A Facile Synthesis of Derivatives of (1,3,4-Thiadiazol-2-yl)glycine and Its Phosphonyl Analogue

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Abstract: The adducts formed by 4-functionally-substituted 2-aryl-5-hydrazino-1,3-oxazoles and aryl isothiocyanates recyclize on heating to produce the hitherto unknown derivatives of (1,3,4-thiadiazol-2-yl)glycine and its phosphonyl analogue.

Key words: α-aminocarboxylic acids, α-aminoalkylphosphonic acids, (1,3,4-thiadiazol-2-yl)glycine, 1,3-oxazoles, 3,3-dichloroacrylates, 2,2,2-trichloroethylphosphonates, aryl isothiocyanates

In recent years, modified α-aminocarboxylic acids containing heterocyclic substituents at the α and β positions relative to the carboxy group have found extensive application in biochemical research as well as in the search for bioactive substances (see recent publications[1–6] and references therein). Systems of this kind can be exemplified by α-amino acid derivatives containing a pyridine,[4,7] pyrimidine,[1,3,8] or purine[3] residue as well as the fragments of some five-membered heterocycles such as pyrazole,[4,6] 1,2-oxazole,[4,9] 1,2-thiazole,[10] 1,2,3-triazole,[6] and 1,2,5-thiadiazole.[11]

We have developed an original synthetic access to the hitherto unknown functional derivatives of 1,3,4-thiadiazol-2-ylglycine starting from previously obtained[12] alkyl 2-acylamino-3,3-dichloroacrylates **1a**–**c** as shown in Scheme 1. First, compounds **1a**–**c** were treated with an excess of hydrazine hydrate to yield substituted 5-hydrazino-1,3-oxazoles **2a**–**c**, whose structures were confirmed by IR and ^{1}H NMR spectroscopy (Table 1). Much the same cyclization was investigated before in the case of 2-acylamino-3,3-dichloroacrylonitriles, the close analogues of compounds **1a**–**c**.[13,14]

Substrates **2a**–**c**, if reacted with aryl isothiocyanates, first produce adducts **3a**–**h** apparently able to form prototropic tautomers **4a**–**h** which recyclize on heating to give the corresponding (1,3,4-thiadiazol-2-yl)glycine derivatives **5a**–**h**. The molecular structure of compound **5d** (Figure 1 and Table 2) was determined by a single-crystal X-ray diffraction. The S(1)N(1)N(2)C(1)C(2)–N(4)H–C(13–18) bond system is approximately planar; the deviation from the least-square plane are in the range 0.009–0.225 Å (average 0.092 Å). The thiadiazole ring S(1)N(1)N(2)C(1)C(2) makes with the N(4)C(2)H(4)C(13) plane dihedral angle of 9.9°, whereas the C(13–18) benzene ring is twisted out of this plane by only 4.6°.

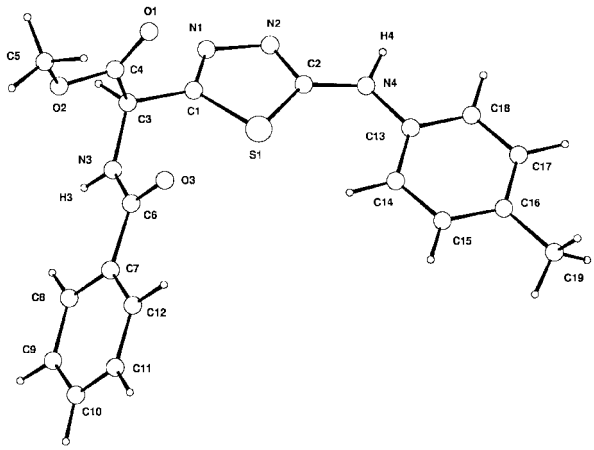

Figure 1 Perspective view and labelling scheme for the molecule **5d** (*S*-enantiomer)

In a crystal of racemate **5d**, (*R*)-enantiomer molecules are joined into centrosymmetric dimers by the hydrogen bonds N(4)–H(4)…N(2) [N(4)…N(2) 2.891(5), H(4)…N(2) 1.93(4), and N(4)–H(4) 0.97(5) Å, N(4)H(4) N(2) 172(2)°]. In turn, the dimers form an endless chain by means of the hydrogen bonds N(3)-H(3)… O(3) with (*S*)-enantiomer molecules [the respective distances and angle are: N(3)…O(3) 2.928(5), H(3)…O(3) 1.99(4), and N(3)–H(3) 1.00(4) Å, N(3)H(3)O(3) 155(2)°].

