An Efficient General Route to Furo-, Pyrido- and Thieno-[*d*][2]benzazepines *via* Pd° Catalysed Cross Coupling Reactions and Nitrile Ylide Cyclisations

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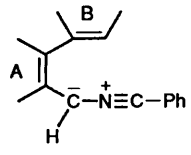
The cyclisation of diene-conjugated nitrile ylides of the general type **1**, in which the conjugated system consists of a benzene ring and a five- or a six-membered heterocyclic ring, provides an effective route to fully unsaturated heterocyclo[*d*][2]benzazepines. The combination of this cyclisation with a direct route to the nitrile ylide precursors *via* Pd° catalysed cross-coupling gives an efficient general synthetic route to these systems from readily available starting materials.

This work is concerned with an investigation into the cyclisation of biaryl-conjugated nitrile ylides of type **1** in which



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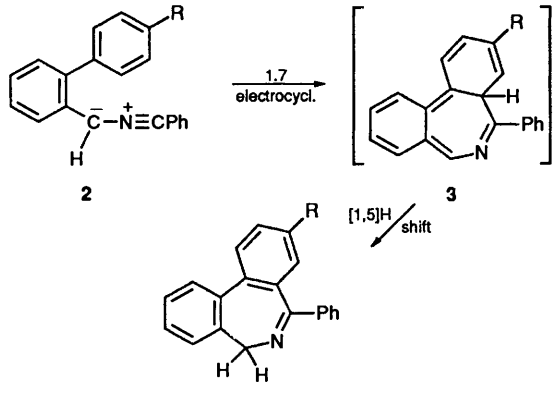
one of the aromatic rings (A or B) is a benzene ring and the other is a five- or six-membered heterocycle. It follows recent work on the analogous system **2**, containing two benzene rings, whose cyclisation provides a good general route to dibenz[*c*,*e*]-azepines **4**.[1] This electrocyclic mode of aromatic substitution has the advantage over electrophilic or nucleophilic substitution in that it is effective for terminal rings carrying substituents (R in **2**) which are *either* electron donating *or*

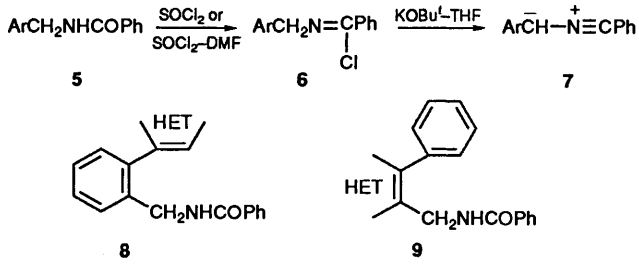


2 **3** **4**

electron withdrawing.[1,2] The objectives of the present work were to find out whether the nitrile ylide cyclisation step was also effective in biaryl systems containing electron rich or electron poor heterocyclic rings and, if so, thus to develop a general route to tricyclic azepines with one fused benzene ring and one fused heterocyclic ring. Compounds of this type and their functionalised derivatives are of interest for their possible interaction with benzodiazepine, cholecystokinin (CCK) and gastrin receptors.

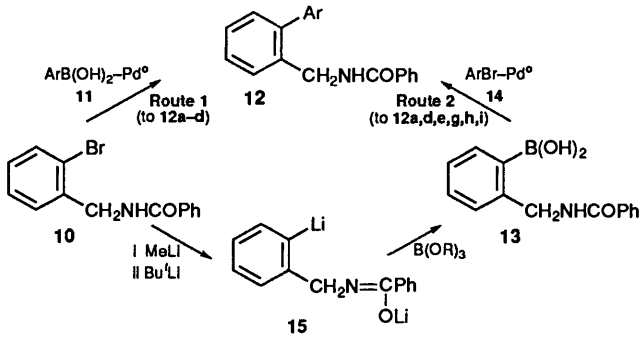
Results and Discussion

The general route to nitrile ylides **7** used in the earlier work[1] involved the base-induced 1,3-dehydrochlorination of imidoyl chlorides **6**, which were themselves simply derived by the chlorination of amides **5**. The intention here was to use the same method and this therefore required the development of efficient routes to amides of the general types **8** and **9**.



5 **6** **7** **8** **9**

(*a*) *Routes to the Amides* **8** *and* **9** *as Precursors to Nitrile Ylides.*—In recent years, several direct routes to biaryls have been developed *via* the palladium(0) catalysed cross-coupling of aryl halides with various organometallic derivatives. Of these, the route developed by Suzuki using arylboronic acids[3], is, perhaps, the most general in respect of its tolerance of a wide range of other functional groups and the ease of preparation of the reactants. Scheme 1 shows the application of this chemistry to the synthesis of biaryls **12** (Ar = aryl) and heterobiaryls **12** (Ar = hetaryl) containing the *o*-benzamidomethyl group required as nitrile ylide precursor. In principle, this substituent could be present in either the halide component **10** or in the boronic acid **13**; both alternatives have some potential advantages and both have been utilised as described below. The first approach was *via* the coupling of *N*-(2-bromobenzyl)-benzamide **10** with a range of heterocyclic boronic acids **11**, Scheme 1 (Route 1). This was attractive in that the amide **10** is



Scheme 1

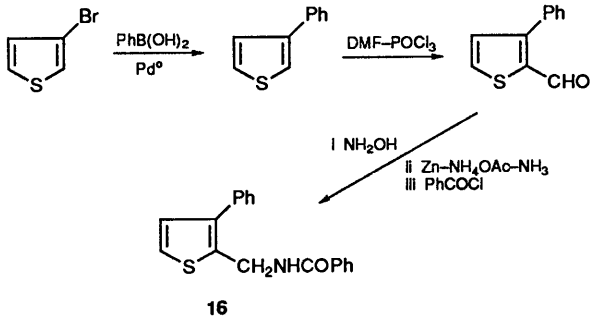
Table 1 Yields and physical data on the amides **12a–i**, **16** and **17**

Compound	Ar	Yield (%) [time (h)] Route 1	Route 2	Cryst. solvent[a]	M.p. (°C)	Molecular formula	C (%) Found	Calc.	H (%) Found	Calc.	N (%) Found	Calc.	*m/z* (M^+) Found	Calc.
12a	Ph	86 [5]	91 [4]	E	95–96[b]									
12b	2-Thienyl	78 [3]		E	119–120	$C_{18}H_{15}NOS$							293.0878	293.0874
12c	3-Thienyl	80 [5]		E	125–126	$C_{18}H_{15}NOS$							293.0865	293.0874
12d	3-Furyl	77 [2]	85 [2]	Eth/H	80–81	$C_{18}H_{15}NO_2$							279.1259[c]	279.1259
12e	4-Pyridyl		73 [1]	E	130–131	$C_{19}H_{16}N_2O$							288.1260	288.1263
12f	3-Pyridyl	74 [5]		E	116–118	$C_{19}H_{16}N_2O$							288.1263	288.1263
12g	2-Pyridyl		81 [3]	EA/H	104–106	$C_{19}H_{16}N_2O$							288.1255	288.1263
12h	2-Pyrimidyl		83 [2]	E/H	124.5–126.5	$C_{18}H_{15}N_3O$	74.2	74.7	5.0	5.2	14.7	14.5	289.1214	289.1215
12i	5-Pyrimidyl		81 [2]	EA/H	150–151	$C_{18}H_{15}N_3O$							289.1212	289.1215
16		see text				$C_{18}H_{15}NOS$	73.4	73.7	5.2	5.2	4.5	4.8	293.0877	293.0874
17		see text				$C_{18}H_{15}NOS$	73.4	73.7	5.2	5.2	4.7	4.8	293.0865	293.0874

[a] H = hexane, E = ethanol, Eth = diethyl ether. [b] Lit.,[1] 94.5–95.5 °C. [c] FAB, glycerol.

