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Extraordinary sulfur/oxygen exchange between P=S and C=O bonds during the reaction of γ-amino ynones with secondary phosphine sulfides

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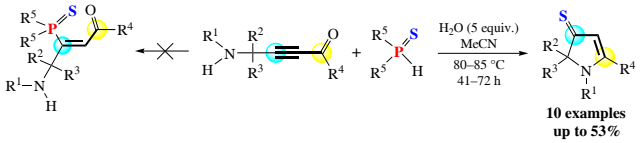
Unknown reactivity patterns of P=S and C=O bonds were observed when γ-amino α,β-ynones reacted with secondary phosphine sulfides affording, instead of the addition/cyclization products, 1,2-dihydro-3*H*-pyrrole-3-thiones and the corresponding secondary phosphine oxides. The reaction mechanism involves the sulfur/oxygen exchange between the P=S and C=O functions. This is the first case of the successful competition between the P=S and P–H moieties as nucleophiles for electrophilic triple bond.



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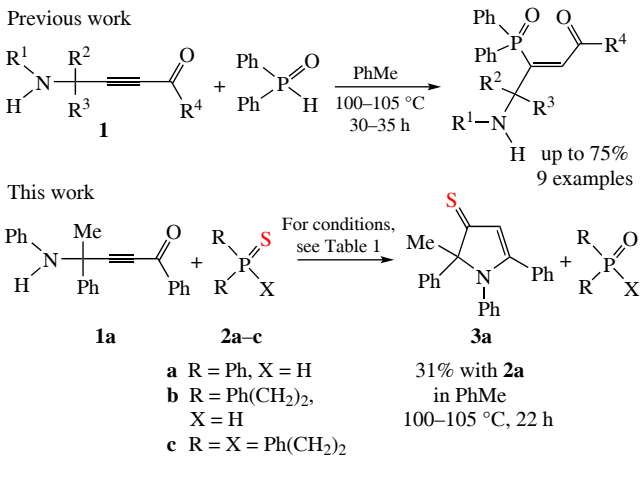
The reactions of secondary phosphine chalcogenides with acetylenes, including electron-deficient ones (alkyl propiolates,[1,2] acetylenedicarboxylates,[3–5] acetylenic ketones,[6–10] cyanoacetylenes[11,12]) are in the focus of modern research.[11–18] Usually, the main products of such reactions are the corresponding mono- or diadducts of secondary phosphine chalcogenides to the triple bond, *i.e.*, tertiary ethenyl phosphine or bisphosphine chalcogenides.[3,4,6,7,11,12] These compounds are employed as precursors of biologically active substances,[13,14] ligands for the design of metal complexes,[15–17] extractants of rare earth metals[18–20] and multifaceted building blocks in organic synthesis.[21–24] Meanwhile, the reactions of secondary phosphine sulfides with electron-deficient acetylenic ketones, particularly those with additional functionality,[25] remain understudied.[6,7] These reactions can produce adducts both at the triple bond[6,7] and carbonyl group.[26]

Recently, the reaction of secondary diphenylphosphine oxide with a novel family of functionalized acetylenic ketones, namely, γ-amino α,β-ynones, was investigated. The latter became readily available from propargylic amines, adducts of acetylene gas to Schiff bases.[27] These propargylic amines are readily cross-coupled with (hetero)aromatic acyl chlorides in the presence of the catalytic system $PdCl_2$/CuI/Ph_3P/Et_3N to afford γ-amino ynones.[28] The thus obtained amino ynones **1** reacted regio-, stereo- and chemoselectively with $Ph_2P(O)H$ (no catalyst, toluene, 100–105 °C) to give *Z*-3-diphenylphosphoryl-1,4-diorganyl-4-(organylamino)alk-2-en-1-ones in yields up to 75% (Scheme 1, upper line).[29] However, when attempted (in the origin of present work) to extend this reaction over secondary phosphine sulfides it turned out, that under similar conditions, the reaction of 1,4-diphenyl-4-(phenylamino)pent-2-yn-1-one **1a** with diphenylphosphine sulfide **2a** took absolutely unexpected pathway. Instead of ordinary addition, the sulfur atom transfer to acetylenic ketone with simultaneous release of oxygen to give 1,2-methyl-1,2,5-triphenyl-1,2-dihydro-3*H*-pyrrole-3-thione **3a** was observed (yield 31%, see Scheme 1, lower line). Diphenylphosphine oxide was detected as the secondary reaction product (^{31}P NMR). The awaited adducts of diphenylphosphine sulfide to the triple bond were fixed in the reaction mixture only in negligible amounts (~5–7%).

