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RUTHENIUM-CATALYSED REARRANGEMENTS OF AZOBENZENES

II *. THE PREPARATION OF 1-PHENYLBENZIMIDAZOLES FROM AZOBENZENE DERIVATIVES AND PRIMARY ALCOHOLS CATALYSED BY RUTHENIUM COMPLEXES

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Summary

$RuCl_3 \cdot 3H_2O$ in presence of PPh_3 and a catalytic amount of a base and under an atmosphere of carbon monoxide catalyses the reaction of azobenzene derivatives and primary alcohols or their esters to give 2-substituted 1-phenylbenzimidazoles. Substituents in the azobenzene derivatives have a marked effect on the product yields. Where isomer formation can occur, all possible isomers of the product are usually formed. In non-symmetrically substituted azobenzene derivatives, *ortho*-metallation occurs preferentially in the aromatic ring having the highest electron density.

Introduction

We have previously described the ruthenium-catalysed synthesis of 1-phenyl-2-alkylbenzimidazoles from azobenzene derivatives and tertiary amines [1,2]. The reaction is believed to involve *ortho*-metallation of the azobenzene derivative followed by its rearrangement to a deprotonated *N*-phenyl-1,2-phenylenediamine (*o*-semidine) intermediate and subsequent attack by ruthenium on the α C–H bond of the tertiary amine. Since ruthenium complexes have long been known to attack the α C–H bond of primary alcohols [3], it was apparent that these might replace tertiary amines in the benzimidazole synthesis. We have discovered conditions under which this is possible [1] and we report here our findings.

Results

The stoichiometry of the synthesis of 1-phenyl-2-(n-propyl)benzimidazole (I) from azobenzene and n-butanol catalysed by ruthenium complexes is given in eq. 1.

* For part I see ref. 2.

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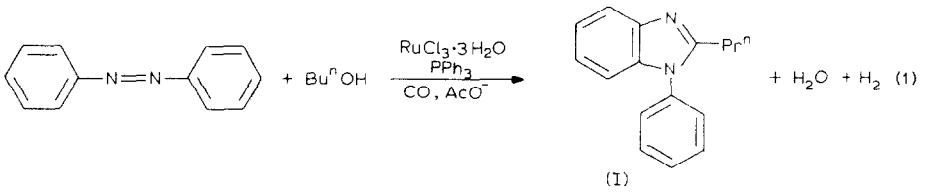


(I)

The rates of reaction and the yields obtained are generally higher than in the tertiary amine version of the reaction [2], and primary alcohols possess the added advantages of being more readily available in greater variety than tertiary amines and of being less expensive.

General conditions and catalysts

A carbon monoxide atmosphere and high temperatures are required for these reactions, which were generally carried out at 180°C. Since this is well above the boiling point of many of the alcohols used and slightly above that of some of the solvents, reactions were carried out in glass pressure tubes sealed at room temperature under normal pressure of carbon monoxide. Variation of the reaction time showed that 8 h was usually sufficient. Polar solvents were again used. Tetramethylurea was preferred, but good results were also obtained with *N*,*N*-dimethylacetamide and *N*-methylpyrrolidone. The alcohol can be used as solvent, but best results were obtained by using it in two- to three-fold excess relative to the azobenzene derivative in one of the above solvents.

Ruthenium trichloride hydrate was used as catalyst precursor. The reaction requires the presence of both a phosphorus ligand, typically triphenylphosphine, and a base. $LiOAc \cdot 2H_2O$ or NaOAc were commonly used. $NaHCO_3$ gave lower yields. Interestingly, tri-n-alkylamines or *N*-benzyldimethylamine could also serve as base for the reaction, with the incorporation of the alkyl group into the benzimidazole product involving only the primary alcohol. NaOAc was the preferred base.

