An Efficient Method for the Preparation of *N*-Alkylamides from Alkyl Diphenylphosphinites and Amides by Using Methyl Acrylate

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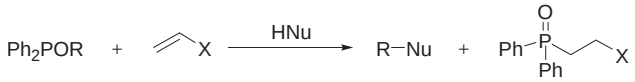
N,*N*-Dibenzyltrifluoroacetamide was formed in good yield by treating benzyl diphenylphosphinite with *N*-benzyltrifluoroacetamide in the presence of easily available methyl acrylate under mild conditions. Yields obtained for the corresponding inverted sulfonamides were good to high in the cases when alkyl diphenylphosphinites derived from chiral secondary alcohols were used.

Recently, it was reported from our laboratory that *N*-alkylated compounds were synthesized under neutral conditions by an oxidation–reduction condensation using alkyl diphenylphosphinites (Ph_2POR),[1] 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ) and weakly acidic compounds having a nitrogen–hydrogen bond such as phthalimide, *N*-benzyltrifluoroacetamide or sulfonamides.[2] Very recently, it was shown that the use of an alkyl diphenylphosphinite and an alkyl azide such as trimethylsilylmethyl azide or 1-azidoadamantane for the oxidant also could afford the monoalkylated product from unsubstituted sulfonamide[3] and nitrogen-containing cyclic compounds such as pyrrolidine or piperidine derivatives.[4] Although DBBQ and the azide compounds efficiently behaved as the oxidants here, the price of those reagents is not low. Therefore, our attention was focused on establishing a practical and convenient method that uses cheaper and simpler oxidants than DBBQ and azide compounds.

It is well known that an electron-rich trivalent phosphorus compound such as trialkylphosphites readily undergoes a conjugate addition to the activated olefins such as α,β-unsaturated nitriles, esters, ketones, aldehydes, or amides in the presence of a proton source such as an alcohol to furnish β-substituted phosphonate esters and ethers.[5] Then, it was expected that an alkylation reaction onto nitrogen atom takes place if an alkyl diphenylphosphinite and a weakly acidic compound having a nitrogen–hydrogen bond are used in place of the above trialkylphosphite and alcohol. However, no *N*-alkylation reactions have yet been reported until present (Scheme 1).

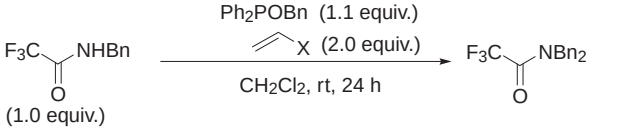
Here, we would like to report a new method of high-yielding *N*-alkylation of amides by using several alkyl diphenylphosphinites with methyl acrylate under neutral conditions.

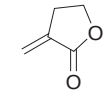
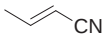
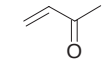
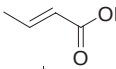
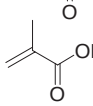
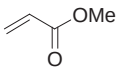
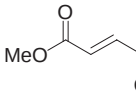
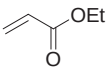
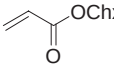
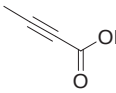
In the first place, *N*-benzylation of *N*-benzyltrifluoroacetamide by using 1.1 equiv. of benzyl diphenylphosphinite and 2.0 equiv. of acrylonitrile was tried and *N*,*N*-dibenzyltrifluoroacetamide was formed in 60% yield (Table 1, Entry 1). This result was found almost the same to that when DBBQ was used as an oxidant (59% yield).[2] Then, the use of other acrylonitrile derivatives was studied next, but the expected product was not obtained in any case (Entries 2–7). Then, other activated olefins were tried in turn (Entries 8–20). Interestingly, the use of methyl acrylate (MA) afforded the desired product in 79% yield whereas no better results were found with other acrylic acid esters (Entries 8–13). On the other hand, the yields remained low when *N*,*N*-dimethylacrylamide and methyl vinyl ketone were used (Entries 14 and 15). The corresponding targeted compounds were obtained in moderate yields with the use of methyl propiolate and methyl tetrolate while the desired product was not afforded when methyl acrylate derivatives were used (Entries



Scheme 1.

