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Efficient synthesis of 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines

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ABSTRACT

We described in this paper an efficient synthesis of variously substituted 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines involving nucleophilic addition of hydrazine on β-ketothioamides as key-step.

1. Introduction

Because of their chemical and/or biological significance, nitrogen containing heterocycles represent an important and attractive area of organic chemistry. Among various series of heterocycles, we focused our attention on indazolyl moieties. As mentioned in literature, numerous examples of indazolyl heterocycles exhibit biological properties as well as anticoagulating agent,[1] topoisomerase bacterium II inhibitor,[2] or for treatment of hypercholesterol,[3] tuberculosis,[4] … (Fig. 1).

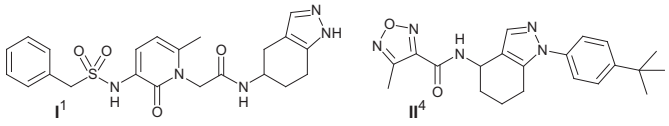
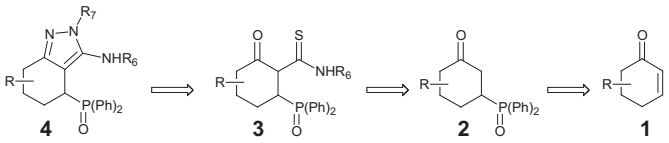


Fig. 1. Examples of imidazolyl heterocycles with inhibiting biological properties.

Given that phosphonate-containing azaderivatives are of biological interest,[5] it seems interesting to combine indazolyl ring and phosphinoyl group in the same skeleton to enhance the potential biological properties. In connection with our interest in synthesizing azaheterocyclic derivatives,[6,7] we then investigated the preparation of various phosphinoyltetrahydroindazolyl amines.

2. Results and discussion

In our knowledge, the most current strategy for the preparation of tetrahydroindazolyl or pyrazolyl rings consists in a cyclocondensation of hydrazines with 1,3-dicarbonyl compounds, unsaturated ketones, β-ketoesters or thioamides.[8–12] Consequently, we envisioned to build 1,2-diazole cycle using a such cyclocondensation step between *N*-substituted hydrazines and desired phosphinoyl β-ketothiamides to success in the preparation of the expected amino tetrahydroindazoles (Scheme 1).



Scheme 1. Retrosynthetic analysis for the elaboration of indazolylamines **4**.

The expected 3-phosphinoylcyclohexanones **2a**–**g** were prepared in good yields (58–81%) by reaction between cyclohex-2-enones **1a**–**g** and *P*-chlorodiphenylphosphine (1 equiv) (Table 1), at room temperature. A mechanism proposal might envision introduction of phosphinoyl group according to Michael addition of

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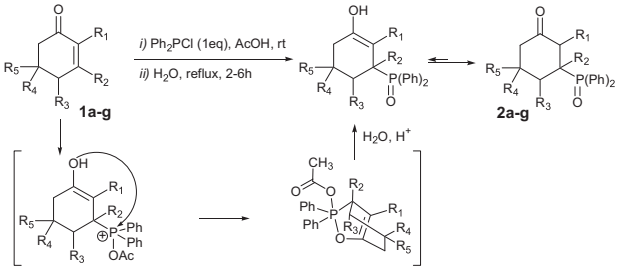
the in situ prepared diphenylphosphinyl acetate, followed by [1,2] oxaphospholane formation and then ring opening by acidic hydrolysis to give **2a**–**g**.

Table 1
Preparation of the 3-phosphinoylcyclohexanones **2a**–**h** and mechanism proposal

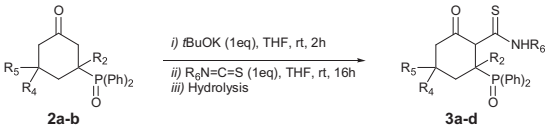


Compound	R_1	R_2	R_3	R_4	R_5	Yields[a] (%)
2a	H	H	H	H	H	81
2b	H	CH_3	H	CH_3	CH_3	79
2c	H	CH_3	H	H	H	76
2d	H	H	H	H	CH_3	72
2e	H	H		H	H	58
2f	Me	H	H	H		64
2g	Me	H	H	H		62

[a] Isolated yield after silica gel chromatography.

In a second step, isothiocyanates were used to introduce the expected thioamide units (Table 2). The sequence was realized within THF by action of potassium *tert*-butoxide (1 equiv) on 3-phosphinoylcyclohexanones **2a**,**b**, for 2 h, followed by the addition of isothiocyanate (1 equiv). The reaction was performed at room temperature overnight. The expected 2-phosphinoyl-6-oxocyclohexanecarbothioamides **3a**–**d** were then isolated in good yields (66–81%).

Table 2
Preparation of the 2-phosphinoyl-6-oxocyclohexanecarbothioamides **3a**–**d**



Compound	R_2	R_4	R_5	R_6	Yields[a] (%)
3a	H	H	H	Ph	81
3b	H	H	H	CH_2Ph	77
3c	H	H	H	*c*-Hex	72
3d	CH_3	CH_3	CH_3	Ph	66

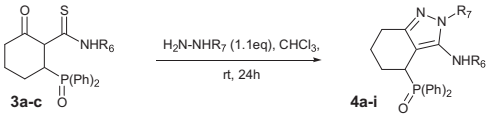
[a] Isolated yield after silica gel chromatography.

