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RUTHENIUM-CATALYSED REARRANGEMENTS OF AZOBENZENES

I. THE PREPARATION OF 1-PHENYLBENZIMIDAZOLES FROM AZOBENZENE DERIVATIVES AND TERTIARY AMINES CATALYSED BY RUTHENIUM COMPLEXES

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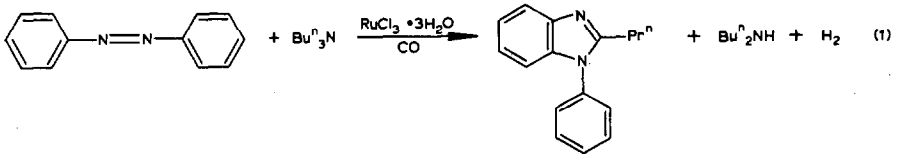
Summary

Carbonyl complexes of ruthenium catalyse the formation of 1-phenyl-2-alkylbenzimidazole derivatives from azobenzenes and tertiary amines. The reaction involves rearrangement of the azobenzene moiety to an *N*-phenyl-1,2-phenylenediamine intermediate which then undergoes alkylation at nitrogen with an alkyl group from the tertiary amine followed by ring closure and aromatization. Various ruthenium complexes serve as catalyst precursors for the reaction and the presence of carbon monoxide is required if good yields are to be obtained. $RuCl_3 \cdot 3H_2O$ is the preferred catalyst precursor. The yields of products formed show a marked dependence on the substituents in the azobenzene derivative. $RhCl_3 \cdot 3H_2O$ also catalyses the reaction, though less efficiently than ruthenium complexes.

Introduction

Benzimidazole derivatives are of considerable importance in agricultural chemistry, particularly as fungicides [1,2]. Some three years ago we discovered a completely new single-step ruthenium-catalysed synthesis of 1-phenyl-2-(n-propyl)benzimidazole from azobenzene and tri-n-butylamine (eq. 1). The di-n-butylamine



(1)

(I)

formed partly undergoes carbonylation to give *N*,*N*-di-n-butylformamide. We have studied this and related reactions in detail in the intervening period [3,4] and we commence here the reports of our findings.

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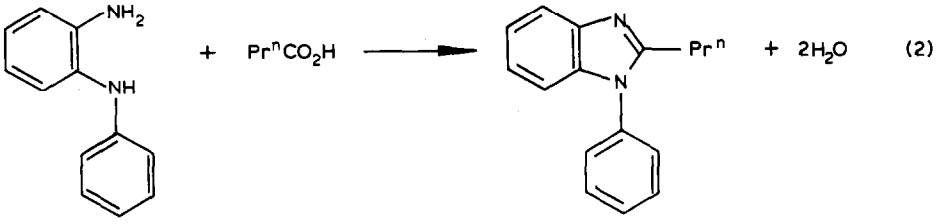
Results

Compound I was fully characterised by elemental analysis, mass spectroscopy and ^{13}C and ^{1}H (250 MHz) NMR spectra. Its IR and ^{1}H NMR spectra were identical with the product obtained from the reaction of *N*-phenyl-1,2-phenylenediamine with n-butyric acid (eq. 2).



General conditions and catalysts

The reaction 1 can be carried out in many solvents, though those of a polar nature are most suitable. We have generally used tetramethylurea, but substituted amides such as *N*,*N*-dimethylacetamide or *N*,*N*-dimethylformamide are also satisfactory. Temperatures in the range of 160–190°C are suitable. The use of tri-n-butylamine in more than stoichiometric amount leads to lower yields of compound I.

Several ruthenium complexes have been used as catalyst precursors, but in general ruthenium trichloride hydrate was preferred. It is important that the reaction be carried out under an atmosphere of carbon monoxide, otherwise the yields of compound I are very poor. The reactions were generally carried out with carbon monoxide being passed slowly through the reaction mixture at normal pressure. We have found no evidence for the involvement of carbon monoxide in the stoichiometry of the reaction and it appears to be needed only as a ligand. This view is supported by the results given in Table 1, where four complexes were compared as catalyst precursors under atmospheres of carbon monoxide and argon. Only the carbonyl complex $Ru_3(CO)_{12}$ gave almost as good a performance under argon. Some of the azobenzene is reduced to aniline by the hydrogen liberated in reaction 1. With certain substituted azobenzenes, transfer hydrogenation of the azobenzene

TABLE 1

COMPARISON OF VARIOUS CATALYST PRECURSORS IN THE SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE UNDER CARBON MONOXIDE AND ARGON

(Azobenzene 25 mmol, tri-n-butylamine 25 mmol, ruthenium 0.25 g.atom, tetramethylurea 12.5 ml, reflux, 8 h, CO or Ar at normal pressure.)