Thus, the conversion **3** → → **5** is supported by solid evidence. A similar recyclization leading to 1,3,4-oxadiazole derivatives has recently been found to occur on heating the 2-aryl-5-hydrazino-1,3-oxazole-4-carbonitriles in acetic acid.[14] By structural features, the conversion **3** → **4** → **5** belongs to a particular rearrangement type studied by Boulton, Katritzky et al.[15] which involves azole side chains. Of great preparative importance is not only the conversion **3** → **4** → **5** but also further modification of recyclization products using sodium hydroxide which furnishes previously unknown 2-acylaminomethyl-5-arylamino-1,3,4-thiadiazoles **6a**,**g** (Scheme 1).

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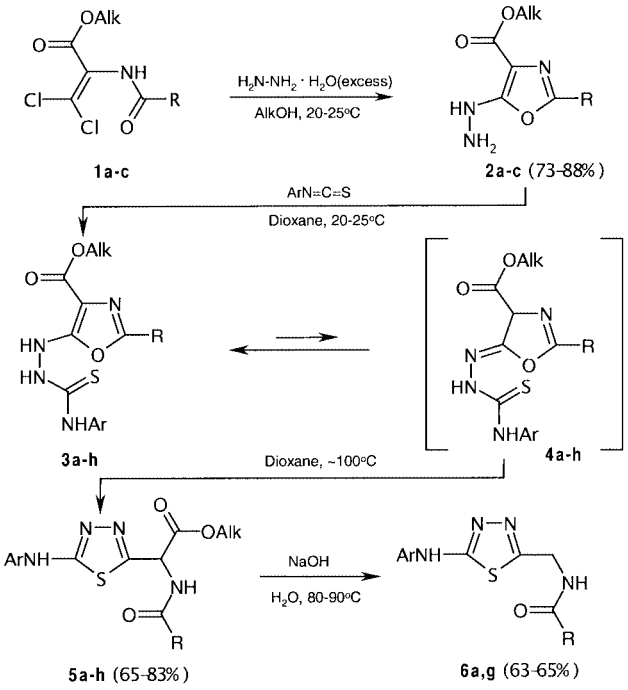


1-6	a	b	c	d	e	f	g	h
R	Ph	4-MeC_6H_4	Ph	Ph	Ph	Ph	4-MeC_6H_4	4-MeC_6H_4
Alk	Me	Me	Et	Me	Me	Et	Me	Me
Ar	Ph	Ph	Ph	4-MeC_6H_4	4-$MeOC_6H_4$	4-MeC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$

Scheme 1

Table 1 Spectroscopic Data of Compounds **2**, **3**, **5**, **6**, **9**, **10**

Compound	IR (KBr) (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, *J* (Hz)
2a	1670 (OC=O), 360 (NH, NH_2)	3.75 (s, 3 H, CH_3), 4.70 (br s, 2 H, NH_2), 7.40–7.88 (m, 5 H, C_6H_5), 8.09 (br s, 1 H, NH)
2b	1665 (OC=O), 3200 (NH, NH_2)	2.34 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 4.80 (br s, 2 H, NH_2), 7.31–7.73 (m, 4 H, C_6H_4), 8.27 (br s, 1 H, NH)
2c	1660 (OC=O), 3320 (NH, NH_2)	1.31 (t, 3 H, CH_3), 4.22 (q, 2 H, CH_2), 4.74 (br s, 2 H, NH_2), 7.18–7.86 (m, 5 H, C_6H_5), 8.09 (br s, 1 H, NH)
3a	1660 (OC=O), 3330 (NH)	3.80 (s, 3 H, CH_3), 7.14–7.83 (m, 10 H, 2 × C_6H_5), 9.35 (br s, 1 H, NH), 9.93 (s, 1 H, NH), 10.04 (s, 1 H, NH)
3d	1660 (OC=O), 3330 (NH)	2.27 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 7.14–7.81 (m, 9 H, C_6H_5, C_6H_4), 9.49 (s, 1 H, NH), 9.95 (s, 1 H, NH), 10.03 (s, 1 H, NH)
5a	1645 (NC=O), 1760 (OC=O), 3330 (NH)	3.73 (s, 3 H, CH_3), 5.91 (d, 1 H, *J* = 7.2, CH), 7.00–7.93 (m, 10 H, 2 × C_6H_5), 9.74 (d, 1 H, *J* = 7.2, NH), 10.37 (s, 1 H, NH)
5b	1645 (NC=O), 1750 (OC=O), 3290 (NH)	2.36 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 5.87 (d, 1 H, *J* = 7.2, CH), 7.00–7.80 (m, 9 H, C_6H_5, C_6H_4), 9.67 (d, 1 H, *J* = 7.2, NH), 10.36 (s, 1 H, NH)
5c	1630 (NC=O), 1745 (OC=O), 3300 (NH)	1.24 (t, 3 H, CH_3), 4.20 (q, 2 H, CH_2), 5.77 (d, 1 H, *J* = 7.2, CH), 6.95–7.93 (m, 10 H, 2 × C_6H_5), 9.66 (d, 1 H, *J* = 7.2, NH), 10.29 (s, 1 H, NH)
5d[a]	1665 (NC=O), 1760 (OC=O), 3350 (NH)	2.27 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3), 5.79 (d, 1 H, *J* = 7.2, CH), 7.09–7.92 (m, 9 H, C_6H_5, C_6H_4), 9.67 (d, 1 H, *J* = 7.2, NH), 10.17 (s, 1 H, NH)
5e	1640 (NC=O), 1750 (OC=O), 3340 (NH)	3.73 (s, 6 H, 2 × CH_3), 5.73 (d, 1 H, *J* = 7.2, CH), 6.85–7.95 (m, 9 H, C_6H_5, C_6H_4), 9.64 (d, 1 H, *J* = 7.2, CH), 10.07 (s, 1 H, NH)