The following stage consisted in adding hydrazines (1.1 equiv) on β-ketothioamides **3a**–**d** to lead to ring closure of the targeted 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines **4a**–**i** (Table 3).

By considering the possible mechanism (Scheme 2), such a cyclisation can lead to the formation of the two isomers **4** and **5**, according to the nucleophilic attack of the primary or the secondary amino site in hydrazine.

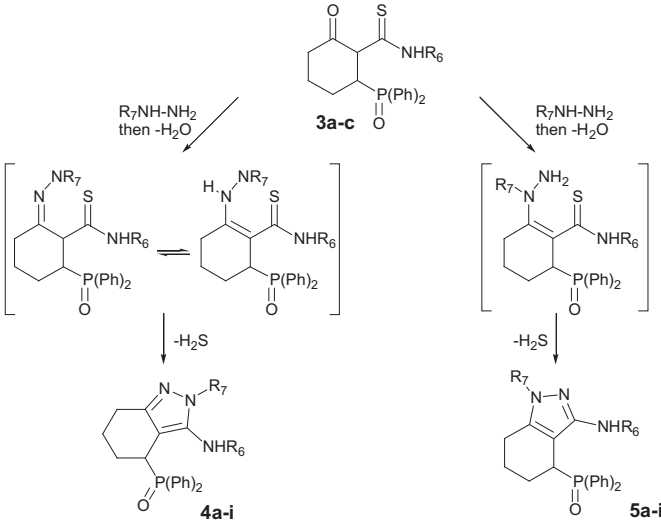
In a general way, it is to be noted that only isomers **4a** and **4c**–**i** were generated in the reaction mixture in good yields (60–76%).

Table 3
Preparation of the 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines **4a**–**i**



Compound	R_6	R_7	Yields[a] (%)
4a	Ph	H	74
4b	Ph	CH_3	51[b,c]
4c	Ph	CH_2CH_2CN	68
4d	CH_2Ph	H	76
4e	CH_2Ph	CH_3	68
4f	CH_2Ph	CH_2CH_2CN	74
4g	*c*-Hex	H	60
4h	*c*-Hex	CH_3	61
4i	*c*-Hex	CH_2CH_2CN	70

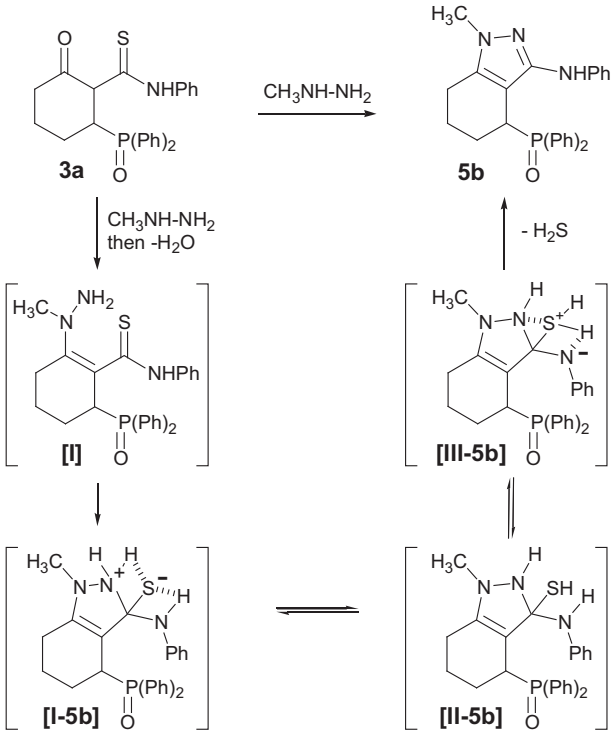
[a] Isolated yield after silica gel chromatography.
[b] Isomer **4b** was obtained in mixture with **5b**.
[c] Yield of **4b** after purification by silica gel chromatography, 23% of **5b** were also obtained as by-product.



Scheme 2. Proposed mechanism for the reaction of **3a**–**c** with hydrazine.

Surprisingly, in the case of the addition of methylhydrazine on β-ketothioamide **3a**, a mixture of isomers **4b** and **5b** was isolated. Isomers **4b** and **5b** were able to be separated by chromatography on silica gel (respectively, 51 and 23% yields). Structures of **4b** and **5b** were determined after a detailed two-dimensional NMR study (see Supplementary data). Potential explanations for these results involve electronic considerations. General behavior could be explained by a nucleophilic addition of the most reactive nitrogen atom present in hydrazine reagents. Due to the overall electron-withdrawing effect of the cyano group, only primary amino group of the propionitrile–hydrazine could react as nucleophile center conducting to the formation of derivatives **4c**, **4f**, and **4i**. In contrast with methylhydrazine, the methyl group slightly increased the electron-density on the central nitrogen atom, and consequently its nucleophile character compared to the terminal one. However, starting from thioamides **3b** and **c**, only isomers **4e** and **4h** were afforded in 68 and 61% yields, respectively, no trace of isomers **5e** and **5h** was detected, electronic effect induced by the methyl group did not affect the reactivity. On the other hand, starting from *N*-phenylthioamide **3a**, mixture of isomers **4b** and **5b** was obtained, nucleophile character of methylamino group was displayed in this case. Considering the proposed mechanism (Scheme 3), the formation of the indazolyl ring may be realized by nucleophilic

addition of the amino group of [**I**] on thioamide substituent; as the result various intermediates [**I**-**5b**] to [**III**-**5b**] might be envisioned. [**III**-**5b**], which presents a strong density of charge on nitrogen atom of the amine, might be favored only in the presence of phenyl as an electronic stabilizing effect substituent. Subsequent H_2S elimination allowed the formation of the compound **5b**.

