Formation of Benzimidazoles at High Pressure

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Benzimidazoles containing bulky 2-substituents, *e.g.* adamantyl and t-butyl, have been synthesized by condensation of *o*-phenylenediamines with carboxylic acids at hydrostatic pressures of up to 8 kbar. Attempts to make the analogous benzothiazoles and benzoxazoles at high pressures were unsuccessful, but an alternative synthesis was devised. A novel diazepinone (18) is reported.

THE mineral acid-catalysed condensation of carboxylic acids with *o*-phenylenediamine has been used extensively in the synthesis of benzimidazoles.[1] However, acids containing bulky substituents, such as adamantane-1-carboxylic [2] and 2,2-dimethylpropionic [3,4] acids either do not react or give low yields of benzimidazoles under the normal conditions. The lack of reactivity [3] was attributed to both steric hindrance and a reduction in the electrophilic reactivity of the carboxy-group. Hamann [5] has shown both theoretically and experimentally that reactions in which ionic intermediates are formed from neutral reactants are generally accelerated in polar solvents at high pressures. Accordingly, the previously mentioned condensations which failed at atmospheric pressure were attempted at pressures of up to 8 kbar (1 kbar = 10^5N m^{-2} ≡ 986.1 atm).

Equimolecular amounts of 2,2-dimethylpropionic acid and *o*-phenylenediamine dihydrochloride in aqueous ethanol at 112 °C and 8 kbar for 24 h gave a 66% yield of 2-t-butylbenzimidazole (1) (Table). Similarly, adamantane-1-carboxylic acid and *o*-phenylenediamine dihydrochloride gave 2-(1-adamantyl)benzimidazole (11) (48% yield) (Table). Although the high pressure reaction was successfully applied to a number of substituted *o*-phenylenediamines and carboxylic acids (Table), alkoxy-substituted compounds were unstable under those conditions, owing to the reaction of hydrochloric acid with the alkoxy-group and subsequent decomposition of the cleavage products. In the absence of hydrochloric acid, condensation takes place giving the expected benzimidazoles (Table).

Furthermore, the benzimidazole reaction proceeds at approximately the same rate in aqueous dimethyl sulphoxide (Table), where no esterification can take place. At ethanol concentrations >90% esterification becomes the dominant reaction.

Condensations of this type are generally considered [6] to take place *via* an *o*-amino-anilide intermediate which undergoes general acid-base catalysed cyclization.

The only evidence we could find of *o*-amino-anilides in our reactions was the diazepinone (18), which is analogous to an anilide. The absence of *o*-amino-anilides can be explained as due to a relatively rapid cyclization under the reaction conditions, which was confirmed as follows.

The effects of acidity and pressure on the cyclization of a probable intermediate, *N*-(1-adamantylcarbonyl)-

[1] J. B. Wright, *Chem. Rev.*, 1951, 397.
[2] T. Sasaki, S. Eguchi, and T. Toru, *Bull. Chem. Soc. Japan*, 1969, **42**, 1617.
[3] G. Holan, E. Samuel, B. C. Ennis, and R. W. Hinde, *J. Chem. Soc.*, 1967, 20.
[4] M. T. Davis, P. Mamalis, V. Petrow, and B. Strugen, *J. Pharm. Pharmacol.*, 1951, **3**, 420.
[5] (*a*) S. D. Hamann, ' Physico-Chemical Effects of Pressure,' Academic Press, New York, 1957; (*b*) S. D. Hamann, *Ann. Rev. Phys. Chem.*, 1964, **15**, 349; (*c*) S. D. Hamann, in ' High Pressure Physics and Chemistry,' ed. R. S. Bradley, vol. 2, Academic Press, New York, 1963, p. 163.
[6] K. J. Morgan and A. M. Turner, *Tetrahedron*, 1969, **25**, 915.

o-phenylenediamine [2] (17), were studied and general acid catalysis was observed. Heating the amino-anilide (17) with hydrochloric acid in ethanol at reflux for 24 h at atmospheric pressure gave the benzimidazole (11) (96.8%). Under similar conditions the weak acid adamantane-1-carboxylic acid (pK_a 6.8) did not produce any detectable amount of (11). However, at 8 kbar adamantane-1-carboxylic acid catalysed the cyclization, giving the benzimidazole in 91% yield. Application of pressure (8 kbar) in the absence of acid to an ethanolic solution of the anilide (17) did not yield the benzimidazole (11).

