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

Laurent Gavara [†], Christelle Petit [†], Jean-Luc Montchamp [*]

Department of Chemistry, Box 298860, Texas Christian University, Fort Worth, Texas 76129, United States

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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

* Corresponding author. Tel.: +1 817 257 6201; fax: +1 817 257 5851.
E-mail address: j.montchamp@tcu.edu (J.-L. Montchamp).
† These two authors contributed equally to this work.

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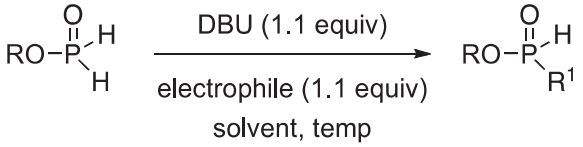
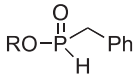
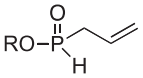
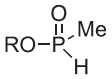
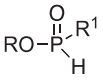
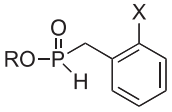
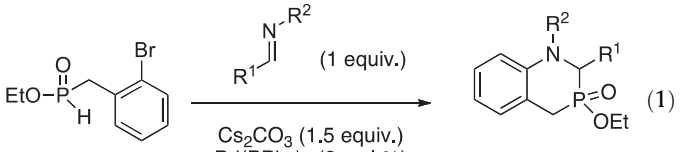
Table 1
DBU-promoted alkylation of phosphinates $ROP(O)H_2$ with electrophiles

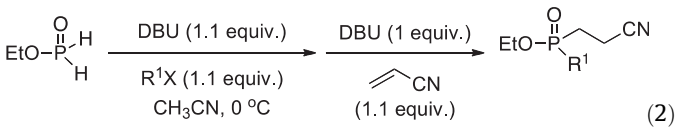


Entry	R[a]	Solvent Temp	Electrophile	Product		^{31}P-NMR yield (%)	Isolated yield (%)[b]
1a	Et	CH_3CN 0 °C	BnCl			15	-
1b	Et		BnBr		**1a**	95	83
1c	Me		BnBr		**1b**	78	67
2	Et	CH_3CN -20 °C	AllylBr		**2**	87	72
3a	Bu	toluene	MeI		**3a**	76	74[c]
3b	Ph_2CH	CH_3CN			**3b**	59	48
3c	Men	Cyclohexane 0 °C			**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]



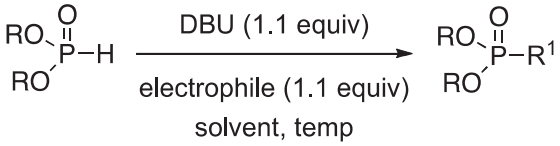


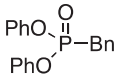
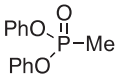
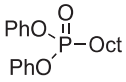
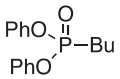
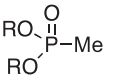
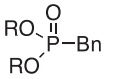
R^1X = BnBr: **6a** 75%
R^1X = 3-$PyrCH_2Br$: **6b** 58%
R^1X = MeI: **6c** 78%

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]

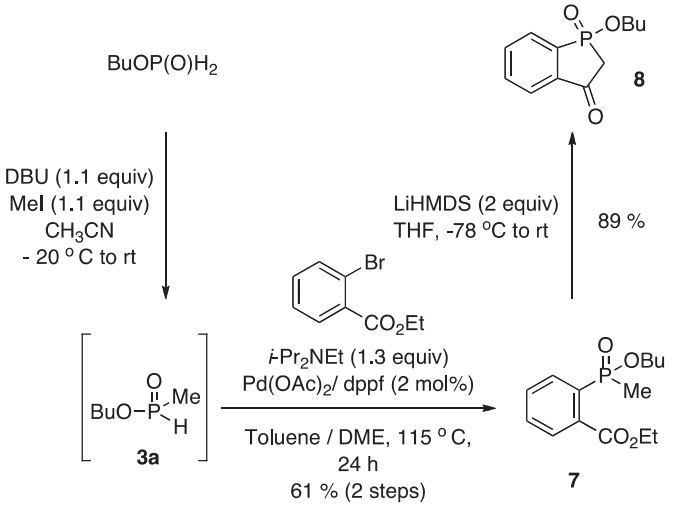
Unlike the alkylation of alkyl phosphinates, the base-promoted alkylation of *H*-phosphonates $(RO)_2P(O)H$ is very well known (Michaelis–Becker reaction) under a variety of basic conditions (NaH, Na, Cs_2CO_3/Bu_4NI, etc.).[14] Because diphenylphosphite is unusually acidic (i.e. the formation of its 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

