Synthesis of Hexasubstituted Carbamimidic Acid Anhydrides and of N^1,N^1,N^2-Trisubstituted Formamidines from 1,1,3-Trisubstituted Ureas

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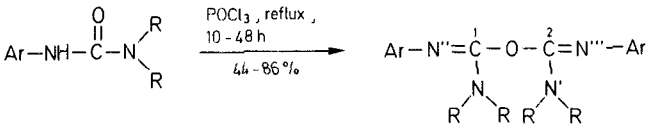
1,1,3-Trisubstituted ureas **1** were converted with phosphoryl chloride to hexasubstituted carbamimidic acid anhydrides **2** which were hitherto unknown or difficult to prepare by other methods. The ureas bearing bulky substituents were converted to amidinoyl chlorides **3** which were reduced to the corresponding formamidines **5** with amine-boranes in acid.

In the course of our research into the preparation of various formamidines[1], we wanted to reduce 1,1,3-trisubstituted ureas to the corresponding formamidines under mild reaction conditions. There is only one report[2] in which three substituted formamidines were synthesized by the reduction of 1,1,3-trisubstituted ureas with lithium aluminium hydride in low to moderate yields.

We have attempted the reduction of 1,1,3-trisubstituted ureas **1** by conversion to the amidinoyl chlorides **3** with phosphoryl chloride and subsequent reduction to the formamidines **5** under the mild reduction conditions as reported in the reduction of amides[3]. Conversion of the ureas to the amidinoyl chlorides was rather difficult in comparison with the chlorination of amides[3], and the reaction proceeded only in the refluxing solutions phosphoryl chloride. As for the



1a-j **2a-j**

1,2	Ar	R	R	1,2	Ar	R	R
a		CH_3	CH_3	f		C_2H_5	C_2H_5
b		CH_3	CH_3	g		C_2H_5	C_2H_5
c		C_2H_5	C_2H_5	h		$-(CH_2)_5-$	
d		C_2H_5	C_2H_5	i		$-(CH_2)_4-$	
e		C_2H_5	C_2H_5	j		$-(CH_2)_2-O-(CH_2)_2-$	

Table 1. Preparation of N^1,N^1-Dicyclohexyl-N^2-phenylformamidine (**5k**)

Reagent	solvent	Yield [%]
$(H_3C)_2NH \cdot BH_3$	HCOOH	73
$(H_3C)_2NH \cdot BH_3$	H_3C—COOH	69
pyridine $\cdot BH_3$	F_3C—COOH	70
$NaBH_4$	dimethoxyethane	32
$LiAlH_4$	dimethoxyethane	50

Table 2. N^1, N^1, N^2-Trisubstituted Formamidines **5** prepared

Product	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	M.S. *m/e*	I.R. (Nujol) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
5k	73	192–193°[d]	$C_{25}H_{31}N_5O_7$[e] (513.5)	284 (M^+, 13.9%); 93 (100)	1630	0.49–2.14 (m, 20H, CH_2); 3.39–4.14 (m, 2H, CH); 6.79–7.59 (m, 5H_{arom}); 7.60 (s, 1H, N=CH—N)
5l	61	56–57°[f]	$C_{13}H_{20}N_2$ (204.3)	204 (M^+, 31.2%); 58 (100)	1625	1.20, 1.30 (2s, 6H each, CH_3); 3.85–4.50 (m, 2H, CH); 6.73–7.37 (m, 5H_{arom}); 7.60 (s, 1H, N=CH—N)
5m	50	195–197°[d]	$C_{20}H_{23}N_5O_7$[e] (445.4)	216 (M^+, 67.4%); 124 (100)	1620	1.23, 1.35 (2s, 6H each, CH_3); 1.30–1.97 (m, 6H, CH_2); 3.80–4.40 (m, 2H, CH); 6.60–7.33 (m, 5H_{arom}); 7.40 (s, 1H, N=CH—N)
5i	trace (92)[g]	–	–	–	–	–

[a] Yield of isolated, pure product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.15, H ±0.23, N ±0.19.
[c] Measured at 60 MHz.
[d] M.p. of picrate.
[e] Molecular Formula of picrate.
[f] In Ref.[3], the m.p. is 56–58°C.
[g] Amount of starting material recovered (%).