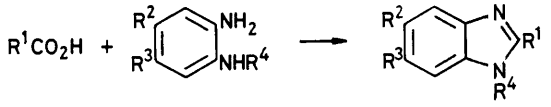
The rate of formation of benzimidazoles increased with increasing pressure. Reactions of equimolecular amounts of 4-chloro-*o*-phenylenediamine dihydrochloride and 2,2-dimethylpropionic acid gave 2-t-butyl-5(6)-chlorobenzimidazole (3) in yields ranging from 18.4 at 2 kbar to 78.5% at 8 kbar. Increasing the molar ratio of diamine to carboxylic acid to 1 : 1.5 gave (3) in yields of up to 92.5% with increasing pressures to 8 kbar.

Variations in solvent composition and the resultant effects on yields were studied, but not in great detail. In the formation of (1) from *o*-phenylenediamine and 2,2-dimethylpropionic acid the optimum solvent composition was 60—75% (v/v) ethanol–water. At higher ethanol or water concentrations the yields diminished appreciably.

The formation of small quantities (<5%) of esters in some reactions indicated that the reaction might take place *via* initial esterification of the carboxylic acid followed by condensation of the ester with the diamine. However, this pathway was discarded when ethyl 2,2-dimethylpropionate failed to condense with *o*-phenyleneamine to yield the 2-t-butylbenzimidazole.

Unexpected compounds were formed in the reactions of *o*-phenylenediamine with 2,2-dichloropropionic and 3-fluoro-2,2-dimethylpropionic acids at 8 kbar. 2-Acetylbenzimidazole [7] was the sole product from the former reaction. Probably the expected 2-(1,1-dichloroethyl)-benzimidazole is formed but then undergoes rapid

Formation of benzimidazoles; reaction conditions



No.	Substituents R¹	R²	R³	R⁴	HCl [a] (mol. equiv.)	Aq. solvent (% v/v)	Pressure (kbar)	Temp. (°C)	Reaction time (h)	Yield (%)
(1)	Bu^t	H	H	H	>10 [b]	H_2O	0.001 [c]	100	67	7.1
					2	EtOH (60)	0.001 2 [c]	107	72	0
					2	EtOH (60)	8.0	112	24	66
					0	EtOH (83)	8.0	107	65	24.0
					0	EtOH (60)	8.0	107	24	19
					0	Me_2SO (80)	8.0	107	24	15.1
					0	Me_2SO (70)	8.0	107	24	13.5
					1	EtOH (50)	0.04 [c]	250	72	0
(2)	$ClCH_2{\cdot}CMe_2$	H	H	H	>10 [b]	H_2O	0.001 [c]	100	65	1.4
					1	EtOH (60)	7.5	107	65	83
(3)	Bu^t	Cl	H	H	2	EtOH (50)	0.001 2 [c]	107	65	0
					>10 [b]	H_2O	0.001 [c]	100	65	6.5
					2	EtOH (50)	2.3	107	24	18.4
					2	EtOH (50)	4.0	107	24	26.8
					2	EtOH (50)	6.3	107	24	61.6
					2	EtOH (50)	8.0	107	24	78.5
					1	Pr^{i}OH (60)	8.0	112	24	30.3
(4)	$ClCH_2{\cdot}CMe_2$	Cl	H	H	1	EtOH (50)	7.7	107	65	30.2
					1	EtOH (50)	8.5	112	65	36.2
(5)	$ClCH_2{\cdot}CMe_2$	Cl	Cl	H	1	EtOH (65)	7.7	107	24	4
(6)	$ClCH_2{\cdot}CMe_2$	Me	H	H	0	EtOH (83)	7.7	107	65	14
(7)	$ClCH_2{\cdot}CMe_2$	Me	Me		1	EtOH (50)	7.7	107	65	10
(8)	$ClCH_2{\cdot}CMe_2$	OMe	H	H	0	EtOH (50)	7.7	107	24	17
(9)	$ClCH_2{\cdot}CMe_2$	H	H	Me	0	EtOH (75)	7.6	107	67	69
(10)	$ClCH_2{\cdot}CMe_2$	H	H	n-$C_{12}H_{25}$	0	EtOH (75)	7.6	107	67	24
(11)	Ad	H	H	H	1	EtOH (60)	8.0	107	24	48
					2	EtOH (60)	8.0	107	24	39
					2	EtOH (60)	8.0	107	1	3.6
					0	EtOH (83)	8.0	107	24	6.5
(12)	Ad	Cl	H	H	2	Pr^{i}OH (60)	7.2	112	74	73
(13)	Ad	Me	H	H	2	Pr^{i}OH (60)	8.0	107	74	72
(14)	Ad	Me	Me	H	2	Pr^{i}OH (60)	8.0	107	74	65
(15)	$FCH_2{\cdot}CMe_2$	H	H	H	1	EtOH (50)	8.0	110	24	10
(16)	$MeO{\cdot}CH_2{\cdot}CMe_2$	H	H	H	0	EtOH (75)	8.0	107	24	25.5

