An Efficient Method for the Preparation of Monoalkylated Sulfonamides from Unsubstituted Sulfonamides and Alkyl Diphenylphosphinites by Oxidation–Reduction Condensation Using Trimethylsilylmethyl Azide

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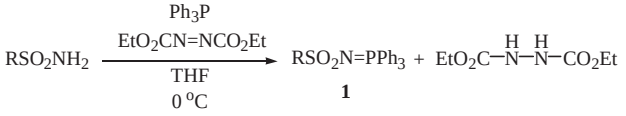
An efficient method for monoalkylation of unsubstituted sulfonamides was established by using alkyl diphenylphosphinites, sulfonamides and trimethylsilylmethyl azide and the monoalkylated sulfonamides were afforded in good yields under neutral conditions.

It was recently reported from our laboratory that a new type of oxidation–reduction condensation reaction by using alkyl diphenylphosphinites (Ph_2POR) that were prepared from alcohols and chlorodiphenylphosphine and quinones can be applied to the synthesis of esters,[1] alkyl aryl ethers,[1b,2] dialkyl ethers,[2] alkyl nitriles,[3] alkyl aryl sulfides,[4] and alkyl amides.[5] In order to extend the scope of this type of condensation reaction, monoalkylation reaction of unsubstituted sulfonamides was studied.

It is generally known that an alkylation of unsubstituted sulfonamides under well-known Mitsunobu conditions (alcohols, triphenylphosphine, and diethyl azodicarboxylate) did not proceed smoothly because the amides react too rapidly with triphenylphosphine to form a phosphazo compound **1** in high yields (Scheme 1).[6] A monoalkylation reaction of unsubstituted sulfonamides by way of oxidation–reduction condensation, on the other hand, is a useful method for the synthesis of primary amines from alcohols under mild conditions. However, there are only few reports except for the alkylation reaction of *p*-toluenesulfonamide ($TsNH_2$) using cyanomethylenetributylphosphorane (CMBP) and alcohols by Tsunoda et al.[7] and a condensation reaction of *o*-nitrobenzenesulfonamide (*o*-$NsNH_2$) and primary alcohols by Fukuyama et al. that proceeded smoothly under Mitsunobu conditions.[8]

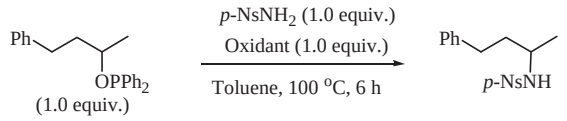
Here, we would like to describe a new method for good-yielding preparation of various monoalkylated sulfonamides by way of a new type of oxidation–reduction condensation using alkyl diphenylphosphinites, sulfonamides, and trimethysilylmethyl azide.

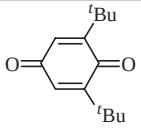
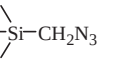
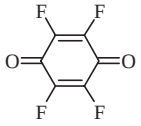
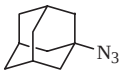
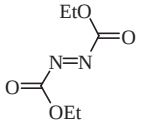
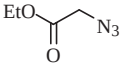
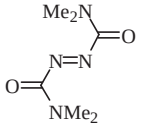
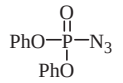
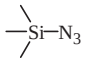
In the first place, introduction of 4-phenyl-2-butyl group to *p*-nitrobenzenesulfonamide (*p*-$NsNH_2$) with 1.0 equiv. of 4-phenyl-2-butyl diphenylphosphinite was tried by using 1.0 equiv. of 2,6-di-*tert*-butyl-1,4-benzoquinone, which was successfully employed in our previous paper,[4,5] and the desired product was obtained in 21% yield within 6 h (Table 1, Entry 1). On the other hand, the corresponding compound was not obtained when tetrafluoro-1,4-benzoquinone, a most suitable oxidant for the synthesis of dialkyl ethers,[2] was used (Entry 2). Then, the reaction was further tried by using other oxidants. Under the above mentioned conditions, the corresponding compound was scarcely obtained when azo compounds such as diethyl azodicarboxylate (DEAD)[9] or *N*, *N*, *N*′, *N*′-tetramethylazodicarboxamide (TMAD)[10] were used (Entries 3 and 4). Interestingly, the yields markedly increased when the alkyl azide compounds such as 3-phenylpropyl azide, trimethylsilylmethyl azide, or 1-azidoadamantane were used, whereas ethyl azidoacetate, diphenylphosphoryl azide, and trimethylsilylazide did not give good results (Entries 5–10).[11]



Scheme 1.

