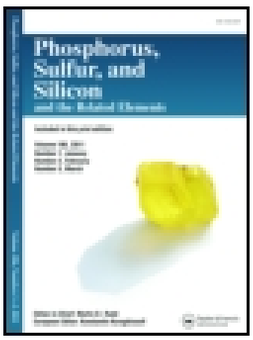

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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

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To cite this article: Angel Zamudio-Medina, Nury Pérez-Hernández, José Luis Castrejón-Flores, Susana Romero-García, Heriberto Prado-García, Angel Bañuelos-Hernández & Marco Franco-Pérez (2021): Obtaining symmetric and asymmetric bisphosphoramidates and bisphosphoramidothioates by a single step multicomponent reaction, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2021.1878358

To link to this article: https://doi.org/10.1080/10426507.2021.1878358

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2021.1878358

Obtaining symmetric and asymmetric bisphosphoramidates and bisphosphoramidothioates by a single step multicomponent reaction

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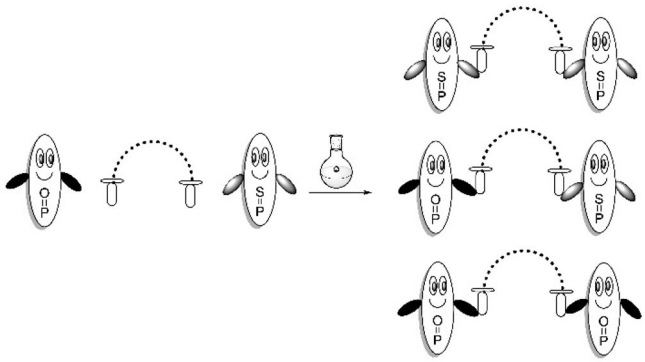
ABSTRACT

We present a new single-step multicomponent reaction strategy for the synthesis of symmetric and (novel) asymmetric bisphosphoramidate and bisphosphoramidothioate derivatives. Reactions proceed under routine experimental conditions, do not require the aid of any catalyst, and provide moderate yields after a short time. We synthesized 18 different compounds, 10 of them for the first time. The cytotoxic activity of our adducts was assessed by measuring their inhibitory capacity (IC_{50}) against two different cell lines, the A549 (lung cancer cells) and the SW1353 (chondrosarcoma cells).

ARTICLE HISTORY
Received 23 November 2020
Accepted 16 January 2021

KEYWORDS
Multicomponent reaction; bisphosphoramidates; bisphosphoramidothioates; symmetric and asymmetric derivatives; cytotoxicity; double addition–elimination

GRAPHICAL ABSTRACT



Introduction

Organophosphates are important organic compounds with broad applications in science and engineering,[1] such as additives in polymers,[2] pesticides in agriculture[3–6] and drugs in pharmaceutics,[7] among others. Particularly, phosphoramidates and bisphosphoramidates, formed by one and two nitrogen–phosphorus–oxygen (N–P = O) bond sequence(s) respectively, display several applications in medical science as antivirals,[8–11] antineoplastics,[12–15] bactericides[16–18] and steroids,[19] as well as DNA intercalators.[20–23] As a representative example, remdesivir, the only approved antiviral against COVID-19,[24–27] the disease caused by the SARC-CoV-2 virus is constituted by a phosphoramidate frame.[28,29] Due to their importance, several strategies have been developed for the synthesis of phosphoramidates and bisphosphoramidates. For instance, Atherton et al. synthesized dibenzyl-aminophosphonates through the reaction between carbon tetrachloride and phosphite species, providing firstly trichloromethylphosphonate and then the forementioned products, once both ammonia and a secondary amine (depending on the desired product) are added to the reaction medium.[30,31] A variant of this strategy was reported by Hackenberger et al. who synthesized several *N,N*-disubstituted phosphoramidates by mixing organic azides with phosphite ions, following a Lewis acid-catalyzed reaction. Although these procedures provide yields from moderate to good, the reactants involved are highly toxic and even explosive in the presence of moisture, requiring stringent experimental

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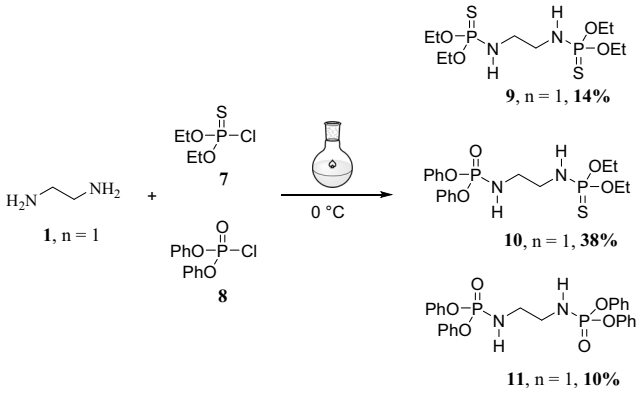
Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2021.1878358.



Scheme 1. MCR procedure to obtain symmetric **9**, **11** and asymmetric **10** derivatives.

conditions, as well as appropriate purification techniques.[32] Phenyl-phosphoramidates are commonly obtained with the aid of a metallic catalyst. Examples of these procedures were reported by Chang et al.[33] and by Fraser et al.,[31] who separately synthesized several derivatives using iridium- and copper-based catalysts, respectively. The use of a catalyst agent substantially improves reaction efficiencies, but at the cost of forming some unwanted secondary products. A few bisphosphoramidates have been synthesized, commonly by mixing aliphatic diamines with a phosphoryl chloride derivative, obtaining symmetric (phosphorous atoms, belonging to each of the two phosphoramidate moieties, display the same connectivity) species according to a double addition–elimination reaction.[34,35] As far as we know, no experimental technique has been designed for the synthesis of asymmetric phosphoramidates.

