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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—VIII*

THE REACTION OF OXIMES WITH HMPA AT ELEVATED TEMPERATURE

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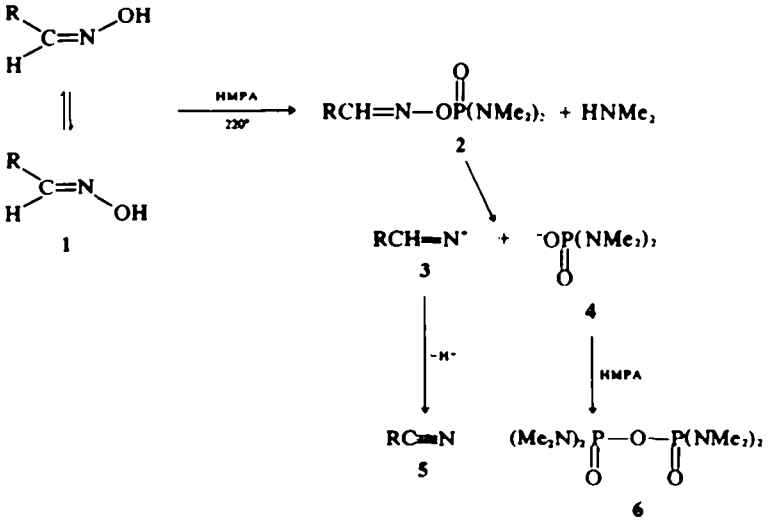
Abstract—A new method for the preparation of nitriles by refluxing aldoximes in HMPA is presented. In the same reaction, almost quantitative yields of octamethylpyrophosphoric amide are formed. Reaction of oximes of aromatic ketones with HMPA produces Beckmann rearrangement products, the corresponding amidines and some quite anomalous products. Cyclohexanone oxime gives no Beckmann rearrangement but several products like octahydroacridines, octahydrocarbazoles, octahydrophenazines, phenazines, lutidines and N,N-dimethyl-anilines.

INTRODUCTION

Hexamethylphosphoric triamide (HMPA) has lately been used as a dehydration reagent[1,2] and has also played a vital role in different types of substitution and fragmentation reactions.[3] A recent note by Monson and Broline[4] on the Beckmann rearrangement in HMPA prompts us to publish our results on reactions of HMPA with some aldoximes and oximes of aromatic ketones and cyclohexanones.



RESULTS

Aldoximes

Oximes **1**, derived from aliphatic and aromatic aldehydes, were heated at about 220° in HMPA, and in general, very high yields of the corresponding nitriles were obtained (Table 1). Besides of the nitriles **5**, high yields of octamethylpyrophosphoric amide, **6**, were found and also bis - (dimethylammonium)dihydrogen pyrophosphate, **7**, was isolated from a gummy precipitate as previously described.[4] Both the *syn*- and the *anti*-forms of benzaldehyde oxime have been studied, but no significant difference in yields was observed. The following mechanism is proposed:

After the initial formation of the phosphorodiamidate, **2**, different routes are imagined. The ions **3** and **4** (free or as ion-pair) are formed after heterolytic cleavage of the N–O bond, and the nitrene, **3**, produces the nitrile after expulsion of a proton. The anion, **4**, will attack another molecule of HMPA to give octamethylpyrophosphoric amide, **6**.

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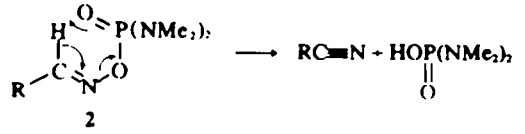
A *cis*-elimination of **2** is also possible, but elimination studies on alcohols in HMPA[5] seem to indicate that C–O fission and proton-loss are not entirely concerted.



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Oximes from alrylketones. In this series oximes of acetophenone, benzophenone, and α-acetonaphthone have been investigated and the same reaction conditions as for the aldoximes have been used.

All these ketoximes underwent the Beckmann rearrangement and in the case of acetophenone oxime both N-phenyl-acetamide and N-methyl-benzamide were isolated. N,N-dimethylamidines were formed from the primarily formed N-phenyl-benzamide and N-phenyl-acetamide (Table 2). In all three cases starting material was recovered, which could not be avoided as too long reaction time produced tarry materials. In the reaction of benzophenone oxime with HMPA, quite unexpectedly benzhydryldimethylamine and benzophenone-methylimine were isolated.

