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Reactions of Phosphoric Anhydride with Acyclic Amides. Synthesis of Amidines and Imides

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ABSTRACT

Acyclic secondary amides such as benzanilides **1a–g,** *acetanilides* **2a–d,** *and benzamide* **1h** *undergo self-condensation in the presence of phosphoric anhydride to produce, in one step, N-substituted aroyl benzamidines* **3a–g,** *acyl acetamidines* **4a–d,** *and imide* **5,** *respectively. Mechanistic evidence is presented for nucleophilic attack by the iminol tautomers on the O-phosphorylated amides to give amidines and on the N-phosphorylated imidates to give imides.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:261–263, 1998

INTRODUCTION

Phosphoric anhydride (P_4O_{10}) is a convenient and widely used reagent for the phosphorylation of alcohols and phenols [1] and can also be used to phosphorylate other nucleophilic compounds such as amines [2]. Amides are biphilic in that both O and N phosphorylation is possible. In the case of barbituric acids, the products were N-phosphorylated [3]. The reaction of phosphoric anhydride with benzanilides was recently reported, and evidence for the formation of both N and O phosphorylated amides was presented [4].

RESULTS AND DISCUSSION

The phosphorylation of seven substituted benzanilides and four acetanilides have been studied. It has been shown that the final products from these reactions are amidines and imides depending on the nature of the amide. While mechanistic rationalization points to the formation of both N- and O-phosphorylated intermediates (see below), these compounds are now believed to be intermediates that are unstable under the reaction conditions. Thus, substituted benzanilides, acetanilides, and benzamide **1a–g, 2a–d,** and **1h,** respectively, with phosphoric anhydride gave N-substituted amidines **3a–g, 4a–d,** and imide **5** [5]. The highest yield of the products was achieved by the use of phosphoric anhydride and amide, in the mole ratio of 1:3, using chloroform as solvent at room temperature (20°C) for 0.3 to 56 hours (see Table 1). The self-condensation was not observed for N-isobutylacetamide.

Infrared, ^1H, and ^{13}C NMR spectra were in accordance with the amidine and imide structures, which were also confirmed by single-crystal X-ray diffraction studies of amidines **3b,d** and **4d** and imide **5.** The NMR spectra showed that there is a large barrier to rotation about both aryl-N bonds compared to the secondary amide group ArNHCOR, and nonequivalence of geminal groups within the ortho-orientated prochiral groups was evident [6]. Variable temperature NMR spectroscopy and molecular me-

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

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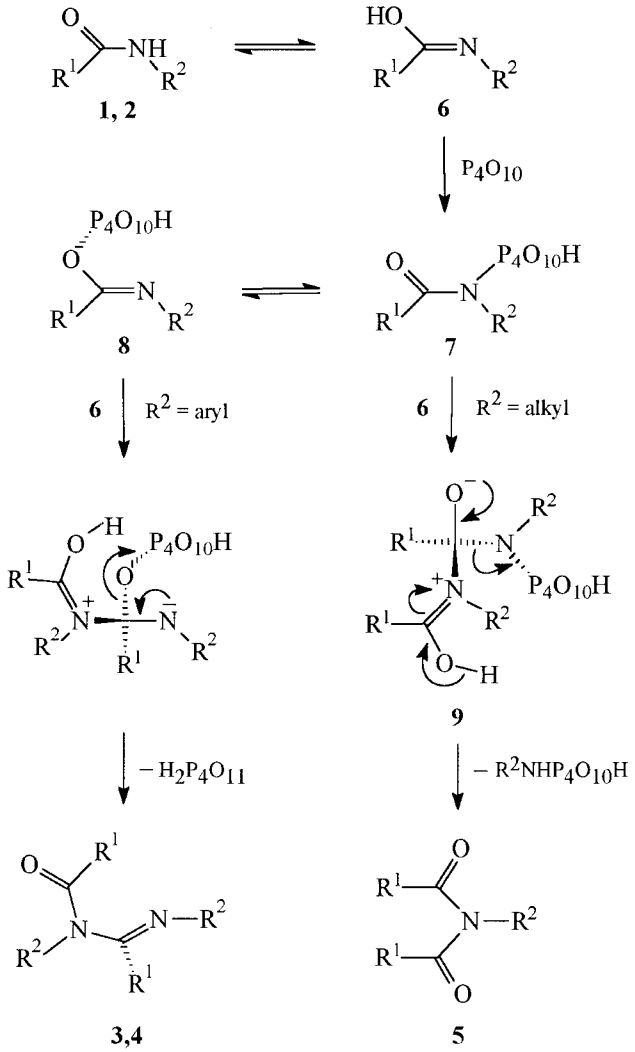
TABLE 1 Reaction Conditions and Melting Points of N-Substituted Acyl Amidines and Imide

R	*Reaction Time, h*	*Yield, %*	*Melting Point °C*
3a Ph	56	64	173–174[a]
3b 2-MeC_6H_4	0.04	83	144–146
3c 2,6-$Me_2C_6H_3$	0.3	84	162–164
3d 2,4,6,-$Me_3C_6H_2$	18	61	188–189
3e 2,6-$Et_2C_6H_3$	27	59	100–102
3f 2,6-$^i Pr_2C_6H_3$	3	41	170–172
3g 4-$OMeC_6H_4$	15	62	144–147[b]
4a 2,6-$Me_2C_6H_3$	24	21	112–113
4b 2,4,6-$Me_3C_6H_2$	4	62	129–130
4c 2,6-$Et_2C_6H_3$	2.5	23	62–64
4d 2,6-$^i Pr_2C_6H_3$	1.2	74	135–137
5 ^{t}Bu	41	24	89–91

[a]Ref. [14]: mp 173–174°C.
[b]Ref. [14]: mp 149–150°C.



