Tetrahedron Letters, Vol.22, No.29, pp 2799 - 2802, 1981
Printed in Great Britain

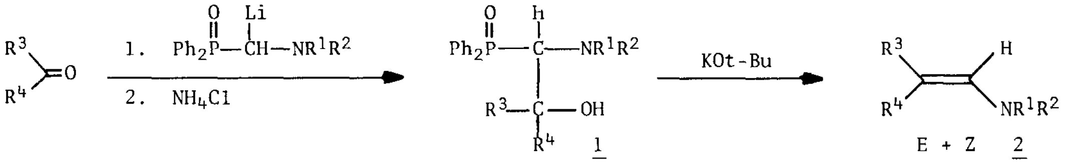
0040-4039/81/292799-04$02.00/0

NOVEL APPLICATIONS OF α-AMINOSUBSTITUTED DIPHENYLPHOSPHINE OXIDES.
THE CONVERSION OF ALDEHYDES INTO α-AMINOMETHYLKETONES.

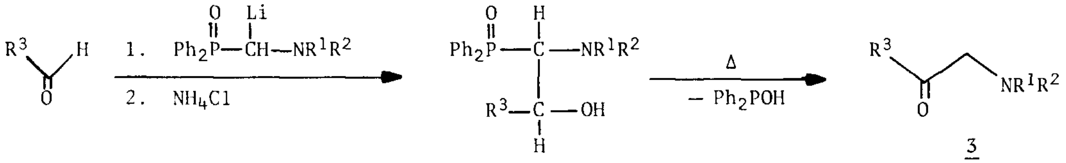
Nico L.J.M. Broekhof and Arne van der Gen.
Gorlaeus Laboratories, Department of Organic Chemistry, University of Leiden,
P.O.Box 9502, 2300 RA Leiden, The Netherlands.

Summary: Aromatic and aliphatic aldehydes (R^3CHO) can be converted into α-aminomethylketones ($R^3COCH_2NR^1R^2$) via reaction with (α-aminomethyl)diphenylphosphine oxides.

Recently we have reported that various types of aldehydes and ketones can be converted into their homologous enamines 2 in excellent yields (75-95%) by Horner-Wittig reaction with (morpholinomethyl)diphenylphosphine oxide[1] or (*N*-methylanilinomethyl)diphenylphosphine oxide.[2]

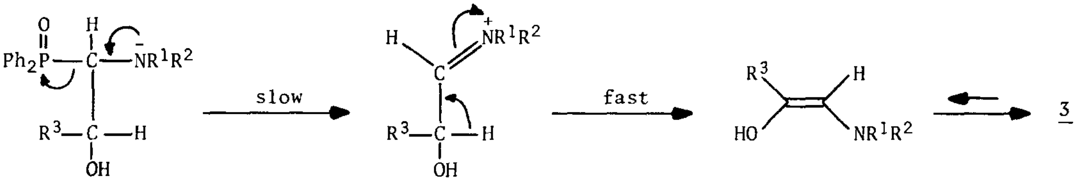


We now wish to report that the adducts 1, which are intermediates in the above reactions, when obtained from aldehydes (R^4 = H), upon thermolysis lose diphenylphosphine oxide (Ph_2POH) to afford α-aminomethylketones 3. The overall sequence thus involves an α-aminomethylation of the parent aldehyde.

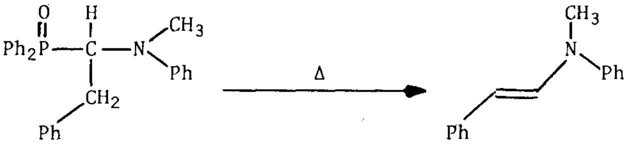


The reaction proceeds without catalysis in protic solvents such as alcohols. Reaction in aprotic solvents like toluene requires the addition of catalytic amounts of acid. Furthermore, the adducts derived from (piperidinomethyl)- or (morpholinomethyl)diphenylphosphine oxide react substantially faster than those derived from (*N*-methylanilinomethyl)diphenylphosphine oxide.[3]