Oximes from cyclohexanones. Cyclohexanone oxime was refluxed in HMPA at about 220°, and in all 15 products have been isolated and characterized (Scheme 1).

It was not possible to isolate all products from one experiment due to the instability and susceptibility of some of the compounds and therefore quite a few experiments were performed. The procedure, after the reaction was complete (followed by GLC and TLC), was to distil the mixture under reduced pressure and the main fractions were then subjected to redistillation and further

Table 1. The reaction of aldoximes with HMPA at 220°C. $RCH{=}N{-}OH \xrightarrow{HMPA} RC{\equiv}N$

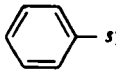
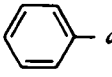
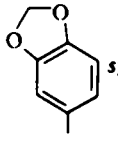
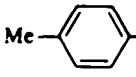
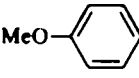
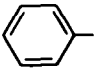
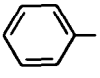
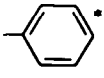
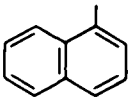
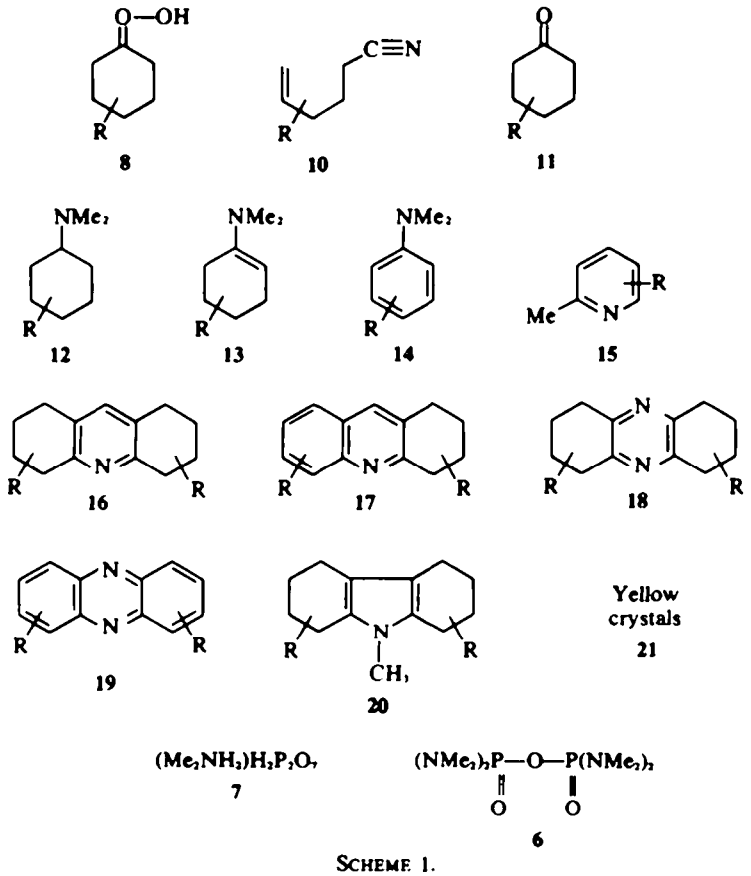
R		Reaction time (h)	Yields %
	*syn*	8	99
	*anti*	8	92
	*syn*	½	86
	*syn*	4	94
	*syn*	3	91
	*anti*	4½	39
n-C_7H_{15}	*syn*	3	89
$(CH_3)_3C$-		½	95

Table 2. The reaction of ketoximes with HMPA at 220°C $\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}N{-}OH \xrightarrow{HMPA}$

R^1	R^2	Reaction time (h)	$R^1{-}\overset{\overset{N-OH}{\|}}{C}{-}R^2$ (%)	$R^1{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R^2$ (%)	$R^2{-}NH{-}\overset{\overset{O}{\|}}{C}{-}R^1$ (%)	$R^1{-}N{=}\overset{\overset{NMe_2}{\|}}{C}{-}R^2$ (%)
	-Me	3	37	17	4	2
	 *	2	42	27	—	5
	-Me	6½	34	15	—	—

* $\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!CHNMe_2$ and $\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}NMe$ were formed in about 1% yield.



