A Facile General Synthesis of Thiocarboxylate *S*-Esters of Glyphosate and Its Derivatives

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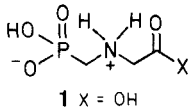
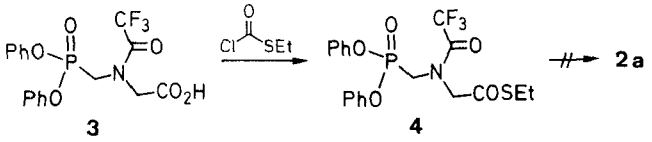
Various glyphosate thiocarboxylate *S*-ester derivatives, e.g. *S*-alkyl 2-(phosphonomethylamino)ethanethioates and *S*-alkyl 2-[(phenoxyphosphorylmethyl)amino]ethanethioates, are readily synthesized from *N*-benzyloxycarbonylglycine using *N*-methylene-*tert*-butylamine as the methylene transfer reagent followed by nucleophilic phosphorylation with tris(trimethylsilyl) phosphite.

N-(Phosphonomethyl)glycine (glyphosate) (**1**) is the active ingredient in Roundup®, a broad spectrum postemergence herbicide.[1-3] In pursuit of discovering new and unique biological properties of glyphosate and its analogs, we initiated an effort to synthesize the thiocarboxylate *S*-esters (*S*-alkyl or *S*-aryl thiocarboxylates) **2** of glyphosate and its dervatives. The labile thiocarboxylate *S*-ester moiety would be readily hydrolyzed *in vivo* and the expected higher lipophilicity of these compounds could provide better penetration through the leaf surface which might convene interesting plant growth regulating properties.

