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The reactivity of arylphosphine oxides under Bouveault-Blanc reaction conditions

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ABSTRACT

Treatment of tertiary arylphosphine oxides with alkali metal/alcohol reagent system lead to the corresponding cyclohexyl-substituted phosphine oxides. This transformation makes use of the inexpensive sodium as the electron donor and an alcohol as the proton source, and provides an attractive alternative to reactions mediated by expensive transition metals. Under optimized conditions numerous mono- and diaryl substituted phosphine oxides were transformed into the corresponding mono- and dicyclohexyl-substituted phosphine oxides in good yields. Furthermore, the formation of 1,2-bis(phosphinoyl)cyclohexanes or unknown 5,10-dialkyltetradecahydrophosphanthrene 5,10-dioxides as side products was observed, which are hardly accessible by other procedures.

1. Introduction

Molecules with incorporated cyclohexane frameworks are very popular in organic chemistry and can be found in many useful substances such as natural products, pharmaceuticals or fuel.[1] One of the possible substrates of these compounds could be the corresponding aromatic compounds which upon treatment with a hydrogen source should undergo saturation of the aromatic ring. Transformation of arenes into the corresponding cycloalkanes could be achieved by three different pathways: reduction with metal hydrides,[2] Birch reduction[3] or catalytic heterogeneous hydrogenation.[4] The use of metal hydrides is usually associated with the formation of large amount of metal salts, while Birch reduction of arenes lead to 1,4-cyclohexadienes which should be further hydrogenated using classic catalysts. From synthetic point of view, catalytic hydrogenation is up to now the most convenient way for the transformation of arenes into cycloalkanes.[4] However, the catalysts used in these reactions are usually active only under high pressures and temperatures, although some progress has been made when using nanoparticle catalysts[5] or water as a solvent.[6]

In the case of functionalized arenes, catalytic hydrogenation might be a good choice if the corresponding cycloalkanes are the target molecules. The examples include hydrogenation of phenols,[4d,6b] simple alkyl-substituted arenes,[6a] phenylalanine and phenylglycine derivatives[7] or monosubstituted benzenes.[5b] Contrary to this, hydrogenation of the aryl fragment in arylphosphorus compounds is relatively underexplored. The first attempted hydrogenation of arylphosphinic and arylphosphonic acids was performed by Freedman and coworkers who used Rh/Al_2O_3 as a catalyst (Scheme 1).[8] Other catalysts used in hydrogenation of aryl substituents in organophosphorus compounds, such as Ru/C, Raney-Ni or $Nb(p\text{-}TolCH_2)_3(2,6\text{-}Ph_2\text{-}C_6H_3O)_2$, appeared to exhibit good activity and selectivity towards complete hydrogenation of aromatic groups.[9]

Reductive dearomatization of arylphosphorus compounds using alkali metals in liquid ammonia could also be regarded as a method for transformation of aryl substituents into their cycloalkyl analogues.[10] Two isolated double bonds in the formed 1,4-cyclohexadiene unit are far more reactive towards hydrogenation than the parent aryl substituent. Despite the obvious advantages of this reaction the main drawback is the use of ammonia due to its irritant odor. Therefore, it would be desirable to develop alternative reaction conditions for Birch reduction where ammonia is replaced by a more friendly solvent. It seems that a good alternative here

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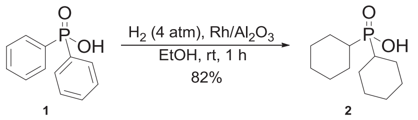


Scheme 1. Hydrogenation of phenyl substituents in **1**.

would be Bouveault-Blanc reduction, a reaction based on the reduction of carbocylic acid esters to the corresponding primary alcohols with an alkali metal in alcohol (Scheme 2).[11]

To the best of our knowledge, no examples of the reduction of other classes of organic compounds under these conditions have been reported.

2. Results and discussion

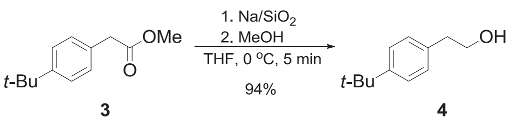
An obvious advantage of Bouveault-Blanc reduction over Birch reduction is the use of readily available and more manipulation-friendly alcohols compared to ammonia. Regarding this, we decided to check the reactivity of a simple tertiary phosphine oxide under Bouveault-Blanc reduction. For initial screening, *t*-butylmethylphenylphosphine oxide (**5**) was used as a model compound (Table 1).

Addition of sodium into a solution of **5** in ethanol led to a vigorous evolution of gas which ceased in ca. 5 min (Table 1, Entry 1). The analysis of the reaction mixture revealed the presence of phosphine oxide **6** as the only reaction product but the overall conversion was moderate. This compound is most probably formed by *in situ* reduction of phenyl substituent by metallic sodium followed by double bond migration and protonation of the carbanion (Scheme 3).