easily prepared from commercially available 2-bromobenzylamine. The boronic acids were generally prepared by adaptations of known routes *via* the reaction of the heterocyclic Grignard reagent or lithium derivative with trimethyl or triisopropyl borate. Using the improved experimental conditions developed by Gronowitz,[4] it was found that the coupling reaction worked well for phenylboronic acid to give compound **12a** (Ar = Ph) which had been prepared previously by other routes and with a range of thienyl- and furyl-boronic acids to give the amides **12b**, **c**, **d**; the substituents are identified and the yields are given in Table 1. This route is, therefore, satisfactory for coupling heterocycles such as thiophene or furan whose boronic acid derivatives are readily available but is not applicable to those such as pyridine where this is not the case. This problem can be avoided in some cases by using other organometallic derivatives of the heterocycle, *e.g.* the commercially available diethyl(3-pyridyl)borane which was used under identical conditions to prepare compound **12f** in good yield. However, such substitutes are not always available and a more general solution was found by adopting the alternative approach *via* the use of compound **13** which has the boronic acid function incorporated in the amide. The development of this route, therefore, required the synthesis of 2-(benzamidomethyl)phenylboronic acid **13** which, it was hoped, would be capable of coupling directly with a range of heterocyclic bromides **14**, which are readily available for most heterocyclic systems. The preparation of the boronic acid **13** involved the formation of the dilithiated derivative **15** and its reaction with a borate ester. The dianion **15** was generated by sequential treatment of **10** with methyllithium to deprotonate selectively the amide and then with butyllithium to effect metal–halogen exchange, a technique used earlier in the preparation of analogous 2-lithiated tosyl hydrazones.[5] A problem encountered in this work was that butyllithium proved unsatisfactory in the second step as its use resulted in the formation of some *N*-(2-butylbenzyl)benzamide *via* the reaction of the dianion **15** with the 1-bromobutane formed in the metal-halogen exchange. This was avoided by the use of *tert*-butyllithium and it was thus possible to prepare compound **13** routinely in isolated yields of *ca.* 85%. It proved to be highly effective in coupling with a range of hetaryl bromides **14**, Scheme 1 (Route 2) (see Table 1 for identification of Ar) and its use, therefore, provides an easy general route to the required amides of the general type **8**. It has also proved to be of much general value in this area of chemistry not only for coupling bromoheterocycles but also for coupling with a range of aryl and alkenyl bromides to give the reactants used in related work.

Only two examples of amides of the general type **9** have been investigated, the two thiophene derivatives **16** and **17** prepared *via* Schemes 2 and 3, respectively.



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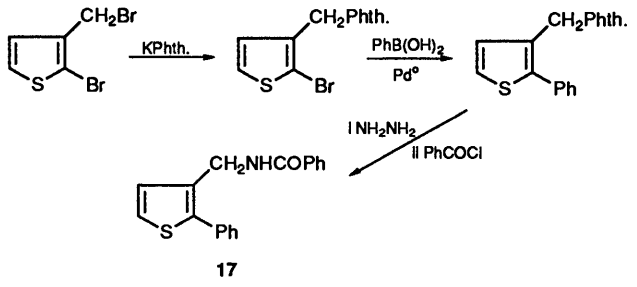
Scheme 2

The physical and spectroscopic properties of the amides are given in Tables 1 and 2, respectively. All showed the expected IR



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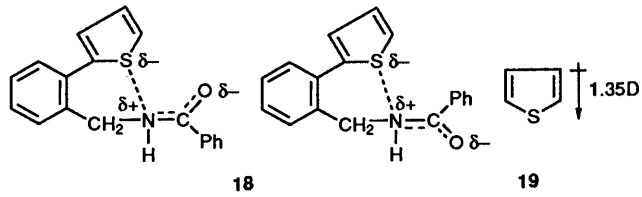
Scheme 3

absorptions for the amide group and all except the 2-thienyl derivative **12b**, had the expected ^{1}H NMR signals for the NH (br) and CH_2 group (doublet) which were similar to those for the phenyl analogue **12a**. The spectrum of the 2-thienyl compound **12b** showed an interesting difference in that both of these signals were doubled, *e.g.* the methylene group gave a pair of doublets at δ 4.68 and 4.71 in the ratio 1:3.8 at 25 °C. It is thought that this effect is due to a non-bonded electrostatic interaction of the sulfur atom of the thiophene with the amide group, as indicated in **18**, which restricts the amide rotation. This explanation is consistent with the fact that the dipole moment of thiophene itself has the negative charge on sulfur and is supported by the observations (*i*) that the two doublets merge when the temperature of the sample is raised to 59 °C and (*ii*) that the integral ratio of the doublets is diminished when the dielectric constant of the solvent is increased by the addition of the more polar solvents perdeuterio-acetone or -dimethylformamide.



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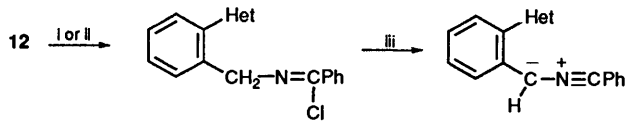
(*b*) *Cyclisation of the Nitrile Ylides to give Heterocyclo*[d][2]*benzazepines.*—In all the cyclisations, except those of **12d** and **12g**, the procedures followed for the cyclisation, work-up and isolation of the products were as described earlier for the analogous biphenyl systems.[1] The generation of the nitrile ylides, shown in Scheme 4 for the general case, involved the conversion of the amide into an imidoyl chloride by reaction with either thionyl chloride in ether at reflux temperature or, in cases of difficulty, by reaction with the more powerful reagent chlorodimethylformiminium chloride at room temp. The latter was generated *in situ* by the reaction of thionyl chloride with DMF. The former method was preferred where possible as any excess of reagent was more easily removed by evaporation under high vacuum. The crude imidoyl chlorides, after evaporation of the reagent and solvent, were not further purified but were dissolved in THF, cooled to 0 °C and treated with an excess of potassium *tert*-butoxide, Scheme 4, to generate the nitrile ylides. In much of this work the potassium *tert*-butoxide used was the fresh commercial reagent (Aldrich) but more recently it has been found that better conversions are obtained when the base is purified by sublimation under high vacuum (at *ca.* 200 °C) before use. The products were isolated by dry-column flash chromatography.[6] In all cases the cyclisations were successful and gave tricyclic azepine systems, Table 3. The cyclisations are discussed in more detail in (*i*) and (*ii*) below. The products were identified by the presence in their ^{1}H NMR spectra (Table 4) of the characteristic[1] pair of doublets (*J ca.* 11)

due to methylene group. These signals showed the expected variation with temperature due to the inversion of the azepine ring; this is discussed in more detail in (*c*) below.



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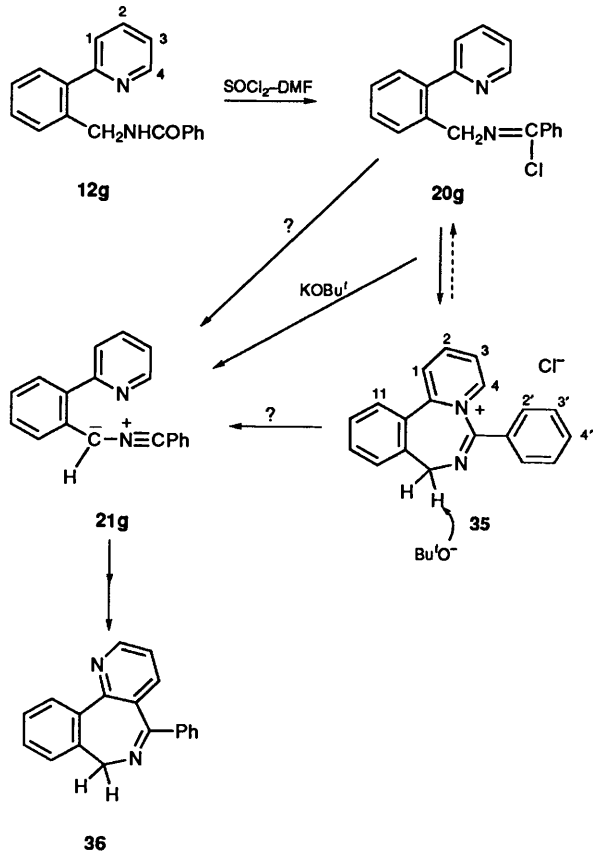
Scheme 4 *Reagents and conditions:* i, $SOCl_2$–ether–reflux; ii, $Me_2\overset{+}{N}=CHCl\ Cl^-$ ($SOCl_2$–DMF), room temp.; iii, KOBu^t–THF