The effect of varying the amount and nature of the base and the phosphorus ligand used and the excess of alcohol were studied in detail. It seems that the best choice depends on the azobenzene-alcohol reactant pair, so that considerable scope for optimisation of the conditions for individual reactions exists. Tables 1, 2, and 3

TABLE 1

EFFECT OF VARYING THE AMOUNT OF SODIUM ACETATE ON THE RUTHENIUM-CATALYSED SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE FROM AZOBENZENE AND n-BUTANOL [a]

Mol. ratio NaOAc/Ru	Yield [b] (%)
1	21
2	36
3	61
5	53
10	48

[a] Azobenzene 25 mmol, n-butanol 75 mmol, NaOAc see above, $RuCl_3 \cdot 3H_2O$ 0.25 mmol, PPh_3 1 mmol, tetramethylurea 12.5 ml, 180°C, 8 h, CO at normal pressure. [b] By gas chromatography.

TABLE 2

EFFECT OF VARYING THE AMOUNT OF TRIPHENYLPHOSPHINE ON THE RUTHENIUM-CATALYSED SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE FROM AZOBENZENE AND n-BUTANOL [a]

Mol. ratio PPh_3/Ru	Yield [b] (%)
0	11
3	63
4	65
5	69
6	39

[a] Azobenzene 25 mmol, n-butanol 50 mmol, $LiOAc \cdot 2H_2O$ 16 mmol, $RuCl_3 \cdot 3H_2O$ 0.25 mmol, PPh_3 see above, tetramethylurea 12.5 ml, 180°C, 8 h, CO at normal pressure. [b] By gas chromatography.

TABLE 3

EFFECT OF VARYING THE AMOUNT OF n-BUTANOL ON THE RUTHENIUM-CATALYSED SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE FROM AZOBENZENE AND n-BUTANOL [a]

Mol. ratio n-butanol/azobenzene	Yield [b] (%)
1	49
2	67
3	64
5	69

[a] Azobenzene 25 mmol, n-butanol see above, $LiOAc \cdot 2H_2O$ 1.6 mmol, $RuCl_3 \cdot 3H_2O$ 0.25 mmol, PPh_3 1 mmol, tetramethylurea 12.5 ml, 180°C, 8 h, CO at normal pressure. [b] By gas chromatography.

TABLE 4

EFFECT OF VARYING THE PHOSPHORUS LIGAND ON THE RUTHENIUM-CATALYSED SYNTHESIS OF 1-PHENYL-2-(n-PROPYL)BENZIMIDAZOLE FROM AZOBENZENE AND n-BUTANOL [a]

Ligand	Yield [b] (%)
$P(p\text{-Tol})_3$	58
PPh_3	57
$P(p\text{-}CH_3OC_6H_4)_3$	55
$P(p\text{-}FC_6H_4)_3$	53
PPh_2Bu^t	41
$P(o\text{-Tol})_3$	36
PCy_3	11
$Ph_2PCH_2PPh_2$	11
$Ph_2P(CH_2)_4PPh_2$	8
$Ph_2P(CH_2)_2PPh_2$	1

[a] Azobenzene 25 mmol, n-butanol 75 mmol, $LiOAc \cdot 2H_2O$ 1.6 mmol, $RuCl_3 \cdot 3H_2O$ 0.125 mmol, PPh_3 0.5 mmol, tetramethylurea 12.5 ml, 180°C, 8 h, CO at normal pressure. [b] By gas chromatography.

give examples of the effect of varying the quantity and nature ($LiOAc \cdot 2H_2O$ or NaOAc) of the base, the PPh_3/Ru ratio and the excess of n-butanol used on the reaction of eq. 1. The results indicate that for azobenzene and n-butanol, $LiOAc \cdot 2H_2O$ should be used in higher concentration than NaOAc and that the ratio of n-butanol to azobenzene to be employed is also base dependent.

