Short Communication

Synthesis of *N,N'*-Dialkylamidines from Heterocyclic Carboxylic Acids

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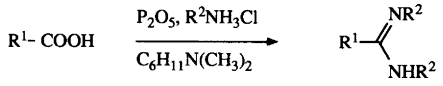
Comparatively little attention has been devoted to *N,N'*-disubstituted furancarboxamidines and *N,N'*-disubstituted thiophenecarboxamidines, especially those with *N,N'*-dialkyl substituents. Degnan and Pope[1] have prepared *N*-alkyl-*N'*-aryl-2-furancarboxamidines that possessed a high anesthetic potency compared with *N,N'*-diaryl-2-furancarboxamidines. Additional *N*-alkyl-*N'*-aryl-2-furancarboxamidines and *N,N'*-diaryl-2-furancarboxamidines have been reported,[2–4] whereas *N*-(*n*-propyl)-*N'*-isopropyl-2-furancarboxamidine[4] is the only known *N,N'*-dialkyl substituted furancarboxamidine. McFarland and Howes[5] have investigated thienylpropionamidines and thienylacrylamidines for anthelmintic activity and showed this to be associated with *N,N*-disubstitution, whereas substitution at the *N'*-position was unfavorable for activity. The only *N,N'*-disubstituted thiophenecarboxamidines found in the literature are *N*-methyl-*N'*-(4-chlorophenyl)-2-thiophenecarboxamidine[6] and *N,N'*-diphenyl-2-thiophenecarboxamidine.[7] Since the procedures for the preparation of the above-mentioned and of symmetrical *N,N'*-dialkyamidines would include multistep procedures, it would be of interest to investigate whether heterocyclic carboxamidines can be prepared in one step under the same vigorous reaction conditions as previously reported for *N,N'*-dialkylbenzenecarboxamidines. In this procedure benzoic acid was heated in a phosphorus pentaoxide amine matrix at 220 °C for several hours.[8]

We have now found that furancarboxylic acids and thiophenecarboxylic acids produce symmetrically substituted *N,N'*-dialkylfurancarboxamidines and *N,N'*-dialkylthiophenecarboxamidines (**1**) when heated in a mixture of phosphorus pentaoxide, *N,N*-dimethylcyclohexylamine, and an appropriate alkylamine hydrochloride at 220 °C for 4 h (Scheme 1). The corresponding thienylacetamidines were similarly prepared. The results of these preparations are given in Table 1. Spectral data are given in Table 2.



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Scheme 1.

Table 1. Properties of *N,N'*-dialkylamidines **1a–i**.

Cpd.[a]	R^1	R^2	Yield (%)	B.p./°C (kPa) or m.p./°C	n_D^{25}
1a	Furan-2-yl	CH_3	22	66–67 (0.16)	1.5469
1b	Furan-2-yl	C_3H_7	72	80–81 (0.04)	1.5074
1c	Furan-2-yl	*iso*-C_4H_9	55	73–74 (0.04)	1.4948
1d	Thiophen-2-yl	CH_3	15	80–82	
1e	Thiophen-2-yl	C_3H_7	58	87–88 (0.07)	1.5365
1f	Thiophen-2-yl	*iso*-C_4H_9	68	90–91 (0.08)	1.5207
1g	Thiophen-2-ylmethyl	*iso*-C_4H_9	54	106–108 (0.12)	1.5170
1h	Thiophen-3-ylmethyl	C_3H_7	49	102–104 (0.06)	1.5343
1i	Thiophen-3-ylmethyl	*iso*-C_4H_9	71	102–103 (0.05)	1.5170

[a]Microanalyses C, H, N.

Table 2. Spectral data of *N,N'*-dialkylamidines **1a–i**.

Cpd.	IR (Film) γ/cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ (ppm)	MS *m/z* (%)
1a	3460 1630	3.10 (6 H, s), 4.90 (1 H, br s), 6.3–7.5 (3 H, m)	138 (M^+, 64) 108 (100)
1b	3460 1630	0.97 (6 H, t), 1.63 (4 H, sextet), 3.33 (4 H, t), 4.50 (1 H, br s), 6.4–7.5 (3 H, m)	194 (M^+, 39) 94 (100)
1c	3470 1635	0.97 (12 H, d), 1.5–2.3 (2 H, m), 3.20 (4 H, d), 4.35 (1 H, br s), 6.4–7.5 (3 H, m)	222 (M^+, 18) 108 (100)
1d	3450[a] 1620[a]	3.00 (6 H, s), 4.50 (1 H, br s), 7.0–7.5 (3 H, m)	154 (M^+, 40) 124 (100)
1e	3450 1630	0.90 (6 H, t), 1.58 (4 H, sextet), 3.25 (4 H, t), 4.37 (1 H, br s), 7.0–7.4 (3 H, m)	210 (M^+, 29) 110 (100)
1f	3450 1635	0.92 (12 H, d), 1.5–2.2 (2 H, m), 3.14 (4 H, d), 4.18 (1 H, br s), 7.0–7.4 (3 H, m)	238 (M^+, 48) 110 (100)
1g	3450 1645	0.93 (12 H, d), 1.5–2.1 (2 H, m), 3.10 (4 H, d), 3.80 (2 H, s), 4.07 (1 H, br s), 6.9–7.4 (3 H, m)	252 (M^+, 71) 97 (100)
1h	3440 1640	0.90 (6 H, t), 1.53 (4 H, sextet), 3.20 (4 H, t), 3.60 (2 H, s), 3.90 (1 H, br s), 6.9–7.4 (3 H, m)	224 (M^+, 79) 97 (100)
1i	3450 1645	0.88 (12 H, d), 1.5–2.1 (2 H, m), 3.03 (4 H, d), 3.58 (2 H, s), 3.87 (1 H, br s), 6.9–7.3 (3 H, m)	252 (M^+, 94) 57 (100)

[a] KBr.

Experimental

General procedure for preparation of **1a–i**: The carboxylic acid (0.10 mol), phosphorus pentaoxide (45 g, 0.32 mol), and an appropriate primary alkylamine hydrochloride (0.38 mol) were mixed by mechanical stirring and protected from moisture. *N,N*-Dimethylcyclohexylamine (50 ml) was added with stirring. The flask was heated in an oil bath at 220 °C for 4 h with continuous stirring. When the temperature of the reaction mixture had decreased to 100 °C, approx. 800–900 ml of 2 M NaOH solution were added until the reaction mixture was strongly alkaline (pH ca. 10). Then the mixture was extracted with ether (3×100 ml), and the combined ether phases were washed with water and dried over potassium carbonate. Ether and *N,N*-dimethylcyclohexylamine were stripped off, and the oily residue was distilled to give yellowish, clear liquids, except for compound **1d** which solidified on being distilled and was recrystallized from toluene.

References

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