(*i*) *Systems containing thiophene or furan rings.* Four systems containing thiophene rings and one containing a furan ring were examined. The first two were the nitrile ylides **21b** and **21c** and in these cases azepine formation requires electrocyclic substitution of the electron-rich thiophene ring. In both cases the amide precursors were easily converted into the imidoyl chlorides using thionyl chloride in ether under reflux. Both of these nitrile ylides cyclised as expected to give the azepines **22** and **23**, respectively. As expected from earlier work on diazo cyclisations,[7] the latter cyclised only at the 2-position of the thiophene ring rather than the 4-position. The other two thiophene systems **25** and **28** both had the thiophene ring in the α,β position, *i.e.* carrying the nitrile ylide group and consequently ring closure required electrocyclisation onto the benzene ring. The conversion of their amide precursors **16** and **17**, respectively, into imidoyl chlorides caused some initial difficulty as the latter, **24** and **27**, seemed to be unusually unstable. Reaction with thionyl chloride in ether at reflux, as used for the two previous thiophene-containing systems, gave little of the expected products and much black tar. The problem was solved by the use of the more reactive reagent chlorodimethylformiminium chloride at a lower temperature. The relatively high instability of compounds **24** and **27** probably has its origins in the electron-rich nature of the thiophene ring. All benzimidoyl chlorides tend to decompose at high temperatures *via* the extrusion of benzonitrile and in these cases this process would be favoured by the effect of the electron-rich thiophene ring in stabilising the incipient thienylmethyl carbocation which, once formed, could then undergo further reactions such as alkylation. Generation of the nitrile ylides was carried out in the usual way and they cyclised to give compounds **26** and **29** in satisfactory yields. All of these thiophene-containing azepines showed a reluctance to crystallise even more marked than some of their dibenzo analogues[1] and it was generally found to be most efficient to purify them by Kugelrohr distillation.

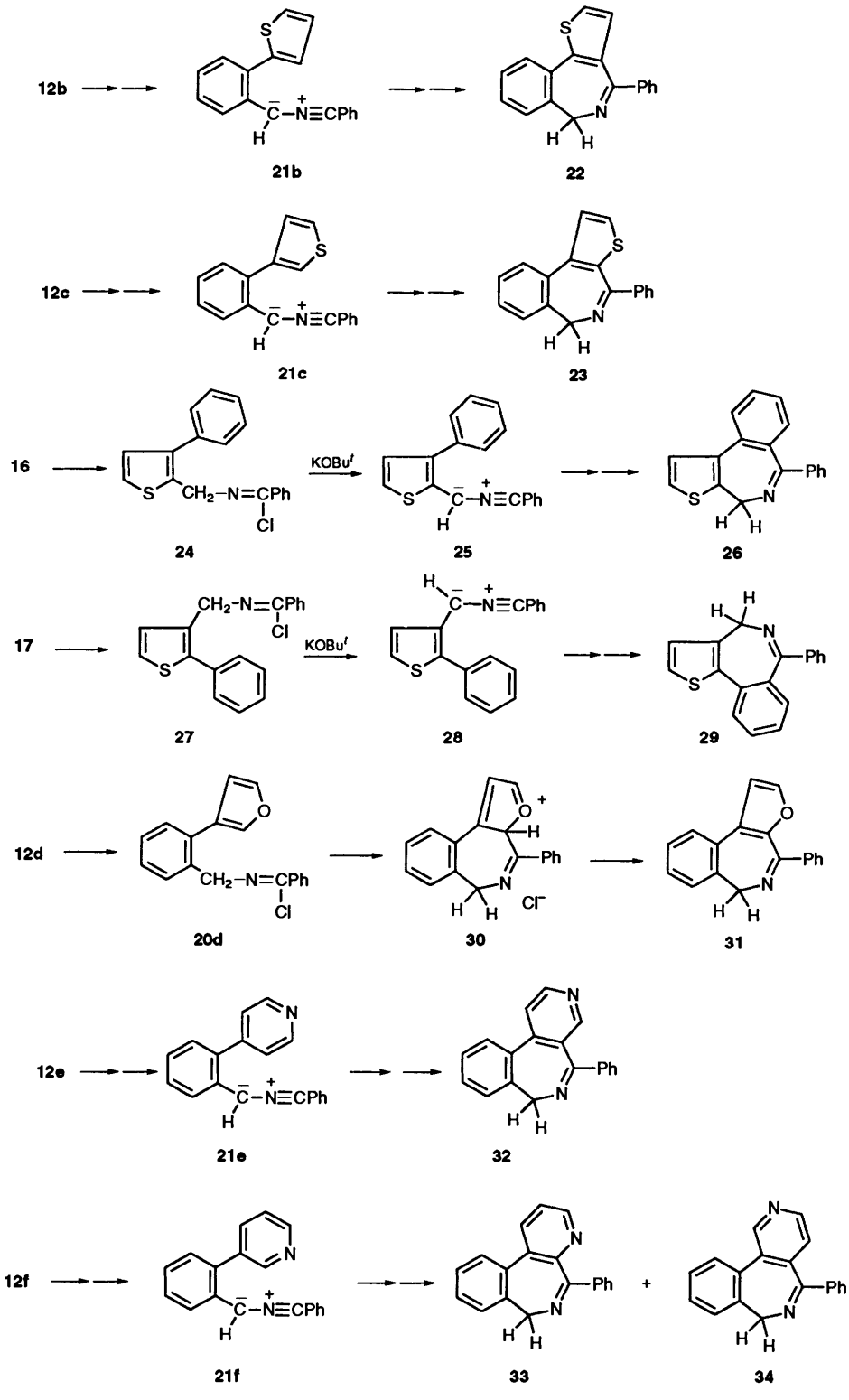
The furan-containing imidoyl chloride **20d** could not be isolated. Both methods were used to generate it from its amide precursor **12d** and in both cases it cyclised spontaneously to give the furobenzazepine **31** in high yield. It seems likely that this takes place by a Bischler–Napieralski type of electrophilic substitution *via* **30** as shown. That this takes place for this compound and not for the thiophene analogue reflects the much higher reactivity of furan than thiophene to electrophilic substitution (*e.g.* 140 × for trifluoroacetylation and 107 × for formylation).[8]

(*ii*) *Systems containing pyridine rings.* The three isomeric pyridine-containing systems **21e**, **21f** and **21g** have been studied. These contrast with the above in that azepine formation now requires the electrocyclic substitution of electron-deficient heterocyclic rings. In all cases the formation of the imidoyl chlorides required the use of chlorodimethylformiminium chloride. The 4-substituted derivative **21e** cyclised to give 5-phenyl-7*H*-pyrido[3,4-*d*][2]benzazepine **32** in good yield. The 3-substituted analogue **21f** cyclised at both of the '*ortho*' positions to give a mixture of the two isomers 5-phenyl-7*H*-pyrido[2,3-*d*][2]benzazepine **33** and 5-phenyl-7*H*-pyrido[4,3-*d*][2]benzazepine **34**. These compounds were formed in a ratio of 1:1.4 but could not be separated and it is not known which of the two is the major product. On the basis of other work[2] which has shown that the reaction rate is increased by the proximity of electron-withdrawing groups to the cyclisation site it seems likely that the major product is compound **33**. One of the main points of interest in looking at this pyridine series was to find out what would happen in the case of the 2-pyridyl compound **21g** (Scheme 5) which has one of the two potential cyclisation sites occupied by the pyridine nitrogen atom. Some initial lack of reproducibility in this series of reactions indicated the need to look closely at the reaction of the amide **12g** with the chlorinating reagent. ^{1}H NMR studies were therefore carried out in which the reaction of compound **12g** with perdeuteriodimethylformamidinium chloride was carried out in perdeuteriodimethylformamide in an NMR tube and monitored until completion. The results from this reaction were compared with similar reactions of two comparators, the phenyl analogue **12a** and the 4-pyridyl analogue **12e**. In the reaction of 'phenyl' amide **12a** the methylene doublet at δ 4.42 had virtually disappeared after 15 min to be replaced by a more deshielded singlet at δ 4.74 due to the CH_2 of the imidoyl chloride. The 4-pyridyl analogue **12e** showed a similar but slower transformation in which the amide doublet at δ 4.42 was replaced by the imidoyl chloride singlet at δ 4.89; the reaction was essentially complete in 1 h. This slower reaction accords with our general observations on the effects of electron withdrawing groups on imidoyl chloride formation.[1] The reaction of the '2-pyridyl' amide **12g** gave a product spectrum, Fig. 1, which was quite different from those of the two comparators. The disappearance of the amide CH_2



Scheme 5

* Experiment designed and carried out by Dr. D. Reed, Chemistry Dept., University of Edinburgh.