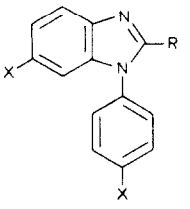
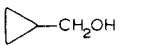
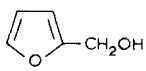
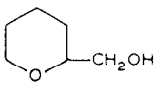
The effect of varying the phosphorus ligand is shown in Table 4. 0.5 mol% ruthenium trichloride hydrate relative to azobenzene was used in these studies. The triarylphosphines that are not sterically hindered in coordinating to ruthenium are most effective and triphenylphosphine was normally used in further reactions.

Primary alcohols

In order to investigate the scope of the reaction, a number of alcohols were caused to react with azobenzene and the results are given in Table 5. For the reasons mentioned above, the choice of conditions is somewhat arbitrary. The alcohol version of the reaction permits a far wider range of groups to be introduced in the 2-position of the benzimidazole product than when tertiary amines are used [2].

TABLE 5

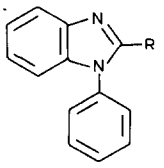
THE SYNTHESIS OF 1-PHENYLBENZIMIDAZOLE DERIVATIVES BY THE RUTHENIUM-CATALYSED REACTION OF AZOBENZENE OR 4,4'-DIMETHYLAZOBENZENE WITH ALCOHOLS

Alcohol	(mmol)	Base	(mmol)	R	X	Yield [b] (%) of 
$n\text{-}C_3H_7OH$	(150)	NaOAc	(1.5)	$n\text{-}C_2H_5$	H	65
$n\text{-}C_5H_{11}OH$	(100)	$LiOAc \cdot 2H_2O$	(32)	$n\text{-}C_4H_9$	H	30
$n\text{-}C_5H_{11}OH$	(150)	NaOAc	(1.5)	$n\text{-}C_4H_9$	H	41
$n\text{-}C_7H_{15}OH$	(150)	NaOAc	(1.5)	$n\text{-}C_6H_{13}$	H	40
	(100)	$LiOAc \cdot 2H_2O$	(32)		H	46
$C_6H_5CH_2OH$	(150)	NaOAc	(1.5)	C_6H_5	H	21
	(150)	$LiOAc \cdot 2H_2O$	(3.2)		H	33
$Me_2CHCH_2CH_2OH$	(150)	NaOAc	(1.5)	Me_2CHCH_2	Me	55
	(150)	NaOAc	(1.5)		Me	33

[a] Azobenzene derivative 50 mmol, alcohol and base see above, $RuCl_3 \cdot 3H_2O$ 0.5 mmol, PPh_3 2 mmol, tetramethylurea 25 ml, 180°C, 8 h, CO at normal pressure. [b] Isolated yield.

TABLE 6

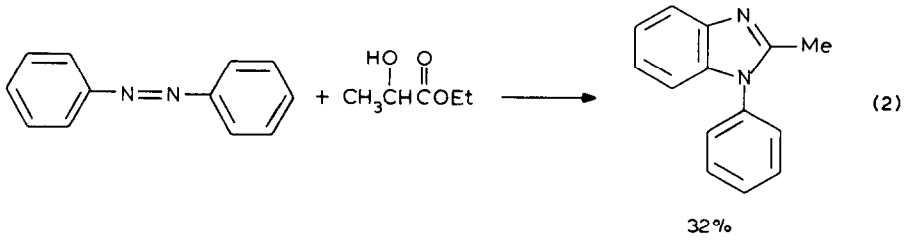
THE RUTHENIUM-CATALYSED SYNTHESIS OF 1-PHENYLBENZIMIDAZOLE DERIVATIVES FROM AZOBENZENE AND ESTERS [a]

Ester	(mmol)	Base	(mmol)	R	Yield [b] (%) of 
$CH_3CH(OH)COEt$	(100)	$LiOAc \cdot 2H_2O$	(32)	CH_3	32
$CH_3CH(OH)CH_2COEt$	(250)	LiOAc	(2)	CH_3	11
CH_3COEt	(100)	$LiOAc \cdot 2H_2O$	(32)	CH_3	35
$HCOEt$	(150)	NaOAc	(1.5)	CH_3	23
$HCOPr^n$	(100)	$LiOAc \cdot 2H_2O$	(32)	C_2H_5	20

[a] Azobenzene 50 mmol, ester and base see above, $RuCl_3 \cdot 3H_2O$ 0.5 mmol, PPh_3 2 mmol, tetramethylurea 25 ml, 180°C, 8 h, CO at normal pressure. [b] Isolated yields.

