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ORGANOPHOSPHORUS ENAMINES II.[1] ENAMINE PHOSPHINE OXIDES. A VERSATILE AND EFFICIENT SYNTHESIS OF α,β-UNSATURATED KETIMINES AND THE CORRESPONDING KETONES

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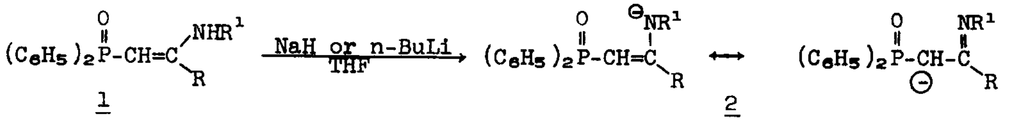
In the course of our investigations into the synthetic utility of organophosphorus compounds, we have studied the use of the enamine phosphine oxides 1a-g as intermediates in a versatile and efficient synthesis of α,β-unsaturated ketones. Herein, we wish to report our preliminary results in this area.

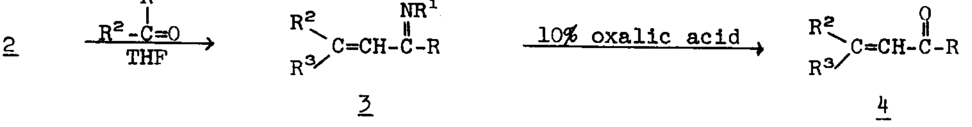
The enamines, 1a-g in THF, were treated with NaH or n-BuLi to produce the anions, 2a-g (eq. 1). Addition of an aldehyde to the THF solutions of 2a-g provided the corresponding α,β-unsaturated ketimine 3 in high yields, as determined by infrared and nmr spectroscopic analysis of the crude product.[5] After addition of the aldehyde, the solution was stirred for 8-10 hr at room temperature or refluxed 1/2-1 hr to complete the reaction. The analogous reaction of anion 2b with cyclohexanone or benzophenone required longer (16-22 hr) reflux periods. Stirring at room temperature or heating an ethereal solution of the crude α,β-unsaturated ketimine with 10% aqueous oxalic acid provided the α,β-unsaturated ketones 4 (eq. 2).[6,7] They were isolated pure in 53-70% overall yield, based on the phosphine oxide, as indicated in Table I.



$$(C_6H_5)_2\overset{\overset{O}{\|}}{P}\text{-CH=C}\genfrac{}{}{0pt}{}{\diagup NHR^1}{\diagdown R}\ \xrightarrow[THF]{NaH\ or\ n\text{-}BuLi}\ (C_6H_5)_2\overset{\overset{O}{\|}}{P}\text{-CH=}\overset{\overset{\ominus NR^1}{|}}{C}\diagdown R \longleftrightarrow (C_6H_5)_2\overset{\overset{O}{\|}}{P}\text{-}\underset{\ominus}{CH}\text{-}\overset{\overset{NR^1}{\|}}{C}\diagdown R \qquad (1)$$

1 2

a. R = C_6H_5, R^1 = $CH_2C_6H_5$
b. R = C_6H_5, R^1 = n-C_4H_9
c. R = C_6H_5, R^1 = $CH_2CH_2(OC_2H_5)_2$
d. R = n-C_3H_7, R^1 = n-C_4H_9
e. R = t-C_4H_9, R^1 = n-C_4H_9
f. R = ⬠, R^1 = n-C_4H_9
g. R = ⬡, R^1 = n-C_4H_9

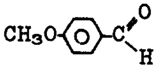
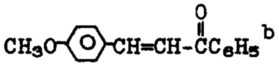
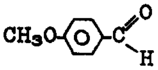
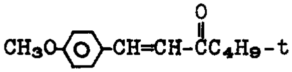
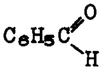
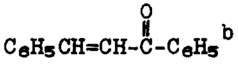
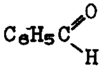
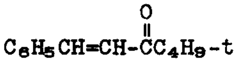
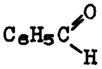
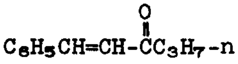
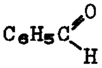
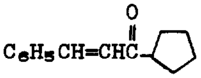
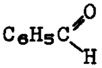
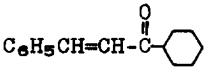
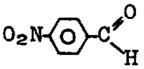
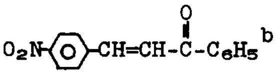
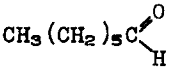
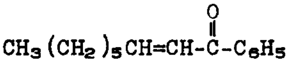
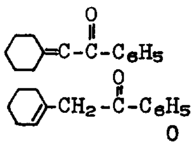
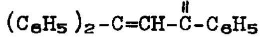


