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The Preparation and Reactions of Protected Glyphosate Imidate, Thioimidate, and Thiono Esters from N-[Diphenoxyphosphinylmethyl]glycinonitrile: Comparative Reactivities of Activated Carboxylate versus Phosphonate Esters

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ABSTRACT:

The highly efficient syntheses of novel protected glyphosate imidate, thioimidate, and thiono ester derivatives are described starting from N-[diphenoxyphosphinylmethyl]glycinonitrile ***3b****. The scope, utility and limitations in using each of these activated carboxylate functionalities for further transformations to new "masked" heterocyclic derivatives are defined. While the solution stability of the imidate and thioimidate series limited the synthetic application of these species, the corresponding thiono ester derivatives were valuable synthetic intermediates, providing a short, efficient route to the first glyphosate derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole ring systems in place of the carboxylate group. These thiono esters thus undergo selective nucleophilic addition at this activated carboxylate center, while retaining the reactive diphenyl phosphonate moiety.*

INTRODUCTION

The commercial success of glyphosate (N-phosphonomethylglycine)[1, 2] **1** as an extremely effective and environmentally friendly herbicide has stimulated the search for other pro-herbicide forms of this material that might exhibit enhanced uptake and penetration properties. Previous attempts to prepare various glyphosate derivatives directly were hampered by its demonstrated low solubility in most common organic solvents [3]. While simple carboxylic ester, [4, 5] amide [6] and hydrazide [7] derivatives have been identified, only a few examples [8, 9] have been reported which incorporate heterocycles as potentially "masked" carboxylate functionalities.

Recently, the reaction between an appropriately substituted hexahydro-1,3,5-triazine **2** and diaryl phosphites has made available a number of versatile glyphosate intermediates **3** which retain their herbicidal properties but have enhanced organic solubility. [10, 11] This reaction is particularly useful for the nearly quantitative synthesis of N-[diphenoxy-phosphinyl]methylglycinonitrile **3b** from commercially available diphenyl phosphite and **2b**. Like similarly activated carboxylate esters, these aromatic phosphodiesters undergo a smooth, stepwise hydrolysis [12] to glyphosate under very mild conditions via the zwitterionic monoaryl esters **4** (Scheme 1). ^{31}P NMR studies of this hydrolysis reaction demonstrate that water addition to **3a** & **3b** occurs preferentially and selectively at phosphorus first [13].

*To whom correspondence should be addressed.
Dedicated to Professor Herbert C. Brown on the Occasion of his 80th Birthday.

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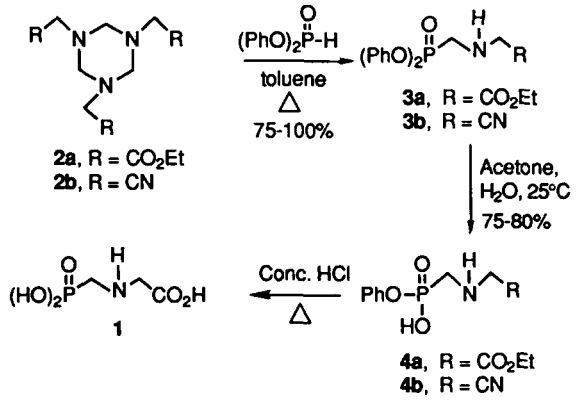


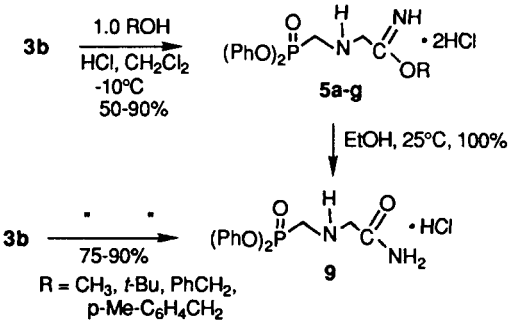
SCHEME 1

The ready availability of **3b** prompted us to explore its utility as a synthetic intermediate for various novel activated carboxylate derivatives of glyphosate. Our desire to introduce subsequently new heterocyclic "masked" carboxylate functionalities **8** imposes another demanding synthetic condition. This strategy requires that we identify isolable activated carboxylate groups which could be conveniently prepared in high yield from **3b** and further modified by preferential reaction at the carboxylate position under conditions that would retain the reactive diphenylphosphonate moiety. This system thus presents a challenging contrast between selective nucleophilic reactions at activated carboxylate versus phosphonate centers in the same molecule. Here we report the efficient and nearly quantitative conversion of **3b** to the corresponding imidate **5**, thioimidate **6**, and thiono ester **7** intermediates, and further define the scope, utility, and limitations of these groups for further conversion to their heterocyclic derivatives **8**, either as the partially or fully unsaturated systems, (Scheme 2).

RESULTS AND DISCUSSION

*Synthesis of Imidate Esters from **3b***

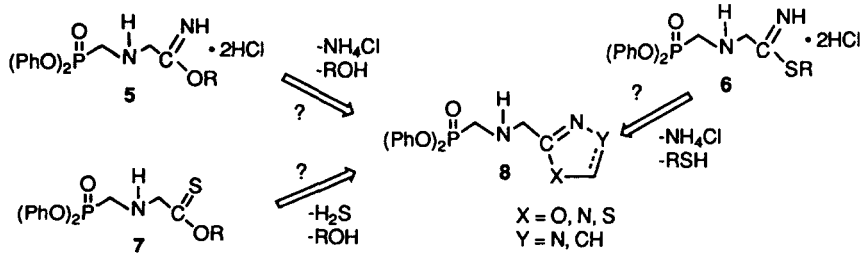
Imidates can generally be prepared from nitriles and alcohols either under basic or acidic conditions [14]. In order to avoid any base-catalyzed decomposition of the diphenylphosphonate group, we restricted our investigation to the acidic process. Typically, nitrile and excess alcohol are mixed in a suitable solvent, and then gaseous HCl is bubbled into the cold reaction mixture. The success of imidate formation is often strongly dependent upon the ability to crystallize selectively the desired imidate from the other reactants in order to drive the equilibrium forward towards product. Conditions must be carefully chosen so as to avoid precipitation of the hydrochloride salt of **3b**. Solubility studies indicated that cold chloroform and methylene chloride would maintain this hydrochloride salt in solution, whereas diethyl ether would not. Completely anhydrous conditions must also be used in order to avoid any hydrolytic side reactions to **4b**. We found that solutions of **3b** in methylene chloride react cleanly and quantitatively with gaseous HCl under anhydrous condi-



SCHEME 3

tions after a few hours with 1–2 equivalents of ethanol at about –10 °C to give the desired imidate dihydrochloride derivative **5a** as the sole product. No significant exchange of the diphenyl phosphonate esters with ethanol occurs under these acid catalyzed conditions (Scheme 3).