In this work, we present a novel experimental procedure for the synthesis of both symmetric and asymmetric (bis)phosphoramidate and (bis)phosphoramidothioate derivatives following a *one-pot* multicomponent reaction (MCR) strategy.[36] MCRs are powerful procedures for the synthesis of organic species with a high structural complexity, involving short reaction times and relative soft experimental conditions. Previously, we designed a new a tricomponent free catalyst reaction strategy for the synthesis of (dihydro-1H-benzo[*d*]imidazole) phosphonate, using benzimidazoles (component one), aliphatic amines (component two), and phosphorous chloride (component three) as starting materials.[37] Unlike other techniques, our methodology requires relative short reaction times (less than 12 h) and routine experimental conditions (room temperature and atmospheric pressure) to obtain the corresponding compound.

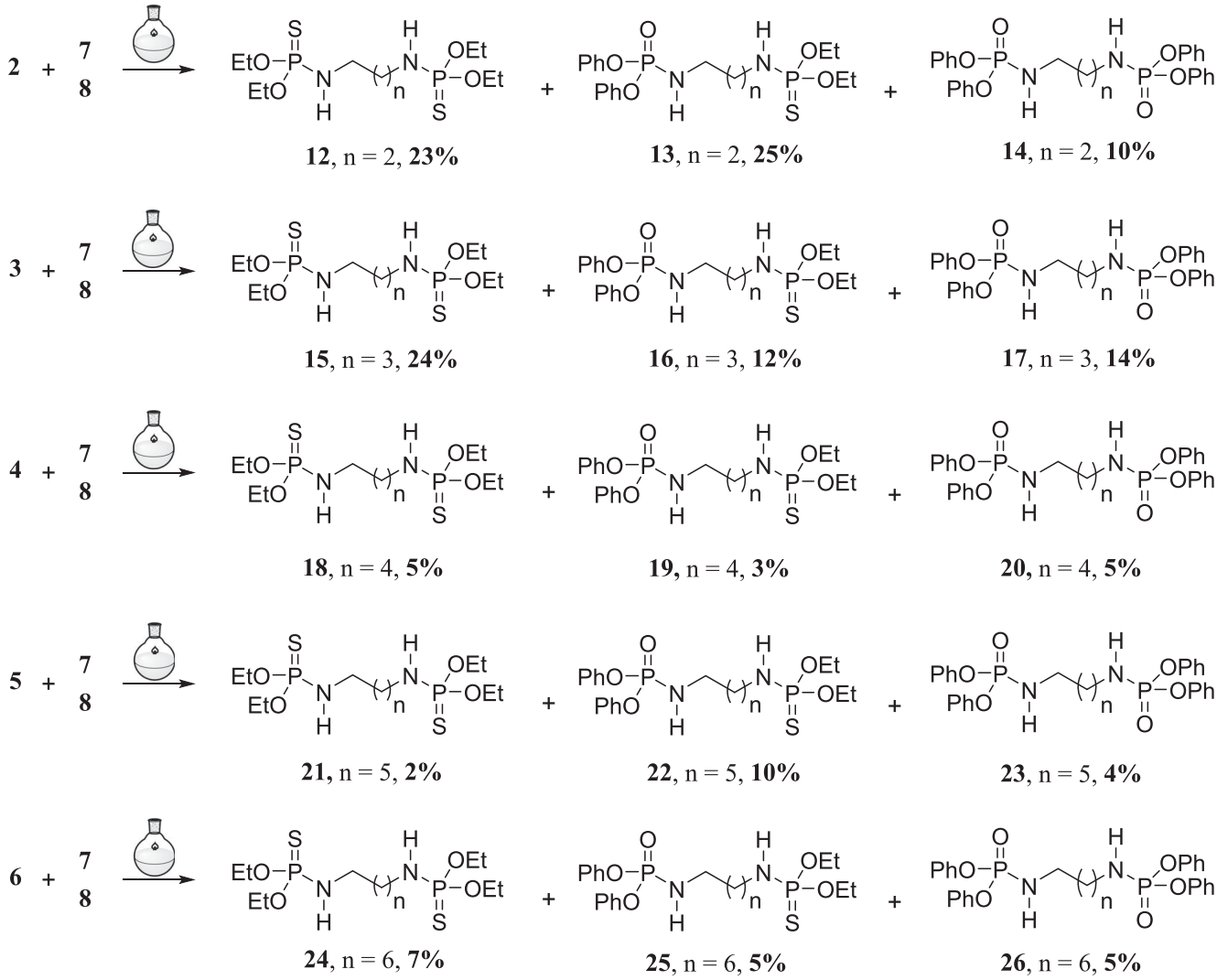
The MCR strategy reported in this work involves reagents with a low toxicity profile without compromising the benefits of these reactions; that is, it requires routine experimental conditions and short reaction times and it proceeds in a single pot, in the absence of catalysts. As an outstanding feature, our procedure is particularly convenient for the synthesis of both symmetric (bisphosphoramidate or bisphosphoramidothioate) and asymmetric (phosphoramidate–phosphoramidothioate) derivatives. Consequently, this work constitutes the first report regarding the synthesis of asymmetric phosphoramidates and phosphoramidothioates. To show the inherent biological features exhibited by compounds synthesized this way, we evaluated the inhibitory capacity of our (symmetric and asymmetric) compounds against two different cell lines: the lung adenocarcinoma cell line A-549 and the human bone chondrosarcoma cell line (SW 1353), as representative of lung cancer malignant cells in bones.[38,39]