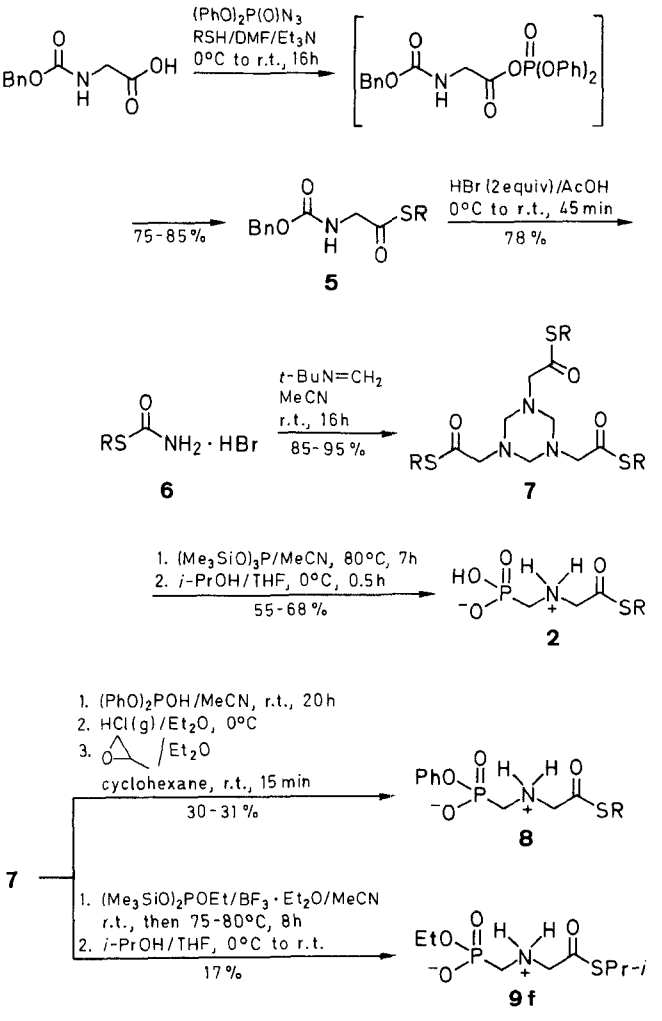


1 X = OH
2 X = SR



3 **4** **2a**

While the *O*-esters of *N*-(phosphonomethyl)glycine are readily synthesized by refluxing the free acid and a catalyst in the corrsponding alcohols, the synthesis of the thiocarboxylate *S*-esters is not trivial. The presence of both the phosphonic acid and the amino moieties in the molecule interfere with the known methodologies for the direct conversion of the carboxylic acid to its thiocarboxylate *S*-esters. Also, the α-substituted nitrogen atom enhances the lability of the thiocarboxylate *S*-esters (*vide infra*) and the poor solubility of glyphosate in organic solvents poses a further restraint on the choice of the reaction conditions. Indeed, attempts using carboxy activating reagents such as thionyl chloride, catecholborane, trimethylsilyl triflate,[4-6] 2-fluoro-1-methylpyridinium tosylate,[7] diphenylphosphoryl azide[8] etc. followed by thiol reagents were tried with no promising results. Chlorothioformate,[9] which itself acts both as the activating and the thiolating reagent, reacted with the protected glyphosate derivative **3** to yield the desired **4** in essentially quantitative yield. However, attempts to remove the trifluoracetyl and the diphenyl ester groups invariably resulted in the destruction of the molecule. In fact, the lability of the molecule and its sensitivity to pH (*vide infra*) make most synthetic routes that involve protecting groups undesirable. A new strategy was sought and is described in the Scheme. *N*-benzyloxycarbonylglycine (Z-glycine) was activated with diphenylphosphoryl azide and the mixed anhydride was reacted with the desired mercaptans to give the corresponding thiocarboxylate *S*-esters **5** in high yields. Control of reaction temperature is critical as too high a temperature causes the Curtius rearrangement to occur and the reaction takes on an entirely different course. The Z-glycine thiol esters thus prepared can be conveniently deprotected (70–90%) with 30% hydrogen bromide in aqueous acetic acid. The products are amine



5–9	R	5–9	R
a	Et	**e**	Ph
b	Me	**f**	*i*-Pr
c	*n*-$C_{10}H_{21}$	**g**	*c*-C_6H_{11}
d	*n*-$C_{18}H_{37}$	**h**	$Me_3SiCH_2CH_2$

Scheme

Table. Glyphosate Thiocarboxylate *S*-Ester Derivatives Prepared

Product	Yield (%)[a]	mp (°C)	Molecular Formula[b]	IR (Nujol) ν (cm^{-1})	NMR (D_2O)	
					^{31}P, δ[c]	^1H, δ, J (Hz)
2a	68	171–172	$C_5H_{12}NO_4PS$ (213.2)	1680, 1430, 1400, 1360, 1300, 1250, 1100	8.42	4.3 (s, 2H), 3.2 (d, 2H, J = 12), 3.1 (q, 2H, J = 6), 1.2 (s, 3H, J = 6)
2b	61	145–155	$C_4H_{10}NO_4PS$ (199.1)	1680, 1480, 1410, 1330, 1250, 1120	8.50	4.3 (s, 2H), 3.2 (d, 2H), J = 13), 2.3 (q, 3H)
2c	55	167–170	$C_{13}H_{28}NO_4PS$ (325.4)	1680, 1530, 1470, 1340, 1270, 1200, 1100	12.4[d]	4.4 (s, 2H), 3.8 (d, 2H, J = 14), 3.1 (t, 2H, J = 6), 1.5–0.9 (m, 19H)[d]
2d	65	145–148	$(C_{21}H_{44}NO_4PS$ (437.6)	1680, 1570, 1540, 1480, 1350, 1260, 1210, 1040	12.69[d]	4.4 (s, 2H), 3.7 (q, 2H, J = 14), 3.0 (t, 2H, J = 6), 1.5–1.0 (m, 35H)[d]
2g	60	195–196	$C_9H_{18}NO_4PS$ (267.2)	1685, 1540, 1320, 1250, 1150, 950	12.40[d]	4.5 (br s, 2H), 3.75 (d, 2H, J = 14), 3.5–3.2 (m, 1H), 2.0–1.2 (m, 10H)[d]
8f	30	174–176	$C_{12}H_{18}NO_4PS$ (303.3)	1680, 1600, 1580, 1430, 1200, 1050	8.40[d]	7.2 (br s, 5H), 4.4 (br s, 2H), 4.0 (br s, 2H, J = 14), 3.5–3.1 (sept, 1H, J = 7), 1.4 (d, J = 7 Hz)[d]
8h	31	198–200	$C_{14}H_{24}NO_4PSSi$ (361.3)	1680, 1520, 1430, 1340, 1250, 1100	8.39[d]	7.15 (br s, 5H), 4.35 (s, 2H), 3.9 (d, 2H, J = 14), 3.3 (m, 2H), 1.0 (m, 1.0 (m, 2H), 0.1 (br s, 9H)[d]
9f	17	184–185	$C_8H_{18}NO_4PS$ (255.2)	1680, 1450, 1380, 1350, 1320, 1270, 1200, 1100	10.2	4.3 (s, 2H), 3.9 (q, 2H, J = 8), 3.7 (sext, 1H, J = 7), 3.2 (d, 2H, J = 12), 1.3 (d, 6H, J = 7), 1.25 (t, 3H, J = 8)

[a] Yield of isolated pure products based on **7** and are not optimized.
[b] All adducts gave satisfactory microanalyses and correct M^+ on FAB-MS.
[c] Chemical shifts (proton decoupled) are reported with positive values being downfield of the ref. standard (85% H_3PO_4).
[d] CF_3CO_2H instead of D_2O as solvent.

hydrobromide salts **6** which are non-hygroscopic and easily isolated. Treatment of the amine salts with *N*-methylene-*tert*-butylamine at room temperature gives the hexahydrotriazines **7** in excellent yields. The novel use of the *N*-methylene-*tert*-butylamine as a methylene group transfer reagent is noteworthy. The reaction is mild, clean and the only byproduct is the *tert*-butylamine hydrobromide which is readily removed by filtration.