The combination of methylene chloride and nearly stoichiometric amounts of ethanol is critical. With excess ethanol (50/50 with CH_2Cl_2) at room temperature, significant quantities (65–82%) of ammonium chloride along with small amounts of



SCHEME 2

TABLE 1 N-{[Diphenoxyphosphinyl]methyl-α-aminoacetamidic esters

Cmpd	*R*	*Yield (%)*	*mp °C (d)*[a]	*Anal. Calcd.*	*Anal. Found*	*^1H NMR Data (DMSO-d_6)*
5a	ethyl[b]	95	159–160	C: 48.47 H: 5.50 N: 6.65 Cl: 16.83	C: 48.25 H: 5.61 N: 6.61 Cl: 16.91	δ: 1.3 (t, 3H); 3.78 (d, 2H, J_{PCH} = 12 Hz); 4.13 (s, 2H); 4.53 (qt, 3H); 7.30 (m, 11H); 10.07 (br s, 3H).
5b	*iso*-propyl	77	150–157	C: 49.67 H: 5.79 N: 6.44 Cl: 16.29	C: 49.66 H: 5.84 N: 6.33 Cl: 16.16	δ: 1.35 (d, 6H); 3.88(d, 2H, J_{PCH} = 12 Hz); 4.23 (s, 2H); 5.18 (m, 1H); 7.35 (m, 10H).
5c	*iso*-amyl	62	155–160	C: 51.84 H: 6.31 N: 6.05 Cl: 15.30	C: 51.62 H: 6.35 N: 6.04 Cl: 15.17	δ: 1.3 (d, 6H); 3.81 (d, 2H, J_{PCH} = 11 Hz); 4.16 (m, 2H); 4.35 (s, 2H); 7.3 (m, 11H).
5d	*neo*-pentyl[c]	79	73–82	C: 51.84 H: 6.31 N: 6.05 Cl: 15.30	C: 51.63 H: 6.30 N: 6.08 Cl: 15.24	δ: 1.0 (s, 9H); 3.85 (s, 2H); 4.2 (m, 2H); 4.4 (s, 2H); 7.28 (m, 11H).

[a] All melted with decomposition.
[b] FDMS: m/e (M^+ -2HCl) = 349.
[c] FDMS: m/e (M^+-2HCl) = 391; IR: 1665 cm^{-1} (C=N)

the amide hydrochloride **9** can be isolated. Presumably, further conversion of **6a** to the corresponding ortho ester with loss of NH_4Cl occurs under these conditions, but all attempts to isolate this ortho ester species failed. A clean, quantitative transformation of isolated **5a** to **9** was observed within a half hour in ethanol at room temperature. When ethanol is the solvent at room temperature, only the hydrochloride salt of **3b** is obtained in high yield (93%). Other primary and secondary aliphatic alcohols also react with varying degrees of success as summarized in Table 1. Occasionally, it is necessary to add small amounts of ether to the reaction medium in order to facilitate imidate crystallization.

Certain other alcohols, notably methanol, *t*-butyl alcohol, benzyl, and p-methylbenzyl alcohol, failed to give any of the desired imidate product. Instead, amide hydrochloride **9** was consistently isolated in high (>75%) yield. Presumably, the expected imidates do form transiently in solution under the reaction conditions, but rapidly degrade to the more stable **9** as shown in Scheme 3. Simple unsubstituted imidate salts normally decompose to amides upon heating [15a]. McElvain and Tate [15b] have investigated the mechanism of this thermal decomposition with acetimidate salts in chloroform and *t*-butyl alcohol. Their kinetic data are consistent with the bimolecular attack of halide ion at the alkoxy carbon. Their observed thermal degradation rate of the methyl ester was nearly twenty fold faster than that of the ethyl analog. Thus, one might expect the methyl ester of **5** to be less stable, but the observed total change in reaction course is surprising.

Attempts to prevent this side reaction and increase the overall stability of these imidates using alcohol reagents with strong electron withdrawing groups (e.g., trichloro- or trifluoroethanol) failed to give any precipitated product. Apparently, the low nucleophilicity of these alcohols hampers imidate formation. The neopentyl-derivative **5c** was also synthesized as a means to mimimize sterically this side reaction. The relatively weak herbicide activity observed for **9** in contrast to derivatives **5a–d** indicates that these imidate species can hydrolyze to glyphosate in vivo, presumably through intermediates **3a** and **4a**, rather than through the corresponding amides [16].

This solution degradation to **9** severely restricted any further synthetic applications of imidates **5a–d**. Essentially, any conditions which could be identified to solubilize these intermediates led quickly to the facile formation of amide **9**. Several imidate ester derivatives of amino acids are known which will react with suitable bifunctional nucleophiles to give heterocyclic products. For example, ethyl N-carbobenzyloxy-iminoglycinate hydrochloride reacts with benzoic acid hydrazide to give the expected 5-phenyl-2-aminomethyl-1,3,4-oxadiazole product in good yield [17]. Because of the stability of the oxadiazole products, this transformation seemed attractive as a model reaction to test the ring-forming capabilities of these analogous glyphosate imidates. Unfortunately, no significant oxadiazole product formation could be observed

TABLE 2 N-{[Diphenoxyphosphinyl]methyl-α-aminoacetamidic thioesters

Cmpd	R	Yield (%)	mp °C	Anal. Calcd.	Anal. Found	^1H NMR Data (DMSO-d_6)
6a	ethyl[a]	95	112–113	C: 46.69 H: 5.30 N: 6.41 Cl: 16.21	C: 46.47 H: 5.32 N: 6.34 Cl: 16.04	δ: 1.23 (t, 3H); 6.63 (s, 2H); 7.28 (m, 11H).
6b	*iso*-propyl[b]	89	104–105	C: 46.06 H: 5.80 N: 5.97 Cl: 15.11	C: 46.07 H: 5.76 N: 6.02 Cl: 15.13	δ: 1.35 (d, 6H); 3.88 (d, 2H); 4.23 (2, 2H); 5.18 (m, 1H); 7.35 (m, 1OH).
6c	benzyl[c]	31	86–92	C: 52.91 H: 5.05 N: 5.61	C: 52.75 H: 5.05 N: 5.59	δ: 3.82 (d, 2H); 4.15 (s, 2H); 4.32 (s, 2H); 5.33 (s, 4H): 7.30 (s, 15H).
6d	m-NO_2-benzyl[d]	89	107–109	C: 48.54 H: 4.44 N: 7.72 Cl: 12.90	C: 48.58 H: 4.46 N: 7.73 Cl: 12.80	Stable, hygroscopic solid. Very unstable in solution. NMR is not definitive.
6e	2-phenyl-ethyl[e]	90	107-109	C: 52.88 H: 5.40 N: 5.36 Cl: 13.57 S: 6.14	C: 52.69 H: 5.29 N: 5.38 Cl: 13.45 S: 6.04	Stable, hygroscopic solid. Very unstable in solution. NMR is not definitive.
6f	phenyl[f]	83	103–105	C: 51.97 H: 4.78 N: 5.77 Cl: 14.61 S: 6.61	C: 51.89 H: 4.76 N: 5.79 Cl: 14.49 S: 6.64	δ: 3.78 (d, 2H); 4.18 (s, 2H); 4.57 (s, 4H); 7.35 (m, 15H).
6g	p-Cl-benzyl[g]	52	87–90	C: 48.41 H: 4.68 N: 5.13	C:48.13 H: 4.47 N: 5.12	Stable, hygroscopic solid. Very unstable in solution. NMR is not definitive.
6h	p-CH_3O-benzyl[h]	74	99–101	C: 52.18 H: 5.14 N: 5.29 Cl: 13.39	C:52.09 H: 5.15 N: 5.29 Cl: 13.30	Stable, hygroscopic solid. Very unstable in solution. NMR is not definitive.