The aim of this work was to study the main features of the above sulfur/oxygen exchange/cyclization process during the reaction between γ-amino α,β-ynones **1** and secondary phosphine sulfides. To determine the basic preparative patterns of the sulfur/oxygen exchange/cyclization found, we investigated the reactions between model 1,4-diphenyl-4-(phenylamino)pent-2-yn-1-one **1a** and diphenyl-, bis(2-phenylethyl)-, and tris(2-phenylethyl)phosphine sulfides **2a–c** (see Scheme 1). Bis(2-phenylethyl)phosphine sulfide **2b** was readily available *via* the reaction of styrene with PH_3/H_2O mixture generated from red phosphorus in superbase media[30] followed by treatment with elemental sulfur. The reaction was monitored by ^{31}P NMR



Scheme 1

spectroscopy until complete conversion of the starting phosphine sulfide, as well as by IR spectroscopy following disappearance of the absorption band at ~2208 cm^{-1} for the C≡C bond. In the reaction mixture, the corresponding phosphine oxide was also identified (^{31}P NMR data).

Diorganylphosphine sulfides **2a**,**b** reacted with amino ynone **1a** (toluene, 100–105 °C, 22 h) to afford 1,2-dihydro-3*H*-pyrrole-3-thione **3a** in 31 and 26% yields, respectively (Table 1, entries 1, 2). A little bit higher yield (32%) was achieved when the reaction **1a**+**2b** was carried out in acetonitrile at 80–85 °C for 60 h (entry 3). At lower temperature (50–55 °C), the yield of thione **3a** considerably decreased (to 10%) despite a longer (80 h) heating (entry 5), while at room temperature no target thione **3a** was detected (entry 4).

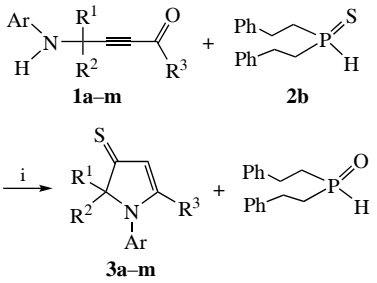
The highest yield of thione **3a** (53%, see Table 1, entry 6) was observed under the following conditions: aqueous MeCN (5 equiv. of water per 1 equiv. of ketone **1a**), 80–85 °C, 48 h. A slightly lower efficiency of the process (46% yield, entry 7) was achieved when the reaction was performed as two-phase process in the presence of 5 equiv. of water (without MeCN) for much shorter time (6 h). However, larger quantity of water (~222 equiv.) negatively affected the process when only traces of product **3a** were detected (entry 8). The replacement of water by Bu^{n}OH (100–105 °C) as a possible proton transfer agent entirely stopped the exchange/cyclization (entry 9). The major products of entries 8, 9 were oligomers of amino ynone **1a** (similar oligomers were also detected in cases with toluene, see entries 1, 2). Applying two-fold excess of phosphine sulfide **2b** (MeCN, 5 equiv. of water, 80–85 °C, 40 h) (see entry 6) did not noticeably influence the process since it increased just slightly (from 53 to 57%) the yield of thione **3a**, the conversion of the initial phosphine sulfide **2b** being ~77% (^{31}P NMR data).

Notably, with diphenylphosphine sulfide **2a** under optimal conditions (5 equiv. H_2O, MeCN, 80–85 °C, 24 h) pyrrole-3-thione **3a** was isolated in only 8% yield (see Table 1, entry 10). Such a considerable substituent effect is possibly associated with a decrease in nucleophilicity of thiophosphoryl sulfur caused by the electron-withdrawing phenyl groups. A steric shielding of the P=S group by *ortho*-hydrogen atoms of phenyl groups may also contribute to low reactivity of diphenylphosphine sulfide **2a**. In the reaction mixture, there were detected (^{31}P NMR) small amounts of thiophosphinic acid and its anhydride, the products of diphenylphosphine sulfide oxidation, along with trace dithiophosphinic acid resulted from disproportionation of diphenylphosphine sulfide **2a** (*cf.* refs. 31, 32). These side reactions reduced efficiency of the sulfur/oxygen exchange that followed from the reduced yields of 1,2-dihydro-3*H*-pyrrole-3-thiones **3**. Apart from these minor side processes, the formation of the expected[28] 1,2-dihydro-3*H*-pyrrol-3-one and a monoadduct of phosphine sulfide **2a** to the triple bond of the starting acetylene **1a** (10–12%) was observed in most of the experiments.