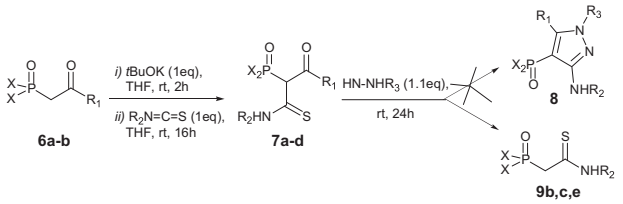


Scheme 3. Proposed mechanism for the formation of 4-phosphinoyl-4,5,6,7-tetrahydro-1*H*-indazol-3-ylamine **5b**.

In the second part of our work, we tried to apply the strategy described above for **4a**–**i** to reach pyrazoles **8** starting from acyclic β-ketophosphonates **6a**,**b**[13–16] (Table 4). The expected ketothioamides **7a**–**d** were easily prepared by addition of potassium enolates derived from **6a**,**b** on phenyl-, benzyl- or *c*-hexylisothiocyanates (77–87% yields). Nevertheless, concerning the second step, in spite of numerous realized experiments, no trace of the expected azaheterocyclic derivatives **8** was observed. Due to the nearness of phosphoryl unit in α-position as electron-withdrawing group, a cleavage of the carbonyl moieties occurred easily and led to the interesting phosphinoylthioamides **9b**, **c**, and **e** in 77, 72, and 76% yields, respectively.

This deacetylation (or debenzoylation for **7a**) sequence, using hydrazine as reagent and at room temperature as condition, turns out an interesting alternative leading to an efficient and versatile preparation of β-phosphorylthioamides from easily accessible substrates.

Table 4
Aliphatic series: preparation of compounds **7a**–**d** and **9b**,**c**,**e**



Compound	X	R_1	R_2	Yields[a] (%)
7a	Ph	Ph	Ph	87
7b	EtO	CH_3	Ph	86
7c	EtO	CH_3	CH_2Ph	77
7d	EtO	CH_3	*c*-Hex	81
9b	Ph		Ph	77
9c	EtO		CH_2Ph	72
9e	EtO		Ph	76

[a] Isolated yield after silica gel chromatography.

3. Conclusion

We succeeded in the synthesis of various 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines with moderate to good over yields (33–47%); an extension of this reaction sequence can be envisioned to allow the preparation of compounds bearing appropriate substituents, which can confer a potential biological activity to these heterocycles.

4. Experimental section

4.1. General

^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 400 or 250 or 200, 100 or 63 or 50 and 300 Mhz, respectively, with $CDCl_3$ as solvent and TMS (for ^1H NMR) or H_3PO_4 (^{31}P NMR) as internal standards. HRMS spectra were recorded on a BRUKER micrOTOF-Q spectrometer. MS were recorded on an SHIMADZU GCMS-QP2010 spectrometer. Melting temperatures are uncorrected.

Cyclohex-2-enones **1a**–**g** were commercially available or prepared according to the procedure described in literature.[16–18]

4.2. General procedure for the preparation of 3-(diphenylphosphinoyl)cyclohexanones (2a–h)

To a solution of cyclohexenones **1a**–**g** (5.0 mmol, 1.0 equiv) in glacial acetic acid (50 mL) was added dropwise *P*-chlorodiphenylphosphine (5.0 mmol, 1.0 equiv) at room temperature, under nitrogen atmosphere. After addition of H_2O (1.5 mL), the reactional mixture was refluxed during a reaction time (t_R). After extraction with chloroforme ($CHCl_3$), the combined organic layers were washed with an aqueous saturated NaCl solution, then with an aqueous saturated $NaHCO_3$ solution. After drying ($MgSO_4$), filtration, and solvent evaporation, the crude product was purified by recrystallisation in diethyl ether (Et_2O).

*4.2.1. 3-(Diphenylphosphinoyl)cyclohexanone (**2a**).* Compound **2a** t_R: 2 h; solid; yield=81%; mp 144–146 °C; ^1H NMR δ_H (ppm) 1.70–2.50 (m, 9H, CH, CH_2), 7.40–7.90 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 22.6, 25.5 (J_{CP} 15.9 Hz), 37.1 (J_{CP} 75.7 Hz), 38.6, 40.3, 128.0–132.0, 208.6 (J_{CP} 14.6 Hz); ^{31}P NMR δ_P (ppm) 31.46; HRMS calcd for $C_{18}H_{19}NaO_2P$ $(M+Na)^+$: 321.1015; found: 321.1014.

*4.2.2. 3-(Diphenylphosphinoyl)-3,5,5-trimethylcyclo hexanone (**2b**).* Compound **2b** t_R: 5 h; solid; yield=79%; mp 116–118 °C; ^1H NMR δ_H (ppm) 1.20–3.10 (m, 6H, CH_2), 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.42 (d, 3H, $^3J_{PH}$ 17.9 Hz, CH_3), 7.20–8.10 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 22.1, 28.8, 33.9, 37.0 (J_{CP} 13.7 Hz), 41.3, 42.1 (J_{CP} 68.9 Hz), 45.0, 53.5, 128.0–133.0, 210.0; ^{31}P NMR δ_P (ppm) 36.74.