Esters

An attempt to use ethyl lactate as the alcohol component (eq. 2) lead to the formation of 1-phenyl-2-methylbenzimidazole, which may also be prepared from ethanol itself.



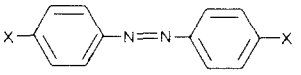
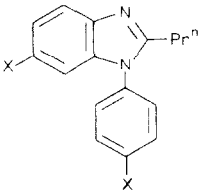
(2)

32%

This result prompted us to investigate the behaviour of a number of other esters and the results are given in Table 6. That it is the alcohol residue of the ester that is incorporated in the product is made clear by the behaviour of ethyl formate and n-propyl formate. The secondary alcohol groups of ethyl lactate and ethyl 3-hydroxybutyrate do not react here. However, some secondary alcohols do enter into a ruthenium-catalysed reaction with azobenzene derivatives [4] and this work is the subject of part III of this series [5].

TABLE 7

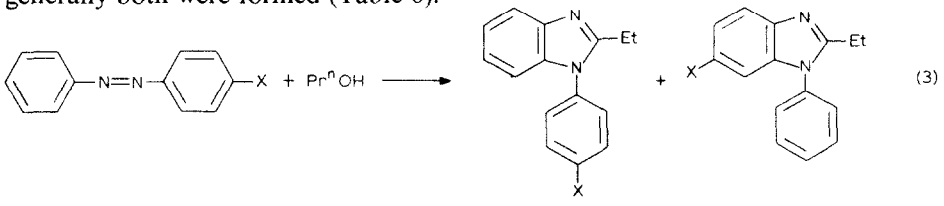
EFFECT OF *para*-SUBSTITUENTS IN THE AZOBENZENE DERIVATIVE ON THE YIELD OF THE BENZIMIDAZOLE PRODUCT [a]

Substituent X in 	Yield [b] (%) of 
H	55
Me	50
F	27
Cl	8

[a] Azobenzene derivative 50 mmol, n-butanol 30 ml, NaOAc 50 mmol, $RuCl_3 \cdot 3H_2O$ 0.5 mmol, PPh_3 2 mmol, 180°C, 8 h, CO at normal pressure. [b] Isolated yield.

Azobenzene derivatives

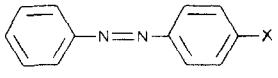
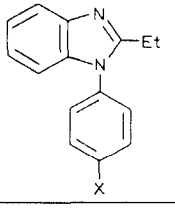
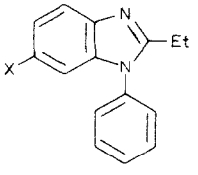
The behaviour of a large number of azobenzene derivatives in the reaction, using the above alcohols and others though mainly with n-propanol and n-butanol, has been studied [1]. A limited representative selection is given here to illustrate the scope of the reaction. As in the case of tertiary amines [2], there is a significant dependence on the substituents in the azobenzene derivative (Table 7). With 4-substituted azobenzenes, two isomers of the product are possible (eq. 3), and generally both were formed (Table 8).