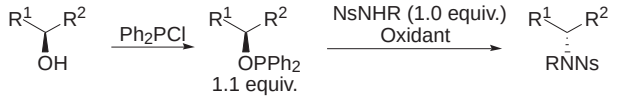
Table 1. Screening of α,β-unsaturated compounds on benzylation of *N*-benzyltrifuluoroacetamide

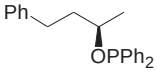
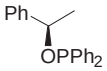


Entry	X	Yield/%	Entry	X	Yield/%
1		60	11		72
2		N.R.	12		53
3		N.D.	13		63
4		N.R.	14		5
5		N.R.	15		3
6		N.R.	16		N.R.
7		N.D.	17		N.R.
8		79	18		N.D.
9		73	19		40
10[a]		73	20		50

[a]Chx = Cyclohexyl.

Table 2. *N*-Alkylations of sulfonamides with alkyl diphenylphosphinites in the presence of methyl acrylate,[a] DBBQ,[b] or trimethylsilylmethyl azide[c]



Entry	Phosphinite	NsNHR	Oxidant	Yield/%	% ee[d]
1		NsNHBoc	MA	83	98[e]
2			DBBQ	77	98
3			$TMSCH_2N_3$	44	97
4		$NsNH_2$	MA	72	96
5			DBBQ	46	92
6			$TMSCH_2N_3$	59	95
7		NsNHBoc	MA	94	98
8			DBBQ	91	99
9			$TMSCH_2N_3$	43	98
10		$NsNH_2$	MA	67	97
11			DBBQ	43	93
12			$TMSCH_2N_3$	65	96
13		NsNHBoc	MA	85	84
14			DBBQ	82	71
15			$TMSCH_2N_3$	54	90
16		$NsNH_2$	MA	52	72[f]
17			DBBQ	32	59
18			$TMSCH_2N_3$	51	73

[a]MA (2.0 equiv.), CH_2Cl_2 (1.2 M), rt, 24 h. [b]DBBQ (1.1 equiv.), CH_2Cl_2 (1.2 M), rt, 1 h. [c]$TMSCH_2N_3$ (1.1 equiv.), 1,2-dichloropropane (0.6 M), 80 °C, 6 h. [d]DAICEL CHIRALPAK AD–H column was used for HPLC analysis. [e]Ee was measured after deprotection of Boc group. [f]DAICEL CHIRALPAK AS–H column was used for HPLC analysis.

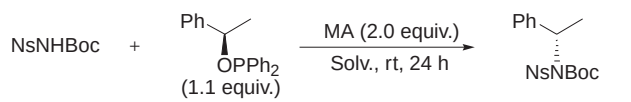
16–20). Thus, it is noted that the methyl acrylate is the most effective oxidant in this reaction.

Next, in order to confirm the usefulness of methyl acrylate, reactions of 2-nitrobenzenesulfonamides[6] with alkyl diphenylphosphinites derived from chiral secondary alcohols were examined. The results are summarized in Table 2. For comparison, the results obtained with DBBQ and trimethylsilylmethyl azide are also listed.[7]

Results shown in Table 2 demonstrate clearly that the methyl acrylate gives better yields than any other oxidants. Good enantiomeric excess was attained by using methyl acrylate especially in the cases with (*S*)-*sec*-butyl diphenylphosphinite and (*R*)-1-methyl-3-phenylpropyl diphenylphosphinite, while a slightly lower enantiomeric excess was recorded in Entry 13 than that obtained with trimethylsilylmethyl azide (Entry 15).