Table 1 Spectroscopic Data of Compounds **2**, **3**, **5**, **6**, **9**, **10** (continued)

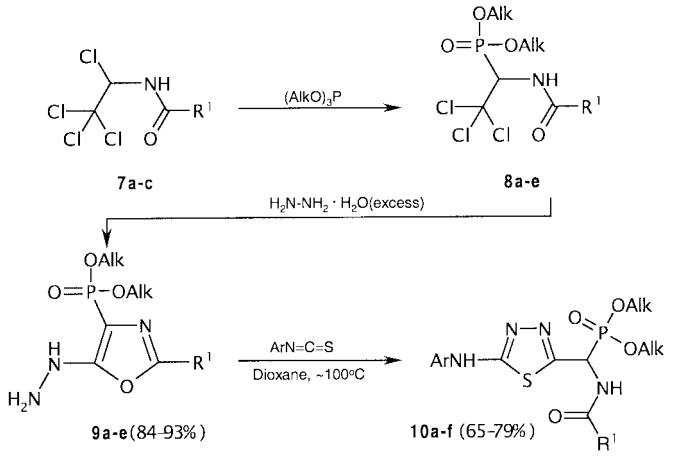
Compound	IR (KBr) (cm^{-1})	^1H NMR (DMSO-d_6/TMS) δ, *J* (Hz)
5f	1645 (NC=O), 1745 (OC=O), 3260 (NH)	1.24 (t, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 4.20 (q, 2 H, CH_2), 5.76 (d, 1 H, *J* = 7.2, CH), 7.10–7.90 (m, 9 H, C_6H_5, C_6H_4), 9.62 (d, 1 H, *J* = 7.2, NH), 10.18 (s, 1 H, NH)
5g	1635 (NC=O), 1745 (OC=O), 3265 (NH)	2.25 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 5.85 (d, 1 H, *J* = 7.2, CH), 7.15–7.82 (m, 8 H, 2 × C_6H_4), 9.65 (d, 1 H, *J* = 7.2, NH), 10.25 (s, 1 H, NH)
5h	1645 (NC=O), 1750 (OC=O), 3290 (NH)	2.36 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 5.82 (d, 1 H, *J* = 7.2, CH), 6.91–7.80 (m, 8 H, 2 × C_6H_4), 9.64 (d, 1 H, *J* = 7.2, NH), 10.14 (s, 1 H, NH)
6a	1645 (NC=O), 3220 (NH)	4.69 (d, 2 H, CH_2), 6.96–7.90 (m, 10 H, 2 × C_6H_5), 9.37 (t, 1 H, NH), 10.26 (s, 1 H, NH)
6g	1640 (NC=O), 3260 (NH)	2.27 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 4.64 (d, 2 H, *J* = 6.8, CH_2), 7.10–7.76 (m, 8 H, 2 × C_6H_4), 9.19 (t, 1 H, NH), 10.04 (s, 1 H, NH)
9a	1250 (P=O), 3260 (NH)	3.69 (d, 6 H, $J_{H,P}$ = 12.1, 2 × CH_3), 4.80 (br s, 2 H, NH_2), 7.45–7.86 (m, 6 H, C_6H_5, NH)
9c	–	3.67 (d, 6 H, $J_{H,P}$ = 12.0, 2 × CH_3), 4.75 (br s, 2 H, NH_2), 7.03–7.64 (m, 8 H, C_6H_5, CH=CH, NH)
10a	–	3.50 (d, 6 H, 2 × CH_3), 5.56 (m, 1 H, CH), 6.90–8.17 (m, 11 H, 2 × C_6H_5, NH), 10.22 (br s, 1 H, NH),
10b	1250 (P=O), 1645 (NC=O), 3220 (NH)	2.38 (s, 3 H, CH_3), 3.77 (d, 6 H, $J_{H,P}$ = 10.8, 2 × CH_3), 6.13 (dd, 1 H, *J* = 9.3, $J_{H,P}$ = 21.5, CH), 6.95–7.83 (m, 9 H, C_6H_5, C_6H_4), 9.40 (d, 1 H, *J* = 9.3, NH), 10.30 (s, 1 H, NH)
10c	–	3.76 (t, 6 H, 2 × CH_3), 5.97 (dd, 1 H, *J* = 6.4, $J_{H,P}$ = 16.0, CH), 6.86–7.59 (m, 12 H, 2 × C_6H_5, CH=CH), 9.29 (d, 1 H, *J* = 6.4, NH), 10.34 (s, 1 H, NH)
10d	–	1.25 (m, 6 H, 2 × CH_3), 4.12 (m, 4 H, 2 × CH_2), 6.06 (dd, 1 H, *J* = 8.3, $J_{H,P}$ = 20.8, CH), 6.97–7.91 (m, 10 H, 2 × C_6H_5), 9.49 (d, 1 H, *J* = 8.3, NH), 10.32 (s, 1 H, NH)
10e	1265 (P=O), 1655 (NC=O), 3240 (NH)	1.20 (m, 6 H, 2 × CH_3), 4.11 (m, 4 H, CH_2), 5.97 (dd, 1 H, *J* = 7.2, $J_{H,P}$ = 19.0, CH), 6.90–7.59 (m, 12 H, 2 × C_6H_5, CH=CH), 9.28 (d, 1 H, *J* = 7.2, NH), 10.42 (s, 1 H, NH)
10f[a]	–	2.28 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.77 (d, 6 H, $J_{H,P}$ = 11.4, 2 × CH_3), 6.04 (dd, 1 H, *J* = 8.1, $J_{H,P}$ = 20.0, CH), 7.09–7.85 (m, 8 H, 2 × C_6H_4), 9.40 (d, 1 H, *J* = 8.1, NH), 10.21 (s, 1 H, NH)

