N-METHYL-N-ANILINOMETHYL DIPHENYLPHOSPHINE OXIDE:
A VERSATILE REAGENT FOR THE SYNTHESIS OF ENAMINES

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Summary: Cyclic as well as acyclic ketones, both saturated and α,β-unsaturated, can be converted into their homologous enamines by Horner-Wittig reaction with N-methyl-N-anilinomethyl diphenylphosphine oxide (3).

Enamines are highly valued intermediates in organic synthesis. They react with a large variety of electrophiles to give, after hydrolysis, α-substituted carbonyl compounds.[1]

We have recently reported that aromatic as well as aliphatic and α,β-unsaturated aldehydes can be converted into their homologous enamines 2 in excellent yields (75-95%) by Horner-Wittig reaction with N-morpholinomethyl diphenylphosphine oxide.[2]
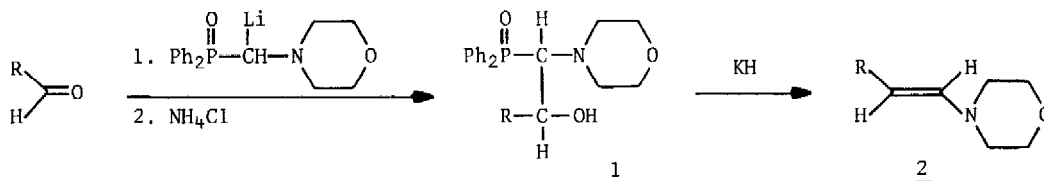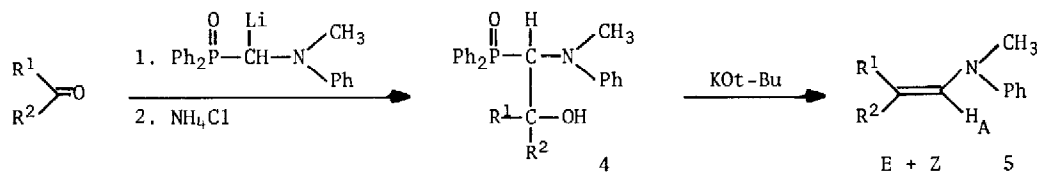

The results with enolisable ketones were less satisfactory, because in that case the ylide acted also as a base, converting part of the carbonyl compound into its lithium enolate. Thus, cyclohexanone afforded only 52% of homologous enamine (^{1}H NMR: vinylic proton at 5.28 ppm), and reactions with acetophenone, cyclopentanone and several acyclic ketones resulted in virtually complete enolisation.[3] It was anticipated that the use of a less strongly basic, but still sufficiently nucleophilic, ylide could circumvent this problem. Thusfar, little attention seems to have been devoted to the influence that an amino substituent exerts on the basicity and nucleophilicity of an adjacent carbanion.[4] Amino substitution would be expected to stabilize a carbanion by induction, while repulsion between the non-bonding pairs of electrons on the hetero-atom and the carbanion should result in destabilization.[5] In phenylamino-substituted carbanions the electron density of nitrogen and thereby the destabilizing effect

upon the ylide should be strongly reduced. Hence the basicity of the ylide from N-methyl-
-N-anilinomethyl diphenylphosphine oxide (3) was expected to be substantially lower than that
of the morpholino-substituted analog. 3 can be conveniently prepared by an Arbusov reaction of
N-methoxymethyl-N-methylaniline[6] with chlorodiphenyl phosphine.[7]