Catalyst precursor	Yield (%) [a]	
	under CO	under Ar
$RuCl_3 \cdot 3H_2O$	67	9
$[Ru_2(OAc)_4]Cl$	58	10
$Ru(OAc)_2(PPh_3)_2$	24	0
$Ru_3(CO)_{12}$	43	34

[a] By gas-chromatography.

TABLE 2

COMPARISON OF DIFFERENT CATALYST PRECURSORS IN THE SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE

(Conditions as for Table 1, under CO).

Catalyst precursor	Yield (%) [a]
$RuCl_2(DMSO)_4$	73
$Ru(acac)_3$	17
$RuCl_3 \cdot 3H_2O$	67
$RuCl_3 \cdot 3H_2O + 2AsPh_3$	67
$RuCl_3 \cdot 3H_2O + 2SbPh_3$	49
$RuCl_3 \cdot 3H_2O + 2PPh_3$	47
$RuCl_3 \cdot 3H_2O + 2P(OPh)_3$	60
$RuCl_3 \cdot 3H_2O + 2PMe_3$	5
$RuCl_3 \cdot 3H_2O$ + diphos	8

[a] By gas-chromatography.

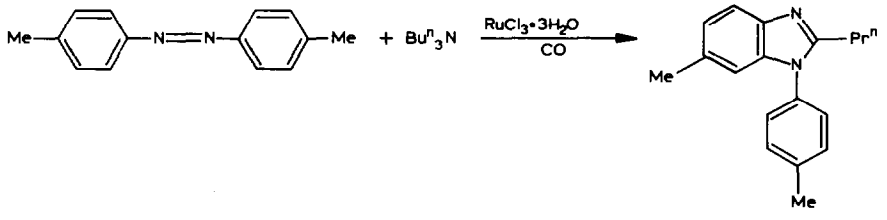
by the tertiary amine may also occur, giving the corresponding aniline derivative (see below).

In Table 2 the results obtained with a range of catalyst precursors, all used under an atmosphere of carbon monoxide, are collected. None shows a significant advantage over $RuCl_3 \cdot 3H_2O$ and this was therefore used for all subsequent reactions. The metals surrounding ruthenium in the periodic table were also checked for catalytic activity for equation 1. The reaction did not occur when the catalyst precursor was one of the complexes $Mo(CO)_6$, $Mn_2(CO)_{10}$, $Re_2(CO)_{10}$, $FeCl_3 \cdot 6H_2O$, $Os_3(CO)_{12}$, $CoCl_2 \cdot 6H_2O$, $IrCl_3 \cdot 3H_2O$, or $PdCl_2$. With $RhCl_3 \cdot 3H_2O$, compound I was obtained in a yield of 28%, compared with 67% using $RuCl_3 \cdot 3H_2O$ under the same conditions. Complexes of technetium were not investigated as all of its isotopes are radioactive. In view of its superior performance compared with its rhodium analogue, we have continued to use $RuCl_3 \cdot 3H_2O$ as catalyst precursor.

Attempts were made to replace the tri-n-butylamine with other compounds containing C_4-residues. Those tried were n-butanol, n-butyraldehyde, n-butyric acid, tri-n-butylphosphine and 1-butene. Although these initial attempts failed in all cases, we have subsequently succeeded in carrying out the synthesis of compound I and derivatives of it using alcohols or even esters (via their alcohol residue) and these studies are the subject of the following reports [5,6].