[a] For compounds **5d** and **10f**, the respective ^{13}C NMR signals for NC=O, C(2)=N, C(5)=N were registered (DMSO-d_6/TMS): δ = 154.26, 166.36, 168.62 and 153.56, 165.97, 166.26.

Table 2 Selected X-Ray Bond Lengths and Bond Angles of Compound **5d**

S(1)–C(1)	1.735(4)	C(1)–S(1)–C(2)	87.3(2)
S(1)–C(2)	1.732(4)	N(2)–N(1)–C(1)	113.4(3)
N(1)–N(2)	1.383(5)	N(1)–N(2)–C(2)	112.1(3)
N(1)–C(1)	1.284(5)	C(3)–N(3)–C(6)	119.5(3)
N(2)–C(2)	1.325(5)	C(2)–N(4)–C(13)	130.5(4)
N(3)–C(3)	1.463(5)	S(1)–C(1)–N(1)	114.1(3)
N(3)–C(6)	1.339(5)	S(1)–C(2)–N(2)	113.1(3)
N(4)–C(2)	1.347(5)		
N(4)–C(13)	1.409(5)		
C(6)–C(7)	1.493(5)		

By analogy with the synthesis of new glycine derivatives **5a**–**h**, we have managed to obtain structurally related compounds, aminomethylphosphonic acid derivatives **10a**–**f** (Scheme 2). At first, the available *N*-(1,2,2,2-tetrachloroethyl)carboxamides **7a**–**c** were subjected to the Arbuzov reaction with trialkyl phosphites and then the resulting phosphonates **8a**–**e** were treated successively with excess hydrazine hydrate[16] and an equimolar amount of the corresponding aryl isothiocyanate. The expected reaction course, namely, the formation of **9** followed by the recyclization **9** → → **10** is corroborated by the ^1H NMR spectra of the final products **10a**–**f** which suggest the presence of the characteristic moiety PCHNH (Table 1). Furthermore, **10f** like its phosphorus-free analogue **5d**, exhibits two downfield ^{13}C NMR signals (δ = >165), which can be assigned to the atoms C-2 and C-5 of the electron-deficient 1,3,4-thiadiazole ring. The conversion **9** → **10** adds to a list of the known methods for the synthesis of hetaryl-substituted α-aminoalkylphosphonic acids, which have been attracting considerable attention recently in search of various bioregulators (see, e.g., the monograph[17] and the main papers[18–22]).



