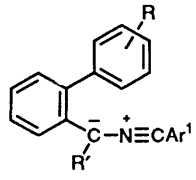
Reactions of Diene-conjugated 1,3-Dipolar Intermediates: A Versatile and Efficient Route to Dibenz[*c,e*]azepines *via* Benzonitrile *o*-Arylbenzyl Ylides[1]

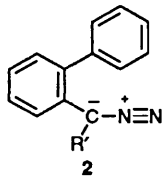
Kevin E. Cullen and John T. Sharp *
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, Scotland

Diene-conjugated nitrile ylides of the type **1** in which both the α,β- and the γ,δ-double bonds are aromatic, and where R is either hydrogen or a *para* substituent, cyclise to give dibenz[*c,e*]azepines **21** (Scheme 2) in high yield. This is in contrast to the analogous diazo system **2** in which cyclisation does not occur. The presence of an *ortho* methyl group in the ring under attack (**1j**, Scheme 3) prevents cyclisation *via* its steric limitation of conjugation in the transition state.

This paper is concerned with the generation and reactions of diene-conjugated nitrile ylides of the type **1** in which both

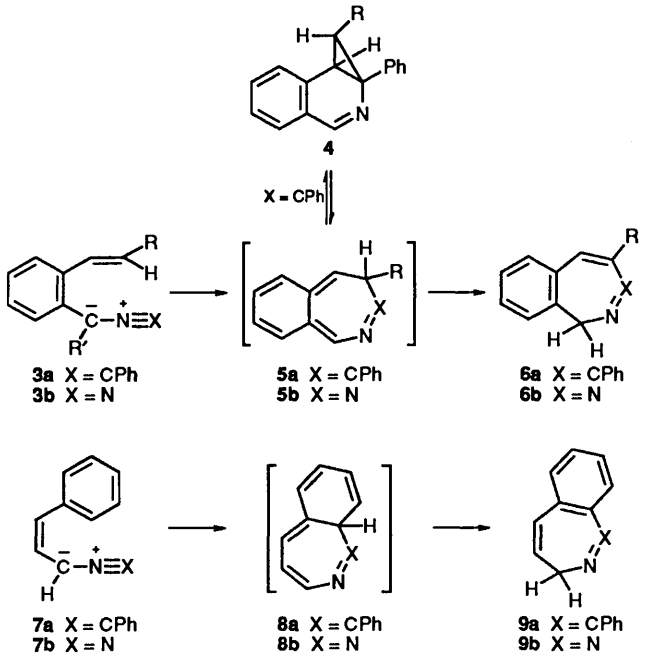


1



2

elements of the diene system are aromatic double bonds. It follows earlier work on analogues **3a**[2] and **7a**[3] in which the diene contains only one aromatic double bond, α,β to the nitrile ylide in **3a** and γ,δ in **7a**. These species cyclised to give the



3a X = CPh
3b X = N

5a X = CPh
5b X = N

6a X = CPh
6b X = N

7a X = CPh
7b X = N

8a X = CPh
8b X = N

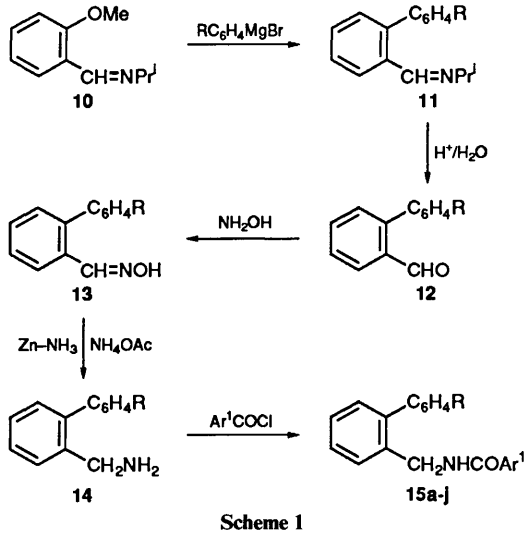
9a X = CPh
9b X = N

benzazepines **6a** and **9a**, respectively. Previous work has also been carried out on the diazo analogues of all these systems **2**,[4] **3b**,[5] and **7b**.[6] Compounds **3b** and **7b** cyclised similarly to give the benzo fused 1,2-diazepines **6b** and **9b**, but **2** failed to cyclise and reacted only *via* loss of nitrogen to give carbene-derived products. It appears that the presence of the two aromatic rings in **2** raises the activation energy for cyclisation above that of the alternative reaction path involving loss of nitrogen. It was, therefore, of interest to study the reactions of the analogous nitrile ylide **1** to find out whether it would cyclise or would also take an alternative path such as dimerisation. Since nitrile ylides seem to be generally more reactive in [1.7] electrocyclisation than diazo compounds and do not have as easy an alternative reaction path; it was hoped, therefore, that **1** would undergo cyclisation to provide a route to dibenz[*c,e*]azepines **21**.

