Formation of 1,2,3,4-dibenzocycl[2.2.3]azines by a novel consecutive 1,3-dipolar cycloaddition of pyridinium dicyanomethylides to benzyne

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A one-pot procedure for the direct and surprisingly simple formation of the title compounds by the reactions of pyridinium dicyanomethylides with benzyne are described together with full details of the ^1H and ^{13}C NMR data for the products.

Since Boekelheide *et al.* reported the first synthesis of cycl[2.2.3]azines,[1] their synthesis and physicochemistry has attracted much interest.[2] Specifically, peripherally conjugated heterocyclic systems such as bridged heteroannulenes and cyclazines are useful in obtaining experimental evidence for recognition of the net energy changes associated with π-electron delocalizations. Although the parent cycl[2.2.3]azine **1**[3] is a typical example, giving a peripheral 10π electron conjugated system, little is known about larger systems, apart from one highly complex system,†[4] despite their potential aromaticity. One of the simplest such possible compounds, having a 18π-perimeter, would be the 1,2,3,4-dibenzocycl[2.2.3]azine system **2**. In connection with the 1,3-dipolar cycloadditions of cycloimmonium ylides, we have investigated the reactions of pyridinium dicyanomethylides with benzyne,[5] and found that the title compounds are formed in a one-pot procedure.[6] This reaction is the subject of the present paper.

The reaction of the pyridinium dicyanomethylide **3a** with benzyne either generated from diphenyliodonium-2-carboxylate monohydrate at *ca.* 200 °C (Method A) or anthranilic acid and isopentyl nitrite in refluxing chloroform–acetone (Method B) gave, after chromatographic purification followed by recrystallization, dibenzocycl[2.2.3]azine **2a** as pure orange coloured needles (mp 130 °C) along with 6-cyanobenzo[*a*]indolizine **5a**.[6] In a similar manner, 4-substituted pyridinium dicyanomethylides **3b–f** afforded the corresponding dibenzocycl[2.2.3]azines **2b–f** *via* 2-substituted 6-cyanobenzo[*a*]indolizine **5b–f**.[6] The former products **2a–f** which constitute the first example of an 18π cyclazine system had microanalytical data which were satisfactory. Electron-impact (EI) mass spectrometry (MS) of the products **2a–f** established their molecular weights. The reaction probably proceeds by a surprising sequence of reactions involving (i) cycloaddition of pyridinium dicyanomethylides with benzyne, (ii) elimination of hydrogen cyanide to give 6-cyanobenzo[*a*]indolizine **5**, (iii) cycloaddition of 6-cyanobenzo[*a*]indolizine **5** with benzyne and (iv) elimination of hydrogen cyanide.[7] Indeed, the reactions of 6-cyanobenzo[*a*]indolizine **5** with benzyne generated from diphenyliodonium-2-carboxylate monohydrate gave the corresponding dibenzocycl[2.2.3]azines **2a–f** in better yields (Method C). The results are summarized along with the ^1H and ^{13}C NMR data in Tables 1–3.

† We are indebted to one of the referees for calling attention to this reference.

