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A NOVEL DIRECT SYNTHESIS OF AMIDINES FROM CARBOXYLIC ACIDS AND AMINES USING POLYPHOSPHORIC ACID TRIMETHYLSILYL ESTER (PPSE) AS CONDENSING AGENT

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It was found that amidines were obtained directly by the reaction of carboxylic acids with amines in the presence of PPSE, and the yields of amidines were dependent on the structure of amines rather than that of carboxylic acids.

Polyphosphoric acid trimethylsilyl ester (PPSE) which is readily prepared by the reaction between phosphorous pentoxide and hexamethyldisiloxane[1)] has been utilized as synthetic reagent.[1,2)] In a series of the reactions, dehydrative condensation reaction was one of the typical feature of PPSE. For example, heterocyclic compounds such as benzimidazoles,[2c)] indoles,[2c)] and 2H-1,2,4-benzothiadiazine 1,1-dioxides[2e)] have been synthesized in better yield compared with the cases of using polyphosphoric acid or polyphosphoric acid ethyl ester (PPE).[2c)]

We describe herein a novel and convenient synthesis of amidines from carboxylic acids and amines using PPSE as condensing agent (Eq. 1). The conventional starting materials for amidine syntheses[3)] are nitriles, amides, imidates, imidohalides, and orthoesters etc., which are derivatives of carboxylic acids and/or amines.

$$R^1COOH + 2R^2NH_2 \xrightarrow[k_1]{PPSE} \left(R^1CONHR^2 \right) \xrightarrow[k_2]{PPSE} R^1C\begin{matrix} \nearrow NR^2 \\ \searrow NHR^2 \end{matrix} \qquad (1)$$

The following example is representative: PPSE was prepared from phosphorous pentoxide (1.42 g, 5 mmol) and hexamethyldisiloxane (2.56 g, 16 mmol) in 3 ml of CH_2Cl_2 at the refluxing temperature for 30 min,[1)] and the solvent was distilled away from the reaction mixture. To the residual syrup, p-methoxybenzoic acid (190 mg, 1.25 mmol) was added, and heated at 160 °C. After aniline (233 mg, 2.5 mmol) was added to the mixture, the solution was stirred at 160 °C for 5 h. The crude product was isolated by pouring the reaction mixture into 200 ml of cold 1M NaOH solution. Recrystallization from aqueous ethanol gave pure N,N'-diphenyl-p-methoxybenzamidine melting at 115-116 °C (328 mg, 87%).[4)]

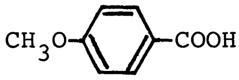
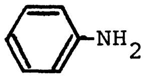
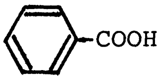
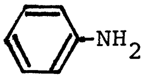
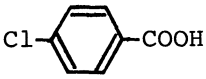
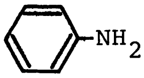
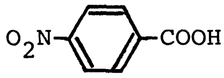
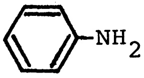
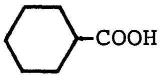
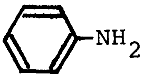
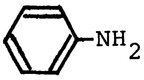
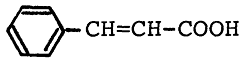
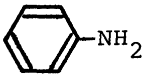
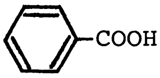
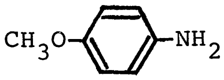
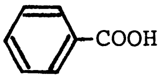
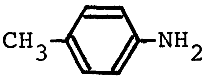
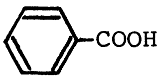
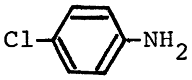
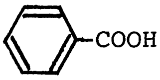
We examined the reaction in two series as depicted in Table 1. The first series is exemplified from entry 1 to 7, where a variety of carboxylic acids were reacted with two equivalents of aniline at 160 °C for 5 h. In the second series from entry 8 to 11, amines were varied and benzoic acid was fixed. N,N'-diphenylamidines were obtained by the reaction between aniline and aromatic, aliphatic, and α,β-unsaturated carboxylic acids in high yields. On the other hand, the reaction of benzoic acid and p-nitroaniline (entry 11) did not afford the corresponding amidines but gave N-p-nitrophenylbenzamide in 59% yield. This amide formation might be caused because of the low nucleophilicity of p-nitroaniline. Contrary to success of the synthesis of N,N'-diaryl-substituted amidines, highly nucleophilic aliphatic amines gave a mixture of amidines and amides in low yield.

In the course of the reaction, an interesting phenomenon was observed. When an equimolar amount of benzoic acid and aniline were reacted in the presence of PPSE at 160 °C for 5 h, N,N'-diphenylbenzamidine was obtained in 82% yield based on aniline, and benzanilide was not isolated from the reaction mixture. N,N'-diphenylbenzamidine was also obtained by the reaction of benzanilide and aniline in 90% yield under the same conditions. The reaction of p-anisidine and benzoic acid using PPE afforded the corresponding amidine in 32% yield, while the reaction with PPSE gave the same product in 88% yield.

These results suggest that, i) the intermediate of this amidine formation should be the corresponding amide or its derivatives such as phosphate or silylated compound, and ii) the rate of the formation of amide (k_1) should be smaller than the rate of the formation of amidine (k_2) (Eq. 1).

The study of the mechanism of the present reaction and applications are under investigation.

Table 1. Synthesis of Amidines Using PPSE

			Amidine	
Entry	Carboxylic acid	Amine	Yield/%[a)]	MP /°C (Lit.)[b)]
1			87	115-116(107-108[5)])
2			83	143-144(144[6)])
3			88	149-150(149[7)])
4			84	151-153(155[8)])
5			81	110-111[e)]
6	$CH_3(CH_2)_4$-COOH		79	91-92(90[9)])
7			65	115.5-116.5[e)]
8			88	120-122(125[10)])
9			87	131-131.5[e)]
10			69	140-141[e)]
11			(59)[c, 12)]	178-181[d)](203[11)])

a) Yields are after recrystallized from aqueous ethanol. b) Melting points are uncorrected. c) Yield of amide. d) Melting point of amide. e) Spectral and analytical results were consistent with the structure.

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4) The following spectra were obtained: IR (KBr) $\nu \mathrm{cm}^{-1}$; 3290, 1625, 1215, 1105, 765. ^{1}H NMR, δppm ($CDCl_3$); 3.67(S, 3H), 5.70(S, 1H), 7.00(m, 14H).

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12) The following spectra were obtained: IR (KBr) $\nu \mathrm{cm}^{-1}$; 3350, 1655, 1530, 1315, MS; m/e 242.

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