ETHYL 4-DIPHENYLPHOSPHINOYL-2-OXOBUTANOATE:

A CONVENIENT REAGENT FOR THE SYNTHESIS OF γ,δ-UNSATURATED β-KETOESTERS

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Summary: Aldehydes and ketones can be converted into γ,δ-unsaturated-β-ketoesters by
reaction with the dianion from phosphine oxide 1.

γ,δ-unsaturated-β-ketoesters are highly valued intermediates in organic synthesis.
Their multifunctionality allows numerous further transformations. Several of these, e.g.: the
Robinson annelation of cycloalkanones[1] or the corresponding enamines,[2] the formation of
4-piperidones by the Mannich reaction[3] and Diels-Alder reactions of the enol-acetates[4] have
received considerable interest in recent years while others, such as decarbalkoxylations and
reactions via the mono- and dianions, appear not to have been explored.

Wider application of γ,δ-unsaturated-β-ketoesters has been greatly hampered by their
limited accessibility. The methods described until recently were not generally applicable,
suffered from low yields or used difficultly accessible starting materials.[5] The condensation
of carbonyl compounds with the dianion of the acetoacetic ester, described by Huckin and
Weiler,[6] appeared to be more general, but no satisfactory method for the dehydration of the
resulting alcohols has been described. The recent report by Bodalski et al.[7] on the synthesis of
these unsaturated esters by the Wittig-Horner-Emmons approach, using diethyl 3-carbethoxy-2-
-oxopropane phosphonate prompts us to disclose our own results, which make use of a Horner-
-Wittig reaction with the dianion from phosphine oxide 1.

This phosphine oxide is easily available by an Arbusov reaction of ethyl 4-bromo-3-
-oxobutanoate[8] with ethyl diphenylphosphinite.
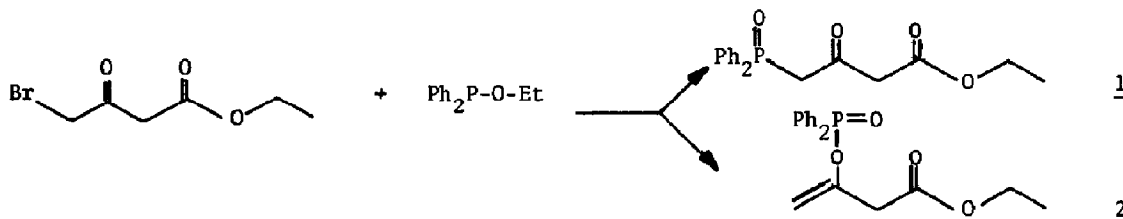
Apart from the desired phosphine oxide 1 a certain amount of vinyl phosphinate 2 is formed
(Perkow reaction) but one crystallization (toluene/ether/ hexane) suffices to obtain the
phosphine oxide in excellent purity mp 95°).[9]

1 (3 mmol in 20 ml of THF/HMPT 3:1 v/v) reacts with 2 equiv of sodium hydride in THF
(10 ml) to give the yellow coloured dianionic species **3**. Addition of HMPT is necessary to allo
complete conversion into the dianion.
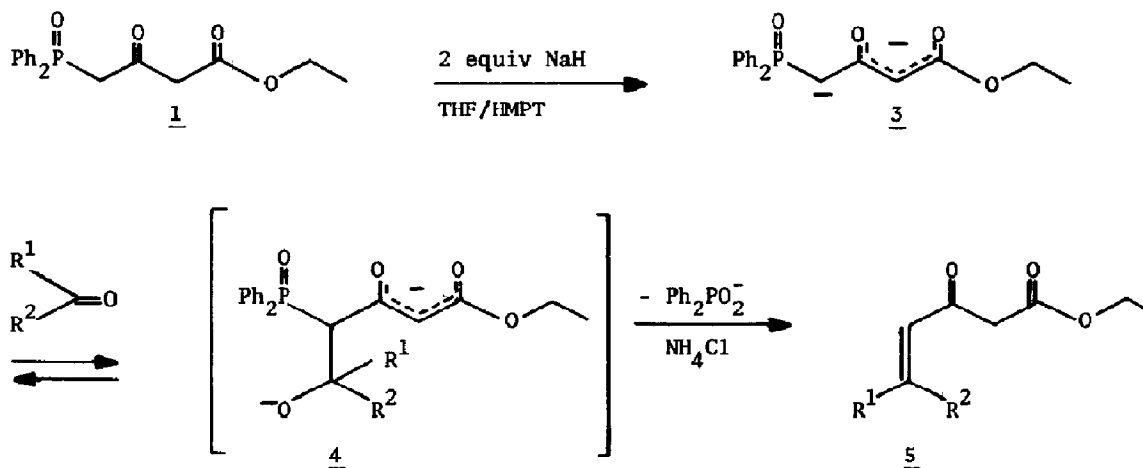
Dianion **3** reacts smoothly with a large variety of aldehydes and ketones (3 mmol in 20 ml of
THF) at room temperature. The resulting betaines **4** loose diphenylphosphinate spontaneously to
afford the unsaturated ketoesters **5** in high yields. The results are presented in the Table.
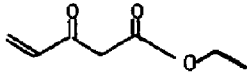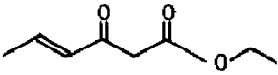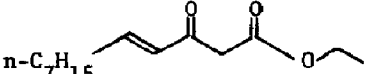The compounds marked with an asterisk were also obtained by Bodalski et al.[7] in comparable
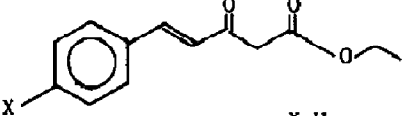yields.
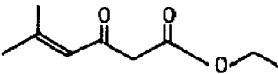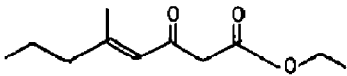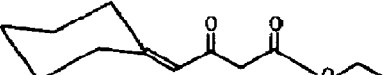
Similar to what is observed in the reactions with the phosphonate reagent,[7] the products
5 derived from aldehydes (R^2 = H) are exclusively formed as E-isomers.[11] This indicates
reversibility of the initial condensation step and exclusive elimination of diphenylphosphinat
from the thermodynamically favoured threo isomer of **4**.[12]