(3)

TABLE 8

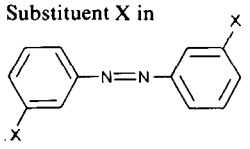
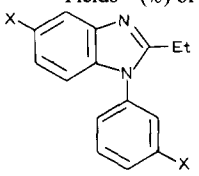
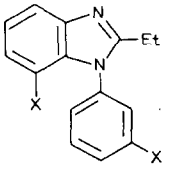
PRODUCT DISTRIBUTION OBTAINED WITH 4-SUBSTITUTED AZOBENZENES [a]

Substituent X in 	Yields [b] (%) of 	
Me	45	30
F	33	33
Cl	14	13
Br	9	12

[a] Azobenzene derivative 50 mmol, n-propanol 150 mmol, NaOAc 1.5 mmol, $RuCl_3 \cdot 3H_2O$ 0.5 mmol, PPh_3 2 mmol, tetramethylurea 25 ml, 180°C, 8 h, CO at normal pressure. [b] Isolated yield of isomer mixture; composition from 250 MHz ^1H NMR spectra.

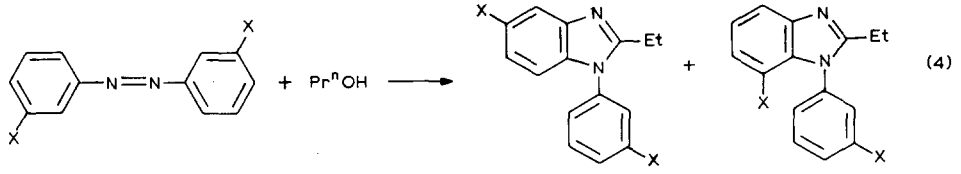
TABLE 9

PRODUCT DISTRIBUTION OBTAINED WITH 3,3′-DISUBSTITUTED AZOBENZENES HAVING LIKE SUBSTITUENTS [a]

Substituent X in 	Yields [b] (%) of 	
MeO	21	17
Me	24	23
Cl	6	6

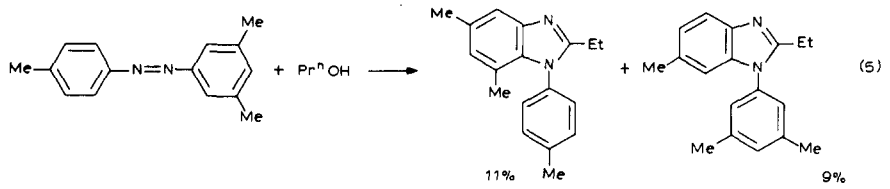
[a] Conditions as for Table 8. [b] Total yield is of isolated isomer mixture; composition from 250 MHz ^{1}H NMR spectra.

The same was true with 3,3′-disubstituted azobenzenes having like substituents (eq. 4, Table 9).

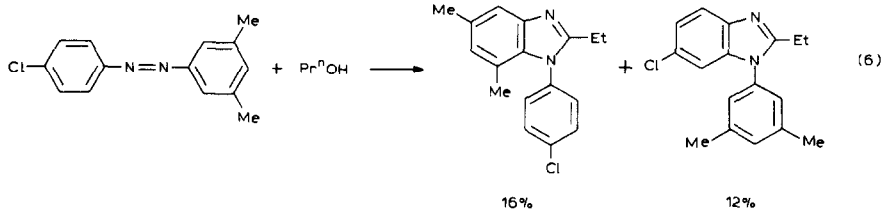


(4)

Even when 3,5,4′-trisubstituted azobenzenes were employed, both possible isomers still formed (eqs. 5, 6). The conditions were as in Table 8.

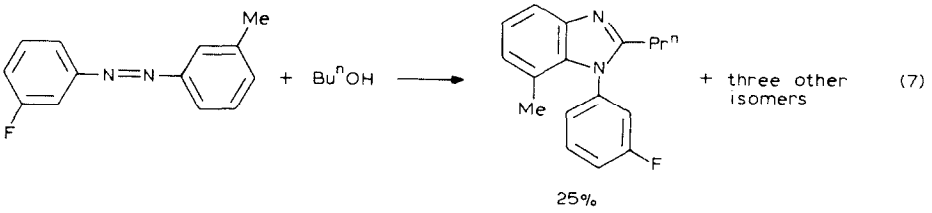


(5)

