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THE THERMAL REARRANGEMENT OF 2-ARYL-1-CYANOINDAZOL-3-ONES

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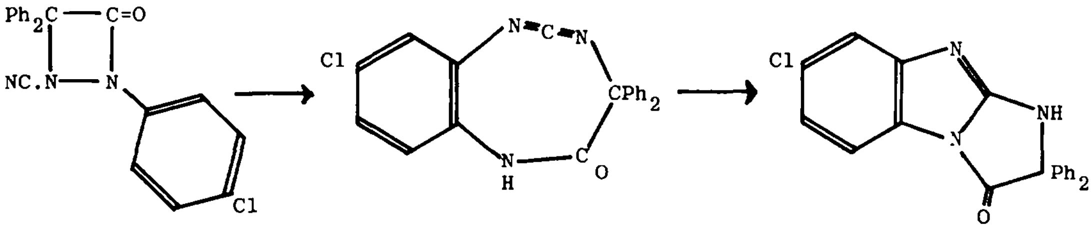
Abstract-A range of 2-aryl-1-cyanoindazol-3-ones has been prepared and their thermal rearrangement to the corresponding benzimidazo[2,1-b]-quinazolones investigated. Quantitative studies using differential scanning calorimetry have provided rates, energies and entropies of activation. The rates of rearrangement of the 2-(p-substituted-phenyl) compounds are shown to be correlated by the Hammett relationship using σ^+ rather than σ substituent constants. In the case of the 2-(2,6-dimethylphenyl) and 2-(2,4,6-trimethylphenyl) comounds rearrangement is accompanied by [1,9] sigmatropic shifts of the obstructing methyl groups.

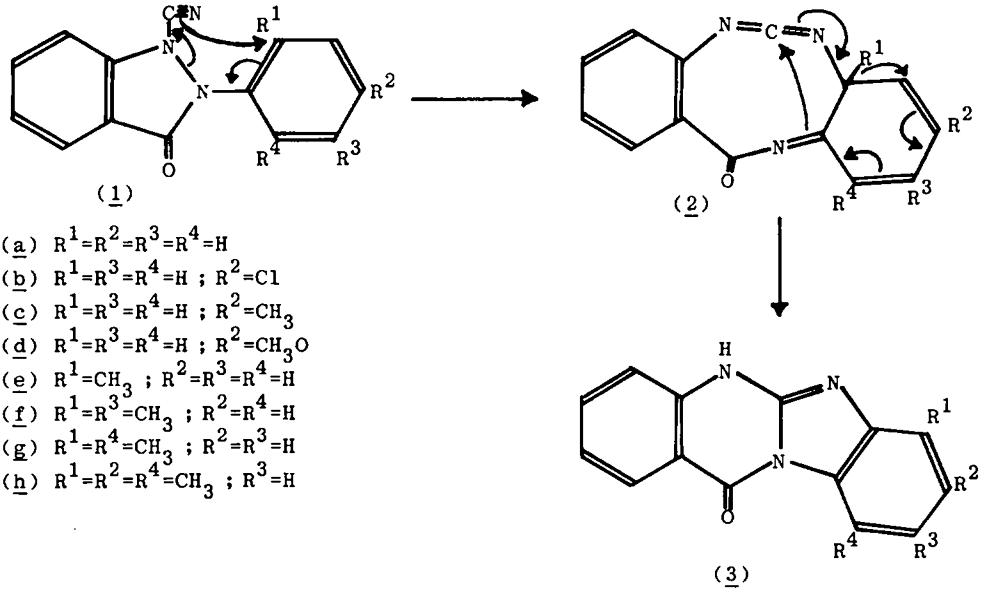
Following the original observation[1] of the facile thermal rearrangement of 1-aryl-2-cyanodiazetidinones to the isomeric imidazo[1,2-a]benzimidazoles, the mechanistic aspects of such transformations have been investigated[2,3,4] extensively and the following pathway conclusively established.



