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DBU-promoted alkylation of alkyl phosphinates and *H*-phosphonates

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ABSTRACT

The alkylation of alkyl phosphinates and some *H*-phosphonate diesters is promoted by the base DBU. Only more reactive alkyl halides react in preparatively useful yields. However, the method provides easy access to important *H*-phosphinate building blocks, without the need for a protecting group strategy or metal catalysts. The reaction is conveniently conducted at, or below, room temperature. The preparation of methyl-*H*-phosphinate esters is particularly interesting as it avoids the heretofore more common use of methyldichlorophosphine $MePCl_2$.

Forming *H*-phosphinates through the direct base-promoted alkylation of alkyl phosphinates [$ROP(O)H_2$] is a known and useful reaction, but is quite rare.[1] This is because of the instability of the corresponding P(III) anion: ROP(OM)H.[2] A few years ago, we reported a method to achieve this transformation, based on *n*-butyllithium deprotonation at low temperature (−78 °C).[1b] Although the reaction was successful on a variety of electrophiles, foul-smelling reaction mixtures were sometimes obtained due to some unavoidable decomposition of the intermediate phosphinate anion. In our report, two examples using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature (instead of *n*-BuLi at −78 °C) were also disclosed. On the other hand, the base-promoted or base-catalyzed conjugate addition of alkyl phosphinates to Michael acceptors is much more common.[3] Alkylation with less reactive electrophiles typically requires a protecting group strategy (Ciba-Geigy reagents $(EtO)_2CRP(O(OEt)H$, R = H, Me; bis(trimethylsilyloxy)phosphine, or (dialkoxy)phosphine-borane complexes $(R^1O)(R^2O)P(BH_3)H$) in order to obtain acceptable yields of *H*-phosphinate esters and avoid extensive decomposition of the phosphinate nucleophile.[4]

Herein, we report on the practical DBU-promoted alkylation of alkyl phosphinates with reactive electrophiles, as well as an extension to diphenylphosphite $(PhO)_2P(O)H$ and other reactive *H*-phosphonates. Because DBU seemed promising in our initial report,[1b] we decided to investigate more thoroughly the scope of this reaction. Using iodomethane (1.1 equiv) as the electrophile, and $EtOP(O)H_2$ as the nucleophile, various bases were tested (1.1 equiv, 0 °C, CH_3CN) and the product formation was established by ^{31}P NMR: DBU (85%), TBD (81%), TMG (65%), DBN (49%), DABCO (0%), and Et_3N (0%).[5] Thus, DBU was retained as the base of choice. For the solvent, CH_3CN was found to be ideal, both for its convenience to prepare the alkyl phosphinate[6] and the subsequent alkylation step. Toluene and DMF could also be employed, but the overall yield was lower.

Based on the above experiments, standard conditions were used with a variety of electrophiles. The results are reported below (Table 1). As expected, less reactive electrophiles such as 1-iodooctane cannot be employed successfully. Other electrophiles tested included bromoacetonitrile, propargyl chloride and bromide, benzyl and allyl chloride, and 1-iodooctane, but in all cases the ^{31}P NMR yield of alkylation was in the 0–15% range. Additionally, very reactive electrophiles ($C_6F_5CH_2Br$, $2\text{-}O_2NC_6H_4CH_2Br$) were also unsatisfactory, perhaps because Atherton-Todd-like P-halogenation becomes the major pathway, resulting in the nearly quantitative formation of $(EtO)_2P(O)H$.[7] Consistent with this, using the less reactive 2-nitrobenzyl chloride is better (48% NMR yield). Although limited in its scope, the present reaction is very convenient to run, does not produce foul-smelling reaction mixtures, and delivers very useful products such as methyl-*H*-phosphinate **3** (entry 3). Whereas we[1b] and Gallagher[1a] have prepared methyl-*H*-phosphinate esters by direct alkylation, the present method is significantly simpler. Additionally, $CH_3P(O)(OR)H$ is still most often made through the esterification/hydrolysis of methyldichlorophosphine CH_3PCl_2 (which is itself made from the Kinnear–Perren reaction: $CH_3Cl + AlCl_3 + PCl_3$ followed by reduction with aluminum).[8] Although available commercially, methyldichlorophosphine is not only hazardous (toxic, pyrophoric) but also expensive.