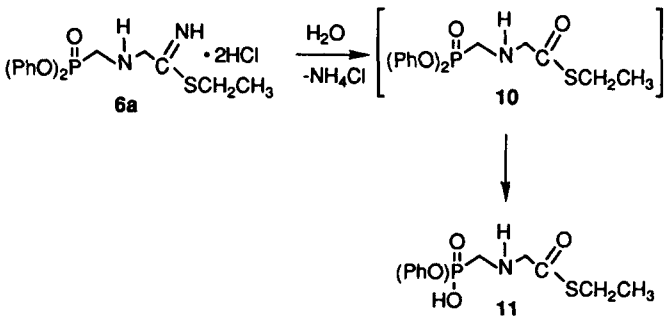
[a] FDMS: m/e (M^+ -2HCl) = 365. [e] FDMS: m/e (M^+ -2HCl) = 441.
[b] FDMS: m/e (M^+ -2HCl) = 380. [f] FDMS: m/e (M^+ -2HCl) = 412.
[c] FDMS: m/e (M^+ -2HCl) = 426. [g] FDMS: mle (M^+ -2HCl) = 460.
[d] FDMS: m/e (M^+ -2HCl) = 472. [h] FDMS: m/e (M^+ -2HCl) = 457.

under any homogeneous conditions using **5a**. With **5d** only copious quantities of ammonium chloride could be isolated from the reaction mixture. Similarly, all attempts to observe ring closure with other bifunctional nucleophiles such as ethylene diamine failed to give any of the desired cyclic imidazolidine derivatives.

Synthesis of Thioimidate Esters from ***3b****.*

Since the degradation to amide **9** seemed to predominate in the solution state reactions of **5a–d**, we also investigated the synthesis and reactions of the corresponding thioimidate derivatives **6.** Decomposition of the thioimidate functionality by any halogen attack at the S-alkyl group should be reduced substantially in these systems and greatly enhance their stability in solution. Indeed, the reverse alkylation of thioamides with alkyl halides is often used as a synthetic procedure to prepare thioimidates [14].

Intermediate **3b** reacts with two equivalents of ethanethiol and HCl at −10 °C in methylene chloride to give the desired ethyl thioimidate **6a** in 95%



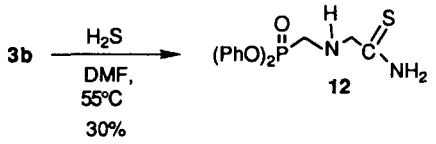
SCHEME 4

yield. A wide variety of alkyl and aryl mercaptans react under similar conditions producing the corresponding thioimidate derivatives **6b–h** as crystalline solids in quite good isolated yields (Table 2). The greater versatility of thioimidate formation is easily demonstrated from the wide variety of thiophenols and substituted benzyl thiols that will generate products. Several substituted benzyl mercaptans gave crystalline products which were isolable as analytically pure, hygroscopic solids that rapidly degraded in DMSO solution. Compounds **6d–e** and **6g–h** could therefore not be definitively characterized by NMR spectroscopy. Certain aliphatic thiols, notably methyl and *t*-butyl mercaptan only gave trace quantities of the desired products.

The greater thermal stability of these thioimidates over their oxygen counterparts was demonstrated in solution using **6a**. Whereas solutions of **5a** in ethanol or DMSO-d_6 converted cleanly and quantitatively to amide **9**, similar solutions of **6a** yielded only mixtures of thioimidate and thioester **10** [18] as determined by NMR and IR spectroscopy. The amount of **10** observed in these solutions was highly variable and appeared to depend on the amount of water present in the DMSO-d_6. Direct treatment of **6a** with water readily hydrolyzes the thioimidate to **10** as evidenced by NMR and IR spectroscopy. All attempts to isolate this derivative in pure form from this mixture failed. However, with acetone as a solvent containing just enough water for hydrolysis, a crystalline solid slowly forms which has been characterized by NMR, IR, and MS determinations as a mixture of the monoaryl thioester derivative **11** and ammonium chloride (Scheme 4). Thus, even this thioimidate appears to undergo competitive hydrolysis at the phosphonate center simultaneously with reaction at the activated carboxyl group.

Even after 24 hr at room temperature, solutions of **6a** in DMSO-d_6 gave no indication of thioamide **12** formation by NMR spectroscopy. Thioalmide **12** can be conveniently prepared in low yield by treating **3b** with H_2S in DMF (Scheme 5). After one hour, this reaction produces essentially a 50/50 mixture of **3b** and **12**. Prolonged reaction times, higher temperatures or the presence of an amine catalyst failed to improve this conversion. However, all of the starting material contaminating the product can be removed conveniently using hot carbon tetrachloride to give the desired thioamide in analytically pure form. As observed previously for **9**, thioamide **12** also displays little significant herbicide activity, again suggesting that these herbicidally active glyphosate thioimidates [19] hydrolyze in vivo to the corresponding active glyphosate thioesters [18].

As before, all attempts to utilize these thioimidates in cyclization processes with benzoic acid

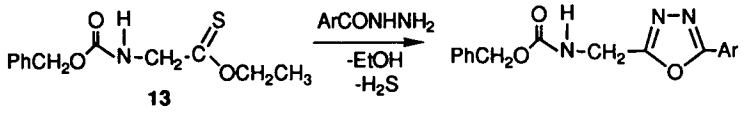


SCHEME 5

hydrazide or ethylene diamine failed to produce any significant quantities of the desired heterocyclic "masked" carboxylate derivatives. In this case, the facile hydrolysis to the corresponding thioester derivatives **10,11** appears to be a major limitation in utilizing these thioimidate intermediates for further conversions.

Synthesis of Thiono Esters from ***5a***

From these results we concluded that any effective transformation at the activated carboxylate center in these systems would require a fairly rapid, irreversible reaction to generate the desired heterocyclic derivatives. Whereas imidate and thioimidate derivatives have seen wide application for the synthesis of new heterocycles, the corresponding thiono esters have been used sparingly, though quite successfully, for similar transformations [20, 21]. In an earlier model study, we demonstrated that the protected ethyl N-carbobenzyloxythiono-glycinate **13** reacts cleanly and irreversibly through loss of H_2S with many aromatic acid hydrazides to generate a



SCHEME 6

wide variety of 1,3,4-oxadiazole products containing 2-aminomethyl side chains (Scheme 6) [22].

