

A NOVEL C-C COUPLING OF BENZAZOLES MEDIATED BY DICHLOROCARBENE -
FORMATION OF BIS-BENZAZOLES

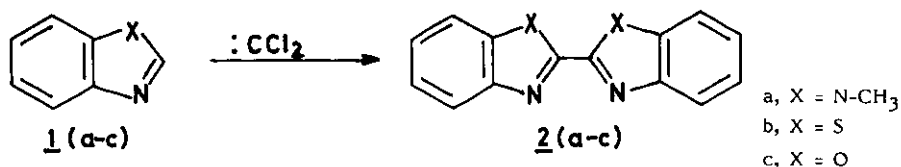
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Abstract - The reaction of dichlorocarbene with benzazoles has led to the formation of bis-benzazoles. A reasonable mechanism has been proposed for this novel C-C coupling induced by dichlorocarbene.

Dichlorocarbenes, derivatives of highly reactive divalent carbon, react with several five-membered heterocyclic systems leading to ring expansion products¹, sometimes along with addition compounds². Addition of dichlorocarbene on C=C bond both under basic and neutral conditions is well documented^{1,3}. Whereas addition on C=N bond in a heterocyclic system describes that addition takes place through gas-phase thermolysis⁴. Recently, such type of compounds have been isolated in the case of benzimidazole⁵, where the insertion of carbene into the N-H bond is the main feature. Further, generation of carbene under classical conditions or two-phase system has produced similar products.

We report now, the reaction of dichlorocarbene obtained under Makosza condition, with benzazole systems, which has resulted in a novel C-C coupling, giving bis-benzazoles in 30-60% yields. Typically the reaction is carried out with the organic base in chloroform, 50% aqueous sodium hydroxide and a catalytical amount of triethylbenzylammonium chloride (TEBA) and triethylenediamine (TEDA) by stirring the mixture vigorously at ambient temperature for 4-6 h. The bis-azoles were isolated from the organic phase, by column chromatography using silica gel. The unreacted starting materials were also recovered. Thus N-methylbenzimidazole gave 2,2'-bis(N-methylbenzimidazole) (2a) in a 30% yield and the reaction proceeded smoothly with benzothiazole, giving the corresponding 2,2'-bisbenzothiazole (2b) in a 60% yield. In the case of benzoxazole the reaction required longer time giving the corresponding bis-compound (2c) in rather low yield (10%) and the unconverted starting material. The involvement of dichlorocarbene in the coupling reaction of azoles has been verified by conducting the reaction in solvents other than chloroform. The above reaction, when conducted in dichloromethane and/or benzene did not give the bis-azoles even in traces.



The structures of the bis-benzazoles were identified on the basis of mass, ^{13}C nmr, and ^1H nmr spectral data. The high resolution mass spectrum of 2a showed an elemental composition of $\text{C}_{16}\text{H}_{14}\text{N}_4$ for the molecular ion at m/z 262.1209 (calcd. m/z 262.1216). ^1H nmr spectrum (, CDCl_3) 7.2-7.9 (m, 8H, aromatic H), 4.3 (s, 6H, N-CH_3). ^{13}C nmr spectrum (, CDCl_3) 32.50 (N-CH_3), 110.13, 120.45, 122.92, 124.04 (benzimidazolyl carbons), 136.35, 142.73, 143.38 (quaternary carbons). Spectral data of 2,2'-bisbenothiazole 2b [ms m/z 268 (M^+); ^1H nmr (, CDCl_3) 7.2-7.7 (m, 8H, aromatic H); ^{13}C nmr (, CDCl_3) 121.63, 123.42, 125.26, 125.98 (benzothiazolyl carbons), 133.55, 153.11, 153.59 (tertiary carbons)]. Spectral data of 2,2'-bisbenzaxozole 2c [ms, m/z 236 (M^+); ^1H nmr (, CDCl_3) 7.2-7.8 (m, 8H, aromatic H)]. The structures of bis-benzazoles were finally substantiated by comparing with authentic samples prepared by literature methods⁸.

The reaction of benzazoles 1 (a-c) with dichlorocarbene generated from sodium trichloroacetate by refluxing in dioxane also proceeds smoothly, giving the bis-compounds 2(a-c). Furthermore, the alkali alone cannot induce C-C coupling, which has been substantiated by conducting the reaction under Makosza conditions by excluding chloroform, where the entire starting materials were recovered. Variation in the reaction temperature and other parameters such as catalyst, stoichiometry did not show any influence on the reaction course. Tributylamine^{6,7} was tried as the catalyst, but there was no significant improvement in the yields of the reaction product.

It is interesting to note that the dichlorocarbene did not give any C=N bond addition product in spite of the presence of an isolated azomethine linkage in all the substrate molecules under study, suggesting the carbenoid insertion to the C=N bond is not a favourable one. The results are tabulated below.