Results and discussion

Our multicomponent reactions proceed from the following three starting materials: aliphatic diamines, **1**, 1,3-diaminopropane **2**, 1,4-diaminobutane **3**, 1,5-diaminopentane **4**, 1,6-diaminohexane **5** and 1,7-diaminoheptane **6**), *O, O′*-diethyl chlorothiophosphate **7**, and diphenyl phosphoryl chloride **8.** It is worthy to mention that this novel procedure is part of a patent, still in process.[40] One may observe that three derivatives are obtained for each of the diamines used as reagent: two symmetric (a phosphoramidate and a phosphoramidothioate) and the asymmetric analog (phosphoramidate-phosphoramidothioate). For instance, note that if diamine **1** is mixed with the two phosphoryl chlorides mentioned above (compounds **7** and **8**), the following two symmetric derivatives are obtained, *O,O,O',O'*-tetraethyl ethane-1,2-diylbis (phosphoramidothioate) **9** and tetraphenyl ethane-1,2-diylbis(phosphoramidate) **11**, conjointly with the asymmetric analogue diphenyl (2-((diethoxyphosphorothioyl)amino)ethyl)phosphoramidate **10** (Scheme 1). The set of MCR reactions performed in this work are summarized in Scheme 2 (Recorded ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts for adducts **9**–**26** are available in the Supplemental data).

As can be seen in diagrams **1** and **2**, the reaction yields are severely affected by the solubility of the diamine used as a reagent. The highest yields were obtained for reactions involving light diamines **1–3** with overall yields of 62%, 58%, and 50%, respectively (short alkyl chain lengths), while the lowest yields were obtained with diamines **4–6** as a reagent with overall yields of 13%, 16%, and 17%, respectively (long alkyl chain lengths). As explained in the text (and represented in diagrams **1** and **2**), our strategy provides a mixture of products constituted by symmetric (**9** (14%), **11** (10%), **12** (23%), **14** (10%), **15** (24%), **17** (14%), **18** (5%), **20** (5%), **21** (2%), **23** (4%), **24** (7%), and **26** (5%)) and asymmetric (**10** (38%), **13** (25%), **16** (12%), **19** (3%), **22** (10%), and **25** (5%)) species.

All our adducts were characterized by ^{1}H, ^{13}C and ^{31}P NMR; As an example, we explain the characterization of compound **10**. Asymmetric bisphosphoramidate **10** has two different bonds, nitrogen–phosphorus–oxygen (N–P=O) and nitrogen–phosphorus–sulfur (N–P=S). In the ^{1}H NMR spectrum, it displayed a signal (dt) at 1.27 ppm with two coupling constants of 7.6 and 14 Hz, for $-CH_2CH_3$. In 3 ppm, we observed a (dt) at $-CH_2NPS$, with two coupling constants of 6.4 and 12.8 Hz. In ^{13}C NMR, a (d) was observed at 15.9 ppm for carbons belonging to $-OCH_2CH_3$, with a coupling constant of 8.1 Hz. At 62.9 ppm, a signal (d) was also observe for carbons in $-OCH_2CH_3$, with a coupling



Scheme 2. Set of three-component reactions performed in this work. Reaction yields are reported as percentage.

Table 1. Half-Growth inhibition (IC_{50}) in lung adenocarcinoma and chondrosarcoma cells. Values are expressed as the mean ± standard error of the mean (SEM).

Compound	IC_{50} A549	IC_{50} SW-1353
9	>100	**
10	111.15 ± 4.53	465.70 ± 2.46
11*	105.51 ± 7.16	>100
12	>100	19.53 ± 1.31
13	47.59 ± 1.97	12.77 ± 1.37
14	>100	10.37 ± 1.31
CDDP	32.93 ± 1.48	**
Doxorubicin	**	8.53 ± 3.35
Colchicine	**	1.69 ± 1.53

*Limited solubility.
**Not determined.

constant of 5 Hz. At 150.64 ppm for the carbon ipso as a signal (d) with a coupling constant of 6.8 Hz. In the ^{31}P NMR spectrum, we observed two signals, one at −2.69 ppm (P═O) and the other at 69.83 ppm (P═S).

From the set of symmetric and asymmetric adducts here obtained, compounds **9**, **11**, **12**, **14**, **15**, **17**, **18**, and **20** were previously synthesized through addition–elimination reactions.[25,34,35] In this context, the symmetric derivatives **21**, **23**, **24**, and **26**, as well as the whole set of asymmetric analogues **10**, **13**, **16**, **19**, **22**, and **25** were synthesized for the first time in this work, through our MCR procedure.