Further efforts were put towards the optimization of the reaction conditions. Replacement of ethanol with *n*-BuOH led to a quite striking change in the product composition (Table 1, Entry 2). Apart from **6**, the presence of *t*-butyl(cyclohex-3-enyl)methylphosphine oxide **7** has been observed which suggests that compound **6** undergoes saturation of conjugated double bond in the presence of an excess of an alkali metal. However, the most intriguing was the presence of trialkylphosphine oxide **8** where the phenyl group underwent complete saturation under the reaction conditions. This reaction could be regarded as the first example of transition metal and hydrogen-free arene hydrogenation. Here, an alkali metal serves as the electron source and the alcohol is the proton source.

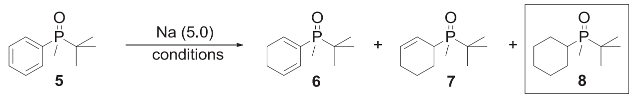
Contrary to *n*-BuOH, the use of *i*-PrOH led to a complete shift of the selectivity towards monohydrogenation product **6**, although the conversions were usually low. One of the reasons for the incomplete conversion of **5** might be the loss of an alkali metal due to its reaction with an excess of an alcohol present in the reaction. Therefore, a slight modification of the reaction conditions was proposed. In this case, the reaction was undertaken in THF as a solvent and 6-fold excess of both alkali metal and *i*-PrOH was used (Table 2).

Under these conditions the main product was fully saturated phosphine oxide **8** along with a remarkable amount of cyclohexenylphosphine oxide **7** which suggests the crucial influence of the amount of used alcohol on the selectivity of the reaction.



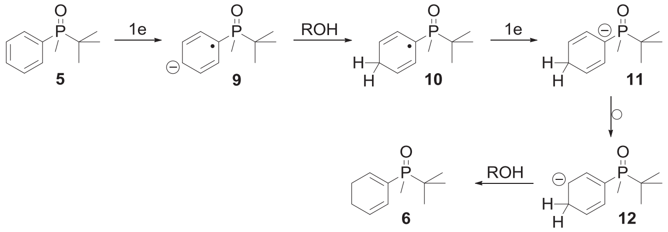
Scheme 2. Bouveault-Blanc reduction of **3**.

Table 1
The reactivity of **5** under Bouveault-Blanc reduction.



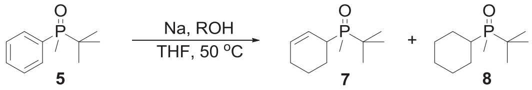
Entry	Conditions	Products[a]		
		6	**7**	**8**
1	EtOH, rt, 1 h	22%	–	–
2	*n*-BuOH, rt, 0.5 h	30%	11%	4%
3	*i*-PrOH, rt, 1 h	23%	–	–
4	*i*-PrOH, rt, 2 h	16%	–	–
5	*i*-PrOH, rt, 3 h	26%	–	–
6	*i*-PrOH, rt, 4 h	22%	–	–
7	*i*-PrOH, rt, 22 h	12%	–	–

[a] Yields based on NMR analysis of the reaction mixtures.



Scheme 3. Plausible mechanism for the formation of **6**.

Table 2
Optimization of reduction conditions for **5**.



Entry	Na (equiv.)	ROH (equiv.)	Time (h)	Products[a]	
				7	**8**
1	6.0	*i*-PrOH (6.0)	48	37%	57%
2	10.0	*i*-PrOH (6.0)	48	40%	60%
3	6.0	*i*-PrOH (6.0)	1	34%	66%
4	6.0	*i*-PrOH (6.0)	2	33%	67%
5	6.0	*i*-PrOH (6.0)	3	30%	70%
6	6.0	*i*-PrOH (6.0)	4	30%	70%
7	6.0	*s*-BuOH (6.0)	4	28%	72%
8	6.0	*t*-BuOH (6.0)	4	30%	70%
9	6.0	*t*-BuOH (6.0)	24	28%	72%

[a] Conversions based on NMR analysis.

It appeared also that the reaction selectivity can be modified slightly by modification of the reaction conditions. The highest conversion of **5** into **8** was observed after 4 h at 50 °C; the reaction temperature was raised in order to shorten the reaction time. The use of different alcohols had some influence on the selectivity of the reaction; the use of *s*-BuOH or *t*-BuOH led to the formation of minor amounts of unidentified by-products. On the other hand, an increase of the amount of alkali metal had no influence on the selectivity of the reaction.

To test the utility of the optimized reaction conditions a set of tertiary phosphine oxides was submitted to the modified Bouveault-Blanc reduction. First, dialkylphenylphosphine oxides were used as substrates (Table 3).

It was a pleasure to conclude that all reductions took place smoothly and afforded complete conversion of substrates within