TABLE

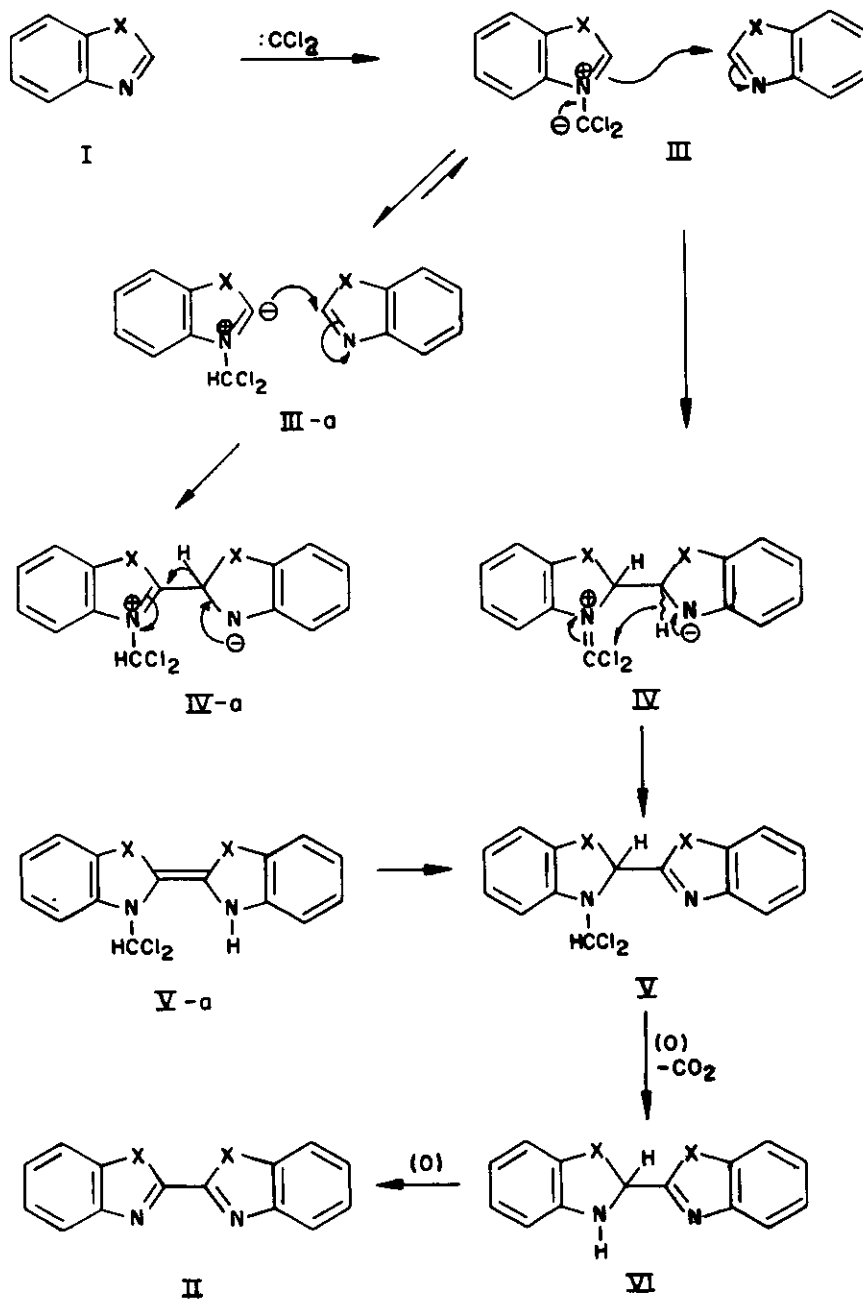
Starting material	Reaction temperature	Reaction time (h)	Catalyst	Yield of the bis-benzazole
N-Methylbenzimidazole	Room temp.	4	TEBA/TEDA	30%
	100°C	5	$\text{CCl}_3\text{CO}_2\text{Na}$	30%
Benzothiazole	Room temp.	4	TEBA/TEDA	60%
	100°C	6	$\text{CCl}_3\text{CO}_2\text{Na}$	60%
Benzazole	Room temp.	24	TEBA/TEDA	10%
	100°C	24	$\text{CCl}_3\text{CO}_2\text{Na}$	10%

Notwithstanding the synthetic limitations, the reaction is interesting for its mechanistic implications.

A possible pathway for the formation of bis-compounds (2a-c) is represented in the scheme.

It is reasonable to assume that the electron deficient dichlorocarbene species makes an electrophilic attack on the azomethine nitrogen of the azole resulting in the formation of an ylide (III). The ylide in turn can

SCHEME



add onto the C-2 position of the neutral azole leading to the 1,4-dipole (IV). Formation of a dihydro bis-azole intermediate (VI) can be visualized from IV in the following way. An intramolecular hydride shift, assisted by the negative charge on the nitrogen to the electron deficient carbon bearing halogens can lead to the formation of a dichloromethyl analogue (V). The resulting chloromethyl intermediate (V) can react with hydroxide ions which are transported to organic phase and subsequent decarboxylation leading to VI. Since the dihydroazoles are not very stable, they undergo air oxidation to give the bis-compound (II). Alternatively, the ylide (III) can be isomerized to the more stable endocyclic ylide (III-a), which then attack the C-2 position of neutral azole leading to the dipole (IV-a). The dipole with a 1,2-hydride shift can give V or the isomeric enediamine (V-a) which can undergo either 1,4-elimination thermally, or the hydrolysis sequence as shown in the Scheme.

Conversion of the precursor to the final product, under anhydrous conditions may be visualized as follows: The undissociated trichloroacetate ions can displace the chlorines to give diacylorthoformate type of intermediate, which can undergo thermal rearrangement to the corresponding formyl compound. Subsequent oxidation followed by decarboxylation can result in the formation of the dihydro compound VI, which on air oxidation leads to II.

The variation in the yields (10 to 60%) of the coupling may reasonably be attributed to the influence of the second heteroatom present in the azole nucleus. The highest yields of bi-benzothiazole may be explained on the basis of the relative basicities⁹ of the azoles and the stabilities of the corresponding ylides¹⁰ coupled with a possible 'd' orbital overlap by sulfur atom. Thus, the formation of bis-azoles starting from monomeric azoles constitute a novel oxidative coupling reaction affected by dichlorocarbene species.

ACKNOWLEDGEMENT

One of the authors (J.S.R.) is grateful to the CSIR, New Delhi for the award of Research Fellowship.

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Received, 2nd December, 1986