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Synthesis of *trans*-N-2-aryl(heteryl)ethenamidines[+]

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Abstract. 2-Amino-2-arylethylamides 1 carrying electron-donating substituents in the *para* position are transformed by hot $POCl_3$ to the the title compounds 2, presumably via iminochlorides 7 and imidazolium derivatives 8. Amides lacking this para-substituent give rise to chloroamidines 11 under these conditions. *m*-Methoxyphenethylamide 1t and $POCl_3$ form, besides 11f, an isoquinoline derivative 3. The involvement of an imidazolium compound 8 in the formation of ethenamidines has been verified by the synthesis of 2a from 10. Reaction of amide 1w with PCl_5 in the cold leads to, besides the chloroamidine 11c, the *cis*-ethenamidine 12 which equilibrates with the *trans*-isomer 2o in hot toluene. Thienylethyl urea 13 is converted by hot $POCl_3$ to the imidazoline 16, while phenylpropylamide 17 forms only the iminochloride 18a.

Keywords. Ethenamidine; α-chloroamidine; anomalous Bischler–Napieralski reaction; imidazoline; 2-azabutadienes.

1. Introduction

Azabutadienes form a class of interesting dienophiles, which are acquiring increasing theoretical and practical importance in (4 + 2) cycloaddition reactions (McKillop and Boulton 1984; Nagarajan *et al* 1988). Some years ago, we reported for the first time, a facile and versatile synthesis of a novel class of 2-azabutadienes, viz. *trans*-N-(β-styryl)amidines or 2-arylethenamidines 2 from 2-aryl-2-aminoethylamides 1 under Bischler–Napieralski conditions, along with structure proof and a speculative mechanism (Advani *et al* 1968). Subsequently a number of syntheses of such azabutadienes have appeared in the literature: Ring opening of 5-substituted-4-chloro-2-phenylpyrimidines by potassium amide in liquid ammonia (Va Meeteren and Van der Plas 1971); Grignard reactions or action of organolithium compounds on benzonitriles (Marxer 1972; Cook and Wakefield 1980; Compagnon *et al* 1982; Cook *et al* 1983); Dimerisation of nitriles having *alpha* hydrogen in the presence of hydrogen chloride

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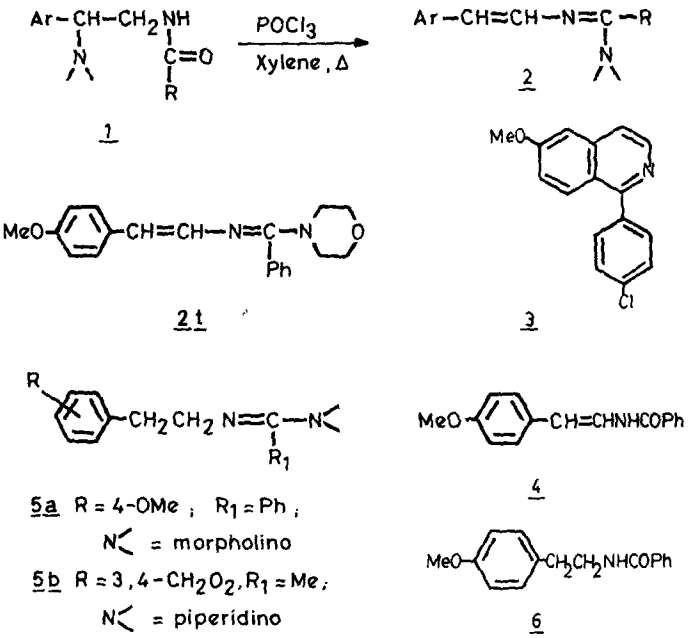
(Yanagida *et al* 1973; Yanagida 1975); Base treatment of N-(*trans*-styrylsulphonyl) amidines (Matier and Comer 1974, 1975, 1977); from N-vinyl-substituted chloroform-amidines (Ried and Erle 1979); Acid decomposition of 5-amino-1-vinyl-4,5-dihydro-1H-1,2,3-triazole (Ito *et al* 1983); Reaction of 2-aryl-4-arylidene-2-oxazolin-5-ones with nucleophiles (Islam *et al* 1983) and reaction of electron-rich aromatics like indoles with 3-dimethylamino-2-(dimethylaminomethyleneamino) acrylic esters (Biere 1983). The last class of ethenamidines has been fruitfully cyclized to *beta*-carbolines.

Since our synthesis offered access to a variety of these azadienes, we have studied it more extensively, probing its generality and limitations and trying to gain insight into its mechanism. We describe in this paper our newer findings along with full details for the syntheses of styrylamidines.

2. Results and discussion

Aryl (heteryl) ethylenediamines obtained by LAH reduction of Strecker nitriles (Rajagopalan and Advani 1965), were converted to the acyl derivatives 1 (scheme 1, table 1) which upon heating with $POCl_3$ in toluene or xylene under reflux generally afforded styryl amidines 2 (table 2). Reaction was facile but was not optimised (15–72% yield) in those cases where Ar was an aryl group with an electron-donating group in the para position to the side-chain or a 2-thienyl group. 3,4-Methylenedioxy- and 3,4-dimethoxyphenyl compounds also responded well, but in the case of one derivative, 1f of the latter group, reaction failed to occur. Likewise, unsubstituted 2-phenyl-2-aminoethyl amides, e.g. 1e, did not form the styryl amidine. Further variation of substituents in the aromatic nucleus was not attempted. It is possible that the R group in 1 has a role in the formation of the styryl amidine. Thus while benzamides



Scheme 1.

Table 1. 2-Aryl-2-aminoethyl amides (1).

