Acta Chemica Scandinavica B 34 (1980) 369 – 373

Phosphoramides. XII.* Diphosphorus Pentaoxide Amine Mixtures as Reagents in a New Synthesis of Formamidines with Potential Pesticidal Activity

BO W. HANSEN and ERIK B. PEDERSEN **

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark

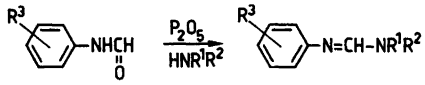
N'-Aryl-*N*,*N*-dialkylformamidines were prepared in a new synthetic manner by treating *N'*-arylformamides with a mixture of diphosphorus pentaoxide and an amine at 210 °C. The mechanism in these reactions is proposed to be the same as for the analogous hexamethylphosphoric triamide, HMPT, reactions. In the synthesis of *N*-aryl-*N'*-alkylformamidines using primary amines the yields were increased by using the corresponding amine hydrochlorides. The procedure was extended to acetamidines, propionamidines and benzamidines.

The development of new acaricides for control of ticks and mites are of increasing interest because these animals often are plasmic organisms which show great ability to make resistant strains.[1] Spider mites have been controlled by insecticides, which unfortunately also act upon the natural enemies to the mites. *N'*-Aryl-*N*,*N*-dialkylformamidines represent a new class of specific acaricides.[2] For example chlordimeform [*N'*-(4-chloro-2-methylphenyl)-*N*,*N*-dimethylformamidine] has been used to control pests on cotton, rice and fruit-trees. The active compounds are usually prepared by a Vilsmeyer condensation reaction of *N*,*N*-dimethylformamide, DMF, and anilines using acyl halides[3–6] as condensing agents. Treatment of arylisocyanates with DMF,[7,8] or reaction of anilines with amines in triethyl orthoformate[9] have also been used. Recently *N*,*N*-dimethylamidines were readily synthesized by refluxing formanilides in hexamethylphosphoric triamide, HMPT.[10] This method was later modified to heating anilines with formic acid to reflux temperature in HMPT.[11]

Oxo groups can be converted to amino groups in good yields by a one-step procedure using diphosphorus pentaoxide amine mixtures.[12,13] This investigation deals with a new synthesis of potentially pesticidal formamidines using a mixture of diphosphorus pentaoxide and an amine as the reagent.

RESULTS AND DISCUSSION

N'-Aryl-*N*,*N*-dialkylformamidines *2* were prepared in 13–96 % yield by heating formanilide *1* in a mixture of diphosphorus pentaoxide and a secondary amine at 210 °C for 2 h (*cf.* Table 1).



1 *2*

High yields are obtained with both electron-withdrawing and electron-donating substituents in the aromatic ring. The alkyl groups in the amine can be changed from one to four carbons without affecting the yields. The reaction with dicyclohexylamine gives a low yield which possibly is a result of steric repulsion in transition state as discussed below. For non-crowded alkyl groups the yields are 57–96 %. Allyl groups led to heat sensitive products. However, by lowering the reaction temperature fair yields were also obtained of *N*,*N*-diallylformamidines. The procedure was extended to trialkyl-

* Part XI, Jensen, K. G. and Pedersen, E. B. *Acta Chem. Scand. B 33* (1979) 319.