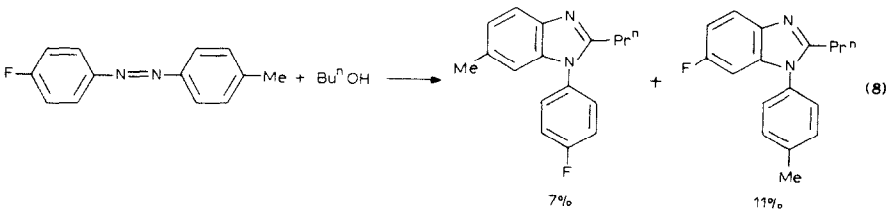


(6)

The worst possible case of isomer formation occurs when a non-symmetrically 3,3′-disubstituted azobenzene is employed. In the reaction of 3-fluoro-3′-methylazobenzene with n-butanol, all four possible isomers were formed as judged from the 250 MHz ^{1}H NMR spectrum of the distilled product. The total yield was 45%, and 1-(3′-fluorophenyl)-2-(n-propyl)-7-methylbenzimidazole was the major product, amounting to roughly half of the mixture (eq. 7).

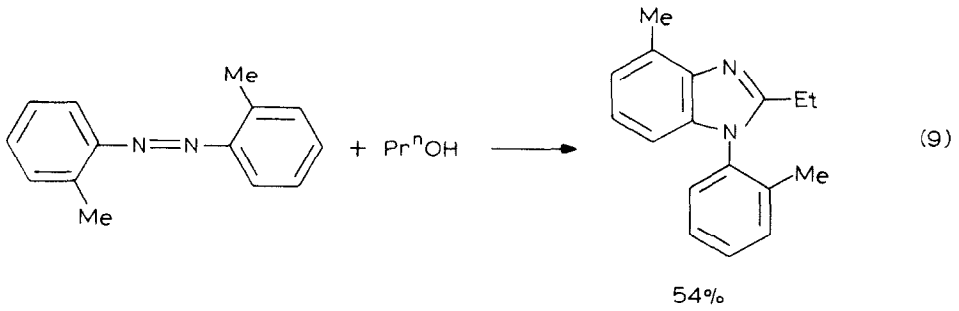


The spectra of the other three isomers could not be unambiguously assigned. 4-Fluoro-4'-methylazobenzene was caused to react under the same conditions, and the product distribution is given in eq. 8.



This and the previous reaction (eq. 7) are of interest as regards the selectivity of the *ortho*-metallation in non-symmetrically substituted azobenzenes (see Discussion).

2,2'-Dimethylazobenzene reacts with n-propanol to give 1-(2'-methylphenyl)-2-ethyl-4-methylbenzimidazole (eq. 9).



The conditions were as in Table 8. On the other hand, no reaction occurred with 2,6-dimethylazobenzene. Mono-*ortho*-substituted azobenzene derivatives again [1] gave mixtures of both possible isomers.