SCHEME 1.

chromatographic separation. The complexity of the reaction is illustrated in Table 3, where many isolated products are recorded after different reaction times.

The yellow crystals **21** were isolated from a very high boiling fraction, but the structure has not yet been determined.

Table 3. Yields (in %) for reaction of cyclohexanone oxime in HMPA at 220°C

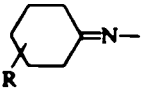
Compounds	3/4 (h)	2 (h)	4 (h)
8	71	32	7
10	2	—	—
11	8	6	1
12	1	5	2
13	4	2	—
14	2	7	5
15	< 1	< 1	—
16	1	5	7
17	—	—	< 1
18	1	2	8
19	—	—	1
20	—	3	5

In Table 4 is given the product distribution from the reaction of substituted cyclohexanone oximes with HMPA. The products were characterized by comparison of spectroscopical data, R_f values and bpts with those obtained for the products from cyclohexanone oxime itself. It should be noted that the mixtures from all reactions of cyclohexanone oximes with HMPA were always very complex.

DISCUSSION

In all reactions of oximes with HMPA it is reasonable to suggest a nucleophilic attack of the oxygen of the oxime on the P atom, a subsequent

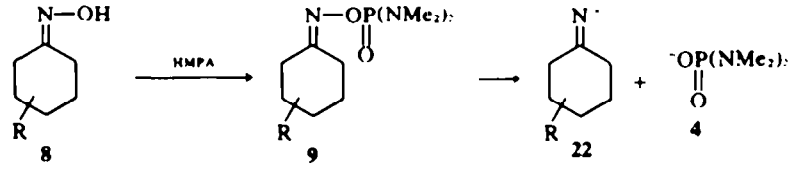
Table 4. Product distribution for reaction of

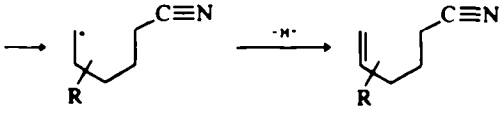


with HMPA at 220° (%)

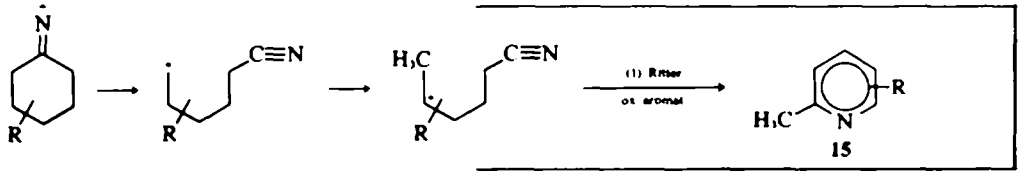
R	11	12	13	14	15	16	18	21
2-Me	5	4	< 2	—	—	3	—	—
3-Me	6	5	2	—	2	6	3	8
4-Me	6	5	3	9	—	13	3	8
4-CMe₃	5	6	—	11	—	5	4	9

expulsion of a dimethylamino group from the HMPA-molecule, and the formation of a phosphorodiamidate. In the reaction of cyclohexanone oxime **8** the intermediate **9** was formed. Compound **9** may have undergone a N–O scission to the corresponding nitrene, **22**, which in theory would give a Beckmann rearrangement or a ring-opened product. However, no caprolactam and only a low yield of **10** was observed:





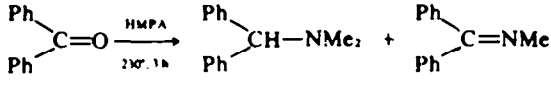
The pyridine **15** would be formed from **22** by ring-opening, hydride shift, Ritter-type reaction, and subsequent oxidative aromatization:



Compound **18** was probably produced from **9** via the corresponding α-amino-cyclohexanone (Neber rearrangement), dimerization and subsequent oxidative aromatization. Compound **19** would then be formed from **18** by oxidative aromatization.

Also cyclohexanone **11** was isolated from the reaction, which can be accounted for by an autooxidation of cyclohexanone oxime(*cf* Ref 8) or by the presence of trace amounts of water in HMPA. But other alternative routes are possible. Thus when cyclohexanone was formed during the reaction, its further reaction with HMPA produced the enamine, **13**, already postulated by Monson[9] and disproportionation of **13** gave N,N-dimethyl–cyclohexylamine, **12**, and the hydroacridine, **16**.[9] The formation of the N,N-dimethylaniline, **14**, was accounted for by the aromatization of **13** and also compound **16** was expected to undergo an oxidative aromatization to give **17**.