** To whom the correspondence should be addressed.

0302-4369/80/050369-05$02.50

Table 1. N'-Aryl-*N,N*-dialkylformamidines *2.*

R^1	R^2	R^3	Yield (%)	B.p. (°C)/Torr (lit. b.p./Torr)	n_D^{25} or m.p.	Insecticidal activity[a,18]
Et	Et	H	81	92–96/0.07 (143–144/15)[19]	1.5728	
Pr	Pr	H	96	99–101/0.09 (108–110/0.3)[20]	1.5523	+ –
Et	Et	4-Me	91	90–93/0.02	1.5612	
Pr	Pr	4-Me	92	95–97/0.03	1.5492	+ –
Pr	Pr	4-Cl	71	117–119/0.03	1.5645	+ –
Allyl	Allyl	4-Cl	84	116–118/0.07	1.5865	+ –
Pr	Pr	4-OMe	80	135–139/0.08	1.5522	–
Me	Cyclohexyl	4-OMe	71	148–150/0.02	50–52[b]	–
Cyclohexyl	Cyclohexyl	4-OMe	13	160–175/0.04	1.5856	
Pr	Pr	4-NO_2	84	169–174/0.1	1.6473	–
Et	Et	4-NMe_2	18	127–129/0.1	1.6045	
Pr	Pr	4-NMe_2	57	130–133/0.06	1.5769	
Pr	Pr	2,6-diMe	90	103–105/0.07	1.5298	
Pr	Pr	2,6-diCl	90	117–119/0.09	1.5632	
Me	Bu	2-Me-4-Cl	76	144–146/0.2 (130–135/0.5)[21]	1.5637	
Pr	Pr	2-Me-4-Cl	73	135–136/0.2 (109–111/0.15)[1]	1.5556	
Bu	Bu	2-Me-4-Cl	73	128–130/0.12	1.5459	–
	$-(CH_2)_5-$	2-Me-4-Cl	82	125–130/0.04	1.5968	+ –
	$-(CH_2)_2O(CH_2)_2-$	2-Me-4-Cl	70	134–138/0.1	1.6001	+ –
Allyl	Allyl	2-Me-4-Cl	48	120–125/0.2	1.5721	
Et	Et	2-Me-5-NO_2	79	166–170/0.5	1.5905	–
Pr	Pr	2-Me-5-NO_2	91	146–148/0.07	1.5716	–
Me	Bu	2-Me-5-NO_2	90	150–155/0.04	1.5820	–

[a] – = no activity, + – = primary test showed some positive results which could not be confirmed in a secondary, more differentiated test. Test material: *Musca domestica, Aedes* larval stage 1, *Spodoptera* eggs and larval stage 3, *Epilachna* larval, *Aphis.* [b] Recrystallized from cyclohexane.

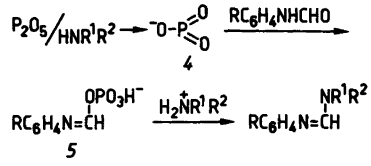
substituted formamidines *3* which have been reported to be very active defoliants.[14] However, for lower alkyl groups a decreased yield was obtained.

$Pr_2N-CH=N-Alkyl$

3

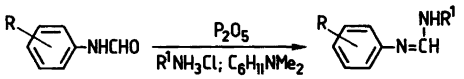
Alkyl: Isobutyl (58 %); Dodecyl (74 %)

Diphosphorus pentaoxide-amine mixtures behave as reagent similar to HMPT.[12] In the reaction of benzyl alcohols with HMPT at 200 °C the metaphosphate ion *4* has been found to be a reactive intermediate which adds to benzyl alcohol with formation of benzyl phosphate undergoing further reactions.[15] The metaphosphate ion was formed in the rate-determining step from the pyrophosphate ion. The phosphoramides produced in the diphosphorus pentaoxide aminolysis may split off the reactive metaphosphate ion. The metaphosphate ion adds to the formamide with formation of the imidoylphosphate *5* which then yields the formamidine.



Yields are low when the reagent is prepared by aminolysis of P_2O_5 using primary amines. The reaction is then modified by heating the corresponding amine hydrochlorides and formanilide in the presence of *N,N*-dimethylcyclohexylamine, *cf.* Table 2.

Table 2. Yields of *N,N'*-disubstituted formamidines *(6a–6d)* (%).



6 (a–d)

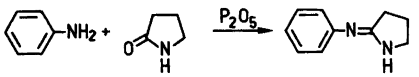
	R	R^1	Procedure A[a]	Procedure B[b]
6a	2-CH_3-4-Cl	Cyclohexyl	25	70
6b	4-CH_3	$CH_2CH_2CH_3$	5	21
6c	4-CH_3	$(CH_2)_3NMe_2$	2	16
6d	4-OCH_3	$C(CH_3)_3$	26	

[a] $R^1NH_2+P_2O_5$. [b] $R^1NH_3Cl+C_6H_{11}NMe_2+P_2O_5$.

The yields increased about five times. The unsuccessful reaction with primary amines is possibly due to formation of phosphoramides which do not easily form the metaphosphate ion. By addition of the corresponding amine hydrochlorides to the reaction mixture the pH changes to give more favourable conditions for its formation.

