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2-Halopyridines in the triple reaction in the P_n/KOH/DMSO system to form tri(2-pyridyl)phosphine: experimental and quantum-chemical dissimilarities

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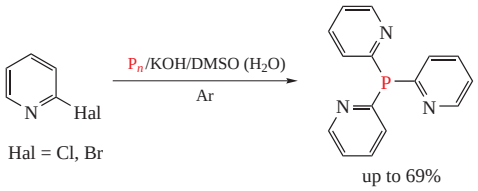
Experimental and quantum-chemical features of the triple nucleophilic substitution of halogen atoms in 2-chloro- and 2-bromopyridines under the action of P-centered nucleophiles generated in the system P_n/KOH/DMSO to afford tri(2-pyridyl)phosphine in a yield of up to 69% have been compared.

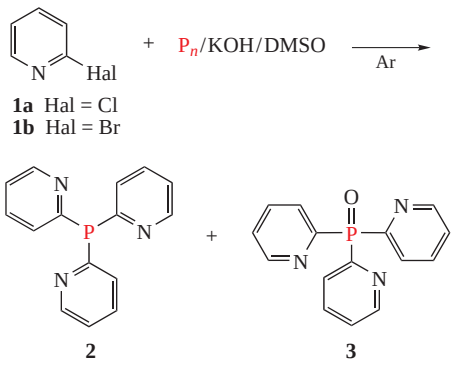


Tri(2-pyridyl)phosphine is an effective in-demand tripodal ligand for the synthesis of scorpionate transition metal complexes[1] and clusters,[2] some of which catalyze important industrial reactions.[3] Complexes of this phosphine and its chalcogenides are used for the design of optoelectronic devices,[4] heat-resistant photomaterials,[5] single molecular or single ion magnets,[1(c)] find application as additives to electrolyte for lithium-ion batteries,[6] precursors to radiopharmacetucals[7] and also as building blocks for organic synthesis.[8]

A wider application of this phosphine is limited by the lack of its expedient syntheses, the known techniques being multistep[9] and based on hazardous, toxic and moisture-sensitive phosphorus halides and organometallic reagents.[4(a),9] Meanwhile, a major trend of modern organic synthesis is a departure from multi-pot procedures using ecologically malignant reagents and metal catalysts to arrive at pot, atom, and step economy (PASE paradigm).[10]

A while ago, tri(2-pyridyl)phosphine has been synthesized from 2-bromopyridine in a one synthetic operation.[11] However, it remains practically important to replace 2-bromopyridine by more accessible and inexpensive 2-chloropyridine in the same synthesis.

In this communication, we have compared experimental and quantum-chemical features of this synthesis including rationalization of the initial step of this unconventional triple nucleophilic substitution at the phosphorus-centered nucleophiles generated *in situ* in the P_n/KOH/DMSO system (Scheme 1).



Scheme 1

After a series of experiments with red phosphorus (P_n) and chloropyridine **1a**, we have found that a synthetically reasonable yield of tri(2-pyridyl)phosphine **2** (69%) and good selectivity (relative to phosphine **2**) can be attained under the conditions shown in Table 1 (entry 3).

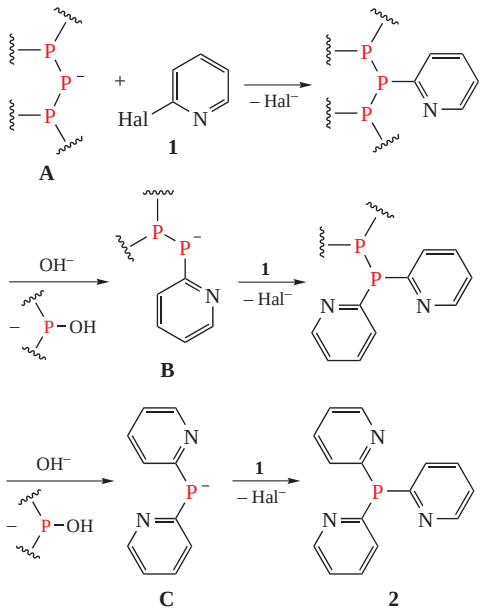
White phosphorus (P_4) allotrope reacted with pyridines **1a**,**b** at lower temperature (100 °C and 75 °C, respectively) to form, in case of chloropyridine **1a**, a 1:1 mixture of both phosphine **2** and its oxide **3** (entry 5), while with bromopyridine **1b** only phosphine **2** was isolated (entry 7).