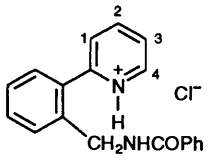


doublet was slower than for the 4-pyridyl analogue and it was replaced largely by a pair of doublets at δ 4.91 and 4.72 (J 11.1) together with a singlet at δ 5.14. The aromatic region also showed major changes, unlike the previous cases. The conversion was virtually complete after 12 h and the spectrum remained unchanged after a further 10 h at room temp. The major product is thought to be the 2,4-benzodiazepinium salt **35** formed by nucleophilic ring closure in the first-formed imidoyl chloride (Scheme 5). This formulation is supported by its ^{1}H NMR spectrum; the methylene group gives the expected pair of doublets (which resonate at positions quite different from those in the final product **36** or its hydrochloride). The major changes in the aromatic region of the spectrum are consistent with the quaternisation of the pyridine nitrogen atom. As a basis for comparison the chemical shifts of the pyridine protons for the amide **12g**, its hydrochloride salt **37**

Table 2 Spectroscopic data for the amides **12a–i**, **16** and **17**

Compound	Ar	Spectroscopic data	
12a	Ph	δ_H	4.62 (d, *J* 5.6, CH_2), 6.23 (br s, NH) and 7.25–7.50 (12 H, m)
		ν_{max}	1625 (C=O) and 3320 (NH)
12b	2-Thienyl	δ_H [b]	4.71 (d, *J* 5.6), 4.68 (d, *J* 5.9; combined integral 2 H, CH_2), 5.36 (br s), 5.79 (br s); combined integral 1 H, NH) and 7.04–7.75 (12 H, m, Ar-H)
		ν_{max}	1630 (C=O) and 3320 (NH)
		m/z	275 (67%), 274 (100) and 171 (25)
12c	3-Thienyl	δ_H	4.65 (d, *J* 5.6, CH_2), 6.28 (br s, NH) and 7.41–7.82 (12 H, m, Ar-H)
		ν_{max}	1625 (C=O) and 3275 (NH)
		m/z	293 (55%), 188 (25), 172 (100), 171 (60) and 122 (55)
12d	3-Furyl	δ_H	4.63 (d, *J* 5.5, CH_2), 6.53 (dd, *J* 1.8 and 0.9, 4'-H), 6.95 (br s, NH), 7.23–7.49 (9 H, m, Ar-H) and 7.61–7.75 (2 H, m, Ar-H)
		ν_{max}	1635 (C=O) and 3250 (NH)
		m/z [c]	279 (M + 1, 48%), 278 (100), 157 (92), 129 (50) and 105 (98)
12e	4-Pyridyl	δ_H	4.54 (d, *J* 5.6, CH_2), 6.80 (br s, NH), 7.18–7.50 (9 H, m, Ar-H), 7.64–7.71 (2 H, m, Ar-H) and 8.56 (2 H, br s, Ar-H)
		ν_{max}	1630 (C=O) and 3375 (N–H)
		m/z	287 (16%), 183 (20), 167 (100), 105 (31), 77 (38) and 69 (48)
12f	3-Pyridyl	δ_H	4.54 (d, *J* 5.6, CH_2), 6.74 (br s, NH), 7.16–7.71 (11 H, m, Ar-H) and 8.48–8.53 (2 H, m, Ar-H)
		ν_{max}	1630 (C=O) and 3375 (NH)
		m/z	183 (18%), 168 (48), 166 (51), 105 (57), 77 (100) and 69 (24)
12g	2-Pyridyl	δ_H	4.55 (d, *J* 6.1, CH_2), 7.25–7.89 (12 H, m, Ar-H and N-H) and 8.64–8.71 (2 H, m, Ar-H)
		δ_C [d]	41.0 (quat.) 121.8, 123.8, 126.6, 126.7, 127.9, 128.0, 128.2, 129.4, 130.7, 134.5 (quat.), 136.6, 137.2 (quat.), 139.4 (quat.), 148.5, 158.8, 161.3, 161.6, 161.8, 161.9 and 165.7 (quat.)
		m/z	289 (69%), 183 (20), 167 (100) and 105 (19)
		ν_{max}	1645 (C=O) and 3320 (NH)
12h	2-Pyrimidyl	δ_H	4.71 (d, *J* 6.3, CH_2), 7.24–7.49 (6 H, m, Ar-H), 7.62–7.69 (1 H, m, Ar-H), 7.77–7.83 (2 H, m, Ar-H), 8.01–8.09 (1 H, m, Ar-H), 8.26 (br s, NH) and 8.86 (2 H, d, *J* 4.9, Ar-H)
		m/z	289 (45%), 184 (18), 168 (100), 131 (17), 119 (23) and 69 (67)
		ν_{max}	1625 (C=O) and 3230 (N-H)
12i	5-Pyrimidyl	δ_H	4.48 (d, *J* 5.7, CH_2), 6.89 (br s, NH), 7.14–7.51 (7 H, m, Ar-H), 7.63–7.70 (2 H, m, Ar-H), 8.66 (2 H, s, 4'-H and 6'-H) and 9.11 (s, 2'-H)
		m/z	288 (5%), 168 (100), 157 (17), 131 (21), 119 (20), 105 (36), 77 (44) and 69 (59)
		ν_{max}	1635 (C=O) and 3350 (NH)
16		δ_H	4.82 (d, *J* 5.4, CH_2), 6.67 (br s, NH), 7.06 (d, *J* 5.2, 4-H), 7.25 (d, *J* 5.2, 5-H), 7.28–7.51 (8 H, m, Ar-H) and 7.68–7.74 (2 H, m, Ar-H)
		m/z	294 (21%), 293 (100), 172 (20) and 69 (97)
		ν_{max}	1635 (C=O) and 3290 (NH)
17		δ_H	4.65 (d, *J* 5.4, CH_2), 6.59 (br s, NH), 7.10 (d, *J* 5.2, 4-H), 7.24 (d, *J* 5.2, 5-H), 7.28–7.49 (8 H, m, Ar-H) and 7.66–7.72 (2 H, m, Ar-H)
		m/z	293 (69%), 105 (100) and 77 (31)
		ν_{max}	1645 (C=O) and 3355 (NH)

[a] *J*-Values are given in Hz. [b] The ^1H NMR spectrum was also run in mixtures of deuteriochloroform and either perdeuterio-acetone or -DMF, the results are discussed in the text. [c] FAB (glycerol). [d] In [$^2H_7$]DMF.



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and the product formulated as **35** have been determined by 2D ^1H NMR COSY experiments.* The results are given in Table 5. The first key point is that all the four pyridine protons are still present in the spectrum of **35** and that they are all strongly deshielded in comparison to those in the amide **12g**. A similar but weaker effect is seen in the spectrum of the hydrochloride salt **37** of the amide **12g**, thus supporting the contention that the new compound contains a quaternised nitrogen atom. Nuclear Overhauser experiments (NOE) on compound **35** also support the proposed structure, irradiation at position 1 produced an effect at positions 2 (1.5%) and 11 (4%) only, and at position 4 produced an effect at positions 3 (2%) and 2' (1%). The singlet at δ 5.14 in Fig. 1 is attributed to the presence of some of the imidoyl chloride **20g**, Scheme 5, present in equilibrium with **35** in the ratio *ca.* 1:3. This interpretation is supported by the fact that hydrolysis of the reaction mixture produced only the amide **12g**. A preparative-scale reaction of the amide with chlorodimethylformiminium chloride was carried out under identical conditions and after 12 h the reaction mixture was diluted with THF and treated with potassium *tert*-butoxide. Work-up gave 5-phenyl-7*H*-pyrido[3,2-*d*][2]benzazepine **36** in *ca.* 70% yield. It seems like that it is formed in the usual way *via* the nitrile ylide **21g** which itself may be formed either directly from the imidoyl chloride **20g** or *via* the deprotonation and ring opening of compound **35**, Scheme 5. The cyclisation of **21g** thus apparently takes place normally at the free '*ortho*' position and the only observable effect of the presence of the pyridine nitrogen atom is in the ring closure/opening equilibration of the imidoyl chloride **20g** with compound **35**.

