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A simple, general and efficient ketone synthesis *via* alkylation and dephosphinoylation of β-keto-diphenylphosphine oxides†

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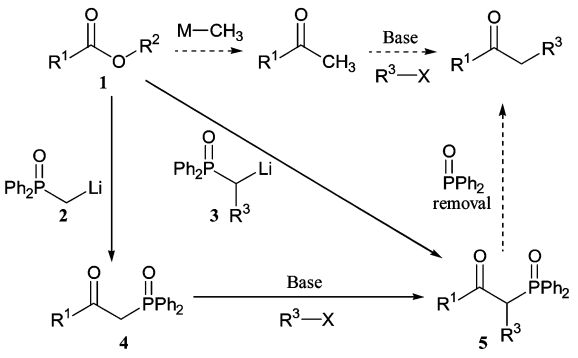
Products of difficult ketone alkylation reactions can be made selectively *via* activation with a diphenylphosphinoyl group; subsequent dephosphinoylation is easily achieved in base.

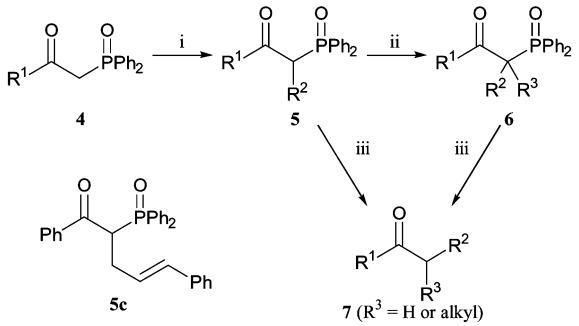
The synthesis of simple ketones by addition of organometallic reagents to carboxylic acid equivalents can be hampered by over-reaction to give tertiary alcohols. Additions of alkylmetal reagents to Weinreb amides[1] do provide methods for selective ketone synthesis. Lithiated phosphine oxides **2** and **3**, however add to simple alkyl esters **1** to give ketones **4** and **5** in high yield (Scheme 1). The β-ketophosphine oxides so formed are useful intermediates in the synthesis of (*E*)-olefins[2] and cyclopropanes.[3] In these syntheses, the phosphinoyl group is removed from the molecule by attack of an intramolecular alkoxide nucleophile.

Current research projects within our group demanded the high-yielding synthesis of simple alkyl and aryl ketones *via* enolate alkylation, but it proved difficult to perform selective mono-alkylations of methyl ketones in standard conditions (Scheme 1). Related hydrazones could be alkylated instead and cleaved to give ketones,[4] but as an alternative we hoped that β-ketophosphine oxides could be selectively alkylated and then dephosphinoylated in basic conditions with hydroxide as the intermolecular nucleophile. Alkylation of (diphenylphosphinoyl)methyl ketones **4** provides an alternative to the addition of more elaborate lithiated phosphine oxides **3** to esters.[3]

Initial investigations involved the treatment of ketone **5c** (R^1 = Ph, R^2 = (*E*)-Ph(CH=CH)CH_2–) with KOH in methanol at reflux. Dephosphinoylation was complete in a few hours and the desired product **7c** was obtained in near quantitative yield (Table 3). To test the generality of this method, (diphenylphosphinoyl)methyl ketones **4** (R^1 = Ph or Me) were alkylated with a range of electrophiles (Scheme 2, Table 1). If one equivalent of base and electrophile was used, only monoalkylation was observed. Treatment of mono-substituted ketones **5** in the same conditions allows for the introduction of a second, different alkyl group (Scheme 2, Table 2). Interestingly, a second alkylation is not possible for aryl ketones (R^1 = Ph), even with heating. This is not currently understood. Base mediated dephosphinoylation occurs in good yield for a wide range of substrates **5** and **6** (Scheme 2, Table 3).



Scheme 1



Scheme 2 *Reagents and conditions*: i, see Table 1; ii, see Table 2; iii, see Table 3.