Table 2
DBU-promoted alkylation of $(RO)_2P(O)H$[a]



Entry	R	Solvent	Temp	Electrophile	Product		^{31}P-NMR yield (%)	Isolated yield (%)[b]
1a	Ph	CH_3CN	rt	BnCl		**9**	50	-
1b				BnBr			96	82
2	Ph	CH_3CN	0 °C	MeI		**10**	97	80
3	Ph	DMF	rt	OctI		**11**	64	-
			-20 °C				87	69
4a	Ph	DMF	0 °C	BuI		**12**	86	63
4b				BuBr			40	-
5a	Et						13	-
5b	CF_3CH_2	CH_3CN	0 °C	MeI		**13a**	72	66
5c	Bn					**13b**	100	98
6a	Et						4	-
6b	CF_3CH_2	CH_3CN	0 °C	BnBr		**14a**	74	69
6c	Bn					**14b**	82	67

[a] Reactions were conducted in the solvent (0.5 M).
[b] Products were isolated by chromatography over silica gel.



Scheme 1. Tandem alkylation/cross-coupling and subsequent heterocyclization.

still useful especially for their simplicity. For example, Stawinski prepared diphenyl benzylphosphonate **9** in 74% yield by Pd-catalyzed cross-coupling (BnBr (1.5 equiv), $(PhO)_2P(O)H$ (1 equiv), $Pd(OAc)_2$ (10 mol %), xantphos (20 mol%), *i*-Pr_2NEt (1.3 equiv) in refluxing THF),[16] whereas we obtained **9** in 82% yield using nearly equimolar amounts of reagents (Table 2, entry 1b). Therefore, our method can certainly be competitive.

As expected, less acidic diethyl *H*-phosphonate failed completely (MeI 13%; BnBr 4%, ^{31}P NMR yields, entries 5a and 6a). However, bis(2,2,2-trifluoroethyl)-*H*-phosphonate (another acidic *H*-phosphonate) worked well (entries 5b and 6b). Perhaps more interestingly, dibenzyl-*H*-phosphonate also reacted successfully (entries 5c and 6c). While the rather dramatic difference in reactivity between dibenzyl-and diethyl-*H*-phosphonates might appear surprising, the benzyl group is electron-withdrawing thus stabilizing the P(III) form, as opposed to the electron-donating ethyl group.[15]

In conclusion, we are reporting a straightforward alkylation protocol using DBU as a stoichiometric base. The reaction is very convenient because it proceeds at or below room temperature with essentially equimolar amounts of reagents. Whereas the scope of this reaction is somewhat limited, very useful reagents can be prepared easily and in a single step, whereas literature methods can employ multistep processes and/or palladium-catalyzed

cross-coupling. The formation of methyl-*H*-phosphinate esters is especially noteworthy because it completely avoids hazardous and expensive methyldichlorophosphine, and it can be used in tandem reactions without intervening chromatographic purification. The possibility to develop an asymmetric alkylation of alkyl phosphinates[17] using a chiral DBU equivalent (amidines, guanidines, etc.)[18] is tantalizing.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures, spectra data, and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.019.

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5. Abbreviations: DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG = 1,1,3,3-tetramethylguanidine; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, DABCO = 1,4-Diazabicyclo[2.2.2]octane.
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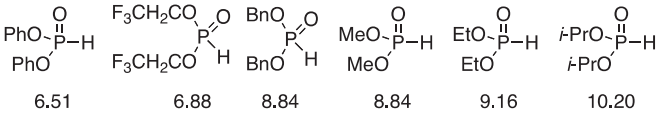
15. The calculated *p*Ka values in aqueous solution (SciFinder, Advance Chemistry Development (ACD/Laboratories) Software V11.02, © 1994-2012 ACD/Labs) are as follows:



In DMSO, the calculated *p*Ka values for $(PhO)_2P(O)H$ and $(MeO)_2P(O)H$ are 9.0 and 18.4, respectively. See: Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453.
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