1-(Triphenylphosphoroylideneaminomethyl)benzotriazole (BETMIP) a Novel $^{+}CH_2N$ = Synthetic Equivalent: Its Application to the Synthesis of Carbodiimides, Imines, Isothiocyanates, Aziridines, and Secondary Amines

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One-carbon homologation has been achieved in novel syntheses of the title compounds by one-pot reaction of 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (**1**) with Grignard reagents followed by *in situ* transformations of the phosphazene functionality with isocyanates, aldehydes, carbon disulfide, ethylene oxide, and alkyl halides, respectively.

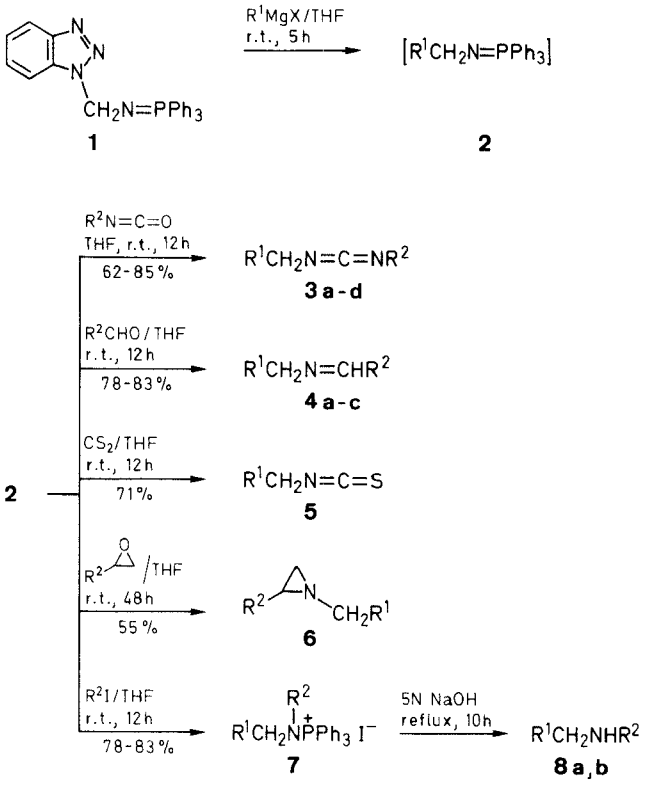
Since the first reported synthesis of iminophosphoranes by the reaction of a tertiary phosphine with organic azides,[1] numerous articles have appeared on the reactions and synthetic applications of these N=P compounds.[3,4,5,6] Iminophosphoranes possess similar structural and chemical characteristics to those of phosphorus ylides, and consequently were shown to react with carbonyl compounds to form Schiff bases and phosphine oxide.[1] Iminophosphoranes also react with carbon dioxide and carbon disulfide to yield isocyanate and isothiocyanate, respectively.[2] Further successful transformations of *N*-substituted iminophosphoranes by reaction with acids,[7] water,[8] alkyl halides,[9] oxiranes,[10] nitrosyl chloride,[11] acetylenedicarboxylates,[12] and ozone,[13] demonstrate their versatility in organic synthesis. Recently, *N*-substituted triphenylphosphoranes have been used in Diels–Alder reactions[14] and in syntheses of heterocyclic compounds.[15]

The *N*-alkyl or aryl substituted iminophosphoranes utilized were almost invariably synthesized by the Staudinger method[16] (the reaction of triphenylphosphine with the corresponding azide). There are a few preparations of iminophosphoranes from amines,[17] amides,[18] and isoxazole,[19] which have some synthetic value. We now describe the first examples in which N=C compounds are prepared from *N*-substituted iminophosphoranes derived from Grignard reactions.

Recently, we reported[20] the preparation of 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (**1**) and the application of this reagent for the synthesis of primary amines. Seven primary amines were prepared (from: four alkyl and three aryl Grignard reagents) in yields of 65–93%. Although the reaction was performed in one-pot, we supposed that the reaction with the Grignard reagent and the hydrolysis step took place consecutively, i.e. there was no reaction between the Grignard reagent and the N=P double bond. Thus after the Grignard step, the N=P intermediate should undergo other phosphazene reactions *in situ*, to yield various other types of *N*-compounds.

We now describe such applications of 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (**1**) for the preparation of carbodiimides **3**, Schiff bases **4**, isothiocyanates **5**, aziridines **6**, and unsymmetrical secondary amines **8**.