$$Ph_2P-Cl \; + \; CH_3O-CH_2-N\overset{\displaystyle CH_3}{\underset{\displaystyle Ph}{}} \longrightarrow \; Ph_2\overset{O}{\overset{\|}{P}}-CH_2-N\overset{\displaystyle CH_3}{\underset{\displaystyle Ph}{}} \; + \; CH_3Cl$$
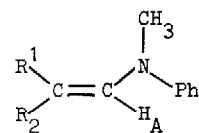
In an atmosphere of dry nitrogen, 3 (1.1 equiv) reacted smoothly at -30° in tetrahydrofuran
(THF) (10 ml/mmol) with n-BuLi (1.1 equiv;as a 1.6 M solution in n-hexane) to give a solution
of the deeply red coloured anion. After 10 min the solution was cooled to -78° and the carbonyl
compound (1.0 equiv) dissolved in THF (2 ml/mmol) was added dropwise. After stirring the
resulting slightly orange solution for 10 min at -78° the reaction was quenched with saturated
aqueous ammonium chloride. After work-up (extraction with CH_2Cl_2) the adducts 4 were obtained
(as mixtures of diastereoisomers when $R^1 \neq R^2$) in almost quantitative yields. The relatively
low basicity, but still sufficient nucleophilicity of the ylide is reflected by the observation
that no starting material is recovered even with highly enolisable ketones such as
cyclopentanone and acetophenone. The only impurity detectable by NMR or TLC was a small amount
of 3, which could easily be removed by chromatography (silicagel/EtOAc).

$$R^1\overset{\displaystyle R^1}{\underset{\displaystyle R^2}{}}{=}O \quad \xrightarrow[\text{2. } NH_4Cl]{\text{1. } Ph_2\overset{O}{\overset{\|}{P}}-\overset{Li}{\overset{|}{C}}H-N\overset{CH_3}{\underset{Ph}{}}} \quad Ph_2\overset{O}{\overset{\|}{P}}-\overset{H}{\overset{|}{\underset{|}{C}}}-N\overset{CH_3}{\underset{Ph}{}} \quad \xrightarrow{KOt-Bu} \quad R^1\overset{R^1}{\underset{R^2}{}}{=}\overset{N\overset{CH_3}{\underset{Ph}{}}}{\underset{H_A}{}}$$

Center column bottom: $R^1{-}\overset{|}{\underset{\displaystyle R^2}{C}}{-}OH$ **4**   E + Z   **5**

In order to complete the Horner-Wittig reaction, the adducts 4 were subsequently treated with
KOt-Bu (1.2 equiv) in THF (10 ml/mmol) at ambient temperature.[8] After 200 min brine was added,
the THF layer separated, and the water layer carefully extracted with ether. The combined
organic layers were washed twice with brine and dried (K_2CO_3). Evaporation of the solvents
afforded the enamines 5. A number of representative examples is compiled in Table I. The
yields are excellent throughout. Because aldehydes already gave good results with the
morpholino-substituted phosphine oxide,[2] only one example is given here (entry M).

The N-methylanilino enamines thus obtained can be easily hydrolyzed to the corresponding
aldehydes.[9] Another interesting property of this type of enamines is their use as precursors of
homo-enolate anions.[10] Because of their difficult accessibility up till now other applications,
especially their behaviour towards electrophiles, have hardly been studied.[11]

TABLE I : Conversion of carbonyl compounds R^1R^2CO into enamines

$$R^1R^2C=C(H_A)N(CH_3)Ph$$

	R^1R^2CO	$\underline{5}$ (yield)[a]	E/Z ratio	$\delta\ H_A$	n_D / mp
A.	cyclopentanone	86 %		5.99 (m)	$n_D^{22} = 1.5578$
B.	cyclohexanone	92 %		5.73 (m)	$n_D^{25} = 1.5628$
C.	2-methylcyclohexanone	84 %	72/28	E 5.75 (m) Z 5.69 (m)	$n_D^{23} = 1.5598$ [c]
D.	4-tert-butylcyclohexanone	86 %		5.73 (m)	mp = 66–67°
E.	adamantanone	85 %		5.75 (s)	mp = 86–87°
F.	cycloheptanone	84 %		5.80 (m)	$n_D^{21} = 1.5608$
G.	acetophenone	80 %	76/24	E 6.42 (q) Z 6.20 (q)	$n_D^{22} = 1.6368$ [c]
H.	benzophenone	81 % [b]		6.65 (s)	$n_D^{20} = 1.6613$
I.	3-pentanone	87 %		5.77 (m)	$n_D^{22} = 1.5402$
J.	2-butanone	85 %	50/50	E 5.82 (m) Z 5.74 (m)	$n_D^{21} = 1.5418$ [c]
K.	2-cyclohexenone	84 % [b]	95/5	E 5.94 (m)	$n_D^{22} = 1.6133$ [c]
L.	β-ionone	81 %	53/47	E 6.17 (m) Z 5.98 (m)	$n_D^{22} = 1.5902$ [c]
M.	2-ethylbutanal	90 %	65/35	E 6.52 (d, J_{AB} = 14 Hz) Z 6.04 (d, J_{AB} = 8 Hz)	$n_D^{22} = 1.5458$ [d]