Compound no.	Ar	R	Yield (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd.) (%) C	H	N
>N = MeNH									
1a, HCl	3,4-diOMeC$_6$H$_3$	Ph	70	$C_{18}H_{23}ClN_2O_3$	EtOAc	144–5(d)	61·31 (61·62)	6·90 (6·61)	7·73 (8·00)
1a	3,4-diOMeC$_6$H$_3$	Ph	85	$C_{18}H_{22}N_2O_3$	EtOAc	128–9	68·52 (68·77)	7·25 (7·05)	8·98 (8·91)
>N = Me$_2$N									
1b	3,4-diOMe–C$_6$H$_3$	4-ClC$_6$H$_4$	79	$C_{19}H_{23}ClN_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	126–7	63·21 (62·89)	6·52 (6·39)	7·48 (7·72)
>N = MeNCH$_2$Ph									
1c	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	66	$C_{25}H_{27}ClN_2O_3$	EtOH–Et$_2$O	119–20	68·24 (68·40)	6·36 (6·20)	6·67 (6·38)
>N = pyrrolidino									
1d	Ph	4-NO$_2$C$_6$H$_4$	61	$C_{19}H_{21}N_3O_3$	C$_6$H$_6$–C$_6$H$_{14}$	135–7	66·90 (67·24)	6·33 (6·24)	12·57 (12·38)
1e	Ph	4-ClC$_6$H$_4$–OCH$_2$	72	$C_{20}H_{23}ClN_2O_2$	—	oil	—	—	—
1f	3,4-diOMeC$_6$H$_3$	Ph	69	$C_{21}H_{26}N_2O_3$	EtOH–H$_2$O	139–40	70·82 (71·16)	7·62 (7·39)	7·93 (7·90)
1g	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	74	$C_{21}H_{25}ClN_2O_3$	EtOAc–C$_6$H$_{14}$	178–80	65·10 (64·86)	6·65 (6·48)	7·31 (7·20)
1h	3,4-diOMeC$_6$H$_3$	2,4-diClC$_6$H$_3$	76	$C_{21}H_{24}Cl_2N_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	124–6	59·44 (59·58)	5·90 (5·72)	— —
1i	3,4-diOMeC$_6$H$_3$	3,4-CH$_2$O$_2$C$_6$H$_3$	69	$C_{22}H_{26}N_2O_5$	EtOAc	142–3	66·28 (66·31)	6·70 (6·58)	— —
1j	3,4-diOMeC$_6$H$_3$	PhCH$_2$	60	$C_{22}H_{28}N_2O_3$	EtOAc–C$_6$H$_{14}$	99–101	72·09 (71·71)	7·51 (7·66)	— —

(Continued)

Table 1. (*Continued*)

Compound no.	Ar	R	Yield (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd.) (%) C	H	N
1k	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$CH$_2$CH$_2$	54	$C_{23}H_{29}ClN_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	103–5	66·55 (66·24)	6·78 (7·01)	6·45 (6·72)
1l	3,4-diOMeC$_6$H$_3$	4-NO$_2$C$_6$H$_4$CH$_2$CH$_2$	67	$C_{23}H_{29}N_3O_5$	—	oil	—	—	—
1m	3,4-CH$_2$O$_2$C$_6$H$_3$	Me	78	$C_{15}H_{20}N_2O_3$	EtOAc–C$_6$H$_{14}$	113–4	64·93 (65·19)	7·14 (7·30)	9·98 (10·14)
1n	3,4-CH$_2$O$_2$C$_6$H$_3$	3,4-CH$_2$O$_2$·C$_6$H$_3$	80	$C_{21}H_{22}N_2O_5$	C$_6$H$_6$–C$_6$H$_{14}$	107–9	65·58 (65·95)	5·96 (5·80)	7·04 (7·33)
1o	3,4-CH$_2$O$_2$C$_6$H$_3$	4-ClC$_6$H$_4$OCH$_2$	69	$C_{21}H_{23}ClN_2O_4$	EtOH	139–41	62·66 (62·60)	5·90 (5·75)	6·87 (6·95)
1p	3,4-CH$_2$O$_2$C$_6$H$_3$	4-ClC$_6$H$_4$CH$_2$CH$_2$	60	$C_{22}H_{25}ClN_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	145–6	65·91 (66·18)	6·28 (6·40)	— —
>N = piperidino									
1q	Ph	4-ClC$_6$H$_4$	65	$C_{20}H_{23}ClN_2O$	EtOH–H$_2$O	142–3	70·20 (70·09)	6·68 (6·71)	8·48 (8·18)
1r	Ph	4-ClC$_6$H$_4$·OCH$_2$	76	$C_{21}H_{25}ClN_2O_2$	C$_6$H$_{14}$	100–2	67·32 (67·64)	6·51 (6·76)	7·18 (7·51)
1s	3-MeOC$_6$H$_4$	Ph	64	$C_{21}H_{26}N_2O_2$	EtOH–H$_2$O	92–3	74·27 (74·52)	7·85 (7·74)	8·01 (8·28)
1t	3-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	80	$C_{21}H_{25}ClN_2O_2$	EtOH–H$_2$O	132–3	67·51 (67·64)	6·93 (6·76)	7·71 (7·51)
1u	3,4-diOMeC$_6$H$_3$	Me	71	$C_{17}H_{26}N_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	127–8	66·18 (66·66)	8·80 (8·86)	9·17 9·15)
1v	3,4-diOMeC$_6$H$_3$	Ph	79	$C_{22}H_{28}N_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	125–6	71·71 (71·71)	7·88 (7·66)	7·98 (7·60)
1w	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	68	$C_{22}H_{27}ClN_2O_3$	C$_6$H$_6$–C$_6$H$_{14}$	140–1	65·32 (65·58)	6·97 (6·75)	6·72 (6·95)

(*continued*)

