Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2019, **29**, 683–685

Mendeleev Communications

Catalyst-free addition of secondary phosphine chalcogenides to pyrazolecarbaldehydes

Svetlana F. Malysheva,[a] Vladimir A. Kuimov,[a] Natalia A. Belogorlova,[a] Nina K. Gusarova,[a] Ilya V. Taydakov,[b] Alexander I. Albanov,[a] Igor L. Eremenko[c] and Boris A. Trofimov*[a]

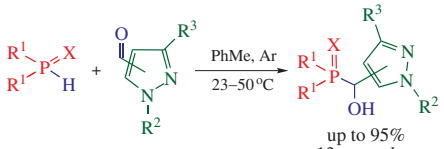
[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. E-mail: boris_trofimov@irioch.irk.ru*

[b] *P. N. Lebedev Physics Institute, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

[c] *N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2019.11.027

(Chalcogenophosphoryl)(hydroxyl)methyl-substituted pyrazoles were obtained by catalyst-free reaction between 4- and 5-pyrazolecarbaldehydes and secondary phosphine chalcogenides $R_2P(X)H$ [R = Ph, $(CH_2)_2Ph$, X = O, S, Se] at 23–50 °C in toluene.



R^1 = Ph, $(CH_2)_2Ph$; X = O, S, Se; R^2 = Me, Pr^i; R^3 = H, Me

Hybrid molecules containing pyrazole cycle and phosphine or phosphine chalcogenide moieties represent attractive objects for medicine, coordination chemistry, fine organic synthesis and advanced materials.[1–4] Platinum, palladium and copper complexes of phosphorylated pyrazoles possess cytotoxic activities against leukemia[5] and melanoma.[6] Today, a particular attention is targeted to lanthanides (specifically, Eu and Tb) pyrazole-tailored complexes as promising candidates for optoelectronics with extremely low energy consumption (OLEDs, displays and the like).[7] In the most known phosphorylated pyrazoles, the heterocycle ring is directly linked with the phosphorus atom, while the congeners wherein the pyrazole and phosphorus counterparts are separated by one carbon spacer are less studied. Among synthetic methods for their preparation are the reaction of 3(5)-chloromethyl pyrazole with lithium diphenylphosphide anion,[8] addition of diarylphosphine oxides to 4-benzylidenepyrazol-5-ones,[9] addition of pyrazole to (2-acylvinyl)(diphenyl)phosphine oxide,[10] and the reaction of phosphorylated diketones with hydrazines.[11]

Herein, we have performed a convenient and efficient synthesis of a new family of functionalized pyrazoles with (chalcogeno)-phosphoryl and hydroxyl groups by the catalyst-free addition of secondary phosphine chalcogenides to 4- and 5-pyrazolecarbaldehydes, which represents a novel (non-catalytic) extension of the classic Abramov reaction.[12]

After a series of experiments with diphenylphosphine oxide **1a** and 1-methylpyrazole-5-carbaldehyde **2a** as model reactants, we have found suitable conditions for the synthesis of [(hydroxyl)-(phosphoryl)methyl]pyrazole **3a** (Scheme 1, Table 1).† The reaction course was monitored by ^{31}P NMR, following the replacement of signal at 19 ppm [$Ph_2P(O)H$] by signal at ~ 30 ppm (adduct **3a**). The best parameters for the reaction providing 95% yield were as follows: the reactant molar ratio **1a**:**2a** = 1:1.05, toluene, 45–50 °C, 6 h (see Table 1, entry 4). Although the reaction can proceed at room temperature (entries 1 and 2), it takes a longer time (8–24 h) with lower yields of the adduct. The positive solvent effect (*cf.* entries 1 and 4) is associated with dilution of the reaction mixture since under solvent-free conditions the precipitate of rapidly formed adduct **3a** would prevent stirring. For aprotic solvents like benzene, toluene, THF, 1,4-dioxane (entries 4–7) no specific solvent effect was observed, the yield being just insignificantly decreased. In polar protic EtOH the reaction slowed down drastically, and the conversion of reactant **1a** and the yield of adduct **3a** for 12 h were only ~10% (entry 8).