Another reason for low yields may be that disubstituted formamidines often hydrolyze more easily than trisubstituted ones in alkaline medium.[16] In the work-up procedure the reaction mixture is adjusted to pH 10, which can explain that anilines often were isolated as the main-products. Also diamines and polyamines gave very low yields.

The formation of the cyclic amidin *7* shows that the method is successful also with aniline and aliphatic amides as substrates.



7

Fair yields are also obtained of benzamidines, acetamidines and propionamidines (*8a–f*, Table 3) starting from the corresponding anilides. A large R^1 group did not lower the yields.

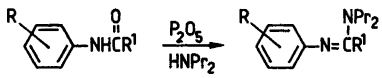
Six of thirteen compounds, which were tested, showed weak insecticidal activity (Table 1). The compounds were inactive as acaricides against *Tetranychus urticae* and *Tetranychus cinnabarinus.*

EXPERIMENTAL

Preparation of formamidines 2

General procedure. P_2O_5 (0.1 mol) and a dialkylamine (0.3 mol) were stirred until the mixture was homogeneous (eventually by heating). *N*-Phenylformamide *1* (0.05 mol) was then added. The reaction mixture was heated on an oil bath at 210 °C for 2 h with stirring. The mixture was then poured onto ice in a separating funnel and 2 M NaOH (250 ml) was added. The water phase was extracted with 3 x 200 ml of ether. At this stage the reaction cake had dissolved completely. The combined ether solutions were washed with water (50 ml), dried over Na_2SO_4 and the ether was stripped off. The oily residue was then distilled. Correct NMR spectra and satisfactory microanalyses of new compounds were obtained.

Table 3. Yields of amidines in the reaction.



8 (a–f)

	R	R^1	Amidine (%)
8a	H	Me	43
8b	3-Cl-4-Me	Me	60
8c	4-NO_2	Me	11
8d	4-OEt	Me	63
8e	4-Me	Et	21
8f	H	Ph	61

N'-(2-Methyl-4-chlorophenyl)-N,N-diallylformamidine. P_2O_5 (10 g) and diallylamine (20 g) were mixed in a strong exothermic process. *N*-(2-Methyl-4-chlorophenyl)formamide (8.5 g) was added and the mixture was heated on an oil bath at 160 °C for 40 min with stirring. The mixture was then poured onto ice and 200 ml 2 M NaOH was added. This alkaline mixture was allowed to stand for 3 h until the reaction cake had dissolved. The water

phase was extracted with 3 × 200 ml ether. The combined ether phases were washed with 100 ml of water, dried over Na_2SO_4 and the ether was stripped off. Distillation at 135–180 °C/0.8 mmHg gave a mixture of products. Preparative silica gel TLC with ether–light petroleum (2:1) for elution afforded 6.00 g (48 %) of the title compound (R_F = 0.85).

N'-*(4-Chlorophenyl)*-N,N-*diallylformamidine*. The same procedure as in the preceding experiment was followed except that preparative silica gel TLC was not used.

N'-*Dodecyl*-N,N-*dipropylformamidine*. The general procedure was followed. However, the reaction mixture was heated on the oil bath at 210 °C for 21 h. Yield 10.9 (74 %). B.p. 128–140 °C/0.04 mmHg, lit.[14] 121–123 °C/0.01 mmHg; n_D^{25} 1.4606. ^{1}H NMR δ($CDCl_3$): 0.88 (9H, t), 1.17–1.83 (24H, m), 3.11 (6H, m), 7.22 (1H, s). MS *m/e* (%): 296 (M^+, 36), 196 (100).

N'-*Isobutyl*-N,N-*dipropylformamidine*. The general procedure was followed. However, the mixture was heated on an oil bath for 17½ h. Yield 5.4 g (58 %). B.p. 50–68 °C/0.06 mmHg. ^{1}H NMR δ ($CDCl_3$): 0.87 (12H, m), 1.20–1.95 (5H, m), 2.93–3.32 (6H, m), 7.20 (1H, s). MS *m/e* (%): 184 (M^+, 27), 100 (100). Found: C 71.27; H 13.16; N 15.03. Calc. for $C_{11}H_{24}N_2$: C 71.68; H 13.13; N 15.20.

