Tetrahedron. Vol. 29, pp. 4215 to 4217. Pergamon Press 1973. Printed in Great Britain

STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—V[a]

PYRIDINES FROM SECONDARY CARBOXAMIDES AND HMPA

T. FREJD,* E. B. PEDERSEN and S.-O. LAWESSON
Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Aarhus C, Denmark

(*Received* 26 *June* 1973; *Accepted for publication* 16 *August* 1973)

Abstract—A new pyridine synthesis has been found by refluxing certain simple secondary carboxamides in HMPA. Thus 2,6-dimethylpyridine, 2-ethyl-6-methylpyridine, 2,3,6-trimethylpyridine, 2-ethyl-3,6-dimethylpyridine, 2-benzyl-6-methyl-3-phenylpyridine, 2-ethyl-3-methyl-5,6,7,8-tetrahydroquinoline and 2-t-butyl-6-methylpyridine were prepared in 15–40% yield.

INTRODUCTION

Recently it was found that gentle reflux of secondary carboxamides[1] (RCONHR', where R or/and R' is an aromatic ring) in hexamethylphosphoric triamide (HMPA) produced the corresponding N,N-dimethylamidines in fair yields. It was also found that the secondary carboxamides upon heating in HMPA could undergo fragmentation reactions if R or R' were able to form sufficiently stable carbonium ions.[2]

Quite unexpectedly we obtained 2,6-dimethylpyridine when N-isopropylacetamide was heated in HMPA. The scope of this new pyridine synthesis has been investigated and this paper describes the results.

DISCUSSION

At first it was not obvious at all what was the source of the two extra C atoms needed for the formation of 2,6-dimethylpyridine from N-isopropylacetamide. However, on heating N-isopropylpropionamide in a similar way as the acetamide in HMPA 2-ethyl-3,6-dimethylpyridine, **1**, was formed in 23% yield. This observation indicated that the pyridine nucleus was formed from the N–C skeleton of one propionamide molecule (the unstared carbons in Fig 1) and from the carbon skeleton of the carboxylic acid part of another propionamide molecule (the stared carbons). A similar condensation accounts for the formation of the 2,6-dimethylpyridine from N-isopropylacetamide. Further proof for this suggested building up of the pyridine skeleton from two carboxamide molecules is found in the reaction between N-sec-butylacetamide and HMPA, which gave two isomeric pyridine derivatives **2** and **3** (Fig 2). This

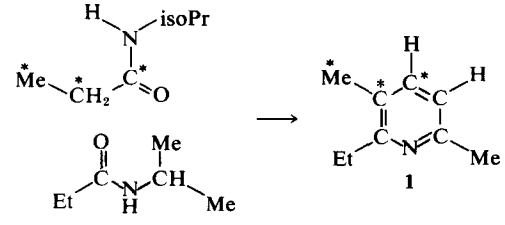


Fig 1.

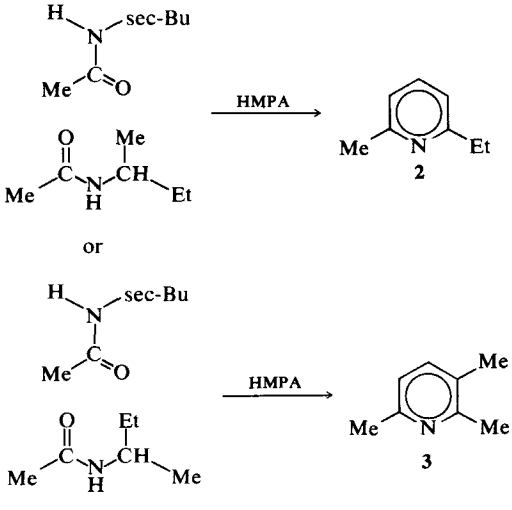


Fig 2.

result showed that the sec-Bu group could react in both ways. Similarly N-isopropyl-phenylacetamide produced 2-benzyl-6-methyl-3-phenylpyridine in 17% yield. Interestingly, this reaction-type can also be used for preparation of tetrahydroquinoline derivatives. So 2-ethyl-3-methyl-5,6,7,8-tetrahydroquinoline was prepared simply by heating N-cyclohexylpropionamide in HMPA.

[a]Part IV, E. B. Pedersen, J. Perregård and S.-O. Lawesson, *Tetrahedron* **29**, 4211 (1973)

*Present address: Department of Organic Chemistry, Chemical Center, University of Lund, Lund, Sweden.