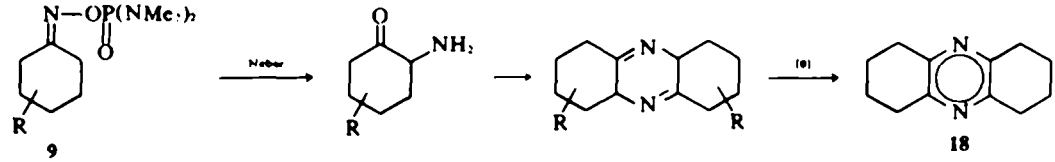
In the reaction of benzophenone oxime with HMPA at elevated temperature there is evidence for the formation of the parent ketone. Thus benzophenone oxime produced the expected Beckmann product and the corresponding amidine, and, in very small yields, the same products were formed as in the reaction of benzophenone with HMPA:[10]



CONCLUSION

There are quite a few procedures known for dehydration of aldoximes[11] to nitriles. The method of heating the aldoxime in HMPA gives almost quantitative yields of the nitrile except for the oxime of furfural. The method may thus offer some advantages.

As to the method of Beckmann rearrangement of ketoximes in HMPA we have never been able to isolate more than half of the yields of amides



claimed by others.[4] However, the main difference between these two investigations are that we dealt at all times with chromatographically pure compounds. In case of the acetophenone oxime we did observe both a Ph and a Me-migration, showing that both the *anti*- and *syn*-substituents can rearrange. Also the expected amidine was isolated in low yields.

Cyclohexanone oxime does not give Beckmann rearrangement products when refluxed in HMPA, but abnormal Beckmann rearrangements have been observed. Also the Neber rearrangement did occur and a series of different heterocyclic compounds have been isolated.

EXPERIMENTAL

Aldoximes. An aldoxime (10 g) in HMPA (60 ml) was refluxed. The formation of nitrile was followed by IR. The nitrile was obtained by distillation (reaction times and yields of nitriles are given in Table 1). Further distillation gave HMPA, b.p. 120°/10 mm, and octamethylpyrophosphoramide b.p. 120–122/0·5 mm, $n_D^{25} = 1{\cdot}4608$; litt.[12] b.p. 100°/0·2 mm, $n_D^{25} = 1{\cdot}4612$.

Acetophenone oxime (10 g) in 60 ml of HMPA was refluxed at 220° for 3 h. Starting material and HMPA was distilled off. This distillate was poured into water and subsequent extraction with ether gave 3·7 g (37%) of acetophenone oxime. The distillation residue was subjected to preparative TLC (silica gel $PF_{254+366}$ (Merck) and elution with ether/light petroleum ether (20:80). Following compounds were isolated in this manner, acetanilide 1·7 g (17%), m.p. 112–115°; lit.[13] m.p. 113–114° and N-methylbenzamide 0·4 g, and N,N-dimethyl-N'-phenylacetamidine 0·3 g (2%), b.p. 83°/0·05 mm, $n_D^{25} = 1{\cdot}5741$; lit.[14] b.p. 75–77°/0·005 mm, $n_D = 1{\cdot}5775$.

Benzophenone oxime (10 g) was heated in 60 ml HMPA for 2 h at 220°. Distillation at 10 mm gave a fraction containing a mixture of benzophenone oxime, 4·2 g (42%), and HMPA. (The separation of starting material and HMPA was performed as above). Continued distillation at reduced pressure gave the second fraction, a mixture of HMPA and benzanilide, which was poured into water and extracted with Et_2O. The yield was 2·7 g (27%) of benzanilide. The distillation residue was subjected to preparative TLC (silica gel $PF_{254+366}$ (Merck) and elution twice with ether/light petroleum ether (20:80)). Following compounds were isolated: 0·6 g (5%) N,N, - dimethyl - N' - phenylbenzamidine, m.p. 73°, lit.[14] m.p. 70–72°, benzhydryldimethylamine, 0·1 g, and benzophenonone methylimine, 0·1 g, b.p. 101°/0·5 mm; lit.[15] 126–128°/2·5 mm. (NMR ($CDCl_3$) δ: aromatic 7·0–7·8, =N–Me: 3·21).