As a final task, we measured the half maximal inhibitory concentration (IC_{50}) values for the six organophosphorus derivatives (**9–14**) here synthesized, against the A-549 and SW-1353 cell lines. In Table 1, we report those species able to inhibit the grown of these cell cultures. Note that three of our compounds (**12**, **13**, and **14**) displayed a good inhibitory capacity over the SW-1353 cell line, in the same concentration rande to doxorubicin, one of the most widely used antineoplastics.[41]

Experimental

The chemical structures corresponding to all our synthesized compounds were revealed by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectroscopic and mass spectrometric records (corresponding data can be found in the supplemental data). ^{1}H, ^{13}C, and ^{31}P NMR data were recorded at room temperature using the Bruker BioSpin GmbH (Billerica, MA). All our experiments were performed using deuterated chloroform ($CDCl_3$) as solvent. Chemical shifts (δ) are reported in parts

per million. Multiplicities were recorded as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), and multiplet (m). Coupling constants (J) are given in Hz. High-resolution mass spectra were recorded on a JEOL AccuTOF JMS-T100LC mass spectrometer with TOF mass analyzer (JEOL USA, Inc., Peabody, MA). FAB + mass spectra were obtained on a 3-nitrobenzyl alcohol matrix in the positive ion mode on a JEOL MStationJMS-700 spectrometer, operated at an accelerating voltage of 10 kV by using Xenon atoms at 6 keV (JEOL USA, Inc., Peabody, MA). Melting points were determined using Fisher Johns melting point apparatus (uncorrected) (168 Third Avenue Waltham, MA). Supplemental data contain sample ^{1}H, ^{13}C, and ^{31}P NMR spectra for the products (Figures S 1–S 54).

General method

The general synthesis procedure was as follows: Under magnetic stirring and at 0 °C, a 50-mL round bottom flask containing the diamine (1 mmol) was placed in CH_2Cl_2 2 mL with NEt_3 (1 mmol) and *O, O′*-diethyl chlorothiophosphate (0.5 mmol) was added dropwise and left stirring for additional 30 min at 0 °C. Subsequently, NEt_3 (1 mmol) was added and left stirring for 5 min, followed by a diphenyl phosphoryl chloride (0.5 mmol) addition, dropwise. The reaction mixture was left stirring for 1 h. The reaction mixture was then concentrated *in vacuo*. The crude products were purified by flash column chromatography. The purification of adducts was carried out using two different mixtures of eluents, i.e., a hexane/EtOAc (4:1) mixture followed by a hexane/EtOAc (1:1) mixture.

O,O,O′,O′-tetraethylethane-1,2diylbis (phosphoramidothioate) (9)

Yield: 23%; solid white; mp: 79–80 °C. (lit [25]). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 1.32$ (dt, J_{HH} = 6.9, 7.2 Hz, $-OCH_2CH_3$, 12H), 3.05 (dt, J_{HH} = 6.8, J_{PNCH} = 9.6 Hz, $-CH_2NP$, 4H), 3.25–3.28 (m, PNH, 2H), 4.05 (dq, J_{HH} = 6.8, J_{POCH} = 7.2 Hz, $-OCH_2CH_3$, 8H) ppm. ^{13}C NMR (100.53 MHz, $CDCl_3$, 298 K): $\delta = 15.94$ (d, $J_{P\text{-}C}$ = 8.1 Hz, $-OCH_2CH_3$, 12 C), 42.79 ($-CH_2CH_2$, 4 C), 63.10 (d, $J_{P\text{-}C}$ = 5.1 Hz, $-OCH_2CH_3$, 8 C) ppm. ^{31}P NMR (161.91 MHz, $CDCl_3$): $\delta = 69.62$ (s) ppm. HRMS (DART) $C_{10}H_{27}N_2O_4P_2S_2$ $[M+H]^+$ calc. 365.0887, found 365.0881.

Diphenyl(2((diethoxyphosphorothioyl)amino) ethyl)phosphoramidate (10)

Yield: 38%; yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 1.27$ (dt, J_{HH} = 7.6, 14 Hz, $-OCH_2CH_3$, 6H), 3.01 (dt, J_{HH}= 6.4, J_{CH2NPS} = 12.8 Hz, CH_2NPS, 2H), 3.11 (dt, J_{HH} = 6, J_{OPOCH2} = 12.9 Hz, $OPNCH_2$, 2H), 3.55–3.56 (m, SPNH), 3.96 (dq, J_{HH} = 7.2, $J_{SPNHCH2}$ = 14.8 Hz, 4H), 4.21–4.22 (m, OPNH), 7.12–7.32 (m, 10H).

^{13}C NMR (100.53 MHz, $CDCl_3$, 298 K): $\delta = 15.82$ (d, J_{PC} = 8.1 Hz, $-OCH_2CH_3$, 2 C), 42.75 (d, J_{PC} = 4.7 Hz, CNPS), 42.90 (d, J_{PC} = 4.9 Hz, CNPO), 62.98 (d, J_{PC} = 5.0 Hz, OCH_2CH_3, 2 C), 120.17 (d, J_{PC} = 4.8 Hz, 4 C_{ortho}), 124.98 (2 C_{para}), 129.71 (4 C_{meta}), 150.70 (d, J_{PC} = 6.8 Hz, 2 C_{ipso}). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = −2.69 (s, P = O), 69.83 (s, P = S). HRMS (DART) $C_{18}H_{27}N_2O_5P_2S$ $[M+H]^+$ calc. 445.1038, found 445.1119.

Tetraphenyl ethane-1,2-diylbis(phosphoramidate) (11)

Yield: 10%; solid white; mp: 134–135 °C. (lit [27]). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS, ppm): $\delta = 3.09$ (dd, J_{HH}= 6.4 Hz, J_{PNCH} = 6.8 Hz, 4H, $-CH_2NH$), 4.33 (dt, J_{PNH} = 6 Hz, 2H, NH), 7.10–7.28 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS, ppm): $\delta = 42.95$ (d, J_{PC} = 5.3 Hz, 2 C, $-CH_2NH-$), 120.20 (s, 8 C_{ortho}), 125.01 (s, 4 C_{para}), 129.72 (s, 8 C_{meta}), 150.67 (d, J_{PC} = 6.8 Hz, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = −0.41 (s). HRMS (DART) $C_{26}H_{27}N_2O_6P_2$ $[M+H]^+$ calc. 525.1344, found 525.1361.