Table 1. *(Continued)*

Compound no.	Ar	R	Yield (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd.) (%) C	H	N
1x	3,4-$CH_2O_2C_6H_3$	Me	76	$C_{16}H_{22}N_2O_3$	—	oil	— —	— —	— —
1y	3,4-$CH_2O_2C_6H_3$	4-$NO_2C_6H_4$	73	$C_{21}H_{23}N_3O_5$	EtOH	92–3	62·96 (63·46)	5·93 (5·83)	10·36 (10·58)
1z	3,4-CH_2O_2·C_6H_3	4-$NO_2C_6H_4CH_2CH_2$	62	$C_{23}H_{27}N_3O_5$	C_6H_6–C_6H_{14}	106–8	64·77 (64·92)	6·69 (6·40)	9·62 (9·88)
1aa	2-Thienyl	4-ClC_6H_4	72	$C_{18}H_{21}ClN_2OS$	C_6H_6–C_6H_{14}	155–6	61·80 (61·98)	6·30 (6·07)	— —
1bb	2-Thienyl	$C_6H_5CH_2$	61	$C_{19}H_{24}N_2OS$	C_6H_{14}	92–5	69·40 (69·49)	7·44 (7·36)	— —
>N = morpholino									
1cc	4-MeO·C_6H_4	Ph	76	$C_{20}H_{24}N_2O_3$	—	oil	— —	— —	— —
1dd	4-MeO·C_6H_4	4-$ClC_6H_4OCH_2$	67	$C_{21}H_{25}ClN_2O_4$	C_6H_6–C_6H_{14}	119–21	62·02 (62·29)	6·37 (6·22)	7·02 (6·92)
1ee	4-MeO·C_6H_4	4-NO_2·C_6H_4	63	$C_{20}H_{23}N_3O_5$	C_6H_6–C_6H_{14}	142–4	62·15 (62·30)	6·19 (6·02)	11·30 (10·90)

Table 2. *Trans*-2-aryl ethenamidines (2).

Compound No.	Ar	R	Yield (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd.) (%) C	H	N
>N = Me₂N									
2a	2,4-diOMeC$_6$H$_3$	Ph	15	$C_{19}H_{22}N_2O_2$	—	Oil	—	—	—
2b	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	20	$C_{19}H_{21}ClN_2O_2$	Et_2O-C_6H_{14}	114–5	66·30 (66·17)	6·47 (6·14)	8·41 (8·12)
>N = MeNCH₂Ph									
2c	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	22	$C_{25}H_{25}ClN_2O_2$	EtOH	125–6	71·05 (71·33)	5·67 (5·99)	6·27 (6·65)
>N = pyrrolidino									
2d	Ph	4-NO$_2$C$_6$H$_4$	27	$C_{19}H_{19}N_3O_2$	C_6H_6-C_6H_{14}	183–5	70·93 (71·01)	6·47 (5·96)	13·30 (13·08)
2e	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$	15	$C_{21}H_{23}ClN_2O_2$	C_6H_{14}	112–3	68·11 (68·00)	6·48 (6·25)	7·93 (7·55)
2f	3,4-diOMeC$_6$H$_3$	2,4-diClC$_6$H$_3$	40	$C_{21}H_{22}Cl_2N_2O_2$	C_6H_{14}	100–2	62·61 (62·22)	5·48 (5·47)	— —
2g	3,4-diOMeC$_6$H$_3$	3,4-CH$_2$O$_2$·C$_6$H$_3$	61	$C_{22}H_{24}N_2O_4$	EtOAc-C_6H_{14}	145–6	69·33 (69·45)	6·56 (6·36)	7·38 (7·36)
2h	3,4-diOMeC$_6$H$_3$	PhCH$_2$	53	$C_{22}H_{26}N_2O_2$	C_6H_6-C_6H_{14}	100–2	75·50 (75·40)	7·69 (7·48)	— —
2i	3,4-diOMeC$_6$H$_3$	4-ClC$_6$H$_4$CH$_2$CH$_2$	49	$C_{23}H_{27}ClN_2O_2$	C_6H_6-C_6H_{14}	112–3	69·04 (69·23)	6·97 (6·82)	7·08 (7·03)
2j	3,4-diOMeC$_6$H$_3$	4-NO$_2$C$_6$H$_4$CH$_2$CH$_2$	37	$C_{23}H_{27}N_3O_4$	C_6H_6-C_6H_{14}	121–4	67·72 (67·46)	6·73 (6·65)	10·16 (10·26)
2k	3,4-CH$_2$O$_2$C$_6$H$_3$	Me	50	$C_{15}H_{18}N_2O_2$	C_6H_6-C_6H_{14}	117–9	69·55 (69·74)	7·13 (7·02)	10·61 (10·85)
2k HCl	3,4-CH$_2$O$_2$C$_6$H$_3$	Me	—	$C_{15}H_{19}ClN_2O_2$	MeOH-Et_2O	266–8	61·21 (61·11)	6·75 (6·50)	9·87 (9·50)

(Continued)

Table 2. (*Continued*)

