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A GENERAL AND CONVENIENT SYNTHESIS OF *N*-[(1-DIPHENYLOXOPHOSPHINYL)ALKYL]CARBOXAMIDES AND SULFAMIDE

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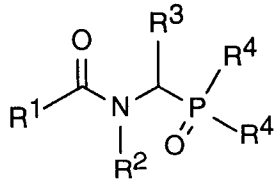
ABSTRACT: A wide range of title compounds were prepared in good yields by amidoalkylation of ethyl diphenylphosphinite with readily available *N*-[α-(benzotriazol-1-yl)alkyl]amides. A more convenient direct one-pot amidoalkylation of ethyl diphenylphosphinite with an amide, an aldehyde and benzotriazole is described.

N-[(1-Diaryloxophosphinyl)alkyl]amides (**1**, R^4 = aryl) and *N*-[(1-dialkyloxophosphinyl)alkyl]amides (**1**, R^4 = alkyl) are of interest due to their biological activities.[1] Several synthetic routes to this class of compounds have



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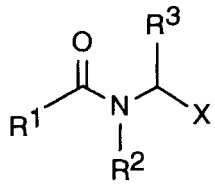
been reported, all of which involve treatment of a trivalent phosphorus species with an electrophilic amidoalkylation reagent of the type **2**. However, previous methods using reagents **2** all possess limitations:



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X = OCH_3, OAc, $NHCOR^1$, Cl

(a) X = OCH_3. *N*-[(1-Diphenyloxophosphinyl)alkyl]carbamates (**1**, R^1 = alkoxy) have been prepared by the reaction of chlorodiphenylphosphine with α-methoxylated carbamates.[2] However, anodic oxidation was required for the preparation of these amidoalkylation reagents. Furthermore, the literature only describes the preparation of cyclic carbamates by this method.

(b) X = OAc. A number of phosphorylated β-lactams have been obtained by the replacement of an α-acetoxy group by a phosphoryl group.[3,4] However, this approach is only applicable to β-lactams, since the acetoxylated lactams are prepared from vinyl esters and chlorosulfonyl isocyanate.[5]

(c) X = $NHCOR^1$. Although the amidoalkylation of chlorodiphenylphosphine with *N,N'*-alkylidene or *N,N'*-arylidene bisamides has provided easy access to *N*-[(1-diphenyloxophosphinyl)alkyl]amides, attempts to extend the scope of this reaction to secondary amides ($R^2 \neq H$) were unsuccessful.[6] In addition, the yields from primary amides were usually around 40%.

(d) X = Cl. Recently, a variety of *N*-[(1-diphenyloxophosphinyl)-methyl]amides have been synthesized by chloromethylation of the appropriate

secondary amides and subsequent treatment with ethyl diphenylphosphinite.[7] However, this methodology was restricted to compounds with methylene linkages between N and P (R^3 = H).