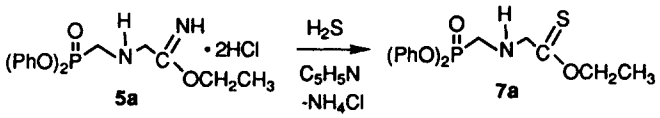
The corresponding glyphosate thiono ester derivatives **7** might be expected to undergo similar reactions, but their ease of preparation and stability are certainly not guaranteed based on literature reports. A search of the literature reveals that certain amino acid thiono esters containing free N—H groups are known, but they all contain some type of amide protecting group to minimize self-condensation and/or polymerization at the thiono ester center [23–27]. Indeed, several publications describe facile condensations between thiono esters and simple primary or secondary amines at room temperature as a general method to prepare the corresponding coupled thioamide derivatives [20, 28, 29]. There are no literature reports of either stable glycine and sarcosine thiono esters or higher homologs containing simple N-alkyl substituents, although such species have been postulated as transient reactive intermediates at low (−78 °C) temperatures [30, 31]. Only weakly nucleophilic primary amines such as anilines can be tolerated with the thiono ester group [32, 33].

The weak basicity and low reactivity of the nitrogen atom in **3b** toward alkylating agents such as trimethyloxonium tetrafluoroborate prompted us to explore the preparation of the corresponding glyphosate thiono ester derivatives **7a–c**. Indeed, imidate **5a** reacts cleanly and nearly quantitatively with H_2S in dry pyridine at 0°C under scrupulously anhydrous conditions to give an excellent isolated yield of the desired thiono ester analog **7a** as a low melting solid (Scheme 7). All spectroscopic data (NMR, IR, MS) were in complete agreement with the indicated thiono ester product. There was no spectroscopic evidence by NMR or IR for any contamination of the isolated material by either the neutralized form of imidate ester **5a** (IR, 1680 cm^{-1}) or the ethyl carboxylate derivative **3a** (IR, 1750 cm^{-1}). In addition, ^1H NMR spectroscopy indicated a significant downfield chemical shift of the ethyl ester methylene protons (δ 4.58) for **7a** in $CDCl_3$ versus those observed for **3a** (δ 4.08) or carefully (DBU/THF) neutralized **5a** (δ 4.32). A distinct downfield chemical shift was also observed for the C=S group (δ 220.8) in **7a** versus the C=O displayed for **3a** (δ 167.3) by ^{13}NMR spectroscopy, consistent with literature shifts of other thiono esters [34]. Similarly, there was no spectral evidence for any thioamide **12** or P=S species contaminating the isolated thiono ester product.

TABLE 3 N-{(Dphenoxyphosphinyl]methyl-α-aminoacetamidic thionoesters

Cmpd	*R*	*Yield (%)*	*mp °C*	*Anal. Calcd.*	*Anal. Found*	*^1H NMR Data ($CDCl_3$):*
7a	ethyl[a]	89	52–54	C: 55.88 H: 5.52 N: 3.83 S: 8.78	C: 55.62 H: 5.60 N: 3.80 S: 8.67	δ: 1.38 (t, 3H); 3.40 (d, 2H, J_{PCH} = 12 Hz); 3.72 (s, 2H); 4.57 (q, 2H); 7.27(m, 11H).
7b	*iso*-propyl[b]	68	40–43	C: 56.98 H: 5.84 N: 3.69 S: 8.45	C: 56.83 H: 5.88 N: 3.66 S: 8.44	δ: 1.30 (d, 6H); 3.42 (d, 2H, J_{PCH}= 13 Hz); 3.65 (d, 2H, $J_{PCHNHCH}$ = 1 Hz); 5.67 (sept, 1H); 7.23 (m, 11H).
7c	*neo*-pentyl[c]	59	oil	C: 58.95 H: 6.43 N: 3.44 S: 7.87	C: 58.90 H: 6.44 N: 3.44 S: 7.79	δ: 1.00 (s,9H); 3.43 (d, 2H, J_{PCH} = 11 Hz); 3.78 (d, 2H, $J_{PCHNHCH}$ = 1 Hz); 4.22 (s, 2H); 7.32 (m, 11H).

[a] FDMS: m/e (M^+) = 365; ^{13}C NMR($CDCl_3$): (C=S) = 220.8 ppm; ^{31}P NMR($CDCl_3$): 18.6 ppm.
[b] FDMS: m/e (M^+) = 379; ^{13}C NMR($CDCl_3$): (C=S) = 219.9 ppm; ^{31}P NMR($CDCl_3$): 18.8 ppm.
[c] FDMS: m/e (M^+) = 407; ^{13}C NMR($CDCl_3$): (C=S) = 221.1 ppm; ^{31}P NMR($CDCl_3$): 18.6 ppm; $n_D^{27.5}$ = 1.6650.



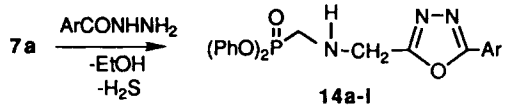
SCHEME 7

These encouraging results led us to pursue the reaction with other members of the imidate series. Both the isopropyl **5b** and neopentyl **5d** derivatives gave good conversions to the corresponding thiono esters **7b–c**. The ^{1}H NMR of **7b–c** again exhibited the characteristic downfield chemical shift for the aliphatic protons alpha to oxygen. However, no pure dithio ester products could be obtained using any of the thioimidate analogs **6a–h** under comparable conditions. To the best of our knowledge, this successful synthesis of thiono esters **7a–c** represents the first reported examples of isolable and relatively stable N-alkyl thiono glycinates.

Each of these compounds was prepared very efficiently in 50–70% isolated yields upon scaleup from >100 g batches of **3b** (Table 3). They all could be maintained for several weeks under nitrogen in a refrigerator with no visible deterioration. However, even minimal exposure of **7a** in acetone/water or dilute acid resulted in rapid loss of H_2S with concomitant formation of the zwitterionic oxodiester **4a**, as evidenced by the reappearance of the C=O band at 1750 cm^{-1} by IR spectroscopy. Similar desulfurization occurs easily under very mild conditions with **7b–c**. Prolonged exposure of toluene solutions containing **7b** to moist air produced a precipitate consisting entirely of the isopropyl oxo ester analog of **4a**, and no thiono ester remained in solution. This desulfurization reaction is a well documented process for other thiono esters [35]. Once again, the observed herbicide activity displayed by **7a–c** suggests that hydrolysis occurs in vivo through a similar process involving the herbicidal intermediate **4a** [36].