Compounds of this type are of interest for their potential activity in the central nervous system and as cholecystokinin (CCK) and gastrin antagonists.[7]

Results and Discussion

Preparation of Precursors and Generation of Nitrile Ylides.— In all cases the nitrile ylides **1** (Scheme 2) were generated from the amides **15** *via* 1,3-dehydrochlorination of the imidoyl chlorides **22**. The amides **15a–j** (Table 2) were prepared by the route shown in Scheme 1. The formation of the unsymmetrical



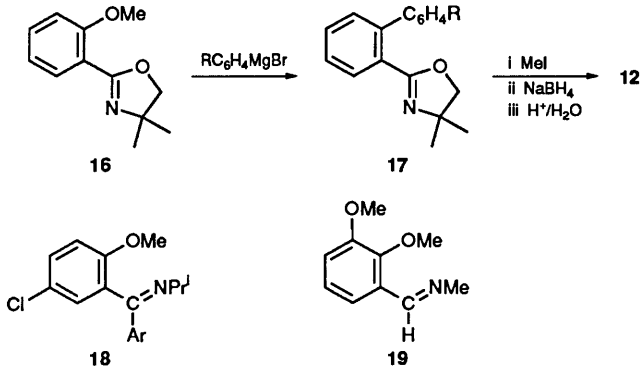
Scheme 1

biaryl, the key step, was achieved by the nucleophilic displacement of the methoxy group in *o*-methoxybenzaldehyde *N*-isopropyl imine **10** using the appropriate aryl Grignard reagent. This was a highly effective reaction and produced the *o*-aryl imines **11** in virtually quantitative yield in most cases. These imines were readily hydrolysed to give the aldehydes **12** which were then converted into the amides **15** *via* the route shown (yields and physical data for compounds **11–14** and **15** are shown in Tables 1 and 2, respectively). The reduction of the oximes **13** using zinc and ammonium acetate was found to be much more convenient and effective than the more common method using lithium aluminium hydride. The use of the *N*-isopropyl imine function in **10** to activate the methoxy group

Table 1 Yields and physical data for imines **11**, aldehydes **12**, oximes **13** and amine hydrochlorides **14**

Compound	R	Yield (%)	Cryst. solvent[a]	M.p./B.p (° C)	Molecular formula	C(%) Found	C(%) Calc.	H(%) Found	H(%) Calc.	N(%) Found	N(%) Calc.	$m/z(M^+)$ Found	$m/z(M^+)$ Calc.
11	H	99	oil		$C_{16}H_{17}N$							223.1347	223.1361
11	4-OMe	81	oil		$C_{17}H_{19}NO$							253.1455	253.1467
11	4-Cl	98	*b*		$C_{16}H_{16}ClN$							257.0970	257.0971[c]
11	2-Me	97	*b*		$C_{17}H_{19}N$							237.1513	237.1517
12	H	77	oil	138–140 (5 mmHg)	$C_{13}H_{10}O$							182.0727	182.0732
12	4-MeO	73	P	52–53	$C_{14}H_{12}O_2$	79.3	79.2	5.7	5.7			212.0836	212.0837
12	4-Cl	69	H	63–65	$C_{13}H_9ClO$	72.0	72.2	4.2	4.2			216.0340	216.0342[c]
12	2-Me	85		94–98[d] (0.25 mmHg)	$C_{14}H_{12}O$							196.0889	196.0888
13	H	83	E	114–116[e]	$C_{13}H_{11}NO$							197.0823	197.0841
13	4-OMe	95	C/E	110–111	$C_{14}H_{13}NO_2$	73.8	74.0	5.8	5.8	6.1	6.2	227.0940	227.0946
13	4-Cl	94	E	161–162	$C_{13}H_{10}ClNO$	67.3	67.4	4.3	4.45	6.0	6.05	233.0413	233.0421[f]
13	2-Me	92	H/E	98–100	$C_{14}H_{13}NO$	79.8	79.6	6.4	6.2	6.7	6.6	211.0996	211.0997
14	H	68			$C_{13}H_{13}N$							183.1050	183.1048
14	4-OMe	57			$C_{14}H_{15}NO$							213.1157	213.1154
14	4-Cl	74			$C_{13}H_{12}ClN$							217.0658	217.0658[c]
14	2-Me	57			$C_{14}H_{15}N$							197.1213	197.1204

[a] P = light petroleum b.p. 60–80 °C, H = hexane, E = ethanol, C = cyclohexane. [b] Amorphous solid which could not be crystallised. [c] For ^{35}Cl isotope. [d] Lit.,[15] 150 °C at 7 mmHg. [e] Lit.,[16] 115 °C. [f] For ^{37}Cl isotope.



to nucleophilic displacement by the Grignard reagent closely parallels the use of the oxazoline ring in the conversion of **16** into **17** devised by Meyers.[8] The advantages of the imine over the oxazoline in this application are simpler preparation and, in particular, the formation of a product **11** whose conversion into the aldehyde **12** is much easier than that of the oxazoline **17**. The Meyers method for the latter conversion, involving the borohydride reduction of the oxazoline methiodide, is a more cumbersome procedure which in our hands gave poor results for compounds **17** in which the aromatic ring contained electron-donating groups. The use of an imine to activate an *ortho*-methoxy group to substitution was first reported by Gschwend[9] in the reaction of the benzophenone imine **18** with an aryl Grignard reagent. The possibility of extending this principle to benzaldehyde imines *e.g.* **10** was attractive but somewhat precarious in view of earlier reports that aldehyde imines react readily with Grignard reagents *via* 1,2-addition to the imine bond and, in particular, that the *N*-methylimine **19** reacted with benzylmagnesium chloride wholly by 1,2-addition rather than by *o*-substitution.[10] In the event, the use of the bulky *N*-isopropyl group in **10** was found to be sufficient to completely disfavour the imine addition reaction. More recently, it has been reported that o-halogenoarylimines undergo a formally similar Grignard cross-coupling reaction.[11] The formation of unsymmetrical biaryls by reactions of this type is a straightforward, high-yielding procedure but it has now been somewhat eclipsed as a method for forming bonds between unsaturated carbon atoms by the range of Pd^0-catalysed coupling reactions which are tolerant of a wider range of substituents.