Azobenzene derivatives

The reaction of 4,4'-dimethylazobenzene with tri-n-butylamine gives as product 1-(4'-methylphenyl)-2-(n-propyl)-6-methylbenzimidazole (eq. 3). Substituents in the phenyl rings of the azobenzene derivatives have a marked effect on the reaction. Strongly electron-releasing substituents retard the reaction considerably. Strongly

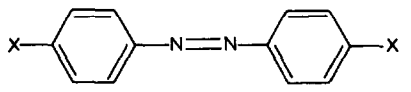
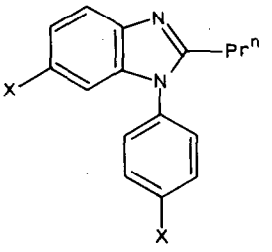


(3)

TABLE 3

EFFECT OF *para*-SUBSTITUENTS IN THE AZOBENZENE DERIVATIVE ON THE YIELD OF THE BENZIMIDAZOLE PRODUCT

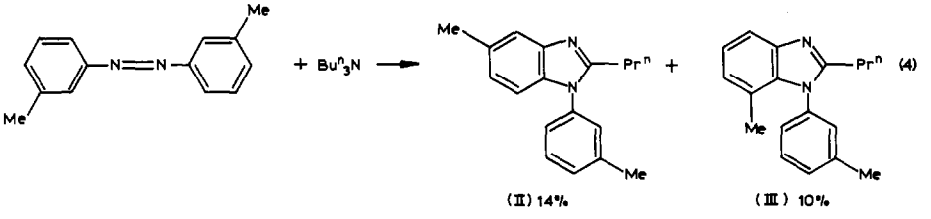
(Azobenzene derivative 100 mmol, tri-n-butylamine 100 mmol, $RuCl_3 \cdot 3H_2O$ 1 mmol, tetramethylurea 50 ml, reflux, CO at normal pressure.)

Substituent X in 	Yield (%) [a] of 	Reaction time (h)
H	60	23
Me	47	21
F	34	22
Cl	10	23

[a] Isolated pure product.

electron-withdrawing substituents accelerate the reduction of the azobenzene compound to the corresponding aniline derivative by transfer hydrogenation. Table 3 shows the effect of *para*-substituents on the yield of the benzimidazole product.

Depending on the pattern of substitution of the azobenzene derivative used, more than one isomer of the benzimidazole product may be formed. Thus 3,3'-dimethylazobenzene gives both II and III in reaction with tri-n-butylamine in the yields shown (eq. 4).



In the case of 3,3',5,5'-tetramethylazobenzene, only one isomer of the product is possible (eq. 5).

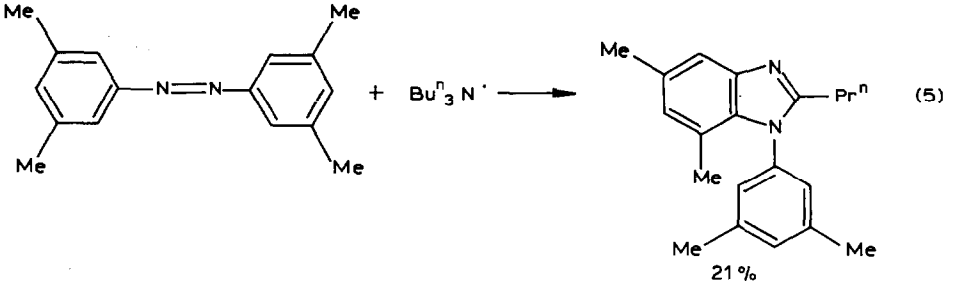
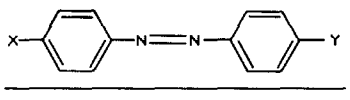
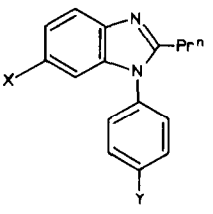
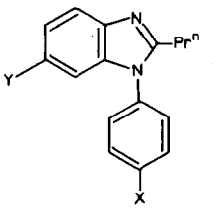


TABLE 4

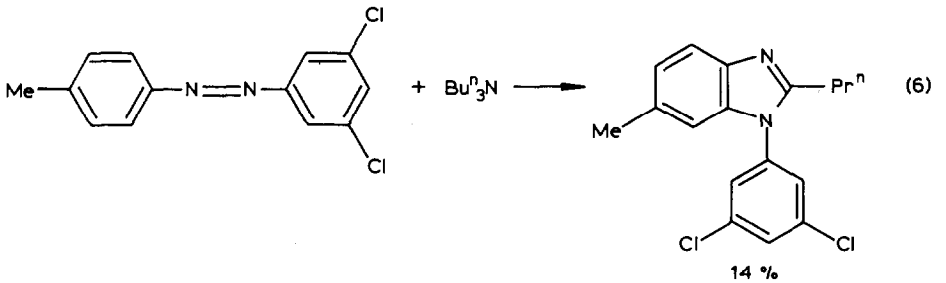
ISOMER DISTRIBUTION IN THE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES FROM 4-MONOSUBSTITUTED OR NON-SYMMETRICALLY 4,4′-DISUBSTITUTED AZOBENZENES

(Azobenzene derivative 50 mmol, tri-n-butylamine 50 mmol, $RuCl_3 \cdot 3H_2O$ 0.5 mmol, tetramethylurea 25 ml, reflux, CO at normal pressure.)

