Tetrahedron 72 (2016) 810–824

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Aryl group – a leaving group in arylphosphine oxides

Marek Stankevič *, Jolanta Pisklak, Katarzyna Włodarczyk

Department of Organic Chemistry, Faculty of Chemistry, Marie Curie-Sklodowska University, Gliniana 33, 20-614 Lublin, Poland

ARTICLE INFO

Article history:
Received 19 September 2015
Received in revised form 8 December 2015
Accepted 21 December 2015
Available online 23 December 2015

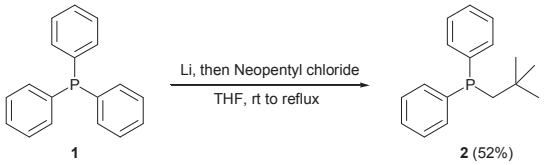
Keywords:
Nucleophilic substitution
Phosphine derivatives
Organolithium compounds
Grignard reagents
Selectivity

ABSTRACT

The treatment of triphenylphosphine oxide with organometallic reagents leads to the substitution of up to three phenyl substituents with the incoming carbon nucleophile. The replacement of the phenyl/aryl group in tertiary diarylalkylphosphine oxides or even aryldialkylphosphine oxides was also observed. Naphthyl-substituted phosphine oxides undergo Michael-type addition at the naphthyl group when treated with organolithium reagent.

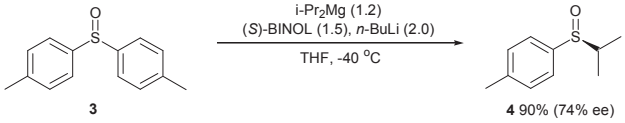
1. Introduction

Modification of the carbon chain in organic molecules through nucleophilic substitution requires the presence of a good leaving group in the molecule which could be replaced by a carbon nucleophile during the reaction. The same trend is observed in phosphorus chemistry, where the organophosphorus compounds possessing a leaving group at the phosphorus atom undergo nucleophilic substitution.[1] Carbon-based groups are regarded as substitution-resistant although the aryl substituents in arylphosphines[2] or phosphine oxides[3] could be replaced through reductive cleavage of *P*-aryl bond with an alkali metal (Scheme 1).



Scheme 1. Replacement of phenyl by reductive cleavage of *P*-aryl bond.

Except for a few observations, the nucleophilic substitution of phenyl (aryl) group in arylphosphorus compounds has never been a subject to intensive research studies.[4] In fact, there is little known about phenyl/aryl group substitution in organic chemistry in general, although a few examples of this kind of transformation can be found in organosulfur chemistry where a treatment of diarylsulfoxides with Grignard (Scheme 2)[5] or organolithium[6] reagents led to substitution of an aryl group.



Scheme 2. Nucleophilic substitution of aryl group in sulfoxides.

The substitution of phenyl/aryl group at phosphorus may be of high importance due to the high availability of arylphosphorus compounds, including triphenylphosphine and its derivatives. With the developed method in hand, the synthesis of new phosphines and derivatives could be achieved by simple replacement of aryl substituents. This approach is much more flexible and convenient compared to the tedious preparation of reactive organophosphorus precursors (halides or esters).

In the course of our research topic, related to the modification of aryl substituent in arylphosphorus compounds, we primarily were interested in the synthetic activation of aryl groups through the dearomatization under Birch reduction conditions[7] or *ortho*-functionalization using directed *ortho*-metallation (DoM)[8] methodology. Considering the results obtained so far we were curious if arylphosphines and their derivatives could be good substrates for

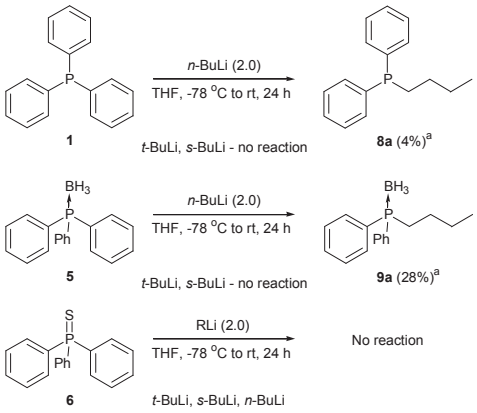
* Corresponding author. Tel.: +48 81 537 77 52; fax: +48 81 524 22 51; e-mail address: marek.stankevic@poczta.umcs.lublin.pl (M. Stankevič).

http://dx.doi.org/10.1016/j.tet.2015.12.043
0040-4020/

the nucleophilic substitution at phosphorus in the case where aryl group is the only potential leaving group. Theoretically, such a substitution could take place in the case where the incoming nucleophile has higher pKa value than the leaving aryl anion. In practice, this process would require the use of the very strong carbon nucleophiles.

2. Results and discussion

Among the available arylphosphorus compounds triphenylphosphine **1** and its derivatives appeared to be very suitable substrates for the test reactions. The symmetrical nature of these molecules exclude the problem of competitive substitution of two different aryl groups. The substitution of phenyl groups in **1** and its derivatives using commercially available organolithium compounds have been checked first (Scheme 3).



Scheme 3. Substitution of phenyl group in **1**, **5** and **6**.