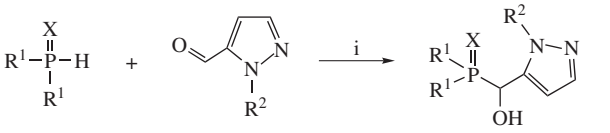
Interestingly, a slight excess of pyrazolecarbaldehyde **2a** favored the clean processing of the reaction, the adduct yield being near to quantitative. The synthesis is easily scaled up five-fold without affecting the yield (see Table 1, entry 9). To evaluate the scope of the reaction, we have varied the nature of both phosphine chalcogenide

Table 1 Optimization of the conditions for the reaction between $Ph_2P(O)H$ **1a** and pyrazolecarbaldehyde **2a**.[a]

Entry	molar ratio **1a**:**2a**	Solvent	*T*/°C	*t*/h	Yield of **3a** (%)
1	1:1	none	23–25	24	65
2	1:1	PhMe	23–25	8	80
3	1:1	PhMe	45–50	6	90
4	1:1.05	PhMe	45–50	6	95
5	1:1.05	PhH	45–50	6	94
6	1:1.05	THF	45–50	6	93
7	1:1.05	dioxane	45–50	6	90
8	1:1.05	EtOH	45–50	12	~10
9[b]	1:1.05	PhMe/CH_2Cl_2	45–50	8	95

[a] Reactants: $Ph_2P(O)H$ **1a** (1 mmol), pyrazolecarbaldehyde **2a** (1–1.05 mmol), solvent (2 ml), argon. [b] Pyrazolecarbaldehyde **2a** (5.25 mmol) and $Ph_2P(O)H$ **1a** (5 mmol) in PhMe (15 ml) were stirred during 6 h (45–50 °C), then CH_2Cl_2 (2 ml) was added, and the resulting solution was stirred at 45–50 °C for 2 h.

† *General procedure for synthesis of chalcogenophosphoryl hydroxymethyl pyrazoles* **3** *or* **5**. A mixture of the corresponding secondary phosphine chalcogenide **1** (1.00 mmol) and carbaldehyde **2** or **4** (1.05 mmol) in toluene (2 ml) was stirred at 23–50 °C for 6 to 94 h in argon atmosphere (see Online Supplementary Materials for details). Toluene was removed under vacuum, and the residue was washed with Et_2O (1 ml), dissolved in $CHCl_3$ and re-preciptated with *n*-hexane. The resulting solid was collected, dried under vacuum to afford alcohols **3** or **5**.

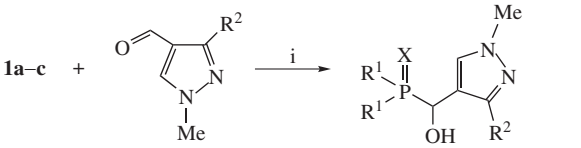


1a–e **2a,b** **3a–h**

a R^1 = Ph, X = O
b R^1 = $(CH_2)_2$Ph, X = O
c R^1 = $(CH_2)_2$Ph, X = S
d R^1 = Ph, X = Se
e R^1 = $(CH_2)_2$Ph, X = Se

a R^2 = Me
b R^2 = Pr^i

	R^1	R^2	X	Yield (%)
a	Ph	Me	O	95
b	Ph	Pr^i	O	93
c	$(CH_2)_2$Ph	Me	O	93
d	$(CH_2)_2$Ph	Pr^i	O	92
e	$(CH_2)_2$Ph	Me	S	92
f	$(CH_2)_2$Ph	Pr^i	S	87
g	Ph	Me	Se	80
h	$(CH_2)_2$Ph	Me	Se	89



4a,b **5a–e**

a R^2 = H
b R^2 = Me

	R^1	R^2	X	Yield (%)
a	Ph	H	O	90
b	Ph	Me	O	90
c	$(CH_2)_2$Ph	H	O	78
d	$(CH_2)_2$Ph	H	S	90
e	$(CH_2)_2$Ph	Me	S	85

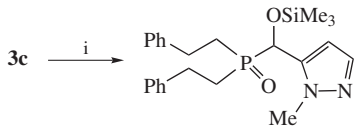
Scheme 1 *Reagents and conditions*: i, toluene, 23–50 °C, 6–90 h.

and pyrazolecarbaldehyde components (see Scheme 1). The reactions proceeded at room temperature or at 45–50 °C in toluene, and the yields of products **3** and **5** ranged within 78–95% (Table S1, see Online Supplementary Materials).