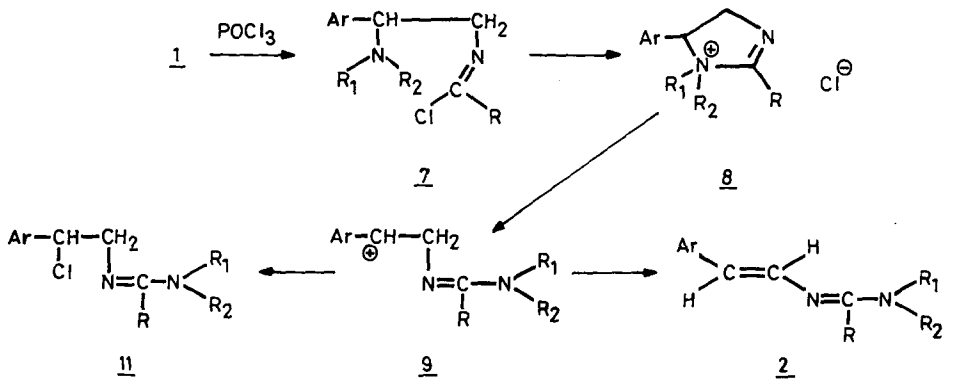
Compound no.	Ar	R	Yield (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd.) (%) C	H	N
2l	3,4-$CH_2O_2C_6H_3$	3,4-$CH_2O_2C_6H_3$	31	$C_{21}H_{20}N_2O_4$	C_6H_6–C_6H_{14}	138–41	69·37 (69·21)	5·80 (5·53)	7·46 (7·69)
2m	3,4-$CH_2O_2C_6H_3$	4-$ClC_6H_4OCH_2$	38	$C_{21}H_{21}ClN_2O_3$	EtOAc–C_6H_{14}	153–5	65·65 (65·53)	5·45 (5·50)	7·54 (7·28)
2n	3,4-$CH_2O_2C_6H_3$	4-$ClC_6H_4CH_2CH_2$	33	$C_{22}H_{23}ClN_2O_2$	C_6H_6–C_6H_{14}	93–5	68·88 (69·01)	6·24 (6·05)	7·45 (7·32)
>N = piperidino									
2o	3,4-di$OMeC_6H_3$	4-ClC_6H_4	57	$C_{22}H_{25}ClN_2O_2$	C_6H_{14}	103–5	68·44 (68·65)	6·87 (6·55)	7·32 (7·28)
2p	3,4-$CH_2O_2C_6H_3$	Me	70	$C_{16}H_{20}N_2O_2$	EtOAc–C_6H_{14}	93–5	70·53 (70·56)	7·52 (7·40)	— —
2q	3,4-$CH_2O_2C_6H_3$	4-$NO_2C_6H_4$	51	$C_{21}H_{21}N_3O_4$	EtOAc	184–5	66·89 (66·48)	5·56 (5·58)	11·03 (11·03)
2r	2-Thienyl	4-ClC_6H_4	61	$C_{18}H_{19}ClN_2S$	EtOAc	142–4	65·63 (65·37)	6·15 (5·79)	— —
2s	2-Thienyl	$PhCH_2$	72	$C_{19}H_{22}N_2S$	C_6H_6–C_6H_{14}	111–4	73·36 (73·52)	7·37 (7·14)	9·18 (9·03)
>N = morpholino									
2t	4-$MeOC_6H_4$	Ph	57	$C_{20}H_{22}N_2O_2$	C_6H_{14}	93–5	74·77 (74·51)	6·92 (6·88)	9·00 (8·89)
2u	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	61	$C_{20}H_{21}N_3O_4$	C_6H_6–C_6H_{14}	165–6	65·38 (65·53)	5·76 (5·89)	11·44 (11·34)
2v	4-$MeOC_6H_4$	4-$ClC_6H_4OCH_2$	37	$C_{21}H_{23}ClN_2O_3$	Et_2O–C_6H_{14}	135–7	65·54 (65·18)	6·16 (5·99)	7·08 (7·24)

1f and 1e, 1q and 1r did not afford styryl amidines, the *p*-chlorobenzamide 1g and *p*-nitrobenzamide 1d did, although in rather low yields. In the case of the *m*-methoxy-phenethylamide 1t, 1-(*p*-chlorophenyl)-6-methoxyisoquinoline 3 was isolated in moderate yield, its structure being supported by analytical and spectral (NMR, Mass) data.

In this study, five different >N groups were used successfully; viz. dimethylamine, methylbenzylamine, morpholine, pyrrolidine and piperidine. The last two have been employed extensively and the first three meagrely. Nevertheless from available results, it appears that wide variations of >N could be permissible. From the limited observations of substituents in Ar in 1 it can be tentatively concluded that a single electron-releasing substituent at the meta position would be detrimental to the formation of styryl amidines.

Proof of structures of amidines 2t and 2p has been given in the earlier communication (Advani *et al* 1968). Apart from NMR spectral data, the proof rested on mild hydrolysis of 2t to known N-β-(*p*-methoxystyryl) benzamide (4) and catalytic hydrogenation to 5a which was independently synthesised from 6. Styryl amidine 2p was likewise hydrogenated to 5b; while with hot mineral acid and 2p, 2-(3,4-methylenedioxyphenyl)6,7-methylenedioxynaphthalene resulted through the presumed intermediacy of 3,4-methylenedioxyphenylacetaldehyde.

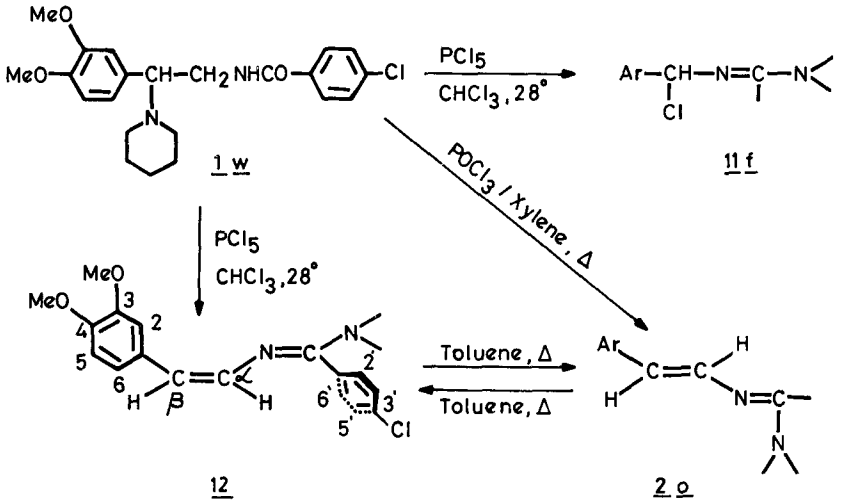
In our earlier paper we had suggested the mechanism depicted in scheme 2. We have synthesised an example of 8 (Ar = 3,4-dimethoxyphenyl, R = phenyl, $R_1 = R_2$ = methyl) as the iodide from the corresponding monomethyl imidazoline 10 (prepared from 1a and $POCl_3$). Heating 8 in toluene alone or in the presence of $POCl_3$ and work up, followed by chromatography, gave the *trans* ethenamidine 2a as an oil, showing the typical AB quartet at 6·80 and 6·35 ppm.