In each case the formation of the new functionality is accompanied by a one-carbon homologation of the original hydrocarbon moiety (R^1) of the Grignard reagent.

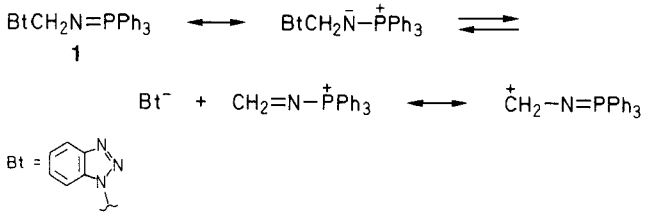


	R^1	R^2		R^1	R^2
3a	Me	*t*-Bu	**5**	Ph	–
3b	Me	Ph	**6**	Me	Ph
3c	Ph	*t*-Bu	**8a**	Ph	Et
3d	Ph	1-naphthyl	**8b**	Ph	Me
4a	Ph	Ph			
4b	Me	Ph			
4c	Ph	*i*-Pr			

Scheme A

Displacement of the benzotriazole moiety in phosphazene **1** by the Grignard reagent can be clearly monitored by the precipitation of the magnesium salt of benzotriazole, which is complete at room temperature, or even at 0 °C, in minutes. This easy displacement of benzotriazole is rationalized by the electron-donation of the nitrogen atom of the N=P group, which leads to an enhanced electrophilicity of the methylene group in compound **1** and to ion pair formation (Scheme **B**).

The benzotriazole magnesium salt, formed as a by-product, can conveniently be removed by filtration, and this is especially advantageous in the preparation of water-sensitive carbodiimides, Schiff bases and isothiocyanates. However, even if it is not removed, this



Scheme **B**

salt does not appear to affect the phosphazene reactions under the conditions employed. For example, when two molar equivalents of phenyl isocyanate were added to the reaction mixture from methylmagnesium iodide and compound **1**, a 1:1 (NMR) mixture of phenyl isocyanate and *N*-ethyl-*N'*-phenylcarbodiimide was isolated; no reaction between the isocyanate and the benzotriazole salt could be detected. Thus one-pot methods could be used for most of the transformations shown in Scheme **A**.

The reaction mixture of the Grignard reagent and the iminophosphorane **1** was treated with either (i) an isocyanate, or (ii) an aldehyde, or (iii) carbon disulfide, or (iv) styrene oxide, or (v) an alkyl halide. The reactions were usually complete at 20 °C, except in the case of aziridine **6**, where 48 hours reflux was employed. After removal of the benzotriazole magnesium salt by filtration, the products were separated from the side product triphenylphosphine oxide by distillation or by column chromatography. In the preparation of secondary amines, the phosphonium salt **7** is isolated before hydrolysis providing a convenient workup procedure (see experimental).

In summary, our new method for the preparation of *N*-substituted iminophosphoranes from 1-(triphenylphosphoroylideneaminomethyl)benzotriazole **(1)** has several advantages and offers versatile applications in organic synthesis. The reagent **1**, a crystalline solid, can be conveniently prepared from benzotriazole in four steps on a large scale and in high overall yield. It is stable at room temperature for at least several months. Reactions with easily accessible (often commercially available) Grignard reagents form a range of *N*-substituted iminophosphoranes, which are conveniently transformed without isolation, and in high yields, into diverse nitrogen compounds as exemplified by carbodiimides **3**, Schiff bases **4**, isothiocyanate **5**, aziridine **6** and secondary amines **8**. The reactions are clean; NMR spectra of the isolated crude products show no side products except triphenylphosphine oxide. Finally, our method provides the first examples of one-carbon homologation of *N*-substituted iminophosphoranes.

Table. Carbodiimides **3**, Schiff Bases **4**, Isothiocyanate **5**, Aziridine **6** and Secondary Amines **8** Prepared.