The reactions of the pyrimidin-2- and 5-yl amides **12h** and **12i** with thionyl chloride–dimethylformamide appear to be more complicated and will be reported in a later publication.

(*c*) *Ring Inversion of the Fused Azepines.*—The results of the VT NMR studies on the tricyclic azepines are given in Table 6. The ease of ring inversion is clearly much affected by the size and nature of the fused heterocyclic ring. The replacement of one of the fused benzene rings in the dibenzazepine **4** (R = H) by pyridine, thiophene or furan makes the system progressively more flexible. The trend is consistent with earlier work on fused diazepines in which it was found that replacement of a fused

Table 3 Yields and physical data on the heterocyclic-fused benzazepines

Compound	Method[a]	Yield (%)	Cryst. solv.[b]	M.p. (°C)	B.p. (°C)	Molecular formula	C (%) Found	Calc.	H (%) Found	Calc.	N (%) Found	Calc.	m/z (M^+) Found	Calc.
22	(*i*)	68			185–190 0.3 mmHg	$C_{18}H_{13}NS$							275.0775	275.0769
Picrate		88		237–238		$C_{24}H_{16}N_4OS$	57.1	57.1	3.2	3.2	11.2	11.1		
23	(*i*)	65			190–195 0.4 mmHg	$C_{18}H_{13}NS$							275.0771	275.0769
Picrate		92		235–236		$C_{24}H_{16}N_4OS$	56.9	57.1	3.15	3.2	11.1	11.1		
26	(*ii*)	69	H	106–108		$C_{18}H_{13}NS$	78.6	78.5	4.7	4.8	4.9	5.1	275.0773	275.0769
28	(*ii*)	74			175–180 0.3 mmHg	$C_{18}H_{13}NS$							276.0847[c]	276.0847
31	(*i*)/(*ii*)[d]	78			170–175 0.3 mmHg	$C_{18}H_{13}NO$							260.1075[c]	260.1075
32	(*ii*)	81			not distilled	$C_{19}H_{14}N_2$							270.1155	270.1157
33–34	(*ii*)	61			205–210 0.1 mmHg	$C_{19}H_{14}N_2$							270.1154	270.1157
1:1.4	(*ii*)													
36[d]	(*ii*)	68	EA/H	186.5–187.5		$C_{19}H_{14}N_2$							270.1143	270.1157

[a] Method of imidoyl chloride formation Scheme 7. [b] H = hexane, EA = ethyl acetate. [c] For (M + 1), FAB, glycerol. [d] For details see text.

Table 4 Spectroscopic data for the fused azepines

Compound			Spectroscopic data[a]
4 (R=H)[b]	δ_H	(298 K)[c]	3.77 (1 H, d, *J* 10.2), 4.87 (1 H, d, *J* 10.2) and 7.24–7.87 (13 H, m, Ar-H)
22	δ_H	(298 K)	4.52 (br s, CH_2) and 7.03–7.70 (11 H, m, Ar-H)
		(280 K)	CH_2 – 3.95 (d *J* 10.75) and 5.10 (d, *J* 10.75)
	m/z		275 (57%), 274 (100), 171 (28), 28 (98)
23	δ_H	(298 K)	4.55 (br s, CH_2) and 7.24–7.71 (11 H, m, Ar-H)
		(280 K)	CH_2 – 3.97 (d, *J* 11.2) and 5.13 (d, *J* 11.2)
	m/z		275 (51%), 274 (100) and 171 (47)
26	δ_H	(298 K)	4.50 (br s, CH_2) and 7.14–7.77 (11 H, m, ArH)
		(275 K)	CH_2 – 3.93 (d, *J* 12.1) and 5.07 (d, *J* 12.1)
	m/z		276 (20%), 275 (90), 274 (100), 171 (37) and 59 (21)
28	δ_H	(307 K)	4.41 (br s, CH_2) and 7.06–7.76 (11 H, m, Ar-H)
		(250 K)	CH_2 – 3.70 (d, *J* 11.3) and 5.12 (d, *J* 11.3)
	m/z[d]		276 (100%), 171 (20), 49 (26), 43 (31), 36 (21), 28 (98)
31	δ_H	(298 K)	4.57 (br s, CH_2), 6.94 (d, *J* 1.8, 4-H fur) and 7.33–7.65 (10 H, m, Ar-H)
		(228 K)	CH_2 – 3.91 (d, *J* 11.2) and 5.23 (d, *J* 11.2)
	m/z		259 (100%), 128 (15), 105 (12), 77 (13), 44 (10), 36 (26) and 32 (25)
32	δ_H	(307 K)[c]	3.83 (d, *J* 10.6, CH_2), 4.95 (d, *J* 10.6, CH_2), 7.41–7.63 (8 H, m, Ar-H), 7.80–7.91 (2 H, m, Ar-H), 8.53 (1 H, s, 2-H pyr) and 8.79 (1 H, d, *J* 5.2, 6-H, pyr)
		(390 K)	4.89 (br s, CH_2)
	m/z		270 (100%), 269 (61), 167 (24), 139 (14) and 120 (9)
33–34	δ_H	(307 K)[c]	3.80 (1 H, d, *J* 11), 3.91 (1 H, d, *J* 11), 4.93 (1 H, d, *J* 11), 4.98 (1 H, d, *J* 11), 7.20–8.00 (21 H, m, Ar-H), 8.18–8.36 (1 H, m, Ar-H) and 8.62–8.76 (2 H, m, Ar-H)
		(288 K)	4.46 (br s, 2 × CH_2)
	m/z		270 (100%), 269 (64), 167 (35) and 32 (21)
36	δ_H	(298 K)[c]	3.99 (1 H, d, *J* 11.7), 4.98 (1 H, d, *J* 11.7), 7.43–7.60 (9 H, m, Ar-H), 7.79 (dd, *J* 7.9 and 1.8, 4-H pyrido) and 8.06–8.16 (1 H, m, Ar-H), 8.95 (dd, *J* 4.5 and 1.8, 6-H, pyridyl)
		(344 K)	4.49 (2 H, br s)
	δ_H (360 MHz)	(298K)[e]	3.81 (1 H, d, *J* 10.6), 4.87 (1 H, d, *J* 10.6), 7.23–7.46 (7 H, m, Ar-H), 7.71 (1 H, dd, *J* 7.9 and 1.8, 4-H, pyr), 7.88 (2 H, br s, Ar-H), 8.02 (1 H, m, Ar-H) and 8.82 (dd, *J* 4.7 and 1.8, 6-H pyr)
	m/z		270 (82%), 269 (100), 205 (23), 167 (42), 143 (27) and 31 (25)

[a] All NMR spectra in $CDCl_3$ at 80 MHz unless otherwise indicated. [b] For preparation and other spectra see ref. 1. [c] [$^2H_6$]DMSO. [d] FAB (glycerol). [e] [$^2H_7$]DMF.

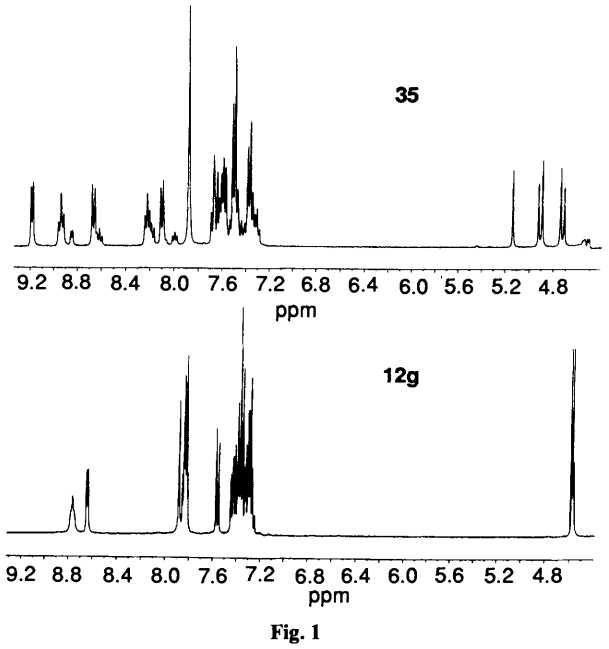

Fig. 1

benzene ring with thiophene decreased the activation energy for ring inversion.[9] This was rationalised in terms of the different effects of five- and six-membered rings on angle strain in the puckered and planar states. Other differences are not so easily explained. For example, it was suggested[1] that the high activation energy for inversion of the dibenzazepine system **4** was due largely to the increased steric interaction of the two hydrogen atoms at positions 1 and 11 in the planar transition state. The lower activation energy for **29** than **26** is consistent with this but the situation is reversed for **22** and **23**.