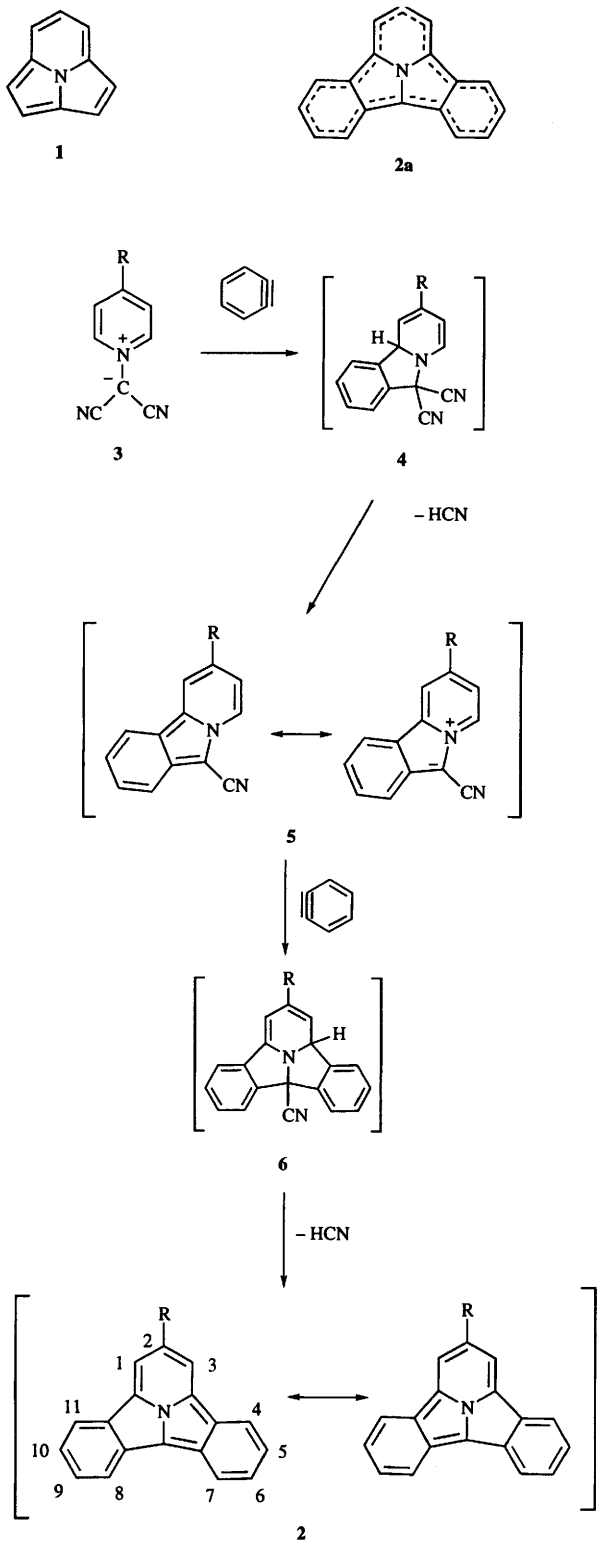
Table 1 Yields of 1,2,3,4-dibenzocyclazines **2**

Comp.	R	Yield (%)[a] Method A	Method B	Method C
2a	H	11[20]	4[35]	39
2b	Me	5[22]	2[12]	33
2c	Ph	3[44]	2[10]	38
2d	PhCO	0.5[21]	17[24]	25
2e	MeOCO	0.3[33]	—	32
2f	MeCO	Trace[27]	—	18

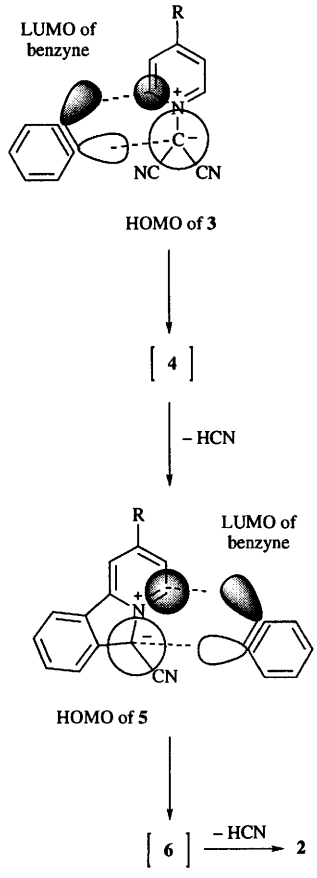
[a] The figure in [ ] shows the yield of 6-cyanoindolizines **5**.

In order to understand the surprisingly facile formation of the system in a one-pot procedure, we have performed PM3 molecular orbital (MO) calculations for the substrates **3** and the intermediates **5**.[8] We tested various LUMO–HOMO overlaps to find effective **3**•benzyne charge transfer (CT) and found a reasonable stacking approach in which there is sufficient overlap on the basis of the FMO (frontier MO) nodal properties, indicating that the 1,3-dipolar cycloaddition of **3** and **5** is likely (see Scheme 2). Since benzyne is a well-known electrophile,[9] it is understandable that the FMO interaction between the LUMO of benzyne and the HOMO of dicyanomethylide **3** controls the addition sites in the exocyclic carbanion position. The benzyne molecule is planar in the C_{2v} point group and the LUMO of benzyne extends in-the-plane.[10] To match this antisymmetric MO, an antisymmetric part of the HOMO in **3** must be prepared for an effective charge transfer. Since the largest extension of the HOMO of **3** is on the C-2 position, the antisymmetric partner site should be the C-2 position in **3**. This in-plane combination leads to a 1,3-cycloadduct **4**. The initial cycloadduct **4** eliminates HCN easily to undergo aromatization and form the indolizine **5**. Similarly, the FMO interaction between the HOMO of **5** and the LUMO of benzyne leads to the formation of 1,3-cycloadduct **6**. The intermediate **6** eliminates HCN easily again to form the final product **2a**. The HOMO energies of **3** and **5** are summarized in Table 4. The pyridinium dicyanomethylides **3** and 6-cyanobenzoindolizines **5** which have an electron-withdrawing group and, therefore, lower HOMO, generally gave poorer yields of **2**.