As seen from Table 1, the conditions for the synthesis of phosphine **2** from 2-chloropyridine are significantly harsher as compared to those for 2-bromopyridine (entries 3, 6). Note that 2-bromopyridine-based synthesis of phosphine **2** from red phosphorus, unlike that with 2-chloropyridine, is not chemoselective: along with the target phosphine **2** (yield 62%), 10% of the corresponding phosphine oxide **3** is formed (entry 6). Besides, the conditions of this synthesis are not transferable to 2-chloropyridine (the yield of **2** is just 30% at 74% conversion, entry 1). The best conditions for the synthesis of phosphine **2** from 2-chloropyridine are the following: the reactants equivalent ratio **1**:P:KOH·0.5H_2O = 1:2:4.6, DMSO, 125 °C, 1 h, argon

Table 1 Phosphorylation of halopyridines **1a**,**b** with elemental phosphorus.

Entry	Substrate	Hal	P	Equivalent ratio of **1**:P_n:KOH·0.5H_2O[a]	*T*/°C	*t*/h	Conversion of **1** (%)	Yield (%)[b]	
								2	**3**
1	**1a**	Cl	P_n	1:2:3	100	3	74	30	traces
2	**1a**	Cl	P_n	1:2:3	125	3	75	51	traces
3	**1a**	Cl	P_n	1:2:4.6	125	1	79	69	traces
4	**1a**	Cl	P_n	1:2:6	125	3	~100	48	traces
5	**1a**	Cl	P_4	1:2:3	100	3	65	10	11
6	**1b**	Br	P_n	1:2:3	100	3	100	62	10
7	**1b**	Br	P_4	1:2:3	75	3	Not determined[11(a)]	50	traces

[a] Additional reaction mixture components: H_2O (2 ml), DMSO (50 ml), argon.
[b] Based on the reacted **1**.

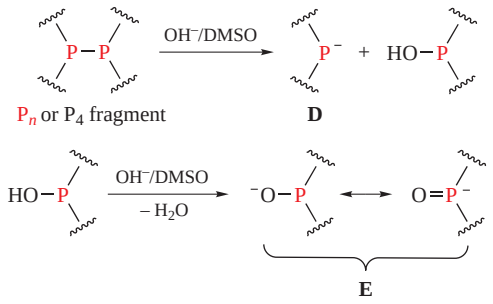


Scheme 2

(entry 3). Under these conditions, the conversion of chloropyridine **1a** was 79% and the isolated yield of phosphine **2** reached 69%.

An advantage and most peculiar feature of this synthesis is that neither primary nor secondary corresponding phosphines were detected (^{31}P NMR). This phenomenon is likely associated with the multiphase nature of the reaction mixture, consisting of the liquid phase (~95% aq. DMSO and 2-halopyridine) and a number of solid phases (red phosphorus, insoluble polyphosphide oligomers originated from the P–P bond cleavage of the polymeric phosphorus network, and some KOH particles). The shorter-chain polyphosphide oligomers **A** are gradually extracted in small quantities to the liquid phase where they would quickly react with excess of haloropyridines. This results in a fast formation of phosphine **2** *via* primary **B** and secondary **C** intermediate phosphine predecessors (Scheme 2). The rate of the each next nucleophilic substitution act should expectedly increase on going from phosphide **A** to the intermediates **B** and **C** due to the progressively enhancing nucleophilicity of the intermediates. Low concentration of KOH in the liquid phase (due to its poor solubility in DMSO) explains the failure of hydroxide ion to compete with the phosphide anionic species **A**–**C** for the nucleophilic substitution of halogen ion in the 2-halopyridine molecule.

Eventually, as it has been previously assumed,[12] the 3D-polymer molecules of elemental phosphorus (P_n and P_4) are actually disassembled in multiphase superbase system of the KOH/DMSO type to initially generate polyphosphide **D** and polyphosphinite **E** particles, including micro, submicro and nanosized ones (Scheme 3). Anions **D** and **E** (as their shorter oligomers, see Scheme 2) are trapped by electrophilic 2-halopyridines to yield the corresponding tertiary phosphine or its oxide.[11–13] In fact,



Scheme 3

the real reaction mixture represents a dynamically changing cocktail of P- and P(O)-centered anions with different number of phosphorus atoms.

This simplest scheme can justify the chosen models for the quantum-chemical evaluation (specified below) of the reaction. It is suggested[12(b),(c)] that the reaction course depends on charge and orbital consistency between the electrophile (in this case, 2-halopyridines) and P-centered anions.