Our suggestion that the pyridine is formed by the reaction of two different carboxamide molecules with each other is further confirmed by the observation that a mixture of acetanilide and N-isopropylpivaloamide heated in HMPA (Fig 3) forms the pyridine **4**. It should be noted that none of the amides used can form a pyridine by itself. It should be mentioned that the above pyridine, **4**, is not easily prepared in other ways. For example Brown and Kanner[3] tried to prepare it by addition of methyllithium to 2-*t*-butylpyridine followed by elimination of lithium hydride. This reaction did not work, however, so the above authors had to use a multistep cyclization procedure as described by Mumm and Böhme.[4]

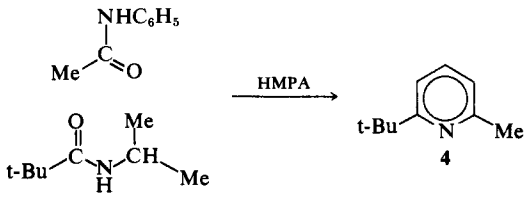


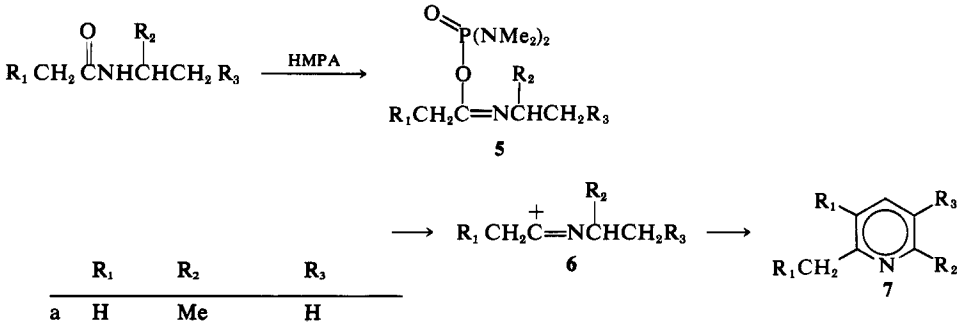
Fig 3.

Concerning the mechanism (Scheme 1) there is some evidence that a phosphorodiamidate derivative **5** and/or a nitrilium carbonium ion **6** are intermediates. When N-isopropyl-phenylacetamide (R_1: C_6H_5, R_2: CH_3 and R_3: H) was heated in HMPA, an equivalent amount of benzylcyanide was isolated besides the pyridine derivative. Also N-cyclohexylpropionamide (R_1: Me_3 and R_2,R_3: $-CH_2CH_2CH_2CH_2-$), when treated in a similar way gave besides a pyridine derivative, **7f**, a small amount of propionitrile and cyclohexene. The fragmentation reactions are typical reactions for nitrilium carbonium ions postulated as intermediates in the Beckmann fragmentation reactions.[5,6]

In order to achieve further evidence for the nitrilium carbonium ion **6** as an intermediate we looked for other reactions where **6** was expected to be formed. One reaction, is heating of the imidoyl chloride of N-cyclohexylpropionamide in tri-n-butylamine at reflux temperature. In fact when the amine was distilled off, a mass spectrum which was identical with the one of the pyridine, **7f**, was obtained, when the mixture was separated by GLC connected with a mass spectrograph. The nitrilium carbonium ion has also been postulated in the Beckmann rearrangement on certain ketoximes initiated by HMPA[7,8] and it was claimed that the carbonium ion was formed from an initially formed bis(dimethylamido)phosphate of the ketoxime. The crude bis(dimethylamido)phosphate of cyclohexyl-ethyl-ketoxime (prepared from the sodium salt of the oxime and N,N,N′,N′-tetramethylphosphorodiamidic chloride in benzene) was heated on an oil bath (245°) and a vigorous reaction took place. An ether extract of the mixture was investigated on GLC connected with a mass spectrograph, and a mass spectrum, which was identical with the one of the pyridine, **7f**, was obtained. As the nitrilium carbonium ion **6f** is formed in both the two above reactions and probably also is formed in the reaction of N-cyclohexylpropionamide with HMPA, it is reasonable to suggest that **6f** in all three cases should account for the formation of the pyridine **7f**. Therefore it is reasonable to suggest that the first step in the reaction is the formation of the phosphorodiamidate **5** which undergoes fragmentation to the nitrilium carbonium ion **6** and what then happens is more obscure.

CONCLUSION

Although the yields in the new pyridine synthesis are quite small, we feel strongly that this method is suitable for the preparation of otherwise not easily available substituted pyridines. It should also be



	R_1	R_2	R_3
a	H	Me	H
b	H	Et	H
c	H	Me	Me
d	Me	Me	H
e	Ph	Me	H
f	Me	$-CH_2CH_2CH_2CH_2-$	

SCHEME 1

noted that very simple starting materials are used for the synthesis. The "mixed" experiment in which 2-*t*-butyl-6-methylpyridine was formed points to a broader scope of the synthesis and is further investigated in this laboratory.

