Tetrahedron Letters No. 26, pp 2433 - 2436. 0040-4039/79/0622-2433$02.00/0

ENAMINE SYNTHESIS BY THE HORNER-WITTIG REACTION

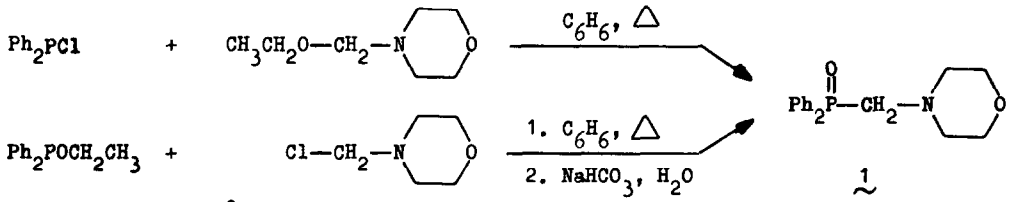
N.L.J.M. Broekhof, F.L. Jonkers and A. van der Gen*
Gorlaeus Laboratories, Department of Organic Chemistry, University of Leiden
P.O. Box 9502, 2300 RA Leiden, The Netherlands.

Summary: Aromatic and aliphatic aldehydes can be converted into their homologous enamines by Horner-Wittig reaction with N-morpholinomethyl diphenylphosphine oxide (1).

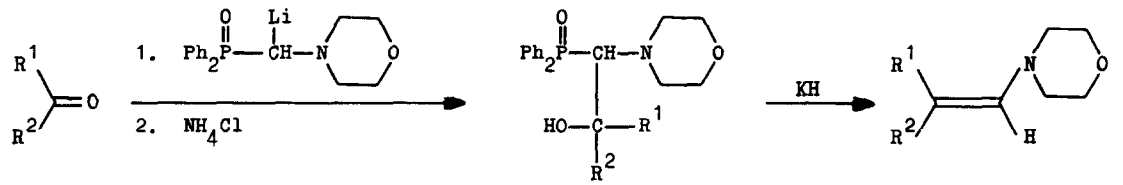
Among the various methods that are used for the homologation of carbonyl compounds, Wittig and Horner-Wittig reactions with α-heterosubstituted ylides occupy a prominent position. A multitude of phosphonium salts, phosphonate esters and phosphine oxides, substituted at the α-carbon atom with aryloxy[1], alkoxy[1-3], aryl- and alkylsulphinyl[2,4,5], sulphonyl[6] and phenylseleno[7] groups, have been described for this purpose. Reaction of the corresponding ylides with aldehydes and ketones, followed by hydrolysis of the (thio or seleno) enolethers, provides the homologous carbonyl compounds.

Thusfar, attempts to effect carbonyl homologation by reaction with α-aminosubstituted Wittig or Horner-Wittig reagents, followed by hydrolysis of the resulting enamines[8] have met with only limited success. In most cases phosphonates have been applied, in which next to the amino group another α-substituent, such as a second phosphonate[9] or an aryl[10], ester[11] or amide[11] function was present and satisfactory reactions were only obtained with aromatic aldehydes. Recently, Martin and coworkers[12] have obtained interesting results with diethyl dialkylaminomethyl phosphonates. In the reaction sequences, leading to various spiro compounds, enamines were thought to be present as intermediates[13].

The often superior properties of diphenylphosphine oxides[5] compared to phosphonates and phosphonium salts in this kind of reactions has led us to investigate the utility of N-morpholinomethyl diphenylphosphine oxide 1[14]. This reagent can be conveniently prepared by an Arbusov reaction of chlorodiphenyl phosphine with N-ethoxymethyl morpholine[15], or by reaction of ethyl diphenylphosphinite[16] with N-chloromethyl morpholine[17,18]. In the latter case the hydrogen chloride salt of 1 is firstly formed[19].