In the last years, halopyridines, due to peculiarities in their electronic structure, became a subject of theoretical investigations to understand their reactivity in terms of orbital localization and photoionization dynamics. These structural features of 2-chloro- and 3-chloropyridines have been recently studied both experimentally and theoretically.[14,15]

In order to rationalize dissimilarities in the reactivity features of 2-chloro- and 2-bromopyridines toward polyphosphide **D** and polyphosphinite **E** anions, we have performed the quantum chemical calculation of the atomic charge values and LUMO/HOMO localization in these electrophiles and P nucleophiles using H_2P^- and $H_2P(O)^-$ as simplest models. The molecular structures were optimized using MP2 method, and the electronic structure was analyzed using natural bond orbital (NBO) and outer-valence Green's function (OVGF) methods. The cc-pVTZ basis sets were used in the calculations. The relevant molecular characteristics selected from whole body of the computed data (see Online Supplementary Materials) are given in Tables 2 and 3.

As follows from Table 2, the charge difference at C(2) is in favor of 2-chloropyridine (0.25 *vs.* 0.19). The difference in LUMO localization at the same carbon (which has no significant component at this atom) is small. The next higher-lying unoccupied orbital (LUMO+1) has pronounced C(2) character which is slightly stronger in 2-chloropyridine **1a** than in 2-bromopyridine **1b**. The negative charge in H_2P^- anion is localized on phosphorus atom (–0.78), while in $H_2P(O^-)$ anion the phosphorus atom is charged positively (+0.79) and the negative charge is localized on the oxygen atom (–1.28). Therefore, in view of the small difference of the positive charges on the C(2) atom in halopyridines **1a**,**b** (see Table 2), the charge-controlled nucleophilic substitution with the participation of H_2P^- and $H_2P(O)^-$ anions in this case seems unlikely. Consequently, the formation of tertiary phosphine **2** should be referred to the orbital-controlled process. The energy gaps between LUMO+1 of electrophiles (halopyridines **1a**,**b**) and HOMO of H_2P^- nucleophile (2.33 and 2.24 eV, respectively) indicate that higher reactivity of 2-bromopyridine **1b** can be expected, which is in agreement with the experimental results

Table 2 Atomic NBO charges on C(2) atom, orbital C(2) character [molecular orbital fraction localized on C(2) atom] and orbital energies computed using the OVGF method for 2-chloropyridine **1a** and 2-bromopyridine **1b**.

Molecule	Charge on C(2) (a.u.)	Orbital C(2) character		Orbital energy/eV	
		LUMO	LUMO+1	LUMO	LUMO+1
2-Chloropyridine **1a**	+0.25	0.07	0.26	1.23	1.63
2-Bromopyridine **1b**	+0.19	0.09	0.24	1.18	1.54

Table 3 Atomic NBO charges, Mulliken atomic populations in HOMO and HOMO energies computed using OVGF method for H_2P^- and $H_2P(O)^-$ anions.

Anion	Charge on P (a.u.)	HOMO atomic populations (electrons)	HOMO energy/eV
H_2P^-	–0.78	1.98	–0.70
$H_2P(O)^-$	+0.79	1.12	–1.94

(see Table 1). Noteworthy, the corresponding LUMO+1/HOMO energy gap for $H_2P(O^-)$ species is much larger (3.57 and 3.48 eV, respectively), which makes their participation in the nucleophilic substitution of halogen atoms in halopyridines **1a**,**b** less favorable, though for 2-bromopyridine **1b** slightly more probable. The latter explains the appearance of the corresponding phosphine oxide **3** in the case of 2-bromopyridine **1b** (see Table 1, entry 6). However, because of simplest approximation accepted here for the complicated P-centered anions, in the real reaction mixture, the effective polyphosphinite $HP(O^-)$ terminated species may have a significantly lower LUMO+1/HOMO energy gap, which can lead to the formation of tertiary phosphine oxides and phosphinic acids, as it was previously reported.[13,16,17] Evidently, the structure and reactivity of the forming polyphosphide anions should depend on phosphorus allotropic state and the reaction conditions. This may explain why tri(2-pyridyl)phosphine oxide **3**, along with the corresponding phosphine **2**, are formed in the reaction with phosphorus white (see Table 1, entry 5).

In conclusion, phosphorylation of 2-halopyridines **1a**,**b** in the multiphase superbase system red phosphorus/KOH/DMSO affords tri(2-pyridyl)phosphine in a yield of up to 69%. The selectivity of this one-pot triple substitution at P-centered nulceophiles is explained by multiphase character of the reaction mixture, in which oligophosphide anionic species are gradually delivered into the liquid phase enriched by large excess of 2-halopyridines. The orbital control is preferred for the first act of the nucleophilic substitution of halogen atoms in 2-chloro- and 2-bromopyridines, being more pronounced for the latter.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.006.