A reaction of triphenylphosphine **1**, triphenylphosphine-borane **5** or triphenylphosphine sulfide **6** with commercially available *t*-BuLi, *s*-BuLi or *n*-BuLi generally failed to produce the corresponding products, except reactions of **1** and **5** with *n*-BuLi where the formation of substitution products **8a** and **9a** was observed to a limited extent.

The case of triphenylphosphine oxide **7** was different (Scheme 4, Table 1).

A reaction of triphenylphosphine oxide **7** with 1.1 equivalent of *t*-BuLi afforded *t*-butyldiphenylphosphine oxide **10a** in 76% yield after 2.5 h (Table 1, entry 10). The use of a higher excess of this organolithium reagent led to a decrease of the yield of **10a** and the formation of phosphafluorene oxide **12**, a formal intramolecular cyclization product, has been observed (Table 1, entry 12). A reaction of **7** with *s*-BuLi was solvent-dependent; in THF, the formation of both substitution and cyclization products **10b** and **12** has been observed, whereas in Et_2O the exclusive formation of the desired product **10b** was detected (Table 1, entries 13 and 14). A similar solvent dependence was observed for the reaction of **7** with *n*-BuLi (Table 1, entries 15 and 16). Here however, a reaction in Et_2O led to the formation of **11a** as a side product, which is formally

Table 1
Substitution in triphenylphosphine **1** and derivatives

Nr	RLi (equiv)	Products		
		10	**11**	**12**
1[a]	***t*-BuLi (1.1)**	**10a (76%)**[b]	—	—
2[c]	*t*-BuLi (2.0)	**10a** (51%)[b]	—	—
3[c]	*t*-BuLi (3.0)	**10a** (10%)[b]	—	46%[b]
4	*s*-BuLi (2.0)	**10b** (54%)[b]	—	26%[b]
5[c]	***s*-BuLi (2.0)**	**10b (86%)**[b]	—	—
6	***n*-BuLi (2.0)**	**10c (97%)**	—	—
7[c]	*n*-BuLi (2.0)	**10c** (85%)[b]	**11a** (8%)[b]	—
8	MeLi (2.0)	**10d** (65%)[b]	**11b** (30%)[b]	—
9[c]	**MeLi (1.0)**	**10d** (89%)[b]	**11b** (9%)[b]	—
10[c]	MeLi (3.0)	**10d** (56%)[b]	**11b** (20%)[b]	—
11	$TMSCH_2Li$ (2.0)	**10e** (80%)[b], **10d** (8%)[a]	—	—
12	***i*-BuLi (2.0)**	**10f** (91%)	—	—

[a] The reaction was run for 5 h.
[b] Yields based on NMR analysis of product mixtures.
[c] Reaction performed in Et_2O.

a product of substitution of two phenyl groups. This trend was even more expressed in the case methyllithium (Table 1, entries 16–18). The use of 2 equivalents of organometallic reagent led to the formation of both monosubstitution and disubstitution products **10d** and **11b** in ca. 2:1 ratio. The selectivity of this particular reaction could be shifted towards monosubstitution product **10d** by lowering the amount of an organometallic reagent. On the other hand, an increase in the amount of methyllithium failed to shift the selectivity towards di- or trisubstitution product.

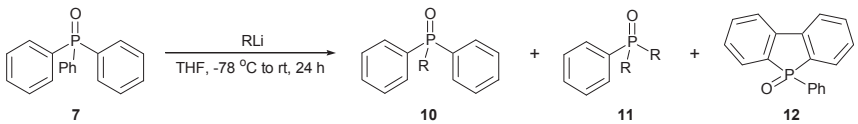
Surprisingly, the problem of overalkylation is not observed using $TMSCH_2Li$, which afforded a mixture of two monoalkylation products (Table 1, entry 20). The formation of **10d** as a side product can be easily explained by the hydrolytic cleavage of the carbon-silicon bond during the aqueous work-up.

The number of commercially available organolithium compounds is relatively low but these reagents could be obtained from the corresponding alkyl/aryl halides using halogen-metal exchange process. In the next step, a set of substitution reactions of **7** with in situ generated organolithium compounds has been performed (Scheme 5, Table 2).

In the case where organometallic species were generated smoothly the substitution went effectively affording the corresponding monosubstitution products **10g** and **10j** (Table 2, entries 1 and 4). The case of aryllithium reagents derived from *m*-iodotoluene and *m*-iodoanisole was different as here the formation of mixtures of mono, di and trisubstitution products has been observed (Table 2, entries 5 and 6). This suggests, that at least for aryllithium reagents the steric crowd generated by the reagent influences the degree of substitution.

Regarding the commercial availability, Grignard reagents are much better candidates for the nucleophilic substitution of phenyl group in triphenylphosphine oxide although they generally exhibit lower reactivity towards nucleophilic substitution. To check the utility of these reagents in phenyl group substitution a set of reactions of **7** with Grignard reagents has been performed (Scheme 6, Table 3).

In accordance with expectations, Grignard reagents appeared to be far less reactive than the corresponding organolithium reagents.



Scheme 4. Substitution in triphenylphosphine **1** and derivatives.