The conversion of the amides **15** into the imidoyl chlorides **22**, Scheme 2, was accomplished in quantitative yield by the use of thionyl chloride in ether for the amides in which the substituent Ar^1 was either Ph or contained an electron-donating group (cases **a**,**c**,**d**–**f**,**i** and **j**). However, this conversion was found to be much more difficult for the amides in which Ar^1 contained an electron-withdrawing group. Attempts to force the reaction by using thionyl chloride neat or in a higher boiling solvent such as chloroform or tetrahydrofuran (THF) had the disadvantage that it always resulted in concomitant partial decomposition of the imidoyl chloride *via* extrusion of the nitrile Ar^1CN. This occurred to only a small extent in the reaction of the *o*-chloro amide **15g** in THF but was a major difficulty with the less reactive *o*-fluoro derivative **15h** particularly when the conversion was attempted in neat thionyl chloride. The problem was solved by the use of chlorodimethylforminium chloride, a much more reactive chlorinating agent known for its use in the preparation of 'difficult' acid chlorides. This was prepared *in situ* by the reaction of thionyl chloride with dimethylformamide and effected the virtually quantitative conversion of the *o*-chloro amide **15b** and the *o*-fluoro amide **15h** on stirring overnight at room temp. In all cases the formation of the imidoyl chlorides was checked by removal of a sample for ^1H NMR spectroscopy and the compounds were then used directly, without purification, after removal of the solvent and excess of reagent on a rotary evaporator at high vacuum.

Cyclisation of the Benzonitrile o-*Arylbenzyl Ylides* **1a**–**i**.—This, the main group of nitrile ylides studied, have either a *para* substituent R or R = H. In all cases these intermediates cyclised to give the dibenz[*c*,*e*]azepines **21** in high yield. The yields and physical data are given in Table 3 and the spectroscopic data in Table 4. The structures of the products follow from comparison of their spectroscopic data with the related benzazepines **6a**[2] and **9a**[3] and by comparison with literature data.[7] In their ^1H NMR spectra the methylene protons showed the expected pair of doublets. A variable

Table 2 Yields and physical data for the amides **15**

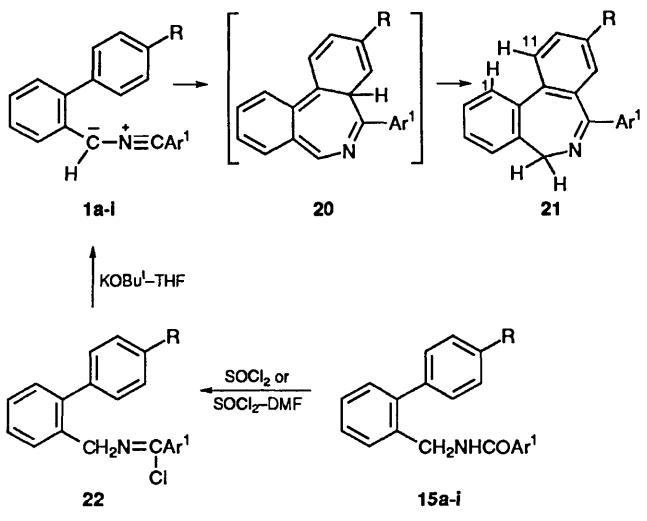
Compound	R	Ar[1]	Yield (%)	Cryst. solvent[a]	M.p. (° C)	Molecular formula	C(%)		H(%)		N(%)		*m/z* (M^+)	
							Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
15a	H	Ph	89	H/E	94.5–95.5	$C_{20}H_{17}NO$	83.6	83.6	5.9	6.0	5.0	4.9	287.1316	287.1310
15b	H	2-ClC_6H_4	83	E	150–151	$C_{20}H_{16}ClNO$	75.05	74.65	5.0	5.0	4.3	4.35		
15c	4-MeO	Ph	61	E	111–112	$C_{21}H_{19}NO_2$	79.4	79.5	6.2	6.0	4.5	4.4		
15d	4-MeO	4-MeC_6H_4	87	H/E	131–133	$C_{22}H_{21}NO_2$	79.7	79.7	6.4	6.4	4.2	4.2	331.1575	331.1572
15e	4-Cl	Ph	63	H/E	118–119	$C_{20}H_{16}ClNO$	74.8	74.65	5.0	5.0	4.4	4.35		
15f	4-Cl	4-MeC_6H_4	64	H/E	149.5–151	$C_{21}H_{18}ClNO$	75.3	75.1	5.7	5.4	4.3	4.2	337.1047	337.1047[b]
15g	4-Cl	2-ClC_6H_4	81	E	140–141	$C_{20}H_{15}Cl_2NO$	67.5	67.6	4.2	4.3	3.9	3.9		
15h	4-Cl	2-FC_6H_4	74	E	99–99.5	$C_{20}H_{15}ClFNO$	70.45	70.8	4.3	4.5	4.0	4.1		
15i	4-Cl	3,4-di-$MeOC_6H_3$	76	E	167–168.5	$C_{22}H_{20}ClNO_3$	68.9	69.3	5.2	5.3	3.7	3.7		
15j	2-Me	Ph	69	H/E	109–110	$C_{21}H_{19}NO$	83.4	83.7	6.4	6.4	4.7	4.7	301.1468	301.1467

[a] H = hexane, E = ethanol. [b] For isotope ^{35}Cl.