EXPERIMENTAL

NMR spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer. TMS was used as internal reference standard and the chemical shifts are expressed in δ-values (ppm), (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). Preparative TLC was carried out on kieselgel $PF_{256+366}$ (Merck) support (20 × 40 cm and 3 mm thick). M.ps and b.ps are uncorrected. The microanalyses were performed by Novo Industry A/S, Copenhagen. HMPA was purified by adding lithium in liquid ammonia until the dark blue colour persisted for longer time than 10 min. The dried HMPA was then distilled twice.[9]

2,6-*Dimethyl-pyridine* (**7a**). N-isopropyl-acetamide (10·1 g; 0·1 mol) and (17·9 g; 0·1 mol HMPA) was heated at reflux temp for 15 hr. The mixture was protected from moisture by a blue silicagel drying tube. The reaction could be followed by a colour change of the silicagel from a light to dark blue colour. Distillation at normal pressure gave 2,6-dimethylpyridine (0·8 g; 15%) and the purity was > 90% (GLC, SE 30, 5%), NMR ($CDCl_3$): $\delta_{\alpha\text{-}CH_3}$, 2·50 (s, 6H); and δ_{aromat}, 6·85, 7·00, 7·32, 7·41, 7·46 and 7·60 (3H, A_2B system). $J_H\beta,_H\gamma = 7{\cdot}5$ Hz; picrate m.p. 158–9°, lit.[10] m.p. 161°.

2-*Ethyl*-6-*methyl-pyridine* (**2**) *and* 2, 3, 6-*trimethyl-pyridine* (**3**). N-sec-butylacetamide (10 g) and 50 ml HMPA were heated at reflux temp for 12 hr. The mixture was allowed to cool to room temp and was then poured into water (400 ml) and extracted 4 times with ether. The combined ether phases were washed with water and dried with $CaCl_2$ and the ether was distilled off. Distillation at 55–60°/14 mm gave 1·5 g (33%) of a mixture of **2** and **3**, 2:5, (calc. from the NMR spectra). NMR ($CDCl_3$) of **2**: $\delta_{\alpha\text{-}CH_3}$, 2·51 (s, 3H); $\delta_{CH_2CH_3}$, 1·28 (t, 3H) and 2·80 (q, 2H); and δ_{aromat}, 6·87, 7·00, 7·36, 7·49, 7·50, 7·79 (3H); NMR ($CDCl_3$) of **3**: $\delta_{\alpha\text{-}CH_3}$, 2·47 (s, 6H); $\delta_{\beta\text{-}CH_3}$, 2·22 (s, 3H); $\delta_H\beta$ and $\delta_H\gamma$, 7·28 (d, 1H) and 6·90 (d, 1H), $J_H\beta_H\gamma = 7{\cdot}5$ Hz. From the mixture of **2** and **3** the picrate of **3** was obtained by repeated recrystallization from EtOH, m.p. 145°, lit.[11] m.p. 147–148°. (Found: C, 47·97; H, 4·21; N, 16·12. $C_{14}H_{14}N_4O_7$ requires: C, 48·0; H, 4·03; N, 16·00%.)

2 - *Ethyl* - 3, 6 - *dimethylpyridine* (**1**). N - isopropyl - propionamide (11·5 g; 0·1 mol) and HMPA (17·9 g; 0·1 mol) was heated at reflux temp for 12 hr. Water steam distillation of the mixture followed by extraction of the distillate several times with ether gave 1·5 g (23%) of the title compound, NMR ($CDCl_3$): $\delta_{CH_2CH_3}$, 1·23 (t, 3H) and 2·69 (q, 2H); $\delta_{\alpha\text{-}CH_3}$, 2·48 (s, 3H); $\delta_{\beta\text{-}CH_3}$, 2·27 (s, 3H); and $\delta_H\beta$ and $\delta_H\gamma$, 7·15 (d, 1H) and 6·90 (d, 1H), $J_H\beta_H\gamma = 7{\cdot}5$ Hz; picrate m.p. 123–4°, lit.[12] m.p. 127°. (Found: C, 49·0; H, 4·43; N, 15·28. $C_{15}H_{16}N_4O_7$ requires: C, 49·4; H, 4·43; N, 15·38%.)