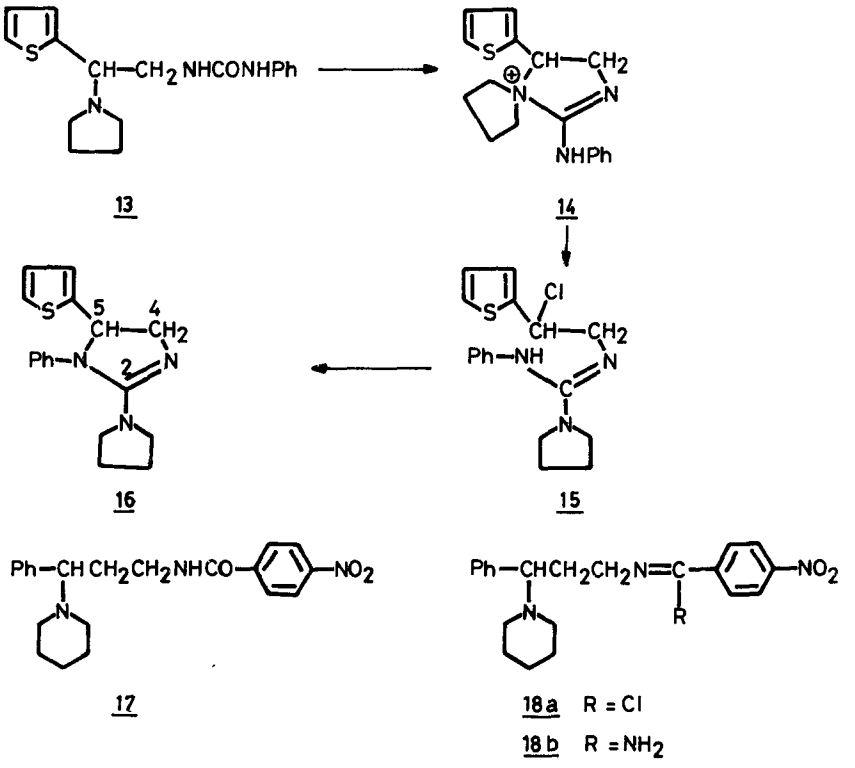
Scheme 2.

Exposure of amide 1w to phosphorous pentachloride in cold $CHCl_3$ and chromatography of the product gave two products one of which was the major slow-moving chloro derivative 11f. The faster-moving minor component obtained in low yield had m.p. 173–4°, and was isomeric with the *trans*-amidine 2o (AB quartet at 6·83 and 6·38 ppm; $J = 14$ Hz), formed from 1w using $POCl_3$ in hot xylene and was identified as the *cis*-amidine 12 (AB quartet at 6·27 and 5·40 ppm, $J = 8$ Hz). Treatment of either with hot toluene gave an equilibrium mixture of the two, but in the presence of $POCl_3$ there was practically no conversion of 2o to 12. The chloro amidine 11f was again transformed to 2o by hot $POCl_3$. On the

other hand, amides 1e and 1q–1t gave only analogues of 11f, considerable amounts of starting materials being recovered in some cases. It is worth noting that the only other reported synthesis of such α-chloroalkylideneiminium salts involves the opening of interesting dichloroaziridines with amines (Ichimura and Ohta 1966;



Scheme 3.



Scheme 4.

Kantlehner 1979). Our method appears to be more versatile and hence its potential merits further exploration.

It is thus possible to speculate that in the chain of events leading to the transformation of 1 to 2, iminochloride 7, imidazoline derivative 8, chloroamidine 11 and *cis*-amidines of the type 12 may be involved (scheme 3). The *cis*-amidine may be the product of kinetic control and isomerises to the *trans*-amidine which is more stable thermodynamically. In the case of amides 1e and 1q–1s and to some extent 1t and 1w, the chloro amidines 11 do not suffer elimination of HCl. 1t evidently partly undergoes Bischler–Napieralski reaction through 7 (or equivalent) to a dihydroisoquinoline which aromatises by loss of piperidine to form 3. Alternative mechanisms are possible such as cyclisation of 11f to a tetrahydroisoquinoline followed by elimination of chloride and amine or of 2 followed by loss of amine. However, these are considered unlikely.

The study was extended in two directions: (a) Reaction of phenylurea 13 with $POCl_3$ in hot solution afforded the imidazoline 16, presumably through intermediates 14 and 15 analogous to 8 and 11; (b) 3-Phenyl-3-aminopropyl amide 17 under these conditions afforded only imino chloride 18a as evidenced by conversion to amidine 18b (scheme 4).

3. Experimental

All melting points are uncorrected. PMR chemical shifts are on the δ scale in ppm downfield from TMS.

3.1 *2-Amino-2-aryl (heteroaryl)ethylamides 1*

General procedure: Acid chloride (0·11 mol) was added dropwise to a solution of amine (0·1 mol) in dry benzene (100 ml) with stirring and the mixture was further stirred with the exclusion of atmospheric moisture for another 30 min. The benzene layer was separated, washed with 10% sodium hydroxide solution (150 ml) and then with water (2 × 150 ml). The organic extract was dried with sodium sulphate and evaporated under reduced pressure; the crude reaction products 1 (table 1) were crystallised from an ethanol or a benzene–hexane mixture. A few were oils. Amide 1a was obtained as its HCl salt by hydrogenation of the chlorobenzamide 1c (5 g in 50 ml ethyl acetate) at atmospheric pressure and room temperature using 10% palladium-on-charcoal catalyst (0·5 g) till the absorption of hydrogen ceased (2 molar equivalent). The free base was obtained from the HCl salt by neutralisation of an aqueous solution with sodium bicarbonate and extraction with methylene chloride.

3.2 *Trans-N-2-aryl(heteroaryl)ethenamidines 2*

General procedure: Phosphorous oxychloride (20 ml) was added to a solution of 1 (5 g) in dry toluene or xylene (30 ml) and the mixture was refluxed with the exclusion of atmospheric moisture for 2·5 h. The volatile components were removed under reduced pressure. The residue was stirred with ice water (100 ml) and made alkaline with 10% NaOH solution (50 ml). The resulting mixture was extracted with chloroform. The chloroform layer was separated and washed with water (2 × 100 ml). The organic extract was dried with sodium sulphate and evaporated under reduced pressure. In

general, the crude reaction products (table 2) were purified by recrystallization from a benzene–hexane mixture. In some cases preliminary purification on basic alumina was necessary (elution with benzene).