Table 1 Conditions for the reaction between amino ynone **1a** and secondary phosphine sulfides **2a**–**c**.[a]

Entry	Phosphine sulfide	Solvent	H_2O added (equiv.)	*T*/°C	*t*/h	Yield of **3a** (%)
1	**2a**	PhMe	none	100–105	22	31
2	**2b**	PhMe	none	100–105	22	26
3	**2b**	MeCN	none	80–85	60	32
4	**2b**	MeCN	none	20–25	120	0
5	**2b**	MeCN	none	50–55	80	10
6	**2b**	MeCN	5	80–85	48 (40[b])	53 (57[b])
7	**2b**	none	5	80–85	6	46
8	**2b**	H_2O[c]	~222[c]	80–85	12	traces
9	**2b**	Bu^{n}OH	none	100–105	21	0
10	**2a**	MeCN	5	80–85	24	8
11	**2c**	MeCN	5	80–85	120	0

[a]Reagents and conditions: 1,4-diphenyl-4-(phenylamino)pent-2-yn-1-one **1a** (0.163 g, 0.5 mmol), phosphine sulfide **2a**–**c** (0.5 mmol), solvent (2 ml), argon. [b]With **1a**/**2b** ratio being 1 : 2, ^{31}P NMR conversion of **2b** was 77%. [c]Amount of water was 1 ml.



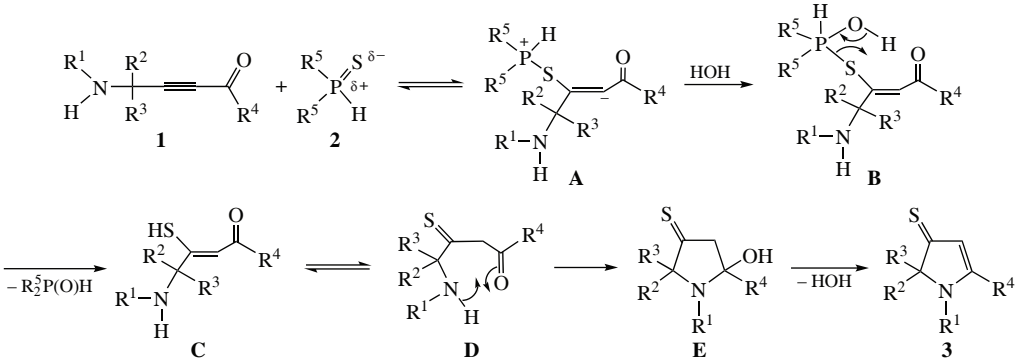
a Ar = R^1 = R^3 = Ph, R^2 = Me, 53%
b Ar = R^1 = Ph, R^2 = Me, R^3 = 4-ClC_6H_4, 35%
c Ar = R^1 = Ph, R^2 = Me, R^3 = 4-EtC_6H_4, 42%
d Ar = R^1 = Ph, R^2 = Me, R^3 = 2-furyl, 20%
e Ar = R^1 = Ph, R^2 = Me, R^3 = 2-thienyl, 25%
f Ar = R^1 = Ph, R^2 = Me, R^3 = Cy, 5%
g Ar = R^3 = Ph, R^1 = 2-thienyl, R^2 = Me, 47%
h Ar = R^3 = Ph, R^1 + R^2 = $(CH_2)_5$, 32%
i Ar = Ph, R^1 + R^2 = $(CH_2)_5$, R^3 = 2-furyl, 35%
j Ar = Ph, R^1 + R^2 = $(CH_2)_5$, R^3 = 2-thienyl, 33%
k Ar = Ph, R^1 + R^2 = $(CH_2)_6$, R^3 = 2-thienyl, 38%
l Ar = R^3 = Ph, R^1 = 2-naphthyl, R^2 = Me, 7%
m Ar = 4-ClC_6H_4, R^1 = 2-furyl, R^2 = Me, R^3 = Ph, 9%

Scheme 2 *Reagents and conditions*: i, amino ynone **1a**–**m** (0.5 mmol), phosphine sulfide **2b** (0.137 g, 0.5 mmol), H_2O (5 equiv.), MeCN (2 ml), 80–85 °C, 41–72 h, argon. For products **3f**,**l**,**m**, ^{1}H NMR yields are given.

