophosphate was added and the reaction mixture was irradiated in the MW reactor at 100 °C for 1 h with stirring. The crude product was extracted with 2 mL of acetonitrile, the acetonitrile solution was filtered, and the solvent from the filtrate was evaporated to afford 0.33 g (80%) of ethylphenothiazine **7**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.13–7.10 (m, 4H), 6.88–6.83 (m, 4H), 3.92–3.87 (m, 2H), 1.39 (t, $J = 7.0$ Hz, 3H) [lit.[27]: ^{1}H NMR ($CDCl_3$): δ = 7.16–7.11 (m, 4H, arom-H), 6.88–6.85 (m, 4H, arom-H), 3.92 (m, 2H, CH_2), 1.42 (t, 3H, CH_3)]; LC-MS: *m*/*z* 228 (M+H).

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