3.3 *N-(2-aryl-2-chloro)ethylamidines 11*

General procedure: Amide 1r (7 g), $POCl_3$ (20 ml) and toluene (50 ml) were heated under reflux for 3 h. Excess $POCl_3$ and solvent were removed *in vacuo*. The residue was treated with ice and made ammoniacal. Extraction with ether, washing of the extract with water, drying and evaporation gave 2-chloroethylamidine 11b (6·8 g) as an oil; ^{1}H NMR($CDCl_3$) 5·0 (CHCl, *t*, $J = 7$ Hz); 4·4 (O–CH_2, *s*); 3·83 CH–CH_2, *d*, $J = 7$ Hz); 3·25 (=C–N$(CH_2)_2$, broad *s*); 1·45 ($CH_2CH_2CH_2$, broad *s*), characterised as the picrate, m.p. 159–161°. 11a, 11c and 11d were prepared similarly (table 3).

p-Chlorobenzamide 1t (2·23 g) was heated with $POCl_3$ (10 ml) in xylene (25 ml) under reflux for 5 h and the product worked up as before and subjected to chromatography on silica. Elution was carried out with $CHCl_3$ and 50 ml fractions collected to give first 1-(*p*-chlorophenyl)-6-methoxyisoquinoline 3, (0·85 g), m.p. 146–7° (from hexane–$CHCl_3$) (Found: C, 71·43, H, 4·78; N, 5·52. M^+ at *m/z* 269, 271. $C_{16}H_{12}ClNO$ requires C, 71·24; H, 4·48; N, 5·52%; *M*, 269, 271); ^{1}H NMR ($CDCl_3$): 8·54 (C–3 H, *d*, $J = 5$ Hz); 3·95 (OMe, *s*) and other aromatic proton signals; subsequently crude unreacted amide 1t (0·85 g) and chloroethylamidine 3e (0·5 g) were obtained (table 3).

3.4 *Cis- and trans-styrylamidines 12 and 2o*

p-Chlorobenzamide 1w (2g) was left with PCl_5 (4 g) in dry chloroform (30 ml) for 6 days at 28°. Solvent was evaporated off and the residue treated with ice cold water and ammonia. Extraction with ether gave gummy material (2 g), from which was obtained by trituration with alcohol, the *cis*-styryl amidine 12 (0·2 g). The mother liquor was evaporated and the residue dissolved in benzene. The solution was poured on to a column of silica gel and elution done beginning with benzene–hexane (3:2) through benzene, benzene–chloroform mixture and finally chloroform. Earlier fractions gave a mixture of mostly 12 with some *trans*-amidine 2o (0·2 g). Then pure 12 (0·2 g), recovered amide 1w (0·6 g) and finally gummy chloroethylamidine 3f (0·8 g) were obtained. 12 was crystallized from alcohol; m.p. 173–174° (Found C, 68·39; H, 6·58; N, 7·32. $C_{22}H_{25}ClN_2O_2$ requires C, 68·65; H, 6·55; N, 7·28%); ^{1}H NMR ($CDCl_3$): 8·15 (C-2 H, *d*, $J = 2$ Hz), 7·50, 7·16 (C-2′–C-6′ H, 2*m*); 7·18 (C-6 H, *dd*, $J = 2$, 8 Hz); 6·80 (C-5 H, *d*, $J = 8$ Hz), 6·27 (C–β H, *d*, $J = 8$ Hz); 5·40 (C–α H, *d*, $J = 8$ Hz); 3·95 (OCH_3, *s*); 3·88 (OCH_3, *s*); 3·50 (CH_2NCH_2, unresolved *m*); 1·65 ($CH_2CH_2CH_2$, unresolved *m*). *Trans* amidine 2o m.p. 103–5°; ^{1}H NMR ($CDCl_3$): 7·50, 7·18 (C-2′–C-6′ H, *m*); 6·73 (C-2, C-5, C-6 H, *m*); 6·83 (C–βH, *d*, $J = 14$ Hz); 6·38 (C–αH, *d*, $J = 14$ Hz); 3·82 (OCH_3, *s*), 3·80 (OCH_3, *s*), 3·40 (CH_2NCH_2, broad *s*); 1·60 ($CH_2CH_2CH_2$, broad *s*). Chloroethyl amidine 11f, gum; ^{1}H NMR ($CDCl_3$): 5·0 ppm (CH–Cl).

3.5 *Formation of styryl amidine 2a from imidazoline 10*

A solution of amide 1a (1 g) in toluene (25 ml) was heated under reflux with $POCl_3$ (15 ml) for 7 h. Solvent and reagent were distilled off. The residue was treated with

Table 3. 2-Aryl-2-chloroethylamidines (11).

Compound no.	R	R_1	Yield[a] (%)	Mol. formula	Crystallised from	m.p. (°C)	Found (Calcd) (%) C	H	N	Cl
>N = pyrrolidino										
11a (maleate)	H	4-$ClC_6H_4OCH_2$	78	$C_{24}H_{25}ClN_2O_5$	MeOH–Et_2O	110–2	62·82 (63·02)	5·21 (5·52)	5·85 (6·13)	7·37 (7·76)
>N = piperidino										
11b (picrate)	H	4-$ClC_6H_4OCH_2$	95	$C_{27}H_{27}Cl_2N_5O_8$	EtOH	159–61	52·70 (52·26)	4·62 (4·39)	10·83 (11·29)	12·03 (11·43)
11c (picrate)	H	4-ClC_6H_4	82	$C_{26}H_{25}Cl_2N_5O_7$	EtOH	166–8	53·29 (52·89)	4·57 (4·27)	12·22 (11·86)	12·19 (12·00)
11d (picrate)	3-MeO	Ph	35	$C_{27}H_{28}ClN_5O_8$	MeOH	173–4	54·90 (55·34)	4·51 (4·82)	12·27 (12·09)	6·72 (6·05)
11e	3-MeO	4-ClC_6H_4	25	$C_{21}H_{24}Cl_2N_2O$	—	gum	— —	— —	— —	18·46 (18·13)
11f	3,4-diMeO	4-ClC_6H_4	38	$C_{22}H_{26}Cl_2N_2O_2$	—	gum	— —	— —	— —	17·75 (16·83)