The cracking of the hexahydrotriazines[10–12] with tris(trimethylsilyl) phosphite to construct the carbon–phosphorus bond and thus the glyphosate skeleton was very successful after some experimentation. Acetonitrile solvent is critical for this reaction and the labile products were isolated by slowly hydrolyzing the reaction mixture at 0°C in a mixture of 2-propanol/tetrahydrofuran. Good yields (60–70%) and more importantly, high purity of the desired glyphosate thiocarboxylate *S*-ester **2** can be obtained in this manner. Hence the whole synthetic sequence is facile and requires no purification of the intermediates or the products. Other glyphosate thiol ester derivatives can also be prepared using suitable alkyl or aryl phosphites. The monophenyl glyphosate thiocarboxylate **8** was obtained in moderate yields using excess diphenyl phosphite. The reaction was conducted at room temperature to minimize the formation of bis(phosphonomethyl)-glycinate and other side products. The resulting diphenoxyphosphoryl intermediate was acidified and allowed to hydrolyze slowly at room temperature to yield the desired thiol ester. The use of ethyl bis(trimethylsilyl) phosphite as the phosphite reagent was also successful and the thiocarboxylate product **9** was conveniently synthesized. However, in this event boron trifluoride–diethyl ether complex catalyst is required to overcome the substantially slower reaction rate.

The mildness of this synthetic methodology is well exemplified by the lability of the thiocarboxylate *S*-esters synthesized. For example, the phenylthio ester **2e** decomposes rapidly upon isolation after the hydrolysis step, the methylthio ester **2b** has a very short half-life and all other glyphosate thiocarboxylate *S*-esters decompose slowly upon prolonged storage at room temperature. Salts of these thiocarboxylate *S*-esters, however, are even more labile than their parent compounds and their shelf lives are usually less than one day. As expected, these interesting glyphosate derivatives show good to excellent glyphosate-type herbicidal activity.

All reagents were of commercial quality from freshly opened containers. *N*-methylene-*tert*-butylamine was purchased from Pfaltz & Bauer, Inc.. Tris(trimethylsilyl) phosphite was purchased from Petrarch Systems and was redistilled before use. Reactions were generally run under a positive pressure of dry N_2 unless indicated otherwise. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H-NMR were recorded on a Varian 400 MHz or Varian EM-360 60 MHz and ^{31}P-NMR were recorded using a Jeol JNM-FX-100. ^{31}P resonances are reported relative to external standard 85% aq H_3PO_4. Mass spectra were recorded on a Finnigan 4535 spectrometer. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Inc.

Benzyl [(Ethylthio)carbonylmethyl]carbamate (5a); Typical Procedure:

N-Benzyloxycarbonylglycine (5 g, 23.9 mmol) is dissolved in DMF (20 mL) at 0°C and diphenylphosphoryl azide (10.3 mL, 2 equiv) is added via a syringe. EtSH (2.1 mL, 1.2 equiv) is added followed by the addition of Et_2N (6.7 mL, 2 equiv). The solution is stirred at 0°C and let gradually warm to r.t. for a period of 16 h. The solution is washed with sat. aq $NaHCO_3$ (2 × 100 mL) and extracted with $CHCl_3$ (300 mL). The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. A simple filtration with a pad of silica gel using CH_2Cl_2 removed the minor impurities to give a clean product as an oil; yield: 4.8 g (80%).

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.3 (s, 5H), 5.2 (s, 2H), 4.1 (d, 2H, J = 6 Hz), 2.9 (q, 2H, J = 7 Hz), 1.2 (t, 3H, J = 7 Hz).

Other alkylthiol esters such as **5b** (mp 68–69 °C), **5c** (mp 168–169 °C), **5f** (oil), **5e** (oil), **5d** (mp 69–72 °C), **5h** (oil), **5g** (mp 86–89 °C), 2-furylmethyl (mp 62–64 °C) and 4-methoxyphenyl (mp 84–85 °C) are prepared similiarly.

S-Ethyl 2-Aminoethanethioate Hydrobromide (6a); Typical Procedure:

Compound **5a** (1 g, 3.95 mmol) is mixed with 30% HBr in AcOH (2.1 mL, 2 equivs.) at 0 °C. The solution is warmed to r.t. and stirred for 45 min. It is then poured into Et_2O (10 mL). The white solid which precipitate out is filtered and washed with Et_2O (2 × 30 mL). The product (0.62 g, 78%) obtained is slightly hygroscopic but otherwise pure (mp 163–166 °C).