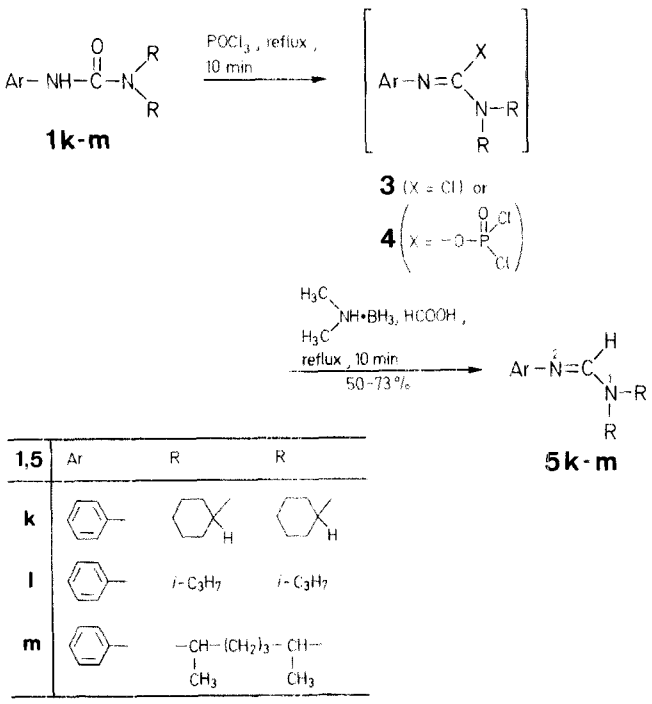
Table 3. Hexasubstituted Carbamimidic Acid Anhydrides **2a–j** prepared

Product	Reaction time [h]	Yield[a] [%]	m.p. [°C]	Molecular Formula[b]	M.S. *m/e*	I.R. (Nujol) [cm^{-1}] $\nu_{C=N}$(s)	ν_{C-O-C}(s)	^{1}H-N.M.R. ($CDCl_3$/TMS; 60 MHz) δ [ppm]
2a	24	86	116–117°	$C_{18}H_{22}N_4O$ (310.4)	310 (M^+, 98.0%); 148 (100)	1670, 1630	1220, 1050	2.32, 2.84 (2s, 6H each, CH_3); 6.58–7.38 (m, 10H_{arom})
2b	24	69	146–148°	$C_{18}H_{20}Cl_2N_4O$ (379.3)	378 (M^+, 6.3%); 181 (100)	1670, 1630	1260, 1060	2.43, 2.87 (2s, 6H each, CH_3); 6.60–7.33 (m, 8H_{arom})
2c	24	71	oil	$C_{24}H_{34}N_4O_3$ (426.6)	426 (M^+, 4.2%); 205 (100)	1655, 1620	1245, 1040	0.77, 0.97 (2t, 6H each, J = 7 Hz, CH_3); 2.80, 3.28 (2q, 4H each, J = 7 Hz, CH_2); 3.65, 3.72 (2s, 3H each, CH_3O); 6.67, 6.73 (2s each, 4H_{arom})
2d	24	69	73–74°	$C_{24}H_{34}N_4O$ (394.6)	394 (M^+, 7.2%); 189 (100)	1660, 1630	1245, 1065	0.67, 0.92 (2t, 6H each, J = 7 Hz, CH_3); 2.18, 2.23 (2s, 3H each, CH_3); 2.87, 3.23 (2q, 4H each, J = 7 Hz, CH_2); 6.57–7.07 (m, 8H_{arom})
2e	24	67	122–125°	$C_{22}H_{28}Cl_2N_4O$ (435.4)	434 (M^+, 20.8%); 209 (100)	1655, 1620	1250, 1080	0.82, 1.02 (2t, 6H each, J = 7 Hz, CH_3); 2.85, 3.30 (2q, 4H each, J = 7 Hz, CH_2); 6.67–7.07 (m, 8H_{arom})
2f	24	44	64–66°	$C_{22}H_{30}N_4O$ (366.5)	366 (M^+, 38.7%); 175 (100)	1660, 1625	1250, 1030	0.70, 0.93 (2t, 6H each, J = 7 Hz, CH_3); 2.73, 3.28 (2q, 4H each, J = 7 Hz, CH_2); 6.67–7.40 (m, 10H_{arom})
2g	24	0(71)[c]	–	–	–	–	–	–
2h	10	66	118–120°	$C_{24}H_{30}N_4O$ (390.5)	390 (M^+, 22.1%); 187 (100)	1660, 1620	1240, 1040	0.80–1.65 (m, 12H, CH_2); 2.60–3.00, 3.15–3.50 (m, 4H each, CH_2); 6.60–7.50 (m, 10H_{arom})
2i	48	59	128–130°	$C_{22}H_{26}N_4O$ (362.5)	362 (M^+, 20.9%); 173 (100)	1660, 1620	1230, 1050	1.20–2.03 (m, 8H, CH_2); 2.53–3.03, 3.03–3.70 (m, 4H each, CH_2); 6.70–7.33 (m, 10H_{arom})
2j	10	57	oil	$C_{22}H_{26}N_4O_3$ (394.5)	394 (M^+, 14.1%); 189 (100)	1670, 1630	1230, 1070	2.60–3.70 (m, 16H, CH_2); 6.70–7.50 (m, 10H_{arom})