[a]of the crude chloro compounds, with the exception of 11a.

ice and aqueous NaOH and extracted with chloroform. The chloroform layer was evaporated and the residual oil chromatographed over silica gel (30 g). Elution was done first with chloroform–5% methanol, approximately 50 ml fractions being collected. After 11 such fractions, chloroform–5% methanol was used to elute the desired 1-methyl-2-phenyl-5-(3,4-dimethoxyphenyl)imidazoline (10) as an oil (0·16 g), ^{1}H NMR ($CDCl_3$) 7·20–7·85 (5 aromatic H, *m*), 7·0 (3 aromatic H, *s*), 5·0 (C-5 H, *t*, $J = 10$ Hz), 4·35 (C-4H, *t*, $J = 10$ Hz), 3·93 (OCH_3, *s*), 3·90 (OCH_3, *s*), 3·75 (C-4 H, *t*, $J = 10$ Hz); 2·85 (NCH_3, *s*). This oil (0·1 g) was heated with methyl iodide (2 ml) in methanol (3 ml) under reflux for 60 h and the solution evaporated. Toluene (6 ml) was added to the gummy methiodide and the mixture heated under reflux for 16 h. Then the solvent was evaporated off and the residue worked up as for 2. The crude product was filtered through a short column of silica gel to give 2a as an oil, M^+ at *m/z* 310; ^{1}H NMR ($CDCl_3$): 6·80, 6·35 (2*d*, $J = 14$ Hz).

3.6 *Phenyl urea 13*

2-(2-Thienyl)-2-(N-pyrrolidinyl) ethyl amine (Rajagopalan and Advani 1965) (3·9 g) was mixed with phenyl isocyanate (2.4 g) in benzene (10 ml). After the initial exothermic reaction subsided, the solution was warmed on a water bath for 15 min, cooled and diluted with hexane. The crystalline precipitate of 13 was filtered off and recrystallised from benzene–hexane; 5·6 g, m.p. 106–8° (Found: C, 65·03; H, 7·05; N, 13·27%. $C_{17}H_{21}N_3OS$ requires C, 64·74; H, 6·71; N, 13·35%). ^{1}H NMR: ($CDCl_3$) 7·70 (PhNH, broad *s*); 6·70–7·50 (8 aromatic H, *m*); 5·80 (CH_2NH, *t*, $J = 5$ Hz), 3·15–4·00 (CH_2CH), 2·50 (H_2C–N–CH_2, unresolved broad *t*), 1·67 (CH_2CH_2, unresolved broad *t*).

3.7 *Action of $POCl_3$ on urea 13 – formation of imidazoline 16*

Urea 13 (2 g) and $POCl_3$ (10 ml) were heated together in toluene (10 ml) for 3 h. The basic product (1·8 g) was worked up as usual and characterised as the HNO_3 salt of 16 (0·7 g), m.p. 206–8° (d) (Found: C, 56·74; H, 5·83; N, 15·78. $C_{17}H_{20}N_4O_3S$ requires C, 56·66; H, 5·59; N, 15·59%). $\nu_{C=N}$ 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6): 6·80–7·80 (8 aromatic H, *m*); 5·80 (C-5 H, *t*, $J = 9$ Hz); 4·30 (C-4 H, *t*, $J = 9$ Hz); 3·75 (C-4 H, *t*, $J = 9$ Hz); 3·20 (H_2CNCH_2, *m*); 1·80 (CH_2CH_2, *m*). The free base was liberated and extracted with ether; oil: M^+ at *m/z* 297 (calculated for $C_{17}H_{19}N_3S$, *M* 297); $\nu_{C=N}$ 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): 6·70–7·50 (8 aromatic H, *m*); 5·00 (C-5 H, *d* × *d*, $J = 5$, 9 Hz); 4·33 (C-4 H, *d* × *d*, $J = 13$, 9 Hz); 3·75 (C-4 H, *d* × *d*, $J = 13$, 5 Hz); 3·25 (CH_2NCH_2; *m*); 1·80 (CH_2CH_2, *m*).

3.8 *3-Phenyl-3-(N-piperidino) propylamine derivative 17*

Cinnamamide (44 g) and piperidine (51 g) were heated together in toluene (300 ml) with Triton B catalyst (4·5 ml) for 24 h to give 3-phenyl-3-(N-piperidino) propionamide (12·5 g), m.p. 156–7° (Found: C, 72·39; H, 8·84; N, 12·17. $C_{14}H_{20}N_2O$ requires C, 72·38; H, 8·68; N, 12·06%). Reduction of the amide (8 g) in THF (150 ml) using LAH (4.5 g) in THF (50 ml) and working up the basic product as usual gave the propylamine as an oil (6·3 g). This was stirred with *p*-nitrobenzoyl chloride (5·6 g) in ether (75 ml) and water (50 ml) containing $NaHCO_3$ (6 g) to give the crude *p*-nitrobenzamide (4·5 g)

which was filtered through a column of silica gel to give pure 17 (1·5 g), m.p. 105–6° (Found: C, 68·47; H, 6·91. $C_{21}H_{25}N_3O_3$ requires C, 68·64; H, 6·86%), yielding a picrate, m.p. 182–4° (from acetone–hexane) (Found: C, 54·57; H, 5·00; N, 14·39. $C_{27}H_{28}N_6O_{10}$ requires C, 54·36; H, 4·73; N, 14·09%). ^{1}H NMR ($CDCl_3$) 8·20, 7·90 ($NO_2C_6\underline{H}_4$, 2*m*) 7·25 ($C_6\underline{H}_5$, *s*) 3.35–3·90 (NC$\underline{H}$, C$\underline{H}_2$N, *m*), 2·10–2·80 (C$\underline{H}_2$N–C$\underline{H}_2$, *m*), 2·15 (C–C$\underline{H}_2$–C, *q*), 1·0–1·8 (C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$, *m*).

