Studies on Organophosphorus Compounds; I. Reaction of Secondary Carboxamides with Hexamethylphosphortriamide (HMPA). – A New Method for the Preparation of Amidines

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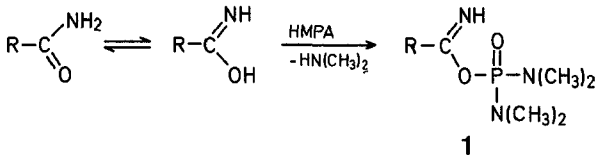
Recently, Monson and Priest[1] found that aliphatic and aromatic carboxamides readily undergo dehydration in hexamethylphosphoric triamide (HMPA) at 220°–240°, producing the corresponding nitriles in good yields. They suggested without proof that the initial step of the reaction is the formation of a phosphorodiamidate derivative **1** of the enol form of the amide.



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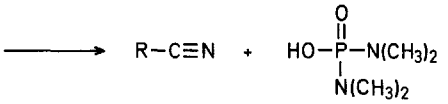
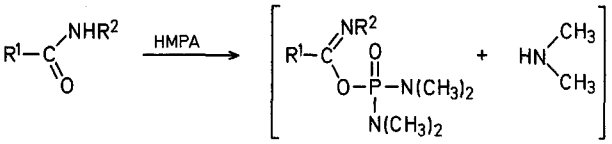


It was then assumed that in an analogous manner the corresponding imidate intermediate **2** could be prepared by treatment of secondary carboxamides with HMPA, but the fate of the intermediate could not be foreseen at that time.

It was now found that gentle refluxing of a series of secondary carboxamides in HMPA produces N,N-dimethylamidines **3** in fair yields.



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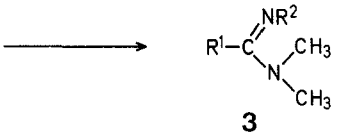

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Although no attempts were made to optimize this new synthesis, the best yield is obtained when R^2 = aryl.

It was also foreseen that heating a secondary carboxamide with HMPA in the presence of a large excess of a secondary amine might give a new amidine **4**. This reaction was achieved when starting from acetanilide, although the yields of **4** were low and appreciable amounts of **3d** were also formed.

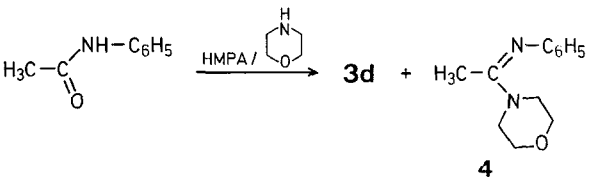

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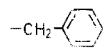
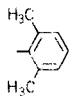
Table 1. Preparation of Amidines (3)

Compound	R^1	R^2	Reaction time hr	Yield %	m.p. or b.p.	n_D^{25}	Elemental analysis
3a		*n*-C_4H_9	2	26	b.p. 72°/0.2 mm	1.5206	$C_{13}H_{20}N_2$ calc. C 76.42 H 9.87 N 13.71 found 76.61 9.84 13.15
3b			6	40	b.p. 118°/0.05 mm	1.5824	$C_{16}H_{18}N_2$ calc. C 80.63 H 7.61 N 11.76 found 80.18 7.60 11.76
3c			6	49	m.p. 73°[a]		
3d	CH_3		2	63	b.p. 85°/0.05 mm	1.5747[b]	
3e	H		3	60	b.p. 62°/0.05 mm	1.5926[c]	
3f	*t*-C_4H_9		5	64	b.p. 80°/0.05 mm	1.5333	$C_{15}H_{24}N_2$ calc. C 77.53 H 10.41 N 12.06 found 77.43 10.41 12.13
3g			4	56	m.p. 89°[d]		$C_{16}H_{16}N_3$ calc. C 75.85 H 7.56 N 16.59 found 75.98 7.52 16.56

[a] From petroleum ether; Ref.[2], m.p. 70–72°.
[b] Ref.[2], b.p. 75–77°/0.005 mm; n_D^{20}: 1.5775.
[c] Ref.[2], b.p. 78–80°/0.1 mm; n_D^{20}: 1.5953.
[d] From petroleum ether.

General Procedure:
A secondary carboxamide (10 g) in HMPA (50 ml) was heated at reflux temperature until the carbonyl-stretching absorption had disappeared in the I. R. The reaction mixture was allowed to cool to room temperature and was then poured into ice water (400 ml) and extracted four times with ether. The combined ether phases were washed with water, dried with calcium sulfate, the ether was distilled, and the amidine purified.

Reaction in the Presence of Morpholine:
Acetanilide (10 g), HMPA (50 ml), and morpholine (15 g) were refluxed for 22 hr and worked up as above.

Yield of **3d**: 1.5 g; b.p. 85°/0.05 mm.

Yield of **4**: 0.5 g; b.p. 110–130°/0.1 mm; m.p. 88° (from petroleum ether b.p. 60–80°).

$C_{12}H_{16}N_2O$ calc. C 70.56 H 7.90 N 13.72
found 70.06 7.90 13.92

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[1] R. S. Monson, D. N. Priest, Can. J. Chem. **49**, 2897 (1971).
[2] H. Bredereck, R. Gompper, K. Klemm, H. Rempfer, Chem. Ber. **92**, 837 (1959).