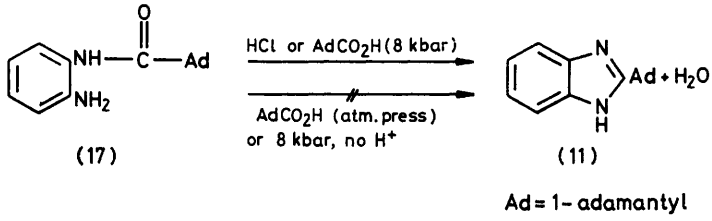
Ad = adamantyl.

[a] The molar ratio of *o*-phenylenediamine to carboxylic acid was 1 : 1. [b] Large excess of 5M-HCl. [c] Closed tube experiments or atmospheric pressure.

[7] G. W. H. Cheeseman, *J. Chem. Soc.*, 1964, 4645.

hydrolysis, analogous to the hydrolysis of 2-trichloromethylbenzimidazole [3] and other 2-halogenomethylbenzimidazoles.[8,9]

In the reaction of *o*-phenylenediamine with 3-fluoro-2,2-dimethylpropionic acid a fluorine free compound was formed. The ^{1}H n.m.r. spectrum indicated two equivalent methyl groups (δ 1.30), a methylene (δ 3.10), two



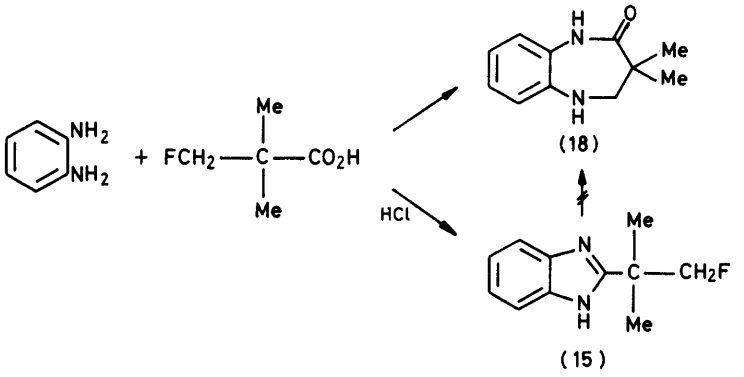
(17) (11)

Ad = 1-adamantyl

SCHEME 1

exchangeable NH protons (δ *ca.* 3.2), and four aromatic protons (δ 6.95). The i.r. spectrum contained a strong amide carbonyl absorption at 1 660 cm^{-1} and NH absorptions at 3 250 and 3 450 cm^{-1}. The compound gave a molecular ion at *m/e* 190 in the mass spectrum and its analytical figures agreed with the formula $C_{11}H_{14}N_2O$. We therefore identified it as 1,3,4,5-tetrahydro-3,3-dimethyl-1,5-benzodiazepin-2-one (18).