References

1 (*a*) T. Gneuß, M. J. Leitl, L. H. Finger, N. Rau, H. Yersin and J. Sundermeyer, *Dalton Trans.*, 2015, **44**, 8506; (*b*) S. Hanf, R. García-Rodríguez, A. D. Bond, E. Hey-Hawkins and D. S. Wright, *Dalton Trans.*, 2016, **45**, 276; (*c*) A. V. Artem'ev, A. V. Kashevskii, A. S. Bogomyakov, A. Yu. Safronov, A. O. Sutyrina, A. A. Telezhkin and I. V. Sterkhova, *Dalton Trans.*, 2017, **46**, 5965; (*d*) R. Suter, H. Sinclair, N. Burford, R. McDonald, M. J. Ferguson and E. Schrader, *Dalton Trans.*, 2017, **46**, 7681.

2 A. V. Artem'ev, I. Yu. Bagryanskaya, E. P. Doronina, P. M. Tolstoy, A. L. Gushchin, M. I. Rakhmanova, A. Yu. Ivanov and A. O. Suturina, *Dalton Trans.*, 2017, **46**, 12425.

3 (*a*) A. Karam, R. Tenia, M. Martinez, F. López-Linares, C. Albano, A. Diaz-Barrios, Y. Sánchez, E. Catarí, E. Casas, S. Pekerar and A. Albornoz, *J. Mol. Catal. A: Chem.*, 2007, **265**, 127; (*b*) F. Lopez-Linares, A. Fuentes, R. Tenia, M. Martinez and A. Karam, *React. Kinet. Catal. Lett.*, 2007, **92**, 285; (*c*) A. N. Kharat, B. T. Jahromi and A. Bakhoda, *Transit. Met. Chem.*, 2012, **37**, 63; (*d*) D. W. Norman and J. L. Laningham, *Patent US 20150080628*, 2015 (*Chem. Abstr.*, 2015, **162**, 438977).

4 (*a*) T. Gneuß, J. Sundermeyer, M. Leitl and H. Yersin, *Patent DE 102014116314*, 2016 (*Chem. Abstr.*, 2016, **164**, 609200); (*b*) A. V. Artem'ev, E. P. Doronina, M. I. Rakhmanova, A. O. Sutyrina, I. Yu. Bagryanskaya, P. M. Tolstoy, A. L. Gushchin, A. S. Mazur, N. K. Gusarova and B. A. Trofimov, *New J. Chem.*, 2016, **40**, 10028.

5 T. Hanyu, *Patent JP 2003057783*, 2003 (*Chem. Abstr.*, 2003, **138**, 195810).

6 K. Amine, L. Zhang and Z. Zhang, *Patent US 20140272607*, 2014 (*Chem. Abstr.*, 2014, **161**, 477212).

7 (*a*) J. J. Liu, P. Galettis, A. Farr, L. Maharaj, H. Samarasinha, A. C. McGechan, B. C. Baguley, R. J. Bowen, S. J. Berners-Price and M. J. McKeage, *J. Inorg. Biochem.*, 2008, **102**, 303; (*b*) J. R. Luque-Ortega, P. Reuther, L. Rivas and C. Dardonville, *J. Med. Chem.*, 2010, **53**, 1788; (*c*) A. N. Kharat, A. Bakhoda, S. Foroutannejad and C. Foroutannejad, *Z. Anorg. Allg. Chem.*, 2011, **637**, 2260; (*d*) A. V. Artem'ev, J. A. Eremina, E. V. Lidera, O. V. Antonova, E. V. Vorontsova and I. Yu. Bagryanskaya, *Polyhedron*, 2017, **138**, 218.

8 (*a*) S. N. Arbuzova, N. K. Gusarova, T. E. Glotova, I. A. Ushakov, S. I. Verkhoturova, A. O. Korocheva and B. A. Trofimov, *Eur. J. Org. Chem.*, 2014, 639; (*b*) S. N. Arbuzova, N. K. Gusarova, S. I. Verkhoturova, T. I. Kazantseva, I. A. Ushakov, A. G. Mal'kina and B. A. Trofimov, *Heteroatom Chem.*, 2015, **26**, 231; (*c*) T. F. Vaughan and J. L. Spencer, *Dalton Trans.*, 2016, **45**, 16826; (*d*) S. F. Malysheva, N. K. Gusarova, N. A. Belogorlova, A. O. Sutyrina, Yu. I. Litvintsev, A. I. Albanov, I. V. Sterkhova and A. V. Artem'ev, *Synlett*, 2016, **27**, 2451; (*e*) N. K. Gusarova, P. A. Volkov, N. I. Ivanova, K. O. Khrapova, A. A. Telezhkin, A. I. Albanov and B. A. Trofimov, *Mendeleev Commun.*, 2017, **27**, 553.

