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Et_3B-induced radical addition of diphenylphosphine oxide to unsaturated compounds

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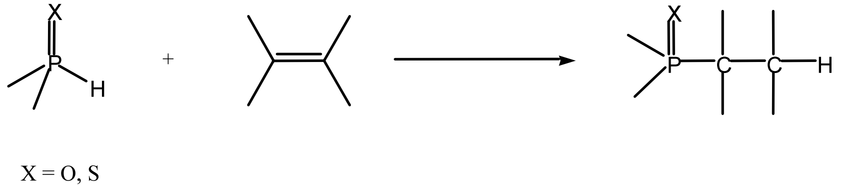
Abstract—Et_3B-catalysed addition of diphenylphosphine oxide to unsaturated compounds, alkenes, unsaturated acids, allylic alcohols, and allylic α-*O*-acetyl nitriles constitutes a practical route to a variety of functionalized diphenylphosphine oxides. The very mild conditions employed, together with the short reaction times, make the procedure highly versatile and tolerant to a range of functionalities.

The Pudovik reaction is one of the most versatile pathways for the formation of carbon–phosphorus bonds (Scheme 1) and involves the addition of compounds containing a labile P–H bond with unsaturated systems (alkenes, alkynes, carbonyls, imines).[1–4]

The products of the reaction find significant applications in a wide range of areas (industrial, biological, and chemical synthetic uses).[5] The Pudovik reaction can progress via an ionic or (and) a radical mechanism. It appears in the literature that the difference of the Pudovik reaction mechanisms depends on the nature of the unsaturated substrates (activated or not). In fact, when the unsaturated compound contains an electron-withdrawing substituent, the main mechanism is ionic. Diethylamine or potassium hydroxide[6–9] are generally used and recently tetramethylguanidine-catalysis has been also employed efficiently under very mild conditions.[10] In a basic medium, the addition occurs by nucleophilic attack of phosphorus anions to olefins by a Michael-type mechanism and the orientation is anti-Markovnikov. Indeed, when the unsaturated substrate used has a nucleophilic character, the mechanism is preferentially radical. In this case, photoactivation[11] or chemical initiation[12] (peroxides, AIBN) is the most efficient method. A major problem of such methods is that the reaction time is long and the reaction conditions are usually drastic.[13] Furthermore, the regioselectivity of the addition is sometimes weak. More recently, ultrasound-induced radical reaction in homogeneous medium has also been used.[14] In the presence of free radical initiators or under photochemical or ultrasound irradiation in a homogeneous medium, the phosphorylated reagents ($R_2P(O)H$) add to a double bond by a free radical mechanism, the orientation of which is also anti-Markovnikov.

In this letter we report our preliminary results concerning the Et_3B-induced radical addition of diphenylphosphine oxide to a variety of unsaturated compounds including alkenes, unsaturated acids, allylic alcohols, as well as an allylic α-*O*-acetyl nitrile (Scheme 2). We have



Scheme 1.

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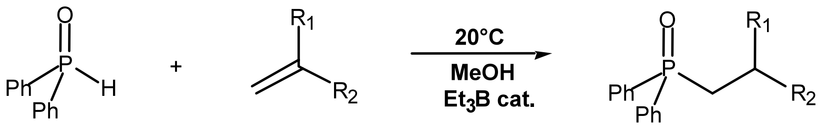

R_1	R_2	Substrate
H	$(CH_2)_5CH_3$	1
H	$(CH_2)_9CH_3$	2
H	CH_3CO_2H	3
H	$CH(CH_3)OH$	4
H	$C(CH_3)_2OH$	5
CH_3	CH_3OH	6
H	CH_2CN	7
H	$CH(OH)CH_2OH$	8
H	$CH(OAc)CN$	9

Scheme 2.

previously reported the use of Et_3B to perform the addition of alkanethiols to unsaturated systems, offering significant advantages especially in terms of experimental simplicity, mild conditions and easy work-up.[15,16]

The addition takes place smoothly (20°C, MeOH) giving rise to the corresponding diphenyl alkylphosphine oxide in good yield (Table 1) on slow addition of catalytic amounts of the triethylborane solution (0.3 mmol) (Aldrich, 1 M in hexane) to the diphenylphosphine oxide (0.5 g; 2.5 mmol) and unsaturated compound (2.5 mmol) in methanol (6 mL).

The regioselective monoaddition reaction can be applied to all unsaturated bifunctionals compounds examined simply through slight modifications of the reaction conditions (see times and temperatures in Table 1). In all cases, good yields were obtained. With other procedures, the reaction proceeds under harsh conditions[12,13] and side reactions were observed. As a general rule, an excess of the diphenylphosphine oxide or unsaturated compounds may be used. Indeed, in these cases, stoichiometric amounts are necessary. We also investigated the influence of the nature of the solvent on the rate of addition of diphenylphosphine oxide and the purity and the yield of the reaction. The nature of the solvent has a prominent effect on the course of the reaction. Actually, when the reaction of diphenylphosphine oxide with unsaturated compounds is carried out in methanol, the yields and the purities of the addition products are better than in hexane and acetone. It is quite obvious that high reaction temperatures (>50°C) during a long reaction time are not favorable for the achievement of high chemical yields. This result is due to the formation of the dimer:

Table 1. Synthesis of alkyl diphenylphosphine oxide by Et_3B-catalysed addition of diphenylphosphine oxide to unsaturated compounds[a]

Unsaturated compounds	Reaction time (h)/and temp. (°C)	Product	Yield (%)
1	2.5/20	$Ph_2P(O)CH_2CH_2(CH_2)_5CH_3$	96
2	2.5/20	$Ph_2P(O)CH_2CH_2(CH_2)_9CH_3$	95
3	3.5/20	$Ph_2P(O)CH_2CH_2CH_2CO_2H$	74
4	3/20	$Ph_2P(O)CH_2CH_2CH(CH_3)OH$	80
5	3.5/20	$Ph_2P(O)CH_2CH_2C(CH_3)_2OH$	94
6	4/20	$Ph_2P(O)CH_2CH(CH_3)CH_2OH$	79
7	2/10	$Ph_2P(O)CH_2CH_2CH_2CN$	72
8	2/20	$Ph_2P(O)CH_2CH_2CH(OH)CH_2OH$	85
9	1.5/10	$Ph_2P(O)CH_2CH_2CH(OAc)CN$	65

[a] Purified compounds.

$Ph_2(O)P\text{-}P(O)Ph_2$. Having demonstrated that Et_3B can afford a facile catalyzed addition of diphenylphosphine oxide to unsaturated system, we are currently investigating the addition of dialkyl or diaryl phosphites and alkyl or aryl phosphinic acids to these unsaturated compounds.

In conclusion, the synthesis of the diphenyl alkylphosphine oxide is realized in good yields by one step via a radical addition of diphenylphosphine oxide to unsaturated compounds initiated by catalytic amounts of molar solution of Et_3B. The solvent and the temperature have an important effect upon the reactivity. Methanol rather than acetone or hexane enhance the activation of Et_3B, favorable to the generation of free radicals.[17] This approach to alkyl diphenylphosphine oxide allies cheapness and simplicity in terms of reagents and experimental procedure (the catalyst is commercially available and inexpensive; short reaction times between 5°C and room temperature, anhydrous solvents or reagents and inert atmosphere conditions are not required).[15,16]

We are currently investigating the Et_3B-catalysed addition of dialkyl or diarylphosphites and aryl or alkylphosphinic acids to unsaturated substrates having as the main focus the synthesis of phosphinothricin derivatives.[18,19]

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