These facts indicate that this Ph_2POH elimination is probably not an intramolecular *syn* process similar to the *N*-oxide elimination (the Cope reaction)[4] or the sulfoxide elimination,[5] in which a five-membered E_i mechanism has been shown to operate, but more likely follows an E_1-type mechanism:



The supposition that the β-hydroxyl group is not directly involved in the elimination step is supported by the observation that a similar elimination proceeds in the absence of this substituent, e.g.:



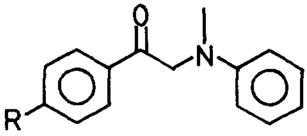
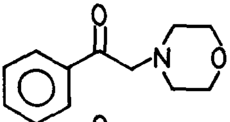
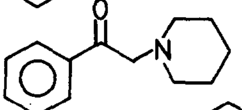
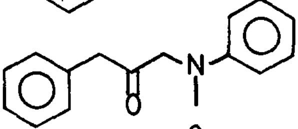
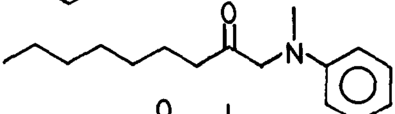
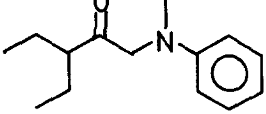
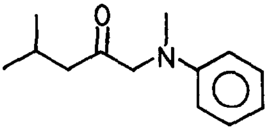
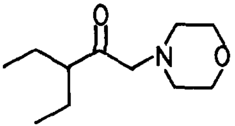
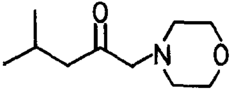
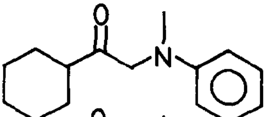
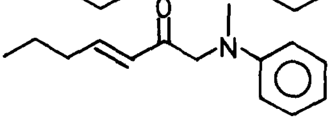
As the requisite phosphine oxides can be prepared by direct alkylation of the unsubstituted (α-aminomethyl)diphenylphosphine oxides, this reaction opens the way to conversion of alkyl halides into homologous enamines.

We have developed two experimental procedures, which are both satisfactory for accomplishing the conversion of adducts 1 (R^4 = H) into α-aminomethylketones 3.

Method A: The adduct, obtained from 5.0 mmol of aldehyde and 5.1 mmol of (α-aminomethyl)-diphenylphosphine oxide in the way described before[1,2] is heated in ethylene glycol (50 ml) at 140-150° for 3h. After cooling, the solution is carefully extracted with hexane.The organic layer is washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield the α-aminomethylketone, which is conveniently purified by column chromatography on silicagel or distillation.

Method B: The adduct is refluxed in toluene (10 ml/mmol) in the presence of a catalytic amount of *p*-TsOH.H_2O (0.04 g/mmol) for 3h. After cooling, the solution is washed twice with saturated $NaHCO_3/H_2O$ and once with brine, dried ($MgSO_4$) and evaporated *in vacuo* to yield a mixture of α-aminomethylketone and Ph_2POH. These are conveniently separated by column chromatography on silicagel. Some representative results obtained with these methods are compiled in Table I. With aromatic as well as aliphatic aldehydes the yields are excellent. In the case of α,β-unsaturated aldehydes, best results were obtained by refluxing the adduct in ethylene glycol for 5 min (entry K).