$$\underline{2}\ \xrightarrow[THF]{R^2\text{-}\overset{\overset{R^3}{|}}{C}\text{=O}}\ \genfrac{}{}{0pt}{}{R^2\diagdown}{R^3\diagup}C\text{=CH-}\overset{\overset{NR^1}{\|}}{C}\text{-R}\ \xrightarrow{10\%\ oxalic\ acid}\ \genfrac{}{}{0pt}{}{R^2\diagdown}{R^3\diagup}C\text{=CH-}\overset{\overset{O}{\|}}{C}\text{-R} \qquad (2)$$

3 4

TABLE I

α,β-UNSATURATED KETONES OBTAINED BY TREATMENT OF 2a-g WITH ALDEHYDES AND KETONES

Enamine Phosphine Oxide	Aldehyde or Ketone	α,β-Unsaturated Ketone	Yield[a] %	Mp or Bp °C/mm Hg
$R = C_6H_5$, $R^1 = C_6H_5CH_2$		 [b]	66	72-74[c]
$R = t\text{-}C_4H_9$, $R^1 = n\text{-}C_4H_9$			52	144-145/.10
$R = C_6H_5$, $R^1 = n\text{-}C_4H_9$		 $C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}C_6H_5$ [b]	57	52-54[d]
$R = t\text{-}C_4H_9$, $R^1 = n\text{-}C_4H_9$		 $C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}C_4H_9\text{-}t$	61	102-104/.50
$R = n\text{-}C_3H_7$, $R^1 = n\text{-}C_4H_9$		 $C_6H_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}C_3H_7\text{-}n$	63	79-81/.05[e]
R = , $R^1 = n\text{-}C_4H_9$			59	132-133/.10[f]
R = , $R^1 = n\text{-}C_4H_9$			70	122-124/.06[g]
$R = C_6H_5$, $R^1 = n\text{-}C_4H_9$		 [b]	69	163-164[h]
$R = C_6H_5$, $R^1 = C_6H_5CH_2$		 $CH_3(CH_2)_5CH{=}CH{-}\overset{O}{\overset{\|}{C}}{-}C_6H_5$	57	118-125/.45
$R = C_6H_5$, $R^1 = C_6H_5CH_2$			53	103-115/35[i]
$R = C_6H_5$, $R^1 = n\text{-}C_4H_9$	$(C_6H_5)_2C{=}O$	 $(C_6H_5)_2{-}C{=}CH{-}\overset{O}{\overset{\|}{C}}{-}C_6H_5$	62	83-85[j]

a. This is the % yield of recrystallized or distilled material, based on the phosphine oxide. Therefore, the crude yield of α,β-unsaturated ketone was considerably higher.

b. The crude ketimine hydrolysis product had an infrared spectrum identical to that for authentic sample, prepared by the usual method; Org. Syn. Coll., Vol. I, p. 78.

c. M. S. Kharasch and H. G. Clapp, J. Org. Chem., 3, 335 (1938), mp 79° C for trans-4-methoxy chalcone.

TABLE I (Cont'd)

d. Org. Syn. Coll., Vol. I, p. 78, mp 55-57° C for trans-chalcone.

e. M. Langlair, A. Bugas, and G. Soussan, Compt. Rend., 261 (15) Group 8 (2920-2) (1965) Fr., bp 116-118° C/2 mm Hg.

f. P. P. Mariella and R. R. Raube, J. Amer. Chem. Soc., 74, 521-4 (1952), bp 166-167° C/8 mm Hg.

g. Ibid., mp 56-56.5° C.

h. W. Davey and J. R. Gwilt, J. Chem. Soc., 1008-14 (1957), mp 164° C for trans-4-nitro chalcone.