9 (*a*) R. J. Bowen, A. C. Garner, S. J. Berners-Price, I. D. Jenkins and R. E. Sue, *J. Organomet. Chem.*, 1998, **554**, 181; (*b*) A. M. Kluwer, I. Ahmad and J. N. H. Reek, *Tetrahedron Lett.*, 2007, **48**, 2999.

10 (*a*) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*b*) A. N. Vereshchagin, M. N. Elinson, Yu. E. Anisina, F. V. Ryzhkov, A. S. Goloveshkin, I. S. Bushmarinov, S. G. Zlotin and M. P. Egorov, *Mendeleev Commun.*, 2015, **25**, 424; (*c*) A. R. Romanov, A. Y. Rulev, I. A. Ushakov, V. M. Muzalevskiy and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2017, 4121; (*d*) A. N. Vereshchagin, M. N. Elinson, Yu. E. Anisina, F. V. Ryzhkov, R. A. Novikov and M. P. Egorov, *ChemistrySelect*, 2017, **2**, 4593.

11 (*a*) B. A. Trofimov, A. V. Artem'ev, S. F. Malysheva, N. K. Gusarova, N. A. Belogorlova, A. O. Korocheva, Yu. V. Gatilov and V. I. Mamatyuk, *Tetrahedron Lett.*, 2012, **53**, 2424; (*b*) B. A. Trofimov, N. K. Gusarova, A. V. Artem'ev, S. F. Malysheva, N. A. Belogorlova, A. O. Korocheva, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Mendeleev Commun.*, 2012, **22**, 187.

12 (*a*) B. A. Trofimov, T. N. Rakhmatulina, N. K. Gusarova and S. F. Malysheva, *Russ. Chem. Rev.*, 1991, **60**, 1360 (*Usp. Khim.*, 1991, **60**, 2619); (*b*) B. A. Trofimov and N. K. Gusarova, *Mendeleev Commun.*, 2009, **19**, 295; (*c*) N. K. Gusarova, S. N. Arbuzova and B. A. Trofimov, *Pure Appl. Chem.*, 2012, **84**, 439.

13 V. A. Kuimov, S. F. Malysheva, N. K. Gusarova, T. I. Vakul'skaya, S. S. Khutsishvili and B. A. Trofimov, *Heteroatom Chem.*, 2011, **22**, 198.

14 A. B. Trofimov, D. M. P. Holland, I. Powis, R. C. Menzies, A. W. Potts, L. Karlsson, E. V. Gromov, I. L. Badsyuk and J. Schirmer, *J. Chem. Phys.*, 2017, **146**, 244307.

15 D. M. P. Holland, I. Powis, A. B. Trofimov, R. C. Menzies, A. W. Potts, L. Karlsson, I. L. Badsyuk, T. E. Moskovskaya, E. V. Gromov and J. Schirmer, *J. Chem. Phys.*, 2017, **147**, 164307.

16 (*a*) A. V. Artem'ev, N. K. Gusarova, A. O. Korocheva, S. F. Malysheva, Yu. V. Gatilov and B. A. Trofimov, *Mendeleev Commun.*, 2014, **24**, 29; (*b*) A. V. Artem'ev, A. O. Korocheva, A. V. Vashchenko, V. I. Smirnov and S. F. Malysheva, *Phosphorus Sulfur Silicon Relat. Elem.*, 2015, **190**, 1455; (*c*) A. V. Artem'ev, S. F. Malysheva, N. K. Gusarova, N. A. Belogorlova, B. G. Sukhov, A. O. Sutyrina, E. A. Matveeva, S. F. Vasilevsky, A. I. Govdi, Y. V. Gatilov, A. I. Albanov and B. A. Trofimov, *Tetrahedron*, 2016, **72**, 443.

17 (*a*) A. V. Artem'ev, S. F. Malysheva, A. O. Korocheva and I. Yu. Bagryanskaya, *Heteroatom Chem.*, 2012, **23**, 568; (*b*) A. V. Artem'ev, A. O. Sutyrina, E. A. Matveeva, A. I. Albanov and L. V. Klyba, *Mendeleev Commun.*, 2017, **27**, 137.

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