Table 3 Yields and physical data for the dibenz[*c,e*]azepines **21**

Compound	R	Ar[1]	Yield (%)	Cryst. solvent[a]	M.p. (° C)	Molecular formula	C(%)		H(%)		N(%)		*m/z* (M^+)	
							Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
21a	H	Ph	76	C	95–96	$C_{20}H_{15}N$	89.4	89.2	5.6	5.6	5.3	5.2	269.1208	269.1204
21b[b]	H	2-ClC_6H_4	76	H/E	141–142	$C_{20}H_{14}ClN$	79.45	79.1	4.7	4.65	4.6	4.6		
21c[c]	4-MeO	Ph	44	H/E	116	$C_{21}H_{17}NO$	84.4	84.2	5.9	5.7	4.8	4.7		
21d	4-MeO	4-MeC_6H_4	90	C	96–97	$C_{22}H_{19}NO$	84.2	84.3	6.1	6.1	4.5	4.5	313.1464	313.1467
21e	4-Cl	Ph	77	M	118–119[e]	$C_{20}H_{14}ClN$	78.85	79.1	4.7	4.65	4.6	4.6		
21f	4-Cl	4-MeC_6H_4	77	C	98–100	$C_{21}H_{16}ClN$	79.2	79.4	5.4	5.1	4.4	4.4	319.0940	319.094[d]
21g	4-Cl	2-ClC_6H_4	67	H/E	124–125	$C_{20}H_{13}Cl_2N$	71.2	71.2	3.8	3.9	4.1	4.1		
21h	4-Cl	2-FC_6H_4	76	H/ET	108–109[f]									
21i	4-Cl	3,4-di-$MeOC_6H_3$	86	H/E	144–145	$C_{22}H_{18}ClNO_2$	72.8	72.7	5.0	5.0	3.9	3.85		

[a] H = hexane, E = ethanol, C = cyclohexane, M = methanol, ET = ether. [b] With P. W. Groundwater and C. Struthers-Semple. [c] With S. D. Jamieson as G.R.S.C. project. [d] For isotope ^{37}Cl. [e] Lit.,[7] 118–119 °C. [f] Lit.,[7] 107–109 °C.



Scheme 2

temperature NMR study on the unsubstituted compound **21a** showed that these doublets coalesced at 149 °C, corresponding to an activation energy for ring inversion of 86 kJ mol^{-1}. This is much higher than for the mono-benzazepines, *e.g.* **6a**, R = Ph, T_c = 62 °C, ΔG = 65 kJ mol^{-1}; and **9a**, T_c = 77 °C, ΔG = 70 kJ mol^{-1}; and must be largely due to the steric interaction of the two aromatic hydrogens at positions 1 and 11.

The cyclisation reactions were all carried out at 0 °C and were complete within a few minutes. There was one interesting difference between these reactions and the earlier cyclisations of **3a** and **7a**; in the latter, the addition of the base produced an immediate deep red/brown coloration which faded over a few minutes. In the reactions of **1** the colour either did not appear at all or was much more transitory under similar reaction conditions and was only prolonged when the reaction was carried out at −20 °C. The colour seen in the reactions of **3a** and **7a** was originally attributed to the presence of the nitrile ylide itself and its duration was taken as a rough indication of the rate of cyclisation. This interpretation is not consistent with the expectation that nitrile ylides of type **1** with two aromatic

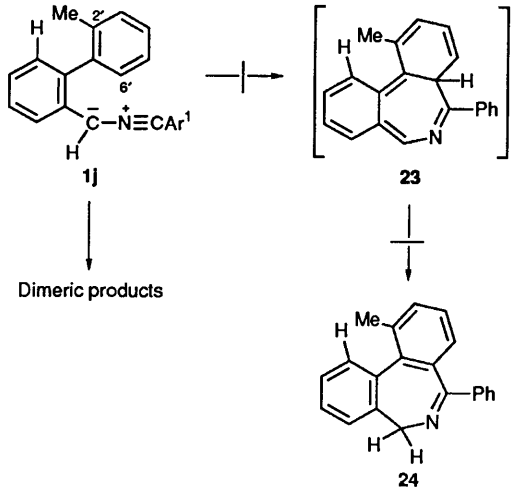
Table 4 Spectroscopic data for amides **15** and dibenz[*c,e*]azepines **21**