The IR spectra of dibenzocycl[2.2.3]azines **2a–f** display absorption at 1610 cm^{-1} (very strong) and around 1595 (strong) cm^{-1} ascribable to the C=C stretching vibrations characteristic



Scheme 1 Formation of 1,2,3,4-dibenzocycl[2.2.3]azine **2** by a novel consecutive 1,3-dipolar cycloaddition to benzyne



Scheme 2 An FMO Interpretation of the consecutive 1,3-dipolar cycloadditions leading to 1,2,3,4-dibenzocycl[2.2.3]azines **2**

of a π-perimeter system. It has been shown that for geometrically similarly disposed groups there is a good correlation between the frequency and the calculated bond order. Thus, we may infer that delocalization of electrons decreases (bond order of C=C increases) and that these dibenzocycl[2.2.3]azines **2** are more aromatic than any other known cyclazine derivatives.

The proton-noise-decoupled ^{13}C NMR spectrum (125.65 MHz) of the cycl[2.2.3]azine **2a** consists of 10 signals of four singlets (δ 125.5, 124.6, 121.9 and 120.7) and six doublets (δ 126.9, 121.9, 120.6, 118.6, 116.7 and 111.9), suggesting a symmetrical form of **2a** in solution. The assignments are based upon the off-resonance and selective decoupling experiments. The downfield-resonating signals at δ 125.5 (s, 2C) and 124.6 (s, 1C) are ascribed to C-3a and C-7b, respectively, since the carbons are attached to the central nitrogen atom. The remaining two singlets at δ 121.9 and 120.7 are due to C-7a and C-3b, respectively. The six doublets are ascribed to the aromatic carbon atoms with hydrogen atoms. The results are summarized in Table 2.

Table 3 lists the ^1H NMR spectral data for the products **2a–f**. The ^1H NMR spectrum of dibenzocycl[2.2.3]azine **2a** has two broad multiplets (intensity ratio 1:2) with AB_2 and ABCD patterns for the three- and four-ring protons around δ 7.8–8.5 and 7.0–6.5. These patterns reduce to one AB_2 and two ABCD spin systems for **2b–f**. The most striking observation is the downfield shift of the outer protons (δ 7.86 and 8.52), a difference of *ca.* 0.3 and 0.7 ppm compared with those of cycl[2.2.3]azine **1**.[11] This is interpreted in terms of the strong anisotropic effect of the system.

The UV–visible spectrum (see Experimental section) of dibenzocycl[2.2.3]azine **2a** consists of six absorption maxima of n–σ* and π–π* transitions around 268, 306, 325, 348, 364, 472 and 504 nm, respectively, whereas the longest wavelength absorption of the parent cyclazine **1** appears at 430 nm.[12] The deep orange colour of dibenzocycl[2.2.3]azines differs from that of cycl[2.2.3]azine which is pale yellow; this is reflected in a 70 nm shift towards the red of the maximum of its longest wavelength absorption compared with that of cycl[2.2.3]-azine.[12] The large bathochromic shift implies that the π delocalization of dibenzocycl[2.2.3]azine is enhanced relative to that of cycl[2.2.3]azine according to the Huckel (4n + 2)π rule for peripherally conjugated systems. It is reasonable to assume that the longest wavelength band (504 nm) is due to in-plane excitation of the molecular plane, whose transition is regarded as of intramolecular charge transfer type.