Discussion

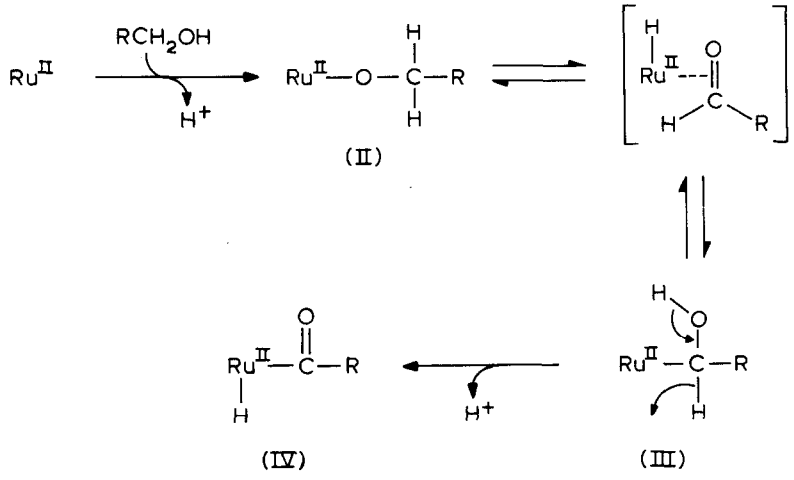
Unlike the ruthenium-catalysed synthesis of 1-phenylbenzimidazoles from azobenzene derivatives and tertiary amines [2], no reaction occurs in the primary alcohol version of the reaction described here if $RuCl_3 \cdot 3H_2O$ alone is used as catalyst under an atmosphere of carbon monoxide. A phosphorus ligand and a catalytic amount of a mild base are required for best results though low yields have been obtained when one or the other was present. The tertiary amine presumably serves as its own base in that version of the reaction. Since the early work of Chatt on reactions of alcohols with ruthenium-phosphine complexes, it is known that a

base (KOH) assists the reactions [3]. It is also known that $RuCl_2(PPh_3)_3$ and $RuCl_3 \cdot 3H_2O$ in the presence of PPh_3 attack refluxing ethanol rapidly in presence of sodium acetate, giving in both cases $RuH(OAc)(PPh_3)_3$ [6]. More recently, the *N*-alkylation of primary and secondary aliphatic amines by alcohols catalysed by the complex $Ru(H)_2(PPh_3)_4$ has been described [7,8]. Finally the *N*-alkylation of aniline by primary alcohols catalysed by $RuCl_2(PPh_3)_3$ has been reported [9]. This reaction did not proceed with $RuCl_3 \cdot 3H_2O$ alone as catalyst, but when $RuCl_2(PPh_3)_3$ was used, no addition of base was necessary. These reactions were carried out at 180°C under argon, whereas in the benzimidazole synthesis, CO is needed, apparently to facilitate the rearrangement of the *ortho*-metallated azobenzene complex to a deprotonated *o*-semidine (*N*-phenyl-1,2-phenylenediamine) derivative [2]. It is thus apparent that, unlike tertiary amines, a phoshorus ligand is needed if ruthenium is to attack a primary alcohol efficiently. It also seems probable that a carbonyl ligand reduces the efficiency of this attack; making the beneficial effect of a base necessary in the benzimidazole synthesis.

In the alkylation of aniline [9], a complex of the type $Ru(H)_2(RCHO)(PPh_3)_n$ was proposed as a possible intermediate, though no evidence for it was provided. In the benzimidazole synthesis, the intact alkyl group of the alcohol is incorporated into the product, and we suggest that the initial attack on the alcohol is as shown in Scheme 1, in which electrophilic attack on the α C–H bond occurs. Intermediates III or IV could then take part in the alkylation step and the release of protons explains the value of a base. Since the final by-products are water and hydrogen (eq. 1) it is clear why only a catalytic amount of base is needed.

The effect of substituents in the azobenzene derivatives on product yields and the isomer distributions observed are similar to those in the tertiary amine version of the reaction, and this may be expected if the azobenzene rearrangement precedes attack on the alcohol.

In general, where the two aromatic rings of the azobenzene derivative are dissimilarly substituted, the major isomer of the benzimidazole product is that



SCHEME 1. Possible mode of attack of ruthenium(II) on the α C–H bond of the alcohol.

arising from *ortho*-metallation of the ring having the highest electron density. This point will be discussed further in part IV of this series [10].

Experimental

Ruthenium trichloride hydrate was obtained from Engelhard and carbon monoxide from Carbagas. Triphenylphosphine, from EGA, was recrystallised from methanol-ethanol under argon. Other phosphines were from Strem and other chemicals from Fluka or Merck. Azobenzene derivatives were synthesised according to the methods already given and the same instrumentation was used [2]. All products and azobenzene derivatives were fully characterised and gave satisfactory elemental analyses.