a. Yields refer to isolated materials after chromatography (silicagel/hexane).[12]
b. After distillation; c. n_D of E/Z-mixture; d. n_D of E-isomer.

Finally we wish to report that the adducts which are derived from aldehydes ($\underline{1}$ and $\underline{4}$, R^1 = H), can undergo a second, completely different, transformation. Upon thermolysis they loose diphenylphosphine oxide (Ph_2POH) to afford, in a clean reaction, the α-aminoketones $\underline{6}$.[13]
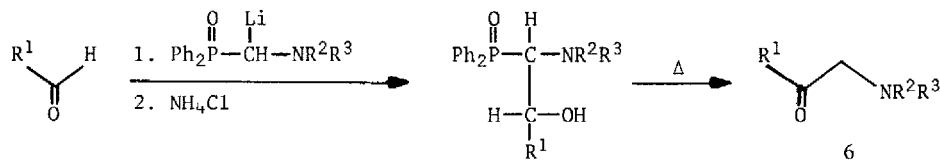
The scope of this net α-aminomethylation is currently being investigated.

REFERENCES AND NOTES

1. See i.a.: A.G. Cook, "Enamines: Synthesis, Structure and Reactions", Ed. Marcel Dekker, New York 1969.

2. N.L.J.M. Broekhof, F.L. Jonkers and A. van der Gen, Tetrahedron Letters $\underline{1979}$, 2433.

3. Performing the reactions in dry THF/hexane (1.1) at -100° in the presence of LiBr, conditions recommanded for the suppression of enolisation, did not substantially improve these results.

4. For a general treatment of the "α-effect", see R.F. Hudson in G. Klopman "Chemical Reactivity and Reaction Paths", 167-252, John Wiley and Sons, New York, 1974.

5. D.J. Peterson, J.Amer.Chem.Soc., $\underline{93}$, 4027 (1971).

6. This compound was prepared in 89% yield (bp: 115-122°/25 mm Hg; n_D^{21} = 1.5397) by adapting the method described by: N. Azerbaev, Yu.G. Bosyakov and S.D. Dzhailauov, J.Gen.Chem.USSR, $\underline{45}$, 2349 (1975).

7. Performing this reaction in THF at ambient temperature we have obtained $\underline{3}$ in 83% yield (mp: 118-119°).

8. With some carbonyl compounds, e.g. acetophenone and β-ionone, we have obtained better results when this step was carried out by stirring at -78° for 120 min, followed by another 120 min at ambient temperature.

9. Stirring enamine B (10 mmol) for 120 min in THF (20 ml)/0.1 N HCl (20 ml) at room temperature resulted in a nearly quantitative conversion into cyclohexanecarboxaldehyde.

10. H. Ahlbrecht, Chimia $\underline{31}$, 391 (1977).

11. G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz and R. Terrell, J.Amer.Chem.Soc., $\underline{85}$, 207 (1963).

12. Satisfactory analytical data were obtained for all compounds described.

13. E.g.: The adduct $\underline{1}$ (R^1 = $(CH_3)_2CHCH_2-$) upon reflux in ethylene glycol solution for 3 min afforded, after work-up, 4-methyl-1-($\underline{N}$-morpholino)pentanone-2 in 83% yield.