Table 5 Chemical shifts of the pyridyl protons in **12g**, **37** and **35**

Compound	Position (δ) 1	2	3	4
12g	7.56	7.83	7.29	8.64
37	8.02	8.44	7.88	8.85
	(+0.46)	(+0.61)	(+0.59)	(+0.21)
35	8.67	8.95	8.23	9.18
	(+1.11)	(+1.12)	(+0.94)	(+0.54)

Table 6 Coalescence temperatures and free energies for ring inversion

Azepine	Solvent	T_c/° C	ΔG kJ mol^{-1}
31	$CDCl_3$	−22	49.6
29	$CDCl_3$	2	54.5
23, picrate	$CDCl_3$	2	55.1
22, picrate	$CDCl_3$	17	58.3
26	$CDCl_3$	23	59.3
23	$CDCl_3$	24	59.5
22	$CDCl_3$	28	60.3
36	$(CD_3)_2SO$	71	69.7
33–34	$(CD_3)_2SO$	112	78.2
32	$(CD_3)_2SO$	115	78.6
4, R = H	$(CD_3)_2SO$	149	86.1

(*d*) *Conclusions.*—This work has shown that electrocyclic aromatic substitution using nitrile ylides is effective in forming azepines fused to a variety of heteroaromatic rings. In combination with the use of Pd° cross-coupling reactions as a route to the nitrile ylide precursors, it provides an efficient general synthetic route from easily available starting materials

to a range of tricyclic azepines with fused benzene and heterocyclic rings. In the case of the furan derivative **12d** it has been shown that azepine formation occurs spontaneously *via* uncatalysed electrophilic cyclisation of the imidoyl chloride **30**. Similar reactions are not observed for the thiophene analogues. These results, in general, illustrate the distinctive features of the electrocyclic substitution process which make ring closure possible on to both electron rich and electron deficient aromatic rings, the latter being particularly important since alternative modes of cyclisation are not easily available.

Experimental

NMR spectra were run as solutions in deuteriochloroform unless otherwise stated. Chemical shifts are recorded as δ values and J values are given in Hz. In the ^{13}C spectra, carbon multiplicity was established by single-frequency, off-resonance decoupling or by DEPT. Mass spectra were obtained using electron ionisation at 70 eV unless otherwise stated. Preparative chromatography was carried out by the 'dry-column flash' technique[6] using silica gel (15 μm, Fluka Fieselgel GF_{254}) and eluting solvents based on light petroleum (b.p. 40–60 °C) admixed with ether or ethyl acetate. Ether refers to diethyl ether. Evaporation of solvents indicates evaporation under reduced pressure using a rotary evaporator. All drying of solutions was done with anhydrous magnesium sulfate.

Solvents, Reagents and Starting Materials.—Tetrahydrofuran (THF) was distilled under nitrogen from sodium diphenylketyl immediately before use. 1,2-Dimethoxyethane (DME) and *N,N*-dimethylformamide (DMF) were distilled from calcium hydride and stored over molecular sieves (4 Å), the former was passed through a column of alumina immediately before use in the coupling reactions. 2-Bromobenzylamine hydrochloride and tetrakis(triphenylphosphine)palladium(0) were obtained from Aldrich Chemical Company and used without further purification.

The following were prepared by literature routes and had the reported physical and spectroscopic properties: 2-thienylboronic acid,[10] 3-thienylboronic acid,[11] phenylboronic acid (also obtained from Aldrich Chemical Company),[12] 3-furylboronic acid.[13]

N-(2-*Bromobenzyl*)*benzamide* **10**.—A mixture of 2-bromobenzylamine hydrochloride (3.92 g, 17.6 mmol), anhydrous sodium carbonate (4.01 g, 37.8 mmol) and benzoyl chloride (2.64 g, 18.8 mmol) in dichloromethane (60 cm^3) was stirred at room temperature for 1 h and then boiled under reflux for 30 min. After it had cooled, the reaction mixture was diluted with water (30 cm^3) and dichloromethane (40 cm^3). The organic phase was then separated, dried and evaporated and the residue recrystallised from ethanol to give the product (4.78 g, 93%) as white crystals, m.p. 133–134 °C (Found: C, 58.0; H, 4.3; N, 4.9. $C_{14}H_{12}BrNO$ requires C, 58.0; H, 4.2; N, 4.8%); δ_H(80 MHz) 4.68 (d, J 6.0, CH_2), 6.81 (br s, NH) and 6.98–7.82 (9 H, m, Ar-H); m/z (FAB), glycerol) 290 (M + 1, 98%), 274 (54) and 257 (100); ν_{max}(Nujol)/cm^{-1} 3300 (N–H) and 1640 (C=O).

2-(*Benzylamidomethyl*)*phenylboronic Acid* **13**.—To a solution of the benzamide **10** (2 g, 7 mmol) in THF (50 cm^3) under nitrogen at −78 °C were added dropwise firstly methyllithium (1.5 mol dm^{-3} solution in diethyl ether; 7.0 cm^3) and then, after stirring for 1 h, *tert*-butyllithium (1.7 mol dm^{-3} solution in pentane; 12.2 cm^3). After 1 h at −78 °C triisopropyl borate (9.2 cm^3, 0.04 mol) was added to the mixture which was then allowed to warm to room temperature. The solution was acidified with hydrochloric acid (2 mol dm^{-3}) and then stirred for 10 min. Separation, drying and evaporation of the organic layer and crystallisation of the resulting residue from dimethyl sulfoxide (DMSO)–water gave the *title compound* (1.50 g, 84%), m.p. 170–173 °C (Found: C, 66.0; H, 5.6; N, 5.4. $C_{14}H_{14}BNO_3$ requires C, 65.9; H, 5.5; N, 5.5%); δ_H(360 MHz; [$^2H_6$]DMSO) 4.63 (d, J 6.1, CH_2), 7.20–7.66 (7 H, m, Ar-H), 7.92 (d, J 7.4, 2′-H), 8.32 (2 H, s, OH) and 9.00 (br s, NH); NOE: irradiation of $B(OH)_2$ affected only 6-H (5%) and CH_2 (3%), and of CH_2 affected only 3-H (4%), $B(OH)_2$ (4%) and NH (10%); δ_B(360 MHz; [$^2H_6$]DMSO) 31.44 (s, B–OH); m/z 238 (11%), 212 (10), 167 (20), 149 (100), 117 (19), 105 (97), 91 (63), 85 (20), 74 (72), 58 (83), 48 (38), 42 (67) and 30 (36); ν_{max}(Nujol)/cm^{-1} 3350 (OH), 3260 (N–H) and 1610 (C=O).

Preparation of the Amides **12** (*Scheme* 1: *Routes* 1 *and* 2).—The general method is exemplified below for the preparation of *N*-(2-phenylbenzyl)benzamide **12a**. Compounds **12a–d** were prepared *via* Route 1 and **12a**, **d**, **e**, **g–i** *via* Route 2. Compound **12f** was prepared by a reaction similar to that in Route 1 but using diethylpyridylborane[14] under the same reaction conditions as below. In all cases the reactions were monitored by HPLC, using conditions similar to those given for **12a** below. The yields, reaction times and physical properties are given in Table 1 and the spectroscopic characteristics in Table 2.

N-(2-*Phenylbenzyl*)*benzamide* **12a**.—The benzamide **10** (3 g, 10.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.3 mmol) were added to DME (50 cm^3) with stirring under dry nitrogen. After 20 min a solution of sodium carbonate (anhydrous, 1.09 g, 10.3 mmol) in water (15 cm^3) and phenylboronic acid (1.51 g, 12.4 mmol) were added to the mixture which was then boiled under reflux. Monitoring by HPLC (5 μm silica ODS, 20% water in methanol) indicated complete consumption of starting material after 5 h. The DME was evaporated and the mixture was extracted with ethyl acetate. Drying and evaporation of the extract gave a brown solid. (In cases where the crude product was very dark, the most effective way to remove the colour was to pre-adsorb the mixture[6] onto alumina before dry-column flash chromatography on silica.) Dry-column flash chromatography (silica, ethyl acetate–hexane, 1:9) gave the *title compound* **12a** as a white crystalline solid (2.54 g, 86%).