7-10	a	b	c	d	e	f
R^1	Ph	4-MeC_6H_4	PhCH=CH	Ph	PhCH=CH	4-MeC_6H_4
Alk	Me	Me	Me	Et	Et	Me
Ar	Ph	Ph	Ph	Ph	Ph	4-MeC_6H_4

Scheme 2

The applicability and scope for the synthetic approaches represented in Schemes 1 and 2 as well as modification aspects for compounds **5** and **10** will be considered elsewhere.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 and 75.43 MHz, respectively, using TMS as an internal standard. IR spectra were measured on a Specord M-80 spectrometer for KBr discs.

Alkyl 2-Aryl-5-hydrazino-1,3-oxazole-4-carboxylates 2a–c; General Procedure

To a solution of enamide **1a–c** (10 mmol) obtained by the known procedure[12] in MeOH or EtOH (20–30 mL) was added hydrazine hydrate (35 mmol). The mixture was allowed to stand at r.t. for 24 h. After filtering off hydrazine hydrochloride, the solvent was evaporated in vacuo, and the residue was treated with H_2O, filtered off, dried, and purified by recrystallization from MeOH or benzene (Table 1).

Methyl 5-Hydrazino-2-phenyl-1,3-oxazole-4-carboxylate (2a)

Compound **2a** was prepared following the general procedure from **1a** (2.74 g) in MeOH (20 mL). The product was purified by recrystallization from MeOH; yield: 1.98 g (85%); colorless crystals; mp 190–191 °C.

Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.84; H, 5.02; N, 18.37.

Methyl 5-Hydrazino-2-(4-methylphenyl)-1,3-oxazole-4-carboxylate (2b)

Compound **2b** was prepared following the general procedure from **1b** (2.88 g) in MeOH (20 mL). The product was purified by recrystallization from MeOH; yield: 2.17 g (88%); colorless crystals; mp 195–196 °C.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.40; H, 5.32; N, 17.19.

Ethyl 5-Hydrazino-2-phenyl-1,3-oxazole-4-carboxylate (2c)

Compound **2c** was prepared following the general procedure from **1c** (2.88 g) in EtOH (30 mL). The product was purified by recrystallization from benzene; yield: 1.8 g (73%); colorless crystals; mp 122–123 °C.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.51; H, 5.47; N, 16.85.

Alkyl 2-Aryl-5-(4-arylthiosemicarbazido)-1,3-oxazole-4-carboxylates 3a–h; General Procedure

To a solution of compound **2a–c** (10 mmol) in anhyd dioxane (20 mL), the corresponding aryl isothiocyanate (10.5 mmol) was added. The mixture was allowed to stand at r.t. for 72 h. The resulting precipitate was filtered off, washed with dioxane, and dried in vacuo. Analytical and spectral data were obtained for compounds **3a**,**d**, whereas their analogues **3b**,**c**,**e**–**h** were immediately used in the preparation of compounds **5b**,**c**,**e**–**h** without isolation (Table 1).

Methyl 2-Phenyl-5-(4-phenylthiosemicarbazido)-1,3-oxazole-4-carboxylate (3a)

Compound **3a** was prepared following the general procedure from **2a** (2.33 g) and phenyl isothiocyanate (1.42 g) in anhyd dioxane (20 mL); yield: 3.17 g (86%); colorless crystals; mp 157–158 °C.

Anal. Calcd for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21; S, 8.70. Found: C, 58.74; H 4.61; N, 15.06; S, 8.43.

Methyl 5-[(4-Methylphenyl)thiosemicarbazido]-2-phenyl-1,3-oxazole-4-carboxylate (3d)

Compound **3d** was prepared following the general procedure from **2a** (2.33 g) and 4-methylphenyl isothiocyanate (1.57 g) in anhyd dioxane (20 mL); yield: 3.09 g (81%); colorless crystals; mp 151–152 °C.

Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; S, 8.38. Found: C, 59.85; H, 4.99; N, 14.59; S, 8.45.

Alkyl 5-Arylamino-1,3,4-thiadiazol-2-yl(acylamino)acetates 5a–h; General Procedure

To a solution of compound **2a–c** (10 mmol) in anhyd dioxane (15 mL) was added the corresponding aryl isothiocyanate (11 mmol). The mixture was refluxed for 8 h and dioxane was removed in vacuo. For crystallization, the residue was treated with H_2O; then it was filtered off and recrystallized from an appropriate solvent (Table 1).