3.9 *Action of $POCl_3$ on propylamide 17 – formation of iminochloride 18a and ammonolysis to 18b*

Amide 17 (1·2 g) and $POCl_3$ (10 ml) were heated together under reflux in xylene (15 ml) for 4 h. The product was worked up as usual to give 18a as a resinous gum (0·9 g) which was stirred with liquor ammonia and the mixture was extracted with methylene chloride. Methylene chloride extract on evaporation under reduced pressure gave a gum which was taken up in MeOH and treated with picric acid; the gummy picrate was crystallised from acetone–methanol removing considerable resinous fractions to give a dipicrate, which was recrystallised from acetone–methanol; 250 mg, m.p. 239–240° (Found: C, 48·01; H, 4·00; N, 16·96; Cl, 0. $C_{33}H_{32}N_{10}O_{16}$ requires C, 48·04; H, 3·88; N, 16·99%). The free base 18b was an oil; ^{1}H NMR ($CDCl_3$) 8·23, 7·80 (2*m*, $NO_2C_6\underline{H}_4$); 7·25 (*m*, $C_6\underline{H}_5$); 3·20–3·80 (N–C$\underline{H}$, C$\underline{H}_2$–N, *m*); 2·10–2·80 (C$\underline{H}_2$–N–C$\underline{H}_2$, *m*); 2·15 (C–C$\underline{H}_2$C, *q*); 1·0–1·7 (C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$, *m*).

3.10 *N-(2-phenethyl)amidine 5a*

3.10a *From reduction of styrylamidine (2t)*: A solution of 2t (1·6 g) in methanol (75 ml) was shaken with hydrogen at room temperature and 1 atmosphere pressure in the presence of 10% Pd–C (0·15 g), until 1 mol of hydrogen was absorbed (3 h). The solution was filtered and concentrated. Addition of picric acid gave 5a picrate, which was recrystallised from alcohol; m.p. and mixed up with authentic sample (see below), 145–6° (Found: C, 56·78; H, 4·99; N, 12·88. $C_{26}H_{27}N_5O_9$ requires C, 56·41; H, 4·92; N, 12·65%).

Similarly the styrylamidine 2p was reduced to phenethyl amidine 5b which was converted into HCl salt; m.p. 223–5° (from methanol–ether) (Found: C, 61·52; H, 7·56; N, 8·61; Cl, 10·99. $C_{16}H_{23}ClN_2O_2$ requires C, 61·83; H, 7·46; N, 9·02; Cl, 11·41%).

3.10b *From N-benzoyl 2-(p-methoxyphenethyl)amide (6)*: 6 (15 g) and thionyl chloride (30 ml) were heated together under reflux for 4 h. After distilling off thionylchloride, the residual iminochloride was taken up in dry ether and treated under cooling and stirring with morpholine (12 g) in ether (50 ml) during 1 h. Ether and morpholine were then distilled off *in vacuo* and the basic product worked up as usual. Crystallisation from ether–hexane gave the phenethyl amidine 5a (10 g), m.p. 45–7° (Found: C, 73·83; H, 7·47; N, 8·28. $C_{20}H_{24}N_2O_2$ requires C, 74·04; H, 7·46, N, 8·64%). ^{1}H NMR ($CDCl_3$) 7·15–7·40 (3 aromatic H, *m*); 6·50–7·10 (5 aromatic H, *m*); 3·67 (OCH_3, *s*); 3.55 (C$\underline{H}_2$OC$\underline{H}_2$, *m*); 3·12 (C$\underline{H}_2$–N–C$\underline{H}_2$; C$\underline{H}_2$–N=, *m*); 2·63 (ArC$\underline{H}_2$, *t*, $J = 7$ Hz). The picrate had m.p. 145–6°. (Found: C, 56·59; H, 4·97; N, 12·91%).

References

Advani B G, Nagarajan K, Rajagopalan P and Ranga Rao V 1968 *Tetrahedron Lett.* **56** 5825
Biere H 1983 *Eur. Patent ammeldung* EP 110 **090A**
Compagnon P L, Gasquez F, Compagnon O and Kimny T 1982 *Bull. Soc. Chim. Belg.* **91** 931
Cook S L, Venayak N D and Wakefield B J 1983 *J. Chem. Res. Synp.* 199
Cook S L and Wakefield B J 1980 *J. Chem. Soc., Perkin Trans. I.* 2392
Ichimura H and Ohta M 1966 *Tetrahedron Lett.* **54** 807
Islam A M, El-Sharief A M S, Ismail I M and Harb A A 1983 *Egypt J. Chem.* **26** 221; 1984 *Chem. Abstr.* **101** 191751g
Ito M M, Nomura Y, Takeuchi Y and Tomoda S 1983 *Bull. Chem. Soc. Jpn.* **56** 641
Kantlehner W 1979 *Advances in organic chemistry methods and results* (series ed.) E C Taylor. Vol. 9, Part 2. *Iminium salts in organic chemistry* (eds) H Bohme and H G Viehe (New York: John Wiley & Sons) p. 99
Marxer A 1972 *Helv. Chim. Acta* **55** 430
Matier W L and Comer W T 1974 *J. Org. Chem.* **39** 3080
Matier W L and Comer W T 1975 *Ger. Offen DE* 2428223; 1975 *Chem. Abstr.* **82** 170425c
Matier W L and Comer W T 1977 *Ger. Offen. DE* 2635121; 1977 *Chem. Abstr.* **87** 22805q
McKillop A and Boulton A J (eds) 1984 *Comprehensive heterocyclic chemistry* (Oxford: Pergamon) vol. 2, p. 442
Nagarajan K, Vunnam V R, Shah R K, Shenoy S J, Fritz H, Richter W J and Muller D 1988 *Helv. Chim. Acta* **71** 77
Rajagopalan P and Advani B G 1965 *Tetrahedron Lett.* **26** 2197
Ried W and Erle H E 1979 *Chem. Ber.* **112** 640
Va Meeteren H W and Van der Plas H C 1971 *Recl. Trav. Chim. Pays-Bas* **90** 105
Yanagida S 1975 *Jpn. Patent* 50/37671; 1976 *Chem. Abstr.* **85** 108660j
Yanagida S, Fujita T, Ohoka M, Katagiri I and Komori S 1973 *Bull. Chem. Soc. Jpn.* **46** 292