Compound	R	Ar^1	Spectroscopic data[a]
15a	H	Ph	δ_H 4.62 (d, *J* 5.6, CH_2), 6.23 (br s, NH), 7.25–7.50 (m, 12 H) ν_{max} 1625 (C=O), 3320 (NH)
15b	H	2-ClC_6H_4	δ_H 4.62 (d, *J* 5.6, CH_2), 6.26 (br s, NH), 7.25–7.70 (m, 13 H) ν_{max} 1630 (C=O), 3248 (NH)
15c	4-MeO	Ph	δ_H 3.85 (s, OCH_3), 4.65 (d, *J* 5.6, CH_2), 6.15 (br s, NH), 6.9–7.7 (m, 13 H) ν_{max} 1625 (C=O), 3275 (N-H)
15d	4-MeO	4-MeC_6H_4	δ_H 2.37 (s, CH_3), 3.83 (s, OCH_3), 4.61 (d, *J* 5.6, CH_2), 6.32 (br s, NH), 6.92–6.99 (m, 2 H), 7.14–7.57 (m, 10 H) ν_{max} 1625 (C=O), 3320 (NH)
15e	4-Cl	Ph	δ_H 4.57 (d, *J* 5.6, CH_2), 6.35 (br s, NH), 7.25–7.70 (m, 13 H) ν_{max} 1632 (C=O), 3283 (N-H)
15f	4-Cl	4-MeC_6H_4	δ_H 2.37 (s, CH_3), 4.56 (d, *J* 5.6, CH_2), 6.33 (br s, NH), 7.16–7.58 (m, 12 H) ν_{max} 1630 (C=O), 3270 (NH)
15g	4-Cl	2-ClC_6H_4	δ_H 4.57 (d, *J* 5.6, CH_2), 6.45 (br s, NH), 7.24–7.63 (m, 12 H) ν_{max} 1642 (C=O), 3287 (N-H)
15h	4-Cl	2-FC_6H_4	δ_H 4.61 (dd, *J* 5.6 and 1.4, CH_2), 6.75 (br, NH), 6.88–7.62 (m, 11 H), 8.06 (td, *J* 7.6 and 2.2, 1 H) ν_{max} 1640 (C=O), 3301 (N-H)
15i	4-Cl	3,4-di-$MeOC_6H_3$	δ_H 3.88 (s, OCH_3), 3.89 (s, OCH_3), 4.57 (d, *J* 5.6, CH_2), 6.19 (br, NH), 6.79 (d, *J* 8.3, 1 H), 7.12 (dd, *J* 8.3 and 2.0, 1 H), 7.2–7.5 (m, 9 H) ν_{max} 1620 (C=O), 3241 (N-H)
15j	2-Me	Ph	δ_H 2.07 (s, CH_3), 4.29 (dd, *J* 14.9 and 5.5, CH), 4.51 (dd, *J* 14.9 and 6.2, CH), 6.19 (br s, NH), 7.14–7.67 (m, 13 H)
21a	H	Ph	δ_H 3.96 (d, *J* 10.4, 5-H), 4.92 (d, *J* 10.4, 5'-H), 7.19–7.81 (m, 13 H) *m/z* 269 (70%), 268(100), 165(30), 134(12) ν_{max} 1600 (C=N)
21b	H	2-ClC_6H_4	δ_H 4.02 (d, *J* 10.5, 5-H), 4.94 (d, *J* 10.5, 5'-H), 7.14–7.56 (m, 10 H), 7.64–7.75 (m, 2 H) δ_C 55.3 (CH_2); 126.5, 126.7, 127.6, 127.8, 128.0, 128.1, 128.7, 129.6, 129.8, 131.0 (all CH); 133.0, 134.8, 138.3, 140.1, 140.4, 140.6 (all quat.); 167.7 (C=N) *m/z* 303(39%), 166(100), 137(63), 102(48), 75(96), 73(50), 63(70), 51(71), 50(72) ν_{max} 1615 (C=N)
21c	4-OMe	Ph	δ_H 3.75 (s, OCH_3), 3.92 (d, *J* 10.4, 5-H), 4.87 (d, *J* 10.4, 5'-H), 6.80–7.70 (m, 12 H) *m/z* 300 (14%), 299(63), 298(60), 268(18), 196(10), 152(16) ν_{max} 1590 (C=N)
21d	4-MeO	4-MeC_6H_4	δ_H 2.33 (s, CH_3), 3.77 (s, OCH_3), 3.92 (d, *J* 10.4, 5-H), 4.86 (d, *J* 10.4, 5'-H), 7.08–7.73 (m, 11 H) *m/z* 313 (20%), 312(16), 69(100) ν_{max} 1600 (C=N)
21e	4-Cl	Ph	δ_H 3.94 (d, *J* 10.5, 5-H), 4.95 (d, *J* 10.5, 5'-H), 7.25–7.75 (m, 12 H) δ_C 55.2 (CH_2); 127.6, 127.7, 127.8, 127.9, 128.2, 129.2, 129.7, 130.2 (all CH); 132.0, 135.3, 137.1, 139.3, 139.8, 140.5 (all quat.); 166.9 (C=N)
21f	4-Cl	4-MeC_6H_4	δ_H 2.35 (s, CH_3), 3.91 (d, *J* 10.5, 5-H), 4.91 (d, *J* 10.5, 5'-H), 7.12–7.16 (m, 2 H), 7.25–7.70 (m, 9 H) *m/z* 319 (27%), 317(100), 282(64), 165(87) ν_{max} 1605 (C=N)
21g	4-Cl	2-ClC_6H_4	δ_H 4.00 (d, *J* 10.5, 5-H), 4.98 (d, *J* 10.5, 5'-H), 7.20–7.75 (m, 11 H) δ_C 55.1 (CH_2); 126.5, 127.6, 127.8, 128.1, 128.2, 129.6, 129.7, 130.0, 130.1, 130.8 (all CH); 132.4, 132.7, 135.9, 137.1, 138.8, 139.2, 139.9 (all quat.); 166.2 (C=N)
21h	4-Cl	2-FC_6H_4	δ_H 3.96 (d, *J* 10.5, 5-H), 5.14 (d, *J* 10.5, 5'-H), 6.9–7.75 (m, 11 H)
21i	4-Cl	3,4-di$MeOC_6H_3$	δ_H 3.87 (s, OCH_3), 3.89 (d, *J* 10.6, 5-H), 3.90 (s, OCH_3), 4.88 (d, *J* 10.6, 5'-H), 6.73–6.88 (m, 2 H), 7.25–7.75 (m, 8 H)

[a] *J* values given in Hz.

rings in the conjugated system should have a higher activation energy and hence a slower rate of cyclisation than those with only one aromatic ring. This inconsistency led to the development of a method of measuring relative rates of cyclisation in these systems[12] which confirmed that cyclisation in systems of the type **3a** is at least 100 × faster than for systems of the type **1**. It seems very unlikely therefore that the transient colour is that of the nitrile ylide but is probably due to the highly conjugated intermediates **5a**, **8a** and **20**. The lifetime of the last of these would be expected to be shorter than that of **5a** or **8a** because the sigmatropic shift in **20** has the driving force of the restoration of the aromatic stabilisation energy of two benzene rings. It is also possible, but less likely, that the colour is that of the benzylic anion produced in the first step of the nitrile ylide generation.