We have previously prepared several allylic- and benzylic-*H*-phosphinates similar to those in Table 1. However, the syntheses use either expensive palladium-catalyzed cross-coupling,[9,10] or multistep reactions.[11] For example, ethyl (2-bromobenzyl)-*H*-phosphinate **5a** (entry 9a) was previously synthesized using the

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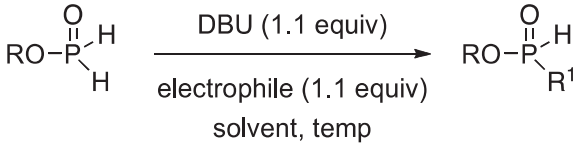
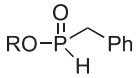
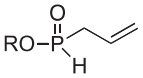
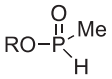
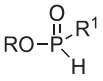
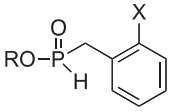
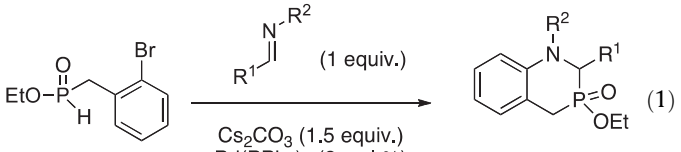
Table 1
DBU-promoted alkylation of phosphinates $ROP(O)H_2$ with electrophiles

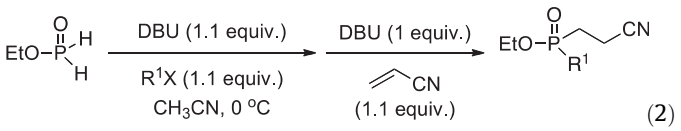


Entry	R[a]	Solvent Temp	Electrophile	Product		^{31}P-NMR yield (%)	Isolated yield (%)[b]
1a	Et	CH_3CN 0 °C	BnCl			15	-
1b	Et		BnBr		**1a**	95	83
1c	Me		BnBr		**1b**	78	67
2	Et	CH_3CN -20 °C	AllylBr		**2**	87	72
3a	Bu	toluene	MeI		**3a**	76	74[c]
3b	Ph_2CH	CH_3CN			**3b**	59	48
3c	Men	Cyclohexane 0 °C			**3c**	100	60[d]
4a	Et	CH_3CN 0 °C	R^1Br	R^1 = prenyl 	**4a**	77	53[e]
4b				cinnamyl	**4b**	83	61
4c				geranyl	**4c**	81	64
5a	Et	CH_3CN - 20 °C	2-$XC_6H_4CH_2Br$	X = Br 	**5a**	72	56
5b				X = I	**5b**	92	78

[a] $ROP(O)H_2$ were prepared from H_3PO_2 as follows: R = Me, $PrSi(OMe)_3$ esterification; R = Et, $Me_2Si(OR)_2$ esterification; R = Bu, Dean-Stark esterification in refluxing toluene; R = $CHPh_2$, esterification with Ph_2CN_2; the typical reaction time was 2 h; R = Men, Dean-Stark esterification in refluxing cyclohexane.
[b] Products were isolated by chromatography over silica gel.
[c] This product was obtained without chromatography and contains 0.5 equiv of residual BuOH.
[d] Obtained as a 1:1 mixture of diastereoisomers.
[e] 1.4 equiv was used.

alkylation of the Ciba-Geigy reagent with LiHMDS in 60% overall yield.[11] Compound **5a** can be converted into interesting *P,N*-heterocycles (Eq. 1).[11]





R^1X = BnBr: **6a** 75%
R^1X = 3-$PyrCH_2Br$: **6b** 58%
R^1X = MeI: **6c** 78%

The present DBU-promoted reaction is significantly simpler and at least comparable in isolated yield to a variety of other approaches based on cross-coupling or alkylation. Furthermore, tandem processes are also possible. Eq. 2 shows some conjugate additions with acrylonitrile. Ethyl(2-cyanoethyl)methylphosphinate **6c** has been prepared previously (starting from $MePCl_2$) as a key intermediate in the synthesis of a potent $GABA_B$ agonist. [4h] Another reaction is the tandem cross-coupling of $CH_3P(O)(OR)H$ **3** with aryl halides. Scheme 1 provides an interesting example. Palladium-catalyzed cross-coupling[12] of **3a** gave product **7**, which was subsequently converted into *P*-heterocycle **8** via Dieckmann-like condensation. Similar cross-coupling products have only been synthesized via the nickel-promoted cross-coupling of methylphosphonites ($MeP(OR)_2$ again derived from $MePCl_2$).[13]

Unlike the alkylation of alkyl phosphinates, the base-promoted alkylation of *H*-phosphonates $(RO)_2P(O)H$ is very well known (Michaelis–Becker reaction) under a variety of basic conditions (NaH, Na, Cs_2CO_3/Bu_4NI, etc.).[14] Because diphenylphosphite is unusually acidic (i.e. the formation of its P(III) tautomer is less unfavorable than with alkyl esters),[15] its DBU-promoted alkylation was investigated under conditions similar to those developed for alkyl phosphinates (Table 2). Since $(PhO)_2P(O)H$ is commercially available, a variety of solvents can be employed directly. This time, even less reactive electrophiles such as 1-iodooctane (entry 3) and 1-iodobutane (entry 4a) reacted in useful yield, and in this case DMF proved superior to acetonitrile. However, 1-bromooctane only gave a 40% NMR yield under a variety of conditions (entry 4b). Despite the fact that numerous methods have been reported for the alkylation of *H*-phosphonates, the present conditions are