Evidently, the reaction occurs as the addition of P-centered nucleophile to the C=O bond. According to previous reasoning,[13] in similar processes four-coordinating phosphine chalcogenides actually react with electrophiles in their three-coordinated tautomeric forms which have a higher nucleophilicity due to the lone electron pair on the phosphorus atom. The substituent effect is in a satisfactory agreement with the mechanism. Indeed, secondary phosphine oxides of higher nucleophilicity[13(*d*)] are more reactive than the corresponding sulfur and selenium analogues. When diphenylphosphine oxide **1a** reacted with carbaldehyde **2a** at room temperature, the reaction lasted 8 h to result in 93% yield of adduct **3a**, while the process with the corresponding selenide **1d** required 7 h and the yield of adduct **3g** was 80%. Steric effects of the substituents in phosphine chalcogenides are noticeable, *i.e.*, addition of diphenylphosphine oxides **1a** to aldehyde **2a** occurs 2.5 times faster than that of bis(2-phenylethyl)phosphine oxide **1b** (Table S1, see Online Supplementary Materials). A similar phenomenon is observed for comparison between phosphine selenides **1d** and **1e**.

The [(chalcogenophosphoryl)(hydroxy)]methylpyrazoles **3** or **5** seem to be prospective building blocks for organic synthesis. Steric, electronic and affinity demands make them prospective ligands that can be easily and diversely modified at hydroxyl function of the methylene spacer. Herein, quantitative O-silylation of adduct **3c** with hexamethyldisilazane leading to silyl ether **6** was accomplished (Scheme 2).

The pharmacophore properties of the pyrazole counterpart and its bio-transport through membranes can be readily improved by their conversion into salts with various acids. In this study, compound **3a** was converted into its hydrotriflate **3a**·TfOH.



6, 95%

Scheme 2 *Reagents and conditions*: i, $(Me_3Si)_2NH$, reflux, 2 h.

In summary, the one-pot atom-economic high-yield synthesis of a new family of pyrazole-phosphine chalcogenide ensembles separated by functionalized one carbon hydroxymethylene spacer has been performed based on catalyst-free reaction between 4- and 5-pyrazolecarbaldehydes and secondary phosphine chalcogenides. The synthesized compounds seem to be promising ligands for metal complexes, key components for optoelectronics with extremely low energy consumption[7] as well as drug precursors.[4]

This work was supported by the Russian Foundation for Basic Research (grant no. 18-02-00653) and the approved plans for research projects at the IPC RAS (state registration no. AAAA-A16-116112510005-7). The authors are grateful to the Baikal Analytical Center of the SB RAS for the spectral measurements.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2019.11.027.

References

1 (*a*) N. S. Goulioukina, N. N. Makukhin and I. P. Beletskaya, *Russ. Chem. Rev.*, 2016, **85**, 667; (*b*) G. A. Abakumov, A. V. Piskunov, V. K. Cherkasov, I. L. Fedushkin, V. P. Ananikov, D. B. Eremin, E. G. Gordeev, I. P. Beletskaya, A. D. Averin, M. N. Bochkarev, A. A. Trifonov, U. M. Dzhemilev, V. A. D'yakonov, M. P. Egorov, A. N. Vereshchagin, M. A. Syroeshkin, V. V. Jouikov, A. M. Muzafarov, A. A. Anisimov, A. V. Arzumanyan, Y. N. Kononevich, M. N. Temnikov, O. G. Sinyashin, Y. H. Budnikova, A. R. Burilov, A. A. Karasik, V. F. Mironov, P. A. Storozhenko, G. I. Shcherbakova, B. A. Trofimov, S. V. Amosova, N. K. Gusarova, V. A. Potapov, V. B. Shur, V. V. Burlakov, V. S. Bogdanov and M. V. Andreev, *Russ. Chem. Rev.*, 2018, **87**, 393.