N'-*(4-Dimethylaminophenyl)*-N,N-*diethylformamidine*. 13.6 g *p*-dimethylaminoaniline (0.1 mol) was mixed with 10 g P_2O_5. 20.2 g *N,N*-diethylformamide (0.2 mol) was added and the reaction mixture was heated on an oil bath at 210 °C for 3 h. Working up was performed as in the general procedure. Distillation at 127–129 °C/0.1 mmHg gave 4.0 g of the title compound (18 %).

Preparation of *N'*-Alkylformamidines *6a–6d*

Procedure A. Equivalent to the general procedure for preparation of formamidines *2*.

Procedure B. P_2O_5 (0.105 mol) and an alkylamine hydrochloride (0.25 mol) were mixed and heated gently until melting. *N,N*-dimethylcyclohexylamine (0.25 mol) was added and the mixture was made homogeneous by stirring. *N*-Arylformamide (0.05 mol) was added and the mixture was then heated on an oil bath at 210 °C for 2 h with stirring. The mixture was then poured onto ice directly in a separating funnel and 2 M NaOH (250 ml) was added. The water phase was extracted with ether (3 × 200 ml). At this stage the reaction cake had dissolved completely. The combined ether phases were washed with water (50 ml), dried over Na_2SO_4 and the ether was stripped off. *N,N*-Dimethylcyclohexylamine and excess of alkylamine were distilled off at 10 mmHg. The residue was then distilled.

N'-*(2-Methyl-4-chlorophenyl)*-N-*cyclohexylformamidine* 6a. B.p. 145–147 °C/0.1 mmHg, m.p. 96–98 °C (cyclohexane). ^{1}H NMR δ ($CDCl_3$): 1.23–1.81 (11H, m), 2.23 (3H, s), 3.63 (1H, br. s), 6.53–7.14 (3H, m), 7.38 (1H, s). MS *m/e* (%): 250 (M^+, 95), 153 (100). Found: C 66.35; H 7.77; N 10.98; Cl 14.31. Calc. for $C_{14}H_{19}ClN_2$: C 67.02; H 7.65; N 11.17; Cl 14.15.

N'-*(4-Methylphenyl)*-N-*propylformamidine* 6b. B.p. 112–120 °C/0.09 mmHg; m.p. 89–90 °C (cyclohexane). ^{1}H NMR δ ($CDCl_3$): 0.95 (3H, t), 1.54 (2H, m), 2.29 (3H, s), 3.28 (2H, m), 4.93 (1H, br, s), 6.73–7.15 (4H, m), 7.54 (1H, s). MS *m/e* (%): 176 (M^+, 100). Anal. $C_{11}H_{16}N_2$: C, H, N.

N'-*(4-Methylphenyl)*-N-*(3-dimethylaminopropyl)formamidine* 6c. Procedure B. The reaction was stopped after 30 min. B.p. 130–140 °C/0.08 mmHg. n_D^{25} 1.5711. ^{1}H NMR δ ($CDCl_3$): 1.74 (2H, m), 2.21 (6H, s), 2.31 (3H, s), 3.41 (4H, m), 6.81–7.22 (4H, m), 7.57 (1H, s). MS *m/e* (%): 219 (M^+, 3), 58 (100). Found: C 71.78; H 9.77; N 19.08. Calc. for $C_{13}H_{21}N_3$: C 71.19; H 9.65; N 19.16.

N'-*(4-Methoxyphenyl)*-N-tert-*butylformamidine* 6d. B.p. 124–127 °C/0.15 mmHg. n_D^{25} 1.5733. ^{1}H NMR δ ($CDCl_3$): 1.37 (9H, s), 3.76 (3H, s), 6.70–7.00 (4H, m), 7.67 (1H, s). MS *m/e* (%): 206 (M^+, 54), 108 (100). Found: C 68.90; H 8.03; N 13.69. Calc. for $C_{12}H_{18}N_2O$: C 69.85; H 8.81; N 13.58.