However, when this reaction was performed with an equivalent amount of hydrochloric acid, the product was 2-(2-fluoro-1,1-dimethylethyl)benzimidazole (15), and no diazepinone (18) was detected (Scheme 2). Heating the



(18) (15)

SCHEME 2

benzimidazole (15) under the same conditions as those used to form the diazepinone (18) failed to produce a rearrangement of (15) to (18) (Scheme 2). Thus the strong acid suppresses nucleophilic substitution of the labile fluorine and favours the benzimidazole reaction.

The role of high pressure in benzimidazole syntheses can be summarized as follows. The much greater yields at high pressure, in the absence of hydrochloric acid, can be partly attributed to the known increase in dissociation of carboxylic acids with pressure.[10] Calculations for pivalic acid indicate that the pK_a should be decreased by 1.5 units at 8 kbar in water and should be reduced further in aqueous ethanol, since the effect depends on the variation of dielectric constant with pressure.[10] The above studies on the cyclization of the *o*-amino-anilide (17) confirm that pressure accelerates the reaction *via* the accepted pathway through an *o*-amino-anilide intermediate. Similarly, a reaction analogous to the anilide formation (the self-catalysed esterification of pivalic acid in ethanol) was accelerated over 100 times by a pressure of 8 kbar at 80 °C,[11] with the reaction having a negative activation volume of 26.2 cm^3 mol^{-1}. Accelerations of cyclization reactions by an increase of pressure have been reported previously,[5] with negative activation volumes of up to *ca.* 26 cm^3 mol^{-1}.

Attempts to prepare 2-(1-adamantyl)-benzoxazole and -benzothiazole by the high pressure condensation of adamantane-1-carboxylic acid with *o*-aminophenol and *o*-aminobenzenethiol, respectively, were unsuccessful: in each case an intractable tar was formed. However, adamantane-1-carbonyl chloride readily condensed at atmospheric pressure with *o*-aminophenol and with *o*-aminobenzenethiol in refluxing *NN*-dimethylaniline giving the benzoxazole and benzothiazole, respectively. The increase in reactivity of the carbonyl group is sufficient to facilitate reaction at atmospheric pressure. A similar approach [2] has been used to overcome the lack of reactivity of adamantane-1-carboxylic acid by using adamantane-1-carbonyl chloride in the synthesis of other

[8] G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 209.
[9] H. Baganz, *Angew. Chem.*, 1956, **68**, 151.
[10] S. D. Hamann, 'Volume Changes for the Ionization of Weak Electrolytes, and the Effects of Pressure on Ionization,' Division of Applied Chemistry Technical Paper No. 3, C.S.I.R.O., Australia, 1972.
[11] M. Linton, Proc. 4th International Conference on High Pressure, Kyoto, 1974, p. 671.

1-adamantyl heterocycles. Thus the reactivity of carboxylic acids containing bulky substituents can be increased by either chemical modification of the carboxy-group or the use of high pressures.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (KBr pellets or liquid films) were recorded with a Unicam SP 200 spectrometer, u.v. spectra with a Beckman DK2 spectrometer (95% ethanol as solvent), ^1H n.m.r. spectra with a Varian T-60 or HA-100 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi-Perkin-Elmer RMU-6D spectrometer. Microanalyses were obtained from the Australian Microanalytical Service, Melbourne.

High-pressure reactions were performed in glass or teflon precision-bore tubes (5—30 ml capacity), sealed with sliding piston caps. The tubes were pressurized (up to 10 kbar with a hydraulic press) in a piston–cylinder apparatus, using a Bridgman unsupported-area packing to seal the cylinder. The ram pressure was measured with a Bourdon standard test gauge. The internal pressure was calibrated (±0.1 kbar) by using the freezing pressures at various temperatures of benzene, chloroform, chlorobenzene, toluene, and water as standards. The vessel was electrically heated and the temperature was regulated (±1 °C) with a Pye Ether Transitrol 12-98B controller.