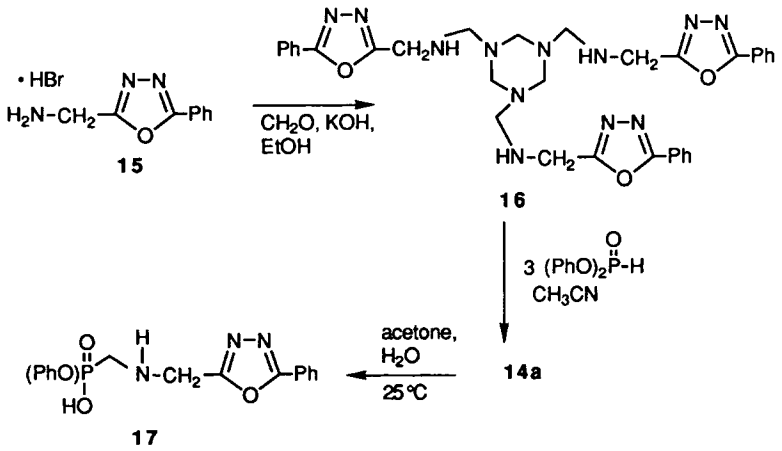
Heterocycle Formation from Thiono Ester **7a**

Having developed a convenient, high yield route to these glyphosate thiono ester intermediates, we turned our attention to defining their synthetic utility for other novel derivatives. Because of their tendency to lose sulfur readily under hydrolytic conditions, water must be scrupulously avoided in all reactions. Like the corresponding glyphosate oxotriesters [10, 37] **3a**, these thiono esters **7a–c** can be converted to their strong acid salts under anhydrous conditions. They will also readily acylate at nitrogen with trifluoroacetic anhydride and base to form their N-trifluoracetyl derivatives [36]. Thus, the nitrogen atom in **7a–c** reacts like other typical glyphosate amines [13].



SCHEME 8

With these encouraging results in hand, we next explored the direct conversion of **7a** to various oxadiazole derivatives. Treatment of **7a** with one equivalent of acid hydrazide substrate in dry acetonitrile under nitrogen at reflux leads to a rapid evolution of H_2S with concomitant formation of the desired 1,3,4-oxadiazoles (Scheme 8). After chromatography, a wide variety of novel oxadiazole derivatives **14a–i** were isolated in good yields, usually as off-white solids as summarized in Table 4. The 5-phenyl-1,3,4-oxadiazole product **14a** formed from **7a** and benzoic acid hydrazide was identical in all respects to a sample independently prepared

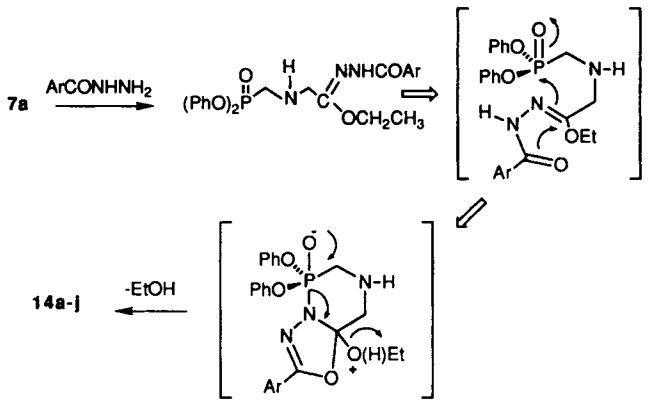


SCHEME 9

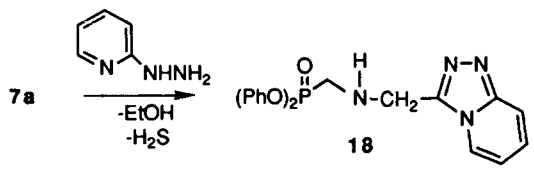
TABLE 4 2-[[N-Diphenoxyphosphonomethyl]-aminomethyl]-1,3,4-oxadiazoles

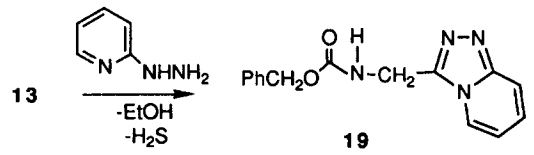
Cmpd	*5-R*	*Yield (%)*[a]	*mp °C*	*Anal. Calcd.*	*Anal. Found*	*^{1}H NMR Data ($CDCl_3$):*
14a	phenyl[b]	50	96–98	C: 62.71 H: 4.78 N: 9.97	C: 62.55 H: 4.87 N: 10.04	δ: 3.52 (d, 2H, J_{PCH} = 12 Hz); 4.30 (d, 2H, $J_{PCHNHCH}$ = 1 Hz); 7.25 (m, 10H); 7.50 (m, 4H); 8.00 (m, 2H).
14b	p-tolyl[c]	57	64–67	C: 63.44 H: 5.09 N: 9.65	C: 63.57 H: 5.15 N: 9.55	δ: 2.40 (s, 3H); 3.46 (d, 2H, J_{PCH} = 12 Hz); 4.26 (s, 2H); 7.23 (m, 11H); 7.67 (ABqt, 4H).
14c	p-CH_3O-phenyl[d]	49	67–69	C: 61.20 H: 4.91 N: 9.31	C: 61.26 H: 4.95 N: 9.25	δ: 3.51 (d, 2H, J_{PCH} = 12 Hz); 3.88 (s, 3H); 4.27 (s, 2H); 6.90, 7.88 (ABqt,4H); 7.26 (m, 11H).
14d	m-NO_2-phenyl[e]	34	122–124	C: 56.66 H: 4.11 N: 12.01	C: 56.57 H: 4.12 N: 11.97	δ: 2.02 (s, 1H); 3.35(d, 2H, J_{PCH}= 11 Hz); 4.10 (s, 2H); 7.03 (m, 11H); 7.48 (m, 1H); 8.17 (m, 2H); 8.60 (m, 1H).
14e	o-Cl-phenyl[f]	52	72–74	C: 57.97 H: 4.20 N: 9.22 Cl: 7.78	C: 58.02 H: 4.03 N: 9.22 Cl: 7.79	δ: 2.00 (s, 1H); 3.50 (d, 2H, J_{PCH} = 12 Hz); 4.28 (d, 2H, $J_{PCHNHCH}$ = 1 Hz); 7.20 (m, 11H); 7.47 (m, 3H); 7.88 (m, 1H).
14f	4-pyridyl[g]	49	104–106	C: 59.72 H: 4.53 N: 13.26	C: 59.47 H: 4.58 N: 13.22	δ: 2.43 (s, 1H); 3.48 (d, 2H, J_{PCH} = 11 Hz); 4.30 (d, 1H, $J_{PCHNHCH}$ = 1 Hz); 7.17 (m, 11H); 7.80 (m, 2H); 8.68 (m, 2H).
14g	3-pyridyl[h]	36	68–70	C: 59.72 H: 4.53 N: 13.26	C: 59.55 H: 4.57 N: 13.23	δ: 2.10 (s, 1H); 3.45 (d, 2H, J_{PCH} = 11 Hz); 4.27 (s, 2H); 7.18 (m, 12H); 8.52 (m, 1H); 8.92 (m, 1H); 9.32 (m, 1H).
14h	2-thienyl[i]	40	80–82	C: 56.20 H: 4.24 N: 9.83 S: 7.50	C: 56.03 H: 4.30 N: 9.75 S: 7.44	δ: 2.25 (s, 1H); 3.46(d, 2H, J_{PCH} = 11 Hz); 4.27 (s, 2H); 7.28 (m, 11H); 7.65 (m, 2H).
14i	2-furyl[j]	20	60–63	C: 58.40 H: 4.41 N: 10.22	C: 58.31 H: 4.59 N: 9.67	δ: 3.48 (d, 2H, J_{PCH} = 12 Hz); 4.25 (d, 2H, $J_{PCHNHCH}$ = 1 Hz); 6.60 (m, 1H); 7.27 (m, 12H); 7.65 (m, 1H).