2 (*a*) T. V. Baiju and I. N. N. Namboothiri, *Chem. Rec.*, 2017, **17**, 939; (*b*) T. E. Ali and S. M. Abdel-Kariem, *Heterocycles*, 2012, **85**, 2073.

3 (*a*) E. Spink, D. Ding, Z. Peng, M. A. Boudreau, E. Leemans, E. Lastochkin, W. Song, K. Lichtenwalter, P. I. O'Daniel, S. A. Testero, H. Pi, V. A. Schroeder, W. R. Wolter, N. T. Antunes, M. A. Suckow, S. Vakulenko, M. Chang and S. Mobashery, *J. Med. Chem.*, 2015, **58**, 1380; (*b*) M. Chang, S. Mobashery, E. Spink, D. Ding, S. Testero, E. Leemans and M. A. Bouderau, *Patent WO 2016049586*, 2016; (*c*) W. Zhang, C. P. Tam, J. Wang and J. W. Szostak, *ACS Central Sci.*, 2016, **2**, 916; (*d*) D. S. Goldfarb, *Patent US 20090163545 A1*, 2009; (*e*) Y. Kim and Y. Yoon, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2256; (*f*) Y. Yoon, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2334; (*g*) M. Lilley, B. Mambwe, M. J. Thompson, R. F. W. Jackson and R. Muimo, *Chem. Commun.*, 2015, **51**, 7305; (*h*) J. M. Kee, R. C. Oslund, A. D. Couvillon and T. W. Muir, *Org. Lett.*, 2015, **17**, 187; (*i*) J. Modranka, R. Jakubowski, M. Rozalski, U. Krajewska, A. Janecka, K. Gach, D. Pomorska and T. Janecki, *Eur. J. Med. Chem.*, 2015, **92**, 565; (*j*) S. K. Nayab Rasool, C. Subramanyam, D. B. Janakiramudu, P. Supraja, R. Usha and C. N. Raju, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2018, **193**, 470; (*k*) O. Gebauer, H. Gayer, U. Heinemann, S. Herrmann, S. Hillebrand, H.-l. Elbe, R. Ebbert, U. Wachendorff-Neumann, P. Dahmen and K.-H. Kuck, *Patent US 20050187224*, 2005; (*l*) U. Doeller, M. Maier, A. Kuhlmann, D. Jans, A. M. Pinchuk, A. P. Marchenko and G. N. Koydan, *Patent WO 2005082917*, 2005; (*m*) P. C. Miller, J. M. Curtis, J. M. Molyneaux and T. J. Owen, *Patent WO 2000046229*, 2000.

4 (*a*) A. F. Shidlovskii, A. S. Peregudov, Y. N. Bulychev and N. D. Chkanikov, *Pharm. Chem. J.*, 2009, **43**, 549; (*b*) N. Sudhapriya, C. Balachandran, S. Awale and P. T. Perumal, *New J. Chem.*, 2017, **41**, 5582; (*c*) N. F. El-Sayed, E. F. Ewies, M. El-Hussieny, L. S. Boulos and E. M. Shalaby, *Z. Naturforsch. B*, 2016, **71**, 765; (*d*) V. E. Rani and L. K. Ravindranath, *Open Pharm. Sci. J.*, 2016, **3**, 49; (*e*) V. E. Rani and L. K. Ravindranath, *Am. J. Org. Chem.*, 2016, **6**, 1; (*f*) E. Leemans, K. V. Mahasenan, M. Kumarasiri, E. Spink, D. Ding, P. I. O'Daniel, M. A. Boudreau,

E. Lastochkin, S. A. Testero, T. Yamaguchi, M. Lee, D. Hesek, J. F. Fisher, M. Chang and S. Mobashery, *Bioorg. Med. Chem. Lett*., 2016, **26**, 1011.

5 (*a*) K. Malinowska, R. Modranka, K. Kubiak, M. Mrowicka, J. Kedziora, A. Klimczak and M. Rutkowski, *Pol. Merkuriusz Lek*., 2009, **26**, 52; (*b*) B. Kupcewicz, K. Sobiesiak, K. Malinowska, K. Koprowska, M. Czyz, B. Keppler and E. Budzisz, *Med. Chem. Res*., 2013, **22**, 2395.