However, mechanistic probing of the rearrangement has been obstructed by the reluctance of diphenylketen to undergo cycloaddition to arenediazocyanides bearing electron donating substituents on the aromatic ring. Thus it has not been possible to assess the relative merits of the use of σ or σ^+ substituent constants in correlating the rates of rearrangement of appropriate diazetidinones using the Hammett relationship[3]. Also, while diazetidinones bearing o,o'-dichloro or dibromo substituents in the aryl group rearrange with migration of one of the obstructing halogen atoms[4,5] it has not been possible to establish whether alkyl groups will undergo comparable migrations. Such rearrangements involving molecules containing the N-aryl-N'-cyanohydrazine moiety have been shown to be of wider generality[6,7], and in particular it has been reported earlier that 2-phenyl-1-cyanoindazolone undergoes thermally initiated conversion into benzimidazo[2,1-b]quinazolin-12-one. The relatively recent report[8] of a more convenient synthetic route to 2-arylindazolones prompted the present work intended to remedy the foregoing omissions.

All of the 2-arylindazolones employed in the present study were synthesised by the base catalysed cyclisation of the corresponding o-azidobenzanilides[8], and were converted into the N-cyano derivatives by treatment of the derived anions with cyanogen bromide. Although this procedure normally gave good yields of the desired (1), the presence of o-substituents in the 2-aryl group led to a marked diminution in yield, presumably due to steric hindrance, and we were unable to obtain any of the N-cyano derivatives from either the 2-(2',5'-dichlorophenyl) or the 2-(2',6'-dichlorophenyl)indazolone.

Each of the cyanoindazolones (1) smoothly rearranged to the isomeric benzimidazoquinazoline (3) on heating to ca. 270°. Of particular note was the conversion of the 2-(2',6'-dimethylphenyl) compound (1g) to (3g). The orientation of (3g) was confirmed by its alternative obtention from 2-(2',5'-dimethylphenyl)-1-cyanoindazolone (1f). A parallel rearrangement was observed also for the 2-(2',4',6'-trimethylphenyl) derivative (1h) giving presumably (3h). These methyl group migrations are conveniently viewed as resulting from a [1,9] sigmatropic shift in the intermediate (2). Apart from the halogen shifts mentioned above[4,5] we are only aware of one other report of the occurrence of [1,9] shifts[9], also involving methyl groups as part of a more complex transformation.



(1)

(a) $R^1=R^2=R^3=R^4=H$
(b) $R^1=R^3=R^4=H$; $R^2=Cl$
(c) $R^1=R^3=R^4=H$; $R^2=CH_3$
(d) $R^1=R^3=R^4=H$; $R^2=CH_3O$
(e) $R^1=CH_3$; $R^2=R^3=R^4=H$
(f) $R^1=R^3=CH_3$; $R^2=R^4=H$
(g) $R^1=R^4=CH_3$; $R^2=R^3=H$
(h) $R^1=R^2=R^4=CH_3$; $R^3=H$

(2)

(3)

The rearrangements of (1a-1h) were also studied by differential scanning calorimetry which provided the rates of reaction over a range of temperatures, as well as the energies and entropies of activation which are recorded in Table 1. No discontinuity was observed in any of the differential enthalpic curves such as might have been anticipated if, for example, the rate of conversion of the intermediate (2) to (3) were slower than its rate of formation from (1). The reproducibility of rate constants from run to run was generally within a range of ±2% and the derived energies of activation probably reproducible to within 4 to 8 KJ/mole. The much higher energies of activation observed for these arylcyanoindazolones than for the diazetidinones (ca. 62KJ/mole) are in line with earlier observations[3] on compound (1a) and ascribed to the much reduced contribution of relief of ring strain in the present case. The failure of substituents in the 2- and 6-positions of the 2-aryl group to show a marked effect on the ease of rearrangement points to a transition state in which bond breaking is more advanced than bond making. This conclusion is supported by the results of correla-

TABLE 1 Rate Constants and Activation Parameters for the Rearrangement of 2-Aryl-1-cyanoindazol-3-ones (1a-h).