O,O,O′,O′-tetraethyl propane-1,3-diylbis(phosphoramidothioate) (12)

Yield: 23%; yellow liquid. (lit [25]). ^{1}H NMR (300 MHz, $CDCl_3$, 298°K): $\delta = 1.32$ (dt, J_{HH} = 6.9, 7.2 Hz, $-OCH_2CH_3$, 12H), 1.63 (dd, J_{HH} = 6.3, 6.6 Hz, $-CH_2CH_2CH_2-$, 2H), 3.05 (dt, J_{HH} = 6, J_{PNCH} = 11.7 Hz, $-CH_2NP$, 4H), 3.09–3.11 (m, PNH, 2H), 4.05 (dq, J_{HH} = 6.9, J_{POCH} = 7.2 Hz, $-OCH_2CH_3$, 8H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$, 298°K): $\delta = 15.98$ (d, $J_{P\text{-}C}$ = 7.5 Hz, $-OCH_2CH_3$, 4 C), 32.88 (d, $J_{P\text{-}C}$ = 5.2 Hz, $-CH_2CH_2CH_2-$, 1 C), 38.49 ($-CH_2NP$, 2 C), 63.0 (d, $J_{P\text{-}C}$ = 4.5 Hz, $-OCH_2CH_3$, 4 C) ppm. ^{31}P NMR (242.95 MHz, $CDCl_3$): $\delta = 72.60$ (s) ppm. HRMS (DART) $C_{11}H_{29}N_2O_4P_2S_2$ $[M+H]^+$ calc. 379.1044, found 379.1041.

Diphenyl (3-((diethoxyphosphorothioyl) amino)propyl)phosphoramidate (13)

Yield: 25%; solid white; mp: 54–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): $\delta = 1.27$ (dt, J_{HH} = 7.2, 14.4 Hz, $-OCH_2CH_3$, 6H), 1.56 (dt, J_{HH} = 6.3, 12.9 Hz, $-CH_2CH_2CH_2-$, 2H), 2.99 (dt, J_{HH} = 6.6, J_{SPOCH2} =12.9 Hz, $SPNCH_2-$, 2H), 3.15 (dt, J_{HH} = 6.6, $J_{OPNHCH2}$ = 11.7 Hz, $OPNCH_2-$, 2H), 3.25–3.27 (m, SPNH), 3.80–3.82 (m, OPNH), 3.98 (dq, J_{HH} = 7.2, J_{POCH2} = 14.0 Hz, $-OCH_2CH_3$, 4H), 7.16–7.35 (m, 10H). ^{13}C NMR (75.48 MHz, $CDCl_3$, 298 K): $\delta = 15.94$ (d, J_{PC} = 7.7 Hz, $-OCH_2CH_3$, 2 C), 32.62 (d, J_{PC} = 4.2 Hz, $-CH_2-$, 1 C), 38.27 (1 C), 38.42 (1 C), 62.91 (d, J_{PC} = 4.7, OCH_2CH_3, 2 C), 120.17 (d, J_{PC} = 4.9 Hz, 4 C_{ortho}), 124.97 (2 C_{para}), 129.73 (4 C_{meta}), 150.7 (d, J_{PC} = 6.8 Hz, 2 C_{ipso}). ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = −2.51 (s, P = O), 69.93 (s, P = S). HRMS (DART) $C_{19}H_{29}N_2O_5P_2S$ $[M+H]^+$ calc. 459.1194, found 459.1272.

Tetraphenyl propane-1,3-diylbis(phosphoramidate) (14)

Yield: 12%; solid white; mp 85-86 °C. (lit [27]). ^{1}H NMR (400 MHz, $CDCl_3$, 298°K): $\delta = 1.49$–1.57 (m, 2H, $-CH_2CH_2CH_2-$), 3.03 (dd, J_{HH}= 6 Hz, J_{PNCH} = 6.8 Hz, 4H,

–CH_2NH), 3.80 (dt, J_{PNH} = 6.4 Hz, 2H, NH), 7.09–7.31 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): δ = 32.47 (s, 1 C, –$CH_2CH_2CH_2$–), 38.06 (s, 2 C, –CH_2NH), 120.20 (s, 8 C_{ortho}), 124.96 (s, 4 C_{para}), 129.70 (s, 8 C_{meta}), 150.79 (d, J_{PC} = 6.7 Hz, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 0.02 (s). HRMS (DART) $C_{27}H_{29}N_2O_6P_2$ $[M+H]^+$ calc. 539.1422, found 539.1503.

O,O,O′,O′-tetraethyl butane-1,4-diylbis(phosphoramidothioate) (15)

Yield: 24%; yellow liquid. (lit [25]). ^1H NMR (400 MHz, $CDCl_3$, 298°K): δ = 1.28 (dt, J_{HH} = 6.9, 7.2 Hz, –OCH_2CH_3, 12H), 1.46–1.48 (m, 4H), 2.91–2.94 (m, 6H), 4.05 (dq, J_{HH} = 6.9, J_{POCH} = 7.2 Hz, –OCH_2CH_3, 8H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): δ = 15.90 (d, $J_{P\text{-}C}$ = 8.1 Hz, –CH_2CH_3, 4 C), 28.60 (d, $J_{P\text{-}C}$ = 6.1 Hz, –$CH_2CH_2CH_2CH_2$–, 2 C), 41.25 (d, J_{PC} =2.9 Hz, –CH_2NP, 2 C), 62.81 (d, J_{PC} = 5.0 Hz, –OCH_2CH_3, 4 C) ppm. ^{31}P NMR (242.95 MHz, $CDCl_3$): δ = 72.40 (s). HRMS (DART) $C_{12}H_{31}N_2O_4P_2S_2$ $[M+H]^+$ calc. 393.1200, found 393.1198.