Table 2 ^{13}C chemical shifts of dibenzocyclazines **2**

Comp.	R	C-1,3	C-2	C-3a	C-3b	C-4	C-5	C-6	C-7	C-7a	C-7b	Substituent
2a	H	112.4	117.2	127.6	114.4	122.3	121.0	127.3	118.9	122.3	125.1	
2b	Me	124.8	113.3	128.1	113.5	122.3	120.5	127.2	118.8	125.1	127.9	22.7 (CH_3)
2c	Ph	131.3	111.3	128.1	114.2	122.3	121.1	127.4	119.1	125.0	126.2	141.6 (ipso-Ph), 128.0 (*o*-Ph) 129.1 (*m*-Ph), 127.1 (*p*-Ph)
2d	PhCO	128.3	114.5	128.1	117.9	122.9	122.5	127.9	119.7	123.9	125.7	139.0 (ipso-Ph), 130.0 (*o*-Ph) 128.5 (*m*-Ph), 131.9 (*p*-Ph)
2e	MeOCO	118.1	113.5	128.3	118.1	122.4	122.7	127.8	119.6	123.9	127.7	52.5 (CH_3O), 167.6 (CO)
2f	MeCO	128.4	112.4	128.4	117.9	122.4	122.9	127.9	119.8	124.0	128.2	27.0 (CH_3), 196.7 (CO)

Table 3 ^{1}H chemical shifts of dibenzocyclazines **2**

Comp.	R	H-1,3 (*J*/Hz)	H-2 (*J*/Hz)	H-4,11 (*J*/Hz)	H-5,10 (*J*/Hz)	H-6,9 (*J*/Hz)	H-7,8 (*J*/Hz)	Substituent
2a	H	8.52 (7.8)	7.86 (7.8)	8.54 (8.5)	7.50 (8.5)	7.75 (8.5)	8.41 (8.5)	
2b	Me	8.31		8.48 (8.8)	7.43 (8.8)	7.71 (8.8)	8.34 (8.8)	2.97 (CH_3)
2c	Ph	8.72		8.56 (7.6)	7.49 (7.6)	7.75 (7.8)	8.39 (7.8)	7.93 (8.5), 7.59 (8.2), 7.44 (7.6)
2d	PhCO	8.96		8.51 (8.0)	7.56 (8.0)	7.78 (8.0)	8.39 (8.0)	7.94 (8.0), 7.60 (8.0), 7.68 (8.0)
2e	MeOCO	9.16		8.58 (7.7)	7.60 (7.7)	7.80 (7.8)	8.34 (7.8)	4.13 (CH_3O)
2f	MeCO	9.07		8.56 (7.9)	7.60 (7.9)	7.80 (7.9)	8.41 (7.9)	2.95 (CH_3CO)

Table 4 HOMO energies (eV) of pyridinium dicyanomethylides **3** and 6-cyanobenzoindolizines **5**[a]

R		HOMO energy		HOMO energy
H	**3a**	−8.653	**5a**	−8.195
Me	**3b**	−8.544	**5b**	−8.114
Ph	**3c**	−8.463	**5c**	−8.073
Ph_5CO	**3d**	−8.839	**5d**	−8.381
MeOCO	**3e**	−8.926	**5e**	−8.447
MeCO	**3f**	−8.880	**5f**	−8.414

[a] Calculated by semiempirical molecular orbital (PM3) method.[8] The LUMO energy of benzyne by the same method (PM3) was −0.902 eV.

Experimental

General

Mps were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ^{1}H NMR spectra were measured either on a JEOL JNM-EX270 (270 MHz) or JNM-ALPHA500 (500 MHz) instrument. ^{13}C NMR spectra were recorded either on a JNM-EX270 or JNM-ALPHA500 spectrometer operating at 67.80 and 125.65 Hz, respectively. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were obtained on a JEOL JMS-DX303 spectrometer at 70 eV of ionization energy for EI-HRMS. The UV–visible spectra were taken on a Hitachi 220A spectrophotometer. Preparative medium-pressure liquid chromatography (MPLC) was carried out using a column (25 × 310 mm) pre-packed with silica gel (Lobar, LiChroprep Si60, Merck). Pyridinium dicyanomethylides **3** were obtained according to a previously reported method.[13] All the solvents used for the preparation of dibenzocycl[2.2.3]azines **2** (benzo[*a*]isoindolo[1,2,3-*cd*]indolizines) were freshly distilled under nitrogen from appropriate drying agents.

General procedures for the preparation of benzo[*a*]isoindolo-[1,2,3-cd]indolizines (dibenzocycl[2.2.3]azines) 2a–f

Method A and Method B. These have already been published.[6]

Method C. A mixture of the 6-cyanobenzo[*a*]indolizine **5** (1 mmol) and diphenyliodonium-2-carboxylate monohydrate (1.1 mmol) in 1,2-bis(2-methoxyethoxy)ethane (15 cm^3) was heated at 190–200 °C in an oil-bath for 3 h. After removal of the solvent, the residue was purified by MPLC (eluent ethyl acetate–hexane, 1 : 10).