Substituents in		Yields (%)[a] of		Reaction time (h)
				
X	Y			
H	Me	32	13	23
Cl	H	19	19	8
CO_2Et	Me	13	0	23
Cl	Me	33	2	23
F	Me	23	9	23
Me	OMe	11	3	23

[a] Isolated yield of isomer mixture: isomer distribution from ^1H NMR spectra (250 MHz).

4-Methyl-3′,5′-dichloroazobenzene gave only one isomer of the product, although here again, two are possible (eq. 6).

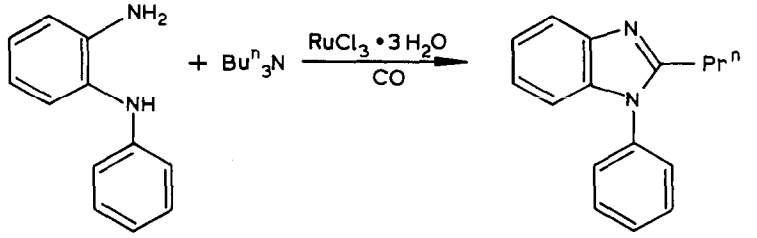


14 %

(6)

With 4-monosubstituted or non-symmetrically 4,4′-disubstituted azobenzenes both possible isomers are generally formed (Table 4). The isomer mixtures were isolated as such and their composition determined from the 250 MHz ^1H NMR spectra.

We have further shown that *N*-phenyl-1,2-phenylenediamine (*o*-semidine) reacts with tri-n-butylamine under the conditions used in Table 3 to give compound I in 53% yield after 4 h (eq. 7).

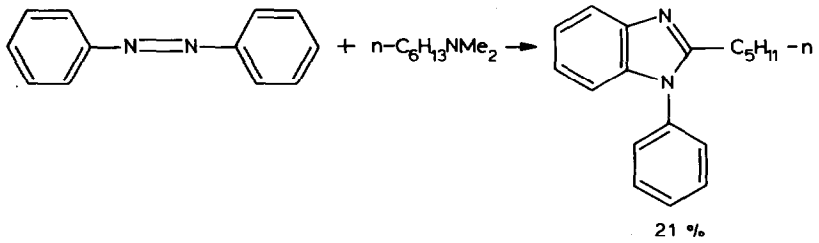


(I) 53 %

(7)

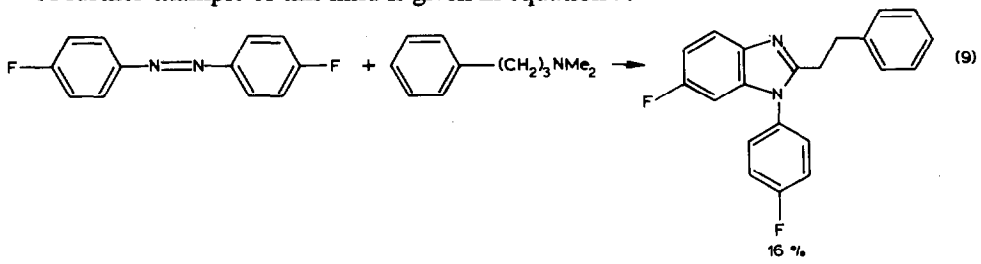
Tertiary amines

Simple tri-n-alkylamines such as tri-n-butylamine or tri-n-propylamine give satisfactory results quite generally. A given alkyl group may also be introduced by use of the appropriate alkyldimethylamine. Here it should be born in mind that the alkyl group in the benzimidazole product has one less carbon atom than the alkyl group of the tertiary amine because of the 2-C atom of the heterocyclic ring. Thus n-hexyldimethylamine reacted with azobenzene to give 1-phenyl-2-(n-pentyl)benzimidazole (eq. 8). The alternative product, 1-phenylbenzimidazole, which would have resulted from incorporation of a methyl group of the tertiary amine, was not observed.



(8)

A further example of this kind is given in equation 9.