Cyclisation of the Benzonitrile o-*Arylbenzyl Ylide* **1j**.—For use in synthesis, the formation of a single reaction product is desirable and this is only possible in this type of cyclisation reaction when the substituent R is in the *para* position (Scheme 2, **1a–i**), or in the *ortho* position (Scheme 3, **1j**). The former type



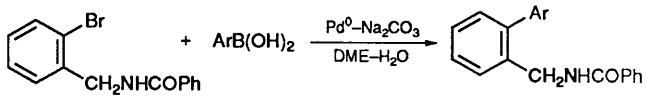
Scheme 3

cyclised readily as discussed above and we report here only some preliminary work on the latter. The results from the first example studied were surprising. It had been expected that the *o*-methyl substituted nitrile ylide **1j** would cyclise at the free *ortho* position to give the dibenzazepine **24** but in the event no cyclisation occurred. Two products were obtained, both of which were shown by mass spectrometry to be nitrile ylide dimers but neither of which have as yet been firmly identified.

The failure of **1j** to cyclise must be due to the steric interaction of the 2'-methyl group with the *ortho*-hydrogen atom in the adjacent ring which restricts rotation about the bond joining the two benzene rings. It is thought that [1.7] electrocyclisation normally takes place *via* a helical transition state[2,5] which involves some twist in the conjugated system, but in this case it appears that the steric effect of the methyl group so much inhibits conjugation between the two benzene rings that an electrocyclisation reaction is not possible. An interesting illustration of the restrictive effect of this methyl group in the precursor amide **15j** is provided by its ^{1}H NMR spectrum (Table 4), in which the methylene protons are seen to be diastereotopic, a unique feature in this set of amides. Further work on this reaction to identify the dimeric products is in progress and on analogous reactants with *ortho* substituents less bulky than methyl in order to establish the lower size limit at which cyclisation is not inhibited.

Conclusions.—This route provides an efficient general synthesis of dibenz[*c*,*e*]azepines **21** which readily allows variation in substituents in both the aromatic ring (Ar^1) and at the 9-position (R). The nature and positions of the substituents in the examples studied were those likely to enhance the CNS activity of the products **21**. One of the attractive features of this kind of electrocyclic aromatic substitution process is that it works well for a wide range of substituents (R) on the aromatic ring onto which cyclisation takes place. The yields are high for both electron-donating and electron-withdrawing substituents, and, in fact, later work[12] has shown that the rate of cyclisation compared to an unsubstituted phenyl ring is enhanced by substituents of both types. This is in contrast to the Bischler–Napieralski type of reaction which is another way of carrying out what is overall a dehydrative cyclisation of an amide onto an aromatic ring. The Bischler–Napieralski reaction is an electrophilic substitution process which works well for electron-rich rings but is ineffective when electron-withdrawing groups are present.

The versatility of this route with respect to the range of substituents (R in **1**) which can be incorporated, could be extended by using the alternative route to the amides **15** *via* Pd^0-catalysed coupling reactions which we have used in more recent work *e.g.* Scheme 4.[12,13] The use of this route to the



Scheme 4

amides **15** followed by the one-pot conversion of **15** into **21** provides a route to the dibenz[*c*,*e*]azepine system which is easier, shorter and as versatile as the best route previously known.[7,8]

Experimental

NMR-spectra were run as solutions in deuteriochloroform unless otherwise stated. Chemical shifts are recorded as δ values. *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[14] using silica gel (15 μm, Fluka Kieselgel 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.

Preparation of the Amides **15a–j**.—The amides were all prepared using the general route shown in Scheme 1. The method is given below in detail for the first example **15a**. The yields and physical data for the imines **11**, aldehydes **12**, oximes **13**, and the amine **14** hydrochlorides are given in Table 1, and for the amides **15** in Table 2. Spectroscopic data for the amides **15** is given in Table 4.

N-*Benzoyl*-2-*phenylbenzylamine* **15a**.—(i) N-(2-*Methoxybenzylidene*)*isopropylamine* **10**. A mixture of *o*-anisaldehyde (40.80 g, 0.30 mol) and isopropylamine (35.40 g, 0.60 mol) was stirred under dry nitrogen at room temp. and concentrated hydrochloric acid (5 drops) was added. The mixture warmed up spontaneously and stirring was continued until the solution cooled to room temp. and then for a further hour at room temp. Sodium hydroxide pellets were added and the mixture was left to stand overnight, filtered and dried. Removal of the excess of isopropylamine on a rotary evaporator followed by distillation

gave *N*-(2-methoxybenzylidene)isopropylamine as a pale green oil (45.55 g, 86%), b.p. 96 °C at 0.3 mmHg (Found: C, 74.5; H, 8.5; N, 7.9. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9%) (Found: *m/z* 177.1159. $C_{11}H_{15}NO$ requires *M*, 177.1154); δ_H(200 MHz) 1.26 (d, *J* 6.3, 2 × CH_3), 3.55 (sept, *J* 6.3, Pr^i-H), 3.82 (s, OCH_3), 6.84–6.99 (m, 2 H), 7.29–7.38 (m, 1 H), 7.96 (dd, *J* 5.9 and 1.8, 1 H) and 8.73 (s, 1 H); *m/z* 176(20%), 162(77), 134(100) and 119(69); ν_{max}(film)/cm^{-1} 1630 (C=N).

(ii) N-(2-*Phenylbenzylidene*)*isopropylamine* **11** (R = H). A solution of *N*-(2-methoxybenzylidene)isopropylamine (14.18 g, 0.08 mol) in THF (30 cm^3) was added dropwise with stirring over 10 min to a Grignard reagent prepared from bromobenzene (16.50 g, 0.104 mol) and magnesium turnings (2.51 g, 0.104 mol) in THF (50 cm^3). The mixture was stirred for a further 10 min and then heated at reflux under dry nitrogen overnight after which GLC (2.5% OV1 at 148 °C) indicated >90% conversion. The mixture was poured, with vigorous stirring into 25% w/v aqueous ammonium chloride (100 cm^3) and stirred at room temp. for 1 h. Extraction with methylene chloride, drying and evaporation gave *N*-(2-phenylbenzylidene)isopropylamine as a yellow oil (17.76 g, 99%); δ_H(200 MHz) 1.25 (d, *J* 6.3, 2 × CH_3), 3.41 (sept, *J* 6.3, Pr^i-H), 7.32–7.48 (m, 8 H), 8.09 (dd, *J* 4.4 and 2.3, 1 H) and 8.27 (s, 1 H); *m/z* 223(20%), 222(100), 180(65) and 165(74); ν_{max}(film)/cm^{-1} 1630 (C=N).