The following two preparations serve as general examples for the two sets of experimental conditions most used in carrying out these reactions. The reactions were performed in 55 or 110 ml glass pressure tubes (Ciba-Geigy) which were fitted with spring-loaded screw caps containing a glass plug and Teflon O-ring. Further examples will be found in ref. 1.

Preparation of 1-(2'-methylphenyl)-2-ethyl-4-methylbenzimidazole

In a 110 ml glass pressure tube were placed 2,2'-dimethylazobenzene (10.5 g, 50 mmol), tetramethylurea (25 ml) and n-propanol (11.21 ml, 150 mmol). Carbon monoxide was passed with magnetic stirring for 5 min, and then ruthenium trichloride hydrate (0.1308 g, 0.5 mmol), triphenylphosphine (0.524 g, 2 mmol) and anhydrous sodium acetate (0.133 g, 1.5 mmol) were added. The tube was capped under normal pressure of carbon monoxide and then stirred for 8 h in an oil bath at 180°C. The reaction mixture was diluted with diethyl ether (100 ml) and extracted three times with water (50 ml). The ether layer was dried with magnesium sulphate (10 g) and the solvents were removed. The residue was chromatographed in dichloromethane on Kieselgel (80 g) and the product so obtained was distilled in vacuo over a Vigreux column. 6.72 g (54%). Pale yellow liquid. b.p. 131–135°C/0.1 mmHg. Anal. Found: C, 81.25; H, 7.18; N, 11.37. $C_{17}H_{18}N_2$ calcd.: C, 81.56; H, 7.25; N, 11.19%.

Preparation of 1-phenyl-2-cyclopropylbenzimidazole

In a 110 ml glass pressure tube were placed azobenzene (9.1 g, 50 mmol) and lithium acetate dihydrate (3.3 g, 32 mmol), and hydroxymethylcyclopropane (7.91 ml, 100 mmol) and tetramethylurea (25 ml) were added. Carbon monoxide was passed with magnetic stirring for 5 min and then ruthenium trichloride hydrate (0.1308 g, 0.5 mmol) and triphenylphosphine (0.524 g, 2 mmol) were added. The tube was capped under normal pressure of carbon monoxide and then stirred for 8 h in an oil bath at 180°C. The reaction mixture was then filtered and the precipitate was washed with dichloromethane (10 ml). After removal of the solvents the residue was distilled in vacuo over a Vigreux column. The crude product was chromatographed in dichloromethane on Kieselgel (100 g) and the product so obtained was redistilled as above. 5.2 g (46%). Yellow viscous liquid. b.p. 144–148°C/0.1 mmHg. Anal. Found: C, 81.73; H, 6.22; N, 12.28. $C_{16}H_{14}N_2$ calcd.: C, 82.02; H. 6.03; N, 11.96%.

References

1 A. Spencer (Ciba-Geigy AG) Eur. Patent Appln., Publication No., 138 750, 1985.
2 Part I. A. Spencer, J. Organomet. Chem., 294 (1985) 357.
3 J. Chatt, B.L. Shaw and A.E. Field, J. Chem. Soc., (1964) 3466.
4 A. Spencer (Ciba-Geigy AG) Eur. Patent Appln., Publication No., 138 760, 1985.
5 Part III. A Spencer, J. Organomet. Chem., 295 (1985) 91.
6 R.W. Mitchell, A. Spencer and G. Wilkinson, J. Chem. Soc., Dalton Trans., (1973) 846.
7 R. Grigg, T.R.B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, J. Chem. Soc., Chem. Commun., (1981) 611.
8 S. Murahashi, K. Kondo and T. Hakata, Tetrahedron Lett., (1982) 229.
9 Y. Watanabe, Y. Tsuji and Y. Ohsugi, Tetrahedron Lett., (1981) 2667.
10 Part IV. A Spencer, J. Organomet. Chem., 295 (1985) 199.