*4.2.3. 3-(Diphenylphosphinoyl)-3-methylcyclohexanone (**2c**).* Compound **2c** t_R: 2 h; solid; yield=76%; mp 131–133 °C; ^1H NMR δ_H (ppm) 1.32 (s, 3H, $^3J_{PH}$ 18.0 Hz, CH_3), 1.00–2.90 (m, 8H, CH_2), 7.30–7.80 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 25.1 (J_{CP} 13.9 Hz),

27.8, 29.6, 32.5 (J_{CP} 69.6 Hz), 44.2, 44.9, 127.0–135.0, 211.5 (J_{CP} 13.2 Hz); ^{31}P NMR δ_P (ppm) 31.56.

*4.2.4. 3-(Diphenylphosphinoyl)-5-methylcyclohexanone (**2d**).* Mixture of diastereoisomers: t_R: 3 h; solid; yield=72%; mp 104–106C; ^{1}H NMR δ_H (ppm) 1.02 (d, 3H, $^3J_{HH}$ 6.4 Hz, CH_3), 1.10–2.80 (m, 8H, CH, CH_2), 7.20–8.00 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 21.7, 21.7, 26.5, 29.8 (J_{CP} 13.2 Hz), 37.4 (J_{CP} 75.6 Hz), 41.9, 42.1, 128.0–132.0, 199.2 and 208.2 (J_{CP} 11.7 Hz); ^{31}P NMR δ_P (ppm) 32.13 (63%) and 34.47 (38%).

*4.2.5. 3-(Diphenylphosphinoyl)-4-isopropylcyclo hexanone (**2e**).* Mixture of diastereoisomers: t_R: 6 h; solid; yield=58%; mp 178–180 °C; ^{1}H NMR δ_H (ppm) 0.44 (d, 3H, $^3J_{HH}$ 6.7 Hz, CH_3), 0.75 (d, 3H, $^3J_{HH}$ 6.7 Hz, CH_3), 1.40–2.80 (m, 9H, CH, CH_2), 7.20–8.00 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 15.9, 16.3, 28.8, 32.4 (J_{CP} 15.4 Hz), 33.2 (J_{CP} 73.1 Hz), 42.3, 43.6, 44.2, 129.0–134.0, 210.3 (J_{CP} 11.2 Hz); ^{31}P NMR δ_P (ppm) 33.60 (51%) and 31.92 (49%).

*4.2.6. (5R)-3-(Diphenylphosphinoyl)-5-isopropenyl-2-methylcyclohexanone (**2f**).* Mixture of diastereoisomers: t_R: 6 h; solid; yield=64%; mp 167–169 °C; ^{1}H NMR δ_H (ppm) 0.97 (m, 3H, $^3J_{HH}$ 6.6 Hz, CH_3), 1.05 (s, 3H, CH_3), 1.20–3.10 (m, 7H, CH, CH_2), 4.76–4.79 (m, 2H, CH_2=C), 7.30–8.00 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 15.6 and 16.3 and 17.9 and 14.0, 19.8, 26.8, 35.2, 39.2 (J_{CP} 71.9 Hz), 40.4, 44.4, 128.0–135.0, 199.6 (J_{CP} 9.2 Hz); ^{31}P NMR δ_P (ppm) 31.45 (66%) and 30.15 (19%) and 34.79 (8%) and 33.39 (7%).

*4.2.7. (5S)-3-(Diphenylphosphinoyl)-5-isopropenyl-2-methylcyclohexanone (**2g**).* Mixture of diastereoisomers: t_R: 6 h; solid; yield=62%; mp 167–168 °C; ^{1}H NMR δ_H (ppm) 1.00 (m, 3H, $^3J_{HH}$ 6.9 Hz, CH_3), 1.08 (s, 3H, CH_3), 1.20–3.20 (m, 7H, CH, CH_2), 4.78–4.81 (m, 2H, CH_2=C), 7.50–8.00 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 15.7 and 12.5, 20.3, 26.8, 35.2, 39.2 (J_{CP} 71.7 Hz), 40.5, 40.6, 120.0–135.0, 199.5 and 210.1 (J_{CP} 9.3 Hz); ^{31}P NMR δ_P (ppm) 31.44 (41%), 33.43 (26%), 34.76 (23%), 31.53 (10%).

4.3. General procedure for the preparation of 2-phosphinoyl-6-oxocyclohexanecarbothioamides (3a–d)

To a solution of potassium *tert*-butoxide (0.01 mol, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise 3-phosphinoylcyclohexanones **2** (0.01 mol, 1.0 equiv) in solution in anhydrous THF (20 mL) at room temperature, under nitrogen atmosphere. After 2 h of stirring, isothiocyanate (0.01 mol, 1.0 equiv) in solution in anhydrous THF (5 mL) was added to the reactional mixture. After 16 h of stirring at room temperature, the hydrolysis was performed with an aqueous saturated NH_4Cl solution. The aqueous layer was then extracted twice with $CHCl_3$ (2×50 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel (0.063–0.200 mm, eluent: 95/5 Et_2O/EtOH).