Diphenyl (4-((diethoxyphosphorothioyl) amino)butyl)phosphoramidate (16)

Yield: 12%; yellow liquid. ^1H NMR (400 MHz, $CDCl_3$, 298°K): δ = 1.27 (dt, J_{HH} = 7.2, 14.4 Hz, –OCH_2CH_3, 6H), 1.36–1.38 (m, –CH_2CH_2–, 4H), 2.78 (dt, J_{HH} = 4 Hz, J_{SPOCH2} =10.4 Hz, SPNCH_2–, 2H), 2.96 (dt, J_{HH} = 6.8, $J_{OPNHCH2}$ = 10.8 Hz, OPNCH_2–, 2H), 3.14–3.15 (m, SPNH), 3.98 (dq, J_{HH} = 7.2, J_{POCH2} = 14.0 Hz, OCH_2CH_3, 4H), 4.12–4.13 (m, OPNH), 7.08 (dd, J_{HH}= 7.6 Hz, 2H), 7.18–7.29 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): δ = 15.90 (d, J_{PC} = 8 Hz, –OCH_2CH_3, 2 C), 28.22 (d, J_{PC} = 6 Hz, –CH_2CH_2–, 2 C), 41.11 (1 C), 41.21 (1 C), 62.60 (d, J_{PC} = 4, OCH_2CH_3, 2 C), 120.10 (d, J_{PC} = 5 Hz, 4 C_{ortho}), 124.80 (2 C_{para}), 129.63 (4 C_{meta}), 150.70 (d, J_{PC} = 7 Hz, 2C_{ipso}). ^{31}P NMR (242.9 MHz, $CDCl_3$): δ = 0.38 (s, P = O), 72.31 (s, P = S). HRMS (DART) $C_{20}H_{31}N_2O_5P_2S$ $[M+H]^+$ calc. 473.1428, found 473.1439.

Tetraphenyl butane-1,4-diylbis(phosphoramidate) (17)

Yield: 14%; solid white; mp: 125-126 °C. (lit [27]). ^1H NMR (300 MHz, $CDCl_3$, 298°K): δ = 1.40–1.42 (m, 4H, –$CH_2CH_2CH_2CH_2$–), 3.03 (dd, J_{HH}= 6.6 Hz, J_{PNCH} = 6.8 Hz, 4H, –CH_2NH), 3.25 (dt, J_{PNH} = 6.3 Hz, 2H, NH), 7.12–7.33 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): δ = 28.25 (d, J_{PC} = 5.9 Hz, 2 C, $CH_2CH_2CH_2CH_2$–), 41.26 (s, 2 C, –CH_2NH), 120.20–120.21 (m, 8 C, C_{ortho}), 124.93 (s, 4 C_{para}), 129.70 (s, 8 C_{meta}), 150.79 (d, J_{PC} = 6.6 Hz, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = –0.69 (s). HRMS (DART) $C_{28}H_{31}N_2O_6P_2$ $[M+H]^+$ calc. 553.1657, found 553.1666.

O,O,O′,O′-tetraethyl pentane-1,5-diylbis(phosphoramidothioate) (18)

Yield: 5%; yellow liquid. ^1H NMR (500 MHz, $CDCl_3$, 298°K): δ = 1.32 (dt, J_{HH} = 7, 7.5 Hz, –OCH_2CH_3, 12H), 1.33–1.36 (m, 2H), 1.47–1.53 (m, 4H), 2.93–2.94 (m, 4H), 3.17–3.18 (m, NH, 2H), 4.05 (dq, J_{HH} = 7, J_{POCH} = 7.5 Hz, –OCH_2CH_3, 8H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): δ = 15.82 (d, $J_{P\text{-}C}$ = 8.1 Hz, –OCH_2CH_3, 4 C), 23.60 (s), 31.02 (d, $J_{P\text{-}C}$ = 6.1 Hz, –$CH_2CH_2CH_2CH_2$–, 2 C), 41.42 (d, $J_{P\text{-}C}$ = 3 Hz, –CH_2NP, 2 C), 62.62 (d, $J_{P\text{-}C}$ = 4.7 Hz, –OCH_2CH_3, 4 C)

^{31}P NMR (202 MHz, $CDCl_3$): δ = 71.52 (s). HRMS (DART) $C_{13}H_{33}N_2O_4P_2S_2$ $[M+H]^+$ calc. 407.1357, found 407.1334.

Diphenyl (5-((diethoxyphosphorothioyl) amino)pentyl)phosphoramidate (19)

Yield: 3%; yellow liquid. ^1H NMR (500 MHz, $CDCl_3$, 298°K): δ = 1.25 (dt, J_{HH} = 6.5, 8.5 Hz, –$CH_2CH_2CH_2CH_2CH_2$–, 2H), 1.29 (dt, J_{HH} =7, 14.5 Hz, 6H), 1.36–1-44 (m, 4H), 2.84 (dd, J_{HH} = 7, 14 Hz, 2H), 2.99–3.05 (m, 3H), 3.65–3.67 (m, OPNH), 3.99 (dq, J_{HH} = 7.2, J_{POCH2} = 14.0 Hz, OCH_2CH_3, 4H), 7.15 (dd, J_{HH}= 7.6 Hz, 2H), 7.25–7.33 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): δ = 15.90 (d, J_{PC} = 8.2 Hz, –CH_2CH_3, 2 C), 23.58 (s, 1 C), 31.03 (s, 2 C), 41.56 (s, 2 C), 62.74 (s, 2 C), 120.18 (d, J_{PC} = 5 Hz, 4 C_{ortho}), 124.88 (s, 2 C_{para}), 129.68 (s, 4 C_{meta}), 150.67 (s, 2 C_{ipso}). ^{31}P NMR (202 MHz, $CDCl_3$): δ = –0.42 (s, P = O), 71.64 (s, P = S). FAB MS m/e 487(MH+, 100); found $C_{21}H_{33}N_2O_5P_2S_1$.