Spectral data for new compounds are available as Supplementary Publication No. SUP 22017 (6 pp.).*

General Method of Preparation of Benzimidazoles at High Pressure.—2-*t-Butylbenzimidazole* (1). A solution of *o*-phenylenediamine (1.0 g) and 2,2-dimethylpropionic acid (1.0 g) in ethanol–water (6 ml; 75% v/v) was heated at 107 °C and 8 kbar for 66 h. Dilution with water and neutralization with ammonia (*d* 0.88) gave the *benzimidazole* (1) (0.73 g, 41.6%), m.p. 334° (from methanol–water) (Found: C, 75.8; H, 8.2; N, 16.2. $C_{11}H_{14}N_2$ requires C, 75.7; H, 8.1; N, 16.1%).

The following benzimidazoles were prepared by using the conditions given in Table 1: 2-(2-*chloro*-1,1-*dimethylethyl*)-*benzimidazole* (2), m.p. 297° (from ethanol–water) (Found: C, 63.3; H, 6.5; Cl, 16.8; N, 13.7. $C_{11}H_{13}ClN_2$ requires C, 63.3; H, 6.2; Cl, 17.0; N, 13.4%); 5(6)-*chloro*-2-*t-butyl*-*benzimidazole* (3), m.p. 291° (from methanol–water) (Found: C, 63.1; H, 6.3; N, 13.3. $C_{11}H_{13}ClN_2$ requires C, 63.3; H, 6.2; N, 13.4%); 5(6)-*chloro*-2-(2-*chloro*-1,1-*dimethylethyl*)-*benzimidazole* (4), m.p. 225° (from ethanol–water) (Found: C, 54.2; H, 5.3; Cl, 28.9; N, 11.3. $C_{11}H_{12}Cl_2N_2$ requires C, 54.3; H, 4.9; Cl, 29.2; N, 11.5%); 5,6-*dichloro*-2-(2-*chloro*-1,1-*dimethylethyl*)*benzimidazole* (5), m.p. 273° (from chloroform) (Found: C, 47.4; H, 3.9; Cl, 38.2; N, 10.0. $C_{11}H_{11}Cl_3N_2$ requires C, 47.6; H, 4.0; Cl, 38.4; N, 10.1%); 2-(2-*chloro*-1,1-*dimethylethyl*)-5(6)-*methylbenzimidazole* (6), m.p. 257° (from ethanol) (Found: C, 65.0; H, 6.7; Cl, 16.0; N, 12.4. $C_{12}H_{15}ClN_2$ requires C, 64.7; H, 6.7; Cl, 16.0; N, 12.6%); 2-(2-*chloro*-1,1-*dimethylethyl*)-5,6-*dimethylbenzimidazole* (7), m.p. 245° (from ethanol–water) (Found: C, 65.8; H, 7.2; Cl, 14.6; N, 11.4. $C_{13}H_{17}ClN_2$ requires C, 66.0; H, 7.2; Cl, 15.0; N, 11.8%); 2-(2-*chloro*-1,1-*dimethylethyl*)-5(6)-*methoxybenzimidazole* (8), m.p. 211° (from ethyl acetate–benzene) (Found: C, 60.8; H, 6.6; N, 11.4. $C_{12}H_{15}ClN_2O$ requires C, 60.4; H, 6.3; N, 11.7%); 2-(2-*chloro*-1,1-*dimethylethyl*)-1-*methylbenzimidazole* (9), b.p. 80° at 5×10^{-6} mmHg (Found: C 65.0; H, 7.1; Cl, 15.7; N, 12.2. $C_{12}H_{15}ClN_2$ requires C, 64.7; H, 6.7; Cl, 16.0; N, 12.6%); 2-(2-*chloro*-1,1-*dimethylethyl*)-1-*dodecylbenzimidazole* (10), b.p. 200° at 5×10^{-6} mmHg (Found: C, 73.7; H, 10.4; N, 7.2. $C_{23}H_{37}ClN_2$ requires C, 73.7; H, 10.0; N, 7.4%); 2-(1-adamantyl)benzimidazole (11), m.p. 420° (from propan-2-ol) (Found: C, 80.9; H, 7.9; N, 11.0. Calc. for $C_{17}H_{20}N_2$: C, 81.0; H, 7.9; N, 11.1%); 2-(1-*adamantyl*)-5(6)-*chlorobenzimidazole* (12), m.p. 364° (from ethanol–water) (Found: C, 71.2; H, 6.8; Cl, 12.3; N, 9.6. $C_{17}H_{19}ClN_2$ requires C, 71.2; H, 6.6; Cl, 12.4; N, 9.8%); 2-(1-*adamantyl*)-5(6)-*methylbenzimidazole* (13), m.p. 295° (from ethanol–water) (Found: C, 80.8; H, 8.4; N, 10.2. $C_{18}H_{22}N_2$ requires C, 81.2; H, 8.3; N, 10.5%); 2-(1-*adamantyl*)-5,6-*dimethylbenzimidazole* (14), m.p. 317° (from dimethyl sulphoxide–water) (Found: C, 81.3; H, 8.3; N, 10.1. $C_{19}H_{24}N_2$ requires C, 81.4; H, 8.6; N, 10.0%); 2-(2-*fluoro*-1,1-*dimethylethyl*)*benzimidazole* (15), m.p. 260° (from ethanol–water) (Found: C, 68.8; H, 7.0; F, 9.5; N, 15.0. $C_{11}H_{13}FN_2$ requires C, 68.7; H, 6.8; F, 9.9; N, 14.6%); 2-(2-*methoxy*-1,1-*dimethylethyl*)*benzimidazole* (16), m.p. 213° (from ethanol–water) (Found: C, 70.7; H, 7.9; N, 13.4. $C_{12}H_{16}N_2O$ requires: C, 70.6; H, 7.9; N, 13.7%).