Noteworthy, tris(2-phenylethyl)phosphine sulfide **2c** appeared to be inert in the reaction providing no target product even upon very long heating at 80–85 °C for 120 h (see Table 1, entry 11). This is in keeping with the above admission about the decrease of thiophosphoryl function reactivity due to steric effect of the adjusting phenylethyl groups.

Next, we evaluated the scope of sulfur/oxygen exchange/cyclization process (Scheme 2). The yields of 1,2-dihydro-3*H*-pyrrole-3-thiones **3a**–**m** strongly depend on the structure of amino ynones **1a**–**m** ranging 5–53%, however no regularity on structure–yield relationship can be here deduced. It is only clear that bulky α-positioned naphthyl substituent at the triple bond almost completely stopped the formation of the target thione **3l**. Also, when phenyl substituent was replaced by electron-donating cyclohexyl one in the acyl part of the ketone, the yield of the corresponding thione **3f** sharply dropped (5%). A small yield (9%) of **3m** was observed as well, when the accepting substituent (Cl) was introduced into the aniline part of ketone **1m**. It should be noted that in cases of thiones **3f**,**l**,**m**, large amount (25–28%) of corresponding oxo analogs, 1,2-dihydro-3*H*-pyrrol-3-ones, was formed.

Mechanistically (Scheme 3), the sulfur/oxygen exchange/cyclization under question is likely initiated by nucleophilic attack of the thiophosphoryl sulfur at the triple bond to generate 1,4-dipole intermediates **A**, which after quenching with water molecule produces phosphoranes **B**. The latter decompose to secondary phosphine oxide and ene thiols **C**, which would prototropically rearrange to thiones **D** further undergoing intramolecular cyclization to 5-hydroxypyrrole-3-thiones **E**, which are dehydrated to final 1,2-dihydro-3*H*-pyrrole-3-thiones **3**. Actually, the transformation of intermediate phosphorane **B** to ene thiol **C** can also proceed *via* six-membered transition state (see four-membered one shown in Scheme 3) with inclusion of an additional molecule of water.



Scheme 3

As far as this reaction was carried out in the commercially grade solvents, traces of water contained in them might be enough to neutralize the carbanionic site of the intermediate **A**. The further reaction progress is due to the water resulted from the cyclization (the dehydration of intermediate **E**).

This reaction cascade corresponds roughly to the observed substituent effects. Indeed, the reaction is strongly hindered by the bulky substituents in the α-position of the triple bond, which is subjected to the initial attack of thiophosphoryl sulfur. Also, slow rate of the process was noticed for amino ynones having more electron-donating substituents in the acyl moiety that hampers the nucleophilic attack at the triple bond. Likewise, the electron-accepting substituents in the aniline part of the ketone retard its addition (cyclization) to the carbonyl group.

In conclusion, the extraordinary sulfur/oxygen exchange/cyclization during the catalyst-free reaction (aq. MeCN, 80–85 °C), between available γ-amino α,β-ynones and secondary phosphine sulfides, particularly bis(2-phenylethyl)-phosphine sulfide, to provide 1,2-dihydro-3*H*-pyrrole-3-thiones has been disclosed. The reaction is assumed to start with the formation of 1,4-dipole intermediate generated by the attack of thione sulfur at the triple bond. The subsequent cascade transformations with participation of water molecules and elimination of phosphine oxides complete the process. The results contribute to better understanding the reactivity of both electron-deficient acetylenes and phosphine chalcogenides and offer an alternative approach to the synthesis of 1,2-dihydro-3*H*-pyrrole-3-thiones, a family of prospective intermediates for pharmaceutical research.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7627.

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