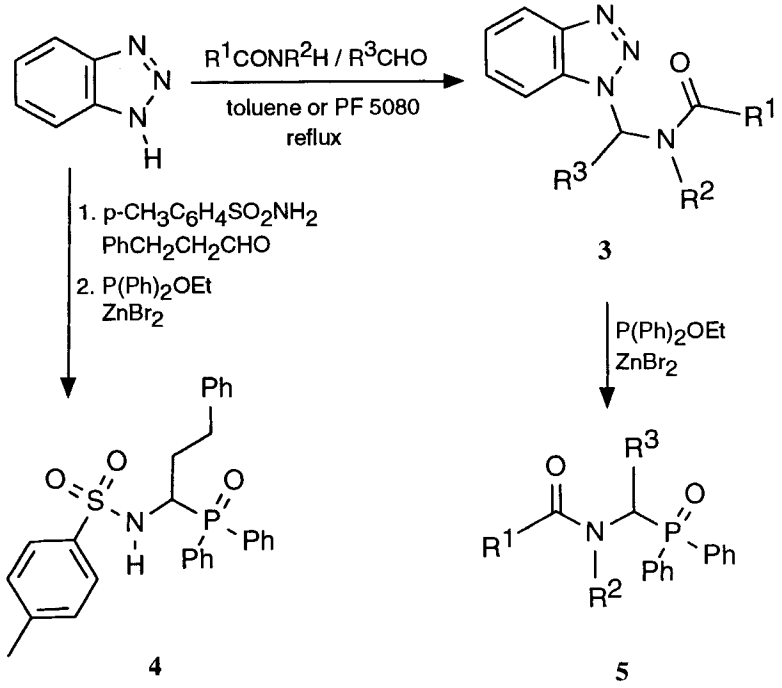
As a continuation of our exploitation of benzotriazole as a synthetic auxiliary, we have demonstrated the versatility of readily available *N*-[α-(benzotriazol-1-yl)alkyl]amides **3** in organic synthesis.[8] We recently reported that amides **3** are convenient precursors of the corresponding acyliminium cations as the benzotriazolate anion is a good leaving group. Derivatives **3** have been successfully used in the amidoalkylation of alkylmalonates and other C-H acids,[9] active aromatic compounds,[10] and in the preparation of tri- and tetra- substituted 4*H*-1,3-oxazines.[11] We have also found that amides **3** react readily with a variety of thiols and sodium sulfide to give *N*-acylhemithioaminals,[12] and with primary and secondary alcohols to afford *N*-(α-alkoxyalkyl)amides.[13]

The present paper reports a general route to *N*-[(1-diphenyloxophosphinyl)alkyl]sulfamide **4** and carboxamides **5** using *N*-[α-(benzotriazol-1-yl)alkyl]amides **3**. A more convenient one-pot procedure employing an amide, an aldehyde and benzotriazole is also described.

Results and Discussion

The amidoalkylation reagents, *N*-[α-(benzotriazol-1-yl)alkyl]amides **3**, were easily prepared by the previously reported method from benzotriazole, an aldehyde, and an amide in toluene[9,14] or performance fluid 5080[15] using Amberlyst® 15 ion exchange resin as a catalyst.[16] Thus, **3a** [R^1R^2 = -$(CH_2)_3$-, R^3 = H], **3b** [R^1R^2 = -$(CH_2)_3$-, R^3 = *i*-propyl], **3c** (R^1 = 2-methylphenyl, R^2 =

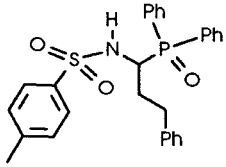
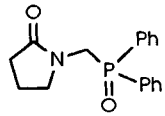
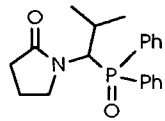
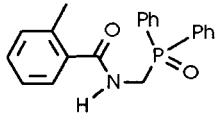
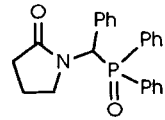
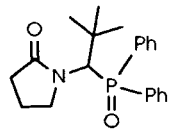
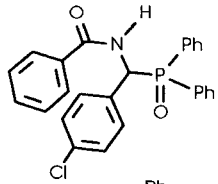
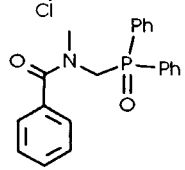
Scheme 1



H, R^3 = H) and **3d** [R^1R^2 = -$(CH_2)_3$-, R^3 = Ph] were synthesized in good yields (Scheme 1).

It was previously reported that benzotriazole adducts are readily assisted by Lewis acids to form the benzotriazole anion and the corresponding carbocations which then react with nucleophiles.[10] Accordingly, compounds **5a-d** were prepared by refluxing the corresponding adducts **3a-d** with ethyl diphenylphosphinite in toluene in the presence of zinc bromide in good yields (Scheme 1 and Table 1). The benzotriazole byproduct formed during the reaction dissolved in dilute alkali and was easily separated by extraction. The crude products were readily purified by recrystallization.