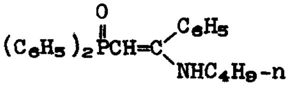
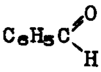
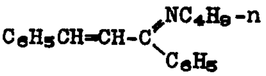
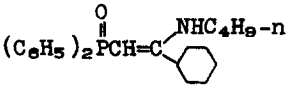
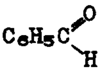
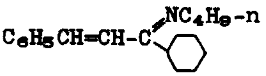
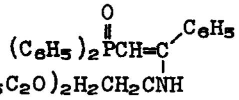
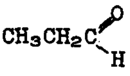
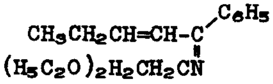
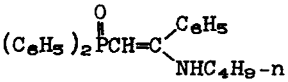
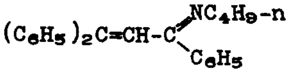
i. E. Winterfeldt, Angew Chem., Int. Ed., 6, 423 (1967), bp endo 176-178° C/ 17 mm; bp exo 140-141° C/2 mm; we isolated a mixture of these two isomers which we did not separate by distillation.

j. J. P. Freeman, J. Amer. Chem. Soc., 80, 1926-30 (1958), mp 85-87° C.

Several of the ketimines were purified by distillation at reduced pressure. The physical data for these compounds is shown in Table II. Of particular interest is the preparation of ketimine 3 (R = C_6H_5, R^1 = $CH_2CH_2(OC_2H_5)_2$, R^2 = CH_3CH_2, R^3 = H; C = N at 6.11 μ neat, 60% pale yellow oil, bp 131-136° C/ 0.3 mm Hg). This and other aminoacetals prepared by our method could be useful as precursors in the Pomeranz-Fritsch synthesis of isoquinolines.

TABLE II

α,β-UNSATURATED KETIMINES[a]

Enamine Phosphine Oxide	Aldehyde or Ketone	Ketimine	Bp °C/mm Hg
2		3	
			170-171/0.05
			151-152/0.10
			131-136/0.30
	$(C_6H_5)_2C=O$		168-172/0.05

a. The ketimines were identifiable by the nmr spectrum which, when R^2 = n-C_4H_9, exhibited a triplet at about 3.3 ppm due to the methylene C=N-CH_2, and a singlet about 4.4 ppm when R was $CH_2C_6H_5$, due to the benzyl protons.

This study represents the first report of the preparation of α,β-unsaturated ketones via enamine phosphine oxide intermediates.[8,9] We feel that the ease of obtaining our starting enamine phosphine oxides adds to the synthetic usefulness of our method since the substituent R can be varied over a wide choice of alkyl, cycloalkyl and aryl moieties. Also, our method allows entry into the t-butyl ketimines and ketones 4 (R = t-butyl) which are otherwise obtained only with difficulty.

Presently, we are investigating the utility of enamine phosphonates and thiophosphonates as well as the enamine phosphine sulfides as intermediates in the preparation of α,β-unsaturated ketimines and α,β-unsaturated ketones and will report these results shortly.

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REFERENCES

1. The preparations of the enamine phosphine oxides appear in Part I submitted for publication.
2. NIH Postdoctoral Fellow, 1970-1971.
3. NASA Predoctoral Fellow, 1966-1969; NDEA Predoctoral Fellow, 1967-1968; NSF Predoctoral Fellow, 1969-1970.
4. To whom correspondence should be addressed.
5. Infrared spectra were obtained in $CHCl_3$ on a Beckman IR 5A or 18A. NMR spectra were obtained in $CDCl_3$ on a Varian A60 and are reported in δ (ppm) downfield from TMS which was an internal standard.
6. Full experimental details will be sent to anyone upon request.
7. Microanalyses performed by Geller Laboratories, P. O. Box 423, Saddle River, New Jersey 07458.
8. W. Nagata and Y. Hayase, *Tetrahedron Lett.*, 4359 (1968).
9. H. Hoffman and H. Förster, *Tetrahedron Lett.*, 983 (1964).