Methyl 5-Anilino-1,3,4-thiadiazol-2-yl(benzoylamino)acetate (5a)

*From **2a***: Compound **5a** was prepared following the general procedure from **2a** (2.33 g) and phenyl isothiocyanate (1.49 g) in anhyd dioxane. The product was recrystallized from MeOH; yield: 2.6 g (71%); colorless crystals; mp 181–182 °C.

Anal. Calcd for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21; S, 8.70. Found: C, 59.03; H, 4.36; N, 14.99; S, 8.79.

*From **3a***: This compound was also obtained from **3a** (3.28 g) by boiling in dioxane (15 mL) for 8 h. The product was isolated as described in the general procedure; yield: 2.53 g (69%); mp 180–181 °C. The IR spectra for the samples of compound **5a** obtained from **2a** and **3a** were identical.

Methyl 5-Anilino-1,3,4-thiadiazol-2-yl(4-methylbenzoylamino)acetate (5b)

Compound **5b** was prepared following the general procedure from **2b** (2.47 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from MeOH; yield: 2.48 g (65%); pale yellow crystals; mp 201–203 °C.

Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; S, 8.38. Found: C, 59.55; H, 4.98; N, 14.53; S, 8.29.

Ethyl 5-Anilino-1,3,4-thiadiazol-2-yl(benzoylamino)acetate (5c)

Compound **5c** was prepared following the general procedure from **2c** (2.47 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from EtOH; yield: 2.78 g (73%); pale yellow crystals; mp 213–214 °C.

Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; S, 8.38. Found: C, 59.45; H, 4.56; N, 14.56; S, 8.37.

Methyl Benzoylamino[5-(4-toluidino)-1,3,4-thiadiazol-2-yl]acetate (5d)

*From **2a***: Compound **5d** was prepared following the general procedure from **2a** (2.33 g) and 4-methylphenyl isothiocyanate (1.64 g). The product was purified by recrystallization from benzene; yield: 2.93 g (77%); pale yellow crystals; mp 173–175 °C.

Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; S, 8.38. Found: C, 59.52; H, 4.87; N, 14.88; S, 8.53.

*From **3d***: This compound was also obtained from **3d** (3.82 g) by boiling in dioxane (15 mL) for 8 h. The product was isolated as described in the general procedure; yield: 3.01 g (79%).

Methyl Benzoylamino[5-(4-methoxyanilino)-1,3,4-thiadiazol-2-yl]acetate (5e)

Compound **5e** was prepared following the general procedure from **2a** (2.33 g) and 4-methoxyphenyl isothiocyanate (1.82 g). The product was purified by recrystallization from MeOH; yield: 3.02 g (76%), colorless crystals; mp 191–192 °C.

Anal. Calcd for $C_{19}H_{18}N_4O_4S$: C, 57.28; H, 4.55; N, 14.06; S, 8.05. Found: C, 59.53; H, 4.62; N, 14.17; S, 7.89.

Ethyl Benzoylamino[5-(4-toluidino)-1,3,4-thiadiazol-2-yl]acetate (5f)

Compound **5f** was prepared following the general procedure from **2c** (2.47 g) and 4-methylphenyl isothiocyanate (1.64 g). The product was purified by recrystallization from EtOH; yield: 3.09 g (78%); pale yellow crystals; mp 193–194 °C.

Anal. Calcd for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13; S, 8.09. Found: C, 60.72; H, 5.15; N, 14.03; S, 8.23.

Methyl 4-Methylbenzoylamino[5-(4-toluidino)-1,3,4-thiadiazol-2-yl]acetate (5g)

Compound **5g** was prepared following the general procedure from **2b** (2.47 g) and 4-methylphenyl isothiocyanate (1.64 g). The product was purified by recrystallization from MeOH; yield: 3.29 g (83%); colorless crystals; mp 207–209 °C.

Anal. Calcd for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13; S, 8.09. Found: C, 60.67; H, 5.03; N, 14.31; S, 8.03.

Methyl 4-Methylbenzoylamino[5-(4-methoxyanilino)-1,3,4-thiadiazol-2-yl]acetate (5h)

Compound **5h** was prepared following the general procedure from **2b** (2.47 g) and 4-methoxyphenyl isothiocyanate (1.82 g). The product was purified by recrystallization from dioxane; yield: 3.13 g (76%); pale yellow crystals; mp 207–209 °C.

Anal. Calcd for $C_{20}H_{20}N_4O_4S$: C, 58.24; H, 4.89; N, 13.58; S, 7.77. Found: C, 58.49; H, 5.11; N, 13.77; S, 8.10.