[a] Yield of isolated, pure product.
[b] The microanalyses or high-resolution M.S. data were in satisfactory agreement with the calculated values: C ±0.26, H ±0.25, N ±0.27, $\Delta m = -0.0005$ (M^+).
[c] Amount of starting material recovered (%).

ureas bearing bulky substituents, the chlorination and the subsequent reduction proceeded smoothly in one pot to give the corresponding formamidines **5** (Tables 1 and 2).

Sterically hindered ureas **1k–m** are easily converted to amidinoyl chlorides **3k–m** or *O*-phosphoryl intermediates **4**, the structures of which are not determined, and subsequently to formamidines **5** by hydride reduction, while sterically unhindered ureas are intact and recovered in good yields under the same reaction conditions. In the case of the prolonged refluxing in phosphoryl chloride, sterically unhindered ureas are converted to the carbamimidic acid



1,5	Ar	R	R
k			
l		i-C_3H_7	i-C_3H_7
m			

anhydrides **2a–j**, while sterically hindered ureas **1k–m** are converted to the corresponding **2** in trace or poor yields in addition to several unidentifiable products. Several trisubstituted ureas were submitted to the carbamimidic acid anhydride formation reaction and the results are presented in Table 3. It is evident from Table 3 that the facility of anhydride formation was enormously affected by the electronic effect of the *para*-substituent on the benzene ring and the steric hindrance of the aliphatic groups (R). An electron-donating substituent (Cl, OCH_3) at the *para*-position facilitates anhydride formation, while an electron-withdrawing substituent (CN) and bulky aliphatic groups retard the reaction.

N',N''-Diphenyl-N,N,N',N'-tetramethylformamimidic Acid Anhydride (2a); Typical Procedure:

A mixture of **1a** (328 mg, 2 mmol) and phosphoryl chloride (6 ml) is heated to reflux for 24 h. Phosphoryl chloride is evaporated in vacuo and 10% sodium carbonate solution (10 ml) is added to the residue with cooling. The aqueous solution is extracted with dichloromethane (2 × 20 ml). The combined extracts are washed with saturated sodium chloride (2 × 20 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue is purified by silica gel flash column chromatography using dichloromethane/methanol (50:1) for elution to give **2a**; yield: 266 mg (86%).

$C_{18}H_{22}N_4O$	calc.	C 69.65	H 7.14	N 18.05
(310.4)	found	69.49	7.26	17.88

N^1,N^1-Dicyclohexyl-N^2-phenylformamidine (5k); Typical Procedure:

A mixture of **1k** (600 mg, 2 mmol) and phosphoryl chloride (6 ml) is heated to reflux for 10 min. Phosphoryl chloride is evaporated in vacuo and formic acid (6 ml) and dimethylamine-borane (254 mg, 6 mmol) are added to the residue with cooling. The mixture is heated at reflux for 10 min. Formic acid is evaporated in vacuo and the excess dimethylamine-borane is decomposed by the addition of 10% sodium hydroxide solution (10 ml). The aqueous solution is extracted with dichloromethane (2 × 20 ml). The combined extracts are washed with saturated sodium chloride (2 × 20 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue is purified by silica gel flash column chromatography using dichloromethane for elution to give **5k**; yield: 412 mg (73%); which is converted to its picrate for analysis.

$C_{25}H_{31}N_5O_9$	calc.	C 58.47	H 6.08	N 13.64
(513.5)	found	58.70	6.14	13.58

This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

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