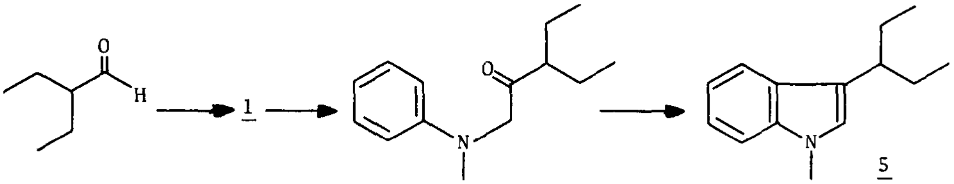
TABLE I : CONVERSION OF ALDEHYDES R^3CHO INTO α-AMINOMETHYLKETONES $R^3COCH_2NR^1R^2$

	PRODUCT[9]		METHOD	YIELD[a]	n_D / mp
A.		R = H	A	82 %	mp = 117.5-118° [b]
		R = H	B	80 %	mp = 117.5-118° [b]
		R = CH_3	A	86 %	mp = 86-87° [c]
		R = OCH_3	A	83 %	mp = 109-110°
B.			B	79 %	n_D^{21} = 1.5661
C.			B	77 %	n_D^{21} = 1.5401
D.			A B	75 % 61 %	n_D^{21} = 1.5914
E.			A	82 %	n_D^{19} = 1.5178
F.			A	82 %	n_D^{21} = 1.5178
G.			A	82 %	n_D^{22} = 1.5201
H.			A	81 %	n_D^{21} = 1.4604
I.			A	90 %	n_D^{21} = 1.4625
J.			B	79 %	n_D^{21} = 1.5445
K.			see text	58 %	n_D^{21} = 1.5442

a. Yields refer to isolated material after chromatography and are based on aldehyde.
b. Litt.[6a]: mp = 122-123° c. Litt.[6b]: mp = 87 %

Thus far, application of tertiary α-aminomethylketones in organic synthesis has been hampered by their difficult accessibility. These compounds were usually prepared from secondary amines and α-halomethylketones[6]—the latter compounds however, are in general only easily accessible when derived from acetone or arylmethylketones—or by spontaneous rearrangement of unbranched aldehydes containing an α-tertiary amino group.[7]

One known application of *N*-methylanilinomethylketones is their use in the Bischler indole synthesis.[8] We have found that (*N*-methylanilinomethyl)diphenylphosphine oxide is an extremely useful reagent for the synthesis of 3-substituted indoles starting from aldehydes. E.g.: refluxing the adduct from 2-ethylbutyraldehyde in xylene for 6h in the presence of p-TsOH.H_2O afforded indole 5 in 69% overall yield.



These and other applications of α-aminomethylketones are currently being investigated and will be reported separately.

REFERENCES AND NOTES

1. N.L.J.M. Broekhof, F.L. Jonkers and A. van der Gen, Tetrahedron Letters 1979, 2433.
2. N.L.J.M. Broekhof, F.L. Jonkers and A. van der Gen, Tetrahedron Letters 1980, 2671.
3. In a competitive reaction the adduct 1, obtained from benzaldehyde and (piperidinomethyl)-diphenylphosphine oxide afforded, after heating in ethylene glycol at 125° for 3h, the expected α-aminomethylketone in good yield, while the corresponding *N*-methylanilinomethyl adduct remained virtually unchanged.
4. a. A.C. Cope and E.R. Trumbull in Organic Reactions 11, 361-370 (1960);
   b. R.D. Bach, D. Andrzejewski and R. Dusold, J. Org. Chem., 38, 1742 (1973).
5. C.A. Kingsbury and D.J. Cram, J. Amer. Chem. Soc., 82, 1810 (1960).
6. e.g.: a. P.E. Verkade and E.F.J. Janetzky, Recl. Trav. Chim. Pays-Bas, 62, 763 (1943);
   b. F. Brown and F.G. Mann, J. Chem. Soc., 1948, 847.
7. L. Duhamel, P. Duhamel and A. Jarry, Bull. Chim. Soc. Fr. 1969, 1797.
8. a. R.K. Brown in'The Chemistry of Heterocyclic Compounds',Volume 25, Part I, p. 317-384, Ed., W.J. Houlihan, John Wiley and Sons, New York, 1972.
   b. M. Julia and J. Lenzi, Bull. Soc. Chim. Fr. 1962, 2263.
9. Satisfactory analytical data 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 1 April 1981)