*4.3.1. 2-(Diphenylphosphinoyl)-6-oxocyclohexane carbothioic acid phenylamide (**3a**).* Solid; yield=81%; mp 202–204 °C; ^{1}H NMR δ_H (ppm) 1.87–1.95 (m, 2H, CH_2), 2.18–2.25 (m, 2H, CH_2), 2.62–2.69 (m, 2H, CH_2), 4.22–4.29 (m, 1H, CHP(O)), 4.53–4.61 (m, 1H, CHC(S)), 7.02–7.83 (m, 15H, CH_{ar}), 11.58 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 21.9 (J_{CP} 13.6 Hz), 22.5, 38.8, 39.6 (J_{CP} 68.6 Hz), 61.8, 123.0–139.0, 196.8 (J_{CP} 2.3 Hz), 205.9 (J_{CP} 8.3 Hz); ^{31}P NMR δ_P (ppm) 35.0; HRMS calcd for $C_{25}H_{25}NO_2PS$ $(M+H)^+$: 434.1338; found: 434.1366.

*4.3.2. 2-(Diphenylphosphinoyl)-6-oxocyclohexane carbothioic acid benzylamide (**3b**).* Solid; yield=77%; mp 195–197 °C; ^{1}H NMR δ_H (ppm) 1.71–1.77 (m, 2H, CH_2), 1.92–1.96 (m, 2H, CH_2), 2.14–2.22 (m, 2H, CH_2), 3.92–3.99 (m, 1H, CHP(O)), 4.15–4.19 (m, 2H, CH_2N), 4.61–4.66 (m, 1H, CHC(S)), 7.03–7.78 (m, 15H, CH_{ar}), 9.67 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 21.9 (J_{CP} 12.8 Hz), 22.2, 38.7, 39.3 (J_{CP} 56.5 Hz), 39.6, 60.4, 127.5–135.7, 197.9 (J_{CP} 3.0 Hz), 205.9 (J_{CP} 7.5 Hz); ^{31}P NMR δ_P (ppm) 35.1; HRMS calcd for $C_{26}H_{26}NNaO_2PS$ $(M+Na)^+$: 470.1314; found: 470.1337.

*4.3.3. 2-(Diphenylphosphinoyl)-6-oxocyclohexane carbothioic acid cyclohexylamide (**3c**).* Solid; yield=72%; mp 213–215 °C; ^{1}H NMR δ_H (ppm) 1.29–1.77 (m, 12H, CH_2), 2.02–2.44 (m, 4H, CH_2), 3.63–3.65 (m, 1H, CHN), 3.81–3.89 (m, 1H, CHP(O)), 4.06–4.11 (m, 1H, CHC(S)), 7.14–7.61 (m, 10H, CH_{ar}), 8.93 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 21.7, 22.1, 23.3, 24.6, 30.6, 37.7 (J_{CP} 59.6 Hz), 41.0, 54.7, 60.4, 128.1–132.4, 195.4 (J_{CP} 4.5 Hz), 205.6 (J_{CP} 13.3 Hz); ^{31}P NMR δ_P (ppm) 35.4; HRMS calcd for $C_{25}H_{31}NO_2PS$ $(M+H)^+$: 440.1808; found: 440.1812.

*4.3.4. 2-(Diphenylphosphinoyl)-2,4,4-trimethyl-6-oxocyclohexanecarbothioic acid phenylamide (**3d**).* Solid; yield=66%; mp 198–200 °C; ^{1}H NMR δ_H (ppm) 1.29–3.14 (m, 4H, CH_2), 1.11 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.49 (d, 3H, $^3J_{PH}$ 18.0 Hz, CH_3), 4.31–4.35 (m, 1H, CHC(S)), 7.29–7.96 (m, 15H, CH_{ar}), 10.28 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 22.1, 27.2, 34.0, 37.1 (J_{CP} 13.6 Hz), 41.2, 42.1 (J_{CP} 68.7 Hz), 45.1, 65.8, 128.4–132.6, 194.2 (J_{CP} 3.0 Hz), 210.4 (J_{CP} 13.6 Hz); ^{31}P NMR δ_P (ppm) 38.7.

4.4. General procedure for the preparation of 4-phosphinoyl-4,5,6,7-tetrahydro-2*H*-indazol-3-ylamines (4a–i)

Hydrazine (0.0011 mol, 1.1 equiv) was added to a solution of β-ketothioamides **3a**–**c** (0.001 mol, 1.0 equiv) in $CHCl_3$. After 24 h of stirring at room temperature, the residue was dried ($MgSO_4$), solvent was evaporated and the crude product was purified by column chromatography on silica gel (0.063–0.200 mm, eluent: 90/10 Et_2O/EtOH).

*4.4.1. [4-(Diphenylphosphinoyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl] phenylamine (**4a**).* Solid; yield=74%; mp 216–218 °C; ^{1}H NMR δ_H (ppm) 1.66–1.73 (m, 2H, CH_2), 1.86–1.98 (m, 2H, CH_2), 2.26–2.40 (m, 2H, CH_2), 3.49–3.55 (m, 1H, CHP(O)), 6.59 (s, 1H, HN–N), 7.07–7.70 (m, 15H, CH_{ar}), 7.74 (s, 1H, NHPh); ^{13}C NMR δ_C (ppm) 24.1, 25.6, 26.3, 34.8 (J_{CP} 78.1 Hz), 99.8 (J_{CP} 6.8 Hz), 128.4–132.1, 144.8; ^{31}P NMR δ_P (ppm) 39.4.