Compd.	Rate constants ($k \times 10^{-3} sec^{-1}$) at indicated temperature(°K)										E_a	S^*
	420	430	440	450	460	470	480	490	500	509	KJ/mol	J/mol°K
1a				0.7	1.9	4.6	9.6	17.4	33.1		146	8
1b					0.6	1.6	3.5	7.9	15.5	28.4	145	-3
1c				2.1	4.6	9.0	16.4	23.0	27.3	29.5	158	41
1d#	2.9	7.7	16.2	26.4	29.8						163	66
1e			1.1	2.6	6.9	16.5	35.1	60.4			159	47
1f		1.4	3.5	8.2	17.2	33.1	46.9				160	56
1g				0.7	1.5	3.1	6.8	17.3	34.4	35.4	144	1
1h			0.9	2.5	7.3	26.4	95.8				157	40

*Calculated for 460°K

#Measured in m-bis(m-phenoxyphenoxy)benzene (OS124) to avoid coincidence of melting endotherm and rearrangement exotherm.

tion of the rate constants utilising the Hammett relationship. Whereas the rates of rearrangement of compounds (1a –1d) at 460° are poorly correlated (r=0.948) using the conventional σ substituent constants, an excellent linear relationship is observed with σ^+ ones (r=0.984) leading to a value of -1.74 for ρ. This is somewhat lower than the value of -2.9 found for the corresponding diazetidinone rearrangement and can be attributed to the availability of the indazolone benzene ring to help to distribute charge developing on N-1 during N-N cleavage. These values point to a reasonable amount of charge separation in the transition state, and lie well within the the range so far observed for [3,3] sigmatropic shifts from 0.5-0.6 for the Claisen rearrangement of allyl aryl ethers[9,10] to 5.8 for the conversion of pyridine N-arylimines to 2-(o-aminobenzyl)pyridines[11]. We also note a recent report providing evidence for pronounced dipolar character of the transition state in the Claisen rearrangement of allyl vinyl ethers[12].

EXPERIMENTAL

N-(o-Azidobenzoyl)arylamines. These compounds were prepared from o-azidobenzoyl chloride and the appropriate arylamine following the literature procedure[13,14]. The following derivatives have not been described previously;- 2,5-dimethyl-, m.p. 129-131° (Found: C, 67.29: H, 5.27: N, 20.85. $C_{15}H_{14}N_4O$ requires: C, 67.67: H, 5.26: N, 21.05%): 2,6-dimethyl-, m.p. 104-106° (Found: C, 67.84: H, 5.34: N, 19.46%): 2,5-dichloro-, m.p. 119-124° (Found: C, 50.68: H, 2.60: N, 18.22: $C_{13}H_8Cl_2N_4O$ requires: C, 50.81: H, 2.60: N, 18.24%): 2,6-dichloro-, m.p.122-125° (Found: C, 50.73: H, 2.59: N, 18.03%).

2-Arylindazol-3-ones. The following new 2-aryl derivatives were prepared by base-catalysed cyclisation[8] of the corresponding N-(o-azidobenzoyl)arylamine:- 2-(2,5-dimethylphenyl)-, m.p. 181-183° (Found: C, 75.61: H, 5.89: N, 11.74. $C_{15}H_{14}N_2O$ requires: C, 75.63: H, 5.88: N, 11.77%): 2-(2,6-dimethyl)-, m.p. 208° (Found: C, 75.53: H, 5.97: N, 11.79%): 2-(2,5-dichlorophenyl)-, m.p. 184-185° (Found: C, 55.65: H, 3.20: N, 10.39. $C_{13}H_8Cl_2N_2O$ requires: C, 55.91: H, 2.87: N, 10.04%): 2-(2,6-dichlorophenyl)-, m.p. 176-184° (Found: C,55.61 : H, 2.55: N, 10.04%).