Table 1. Preparation of *N*-[(Diphenyloxophosphinyl)alkyl]amides **4, 5a - g**

Cpd	Structure	Method	Yield (%)	Solvent
4		one pot	52	toluene
5a		two steps	46[a]	toluene
5b		two steps	64[a]	toluene
5c		two steps	78[a]	toluene
5d		two steps one pot	79[a] 76	toluene PF5080 toluene
5e		one pot	61	PF5080 toluene
5f		one pot	55	PF5080 toluene
5g		one pot	58	PF5080 toluene

[a] Yield of the second step

In practice, it is not necessary to isolate the benzotriazole derivatives **3**. Accordingly, *N*-[(1-diphenyloxophosphinyl)alkyl]sulfamide **4** and *N*-[(1-diphenyloxophosphinyl)alkyl]carboxamides **5** were synthesized in a more convenient one-pot procedure directly from benzotriazole, an amide, an aldehyde and ethyl diphenylphosphinite. Thus, the mixture of benzotriazole, amide and aldehyde was first refluxed in toluene and / or performance fluid for 6 hours. Zinc bromide and ethyl diphenylphosphinite were added subsequently. Upon further refluxing overnight, the expected products **4** and **5d-g** were obtained in good yields (Table 1).

Compounds **4** and **5a-g** were characterized by ^{1}H NMR spectra and elemental analyses as illustrated in Table 2. All compounds except **5a** and **5g** are novel.

In summary, an alternative approach to *N*-[(1-diphenyloxophosphinyl)-alkyl]amides has been developed. The wide generality of this methodology and the simplicity of the work-up procedure offer considerable advantages over previous reported literature procedures.

Experimental Section

Melting points were determined with a Kofler hot stage apparatus without correction. ^{1}H NMR spectra were recorded at 300 MHz with tetramethylsilane as the internal standard. Microanalyses were caried out using a Carlo Erba 1106 elemental analyser.

N-[α-(Benzotriazol-1-yl)alkyl]amides **3a-d** were prepared as previously reported.[9,14,16]

Table 2. Physical Data for *N*-[(Diphenyloxophosphinyl)alkyl]amides **4**, **5a** - **g**