*4.4.2. [4-(Diphenylphosphinoyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]phenylamine (**4b**).* Solid; yield=51%; mp 223–225 °C; ^{1}H NMR δ_H (ppm) 1.50–1.79 (m, 2H, CH_2), 1.85–2.00 (m, 2H, CH_2), 2.30–2.55 (m, 2H, CH_2), 3.65 (s, 3H, CH_3), 3.78–3.90 (m, 1H, CHP(O)), 6.70–7.87 (m, 15H, CH_{ar}), 8.62 (s, 1H, NHPh); ^{13}C NMR δ_C (ppm) 21.5, 21.6, 25.1, 35.0, 35.8 (J_{CP} 64.1 Hz), 97.3 (J_{CP} 5.3 Hz), 116.2–144.1, 149.2; ^{31}P NMR δ_P (ppm) 38.6; HRMS calcd for $C_{26}H_{26}N_3NaOP$ $(M+Na)^+$: 450.1706; found: 450.1703.

*4.4.3. [4-(Diphenylphosphinoyl)-1-methyl-4,5,6,7-tetrahydro-1H-indazol-3-yl]phenylamine (**5b**).* Solid; yield=23%; mp 222–224 °C; ^{1}H NMR δ_H (ppm) 1.41–1.57 (m, 2H, CH_2), 1.78–2.04 (m, 2H, CH_2), 2.30–2.65 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 3.71–3.85 (m, 1H, CHP(O)), 6.52–7.86 (m, 15H, CH_{ar}), 8.08 (s, 1H, NHPh); ^{13}C NMR δ_C (ppm) 20.2, 22.2, 23.3, 31.5 (J_{CP} 48.3 Hz), 34.7, 99.9 (J_{CP} 6.8 Hz), 113.9–144.0, 147.8; ^{31}P NMR δ_P (ppm) 40.1; HRMS calcd for $C_{26}H_{27}N_3OP$ $(M+H)^+$: 428.1886; found: 428.1896.

*4.4.4. 3-[4-(Diphenylphosphinoyl)-3-phenylamino-4,5,6,7-tetrahydro-2H-indazol-2-yl]propionitrile (**4c**).* Solid; yield=68%; mp 228–230 °C; ^{1}H NMR δ_H (ppm) 1.45–1.49 (m, 2H, CH_2), 1.81–1.93 (m, 2H, CH_2), 2.23–2.52 (m, 2H, CH_2), 2.76–2.88 (m, 2H, CH_2), 3.67–3.76 (m, 1H, CHP(O)), 4.03–4.09 (m, 2H, CH_2CN), 6.51–7.74

(m, 15H, CH_{ar}), 7.89 (s, 1H, NHPh); ^{13}C NMR δ_C (ppm) 15.2, 18.1, 20.9, 24.1, 33.1 (J_{CP} 70.1 Hz), 43.6, 102.0 (J_{CP} 6.8 Hz), 114.7, 119.9–144.9, 150.5; ^{31}P NMR δ_P (ppm) 40.3.

*4.4.5. Benzyl-[4-(diphenylphosphinoyl)-4,5,6,7,-tetrahydro-2H-indazol-3-yl]amine (**4d**).* Solid; yield=76%; mp 219–211 °C; ^1H NMR δ_H (ppm) 1.33–1.41 (m, 2H, CH_2), 1.61–1.68 (m, 2H, CH_2), 2.43–2.49 (m, 2H, CH_2), 3.60–3.97 (m, 3H, CHP(O), CH_2N), 5.13 (s, 1H, HN–N), 6.33 (s, 1H, NHBn), 7.25–7.52 (m, 15H, CH_{ar}); ^{13}C NMR δ_C (ppm) 21.0, 23.5, 25.1, 34.1 (J_{CP} 115.5 Hz), 52.8, 100.4 (J_{CP} 6.9 Hz), 128.0–143.8, 146.8; ^{31}P NMR δ_P (ppm) 39.6; HRMS calcd for $C_{26}H_{27}N_3OP$ $(M+H)^+$: 428.1886; found: 428.1876.

*4.4.6. Benzyl-[4-(diphenylphosphinoyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]amine (**4e**).* Solid; yield=68%; mp 227–229 °C; ^1H NMR δ_H (ppm) 1.26–1.39 (m, 2H, CH_2), 1.51–1.64 (m, 2H, CH_2), 2.36–2.43 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 3.70–4.00 (m, 3H, CHP(O), CH_2N), 6.13 (s, 1H, NHBn), 7.15–7.42 (m, 15H, CH_{ar}); ^{13}C NMR δ_C (ppm) 21.6, 23.5, 24.7, 34.2, 35.1 (J_{CP} 145.5 Hz), 52.7, 100.0 (J_{CP} 6.8 Hz), 127.0–145.8, 147.8; ^{31}P NMR δ_P (ppm) 39.1; HRMS calcd for $C_{27}H_{29}N_3OP$ $(M+H)^+$: 442.2043; found: 442.2039.

*4.4.7. 3-[3-Benzylamino-4-(diphenylphosphinoyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl]propionitrile (**4f**).* Solid; yield=74%; mp 233–235 °C; ^1H NMR δ_H (ppm) 1.29–1.38 (m, 2H, CH_2), 1.50–1.59 (m, 2H, CH_2), 2.34–2.41 (m, 2H, CH_2), 2.75–2.81 (m, 2H, CH_2), 3.72–4.00 (m, 3H, CHP(O), CH_2N), 4.06–4.10 (m, 2H, CH_2CN), 7.01 (s, 1H, NHBn), 7.15–7.52 (m, 15H, CH_{ar}); ^{13}C NMR δ_C (ppm) 18.1, 21.6, 22.7, 24.3, 35.1 (J_{CP} 90.5 Hz), 42.9, 52.7, 102.1 (J_{CP} 6.3 Hz), 128.3–144.6, 148.9; ^{31}P NMR δ_P (ppm) 39.8; HRMS calcd for $C_{29}H_{29}N_4NaOP$ $(M+Na)^+$: 503.1971; found: 503.1986.