Methyl-1-naphthyl ketoxime (10 g) was refluxed in 60 ml HMPA at 220° for 6½ h. Distillation at 10 mm gave a mixture of the starting material, 3·4 g (34%) and HMPA (starting material and HMPA were separated as above). After all HMPA has been removed, the residue is subjected to preparative TLC (silica gel $PF_{254+366}$ (Merck) and elution twice with ether/light petroleum ether (15:85)). The only compound isolated was 1-naphthyl acetamide, 1·5 g (15%) m.p. 159–160°C; lit.[16] m.p. 159°.

Cyclohexanone oxime (10 g) was refluxed in HMPA (60 ml) for 1 h at 220°. The mixture was fractionated under diminished pressure and five main fractions A, B, C, D and E. Fraction A was collected at 10 mm, the lower boiling compounds were collected in a freezing trap with liquid air. This fraction was redistilled and three new fractions were collected, No. 1, b.p. 100–150°, No. 2, b.p. 150–180°, and No. 3, b.p. 180–190°. The first of these fractions, No. 1, was subjected to a preparative TLC (silica gel as supporting material and eluted once with ether/light petroleum ether (1:9)). The following three compounds were isolated: 5-Cyano-1-pentene, NMR ($CDCl_3$) δ: 4·85–6·1 (typical allyl system) and 1·4–2·1 (multiplet). IR (CCl_4): 2230 cm^{-1}, C≡N stretching. Cyclohexanone, IR and NMR spectra were identical with those of authentic sample. 2-Methylpyridine, picrate m.p. 165°, lit.[17] m.p. 165°. Fraction no. 2 contained N,N-dimethylaniline and trace of cyclohexanone, IR and NMR spectra of N,N-dimethylaniline were identical with those of authentic sample. Fraction no. 3 contains N,N-dimethylcyclohexylamine. (NMR (δ) NMe_2 = 2·19, aliph. = 1·0–1·8) and 1-dimethylaminocyclohexene. (NMR (δ) NMe_2 2·31, vinylic proton C^2H – 5·12 (triplet), aliph. – 1·0–1·9). Fraction B was HMPA collected at 105–120°C/10 mm. Fraction C which was collected over a b.p. range from 120–160°/10 mm, contains HMPA and octamethyl pyrophosphoramide. Fraction D was collected in the range 85–140°/0·03 mm, then the distillation was continued until a yellow oil distilled. Fraction D contains some octamethylpyrophosphoramide and octahydroacridine, the octahydroacridine precipitates in the octamethylpyrophosphoramide after some time, m.p. 74–75°; lit.[18], m.p. 69°. Fraction E was collected as a yellow oil. The yellow oil wad dissolved in Et_2O, cooled to −70°C, and yellow crystals precipitated; NMR ($CDCl_3$) δ: 1·8 (m), 2·4 (m) and 2·9 (m) with the relative proton ratio 7:5:3; IR (CCl_4): 3480 (w), 2900 (s), 1430 (m), 1390 (m) and 1210 (m); UV (EtOH) λ_{max}: 224 nm; 289 nm and 310 nm (shoulder); M.S. m/e: 188 and 175 (indicates a molecular complex). The mother liquid was subjected to preparative TLC (silica gel as supporting material and eluted twice with ether/light petroleum ether (1:1)). An examination of the separated bands gave the following compounds: 1,2,3,4 - tetrahydroacridine, m.p. 56°; lit.[4] m.p. 54·5°. Octahydrophenazine (NMR ($CDCl_3$): aliphatic: δ = 1·90 and 2·89 (8H:8H), m.p. 108°; lit.[7] m.p. 108°). Phenazine (NMR ($CDCl_3$): aromatic: δ = 7·49–8·15 (4H:4H), the spectrum shows a A_2B_2 system, m.p. 169°; lit.[19] m.p. 171°). N - methyl - octahydrocarbazole (NMR ($CDCl_3$): NMe: δ = 2·35, aliphatic: δ = 1·75–2·40, integration: 3:8:8, m.p. 93°; lit.[20] m.p. 94–95°).

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