[a] Isolated after chromatography.
[b] FDMS: m/e (M^+) = 421.
[c] FDMS: m/e (M^+) = 435.
[d] FDMS: m/e (M^+) = 451.
[e] FDMS: m/e (M^+) = 466.
[f] FDMS: m/e (M^+) = 4.54.
[g] FDMS: m/e (M^+) = 422.
[h] FDMS: m/e (M^+) = 422.
[i] FDMS: m/e (M^+) = 427.
[j] FDMS: m/e (M^+) = 411.

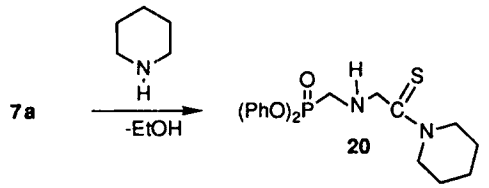


SCHEME 10





SCHEME 11



SCHEME 12

from the known hydrobromide salt of 5-phenyl-2-aminomethyl-1,3,4-oxadiazole [16, 22] **15** via the hexahydrotriazine intermediate **16** (Scheme 9). This product also underwent hydrolysis in aqueous acetone to give the corresponding monoaryl ester derivative **17** in modest yield.

Thus, thiono ester **7a** provides direct access to a number of novel glyphosate analogs containing 1,3,4-oxadiazole functionality in place of the carboxylate group. The reaction tolerates benzoic acids bearing a wide variety of substituents as well as several heterocyclic components. In each case the isolated product is an oxadiazole. This is an expected result based on model studies between **13** with all of the benzhydrazides and either nicotinic or iso-nicotinic acid hydrazides [22]. However, the predominant product observed between **13** and 2-thienyl or 2-furyl hydrazide is an unexpected 2:1 N-amino-1,2,4-triazole adduct. In contrast, reactions between 2-furyl or 2-thienyl hydrazide with **7a** gave no evidence for the formation of any such 2:1 species. The preferential and fairly clean cyclizations of **7a** to oxadiazole products may indicate that the phosphonate moiety provides some anchimeric assistance to the overall cyclization as shown in Scheme 10.

Similar cyclizations to the expected fused 1,2,4-triazole product were also observed between **7a** and other reactive hydrazine derivatives, such as 2-hydrazinopyridine. In a reaction paralleling that observed with model compound **13**, good yields of the desired fused triazolo[4,3,a]pyridine adducts **18,19** are obtained in each case (Scheme 11).

Unfortunately, all attempts to utilize these thiono ester intermediates in cyclizations under similar conditions with less reactive bifunctional nucleophiles, such as ethylenediamine, that could produce the corresponding imidazolidine as a partially unsaturated analog, gave no pure isolable products. Instead, complex mixtures containing imidate, thioamide and other intermediates were observed by NMR spectroscopy, and that prevented further application of these materials. Thiono ester **7a** will react with piperidine to give modest isolated yields of the corresponding thioamide derivative **20** (Scheme 12).

Thus, the utility of **7a–c** appears to be restricted to reactions with fairly reactive bifunctional nucleophiles, particularly hydrazine-based reagents, for the direct synthesis of glyphosate derivatives containing stable, fully unsaturated, or nearly aromatic heterocycles in place of the carboxylate group. The desired preferential attack by the hydrazine nucleophiles is observed to occur at the thiono ester center with retention of the activated diphenylphosphonate moiety. As such, this direct three step synthesis of these glyphosate 1,3,4-oxadiazole and 1,2,4-triazole derivatives from **3b** via **7a** represents an extremely efficient route to the desired molecules compared with the corresponding six step process using 1,3,5-hexahydrotriazine intermediates (Scheme 9).

CONCLUSIONS

In this study we have identified and prepared a variety of novel glyphosate derivatives containing imidate **5a–d** and thioimidate **6a–h** groups as activated carboxylate functionalities. The limited stability of these interesting derivatives in solution has been defined and prevents their further application as viable synthetic intermediates. However, the corresponding glyphosate thiono esters **7a–c** represent a completely novel class of activated sarcosine derivatives, with sufficient stability to be useful for further synthetic transformations by preferential nucleophilic reaction at this activated carboxylate center. As such, they provide an efficient route to a wide variety of new 1,3,4-oxadiazole and 1,2,4-triazole analogs containing the desired 2-[N-phosphonomethyl]aminomethyl sidechains.

Acknowledgments

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EXPERIMENTAL SECTION

General

Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian EM-360L (60 MHz) or Bruker WM-360 (360 MHz) spectrometer. All carbon NMR spectra were obtained on a Bruker WM-360 spectrometer. All proton and carbon chemical shifts are recorded in ppm (δ) relative to tetramethylsilane (TMS). ^{31}P NMR spectra were obtained on a Jeol EX-100 spectrometer and are referenced to H_3PO_4. Radial chromatography was performed on silica (4mm) plates using a Harrison Research model 7924 Chromatotron. All solvents were Aldrich Gold Label grade. All of the thiol and carboxylic acids employed in this study were obtained from commercial sources. Micro-analyses were performed by Atlantic Microlabs, Inc.

Preparation of Diphenoxyphosphinylmethyl-glycinonitrile, ***3b***

A solution of 1,3,5-tris-(cyanomethyl)-hexahydrotriazine (13.6 g, 0.066 mol) and diphenyl phosphite (46.8 g, 0.2 mol) in 100 mL of acetonitrile was heated at 55 °C for 48 hr. ^{31}P NMR examination of the crude reaction mixture indicated complete conversion to product. The acetonitrile was removed *in vacuo* to yield 57 g (94%) of a viscous black oil. Chromatographic purification followed on silica gel eluting with $CHCl_3$. The chloroform eluents were concentrated, dissolved in methylene chloride, washed twice with cold aqueous KOH (5%) and water, dried over $MgSO_4$, filtered and evaporated to give 37.9 g (75%) of diphenoxyphosphinylmethyl-glycinonitrile **3b** as a light yellow oil which crystallized on standing, m.p. 64–67.5°C. This solid was easily recrystallized from CCl_4 using activated charcoal to give white needles, m.p. 66–68°C. ^{31}P NMR ($CDCl_3$) δ: 14.48 ($J_{P\text{-}CH}$ = 12 Hz). ^1H NMR ($CDCl_3$) δ: 1.97 (br s, 1H, N-*H*); 3.27 (d, 2H, $J_{P\text{-}CH}$ = 12 Hz); 3.58 (d, 2H, $J_{P\text{-}CHNHCH}$ = 1 Hz); 7.27 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 150.33 (d, $J_{P\text{-}C}$ = 9Hz), 130.24, 125.86, 120.90 (d, $J_{P\text{-}C}$ = 4.3 Hz), 117.43 (CN), 43.87(d, $J_{P\text{-}C}$ = 162 Hz), 38.39 (d, $J_{P\text{-}CHNH\text{-}C}$ = 16 Hz). Anal. Calcd. for $C_{15}H_{15}N_2O_3P$: C, 59.60; H, 5.00; N, 9.27. Found: C, 59.65; H, 5.02; N, 8.96.