With non-symmetric ketones, both E-and Z-isomers are formed, although a large
preponderance of E-isomer is observed in all cases (entries J,L and O). Acyclic ketones gave
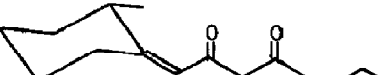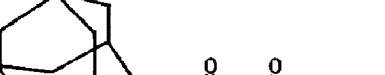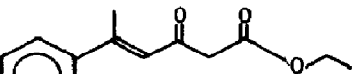quite satisfactory results (entries I,J and O). Cyclohexanones reacted smoothly and provided
the previously unknown derivates (entries K through N) in excellent yields. These compounds
show obvious potential for the synthesis of spiro compounds. Also the simplest member of the
family, the "Nazarov reagent",[1a] is accessible by reaction of **1** with (para)formaldehyde
(entry A). Although the yield in this case is lower (52 %), this provides a convenient route
to this important reagent. In contrast with the preceeding examples, cyclopentanone, reported
to give a 65 % yield,[7] gave less satisfactory results with our method.[13]

As expected, the position of the keto-enol equilibria in which compounds **5** engage, show
a strong solvent dependency. The ratios given in the table have been determined in deutero-
chloroform solution by NMR-analysis.

Preliminary experiments indicate that the unsaturated ketoesters **5**/ can be alkylated at
the α-, γ- or ε-position, depending on the reaction conditions.

Table: Conversion of carbonyl compounds R^1R^2CO into γ,δ-unsaturated β-ketoesters $\underline{5}$.

	Product	Yield [a]	n_D^{20} / mp	E/Z ratio	keto/enol ratio
A.		52 %	n_D 1,4788		50/50
B.*		81 %	n_D 1,4512		75/25
C.	n-C$_7$H$_{15}$	73 %	n_D 1,4638		75/25
D.*	X=H	90 %	mp 53°		60/40
E.	X=CH$_3$	80 %	mp 52°		70/30
F.	X=OCH$_3$	80 %	mp 48°		75/25
G.	X=NO$_2$	81 %	mp 108°		35/65
H.	X=N(CH$_3$)$_2$	84 %	mp 84°		85/15
I.*		72 %	n_D 1,4676		95/5
J.		65 %	n_D 1,4655	85/15	90/10
K.		85 %	n_D 1,4980		95/5
L.		63 %	n_D 1,4980	85/15	95/5
M.		89 %	n_D 1,4898		95/5
N.		73 %	n_D 1,5274		90/10
O.*		65 %	n_D 1,5632	90/10	80/20

a) Yields refer to isolated products after short-column chromatography.

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9. A similar phenomenon has been described for the reaction of ethyl 4-bromo-2-oxobutanoate with triethylphosphite.[10] In that case however the Perkow product is predominantly forme

10. V. Jagodić, Croat.Chem.Acta 49, 490 (1977).

11. Note that dehydratation of the condensation products obtained by Huckin and Weiler[6] affords mixtures of E- and Z-isomers.

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13. Under the conditions used, part of the starting material is converted into condensation products that contaminate the reaction product.