2-(*Benzamidomethyl*)-3-*phenylthiophene* **16** via *Scheme* 2.—3-*Phenylthiophene-2-carbaldehyde oxime*. 3-Phenylthiophene, m.p. 88–89 °C (lit.,[10] 89.5–90.5 °C), was prepared (91%) by the method of Suzuki[3] and converted into 3-phenylthiophene-2-carbaldehyde (76%), m.p. 35–36 °C (lit.,[4] 36–36.5 °C) by the Gronowitz method. The latter (4.5 g, 24 mmol), on reaction at room temp. with a solution of hydroxylamine hydrochloride (1.81 g, 26 mmol) and sodium acetate (2.21 g, 26 mmol) in water (20 cm^3) gave the corresponding oxime (2.98 g, 61%), m.p. 115–116 °C (from ethanol) (Found: C, 64.9; H, 4.3; N, 6.9%; M^+, 203.0408. $C_{11}H_9NOS$ requires C, 65.0; H, 4.5; N, 6.9%; M, 203.0405); δ_H(80 MHz) 7.11 (d, J 5.2, 4-H), 7.33 (dd, J 5.2 and 0.7, 5-H), 7.40 (5 H, m, phenyl), 8.30 (d, J 0.7, CH) and 8.45 (br s, OH); m/z 203 (65%), 202 (96), 186 (100) and 115 (37); ν_{max}(Nujol) 3180 cm^{-1} (OH).

2-(*Aminomethyl*)-3-*phenylthiophene*. The above oxime (3.30 g, 16.2 mmol), zinc dust (8.49 g, 0.13 mol), ammonium acetate (1.00 g, 13 mmol), aqueous ammonia (d 0.88; 97 cm^3) and ethanol (50 cm^3) were boiled under reflux for 18 h. The mixture was then evaporated and the residue stirred with aqueous potassium hydroxide (33% w/v; 100 cm^3). Ether (30 cm) was added to the mixture which was then filtered through a pad of Celite. The organic layer was then separated, dried and evaporated to leave 2-(*aminomethyl*)-3-*phenylthiophene* as a brown oil (2.89 g, 94%). This product was used without further purification (Found: M^+, 189.0609. $C_{11}H_{11}NS$ requires M,

189.0612); δ_H(200 MHz) 1.62 (br s, NH_2), 4.10 (s, CH_2), 7.06 (d, *J* 5.2, 4-H), 7.23 (d, *J* 5.2, 5-H) and 7.24–7.47 (5 H, m, Ar-H); *m/z* 189 (100%), 188 (78), 173 (27), 171 (32) and 112 (24); ν_{max}(film)/cm^{-1} 3375 (NH).

The thiophene **16**. The crude amine obtained above (2.8 g, 14.8 mmol) was benzoylated by the method described above for compound **10**. Dry-column flash chromatography (silica, ethyl acetate–petroleum, 1:3) gave the product as white crystals (3.63 g, 88%), m.p. 117–118 °C (from ethanol–cyclohexane). Its physical and spectroscopic properties are given in Tables 1 and 2.

3-(*Benzamidomethyl*)-2-*phenylthiophene* **17** (*Scheme* 3).—2-*Bromo*-3-(*bromomethyl*)*thiophene*. A mixture of *N*-bromosuccinimide (19.58 g, 0.11 mol) and benzoyl peroxide (0.4 g, 1.65 mmol) was added portionwise to a refluxing solution of 2-bromo-3-methylthiophene (20 g, 0.11 mol)[15] and benzoyl peroxide (0.4 g, 1.65 mmol) in dry carbon tetrachloride. The solution was boiled under reflux for a further 3 h, cooled and the succinimide filtered off. The filtrate was evaporated and the residue fractionated to yield 2-bromo-3-(bromomethyl)thiophene (22.74 g, 81%), b.p. 78–82 °C/1 mmHg (lit., 88–90 °C/4 mmHg); δ_H(60 MHz) 4.47 (s, CH_2), 7.00 (d, *J* 6, 4-H) and 7.25 (d, *J* 6, 5-H).

2-*Bromo*-3-(*phthalimidomethyl*)*thiophene*. A solution of 2-bromo-3-(bromomethyl)thiophene (8 g, 0.03 mol) and potassium phthalimide (12.97 g, 0.07 mol) in DMF (50 cm^3) was stirred at room temperature for 90 min and then warmed to 45 °C for 90 min. The mixture was evaporated under high vacuum and dichloromethane (30 cm^3) was added to the residue. The mixture was washed with aqueous sodium hydroxide (2 mol dm^{-3}; 2 × 20 cm^3) and water (2 × 10 cm^3), dried, and evaporated and the residue recrystallised from ethanol to give 2-bromo-3-(phthalimidomethyl)thiophene (7.58 g, 79%), m.p. 97–99 °C (Found: C, 48.4; H, 2.4; N, 4.2; M^+ + H (FAB, glycerol), 321.9537. $C_{13}H_8BrNO_2S$ requires C, 48.6; H, 2.5; N, 4.4%; *M* + H, 321.9537); δ_H(200 MHz) 4.80 (s, CH_2), 6.96 (d, *J* 5.7, 4-H), 7.17 (d, *J* 5.7, 5-H), 7.66–7.74 (2 H, m, Ar-H) and 7.78–7.88 (2 H, m, Ar-H); *m/z* (FAB, glycerol) 322 (M + 1, 96%), 321 (100), 274 (47), 257 (50) and 160 (26); ν_{max}(Nujol)/cm^{-1} 1710 (C=O).

3-*Aminomethyl*-2-*bromothiophene*. A solution of 2-bromo-3-(phthalimidomethyl)thiophene (3.5 g, 11 mmol) and hydrazine hydrate (100% solution; 3.4 cm^3) in methanol (40 cm^3) was stirred for 1 h at room temp. and then at reflux for 10 min. The insoluble phthaloylhydrazide was filtered off and the filtrate evaporated. Ether (20 cm^3) and water (20 cm^3) were added to the residue after which the organic layer was separated and extracted with aqueous hydrochloric acid (2 mol dm^{-3}; 2 × 10 cm^3). The acidic extract was basified with aqueous sodium hydroxide (2 mol dm^{-3}; 2 × 25 cm^3) and extracted with dichloromethane (2 × 20 cm^3). Separation, drying and evaporation of the organic layer gave a brown oil which was distilled (Kugelrohr) to give 3-*aminomethyl*-2-*bromothiophene* as a brown oil (1.15 g, 55%); b.p. 94–97 °C/0.03 mmHg (Found: M^+, 190.9388. C_5H_6BrNS requires *M*, 190.9404; δ_H(200 MHz) 1.74 (br s, NH), 3.72 (s, CH_2) and 6.94 (2 H, m, Ar-H); *m/z* 191 (78%), 190 (77), 112 (49), 84 (52) and 69 (100); ν_{max}(Nujol)/cm^{-1} 3140 (NH).

The thiophene **17**. 3-Aminomethyl-2-phenylthiophene (0.84 g, 4.4 mmol) was benzoylated by the method described above for compound **10**. Dry-column flash chromatography (silica, ether–petroleum, 1:4) gave the product as white crystals (0.79 g, 61%), m.p. 111–112 °C (from ethanol–hexane). Its physical and spectroscopic properties are given in Tables 1 and 2.

Preparation of the Imidoyl Chlorides from Amides **12b**, **e**, **f**, **16** *and* **17** *and their Base-promoted Cyclisation to give Heterocyclic-fused Benzazepines*.—The amides were converted into imidoyl chlorides by either of the two general methods shown in Scheme 4 and illustrated below for compounds **12b** and **16**. The method used in each case is indicated in Table 3. The imidoyl chlorides were then cyclised by the general method given below to give the fused azepines **22**, **23**, **26**, **29**, **32**, **33** and **34**. The yields and physical characteristics of the products are given in Table 3.