6 (*a*) E. Budzisz, U. Krajewska, M. Rozalski, A. Szulawska, M. Czyz and B. Nawrot, *Eur. J. Pharmacol*., 2004, **502**, 59; (*b*) E. Budzisz, M. Miernicka, I. P. Lorenz, P. Mayer, U. Krajewska and M. Rozalski, *Polyhedron*, 2009, **28**, 637.

7 (*a*) E. A. Varaksina, I. V. Taydakov, S. A. Ambrozevich, A. S. Selyukov, K. A. Lyssenko, L. T. Jesus and R. O. Freire, *J. Lumin.*, 2018, **196**, 161; (*b*) A. G. Vitukhnovsky, S. A. Ambrozevich, V. M. Korshunov, I. V. Taydakov, K. A. Lyssenko, M. T. Metlin and A. S. Selyukov, *J. Lumin*., 2018, **201**, 509; (*c*) D. A. Metlina, M. T. Metlin, S. A. Ambrozevich, I. V. Taydakov, K. A. Lyssenko, A. G. Vitukhnovsky, A. S. Selyukov, V. S. Krivobok, D. F. Aminev and A. S. Tobokhova, *J. Lumin*., 2018, **203**, 546.

8 (*a*) D. B. Grotjahn, D. Combs, S. Van, G. Aguirre and F. Ortega, *Inorg. Chem.*, 2000, **39**, 2080; (*b*) I. D. Alshakova, I. Korobkov, L. G. Kuzmina and G. I. Nikonov, *J. Organomet. Chem.*, 2017, **853**, 68.

9 Z.-C. Geng, J.-X. Zhang, N. Li, J. Chen, X.-F. Huang, S.-Y. Zhang, H.-Y. Li, J.-C. Tao and X.-W. Wang, *Tetrahedron*, 2014, **70**, 417.

10 M. A. Galkina, G. V. Bodrin, E. I. Goryunov, I. B. Goryunova, A. A. Ambartsumyan, T. T. Vasil'eva, P. S. Protopopova, A. E. Saifutiarova, A. B. Uryupin, V. K. Brel and K. A. Kochetkov, *Russ. Chem. Bull., Int. Ed*., 2016, **65**, 1855 (*Izv. Akad. Nauk., Ser. Khim.*, 2016, 1855).

11 A. A. Ambartsumyan, L. A. Sviridova, N. I. Vorozhtsov, E. I. Goryunov, G. V. Bodrin, I. B. Goryunova, A. B. Uryupin, T. T. Vasil'eva, O. V. Chakhovskaya, K. A. Kochetkov and E. E. Nifant'ev, *Dokl. Chem.*, 2013, **448**, 35.

12 (*a*) V. S. Abranmov, *Dokl. Akad. Nauk SSSR*, 1950, **73**, 487; (*b*) *Organophosphorus Reagents. A Practical Approach in Chemistry*, Oxford University Press, New York, 2004; (*c*) J. Guin, Q. Wang, M. van Gemmeren and B. List, *Angew. Chem., Int. Ed.*, 2015, **54**, 355.

13 (*a*) N. K. Gusarova, A. M. Reutskaya, N. I. Ivanova, A. S. Medvedeva, M. M. Demina, P. S. Novopashin, A. V. Afonin, A. I. Albanov and B. A. Trofimov, *J. Organomet. Chem.*, 2002, **659**, 172; (*b*) N. I. Ivanova, N. K. Gusarova, E. A. Nikitina, A. I. Albanov, L. M. Sinegovskaya, M. V. Nikitin, N. A. Konovalova and B. A. Trofimov, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 7; (*c*) N. K. Gusarova, N. I. Ivanova, N. A. Konovalova, B. G. Sukhov, L. V. Balkalova, L. M. Sinegovskaya, D. V. Pavlov and B. A. Trofimov, *Synthesis*, 2006, 4159; (*d*) N. K. Gusarova, N. I. Ivanova, P. A. Volkov, K. O. Khrapova, L. I. Larina, V. I. Smirnov, T. N. Borodina and B. A. Trofimov, *Synthesis*, 2015, **47**, 1611.

Received: 8th May 2019; Com. 19/5916