(9)

The yields obtained in this tertiary amine version of the synthesis of benzimidazole derivatives are often low and the reaction times relatively long. The reaction of azobenzene derivatives with primary alcohols (part II of this series [5]) represents a more efficient and economic route to the synthesis of such benzimidazoles and the use of tertiary amines in this reaction was therefore not investigated further.

Discussion

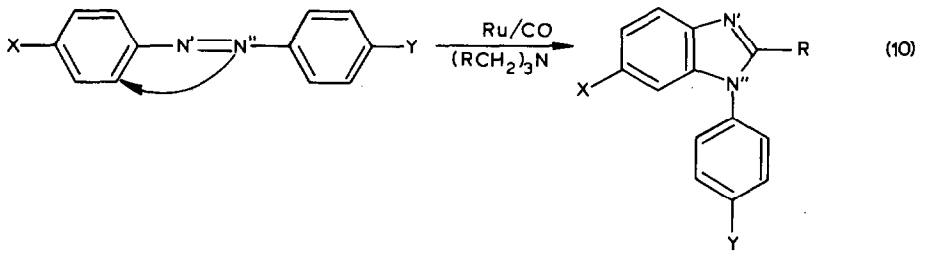
We consider here the basic sequence of reaction steps constituting the mechanism and certain other characteristics of the benzimidazole synthesis described above. A more detailed study of the mechanism will be presented in the fourth paper in this series.

A point of prime importance is whether the ruthenium catalyst first reacts with the azobenzene or the tertiary amine. Two independent pieces of evidence indicate that the catalyst first effects the rearrangement of the azobenzene to an *o*-semidine (i.e. *N*-phenyl-1,2-phenylenediamine) derivative, after which an alkyl residue from the tertiary amine is incorporated.

The first indication comes from the reaction of *o*-semidine with tri-n-butylamine catalysed by $RuCl_3 \cdot 3H_2O$ under carbon monoxide, giving compound I. Although

the protonation state of the nitrogen atoms of the semidine derivatives formed from the azobenzenes is probably different to that of *o*-semidine itself, eq. 7 strongly supports the view that the rearrangements precedes the reaction with the tertiary amine. The second indication of this comes from the stoichiometric reaction of azobenzene with ruthenium complexes such as $Ru_3(CO)_{12}$. Stone and co-workers have shown that both *ortho*-metallation of the azobenzene [7–9] and rearrangement to (deprotonated) *o*-semidine complexes [10] can occur. No tertiary amine was present in these stoichiometric reactions. Stone further showed that complexes containing deprotonated *o*-semidine could be obtained from $Ru_3(CO)_{12}$ and *o*-semidine itself [10]. This would seem to reinforce the evidence of eq. 7. One may thus readily envisage the initial steps of the benzimidazole synthesis involving *ortho*-metallation of the azobenzene followed by its rearrangement to a deprotonated *o*-semidine complex. At this time we have no evidence regarding whether the catalytically active ruthenium complexes are mono- or poly-nuclear.

The use of substituted azobenzene derivatives shows that their rearrangements occurs as shown in eq. 10. The nitrogen atom of one aniline residue in the