1 reacts smoothly at 0°C with n-BuLi in THF to give a solution of the deeply red coloured anion. This lithiated anion reacts with aromatic as well as aliphatic and α,β-unsaturated aldehydes to give after protonation the adducts 2 (obtained as mixtures of diastereoisomers) in almost quantitative yields. Treatment of these adducts with potassium hydride leads to completion of the Horner-Wittig reaction, giving the desired enamines 3 in excellent yields.



Generally, only E-isomers are observed. In the case of 2-ethylbutanal 40% of Z-isomer, present in the crude enamine, is converted into E-isomer upon distillation. Some representative results are compiled in Table I.

Table I: Conversion of carbonyl compounds R^1R^2CO into homologous enamines 3.

R^1	R^2	2 (mp) [a]	3 (yield) [b]	3 (mp/n_D)
p-BrC_6H_4-	H	176- 7°C	93 %	137- 8°C
p-$CH_3C_6H_4$-	H	155- 8°C	96 %	68-70°C
p-$OCH_3C_6H_4$-	H	146- 7°C	91 %	84- 6°C
C_6H_5-	H	168-70°C	99 %	73- 5°C [f]
(E)-C_6H_5CH=CH-	H	167- 9°C	d	d
(E)-C_2H_5CH=$C(CH_3)$-	H	oil	72 % [e]	n_D^{23}=1.5057
C_6H_5	C_6H_5	c	90 % [e]	78-81°C
$CH_3CH(CH_3)CH_2$-	H	149-50°C	83 % [e]	n_D^{21}=1.4720
$CH_3CH_2CH(CH_2CH_3)$-	H	136- 7°C	63 % [e]	n_D^{24}=1.4688

a. mp after one crystallization (MeOH/H_2O or CH_2Cl_2/hexane) of the diastereoisomeric mixture. No impurities were detectable by NMR.

b. The yields refer to enamines of better than 95% purity (GLC/NMR).

c. We were unable to isolate this adduct, even at low temperature (-78°C).

d. Reaction with KH has led to recovery of cinnamic aldehyde and 1.

e. After distillation. f. Lit.[22]: mp 77-8°C (ether).

The results obtained with ketones (cyclohexanone: 52% homologous enamine; 2-methylcyclohexanone: 50% homologous enamine) are less satisfactory, because proton abstraction to give the enolates becomes an important side reaction. It was reasoned, that this problem might be circumvented by applying a less strongly basic amino substituent. Preliminary results indicate, that this is indeed the case[20].

Since morpholino enamines are known to be easily hydrolyzed[21], the anion of 1 can be regarded as a new formyl anion equivalent. Since the lithiated anion of 1 can be alkylated in excellent yields by reaction with alkyl halides (CH_3I: 95%, mp 153-5°C; C_2H_5I: 93%, mp 154-5°C), extension to an acyl anion equivalent appears feasible. Reaction with diphenyldisulfide likewise affords the α-sulfenylated derivative (mp 198-202°C). Also the lithiated anions of the adducts 2, appeared to be amenable to further transformations. Upon quenching with acetylchloride or chlorotrimethylsilane, they afford the corresponding acetates and trimethylsilylethers, respectively. Synthetic applications of these compounds are currently being investigated.

General procedures

N-morpholinomethyl diphenylphosphine oxide (1): In an atmosphere of dry nitrogen, ethyl diphenylphosphinite[16] (0.05 mol, 11.6 g) was added dropwise at room temperature to N-chloromethyl morpholine (0.052 mol, 7.0 g) in 10 ml of benzene. An exothermic reaction ensued. After addition of 50 ml of benzene the solution was heated at reflux for 60 min. Evaporation of the solvent and drying in vacuo at 50°C yielded 14.8 g (88%) of the HCl salt of 1[23]. Direct treatment of the benzene solution with aqueous sodium bicarbonate afforded after work-up and crystallization (CH_2Cl_2/hexane) 12.9 g (86%) of 1 as white crystals. mp 158-9°C (lit.[14a] mp 158-60°C).