Conversion of N-[2-(2-*thienyl*)*benzyl*]*benzamide* **12b** *into* N-[2-(2-*thienyl*)*benzyl*]*benzimidoyl chloride* **20b** *and cyclisation to give* 4-*phenyl*-6H-*thieno*[3,2-d][2]*benzazepine* **22**. *N*-[2-(2-Thienyl)benzyl]benzamide (0.50 g, 1.7 mmol), dry ether (30 cm^3) and thionyl chloride (10 cm^3, 0.14 mol) were heated overnight at reflux, under a dry nitrogen atmosphere. The solvent was evaporated and the residue kept under high vacuum for 3 h. Dry THF (25 cm^3) was added to the residue and the mixture cooled to 0 °C. Solid potassium *tert*-butoxide (0.38 g, 3.4 mmol) was then added to it in one portion with rapid stirring under dry nitrogen. The mixture was stirred for 30 min at 0 °C, allowed to warm to room temp. and stirred for a further 30 min. The solution was treated with aqueous ammonium chloride (25% w/v) and stirred for 10 min and then diluted with dichloromethane (20 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 cm^3). The combined organic layer and extracts were dried and evaporated to provide an oil. Dry-column-flash chromatography of this (silica, ethyl acetate–petroleum, 1:9) followed by Kugelrohr distillation gave compound **22** as an oil (0.32 g, 68%), b.p. 185–190 °C/0.3 mmHg.

Picrate salt of compound **22**. Picric acid (1.17 g, 5.1 mmol) was washed with ethanol (3 × 3 cm^3), dried on filter paper and dissolved in acetone (4 cm^3). To this was added compound **22** (0.25 g, 0.9 mmol) in acetone (2 cm^3). After 30 min stirring at room temp., the product was filtered off to give yellow needles (0.40 g, 88%), m.p. 237–238 °C.

Conversion of compound **16** *into* N-(3-*phenyl*-2-*thienylmethyl*)*benzimidoyl chloride* **24** *and cyclisation to give* 6-*phenyl*-4H-*thieno*[2,3-d][2]*benzazepine* **26**. Thionyl chloride (0.46 cm^3, 6.3 mmol) was added dropwise to a solution of 2-benzamidomethyl-3-phenylthiophene (1.50 g, 5.1 mmol) in dry DMF (6.14 g, 0.08 mol) at room temp. and the mixture was then stirred for 30 min. The solvent was removed under high vacuum at 30–35 °C for 3 h. THF (60 cm^3) was added to the residue and the mixture cooled to 0 °C under nitrogen. Solid potassium *tert*-butoxide (3.24 g, 0.03 mol) was added in one portion to the mixture which was stirred for 30 min at 0 °C, and then 30 min at room temp. The solution was treated with aqueous ammonium chloride (25% w/v), stirred for 10 min and then diluted with dichloromethane (30 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 10 cm^3). The combined organic layer and extracts were dried and evaporated. Dry flash chromatography of the residual oil (silica, ether–petroleum, 1:9) followed by crystallisation gave fawn crystals of compound **26** (0.97 g, 69%), m.p. 106–108 °C (from hexane).

Cyclisation of N-[2-(3-*Furyl*)*benzyl*]*benzamide* **12d** *to give* 4-*Phenyl*-6H-*furo*[2,3-d][2]*benzazepine* **31**.—*Using thionyl chloride–DMF*. A mixture of compound **12d** (100 mg, 0.36 mmol), dry DMF (2 cm^3) and thionyl chloride (60 mg, 0.54 mmol) was stirred overnight at room temp., after which the solvent was removed under high vacuum at 30–35 °C for 3 h. Dichloromethane (10 cm^3) and water (10 cm^3) were added to the mixture and the organic layer was separated; the aqueous layer was then extracted with dichloromethane (2 × 5 cm^3). The combined organic layer and extracts were dried and evaporated and the residue was distilled (Kugelrohr) to give compound **31** as an oil (73 mg, 78%), b.p. 170–175 °C/0.3 mmHg.

Using thionyl chloride–ether. This conversion was also carried out in 83% yield by heating under reflux overnight a mixture of compound **12d** (50 mg, 0.18 mmol) dry ether (5 cm^3) and thionyl chloride (1.71 g, 14.4 mmol).

Reaction of N-[2-(2-*Pyridyl*)*benzyl*]*benzamide* **12g** *with Chlorodimethylformiminium Chloride and Cyclisation to give* 5-*Phenyl*-7H-*pyrido*[3,2-d][2]*benzazepine* **36**.—The first part of this reaction was carried out under similar conditions and with the same relative concentrations of reagents as in the NMR study below. A solution of chlorodimethylformiminium chloride in DMF was prepared in a flask equipped with a Suba-seal by adding thionyl chloride (0.908 g, 7.63 mmol) to dry DMF (9.719 g, *ca.* 10 cm^3). After this solution had been kept at room temp. for 20 min a portion (3.70 cm^3, 2.69 mmol) was added by syringe to compound **12g** (0.516 g, 1.79 mmol) in a flask equipped with a Suba-seal. The amide dissolved rapidly to give a clear yellow solution. After 12 h at room temp. the solution was diluted with dry THF (20 cm^3), cooled to 0 °C and potassium *tert*-butoxide (freshly sublimed) (0.91 g, 8.07 mmol) was added in one batch with vigorous magnetic stirring. A dark and persistent colour developed immediately. The solution was kept at 0 °C for 15 min and then at room temp. overnight. Work-up (see above) gave, after dry-column flash chromatography (silica, ethyl acetate–hexane, 1:4), compound **36** (0.33 g, 68%), m.p. 186.5–187.5 °C (from hexane–ethyl acetate).

NMR Studies of the Reactions of the Amides **12a**, **12e** *and* **12g** *with Chlorodimethylformiminium Chloride.*—The spectra obtained in these experiments are discussed in the Results and Discussion section and, for **12g**, shown in Fig. 1.

N-(2-*Phenylbenzyl*)*benzamide* **12a**. Thionyl chloride (36 mg, 0.3 mmol) was added by syringe to [$^2H_7$]DMF (0.25 cm^3) contained in a glass vial fitted with a Suba-seal closure. After 5 min, the solution syringed into a solution of compound **12a** (50 mg, 0.2 mmol) in [$^2H_7$]DMF (0.40 cm^3) contained in an NMR tube equipped with a septum cap. The resultant mixture was examined by ^1H NMR over 12 h. The first spectrum was obtained after 15 min, the last after 12 h.

N-[2-(4-*Pyridyl*)*benzyl*]*benzamide* **12e**. A similar experiment was carried out using compound **12e** (50 mg, 0.2 mmol) in [$^2H_7$]DMF (0.40 cm^3) and thionyl chloride (36 mg, 0.3 mmol) in [$^2H_7$]DMF (0.25 cm^3). The resultant mixture was examined by ^1H NMR over 16 h.

N-[2-(2-*Pyridyl*)*benzyl*]*benzamide* **12g**. (a) A similar experiment was carried out using compound **12g** (50 mg, 0.2 mmol) in [$^2H_7$]DMF (0.40 cm^3) and thionyl chloride (36 mg, 0.3 mmol) in [$^2H_7$]DMF (0.25 cm^3). The resultant mixture was examined by ^1H NMR over 22 h. (b) A COSYPHDQ.AU experiment was also run on the sample after 22 h using the following parameters: (360 MHz) SI2 = 1024, SI1 = 512; SW2 = 1098.901, SW1 = SW2/2 = 549.451; recycle delay (DI) = 3 s, DO = 3 ms, D3 = 3 ms; incremented delay (IN) = 455 ms; PI = 90° pulse, 8 ms; no. of FIDs (NE) = 256; no. of scans (NS) = 48. An NOE experiment was carried out. Irradiation of the doublet at δ 4.73 was carried out in an attempt to observe a saturation transfer effect on the doublet at δ 4.91, however, this experiment resulted only in an NOE of 14%. This sample was also warmed but no coalescence of the doublets was observed up to 80 °C when the compound degraded. (c) After a similar experiment monitored by NMR, the reaction mixture was treated with aqueous sodium carbonate and gave a product which by ^1H NMR contained only the amide **12g**.

For comparison purposes 2D ^1H NMR spectra were also run on the amide **12g** and its hydrochloride salt **37**. The chemical shifts of the pyridyl protons are shown in Table 5.

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