General Procedure for the Preparation of Glyphosate Imidate ***(5a–g)*** *and Thioimidate Esters Dihydrochlorides* ***(6a–h)*** *from* ***3b***

To an oven-dried 250 mL 3-necked flask equipped with nitrogen inlet, magnetic stirring bar, thermometer and gas sparge was added **3b** (6.04 g, 0.02 mol), the requisite corresponding alcohol or thiol (0.04 mol) and 150 mL of CH_2Cl_2. The resulting solution was cooled to −10 °C in an ice-salt bath, and then gaseous HCl was bubbled through the solution for 90 min. The reaction mixture was stirred overnight under nitrogen at 0 ± 5 °C. If the desired imidate failed to crystallize, 10 mL of absolute diethyl ether was added. The white solid products then crystallized from solution after a few hours at 0°C. The supernatant liquid was removed under nitrogen using the sparge as a filter stick. The solid imidates were then washed successively with 2 × 200 mL of CH_2Cl_2 and 2 × 200 mL of absolute diethyl ether, then dried and stored *in vacuo*. ^1H NMR, FDMS and C,H,N elemental analyses were all consistent with pure products, as summarized in Tables 1 and 2.

*General Procedure for the Preparation of Glyphosate Thiono Esters (****7a–c****) from* ***3b***

To an oven-dried 500 mL 3-necked flask equipped with nitrogen inlet, magnetic stirring bar, thermometer and gas sparge was added **3b** (24.2 g, 0.08 mol), the corresponding alcohol (0.16 mol) and 300 mL of CH_2Cl_2. The resulting solution was cooled to −10 °C in an ice-salt bath, and then HCl gas was bubbled through the solution for 90 min. The reaction mixture was stirred overnight under nitrogen at 0 ± 5 °C. If the desired imidate failed to crystallize, 50 mL of absolute diethyl ether was added. The solid products then crystallized from solution after a few hours at 0 °C. The supernatant liquid was removed under nitrogen with a filter stick. The solid imidate cake was then washed successively with 2 × 200 mL of CH_2Cl_2 and 2 × 200 mL of absolute diethyl ether, then dried *in vacuo*. When all of the volatiles had been removed, the solid was cooled to −20 °C and dissolved under nitrogen in 300 mL of dry pyridine. Then H_2S gas was bubbled into the solution for 3 hr. The resulting mixture was then briefly degassed with nitrogen, and the pyridine was removed under vacuum. A yellow oil generally resulted which was slurried in 300 mL of water and extracted twice with equal volumes of ether to remove any traces of pyridine. The ether extracts were combined, dried over $MgSO_4$, filtered and concentrated to give the desired thiono esters **7a–c** as essentially pure, lightly yellow oils, which could slowly crystallize on standing in the freezer under nitrogen. Satisfactory ^1H NMR, FDMS, and C,H,N elemental

analyses were obtained for each product, as summarized in Table 3. In all cases, these compounds were stored under nitrogen at 0°C to minimize degradation.

*General Procedure for the Preparation of Glyphosate 1,3,4-Oxadiazole Derivatives (**14a–j**) from **7a***

The thiono ester **7a** (8.0 g, 0.022 mol) and the appropriate carboxylic acid hydrazide (0.022 mol) were combined under nitrogen in an oven-dried flask with 150 mL of dry acetonitrile. The resulting solution was refluxed under a nitrogen atmosphere for 8–12 hr, until TLC indicated that all of **7a** was consumed, then cooled to room temperature. The resulting product was purified by either column or radial chromatography on silica gel, eluting with EtOAc/cyclohexane mixtures. The appropriate fractions were combined and concentrated to give the desired 1,3,4-oxadiazoles, generally as off-white solids. ^{1}H NMR, FDMS and C,H,N elemental analyses were all consistent with pure products, as summarized in Table 3.

*Preparation of Glycinamide, N- (diphenoxyphosphinylmethyl)-, hydrochloride, **9**.*

A solution of **3b** (4.53 g, 0.015 mol) and p-methylbenzyl alcohol (5.5 g, 0.045 mol) in 150 mL of CH_2Cl_2 was cooled to 0–5°C under a nitrogen atmosphere. Dry HCl gas was bubbled through the solution over a 4 hr period. A white solid began to form which was allowed to crystallize over another 2 hr. The resulting precipitate was collected by filtration, washed with cold CH_2Cl_2 and ether and recrystallized from absolute ethanol to give **9** as a white solid (4.25 g, 79%), m.p. 168–169.5°C(d). ^{1}H NMR (DMSO-d_6) δ: 3.92 (br s, 4H); 4.20 (s, 2H); 7.33 (m, 10H); 8.25 (br s, 2H). Anal. Calcd. for $C_{15}H_{17}N_2O_3P$ • HCl: C, 50.50; H, 5.09; N, 7.85; Cl, 9.94. Found: C, 50.64; H, 5.10; N, 7.94; Cl, 9.88.

Preparation of Glycine thioamide, N-(diphenoxyphosphinylmethyl)-, **12**

To an oven-dried, 2-L four-necked flask equipped with nitrogen inlet, mechanical stirrer, thermometer, gas sparge and condenser, was added, after cooling under nitrogen, **3b** (100.0 g, 0.33 mol) and 1 L of dry DMF. The resulting orange solution was warmed to 60°C with an oil bath. Then 2 mL of diethylamine was added as a catalyst, and H_2S gas was bubbled through the solution over a 2 hr period. The resulting blue-green solution was poured hot onto ~1 Kg of crushed ice with rapid stirring. A white solid formed quickly which was collected by filtration, washed several times with cold water and dried *in vacuo* overnight. The ^{1}H NMR spectrum of this solid showed it to be a mixture of the desired product contaminated with nearly an equal amount of **3b**, which could be removed completely by heating this solid mixture in about 200 mL of hot CCl_4 . The remaining insoluble material was collected by filtration and air dried to give pure **12** as an off-white solid (31.0 g, 28%), m.p. 98–100°C. FDMS (M^+ = 336). ^{1}H NMR (DMSO-d_6) δ: 3.30 (br s, 2H); 3.38 (d, 2H, $J_{P\text{-}CH}$ = 10 Hz); 3.63 (s, 2H); 7.27 (m, 11H). Anal. Calcd. for $C_{15}H_{17}N_2O_3PS$: C, 53.56; H, 5.09; N, 8.33; S, 9.53. Found: C, 53.42; H, 5.11; N, 8.31; S, 9.63.