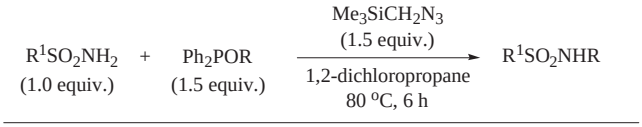
Table 1. 4-Phenyl-2-butylation of *p*-nitrobenzenesulfonamide with 4-phenyl-2-butyl diphenylphosphinite and oxidant

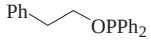
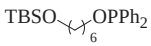
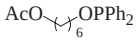
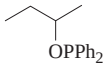
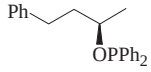
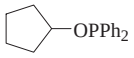
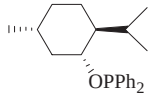
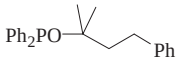


Entry	Oxidant	Yield/%	Entry	Oxidant	Yield/%
1		21	6		61
2		N.D.	7		56
3		N.D.	8		26
4		1	9		N.D.
5	$Ph(CH_2)_3N_3$	61	10		N.D.

After the reaction conditions were optimized, an alkylation reaction of sulfonamides by using various alkyl diphenylphosphinites[12] and commercially-available trimethylsilylmethyl azide was tried. When the reaction was tried with primary alkyl diphenylphosphinites, the desired products were obtained in good yields (Table 2, Entries 1–3). In these cases, the dialkylated amides were observed in about 10% yield as by-products. It was also demonstrated that the useful protecting groups such as ace-

Table 2. *N*-Alkylation of sulfonamides using alkyl diphenylphoshinites[a]

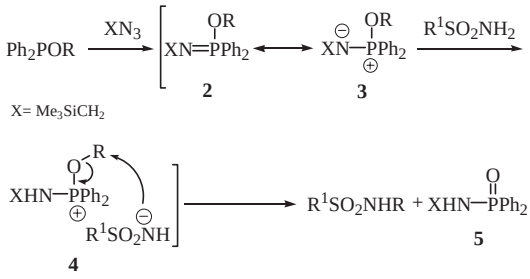


Entry	Ph_2POR	$R^1SO_2NH_2$	Yield/%
1		*p*-$NsNH_2$	70
2		*o*-$NsNH_2$	78
3		*p*-$NsNH_2$	85
4		*o*-$NsNH_2$	82
5		*p*-$NsNH_2$	89
6		$TsNH_2$	37
7[b,c]		*p*-$NsNH_2$	76[d,e]
8		*o*-$NsNH_2$	84
9		*p*-$NsNH_2$	12[f]
10		*p*-$NsNH_2$	5

[a]Reactions were carried out on a 0.3 mmol scale. [b]The phosphinite was prepared from the (*R*)-(−)-4-phenyl-2-butanol (99% ee). [c]DAICEL CHIRALCEL OD column was used for HPLC analysis. [d]The desired product was obtained in 96% ee. [e]DAICEL CHIRALCEL AD column was used for HPLC analysis. [f]The corresponding compound was obtained with perfect inversion.

tyl or *tert*-butyldimethylsilyl group survived under the reaction conditions (Entries 2 and 3). On the other hand, the reaction with secondary alkyl diphenylphosphinites including acyclic/cyclic ones smoothly proceeded to give the corresponding alkyl sulfonamides in good yields without forming dialkylated compounds (Entries 4–8). The reactions with bulky L-menthyl diphenylphosphinite and *tert*-alkyl diphenylphosphinite gave the desired products in low yields (Entries 9 and 10). When the reactions with (*R*)-4-phenyl-2-butyl diphenylphosphinite and L-menthyl diphenylphosphinite were tried, the inverted products were obtained (Entries 7 and 9). This suggests that the reaction proceeded basically via S_N2 mechanism. In order to compare the reactivities of sulfonamides, *sec*-butylations of *o*-$NsNH_2$, *p*-$NsNH_2$ and $TsNH_2$ were examined and the reactivities of *o*-$NsNH_2$ and *p*-$NsNH_2$ were found to be almost the same, which was higher than that of $TsNH_2$ having a higher pK_a value (Entries 4–6).

A proposed reaction mechanism is shown in Scheme 2: Alkyl diphenylphosphinites reacted initially with trimethylsilylmethyl azide to form the phosphinimidate **2** or **3**,[13] which is in turn transformed to the phosphonium salt **4** by the interaction with sulfonamides. An attack of the sulfonamide anion to the carbon atom adjacent to an oxygen atom of the alkoxy group afforded the corresponding alkyl sulfonamides along with *N*-(trimethylsilylmethyl)diphenylphosphinamide **5**.



Scheme 2.

Typical experimental procedure is as follows: to a mixture of sulfonamides (0.3 mmol) and alkyl diphenylphosphinites (0.45 mmol) was added a solution of trimethylsilylmethyl azide (0.45 mmol) in 1,2-dichloropropane (0.6 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 6.0 h at 80 °C. After completion of the reaction (detected by TLC), the crude product was purified by preparative TLC to afford the corresponding sulfonamides.

Thus, it is noted that trimethylsilylmethyl azide is the suitable oxidant in preparing monoalkylated sulfonamides by way of oxidation–reduction condensation using alkyl diphenylphosphinites and unsubstituted sulfonamides and various monoalkylated sulfonamides were obtained in good yields under neutral conditions. Further study on this type of condensation reaction is now in progress.

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References and Notes

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