2-Aryl-1-cyanoindazol-3-ones. The 2-arylindazolone (10.5 mmol) was dissolved in ethanol (30 ml) containing sodium ethoxide (13 mmol). This solution was then added dropwise to a stirred solution of cyanogen bromide (19.8 mmol) in ethanol (10 ml), and stirring continued overnight. The reaction mixture was then diluted with water and the precipitated solid filtered off and recrystallised. The following *2-aryl-* derivatives were prepared by this method and all showed characteristic absorption bands at 1690-1720 (CO) and 2200-2240 (CN) cm^{-1} in their infrared spectra:- *2-methylphenyl-* (49%), m.p. 86-87° from EtOAc/Pet ether (Found: C, 72.39: H, 4.39: N, 17.16. $C_{15}H_{11}N_3O$ requires: C, 72.29: H, 4.42: N, 16.86%): *4-methylphenyl-* (76%), m.p. 148-150° from EtOAc/Pet ether (Found: C, 72.01: H, 4.42: N, 15.70%): *4-methoxyphenyl-* (67%), m.p. 153° from MeOH (Found: C, 67.29, H, 4.25: N, 15.83. $C_{15}H_{11}N_3O$ requires: C, 67.92: H, 4.15: N, 15.85%): *4-chlorophenyl-* (69%), m.p. 138-139° from MeOH (Found: C, 62.92: H, 3.12: N, 15.97. $C_{14}H_8ClN_3O$ requires: C, 62.34: H, 2.97: N, 15.58%): *2,5-dimethylphenyl-* (65%), m.p. 94-97° from MeOH (Found: C, 72.79: H, 4.70: N, 15.54. $C_{16}H_{13}N_3O$ requires: C, 73.00: H, 4.94: N, 15.96%): *2,6-dimethylphenyl-* (58%), m.p. 132-133° from MeOH (Found: C, 72.41: H, 5.03: N, 16.21%): *2,4,6-trimethylphenyl-* (74%), m.p.147-148° from MeOH (Found: C, 73.11: H, 5.39: N, 15.26. $C_{17}H_{15}N_3O$ requires: C, 73.65: H, 5.42: N, 15.16%).

Preparative rearrangements. In each case the 2-aryl-1-cyanoindazolone was slowly heated to 270° and the resulting solid recrystallised from pyridine to give the corresponding benzimidazo[2,1-b]quinazolin-12(5H)-one whose infrared spectrum showed characteristic bands at 2500-3200 (NH), 1680-1710 (CO) and 1640-1670 (C=N) cm^{-1}:- *8-methyl-* (82%), m.p. 305-311° (Found: C, 72.30: H, 4.38: N, 16.87. $C_{15}H_{11}N_3O$ requires: C, 72.29: H, 4.42: N,16.87%) m/z 249(M$^+$,31), 224(10), 79(100): *10-methyl-* (64%), m.p. 309-316° (Found: C, 72.93: H, 4.41: N, 17.06%) m/z 250(M$^+$+1, 100), 221(11), 125(13), 77(11): *8-methoxy-* (84%), m.p. 289-296° (Found: C, 66.82: H, 4.12: N, 15.59. $C_{15}H_{11}N_3O$ requires: C, 67.26: H, 4.15: N, 15.84%) m/z 266(M$^+$+1, 100), 251(38), 223(42), 130(10), 76(10): *8-chloro-* (76%), m.p. 338-342° (Found: C, 61.51: H, 3.03: N, 15.61. $C_{14}H_8ClN_3O$ requires: C, 62.33: H, 2.97: N, 15.58%) m/z 271(M$^+$,35), 269(M$^+$,100), 240(17), 222(19), 206(12), 102(15), 90(10), 76(11): *7,10-dimethyl-* (68% from *1f*, 72% from *1g*), m.p. 275-279° (Found: C, 72.59: H, 4.92: N, 16.04. $C_{16}H_{13}N_3O$ requires: C, 73.00: H, 4.94: N, 15.97%) m/z 263(M$^+$,40), 238(65) 221(26), 209(22), 194(15), 105(100), 104(11), 103(13), 91(16), 84(12), 79(94), 78 (25), 77(36), 76(10): *7,8,10-trimethyl-* (60%), m.p. 294-306° (Found: C, 73.92: H, 4.85: N, 15.38. $C_{17}H_{15}N_3O$ requires: C, 73.65: H, 5.41: N, 15.16%) m/z 277(M$^+$, 79), 262(32), 120(15), 91(12), 77(15).

Quantitative measurements. These were carried out following the method of Barrett[15] but using a Du Pont 900 Thermal Analyser equipped with a Differential Scanning Calorimeter Cell.

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