Tetraphenyl pentane-1,5-diylbis(phosphoramidate) (20)

Yield: 5%; solid white; mp: 96–97 °C. ^1H NMR (500 MHz, $CDCl_3$, 298°K): δ = 1.10 (dt, J_{HH} = 8, 15 Hz, 2H), 1.24–1.30 (m, 4H), 2.87 (dt, J_{HH} = 7, 13.5 Hz, 4H), 4.26 (dt, J_{PNH} = 6.3 Hz, 2H, NH), 7.07 (dd, J_{HH}= 7 Hz, 4H), 7.21–7.26 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): δ = 23.21 (s, 1 C), 30.37 (s, 2 C), 41.47 (s, 2 C), 119.88 (s, 8 C_{ortho}), 124.83 (s, 4 C_{para}), 129. 47 (s, 8 C_{meta}), 150.99 (s, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 0.0 (s). FAB MS m/e 567(MH^+, 100); found $C_{29}H_{33}N_2O_6P_2$.

O,O,O′,O′-tetraethyl hexane-1,6-diylbis(phosphoramidothioate) (21)

Yield: 2%; yellow liquid. ^1H NMR (500 MHz, $CDCl_3$, 298°K): δ = 1.31–1.34 (m, 16H), 1.48–1.50 (m, 4H), 2.91–2.96 (m, 6H), 4.06 (dq, J_{HH} = 7.5, J_{POCH} = 8 Hz, –OCH_2CH_3, 8H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): δ = 15.90 (d, J_{PC} = 8.3 Hz, –OCH_2CH_3, 4 C), 26.29 (s, 2 C), 31.44 (d, J_{PC} = 6.3 Hz, –$CH_2CH_2CH_2CH_2CH_2CH_2$–, 2 C), 41.52 (d, J_{PC} = 3.5 Hz, –CH_2NP, 2 C), 62.79 (d, J_{PC} = 5.1 Hz, –OCH_2CH_3, 4 C) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 72.3 (s). HRMS (DART) $C_{14}H_{35}N_2O_4P_2S_2$ $[M+H]^+$ calc. 421.1513, found 421.1513.

Diphenyl(6-((diethoxyphosphorothioyl)amino)hexyl) phosphoramidate (22)

Yield: 5%; solid white; mp: 42–43 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298°K): $\delta = 1.15–1.23$ (m, 2H), 1.25 (dt, J_{HH} = 7.2, 14.4 Hz, –OCH_2CH_3, 6H), 1.32–1.38 (m, 4H), 2.77–2.84 (m, 2H), 2.93–2.98 (m, 2H), 3.22–3.27 (m, SPNH), 3.95 (dq, J_{HH} = 7.2, J_{POCH2} = 14.0 Hz, OCH_2CH_3, 4H), 4.02–4.13 (m, OPNH), 7.08 (dd, J_{HH}= 7.6 Hz, 2H), 7.20–7.28 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): $\delta = 15.90$ (d, J_{PC} = 8.7 Hz, –OCH_2CH_3, 2 C), 26.10 (d, J_{PC} = 8.7 Hz, 2 C), 31.22 (d, J_{PC} = 6 Hz, 2 C), 41.50 (d, J_{PC} = 6.2 Hz, 2 C), 62.63 (d, J_{PC} = 5, OCH_2CH_3, 2 C), 120.14 (d, J_{PC} = 5 Hz, 4 C_{ortho}), 124.76 (2 C_{para}), 129.60 (4 C_{meta}), 150.88 (d, J_{PC} = 6.2 Hz, 2 C_{ipso}). ^{31}P NMR (202 MHz, $CDCl_3$): δ = −0.23 (s, P = O), 71.69 (s, P = S). HRMS (DART) $C_{22}H_{35}N_2O_5P_2S$ $[M+H]^+$ calc. 501.1741, found 501.1737.

Tetraphenyl hexane-1,6-diylbis(phosphoramidate) (23)

Yield: 4%; solid white; mp: 116–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298°K): $\delta = 1.15–1.20$ (m, 4H), 1.38 (dd, J_{HH} = 7, 15.5 Hz, 4H), 3.04 (dt, J_{HH} = 7, 15 Hz, 4H), 3.50 (dt, J_{PNH} = 6.3 Hz, 2H, NH), 7.14–7.34 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): $\delta = 25.93$ (s, 2 C), 31.20 (d, J_{PC} = 6 Hz, 2 C), 41.54 (s, 2 C), 120.20 (s, 8 C_{ortho}), 124.86 (s, 4 C_{para}), 129. 66 (s, 8 C_{meta}), 150.90 (d, J_{PC} = 6.7 Hz, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = −0.44 (s). HRMS (DART) $C_{30}H_{35}N_2O_6P_2$ $[M+H]^+$ calc. 581.1970, found 581.1970.