2-*Benzyl*-6-*methyl*-3-*phenylpyridine* (**7e**). N-isopropyl-phenylacetamide (17·7 g; 0·1 mol) and HMPA (17·9 g; 0·1 mol) were refluxed for 17 hr and the mixture was poured into water and extracted with ether. The ether was distilled off and preparative TLC using silicagel as supporting material and acetone/light petroleum (60–80°) 1:9 for elution gave 1·1 g benzyl cyanide, $R_f = 0{\cdot}28$ (IR and NMR spectra were identical with authentic sample) and 2·2 g of title compound $R_f = 0{\cdot}36$, NMR ($CDCl_3$): δ_{CH_3}, 2·57 (s, 3H); δ_{CH_2}, 4·12 (s, 2H) (lit.[13] $C_6H_5CH_2C_5H_4N$, $\delta_{CH_2} = 4{\cdot}16$); δ_{aromat}, 6·81–7·50 (m, 12H). Picrate m.p. 182–3°. (Found: C, 61·41; H, 4·19; N, 11·49. $C_{25}H_{20}N_4O_7$ requires: C, 61·47; H, 4·13; N, 11·47%.)

2-*Ethyl*-3-*methyl*-5, 6, 7, 8-*tetrahydroquinoline* (**7f**). N-cyclohexylpropionamide (15·4 g; 0·1 mol) and HMPA (17·9 g; 0·1 mol) were refluxed for 12 hr. A low-boiling fraction collected in a cooling trap was added to the mixture. This was poured into water, the water phase was made neutral with 10% HCl, extracted with ether, and dried over $MgSO_4$. The ether was distilled off. Distillation at normal pressure gave a mixture (0·2 g) of cyclohexene and propionitrile (identified by comparison of NMR spectra and GLC retention times with those of authentical samples) and distillation at 120–3°/12 mm gave 2·0 g (23%) of the title compound. NMR ($CDCl_3$): $\delta_{CH_2CH_3}$, 1·20 (t, 3H) and 2·75 (q, 2H); δ_{CH_3}, 2·21 (s, 3H); δ_{CH_2}, 1·5–2·0 (m, 4H) and 2·5–3·0 (m, 4H); δ_{aromat}, 7·09 (s, 1H), picrate m.p. 113–115°. (Found: C, 53·50; H, 4·89; N, 13·71. $C_{18}H_{20}N_4O_7$ requires: C, 53·46; H, 4·99; N, 13·86%.)

2-t-*Butyl*-6-*methylpyridine* (**4**). N-isopropyl-pivaloamide, (7·1 g; 0·05 mol), acetanilide (6·7 g; 0·05 mol) and HMPA (17·9 g; 0·1 mol) were refluxed for 17 hr. The cooled mixture was poured into water and extracted with ether. By distillation (b.p. < 165°) of the raw material 3·2 g (43%) of almost pure title compound were obtained. Pure compound was obtained by preparative TLC (silicagel, acetone/light petroleum (60–80°) (1:4)); NMR ($CDCl_3$): $\delta_{t\text{-}Bu}$, 1·32 (s, 9H) δ_{CH_3}, 2·25 (s, 3H), δ_{aromat}, 6·82–7·59 (m, 3H). UV (MeOH), λ_{max} (log ϵ_{max}): 219 nm (3·1), 260 nm (shoulder), 267 nm (3·4) and 274 (shoulder). Picrate m.p. 151–3°. (Found: C, 50·79; H, 5·01; N, 14·71. $C_{16}H_{18}N_4O_7$ requires: C, 50·79; H, 4·80; N, 14·81%.)

REFERENCES

[1]E. B. Pedersen, N. O. Vesterager and S.-O. Lawesson, *Synthesis* 547 (1972)

[2]E. B. Pedersen and S.-O. Lawesson, *Tetrahedron* **29**, 4205 (1973)

[3]H. C. Brown and B. Kanner, *J. Am. Chem. Soc.* **88**, 986 (1966)

[4]O. Mumm and R. Böhme, *Ber. Dtsch. Chem. Ges.* **54**, 734 (1921)

[5]R. T. Conley and S. Ghosh, *Mechanisms Molecular Migrations* (Edited by B. S. Thyagarajan) Part **4**, 197. Wiley-Intersciences (1971)

[6]C. A. Grob, H. P. Fischer, W. Randenbush and J. Zergenyi, *Helv. Chim. Acta* **47**, 1003 (1964)

[7]R. S. Monson and B. M. Broline, *Canad. J. Chem.* **51**, 942 (1973)

[8]N. O. Vesterager, E. B. Pedersen and S.-O. Lawesson, *Tetrahedron.* To be submitted

[9]L. Brandsma, *Prep. Acetylenic Chemistry.* Elsevier, (1971)

[10]W. Epstein, *Liebigs Ann.* **231**, 1 (1885)

[11]T. Eguchi, *Chem. Zentral I*, 330 (1929)

[12]U. Basu and B. Banerjee, *J. Ind. Chem. Soc.* **12**, 665 (1935)

[13]W. Brügel, *Z. Elektrochem.* **66**, 159 (1962)