N'-*Phenyl*-N,N-*dipropylacetamidine* 8a was prepared from P_2O_5 (20 g), dipropylamine (30 g), and acetanilide (13.5 g) by heating at 210 °C for 6 h in a similar way as described for *8b* below. Yield 9.4 g (43 %) of *8a*, b.p. 95–96 °C/0.1 mmHg, n_D^{25} = 1.5416. ^{1}H NMR δ ($CDCl_3$): 0.93 (6H, t), 1.3–2.0 (4H, m), 2.80 (3H, s), 3.33 (4H, t), 6.5–7.5 (5H, m). MS *m/e* (%) 218 (M^+, 43), 175 (24), 118 (100), 100 (11), 93 (13), 84 (59), 77 (67), 72 (20), 51 (13), 42 (54). Anal. $C_{14}H_{22}N_2$: C, H, N.

N'-*(3-Chlor-4-methylphenyl)*-N,N-*dipropylacetamidine* 8b. 15 g P_2O_5 (0.105 mol) and 30.3 g dipropylamine (0.30 mol) were mixed and made homogeneous by stirring. 9.2 g *N*-(3-chloro-4-methylphenyl)acetamide (0.05 mol) were added to this mixture. The mixture was heated on an oil bath at 240 °C for 8½ h with stirring. The mixture was then poured onto ice and 250 ml 2 M NaOH was added. The water phase was extracted with 2 × 200 ml ether. The combined ether phases were washed with 100 ml water, dried over Na_2SO_4 and the ether was stripped off. The oily residue was distilled to obtain the title compound. B.p. 120–130 °C/0.04 mmHg. Yield 8.0 g (60 %). ^{1}H NMR δ ($CDCl_3$): 0.92 (6H, t), 1.20–1.95 (4H, m), 1.86 (3H, s), 2.31 (3H, s), 3.30 (4H, m), 6.36–7.18 (3H, m). MS *m/e* 266 (M^+, 85), 84 (100). n_D^{25} 1.5515. Anal. $C_{15}H_{23}ClN_2$: C, H, N, Cl.

N'-*(4-Nitrophenyl)*-N,N-*dipropylacetamidine* 8c. The same procedure as for *8b* was followed. The

reaction mixture was heated at 210 °C for 26 h. Recrystallization from toluene–light petroleum (1:1) yielded 4.25 g (62 %) of *p*-nitroaniline, m.p. 145–149 °C. Toluene and light petroleum were then evaporated from the mother liquid and the remaining oil was distilled giving three products. 0.55 g *N,N*-dipropylacetamide (55–65 °C/0.1 mmHg); 1.4 g *p*-nitroacetanilide (16 %), b.p. 150–165 °C/0.09 mmHg, m.p. 195–210 °C; and 1.50 g (11 %) of the title compound. B.p. 148–151 °C/0.04 mmHg. n_D^{25} 1.6090. ^{1}H NMR δ ($CDCl_3$): 0.93 (6H, t), 1.37–2.10 (4H, m), 1.95 (3H, s), 3.35 (4H, m), 6.60–8.27 (4H, m). MS *m/e* (%): 263 (M^+, 48), 262 (15), 248 (3), 220 (30), 163 (97), 151 (36), 138 (53), 117 (57), 84 (87), 76 (30), 72 (66), 65 (36), 43 (33), 42 (100). Found: C 64.85; H 8.22; N 15.47. Calc. for $C_{14}H_{21}N_3O_2$: C 63.85; H 8.04; N 15.96.

N′-*(4-Ethoxyphenyl)*-N,N-*dipropylacetamidine* 8d. The same procedure as for *8b* was followed. The reaction mixture was heated for 26 h at 210 °C. B.p. 124–125 °C/0.05 mmHg, yield 8.2 g (63 %). n_D^{25} 1.5391. ^{1}H NMR δ ($CDCl_3$): 0.91 (6H, t), 1.37 (3H, t), 1.35–1.97 (4H, m), 1.84 (3H, s), 3.32 (4H, m), 3.98 (2H, q), 6.48–6.87 (4H, m). MS, *m/e* (%): 262 (M^+, 79), 162 (100), Anal. $C_{16}H_{26}N_2O$: C, H, N.

N′-*(4-Methylphenyl)*-N,N-*dipropylpropionamidine* 8e. The same procedure as in *8b* was followed. The reaction mixture was heated for 23½ h at 240 °C. Distillation gave 2.5 g of the title compound (21 %). B.p. 110–125 °C/0.08 mmHg. n_D^{25} 1.5330. ^{1}H NMR δ ($CDCl_3$): 0.95 (9H, m), 1.18–1.97 (4H, m), 2.10–2.50 (2H, m), 2.29 (3H, s), 3.28 (4H, m), 6.50–7.17 (4H, m). MS *m/e* (%): 246 (M^+, 32), 72 (100), 56 (32). Anal. $C_{16}H_{26}N_2$: C, H, N.

