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THE REACTIONS OF SOME KETONES WITH HEXAMETHYLPHOSPHORIC TRIAMIDE
A NOVEL SYNTHESIS OF 3,5-DIALKYL-2,6-DIPHENYLPYRIDINES

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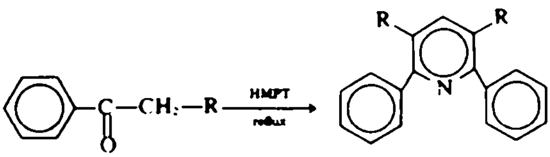
Abstract—Alkylphenones other than acetophenones are found to react with refluxing HMPT over a reaction time of 5–10 hr affording 3,5-dialkyl-2,6-diphenylpyridines in 8–23% yields. The reaction of acetophenones with the same reagent affords only the corresponding 1,3,5-triarylbenzenes. 1-Acetyladamantane similarly affords 1-methyl-2,6-di-(1-adamantyl)-6-dimethylamino-1,4,5,6-tetrahydropyridine, a possible intermediate in the formation of the pyridine products.

Recent work in these laboratories[1] as well as those of Pedersen[2] and Kawanisi[3] has demonstrated that hexamethylphosphoric triamide (HMPT) is a useful reagent for the preparation of a variety of organic compounds by previously unknown routes. Continuing our investigation of this interesting substance, we report herewith the results of our studies on the reaction of HMPT with various ketones.

When alkylphenones other than acetophenones are refluxed in excess HMPT, a slow reaction occurs resulting in the disappearance of the original ketone after 5–10 hr. After a water workup, it is possible to isolate 3,5-dialkyl-2,6-diphenylpyridines in modest yields (Scheme 1). The reaction times and yields are shown for several such compounds in Table 1.

Although the yields from the reaction are small, another route to this series of compounds[4] requires four separate steps from the same starting ketone and results in only a marginal improvement in overall yield.

The reaction of acetophenones with HMPT appears to be much more rapid. The reaction mixture darkens appreciably soon after the onset of reflux, and the reaction is best discontinued after only 0·5–1 hr reflux time. We were unable to isolate pyridines from the reaction mixture, but chromatographic separation of the complex reaction mixture gave traces (< 3%) of the corresponding triarylbenzenes (Scheme 2). Prior work in these laboratories had suggested that tetramethyldiamidophosphoryl chloride 5, might function as a somewhat more reactive substitute for HMPT allowing the reactions to be carried out at lower temperatures. Because of the apparent sensitivity of acetophenones to refluxing HMPT, we undertook to investigate the reactions of this series of compounds in 5 at 160°. This study too failed to reveal the formation of pyridines, but we were able to isolate the corresponding triarylbenzenes in fair yield (27–36%). Although the method seems to offer no advantage over previously published methods[6,7] for the conversion of acetophenones to 1,3,5-triarylbenzenes from the point of view of yield, the simple work up may be somewhat more convenient. Our results on the reactions of acetophenones with tetramethyldiamidophosphoryl chloride are summarized in Table 2.

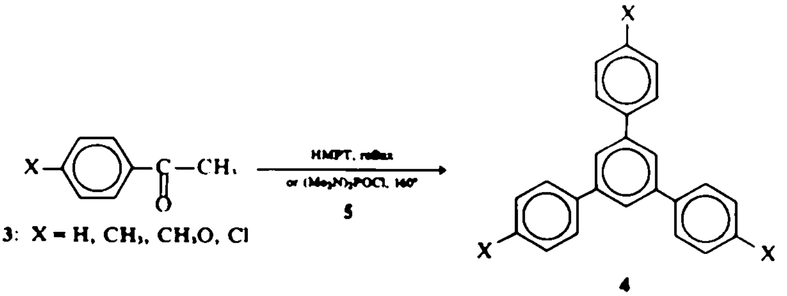


1: R ≠ H 2

Scheme 1.

The most interesting example that we have studied from the point of view of understanding the mechanism of pyridine formation is the reaction of 1-acetyladamantane 6, in refluxing HMPT. The product of this reaction is formed in 25% yield, and all the evidence obtained suggests it is 1-methyl-2,6-di(1-adamantyl)-6-dimethylamino-1,4,5,6,-tetrahydropyridine 7 (Scheme 3).

The IR spectrum of 7 shows a weak band at 6·14 μ. The NMR of 7 shows a triplet at δ 5·07 (1 H), a singlet at δ 2·76 (9 H), and an unresolved broad multiplet plus a doublet centered about δ 1·90 (34 H). These bands can be assigned to the vinylic proton, the N-methyl protons, and the adamantyl plus ring protons respectively. The mass spectrum shows no molecular ion at m/e 408 correspond-



3: X = H, CH_3, CH_3O, Cl

4

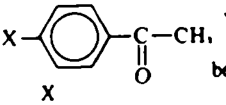
Scheme 2.