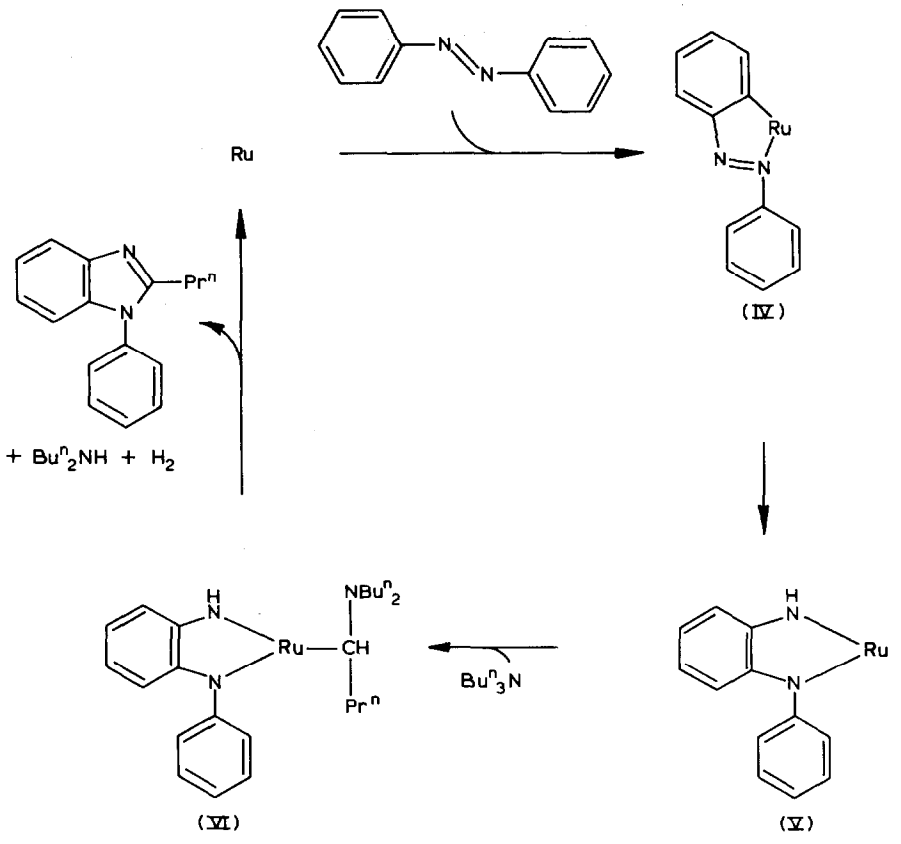


(10)

azobenzene derivatives migrates to an *ortho*-carbon atom of the other aniline residue. We have prepared more than seventy different benzimidazoles by this reaction [3] and the primary alcohol version of it [3,5] and no exception to this rule has been found. The rearrangement in stoichiometric reactions of an *ortho*-metallated azobenzene complex to a deprotonated *o*-semidine derivative is known for the metals molybdenum [8], iron [11,12], ruthenium [10], osmium [13] and rhodium [14]. In all cases, carbon monoxide was present as ligand in the reaction. The strong dependence on carbon monoxide shown in Table 1 therefore is presumed to arise from its beneficial effect on the rearrangement IV → V in Scheme. 1.

As regards the activation of the tertiary amine, the ruthenium-catalysed exchange of alkyl groups between nitrogen centres is known for primary [15], secondary [16] and tertiary [16,17] amines. $Ru_3(CO)_{12}$ [17] and $RuCl_2(PPh_3)_3$ [15,16] were the catalyst precursors. In all cases, the abstraction of hydrogen from an α-carbon atom of the amine was believed to occur, and bonding of the α-carbon atom to ruthenium is therefore probable. To give the observed benzimidazole product such a ruthenium species must then alkylate one of the nitrogen atoms of the deprotonated *o*-semidine after which ring-closure and aromatisation by loss of hydrogen must occur. The latter may be a purely thermal process at the temperature involved here.

The question of which nitrogen atom is first alkylated is difficult to answer. The primary nitrogen atom of the deprotonated *o*-semidine intermediate is more basic and less sterically hindered than the secondary one. However, these factors also favour a stronger bond to ruthenium. Nevertheless, since the activated tertiary amine would also be sterically hindered, we feel that the primary nitrogen atom is most



SCHEME 1. Probable basic steps of the mechanism of the ruthenium-catalysed formation of 1-phenyl-2-(n-propyl)benzimidazole from azobenzene and tri-n-butylamine, assuming a single ruthenium centre is involved. (Oxidation state and other ligands omitted.)

probably the one at which alkylation first occurs. From the above considerations, the basic steps of the mechanism of the benzimidazole synthesis may be postulated to be as shown in Scheme 1, in which the oxidation state of the ruthenium is deliberately not specified.

The benzimidazole synthesis requires the catalytic activation of two different C–H bonds, the first being an *ortho*-C–H bond of the azobenzene derivative and the second an α-C–H bond of the tertiary amine. It is at present not known whether these reactions involve oxidative addition of the C–H bonds to ruthenium(0), electrophillic attack by ruthenium(II) or some other mechanism. Further we do not yet know whether the entire reaction occurs at a single ruthenium centre, in a cluster complex or is of an intermolecular nature. Finally, there remains the interesting question of whether the activation of the azobenzene and tertiary amine C–H bonds occur at the same or different ruthenium atoms. We hope to be able to elucidate some of these points in the fourth paper in this series.