Synthesis of enamines 3. In an atmosphere of dry nitrogen, n-BuLi (5.5 mmol; as a ca. 13% solution in n-hexane) was added at 0°C to a suspension of 1 (5.5 mmol, 1.65 g) in 25 ml of THF. The resulting clear, red solution was stirred for 10 min at 0°C and aqueous saturated ammonium chloride was added. The THF layer was separated and the water layer extracted three times with CH_2Cl_2. The combined organic layers were washed with water and dried ($MgSO_4$). Evaporation of the solvents afforded in almost quantitative yields the adducts 2, which were used without further purification in the next step. Crystallization (CH_2Cl_2/hexane) afforded the pure adducts 2[23] (Table I).

The crude adducts 2 were added to a 6 mmol suspension of KH (the commercially available 24.4% oil dispersion was washed three times with sodium-dry n-pentane) in 50 ml of THF. After

stirring for 180 min (r.t.) the potassium salt of diphenylphosphinic acid had precipitated. 250 Ml of n-pentane and 50 ml of water were added and the mixture was stirred overnight. Separation of the organic layer, drying ($MgSO_4$) and evaporation of the solvents afforded the enamines. These were further purified by crystallization ($MeOH/H_2O$) or distillation[23].

REFERENCES AND NOTES

1. G.Wittig, W.Böll and K.H.Krück, Chem.Ber. 95, 2514, 2526 (1962)
2. G.Wittig and M.Schlosser, Chem.Ber., 94, 1373 (1961)
3. C.Earnshaw, C.J.Wallis and S.Warren, J.C.S.Chem.Comm., 1977, 314
4. H.J.Bestmann and J.Angerer, Annalen, 1974, 2085
5. J.I.Grayson and S.Warren, J.C.S.Perkin I, 1977, 2263
6. M.Mikolajczyk, S.Grzejszczak and A.Zatorski, J.Org.Chem., 40, 1979 (1975)
7. J.V.Comasseto and N.Petragnani, J.Organomet.Chem., 152, 295 (1978)
8. A.G.Cook, "Enamines: Synthesis, Structure and Reactions", Ed. Marcel Dekker, New York 1969.
9. H.Gross and B.Costisella, Ang.Chem., 80, 364 (1968)
10. H.Zimmer and J.P.Bercz, Annalen, 686, 107 (1965)
11. H.Gross and W.Bürger, J.Prakt.Chem., 311, 395 (1969)
12. S.F.Martin, T.-S.Chou and C.W.Payne, J.Org.Chem., 42, 2520 (1977)
13. We have not been able to confirm the presence of enamines in reaction mixtures obtained from 2-methylcyclohexanone and the anion of N-morpholinomethyl phosphonate under the conditions described by Martin et al.[12].
14. Previous preparations of 1 do not appear to offer a synthetically attractive route:
    a. M.J.Gallagher, Austr.J.Chem., 21, 1197 (1968)
    b. A.Burger and W.H.Shelver, J.Med.Pharm.Chem., 4, 225 (1961)
15. N.Azerbaev, Yu.G.Bosyakov and S.D.Dzhailauov, J.Gen.Chem.USSR, 45, 2349 (1975)
16. R.Rabinowitz and J.Pellon, J.Org.Chem., 26, 4623 (1961)
17. H.Böhme, L.Koch and E.Köhler, Chem.Ber., 95, 1849 (1962)
18. The latter procedure is recommended, because it affords a better product.
19. This result may be explained by assuming an intramolecular Arbusov reaction, in which the morpholine nitrogen atom abstracts a proton from the ethyl group and ethene is eliminated.
20. Using N-methylaniline (pKa = 4.85) in stead of morpholine (pKa = 8.33) as amino substituent a 86% yield of the homologous enamine of 4-methylcyclohexanone (n_D^{21} = 1.5373) was obtained.
21. Refluxing the enamines with 1.0 N HCl (10 ml) in THF (50 ml) for 60 min effected quantitative conversion to the homologous aldehydes.
22. W.Ziegenbein and W.Franke, Chem.Ber., 90, 2291 (1957)
23. Satisfactory analyses (GLC, NMR, IR) were obtained for all compounds described.

Acknowledgement: The investigations were supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

(Received in UK 7 March 1979)