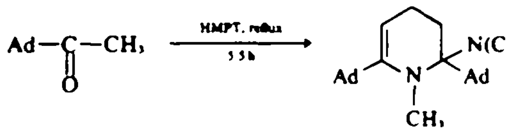
Table 1. Reaction of alkylphenones ($C_6H_5COCH_2$–R) with refluxing HMPT

R	Reaction time (hr)	Yield of 2 (%)	mp (°C)	Lit. mp (°C)
$-CH_3$	5	23	136–7	136–7[4]
$-CH_2CH_3$	5	12	146–7	146–7[4]
$-(CH_2)_2CH_3$	10	10	134–5	a
$-(CH_2)_3CH_3$	10	8	87–8	b
$-(CH_2)_6CH_3$	12	0	—	—
$-C_6H_5$	5	4[5]	238–9	240–1[11]

[a] Anal Calc. for $C_{23}H_{25}N$: C, 87·6; H, 7·9; N, 4·4. Found: C, 87·4; H, 7·8; N, 4·3.
[b] Anal Calc. for $C_{25}H_{29}N$: C, 87·4; H, 8·4; N, 4·0. Found: C, 87·3; H, 8·5; N, 3·9.

Table 2. The reaction of acetophenones with tetramethyldiamidophosphoryl chloride to yield 1,3,5-triarylbenzenes (160° for 20 hr)

 X	Yield of triarylbenzenes 4 (%)	m.p.(°C)	lit.[7] mp(°C)
-H	28	172–3	172
$-CH_3$	28	172–3	178
$-OCH_3$	36	142–3	143
-Cl	27	244–5	246



6: (Ad = 1-adamantyl)

7

Scheme 3.

ing to 7; the highest peak observed is at m/e 364, corresponding to 7 with loss of the $N(CH_3)_2$ group, an observation that has been rationalized elsewhere.[4]

DISCUSSION

It is likely that the reaction of enolizable ketones with HMPT proceeds initially by attack of HMPT on the carbonyl carbon to give the corresponding dimethylamine enamine, perhaps by the route suggested by Pedersen[8] (Scheme 4). Pederson's observations, as well as those of Kawanisi[9] and ourselves[10] confirm that enamine products are formed under the reaction conditions.

Our earlier observation[10] that the corresponding saturated amine forms subsequent to the formation of the enamine suggests a disproportionation of the enamine. This suggestion, combined with a proposal by Newkome and Fishel[4] for the mechanism of a related reaction, leads to the following mechanism for the formation of products related to 7 (Scheme 5).

EXPERIMENTAL

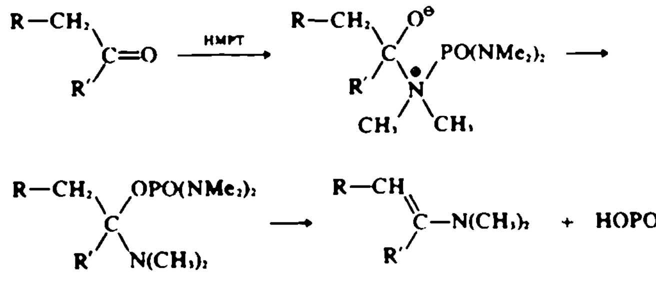
M.ps were determined on a Fisher-Johns apparatus and are corrected, b.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer, NMR spectra on a Jeolco Model C-60 spectrometer with chemical shifts expressed in δ (ppm) relative to TMS as internal standard. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, California. Mass spectra were measured on an AEI MS-12 medium resolution mass spectrometer, direct inlet method at 200° source temperature, 70 eV, by Chemical Analytical Services, University of California, Berkeley, California. Commercial HMPT was distilled before use, b.p. 120–122°/21 mm. All other compounds unless otherwise indicated were commercially available and were used without further purification.

3,5-Dialkyl-2,6-diphenylpyridines 2. The alkylphenone (0·1 mol) was mixed with 65 ml of HMPT and refluxed in a standard reaction vessel with openings protected from moisture for 5–10 hr (Table 1). After cooling, the reaction mixture was poured into 150 ml of ice water and the mixture saturated with sodium chloride. The aqueous solution was extracted three times with ether and the ethereal solution washed twice with brine and finally dried (Na_2SO_4). Evaporation of the solvent afforded the crude product, which was recrystallised from ethanol.