Benzo[a]*isoindolo*[1,2,3-cd]*indolizine* **2a**.—Mp 130–131 °C (Found: C, 89.4; H, 4.3; N, 5.9. $C_{18}H_{11}N$ requires C, 89.6; H, 4.6; N, 5.80%); $\lambda_{max}(CHCl_3)$/nm 268 (ε/dm^3 mol^{-1} cm^{-1} 61 200), 306 (7120), 325 (11 000), 348 (7230), 364 (11 100), 472 (4510) and 504 (6600); $\nu_{max}(KBr)/cm^{-1}$ 1616, 1600, 1415 and 1336; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2 (Found: M^+, 241.0879. $C_{18}H_{11}N$ requires *M*, 241.0891).

2-*Methylbenzo*[a]*isoindolo*[1,2,3-cd]*indolizines* **2b**.—Mp 194–197 °C (Found: C, 89.4; H, 4.9; N, 5.4. $C_{19}H_{13}N$ requires 89.4; H, 4.6; N, 5.5%); $\lambda_{max}(CHCl_3)$/nm 270 (ε/dm^3 mol^{-1} cm^{-1} 62 700), 330 (12 300), 352 (7650), 368 (11 400), 484 (4170) and 516 (6950); $\nu_{max}(KBr)/cm^{-1}$ 2920, 1611, 1434 and 1348; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2 (Found: 255.1062. $C_{19}H_{13}N$ requires 255.1048).

2-*Phenylbenzo*[a]*isoindolo*[1,2,3-cd]*indolizines* **2c**.—Mp 174–180 °C (Found: C, 90.7; H, 4.9; N, 4.5. $C_{24}H_{15}N$ requires 90.8; H, 4.8; N, 4.4%); $\lambda_{max}(CHCl_3)$/nm 272 (ε/dm^3 mol^{-1} cm^{-1} 53 500), 290 (44 600), 332 (11 800), 381 (18 300), 482 (4060) and 515 (6720); $\nu_{max}(KBr)/cm^{-1}$ 1610, 1593 1431 and 1130; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 1 (Found: 317.1232. $C_{24}H_{15}N$ requires 317.1204).

2-*Benzoylbenzo*[a]*isoindolo*[1,2,3-cd]*indolizines* **2d**.—Mp 216–217 °C (Found: C, 87.0; H, 4.5; N, 4.2. $C_{25}H_{15}NO$ requires C, 86.9; H, 4.4; N, 4.1%); $\lambda_{max}(CHCl_3)$/nm 273 (ε/dm^3 mol^{-1} cm^{-1} 49 500), 284 (28 500), 426 (18 200), 432 (10 600) and 484 (6700); $\nu_{max}(KBr)/cm^{-1}$ 1641, 1618, 1589 and 1368; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2 (Found: 345.1175. $C_{25}H_{15}NO$ requires 345.1153).

2-*Methoxycarbonylbenzo*[a]*isoindolo*[1,2,3-cd]*indolizines* **2e**.—Mp 233–234 °C (Found: C, 80.3; H, 4.2; N, 4.6. $C_{20}H_{13}NO_2$ requires C, 80.3; H, 4.4; N, 4.7); $\lambda_{max}(CHCl_3)$/nm 272 (ε/dm^3 mol^{-1} cm^{-1} 53 200), 284 (51 800), 322 (5230), 396 (18 600), 461 (5230) and 492 (6230); $\nu_{max}(KBr)/cm^{-1}$ 2925, 1701, 1615 and 1598; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2 (Found: 299.0930. $C_{20}H_{13}NO_2$ requires 299.0793).

2-*Acetylbenzo*[a]*isoindolo*[1,2,3-cd]*indolizines* **2f**.—Mp 249–252 °C (Found: C, 85.0; H, 4.5; N, 4.7. $C_{20}H_{13}NO$ requires C, 84.8; H, 4.6; N, 4.9%); $\lambda_{max}(CHCl_3)$/nm 273 (ε/dm^3 mol^{-1} cm^{-1} 47 100), 288 (43 400), 412 (18 700), 462 (5800) and 493 (6100); $\nu_{max}(KBr)/cm^{-1}$ 2912, 1655, 1620 and 1586; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2 (Found: 283.1007.$C_{20}H_{13}NO$ requires 283.0997.

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