Experimental

Ruthenium trichloride hydrate was obtained from Engelhard and triruthenium dodecacarbonyl from Fluka. The following complexes were prepared by standard

literature methods: $Ru(acac)_3$ [18], $[Ru_2(OAc)_4]Cl$ [19], $Ru(OAc)_2(PPh_3)_2$ [19], $RuCl_2(DMSO)_4$ [20]. Carbon monoxide was from Carbagas. Other chemicals were from Fluka, Merck or Strem.

Symmetrically substituted azobenzenes were generally prepared by the oxidation of the corresponding aniline derivatives with activated manganese dioxide [21]. In a few cases, the reduction of the appropriate nitrobenzene derivative with zinc was employed [22]. Non-symmetrically substituted azobenzenes were prepared by the reaction of nitrosobenzenes with aniline derivatives [23].

^1H NMR spectra (250 MHz) were recorded on a Bruker WM 250 instrument and ^{13}C spectra with a Varian XL-100. IR spectra were obtained with a Perkin–Elmer 298 and mass spectra with Varian CH5 and CH7 instruments. Elemental analyses were performed by the Microanalytical Laboratory at Ciba-Geigy. All products and the azobenzene derivatives prepared as above were fully characterised and gave satisfactory elemental analyses. Gas chromatography studies employed a Varian 3700 instrument using OV 101 and OV 225 columns, and equipped with a Shimadzu Chromatopac E1A integrator.

The following preparation is representative. More examples will be found in ref. 3.

Preparation of 1-phenyl-2-(n-propyl)benzimidazole from azobenzene and tri-n-butylamine (General method for the ruthenium-catalysed reaction)

In a reflux apparatus having a three-necked flask equipped with a thermometer and a gas inlet tube and with a Nujol bubbler on top of the condenser were placed tetramethylurea (50 ml), azobenzene (18.2 g, 100 mmol) and tri-n-butylamine (23.86 ml, 100 mmol). The mixture was stirred magnetically and carbon monoxide was passed for 5 min (ca. 2 bubbles/s). Ruthenium trichloride hydrate (0.2615 g, 1 mmol) was added and the mixture was refluxed (ca. 174–177°C) for 23 h with carbon monoxide passing. After removal of the solvent, the residue was distilled in vacuo. The crude product was then redistilled to give pure 1-phenyl-2-(n-propyl)-benzimidazole; 14.1 g (60%). Pale yellow viscous liquid, which slowly crystallises. b.p. 145–148°C/0.2 mmHg. Anal. Found: C, 80.87; H, 6.65; N, 11.92. $C_{16}H_{16}N_2$ calcd.: C, 81.32; H, 6.82; N, 11.86%.

Preparation of 1-phenyl-2-(n-propyl)benzimidazole from N-phenyl-1,2-phenylenediamine and n-butyric acid

The method is analogous to that previously used to prepare 1-phenylbenzimidazole [24]. A mixture of *N*-phenyl-1,2-phenylenediamine (18.4 g, 100 mmol) and n-butyric acid (73.5 ml, 800 mmol) was stirred in a reflux apparatus equipped with a Dean-Stark separator at 140–145°C for 5 h. The reaction mixture was then distilled in vacuo to give the crude product, which was redistilled in vacuo over a short Vigreux column to give pure 1-phenyl-2-(n-propyl)benzimidazole; 15.4 g (65%). Almost colourless oil, which slowly solidifies. b.p. 144–145°C/0.3 mmHg. Its IR and 250 MHz ^1H NMR spectra was identical with those of the product obtained by the above method.

Preparation of 1-phenyl-2-(n-propyl)benzimidazole from N-phenyl-1,2-phenylenediamine and tri-n-butylamine

A reflux apparatus as used for the above ruthenium-catalysed reaction was employed. Tetramethylurea (12.5 ml) was stirred for 5 min with carbon monoxide

passing and then ruthenium trichloride hydrate (0.0654 g, 0.25 mmol), *N*-phenyl-1,2-phenylenediamine (4.60 g, 25 mmol) and tri-n-butylamine (5.96 ml, 25 mmol) were added. The mixture was then refluxed with carbon monoxide passing for 4 h. After an initial distillation in vacuo, the crude product was chromatographed on Kieselgel using diethyl ether as solvent and then redistilled in a Kugelrohr apparatus set at 130°C/0.05 mmHg, to give 1-phenyl-2-(n-propyl)benzimidazole; 3.12 g, (53%). Pale yellow oil, which slowly solidified. Its IR spectrum was identical with those of the above two products.

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