*4.4.8. Cyclohexyl-[4-(diphenylphosphinoyl)-4,5,6,7-tetrahydro-2H-indazol-3-yl]amine (**4g**).* Solid; yield=60%; mp 218–220 °C; ^1H NMR δ_H (ppm) 1.09–1.25 (m, 6H, CH_2), 1.45–1.88 (m, 8H, CH_2), 2.22–2.43 (m, 2H, CH_2), 3.18–3.26 (m, 1H, CHN), 3.58–3.67 (m, 1H, CHP(O)), 4.90 (s, 1H, HN–N), 6.10 (s, 1H, NH–*c*Hex), 7.34–7.72 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 18.4, 20.9, 21.8, 24.9, 25.4, 32.2 (J_{CP} 113.1 Hz), 35.3, 51.9, 94.1 (J_{CP} 5.9 Hz), 128.3–132.1, 152.2; ^{31}P NMR δ_P (ppm) 37.3; HRMS calcd for $C_{25}H_{31}N_3OP$ $(M+H)^+$: 420.2199; found: 420.2197.

*4.4.9. Cyclohexyl-[4-(diphenylphosphinoyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazol-3-yl]amine (**4h**).* Solid; yield=61%; mp 220–222 °C; ^1H NMR δ_H (ppm) 1.09–1.28 (m, 6H, CH_2), 1.42–1.78 (m, 8H, CH_2), 2.26–2.39 (m, 2H, CH_2), 3.23–3.31 (m, 1H, CHN), 3.56 (s, 3H, CH_3), 3.53–3.62 (m, 1H, CHP(O)), 6.23 (s, 1H, NH–*c*Hex), 7.31–7.70 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 18.9, 20.2, 21.8, 23.9, 25.7, 32.8 (J_{CP} 113.1 Hz), 34.7, 35.3, 52.6, 97.4 (J_{CP} 7.0 Hz), 127.3–135.4, 151.2; ^{31}P NMR δ_P (ppm) 38.3; HRMS calcd for $C_{26}H_{33}N_3OP$ $(M+H)^+$: 434.2356; found: 434.2347.

*4.4.10. 3-[3-Cyclohexylamino-4-(diphenylphosphinoyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl] propionitrile (**4i**).* Solid; yield=70%; mp 224–226 °C; ^1H NMR δ_H (ppm) 1.14–1.28 (m, 6H, CH_2), 1.39–1.93 (m, 8H, CH_2), 2.30–2.41 (m, 2H, CH_2), 2.79–2.85 (m, 2H, CH_2), 3.22–3.31 (m, 1H, CHN), 3.58–3.69 (m, 1H, CHP(O)), 4.07–4.12 (m, 2H, CH_2CN), 6.80 (s, 1H, NH–*c*Hex), 7.24–7.78 (m, 10H, CH_{ar}); ^{13}C NMR δ_C (ppm) 16.9, 18.4, 20.7, 21.8, 24.7, 26.0, 32.2 (J_{CP} 103.2 Hz), 35.7, 44.6, 51.8, 98.3 (J_{CP} 7.2 Hz), 127.3–137.1, 150.4; ^{31}P NMR δ_P (ppm) 37.3.

4.5. General procedure for the preparation of the derivatives 7a–d

To a solution of potassium *tert*-butoxide (0.01 mol, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise β-phosphorylketones **6a**,**b**[13–16] (0.01 mol, 1.0 equiv) in solution in anhydrous THF (20 mL) at room temperature, under nitrogen atmosphere. After 2 h of stirring, isothiocyanate (0.01 mol, 1.0 equiv) in solution in anhydrous THF (5 mL) was added to the reactional mixture. After 16 h of stirring at room temperature, the hydrolysis was performed with an aqueous saturated NH_4Cl solution. The aqueous layer was then extracted twice with $CHCl_3$ (2 x 50 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on silica gel (0.063–0.200 mm, eluent: 98/2 Et_2O/EtOH).

*4.5.1. 2-(Diphenylphosphinoyl)-3-oxo-3, N-diphenyl thiopropionamide (**7a**).* Solid; yield=87%; mp 184–186 °C; ^1H NMR δ_H (ppm) 6.45 (d, 1H, $^2J_{PH}$ 21.0 Hz, CHP(O)), 7.22–8.02 (m, 20H, CH_{ar}), 11.35 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 67.3 (J_{CP} 44.5 Hz), 125.1–139.0, 186.4 (J_{CP} 6.0 Hz), 190.6 (J_{CP} 4.5 Hz); ^{31}P NMR δ_P (ppm) 28.3; HRMS calcd for $C_{27}H_{22}NNaO_2PS$ $(M+Na)^+$: 478.1001; found: 478.0994.