2-Acylaminomethyl-5-arylamino-1,3,4-thiadiazoles 6a,g; General Procedure

A solution of compound **5a**,**g** (10 mmol) in 10% aq NaOH (80 mL) was heated at 80–90 °C under stirring for 8 h. The mixture was acidified with glacial AcOH to pH ca. 4–5. The precipitate formed was filtered off and recrystallized from MeOH (Table 1).

5-Anilino-2-(benzoylamino)methyl-1,3,4-thiadiazole (6a)

Compound **6a** was prepared following the general procedure from **5a** (3.67 g). The product was purified by recrystallization from MeOH; yield: 1.95 g (63%); colorless crystals; mp 221–222 °C.

Anal. Calcd for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05; S, 10.33. Found: C, 62.17; H, 4.61; N, 17.85; S, 10.25.

2-(4-Methylbenzoylamino)methyl-5-(4-toluidino)-1,3,4-thiadiazole (6g)

Compound **6g** was prepared following the general procedure from **5g** (3.96 g). The product was purified by recrystallization from MeOH; yield: 2.16 g (65%); colorless crystals; mp 249–250 °C.

Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.55; S, 9.47. Found: C, 64.07; H, 5.53; N, 16.64; S, 9.39.

Dialkyl 2-Aryl(styryl)-5-hydrazino-1,3-oxazol-4-ylphosphonates 9a–e; General Procedure

To a solution of compound **8a**–**e** (10 mmol) in THF (15 mL) was added hydrazine hydrate (45 mmol) and the mixture was stirred at 20–25 °C for 72 h. Then the solvent was removed in vacuo and the residue was treated with H_2O. Compounds **9a**–**d** were purified by crystallization; compound **9e** was extracted from aq emulsion with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), and freed of the solvent in vacuo to give a thick oily substance which was used further without additional purification (Table 1).

Dimethyl 5-Hydrazino-2-phenyl-1,3-oxazol-4-ylphosphonate (9a)

Compound **9a** was prepared as described before.[16]

Dimethyl 5-Hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-ylphosphonate (9b)

Compound **9b** was prepared following the general procedure from **8b** (3.74 g). The product was purified by recrystallization from aq EtOH; yield: 2.58 g (87%); colorless crystals; mp 120–121 °C.

Anal. Calcd for $C_{12}H_{16}N_3O_4P$: C, 48.49; H, 5.43; N, 14.14; P, 10.42. Found: C, 48.56; H, 5.58; N, 13.86; P, 10.12.

Dimethyl 5-Hydrazino-2-styryl-1,3-oxazol-4-ylphosphonate (9c)
Compound **9c** was prepared as described before.[16]

Diethyl 5-Hydrazino-2-phenyl-1,3-oxazol-4-ylphosphonate (9d)
Compound **9d** was prepared following the general procedure from **8d** (3.88 g). After evaporating the solvent in vacuo, the residue was treated with hexane, filtered off, and recrystallized from benzene; yield: 2.6 g (84%); colorless crystals; mp 78–80 °C.

Anal. Calcd for $C_{13}H_{18}N_3O_4P$: C, 50.16; H, 5.83; N, 13.50; P, 9.95. Found: C, 50.33; H, 6.02; N, 13.45; P, 9.91.

Diethyl 5-Hydrazino-2-styryl-1,3-oxazol-4-ylphosphonate (9e)
Compound **9e** was prepared following the general procedure from **8e** (4.14 g); yield: 3.13 g (93%); pale yellow oil which was used without purification in the preparation of **10e**.

Anal. Calcd for $C_{15}H_{20}N_3O_4P$: C, 53.41; H, 5.98; N, 12.46; P, 9.18. Found: C, 53.62; H, 6.13; N, 12.45; P, 9.31.

Dialkyl 5-(Arylamino-1,3,4-thiadiazol-2-yl)(acylamino)methylphosphonates 10a–f; General Procedure
A solution of compound **9a–e** (10 mmol) and aryl isothiocyanate (11 mmol) in dioxane (10 mL) was boiled for 12 h. The precipitate formed was filtered off, dried in vacuo, and recrystallized from MeOH or EtOH (Table 1).

Dimethyl 5-(Anilino-1,3,4-thiadiazol-2-yl)(benzoylamino)methylphosphonate (10a)
Compound **10a** was prepared following the general procedure from **9a** (2.83 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from MeOH; yield: 3.3 g (79%); colorless crystals; mp 194–195 °C.

Anal. Calcd for $C_{18}H_{19}N_4O_4PS$: C, 51.67; H, 4.58; N, 13.39; P, 7.40; S, 7.66. Found: C, 51.83; H, 4.61; N, 13.31; P, 7.40; S, 7.66.