(iii) 2-*Phenylbenzaldehyde* **12** (R = H). A mixture of *N*-(2-phenylbenzylidene)isopropylamine (17.76 g, 0.08 mol) and 2 mol dm^{-3} sulfuric acid (100 cm^3) was heated at reflux under nitrogen for 1.5 h. After cooling, extraction with methylene chloride, drying, evaporation of the solvent and distillation gave 2-phenylbenzaldehyde as a pale green oil (11.20 g, 77%), b.p. 138–140 °C at 5 mmHg (lit.,[15] 150 °C at 7 mmHg); δ_H(200 MHz) 7.35–7.68 (m, 8 H), 8.04 (dd, *J* 6.3 and 0.8, 1 H) and 9.96 (d, *J* 0.8, CHO); ν_{max}(film)/cm^{-1} 1690 (C=O).

(iv) 2-*Phenylbenzaldehyde oxime* **13** R = H. A solution of sodium acetate (5.60 g, 0.066 mol) in water (25 cm^3) was added to a solution of hydroxylamine hydrochloride (4.60 g, 0.066 mol) in water (25 cm^3) and the mixture added rapidly with stirring to a warm (35 °C) solution of 2-phenylbenzaldehyde (11.00 g, 0.06 mol) in ethanol (120 cm^3). A light coloured solid was precipitated, water (60 cm^3) was added and the mixture stored in the cold overnight. Filtration gave 2-phenylbenzaldehyde oxime as a white powder (9.92 g, 83%), m.p. 114–116 °C (from ethanol) (lit.,[16] 115 °C); δ_H(360 MHz) 7.32–7.47 (m, 8 H), 7.89–7.92 (m, 1 H), 8.14 (s, H-C=N) and 8.66 (br s, OH); ν_{max}(Nujol)/cm^{-1} 3170 (OH).

(v) 2-*Phenylbenzylamine hydrochloride* **14** (R = H). 2-Phenylbenzaldehyde oxime (1.58 g, 0.008 mol), zinc dust (4.0 g), ammonium acetate (0.51 g), ethanol (25 cm^3) and concentrated aqueous ammonia (*d* 0.88; 55 cm^3) were heated at reflux under dry nitrogen overnight. The solvent was evaporated and the residue stirred with 33% w/v aqueous potassium hydroxide for 1 h. Ether (50 cm^3) was added, the mixture was filtered through a pad of Celite and the ether layer was separated off and dried. Dry hydrogen chloride was bubbled through the solution to give 2-phenylbenzylamine hydrochloride as a white powder (1.20 g, 68%); δ_H(360 MHz; D_2O) 3.97 (s, CH_2) and 7.23–7.67 (m, 9 H, Ar-H); *m/z* 183(24%), 182(52), 166(100), 165(82) and 69(68).

(vi) N-*Benzoyl*-2-*phenylbenzylamine* **15a**. Benzoyl chloride (0.78 g, 5.5 mmol) was added dropwise with stirring to a mixture of 2-phenylbenzylamine hydrochloride (1.10 g, 5 mmol) and sodium carbonate (1.20 g, 12 mmol) in methylene chloride (15 cm^3) and the mixture was stirred at room temp. under nitrogen overnight. Aqueous sodium hydroxide (5 mol dm^{-3}, 20 cm^3) was added and the mixture was stirred for 0.5 h. Separation of the organic layer, washing with water, drying, evaporation of the solvent, and crystallisation of the residue from hexane–ethanol gave *N*-benzoyl-2-phenylbenzylamine (1.28 g, 89%).

Preparation of the Imidoyl Chlorides **22**.—The amides **15a**, **c–f**, **i**, **j** were converted into imidoyl chlorides by reaction with thionyl chloride in ether as exemplified below for **15a**.

N-(2-*Phenylbenzyl*)*benzimidoyl chloride* **22a**. *N*-Benzoyl-2-phenylbenzylamine **15a** (0.90 g, 3.13 mmol), dry ether (45 cm^3) and thionyl chloride (15 cm^3) were heated under reflux under nitrogen for 20 h. The solvent and excess of thionyl chloride were removed on a rotary evaporator and the residue was kept under high vacuum in the reaction flask for 4 h. The crude product was used directly for generation of the nitrile ylide (see below).

The other imidoyl chlorides were prepared as described below.

N-[2-(4-*Chlorophenyl*)*benzyl*]-2-*chlorobenzimidoyl chloride* **22g**. *N*-(2-Chlorobenzoyl)-2-(4-chlorophenyl)benzylamine **15g** (0.6 g), dry THF (3 cm^3) and thionyl chloride (1.5 g) were heated under reflux for 14 h. Evaporation as described above gave the crude imidoyl chloride.

N-[2-(4-*Chlorophenyl*)*benzyl*]-2-*fluorobenzimidoyl chloride* **22h**. Thionyl chloride (0.46 g) was added to a solution of *N*-(2-fluorobenzoyl)-2-(4-chlorophenyl)benzylamine **15h** (1.06 g) in *N*,*N*-dimethylformamide (4.1 g) at room temp. The mixture was stirred at room temp. for 17 h and the solvent was removed by evaporation under high vacuum using a bath temperature of *ca.* 40 °C to leave the crude imidoyl chloride.