*4.5.2. (2-Oxo-1-phenylthiocarbamoylpropyl) phosphonic acid diethyl ester (**7b**).* Solid; yield=86%; mp 170–172 °C; ^1H NMR δ_H (ppm) 1.35 (t, 6H, $^3J_{HH}$ 6.0 Hz, CH_3CH_2O), 2.48 (s, 3H, CH_3), 4.22 (qp, 4H, $^3J_{HH}$ 6.0 Hz, $^3J_{PH}$ 6.0 Hz, CH_2O), 5.24 (d, 1H, $^2J_{PH}$ 24.0 Hz, CHP(O)), 7.23–7.42 (m, 5H, CH_{ar}), 10.65 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 16.2, 32.2, 63.3, 71.6 (J_{CP} 113.9 Hz), 123.0–139.1, 186.0 (J_{CP} 8.3 Hz), 198.9 (J_{CP} 5.3 Hz); ^{31}P NMR δ_P (ppm) 14.1.

*4.5.3. 1-(Benzylthiocarbamoyl-2-oxopropyl) phosphonic acid diethyl ester (**7c**).* Solid; yield=77%; mp 175–177 °C; ^1H NMR δ_H (ppm) 1.28 (t, 6H, $^3J_{HH}$ 6.0 Hz, CH_3CH_2O), 2.43 (s, 3H, CH_3), 4.17 (qp, 4H, $^3J_{HH}$ 6.0 Hz, $^3J_{PH}$ 6.0 Hz, CH_2O), 4.73–4.79 (m, 2H, CH_2N), 5.20 (d, 1H, $^2J_{PH}$ 24.0 Hz, CHP(O)), 7.33–7.36 (m, 5H, CH_{ar}), 9.29 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 16.1, 32.2, 50.7, 62.2, 68.4 (J_{CP} 86.7 Hz), 127.6–135.8, 188.0, 198.4 (J_{CP} 5.3 Hz); ^{31}P NMR δ_P (ppm) 14.4.

*4.5.4. 1-(Cyclohexylthiocarbamoyl-2-oxopropyl) phosphonic acid diethyl ester (**7d**).* Solid; yield=81%; mp 172–174 °C; ^1H NMR δ_H (ppm) 1.37 (t, 6H, $^3J_{HH}$ 6.0 Hz, CH_3CH_2O), 1.60–2.01 (m, 10H, CH_2), 2.43 (s, 3H, CH_3), 4.17 (qp, 4H, $^3J_{HH}$ 6.0 Hz, $^3J_{PH}$ 6.0 Hz, CH_2O), 4.30–4.36 (m, 1H, CHN), 5.11 (d, 1H, $^2J_{PH}$ 24.0 Hz, CHP(O)), 9.02 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 16.2, 24.1, 25.4, 30.7, 32.1, 54.7, 63.7, 69.0 (J_{CP} 114.3 Hz), 185.9 (J_{CP} 7.5 Hz), 198.4 (J_{CP} 5.3 Hz); ^{31}P NMR δ_P (ppm) 14.2.

4.6. General procedure for the preparation of the derivatives 9b, c and e

Hydrazine (0.0011 mol, 1.1 equiv) was added to a solution of β-ketothioamides **7a**–**d** (0.001 mol, 1.0 equiv) in ethanol. After 24 h of stirring at room temperature, the residue was dried ($MgSO_4$), solvent was evaporated and the crude product was purified by column chromatography on silica gel (0.063–0.200 mm, eluent: AcOEt).

*4.6.1. 2-(Diphenylphosphinoyl)-N-phenylthio acetamide (**9b**).* Gummy liquid; yield=77%; ^1H NMR δ_H (ppm) 4.09 (d, 2H, $^2J_{PH}$ 12.0 Hz, CH_2P), 7.12–7.81 (m, 15H, CH_{ar}), 11.47 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 49.2 (J_{CP} 55.0 Hz), 123.2–139.2, 191.4 (J_{CP} 7.4 Hz); ^{31}P NMR δ_P (ppm) 33.1; HRMS calcd for $C_{20}H_{18}NNaOPS$ $(M+Na)^+$: 374.0739; found: 374.0742.

*4.6.2. (Benzylthiocarbamoylmethyl)phosphonic acid diethyl ester (**9c**).* Gummy liquid; yield=72%; ^1H NMR δ_H (ppm) 1.18 (t, 6H, $^3J_{HH}$ 6.0 Hz, CH_3CH_2O), 3.36 (d, 2H, $^2J_{PH}$ 24.0 Hz, CH_2P), 3.96 (qp, 4H, $^3J_{HH}$ 6.0 Hz, $^3J_{PH}$ 6.0 Hz, CH_2O), 4.72–4.74 (m, 2H, CH_2N), 7.17–7.27 (m, 5H, CH_{ar}), 9.39 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 15.3, 43.0 (J_{CP} 126.7 Hz), 49.3, 62.0, 124.4–135.2, 191.3 (J_{CP} 6.0 Hz); ^{31}P NMR δ_P (ppm) 21.1.

*4.6.3. Phenylthiocarbamoylmethylphosphonic acid diethyl ester (**9e**).* Gummy liquid; yield=76%; ^1H NMR δ_H (ppm) 1.34 (t, 6H, $^3J_{HH}$ 6.0 Hz, CH_3CH_2O), 3.65 (d, 2H, $^2J_{PH}$ 24.0 Hz, CH_2P), 4.19 (qp, 4H, $^3J_{HH}$

6.0 Hz, $^{3}J_{PH}$ 6.0 Hz, CH_2O), 7.11–7.72 (m, 5H, CH_{ar}), 11.09 (s, 1H, NH); ^{13}C NMR δ_C (ppm) 16.3, 46.3 (J_{CP} 126.7 Hz), 63.4, 122.8–139.2, 190.5 (J_{CP} 6.8 Hz); ^{31}P NMR δ_P (ppm) 21.2.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.093.

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