Table 1 Selective mono-alkylation of ketones **4** (Scheme 2)

4 R^1	Alkylating agent R^2-X	Product (method)[a]	Yield (%)
Me	(*E*)-PhCH=CHCH$_2$Br	**5a** (a)	87
Me	PhCH$_2$Br	**5b** (a)	72
Ph	(*E*)-PhCH=CHCH$_2$Cl	**5c** (b)	97
Ph	CH$_3$(CH$_2$)$_{11}$I	**5d** (c)	71
Ph	PhC(O)CH$_2$Br	**5e** (a)	86
Ph	(*Z*)-PhCH=CHCH$_2$Br	**5f** (a)	85

[a] Alkylation conditions: a) NaOMe, R^2-X, THF, 20 °C; b) NaOMe, R^2-X, NaI, THF, 20 °C; c) NaH, R^2-X, DMF.

The addition to an ester and alkylation of the product at the activated methylene or methine carbon followed by hydrolytic removal of the activating group is reminiscent of a Claisen ester-condensation, alkylation and decarboxylation.[5] Simple Claisen condensations are complicated by the synthesis of mixtures of cross-condensed and self-condensed β-keto-ester products, which are often difficult to separate and would give mixtures of ketones. The phosphine oxide mediated method avoids the use of a second carbonyl group, providing selective intermediate synthesis and alkylations, and a non-acidic ketone synthesis, ideal for products

Table 2 Alkylation of ketones **5** (Scheme 2)

Starting material **5**		Alkylating agent R^3-X	Alkylation product[a]	Yield (%)
R^1	R^2			
Ph	Me	(*E*)-PhCH=CHCH$_2$Br	**6a**	0
Me	Me	(*E*)-PhCH=CHCH$_2$Br	**6b**	97
Et	Me	(*E*)-PhCH=CHCH$_2$Br	**6c**	81
i-Pr	Me	(*E*)-PhCH=CHCH$_2$Br	**6d**	80
(CH$_2$)$_2$Ph	(*E*)-PhCH=CHCH$_2$	(CH$_3$)$_2$C=CHCH$_2$Br	**6e**	87
Me	(*E*)-PhCH=CHCH$_2$	CH$_2$=CHCH$_2$Br	**6f**	54

[a] Alkylation conditions: NaOMe, R^2-X, THF, 20 °C.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b410144h/

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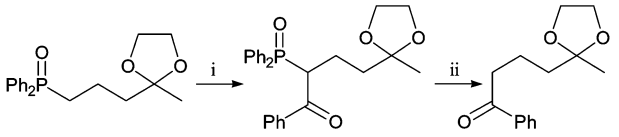
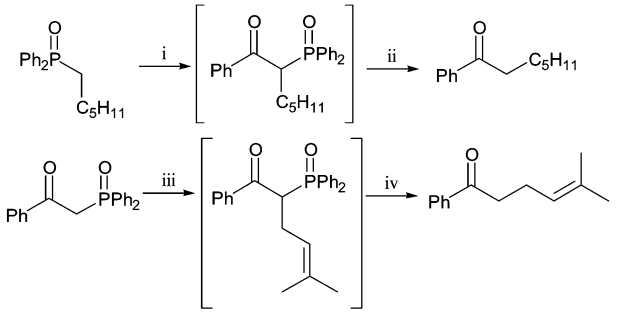
Table 3 Dephosphinoylation of ketones **5** (see Table 1) and **6** (see Table 2) (Scheme 2). Representative procedure for dephosphinoylation: the substrate (1 mmol) was dissolved in ethanol (5 ml) and 4 M NaOH (5 ml) was added. The reaction was heated at reflux until the reaction was complete (by TLC), then allowed to cool, and extracted with EtOAc to give nearly pure product.

Starting material	Ketone product	Yield (%)	Conditions
5a	**7a**	92	$NaOH/H_2O/EtOH$/reflux
5b	**7b**	86	$NaOH/H_2O/EtOH$/reflux
5c	**7c**	96	KOH/MeOH/reflux
5d	**7d**	68	$NaOH/H_2O/EtOH$/reflux
5e	**7e**	68	$NaOH/H_2O/EtOH$/reflux
5f	**7f**	93	$NaOH/H_2O/EtOH$/reflux
6b	**7g**	96	$NaOH/H_2O/EtOH$/reflux
6c	**7h**	91	$NaOH/H_2O/EtOH$/reflux
6d	**7i**	97	$NaOH/H_2O/EtOH$/reflux
6e	**7j**	80	$NaOH/H_2O/EtOH$/reflux
6f	**7k**	71	$NaOH/H_2O/EtOH$/reflux
5a	**7a**	95	$K_2CO_3/H_2O/EtOH$/reflux
5c	**7c**	95	$K_2CO_3/H_2O/EtOH$/reflux
5c	**7c**	0	$KF/H_2O/EtOH$/reflux
5c	**7c**	>95%[a]	NaOMe/MeOH/reflux

[a] Conversion by NMR with $Ph_2P(O)OMe$ as the other product.