Cpd	Molecular Formula	C H N found (required)	mp (°C) (lit)	^{1}H NMR data (δ, ppm; J, Hz)	
				CH-P or CH_2-P	Other signals
4	$C_{28}H_{28}NO_3PS$	68.33 5.74 2.82 (68.69 5.76 2.86)	253-254	4.57-4.62(m, 1H)	1.50-1.69(m, 2H), 2.20-2.60(overlapped s, 3H & m, 2H), 6.64 -6.67(m, 2H), 7.11-7.19(m, 3H), 7.32(d, 2H, J=8.3), 7.49-7.74 (m, 8H), 7.88-8.00(m, 4H), 8.40(d, 1H, J=9.6)
5a	$C_{17}H_{18}NO_2P$	68.27 6.06 4.59 (68.22 6.06 4.68)	145-146 (115-116)[7]	4.25(d, 2H, J=5.7)	1.86-1.91(m, 2H), 2.18-2.24(m, 2H), 3.64-3.68(m, 2H), 7.47 -7.59(m, 6H), 7.81-7.88(m, 4H)
5b	$C_{20}H_{24}NO_2P$	69.98 7.14 4.00 (70.37 7.09 4.10)	106-107	4.87(dd, 1H, J_1= 10.1, J_2=3.3)	0.85(d, 3H, J=6.6), 0.96(d, 3H, J=6.6), 1.15-1.30(m, 1H), 1.69 -1.81(m, 2H), 2.16-2.27(m, 1H), 2.49-2.58(m, 1H), 3.38-3.44 (m, 2H), 7.39-7.60(m, 6H), 7.82-7.89(m, 2H), 7.97-8.04(m, 2H)
5c	$C_{21}H_{20}NO_2P$	71.59 5.73 4.01 (72.20 5.77 4.01)	213-214	4.44(t, 2H, J=6.1)	2.15(s, 3H), 7.07-7.30(m, 4H), 7.42-7.70(m, 6H), 7.72-7.80 (m, 5H)
5d	$C_{23}H_{22}NO_2P$	73.28 5.91 3.65 (73.59 5.91 3.73)	228-229	6.21(d, 1H, J=6.6)	1.68-1.83(m, 2H), 2.01-2.06(m, 1H), 2.12-2.21(m, 1H), 3.45-3.49(m, 1H), 4.01-4.08(m, 1H), 7.28-7.42(m, 6H), 7.50-7.74 (m, 7H), 7.95-8.02(m, 2H)
5e	$C_{21}H_{26}NO_2P$	70.75 7.37 3.89 (70.97 7.37 3.94)	170-171	5.07(d, 1H, J=7.5)	0.75-0.95(m, 1H), 1.09(s, 9H), 1.60-1.90(m, 2H), 2.15-2.30 (m, 1H), 3.50-3.80(m, 2H), 7.40-7.60(m, 6H), 7.82-8.00(m, 2H), 8.00-8.15(m, 2H)
5f	$C_{26}H_{21}NO_2PCl$	70.29 4.83 3.01 (70.04 4.75 3.14)	257-258	6.51(dd, 1H, J_1= 9.6, J_2=7.2)	7.25(d, 2H, J=8.3), 7.34(t, 2H, J=7.6), 7.40-7.54(m, 9H), 7.61 (d, 2H, J=7.7), 7.74-7.81(m, 2H), 7.96-8.03(m, 2H), 9.50(d, 1H, J=9.8)
5g	$C_{21}H_{20}NO_2P$	72.49 5.69 3.88 (72.20 5.77 4.01)	190-191 (126-127)[7]	4.62(d, 2H, J=5.4)	3.15(s, 3H), 6.98(d, 2H, J=6.8), 7.32-7.40(m, 3H), 7.50-7.63 (m, 6H), 7.90-8.00(m, 4H)

Preparation of *N*-[(1-Diphenyloxophosphinyl)alkyl]amides **5a-d** from **3a-d**. General Procedure.

To a mixture of the corresponding *N*-[α-(benzotriazol-1-yl)alkyl]amide (5 mmol) and toluene (20 ml) was added zinc bromide (5 mmol) and the mixture refluxed for 0.5 h under argon. Ethyl diphenylphosphinite (5 mmol) was then added and the mixture refluxed for a further 24 h. The precipitate was filtered off and washed with toluene. The filtrate was washed with aqueous hydrochloric acid (2 N, 10 ml), aqueous sodium hydroxide (2 N, 10 ml) and water (10 ml). The solution was dried over $MgSO_4$, and the solvent evaporated. The crude product was recrystallized from ethyl acetate and hexanes to give the analytically pure product.

One-Pot Preparation of *N*-[(1-Diphenyloxophosphinyl)alkyl]amides **4** and **5d-g**. General Procedure.

To a mixture of aldehyde (5 mmol), amide (5 mmol), benzotriazole (0.60 g, 5 mmol) and Amberlyst® 15 ion exchange resin (0.01 g) was added performance fluid 5080 (30 ml) (in the case of **4** toluene was used instead of performance fluid). The mixture was refluxed for 6 h under argon using a Dean-Stark aparatus to remove the water formed. Zinc bromide (1.13 g, 5 mmol), ethyl diphenylphosphinite (1.15 g, 5 mmol) and toluene (20 ml) were then added and the mixture was further refluxed under argon for 24 h. The precipitate was filtered off and washed with toluene. The filtrate was washed with aqueous hydrochloric acid (2 N, 10 ml), aqueous sodium hydroxide (2 N, 10 ml) and water (10 ml). After drying over $MgSO_4$, the solvent was evaporated. The crude product was recrystallized from ethyl acetate and hexanes to give the analytically pure product.

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