O,O,O′,O′-tetraethyl heptane-1,7-diylbis(phosphoramidothioate) (24)

Yield: 2%; yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, 298°K): $\delta = 1.28–1.30$ (m, 6H), 1.33 (dt, J_{HH} = 7, 14 Hz, 12H), 1.47 (dt, J_{HH} = 11 Hz, 4H), 2.91–2.95 (m, 6H), 4.06 (dq, J_{HH} = 7.5, J_{POCH} = 8 Hz, –OCH_2CH_3, 8H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): $\delta = 15.95$ (d, $J_{P\text{-}C}$ = 8.5 Hz, –OCH_2CH_3, 4 C), 26.57 (s, 1 C), 28.89 (s, 2 C), 31.44 (d, $J_{P\text{-}C}$ = 6.6 Hz, –$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$–, 2 C), 41.63 (d, J_{PC} = 3.6 Hz, –CH_2NP, 2 C), 62.79 (d, $J_{P\text{-}C}$ = 5.1 Hz, –OCH_2CH_3, 4 C) ppm.^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 71.6$ (s).

Diphenyl (7-((diethoxyphosphorothioyl) amino)heptyl)phosphoramidate (25)

Yield: 5%; yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, 298°K): $\delta = 1.12–1.25$ (m, 6H), 1.30 (dt, J_{HH} = 7.2, 14.4 Hz, –OCH_2CH_3, 6H), 1.38–1.44 (m, 4H), 2.84–2.91 (m, 2H), 2.98–3.04 (m, 2H), 3.07–3.11 (m, SPNH), 3.65–3.71 (m, OPNH), 4.05 (dq, J_{HH} = 7.2, J_{POCH2} = 14.0 Hz, –OCH_2CH_3, 4H), 7.15 (dd, J_{HH}= 7.6 Hz, 2H), 7.24–7.33 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, 298°K): $\delta = 15.90$ (d, J_{PC} = 8.7 Hz, –OCH_2CH_3, 2 C), 26.10 (d, J_{PC} = 8.7 Hz, 2 C), 31.22 (d, J_{PC} = 6 Hz, 2 C), 41.50 (d, J_{PC} = 6.2 Hz, 2 C), 62.63 (d, J_{PC} = 5, –OCH_2CH_3, 2 C), 120.14 (d, J_{PC} = 5 Hz, 4 C_{ortho}), 124.76 (2 C_{para}), 129.60 (4 C_{meta}), 150.88 (d, J_{PC} = 6.2 Hz, 2 C_{ipso}). ^{31}P NMR (202 MHz, $CDCl_3$): δ = −0.23 (s, P = O), 71.69 (s, P = S). HRMS (DART) $C_{23}H_{37}N_2O_5P_2S$ $[M+H]^+$ calc. 515.1898, found 515.1916.

Tetraphenyl heptane-1,7-diylbis(phosphoramidate) (26)

Yield: 5%; solid white; mp: 77–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298°K): $\delta = 1.09–1.23$ (m, 6H), 1.38 (dt, J_{HH} = 6, 13 Hz, 4H), 3.03 (dt, J_{HH} = 7, 14 Hz, 4H), 3.40 (dt, J_{PNH} = 6.3 Hz, 2H, NH), 7.13–7.32 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$, 298°K): $\delta = 26.33$ (s, 1 C), 28.69 (s, 2 C), 31.20 (d, J_{PC} = 6 Hz, 2 C), 41.70 (s, 2 C), 120.20 (s, 8 C_{ortho}), 124.89 (s, 4 C_{para}), 129. 69 (s, 8 C_{meta}), 150.90 (d, J_{PC} = 6.7 Hz, 4 C_{ipso}). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = −0.51 (s). HRMS (DART) $C_{31}H_{37}N_2O_6P_2$ $[M+H]^+$ calc. 595.2126, found 595.2149.

Cell culture

Two human cancer cell lines were used for our inhibitory tests, the lung adenocarcinoma cell line (A-549) and the human bone chondrosarcoma cell line (SW 1353). Both cell lines were purchased from ATCC (Manassas, VA, USA). A-549 cells were cultured in RPMI-1640 medium (Sigma-Aldrich, St. Louis, MO, USA), while SW-1353 cells were cultured in Leibovitz's L-15 medium, both media were supplemented with 10% heat-inactivated FCS (fetal calf serum, Hyclone, Logan, UT, USA), 100 μ/mL of penicillin and 100 μg/mL of streptomycin. Tumor cells were incubated in a humidified chamber at 37 °C with filtered atmospheric air (21% oxygen) and 5% CO_2.

Conclusion

We designed an MCR strategy for the synthesis of biphosphoramidate and biphosphoramidothioate derivatives. This new synthesis procedure requires low reaction times and is carried out under standard conditions. Three different derivatives are synthesized simultaneously: the symmetric biphosphoramidate and biphosphoramidothioate species and their asymmetric counterpart, a phosphoramidate-phosphoramidothioate derivative. A total of 18 different compounds were synthesized in this way, 10 of them for the first time. Among the set of synthesized compounds, biphosphoramidates **12**–**14** showed significant cytotoxic activity against SW-1353 cells. The overall yields can be considered low to good, and these were affected to the low solubility of diamines. Using this methodology, we are currently synthesizing new symmetric and asymmetric biphosphoramidates and phosphoramidothioates, using diamines with different solubility profiles, in different reaction media.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was supported by Secretaría de Investigación y Posgrado del Instituto Politécnico Nacional (SIP-IPN), for financial support (Grant Nos. 20195476 and 20200192).

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