Scheme 3 *Reagents and conditions*: i, *n*-BuLi, THF, −78 °C, $PhCO_2Me$, 74%; ii, KOH, MeOH, reflux, 82%.

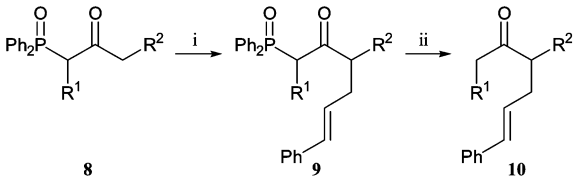


Scheme 4 *Reagents and conditions*: i, *n*-BuLi, −78 °C, $PhCO_2Me$; ii, NaOH, H_2O, EtOH, reflux, 66% (2 steps); iii, NaOMe, $(CH_3)_2C{=}CHCH_2Br$, THF, 20 °C; iv, NaOH, H_2O, EtOH, reflux, 89% (2 steps).

with acetal or ketal functionality (Scheme 3). One-pot reactions are possible with this methodology: lithiated phosphine oxide addition to esters with basic work-up provides ketones in good yield. Alternatively a selective mono-alkylation product can be dephosphinoylated without isolation in excellent combined yield (Scheme 4).

Dephosphinoylation of β-keto-phosphonates is possible with lithium aluminium hydride followed by highly acidic workup, but this method is not compatible with a range of common functional groups.[6] Removal with base[7] or mild acid[8] has been reported only with highly activated substrates containing other significant electron-withdrawing groups. Standard keto-phosphine oxides, however, are nucleophilically cleaved using carbonate, but not fluoride. Sodium methoxide can be used as an alternative; this may be useful if methyl esters are present, avoiding unwanted hydrolysis (Table 3).

Alkylations of α,γ-dilithiated-β-ketophosphine oxides can also lead to the synthesis of interesting ketones.[9] The treatment of variously substituted keto-phosphine oxides with two equivalents of LDA produces a dianion equivalent that selectively reacts at the less stabilised γ-position (Scheme 5). Systematic investigation into the effect on reaction of the substitution of phosphine oxide using cinnamyl bromide shows that increasing methylation at either the α- or γ-position reduced the yield of the γ-alkylation. These products can also be dephosphinoylated (Scheme 5). The same α- or γ-disubstituted keto-phosphine oxide can be produced with alkylation in either order. Comparison of the two routes to ketone **11** shows that both alkylation yields are higher if the γ-substituent is introduced first (Scheme 6).

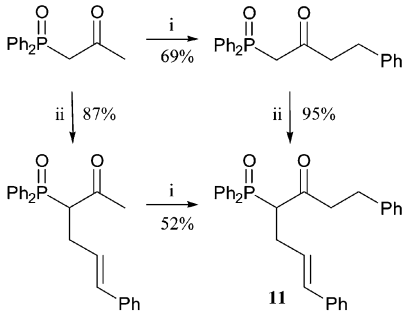


Scheme 5 *Reagents and conditions*: i, LDA (2 eq.), THF, −78 °C, (*E*)-$PhCH{=}CHCH_2Br$; ii, a, NaOH, H_2O, EtOH, reflux, or b, KOH, MeOH, reflux (see Table 4).

Table 4 Alkylation of ketones **8** and dephosphinoylation of ketones **9** (Scheme 5)

R^1	R^2	Yield **9** (%)	Ph_2PO removal method[a]	Yield **10** (%)
H	H	65	a	91
H	Me	45	b	93
Me	H	55	a	85
Me	Me	22	a	70

[a] See Scheme 5.



Scheme 6 *Reagents and conditions*: i, LDA (2 eq.), THF, −78 °C, BnBr; ii, NaOMe, (*E*)-$PhCH{=}CHCH_2Br$, THF.

Overall, selective activation of ketones towards regioselective alkylation with a removable diphenylphosphinoyl group is a general practical method with advantages over existing procedures.

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