Preparation of 1,3,4-Oxadiazole, 2,2',2''-[1,3,5-Triazine-1,3,5(2H,4H,6H)triyltris(methylene)]-tris[5-phenyl]-, **16**

To a slurry of **15** [17] (10.0 g, 0.039 mol) in 350 mL of ethanol was added at room temperature aqueous 37% formalin (3.2 g, 0.039 mol). Then solid KOH was added until a pH of 7.0 was attained using a pH meter. The resulting mixture was stirred overnight at room temperature. The precipitate of KCl was removed by filtration. The resulting filtrate was concentrated and extracted twice with 100 mL portions of CH_2Cl_2. These CH_2Cl_2 extracts were combined, dried over $MgSO_4$, filtered and concentrated to give **16** as a white solid (6.0 g, 82%), m.p. 64–66°C. FDMS (M^+ = 561). ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 2H); 4.12 (s, 2H); 7.42 (m, 3H); 7.97 (m, 2H). Anal. Calcd. for $C_{30}H_{27}N_9O_3$: C, 63.82; H, 4.82; N, 22.33. Found: C, 63.57; H, 5.28; N, 22.25.

*Preparation of Phosphonic acid, {[[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl] amino]methyl}-, diphenyl ester, **14a** from **16***

A stirred solution of **16** (8.4 g, 0.015 mol) and diphenyl phosphite (10.5 g, 0.045 mol) was combined under nitrogen in 500 mL of dry acetonitrile and refluxed overnight. The resulting mixture was concentrated to a dark brown oil, which could be purified by flash column chromatography on silica, eluting with ethyl acetate. Fractions containing **14a** were identified by TLC, combined and concentrated to give the desired product as an off-white solid (67%), m.p. 95–97°C, which was identical in all respects to the material described in Table 4 as prepared from **7a**.

Preparation of Phosphonic acid, {[[(5-Phenyl, 1,3,4-oxadiazol-2-yl)methyl] amino)methyl}-, monophenyl ester, **17**

A solution of **14a** (2.5 g, 0.006 mol) in 100 mL of acetone was stirred at room temperature overnight. A flocculent white precipitate formed slowly, which was collected by filtration, washed with acetone

and air dried to give **17** as a hygroscopic off-white solid (0.75 g, 35%), m.p. 207–209°C. This material was too insoluble in DMSO-d_6 to be characterized by NMR spectroscopy. Anal. Calcd. for $C_{16}H_{16}N_3O_4P \cdot 1/2H_2O$: C, 54.24; H, 4.84; N, 11.86. Found: C, 54.09; H, 4.80; N, 11.92. FDMS (M^+ = 345).

Preparation of Phosphonic acid, {[(1,2,4-Triazolo[4,3,a]pyridin-3-yl-methyl)amino]methyl}-, diphenyl ester, **18**

A solution of **7a** (7.3 g, 0.02 mol) and 2-hydrazinopyridine (2.2 g, 0.02 mol) in 250 mL of dry acetonitrile was refluxed under nitrogen for 2 hr, then allowed to come to room temperature overnight. A fairly instantaneous reaction was observed with evolution of H_2S. The resulting solution was then concentrated on a rotovap to give a dark red oil which could be crystallized from CH_2Cl_2/diethyl ether. The resulting solid was collected by filtration and air dried to give **18** as a yellow solid (5.2 g, 65%), m.p. 136–139°C. FDMS (M^+ = 394). ^{1}H NMR (DMSO-d_6) δ: 3.42 (d, 2H, $J_{P\text{-}CH}$ = 10 Hz); 4.43 (d, 2H, $J_{P\text{-}CHNHCH}$ = 1 Hz); 7.23 (m, 13H); 7.75 (d, 1H); 8.52 (d, 1H). Anal. Calcd. for $C_{20}H_{19}N_4O_3P$: C, 60.91; H, 4.86; N, 14.21. Found: C, 60.89; H, 4.90; N, 14.21.

Preparation of Carbamic acid, N-(1,2,4-Triazolo[4,3-a]pyridin-3-yl-methyl)-, phenyl-methyl ester, **19**

A yellow solution of **13** [22] (10.1 g, 0.04 mol) and 2-hydrazinopyridine (4.36 g, 0.04 mol) in 200 mL of dry acetonitrile was refluxed under nitrogen for 2 hr, then allowed to come to room temperature overnight. A fairly instantaneous reaction was observed with evolution of H_2S. The resulting orange solution was then concentrated on a rotovap to give an orange oil which could be crystallized from diethyl ether. The resulting solid was collected by filtration, washed with ether and air dried to give **19** as an off-white solid (8.5 g, 75%), m.p. 135–137°C. FDMS (M^+ = 282). ^{1}H NMR ($CDCl_3$) δ: 4.93 (d, 2H); 5.15 (s, 2H); 6.75 (q, 2H); 7.32 (m, 6H); 7.67 (d, 1H); 8.38 (d, 1H). ^{13}C NMR (DMSO-d_6) δ: 156.5, 149.4, 144.6, 136.8, 128.3, 127.7, 127.5, 124.0, 115.2, 113.3, 65.8, 34.8. Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.70; H, 5.06; N, 19.80.

Preparation of Phosphonic acid, {([2-(1-Piperidinyl)-2-thioxoethy]amino}methyl}-, diphenyl ester, **20**

A solution of **7a** (8.8 g, 0.024 mol) and piperidine (2.05 g, 0.024 mol) in 200 mL of absolute diethyl ether was combined under nitrogen at room temperature, then allowed to stir at room temperature overnight. The resulting mixture was concentrated on a rotovap to give a dark red oil which could be purified by flash column chromatography on silica, eluting with 70% cyclohexane/30% ethyl acetate in 20 mL fractions. Fractions 22–43 were combined and concentrated to give **20** as a yellow oil (1.9 g, 23%), $n_D^{26.5}$ = 1.5870, which crystallized on standing in the freezer, m.p. 51–54 °C. FDMS (M^+ = 403). ^{31}P NMR ($CDCl_3$) δ: 19.0. ^{1}H NMR ($CDCl_3$) δ: 1.68 (m, 6H); 3.40 (d, 2H, $J_{P\text{-}CH}$ = 11 Hz); 3.63 (m, 2H); 3.80 (s, 2H); 4.25 (m, 2H); 7.30 (m, 11H). Anal. Calcd. for $C_{20}H_{25}N_2O_3PS$: C, 59.39; H, 6.23; N, 6.93; S, 7.93. Found: C, 59.32; H, 6.29; N, 6.77; S, 7.76.

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