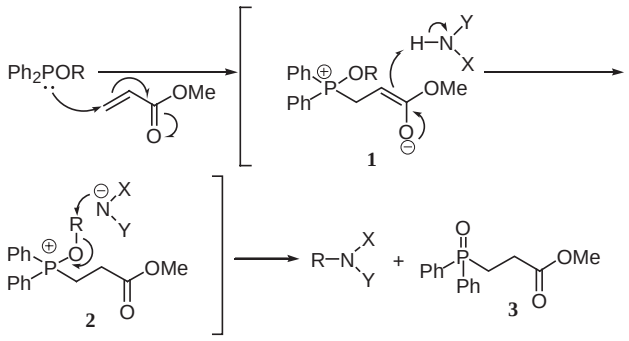
Then, the reaction of (*R*)-1-phenylethyl diphenylphosphinite

Table 3. The reaction of NsNHBoc with (*R*)-1-phenylethyl diphenylphosphinite using methyl acrylate



Entry	Solvent	Yield /%	% ee	Entry	Solvent	Yield /%	% ee
1	CH_2Cl_2	85	84	5	Benzene	85	95
2	$CHCl_3$	87	91	6	Toluene	81	95
3	THF	71	84	7[a]	None	88	93
4	1,4-Dioxane	84	89	8[a,b]	None	88	95

[a]12.0 equiv. of methyl acrylate was used. [b]The reaction was carried out at −10 °C.



Scheme 2.

with NsNHBoc[8] was further studied under various conditions so as to improve the enantiomeric excess (Table 3). As a result, it was found that the desired product was obtained with 95% ee if the reaction was carried out in benzene or toluene (Entries 5 and 6). Interestingly, the same result was also obtained if the reaction was carried out in the absence of solvent at −10 °C (Entry 8).

A proposed reaction mechanism is shown in Scheme 2: An alkyl diphenylphosphinite reacts initially with methyl acrylate to form adduct **1** which is in turn transformed to the phosphonium salt **2** by the interaction with an amide. An attack of thus formed amide anion to the carbon atom adjacent to an oxygen atom of the alkoxy group affords the corresponding amide along with methyl 3-diphenylphosphinoylpropionate (**3**).[9,10]

Thus, it is noted that a simple and easily available methyl acrylate was efficient to work as an oxidant in the preparation of *N*-alkylated compounds from alkyl diphenylphosphinites and weakly acidic compounds having a nitrogen–hydrogen bond. Further study on this type of condensation reaction is now in progress.

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References and Notes

1 For the preparation of alkyl diphenylphosphinites, See: K. Ikegai, W. Pluempanupat, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 638.
2 T. Mukaiyama, H. Aoki, *Chem. Lett.* **2005**, *34*, 142.
3 H. Aoki, K. Kuroda, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1266.
4 T. Mukaiyama, K. Kuroda, H. Aoki, *Chem. Lett.* **2005**, *34*, 1644.
5 R. G. Harvey, *Tetrahedron* **1966**, *22*, 2251.
6 T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373.
7 General experimental procedure is as follows: To a stirred solution of an amide (0.3 mmol) and an alkyl diphenylphosphinite (0.33 mmol) in dichloromethane (0.25 mL) was added methyl acrylate (0.6 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 24 h at room temperature. After completion of the reaction (detected by TLC), it was purified by preparative TLC to afford the corresponding *N*-alkyl amide.
8 T. Fukuyama, M. Cheung, T. Kan, *Synlett* **1999**, 1301.
9 Spectral data for **3**; IR (ATR, cm^{-1}) 3055, 2948, 1742, 1436, 1239, 1174, 1166, 742, 694, 533, 507, 449, 427; ^1H NMR (270 MHz, $CDCl_3$) δ7.78–7.71 (m, 4H), 7.57–7.44 (m, 6H), 3.63 (s, 3H), 2.70–2.55 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ172.6 (d, $J = 16.8$ Hz), 132.1 (d, $J = 99.5$ Hz), 131.8 (d, $J = 2.8$ Hz), 130.6 (d, $J = 9.5$ Hz), 128.6 (d, $J = 11.7$ Hz), 52.0, 26.3 (d, $J = 2.2$ Hz), 25.1 (d, $J = 72.7$ Hz); HRMS ($APCI^+$) calcd for $C_{16}H_{18}O_3P$ $[M + H]^+$ 289.0994, found *m/z* 289.0990.
10 A. Bell, A. H. Davidson, C. Earnshaw, H. K. Norrish, R. S. Torr, D. B. Trowbridge, S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2879.

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