Product	Yield[a] (%)	bp (°C)/Torr[b]	Molecular Formula or Lit. bp (°C)/Torr or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)[9]	^{13}C-NMR ($CDCl_3$/TMS) δ
3a	61	80–82/105	137–139/60[21]	1.15 (t, 3H, CH_3), 1.29 (s, 9H, *t*-Bu), 3.25 (q, 2H, CH_2CH_3)	16.4, 30.9, 41.2 (CH_2), 54.5, 139.9
3b	62	95–97/2.0	43/005[22]	1.28 (t, 3H, CH_3), 3.36 (q, 2H, CH_2CH_3), 7.01–7.20 (m, $5H_{arom}$)	16.8, 41.6 (CH_2), 123.3, 124.5, 129.2, 136.1, 140.6
3c	65	95–97/0.8	123–125/23[21]	1.12 (s, 9H, $C(CH_3)_3$), 4.30 (s, 2H, CH_2), 7.20–7.45 (m, $5H_{arom}$)	30.9, 50.6 (CH_2), 55.0, 127.3, 127.8, 128.3, 138.6, 140.5
3d	85[c]	oil	$C_{18}H_{14}N_2$[d] (258.12)	4.50 (s, 2H, CH_2), 7.05–8.20 (m, $12H_{arom}$)	50.1 (CH_2), 119.7, 123.2, 124.5, 125.5, 125.7, 126.1, 126.9, 127.1, 127.5, 128.3, 128.5, 134.0, 136.2, 137.6, 140.6
4a	83[c]	oil	205/20[23a]	4.65 (s, 2H, CH_2), 7.10–7.78 (m, 10_{arom}), 8.14 (s, 1H, =CH)	67.4 (CH_2), 126.8, 127.8, 128.2, 128.3, 128.4, 130.5, 136.1, 139.3, 161.6
4b	78	54–55/0.7	207/144[23b]	1.28 (t, 3H, CH_3), 3.60 (s, 2H, CH_2), 7.33–7.72 (m, $5H_{arom}$), 8.22 (s, 1H, =CH)	16.1, 55.6 (CH_2), 127.7, 128.3, 130.2, 136.1, 160.1
4c	68	82–84/1.2		1.1 (d, 6H, $CH(CH_3)_2$), 2.5 (m, 1H, $CH(CH_3)_2$), 4.52 (s, 2H, CH_2), 7.20–7.40 (m, $5H_{arom}$), 7.6 (m, 1H, =CH)	19.1, 33.8, 64.4 (CH_2), 127.5, 128.2, 131.8, 139.5, 170.8
5	71	98–100/3.5	140–141/17[23c]	4.63 (s, 2H, CH_2), 7.20–7.40 (m, $5H_{arom}$)	48.5 (CH_2), 126.6, 128.2, 128.8, 134.0, 141.1
6	55	55–57/0.6	68–72/2.5[10c]	1.17 (t, 3H, CH_3), 1.63 (d, 1H, J = 6.5), 1.88 (d, 1H, J = 3), 2.29 (q, 1H, J = 3), 4.63 (q, 2H, CH_2), 7.15–7.30 (m, $5H_{arom}$)	14.4, 37.4 (CH_2), 41.1, 55.8, 126.1, 126.7, 128.1, 140.3
8a	65[e,f]	167.5–168.5	169[23c]	1.30 (t, 3H, CH_2CH_3), 2.83–3.02 (m, 2H, CH_2CH_3), 4.11 (t, 2H, CH_2), 7.39–7.66 (m, $5H_{arom}$), 9.38 (br s, 2H)	11.0, 41.0, 50.0 (CH_2), 128.9, 129.2, 130.0, 130.2
8b[h]	55[g]	40–42/0.7	184–185/749[23d]	1.32 (s, 1H, NH), 2.42 (s, 3H, CH_3), 3.71 (m, 2H, CH_2), 7.20–7.35 (m, $5H_{arom}$)	35.8, 55.9 (CH_2), 126.7, 127.9, 128.1, 140.0

[a] Based on distilled product.
[b] Not corrected.
[c] After column chromatography.
[d] Satisfactory HRMS obtained: calc.: 258.1157; found: 258.1157.
[e] Yield of hydrochloride.
[f] Overall yields; the intermediate phosphonium salts were isolated in 78% **(1a)** and 83% **(1b)**.
[g] Vicinal coupling constants are J = 1 Hz.
[h] In DMSO-d_6.

Benzaldehyde, propionaldehyde, and phenyl isocyanate, were purchased from Eastman Kodak Co. *tert*-Butyl isocyanate and 1-naphthyl isocyanate, from Aldrich, were purified by distillation before use. Carbon disulfide, MeI, and EtI were purchased from Fischer Scientific Co., and styrene oxide from Aldrich and were used without purification. Methylmagnesium iodide (3 M, in THF) and phenylmagnesium bromide (2 M, in THF) were purchased from Aldrich. THF was distilled under nitrogen from sodium/benzophenone ketyl immediately before use.