Dimethyl 5-(Anilino-1,3,4-thiadiazol-2-yl)(4-methylbenzoylamino)methylphosphonate (10b)
Compound **10b** was prepared following the general procedure from **9b** (2.97 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from MeOH; yield: 3.07 g (71%); colorless crystals; mp 133–135 °C.

Anal. Calcd for $C_{19}H_{21}N_4O_4PS$: C, 52.77; H, 4.89; N, 12.96; P, 7.16; S, 7.41. Found: C, 52.58; H, 5.08; N, 12.79; P, 7.05; S, 7.31.

Dimethyl 5-(Anilino-1,3,4-thiadiazol-2-yl)(cinnamoylamino)methylphosphonate (10c)
Compound **10c** was prepared following the general procedure from **9c** (3.09 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from MeOH; yield: 3.34 g (75%); pale yellow crystals; mp 160–161 °C.

Anal. Calcd for $C_{20}H_{21}N_4O_4PS$: C, 54.05; H, 4.76; N, 12.61; P, 6.97; S, 7.21. Found: C, 54.15; H, 4.58; N, 12.52; P, 6.86; S, 7.10.

Diethyl 5-(Anilino-1,3,4-thiadiazol-2-yl)(benzoylamino)methylphosphonate (10d)
Compound **10d** was prepared following the general procedure from **9d** (3.11 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from EtOH; yield: 3.48 g (78%); pale yellow crystals; mp 186–187 °C.

Anal. Calcd for $C_{20}H_{23}N_4O_4PS$: C, 53.81; H, 5.19; N, 12.55; P, 6.94; S, 7.18. Found: C, 54.11; H, 5.43; N, 12.43; P, 6.83; S, 7.09.

Diethyl 5-(Anilino-1,3,4-thiadiazol-2-yl)(cinnamoylamino)methylphosphonate (10e)
Compound **10e** was prepared following the general procedure from **9e** (3.37 g) and phenyl isothiocyanate (1.49 g). The product was purified by recrystallization from EtOH; yield: 3.63 g (77%); pale yellow crystals; mp 171–173 °C.

Anal. Calcd for $C_{22}H_{25}N_4O_4PS$: C, 55.92; H, 5.33; N, 11.86; P, 6.56; S, 6.79. Found: C, 56.10; H, 5.58; N, 11.74; P, 6.42; S, 6.60.

Dimethyl (4-Methylbenzoylamino)[5-(4-toluidino)-1,3,4-thiadiazol-2-yl]methylphosphonate (10f)
Compound **10f** was prepared following the general procedure from **9b** (2.97 g) and 4-methylphenyl isothiocyanate (1.64 g). The product was purified by recrystallization from MeOH; yield: 2.91 g (65%); colorless crystals; mp 130–132 °C.

Anal. Calcd for $C_{20}H_{23}N_4O_4PS$: C, 53.81; H, 5.19; N, 12.55; P, 6.94; S, 7.18. Found: C, 53.97; H, 4.91; N, 12.45; P, 6.82; S, 7.03.

X-Ray Structure Determination of 5d
Crystal Data: $C_{19}H_{18}N_4O_3S$, M = 382.44, monoclinic, a = 9.747(3), b = 20.078(7), c = 9.931(2) Å, β = 100.85(3), V = 1908.8 Å^3, Z = 4, d = 1.331 gcm^{-3}, space group $P2_1/c$, μ = 1.87 cm^{-1}, F(000) = 800.6, sphere with d = 0.36 mm.

Data Collection: All crystallographic measurements were performed at 20 °C on a CAD-4 Enraf-Nonius diffractometer operating in the ω-2θ scan mode (the ratio of the scanning rates ω/2θ = 1.2). Intensity data were collected within the range $2 < \theta < 25°$, ($0 < h < 11$, $0 < k < 23$, $-11 < l < 11$) using graphite-monochromated Mo-K_α radiation (λ = 0.71069 Å). Intensities of 3674 reflections (3341 unique reflections, R_{int} = 0.033) were measured. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction based on azimuthal scan data was applied.[23]

Structure Solution and Refinement: The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package.[24] In the refinement 1655 reflections with $I > 3\sigma(I)$ were used.

All hydrogen atoms were located in the difference Fourier maps and included in the final refinements with fixed positional and thermal parameters [only H (3) and H(4) atoms participating in hydrogen bonding were refined isotropically]. Convergence was obtained at $R1$ = 0.053 and $wR2$ = 0.053, GOF = 1.162 (252 refined parameters; obs/variabl. = 6.6; the largest and minimal peaks in the final difference map, 0.33 and –0.27 eÅ^{-3}). Chebyshev weighting scheme[25] with the parameters 1.26, 0.82, and 1.00 was used.[26]

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