^{1}H-NMR (DMSO-d_6): δ = 4.1 (s, 2H), 3.0 (q, 2H, J = 7 Hz), 1.2 (t, 3H, J = 7 Hz).

Other *S*-alkyl thioester amine hydrobromide salts prepared by this procedure include **6b** (mp 198–199 °C), **6c** (mp 117 °C), **6d** (mp 69–72 °C), **6e** (mp 195–197 °C), **6f** (mp 183–185 °C), **6g** (mp 215 °C).

S,S,S-Triphenyl Hexahydro-1,3,5-triazine-1,3,5-triethanethioate (7e); Typical Procedure:

Compound **6e** (4 g, 16.1 mmol) is mixed with MeCN (50 mL) at r.t. and *N*-methylene-*tert*-butylamine (1.37 g, 1 equiv) is added. A homogeneous solution is obtained which gradually turned cloudy and after ~ 0.5 h, a precipitate is formed. The reaction is stirred overnight for a total of 16 h and Et_2O (50 mL) is added. The precipitate is filtered and washed with another portion of Et_2O (50 mL). The byproduct, *tert*-butylamine hydrobromide (2.1 g, 84.5%) is thus obtained. The filtrate is concentrated *in vacuo*, diluted with CH_2Cl_2 and filtered again to remove the remaining hydrobromide salt. A total of 2.5 g (86%) of pure product (mp 63–64 °C) is obtained in this manner.

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.3 (s, 5H), 3.8 (s, 2H), 3.6 (s, 2H).

Other analogs such as **7d** (mp 63–65 °C) and the **7f** (mp 74–76 °C) are prepared similarly.

S-Ethyl 2-(Phosphonomethylamino)ethanethioate (2a); Typical Procedure:

Compound **7a** (720 mg, 1.83 mmol) is mixed with dry MeCN (6 mL) and 1.6 g (5.4 mmol) of tris(trimethylsilyl) phosphite is added. The solution is then heated to 80 °C. After 5 h, ^{31}P-NMR shows total consumption of tris(trimethylsilyl) phosphite. Another portion of the reagent (0.6 g, 2 mmol) is added and the solution is heated for another 2 h. The reaction is cooled and added dropwise into a mixture of *i*-PrOH (10 mL) and THF (15 mL) at 0 °C. After ~ 0.5 h, a precipitate appears. The solid is centrifuged and washed with Et_2O (2 × 20 mL). It is then dried on a porous plate to give 68% of pure product (mp 171 °C). Other thiol esters of glyphosate (see Table) are synthesized in a similar fashion.

S-Isopropyl 2-[(Phenoxyphosphorylmethyl)amino]ethanethioate (8f); Typical Procedure:

Compound **7f** (1 g, 2.3 mmol) is mixed with dry MeCN (4 mL) and diphenyl phosphite (5.3 mL, 4 equivs.) is added in one portion. The reaction is stirred at r.t. for a total of 20 h. MeCN is removed *in vacuo* and replaced with Et_2O (10 mL). HCl gas was bubbled in at 0 °C for a minute until saturation occurred. Enough cyclohexane is added until a viscous oil separates from the solvent. The oil is then washed 3–4 times with Et_2O/cyclohexane (1:1, 10 mL) to remove excess HCl and diphenyl phosphite. Propylene oxide (5 mL) is added and the solution is stirred to give a homogenous solution (a warm water bath is used). After ~ 15 min volatile components are removed by concentrated *in vacuo* and wet acetone (5 mL, 5% H_2O content) is mixed with the remaining oil. After 5 d, the white crystals are collected, washed with Et_2O (10 mL) and dried to give 660 mg (30%) of monophenyl isopropylthiol ester of glyphosate (see Table).

S-Isopropyl 2-[(Ethoxyphosphorylmethyl)amino]ethanethioate (9f):

Compound **7f** (400 mg, 0.92 mmol) is mixed with dry MeCN (4 mL) and ethylbis(trimethylsilyl)phosphite (981 mg, 1.4 equiv) is added followed by a drop of $BF_3 \cdot Et_2O$ solution at r.t. The solution is then heated to 75–80 °C. The reaction is ~ 80% complete after 4.5 h according to ^{31}P-NMR. After heating for a total of 8 h, the solution is cooled and added dropwise to a mixture of *i*-PrOH (15 mL) and THF (10 mL) at 0 °C. The solution is warmed to r.t. and concentrated to half of the original volume with N_2. Et_2O (15 mL) is added and the mixture is allowed to stand for 4 h. The solution is centrifuged and the residue washed several times with Et_2O (10 mL) to remove residual impurities. The product is obtained as a white solid (see Table).

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