Cyclisation of N-(1-*Adamantylcarbonyl*)-o-*phenylenediamine* (17) *to* 2-(1-*Adamantyl*)*benzimidazole* (11).—(*a*) A solution of the anilide (17) (0.52 g) and adamantane-1-carboxylic acid (0.35 g) in ethanol–water (5 ml; 83% v/v) was heated at 107 °C and 8 kbar for 24 h. Concentration under reduced pressure and neutralization with ammonia (*d* 0.880) gave the benzimidazole (11) (0.44 g, 91.4%), m.p. 420°.

(*b*) A solution of the anilide (17) (0.10 g) and concentrated hydrochloric acid (0.04 g; *d* 1.18) in ethanol–water (2 ml; 50% v/v) was heated under reflux for 24 h. Work-up as in (*a*) gave the benzimidazole (11) (0.09 g, 96.8%), m.p. 420°.

1,3,4,5-*Tetrahydro*-3,3-*dimethyl*-1,5-*benzodiazepin*-2-*one* (18).—A solution of *o*-phenylenediamine (0.54 g) and 3-fluoro-2,2-dimethylpropionic acid (1.17 g) in ethanol–water (5 ml; 75% v/v) was heated at 110 °C and 8 kbar for 24 h. Dilution with water and filtration gave the *diazepinone* (18) (0.21 g, 22.1%), m.p. 191° (from benzene) (Found: C, 69.3; H, 7.2; N, 14.5. $C_{11}H_{14}N_2O$ requires C, 69.5; H, 7.4; N, 14.7%).

2-(1-*Adamantyl*)*benzoxazole* (19).—Adamantane-1-carbonyl chloride (19.0 g) was slowly added to a solution of *o*-aminophenol (10.9 g) in *NN*-dimethylaniline (100 ml). The mixture was heated at reflux for 45 min, cooled, and poured into 4M-hydrochloric acid. Filtration gave the *benzoxazole* (21) (22.7 g, 89.7%), which crystallized as plates from ethanol–water, m.p. 100° (Found: C, 80.9; H, 7.5; N, 5.4; O, 6.7. $C_{17}H_{19}NO$ requires C, 80.6; H, 7.6; N, 5.5; O, 6.3%).

2-(1-*Adamantyl*)*benzothiazole* (20).—The *benzothiazole* (20) was prepared in 72% yield as for the benzoxazole (19); m.p. 106° (from methanol) (Found: C, 75.8; H, 7.1; N, 5.2; S, 11.9; $C_{17}H_{19}NS$ requires C, 75.9; H, 7.4; N, 5.2; S, 11.9%).

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* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.