N-(2-*Phenylbenzyl*)-2-*chlorobenzimidoyl chloride* **22b** was prepared by a similar method to **22h** using the amide **15b** (0.66 g), *N*,*N*-dimethylformamide (5 cm^3) and thionyl chloride (0.31 g) for 17 h at room temp.

Generation and Reactions of the Nitrile Ylides **1a–j**.—The general method, exemplified below, was used for the nitrile ylides **1a–i** which all cyclised to give the dibenz[*c*,*e*]azepines **21**. The crude products contained predominantly the dibenzazepines **21** together with up to *ca.* 5% of the amide starting material and very small amounts of a bright yellow by-product seen as the highest R_f spot on TLC. The dibenz[*c*,*e*]azepines were separated by dry-column flash chromatography. In general, these compounds, particularly those with no or non-polar substituents, showed a strong tendency to form glasses and were difficult to crystallise with good recovery. The yields, after crystallisation, and the physical characteristics of the products are given in Table 3 and their spectroscopic data in Table 4. The THF used in these reactions was distilled under nitrogen from sodium diphenylketyl immediately before use and the reactions were carried out under dry nitrogen. The potassium *tert*-butoxide was fresh commercial reagent (Aldrich).

α-(*Benzonitril*-N-*io*)-o-*phenylbenzylide* **1a**. The crude imidoyl chloride **22a**, prepared as described above from the amide **15a** (0.90 g, 3.13 mmol) was dissolved in dry THF (40 cm^3) and the solution, under nitrogen, was cooled in an ice–water bath over a magnetic stirrer. Solid potassium *tert*-butoxide (0.70 g, 6.27 mmol) was added in one batch to the briskly stirred solution, giving an immediate bright yellow colour. The mixture was stirred for a further 10 min at 0 °C, allowed to warm up to room temp. and then stirred for a further 30 min. Aqueous ammonium chloride (25% w/v, 25 cm^3) was added, and the mixture was then extracted with methylene chloride (40 cm^3). The organic extract was dried and evaporated to give the crude product. Dry-column flash chromatography (silica, ethyl acetate–light petroleum 1:10 to 2:10) gave 7-phenyl-5*H*-dibenz[*c*,*e*]azepine **21a** (0.80 g, 2.97 mmol, 95%) as pale yellow glass pure by NMR spectroscopy and TLC. Crystallisation from cyclohexane gave the product as a white crystalline solid (76%) m.p. 95–96 °C. (In this case only, in a variation of the above procedure, it was found that the product after

chromatography could be distilled without decomposition in a Kugelrohr apparatus at an oven temperature of 180–200 °C at 0.05 mmHg to give 7-phenyl-5*H*-dibenz[*c*,*c*]azepine **21a** as a colourless glass.)

α-(*Benzonitril*-N-*io*)-o-(2-*methylphenyl*)*benzylide* **1j**. (This reaction was carried out by Mr D. J. Sloan as part of a final-year project). The nitrile ylide was generated from the amide **15j** (0.30 g) and treated and worked-up as described above. Dry-column flash chromatography (silica, ethyl acetate–light petroleum 1 : 19 to 1 : 9) gave two unidentified dimeric products (i) a yellow solid (0.12 g) which could not be crystallised, *m*/*z* 567(13%), 565(78), 550(20), 387(60), 385(60), 178(100) and 165(94); and (ii) a pale yellow oil (0.20 g), *m*/*z* 567(33%), 566(82), 551(41), 385(100), 283(36), 178(40) and 165(95).

Acknowledgements

We thank the University of Edinburgh for financial support *via* a Faculty of Science Studentship for K. E. C.

References

1 P. W. Groundwater, C. Struthers-Semple and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1987, 1367.
2 K. R. Motion, I. R. Robertson, J. T. Sharp and M. D. Walkinshaw, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1709.
3 P. W. Groundwater and J. T. Sharp, *Tetrahedron*, 1992, **48**, 7951.
4 J. T. Sharp, unpublished observations.
5 D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 849 and references cited therein.
6 T. K. Miller, J. T. Sharp, H. R. Sood and E. Stefaniuk, *J. Chem. Soc., Perkin Trans. 2*, 1984, 823 and references cited therein.
7 H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, 1982, **47**, 3652; and U.S. Pat. 4315926/1982 (Ciba-Geigy Corporation).
8 A. I. Meyers and E. D. Mihelich, *J. Am. Chem. Soc.*, 1975, **97**, 7383.
9 J. J. Fitt, H. W. Gschwend, A. Hamdan, S. K. Boyer and H. M. Haider, *J. Org. Chem.*, 1982, **47**, 3658.
10 R. B. Moffet and W. M. Hoehn, *J. Am. Chem. Soc.*, 1947, **69**, 1792.
11 L. N. Pridgen, L. Snyder and J. Prol, Jr., *J. Org. Chem.*, 1989, **54**, 1523.
12 K. E. Cullen and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1991, 658.
13 H. Finch, D. H. Reece and J. T. Sharp, unpublished observations.
14 *Practical Organic Chemistry, a Student Handbook of Techniques*, J. T. Sharp, I. Gosney and A. G. Rowley, Chapman and Hall, London, 1989, p. 160.
15 A. I. Meyers, *J. Org. Chem.*, 1983, **48**, 4053; A. Zaheer and A. Faseeh, *J. Indian Chem. Soc.*, 1944, **21**, 381.
16 R. Fanto, *Monatsh. Chem.*, 1898, **19**, 588.

Paper 3/03621I
Received 24*th June* 1993
Accepted 2*nd July* 1993