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian VXR-300 (300 Hz or 75 Hz, FT mode) spectrometer as solutions in $CDCl_3$ or DMSO-d_6. As internal standards TMS ($\delta = 0.0$) was used for ^{1}H-NMR spectra and the solvent signal ($CDCl_3$, $\delta = 77.0$; or DMSO-d_6, $\delta = 39.5$) for ^{13}C-NMR spectra. HRMS were recorded on a AEI MS-30 mass spectrometer.

1-(Triphenylphosphoroylideneaminomethyl)benzotriazole (1):
To a stirred solution of 1-azidomethylbenzotriazole[25] (11.8 g, 68 mmol) in Et_2O (100 mL) was added dropwise PPh_3 (18.0 g, 68.6 mmol) in Et_2O (50 mL). After stirring for 3 h at r.t., the precipitate is collected to give the product yield: 26 g (95%) as a colorless solid; mp 99–101 °C.

$C_{25}H_{21}N_4P$	calc.	C 73.52	H 5.18	N 13.72
(408.5)	found	73.30	5.16	13.60

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 6.11$ (d, 2H, J = 30 Hz, CH_2), 7.24–7.92 (m, 19 H_{arom}).

^{13}C-NMR ($CDCl_3$): $\delta = 62.40$, 62.45 (CH_2), 116.6, 119.3, 123.2, 126.2, 132.7, 146.2 (Bt), 128.4, 128.5, 129.1, 130.4, 131.6, 131.7, 132.4, 132.5 (Ph).

Carbodiimides 3a–d, Schiff Bases 4a–c, Isothiocyanate 5, and Aziridine 6; General Procedure:
To a solution of **1** (5.0 g, 12.2 mmol) in dry THF (50 mL), a commercial Grignard reagent (solution in THF, 13 mmol) is added at r.t. over 5 min. Precipitation of a white solid occurs almost instantaneously. The suspension is stirred at r.t. for 5 h, then the appropriate reagent [(i) isocyanates for carbodiimides **3** (12.2 mmol), (ii) aldehydes for Schiff bases **4**, (12.2 mmol), (iii) CS_2 for isothiocyanide **5** (40 mmol), or (iv) styrene oxide for aziridine **6** (12.2 mmol)] is added, and the stirring is continued overnight (for compounds **3**, **4** and **5**), or the reaction mixture refluxed for 48 h (for aziridine **6**). Then the mixture is diluted with anhydrous Et_2O (50 mL), the precipitate is filtered and washed with anhyrous Et_2O. The combined filtrate is dried ($MgSO_4$). Evaporation of the solvent gives a mixture of Ph_3PO and the desired product, which is isolated by vacuum distillation **(3a–c, 4b,c)** or column chromatography **(3d, 4a)** (see Table 1).

Secondary Amines 8a and 8b:
To a solution of **1** (10 g, 25 mmol) in dry THF (150 mL) commercial phenylmagnesium bromide (2 M in THF, 12.5 mL, 25 mmol) is added at r.t. The suspension is stirred for 5 h, then a solution of (i) EtI (12.7 g, 8.3 mmol) for **8a**, or (ii) MeI (11.3 g, 8.1 mmol) for **8b**, in dry THF (35 mL) is added. The reaction mixture is stirred overnight, and filtered. The solid is washed with sat. aq NH_4Cl and then with Et_2O, and dried to give phosphonium salt **7a** (10.1 g, 78%) or **7b** (9.0 g, 73%), respectively. The phosphonium salt is heated under reflux in aq NaOH (5 M, 250 mL) for 10 h. The product is extracted with Et_2O (3 × 40 mL) and the combined ethereal solution is washed with water (2 × 20 mL), dried ($MgSO_4$) and evaporated. Secondary amine **8a** is isolated as the hydrochloride salt by treating the residue with sat. ethereal HCl solution (50 mL), filtering the resulting precipitate and washing it with acetone yield: 2.7 g (83%). Secondary amine **8b** is isolated by vacuum distillation (40–42 °C/0.6 Torr), yield: 1.6 g (76%).

We thank Dr. P.A. Harris for help with this manuscript.

Received: 11 September 1989; revised: 12 February 1990

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