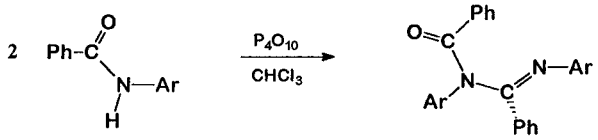
SCHEME 1 Proposed mechanism for self-condensation of acyclic amides promoted by phosphoric anhydride [7].

chanics modeling was used to study the relative barriers to rotation about the amide and imine N-aryl bonds (a subject of separate publication).

The formation of different products (amidine and imide), depending on the aryl or alkyl nature of the N-substituent, indicates that the reaction mechanism involves a divergent pathway. Thus, it is proposed that the mechanism of self-condensation (Scheme 1) proceeds via nucleophilic attack of the iminol tautomer **6** on either an N-phosphorylated amide **7** or an O-phosphorylated imidate **8**, depending on the presence or absence of conjugation with the imino nitrogen; that is, the reaction proceeds by iminol attack on the O-phosphorylated imidate **8** when R^2 is aryl, whereas reaction proceeds by iminol attack on the N-phosphorylated amide **7** when R^2 is alkyl [7]. The divergence in the pathway is attributed primarily to a difference in the reactivities of the intermediates **7** and **8**. When R^2 is aryl, the imino bond of the latter intermediate **8** is expected to be more prone to nucleophilic attack due to the generation of an aryl-stabilized anion on nitrogen. In contrast, when R^2 is alkyl, the imino bond of intermediate **8** is less reactive and the iminol tautomer reacts faster with the carbonyl bond of the intermediate **7** to generate the oxyanion **9**. Evidence has previously been presented in support of facile phosphoryl migration from nitrogen to oxygen, which can be reversible [8]. While phosphorus is renown for its strong bonds to oxygen (which would favor attack of phosphoric anhydride at the carbonyl oxygen of amides), it is possible that the N-phosphorylated intermediate is also formed via the iminol tautomer of the amide **6**, which would be expected to be more nucleophilic than the amide [9]. Indeed, the lack of reactivity of N-isobutylacetamide can be attributed to a reduction in the stability of the iminol tautomer due to absence of conjugation between the imino group and an aryl ring (R^2).

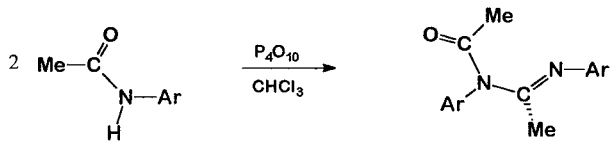
A proposed mechanism for a related Bischler–Napieralski reaction [10] also involved an O-phosphorylated imidate group. However, in this case, the reaction proceeded via attack by a carboxylic oxygen at the N-methylene carbon atom with the generation of phosphate and a nitrile.

There are few examples concerning the condensation of two amide functional groups [11–14]. Amides such as α-bromolactams and thioamides have been converted to cyclic 4-aminothiazole derivatives [11], and N-hydroxyalkyl-2-aminocarboxamides in the presence of Vilsmeier reagent ($DMF/POCl_3$) afford 3-(ω-chloroalkyl)pyrimidine-4(3H)-ones [12]. Formanilides have been shown to give formimidate



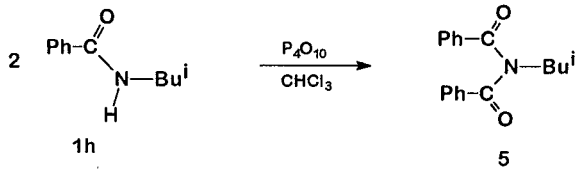
1a Ar = Ph
b Ar = 2-Me C_6H_4
c Ar = 2, 6-Me $_2C_6H_3$
d Ar = 2, 4, 6-Me $_3C_6H_2$
e Ar = 2, 6-Et $_2C_6H_3$
f Ar = 2, 6-^{i}Pr $_2C_6H_3$
g Ar = 4-OMe C_6H_4

3 a-g



2a Ar = 2, 6-Me $_2C_6H_3$
b Ar = 2, 4, 6-Me $_3C_6H_2$
c Ar = 2, 6-Et $_2C_6H_3$
d Ar = 2, 6-^{i}Pr $_2C_6H_3$

4 a-d



1h

5

SCHEME 1

salts via O-methylation using dimethyl sulfate followed by further reaction with amide to produce formamidines [13]. N-Substituted acyl benzamidines have been produced by self-condensation of benzanilides in the presence of the phosphorane Ph_3PBr_2 [14].

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