N′-*Phenyl*-N,N-*dipropylbenzamidine* 8f. 15 g P_2O_5 and 30.3 g dipropylamine were mixed and made homogeneous by stirring. 9.85 g benzanilide (0.05 mol) was added. The mixture was heated on an oil bath at 240 °C for 19 h. The reaction mixture was worked up as for *8b*. Benzanilide (2.60 g) crystallized from the residue. Distillation at 105–125 °C/0.04 mmHg of the remaining oil gave 8.6 g (61 %) of *8f*. n_D^{25} 1.5562. ^{1}H NMR δ ($CDCl_3$): 0.84 (6 H, t) 2.61 (4 H, m), 3.30 (4 H, t), 6.43–7.33 (10 H, m). MS *m/e* (%): 280 (M^+, 15), 104 (100). Found: C 80.93; H 9.08; N 9.82. Calc. for $C_{19}H_{24}N_2$: C 81.38; H 8.63; N 9.99.

2-Phenyliminopyrrolidine 7. 15 g P_2O_5 (0.105 mol) and 28 g aniline (0.3 mol) were mixed and made homogenous by stirring and gentle heating. 4.25 g α-pyrrolidone (0.05 mol) was added and the mixture was heated on an oil bath at 210 °C for 2 h. The mixture was worked up as for *8b*. Distillation at 110–210 °C/0.6 mmHg and subsequent recrystallization from cyclohexane gave white crystals. Yield 4.2 g (53 %); m.p. 112–113 °C, lit.[17] m.p. 114–115 °C.

REFERENCES

1. Chang, K.-M. and Knowles, C. O. *J. Agric. Food Chem. 25* (1977) 493.
2. Dittrich, V. *J. Econ. Entomol. 59* (1966) 889.
3. Duerr, D. and Pissiotas, G. *Ger. Offen.* 2,139,046; *Chem. Abstr. 77* (1972) 34167q.
4. Arndt, H. and Steinhausen, W. *Ger.* 1,172,081; *Chem. Abstr. 61* (1964) 11274d.
5. Bredereck, H., Gompper, R., Klemm, K. and Rempfer, H. *Chem. Ber. 92* (1959) 837.
6. Mandel, H. G. and Hill, A. J. *J. Am. Chem. Soc. 76* (1954) 3978.
7. Weiner, M. L. *J. Org. Chem. 25* (1960) 2245.
8. Neymeyer, J. L. *J. Pharm. Sci. 53* (1964) 1539.
9. Tayler, E. C. and Ehrhart, W. A. *J. Org. Chem. 28* (1963) 1108.
10. Pedersen, E. B., Vesterager, N. O. and Lawesson, S.-O. *Synthesis* (1972) 547.
11. Pedersen, E. B. *Acta Chem. Scand. B 31* (1977) 261.
12. Pedersen, E. B. and Carlsen, D. *Synthesis* (1978) 844.
13. Osbirk, A. and Pedersen, E. B. *Acta Chem. Scand. B 33* (1979) 313.
14. Gätzi, K. and Fischer, H. *Swiss* 563109; *Chem. Abstr. 83* (1975) 189327q.
15. Pedersen, E. B. and Jacobsen, J. P. *J. Chem. Soc. Perkin Trans. 2* (1979) 1477.
16. DeWolfe, R. H. *J. Am. Chem. Soc. 86* (1964) 864.
17. Bredereck, H. and Bredereck, K. *Chem. Ber. 94* (1961) 2278.
18. *Report from CIBA-GEIGY*, Basel 1979.
19. Larizza, A., Brancaccio, G. and Lettieri, G. *J. Org. Chem. 29* (1964) 3697.
20. Tapszergyar, E. G. *French* 1,568,957; *Chem. Abstr. 72* (1970) 121376x.
21. Dousse, R. and Nebel, R. *Ger. Offen.* 2,708,616; *Chem. Abstr. 88* (1978) 120818m.

Received January 10, 1980.