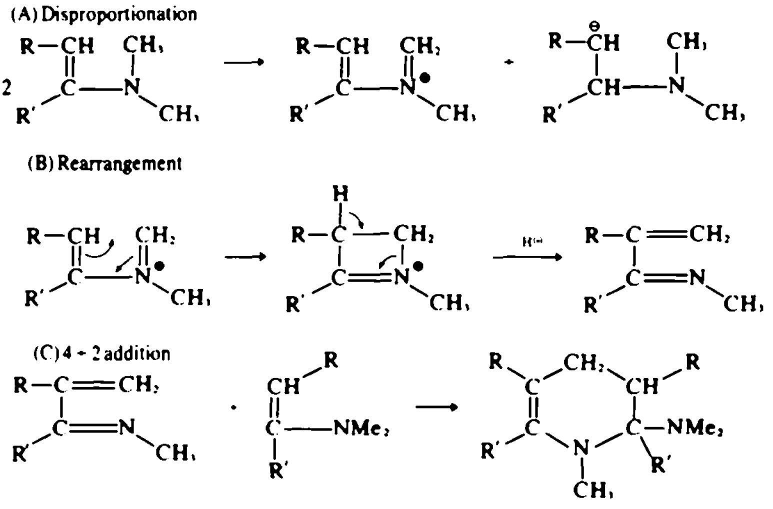
Acetophenones with HMPT. The acetophenone 3 (0·1 mol) was dissolved in 65 ml of HMPT and refluxed for 0·5–1 hr in a standard reaction vessel with openings protected from moisture. The cooled reaction mixture was worked up as in the preceding case. After removal of the solvent, the crude product was chromatographed on activity III alumina with 30–60° petroleum ether-benzene (70:30) as eluant. Recrystallisation of the eluted materials from 60–90° petroleum ether gave a trace of the corresponding 1,3,5-triarylbenzene 4, which was identified by comparison of its physical properties with published[7] values.

Tetramethyldiamidophosphoryl chloride 5 *in HMPT.* HMPT (360 g, 2 mol) was heated to 110° and phosphoryl chloride (77 g, 0·5 mol) added dropwise, the temperature being maintained below 150°. After the addition was complete, the solution was maintained at 150° for 2 hr. Distillation at 110–130° (23 mm) afforded a solution which was approximately 4 molar tetramethyldiamidophosphoryl chloride in HMPT, free of other compounds by GLPC analysis. The solution is stable for long periods when protected from moisture.

Acetophenones with tetramethyldiamidophosphoryl chloride. The acetophenone (0·03 mol) was mixed with 40 ml of tetramethyldiamidophosphoryl chloride solution in HMPT in a



Scheme 4.



7 (R = H, R′ = 1-adamantyl)

Scheme 5.

standard reaction vessel with openings protected from moisture. The mixture was maintained at 160° for 20 hr. After cooling, the reaction mixture was poured into 150 ml of ice water and worked up as for the dialkyldiphenylpyridines. After removal of the solvent, the oily residue was crystallised by treatment with hot ethanol. The product triarylbenzene 4 was recrystallised from benzene-ethanol.

1 - *Methyl* - 2,6 - *di* - (1-*adamantyl*) - 6 - *dimethylamino* - 1,4,5,6 - *tetrahydropyridine* 7. 1-Acetyladamantane (3 g, 17 mmol) was refluxed in 50 ml of HMPT as described above. The cooled reaction mixture was poured into water, saturated with sodium chloride, and the mixture extracted with pentane. The pentane solution was washed with brine, dried (Na_2SO_4), and the solvent evaporated. The residue was dissolved in ca. 100 ml of ethanol and cooled at 10° for several hours affording 0·85 g (25%) of the product 7, which was recrystallised from ethanol-benzene, m.p. 140–1°, IR (film) 6·14 (C=C), 6·91, 7·45 μ; NMR (CCl_4) δ 5·07 (t, 1, J 7 Hz), 2·76 (s, 9), 1·90 (m, 34); mass spectrum (70 eV) *m/e* (rel intensity) 364 (4), 279 (71), 204 (45), 135 (91), 93 (74), 79 (100). (Found: C, 82·1; H, 11·0; N, 6·6. $C_{28}H_{44}N_2$ requires: C, 82·3; H, 10·8; N, 6·8.)

REFERENCES

[1] R. S. Monson and B. M. Broline, *Can. J. Chem.* 51, 942 (1973); and references cited therein
[2] N. O. Vesterager, E. B. Pederson and S.-O. Lawesson, *Tetrahedron* 30, 2509 (1974); and references cited therein
[3] M. Kawanisi, S. Arimatsu and R. Yamaguchi, *Bull. Chem. Soc. Japan* 47, 1693 (1974); and references cited therein
[4] G. R. Newkome and D. L. Fishel, *J. Org. Chem.* 37, 1329 (1972)
[5] A similar yield, along with other products, is reported by Kawanisi[9]
[6] H. O. Wirth, W. Kern and E. Schmitz, *Makromol. Chem.* 68, 69 (1963)
[7] R. E. Lyle, E. J. DeWitt, N. M. Nichols and W. Cleland, *J. Am. Chem. Soc.* 75, 5959 (1953)
[8] E. B. Pederson and S.-O. Lawesson, *Tetrahedron* 30, 875 (1974).
[9] S. Arimatsu, R. Yamaguchi and M. Kawanisi, *Bull. Chem. Soc., Japan* 47, 1553 (1974)
[10] R. S. Monson, D. N. Priest and J. C. Ullrey, *Tetrahedron Letters* 929 (1972)
[11] V. J. Traynelis and R. H. Ode, *J. Org. Chem.* 35, 2207 (1970).