SYNTHESIS OF 2-ARYL-BENZIMIDAZOLES VIA CYCLIC N-DIAZONIUM IONS [1)]

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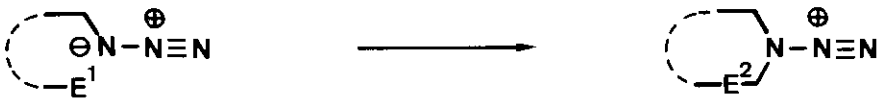
Condensation of 2-azido-aniline with aromatic aldehydes and protonation with tetrafluoroboric acid lead to *phenylogous* azidoiminium salts. Subsequent cyclisation to cyclic N-diazonium ions and N_2-elimination give rise to the formation of 2-aryl-benzimidazoles. In the same manner 2-azido-N-methylaniline can be converted with aromatic aldehydes through a one step procedure into the corresponding 1-methyl-2-aryl-benzimidazoles. The common reaction principle is the intermediate formation of cyclic N-diazonium salts as precursors for 5-membered heterocycles.

α,ω-Bifunctional compounds (1) containing both a terminal azido group and an electrophilic centre (E^1 = nitrilium- [3a)] or E^1 = iminium-group [3b)]) seemed to be attractive precursors for the generation of cyclic N-diazonium ions (2). Nucleophilic addition of the azido group to the polarized carbon nitrogen multiple bond was expected to be a promising route for the formation of these reactive cationic intermediates (2).



(1) (2)

$E^1 = -\overset{\oplus}{N}\equiv C-R$ $E^2 = -N=C(H)-R$

$E^1 = -\overset{\oplus}{H}N=CH-R$ $E^2 = -HN-CH-R$

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In order to evaluate the scope of this simple synthetic principle it was tested if the intramolecular reaction of the phenylogous azido-iminium-salts (5) - via the 5-membered N-diazonium ions (6) and subsequent N_2-elimination to substituted benzimidazoles (7) - could be realized. For this end 2-azido-aniline (3.1) was condensed with substituted aromatic aldehydes via (r_1). The formed azomethines (4) are isolable and can be converted by treatment with tetrafluoroboric acid into the reactive azido-iminium-salts (5.1).

These cationic intermediates lose nitrogen in the range of 95 - 125 °C - depending on the electronic properties of the substituent R' in p-position - giving rise to the formation of 2-aryl-benzimidazoles (7.1, cf. table 1). The cyclisation is obviously favored by the nitro group (R' = NO_2). This electron attracting substituent enhances the electrophilic reactivity of the iminium salt (5.1a) and increases the tendency for cyclisation through intramolecular addition of the azido group to the polarized CN-double bond. The reverse effect is observed for the methyl group (R' = CH_3) in p-position. The reactivity of the azido-iminium-salt (5.1c) is diminished and a higher reaction temperature is afforded for cyclisation.

Table 1: 2-(4'-R'-Aryl)benzimidazoles (7.1, R = H) via cyclisation of 2-azido-N-(4'-R'-benzylidene)anilines (4) in the presence of tetrafluoroboric acid

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2-Azido-N-(4'-R'-benzylidene)anilines (4.1a) - (4.1c) were treated with equimolar amounts of tetrafluoroboric acid in absolute benzonitrile at room temperature. The resulting azido-iminium-salts (5.1a) - (5.1c) were heated for 30-60 min up to 95 - 125 °C until N_2-evolution was completed. The formed 2-aryl-benzimidazoles (7.1) were isolated by standard procedures (distillation, extraction, crystallization) and characterized by comparison with the authentic materials [4].

(7.1a) R' = NO_2, 60 min/ 95-100 °C; yield 73 %, mp = 316 - 318 °C.
(7.1b) R' = Cl, 30 min/110-115 °C; yield 90 %, mp = 295 - 296 °C.
(7.1c) R' = CH_3, 30 min/120-125 °C; yield 96 %, mp = 276 - 279 °C.

The electrophilic activation of the CN-double bond can also be achieved through N-alkylation. Treatment of the phenylogous azido-azomethines (4) with methyl trifluoromethanesulfonate in 1,2-dichloroethane (5 h/0 °C) leads to the reactive azido-iminium-salts (5.2, R = CH_3) via ($r_{1,2}$). Cyclisation to the 5-membered N-diazonium ions (6.2, R = CH_3) and subsequent N_2-elimination is induced by heating at reflux temperature. The anticipated 1-methyl-2-aryl-benzimidazoles (7.2) are obtained with yields of 50 %. In this case no significant dependence of the reaction conditions on the substituents could be detected. In a similar manner 1-ethyl-2-aryl-benzimidazoles are produced by treatment of the phenylogous azido-azomethines (4) with triethyloxonium tetrafluoroborate.

The cyclisation products (7.2) independently arise via a two step reaction (r_2/r_3) from 2-azido-N-methyl-aniline (3.2) by subsequent treatment with tetrafluoroboric acid and the same aromatic aldehydes (cf. table 2). Under the condensation conditions the initially formed azido-iminium-salts (5.2) are not isolable; ring closure to cyclic N-diazonium ions (6.2) accompanied by N_2-elimination provides a convincing explanation for the formation of 1-methyl-2-aryl-benzimidazoles.

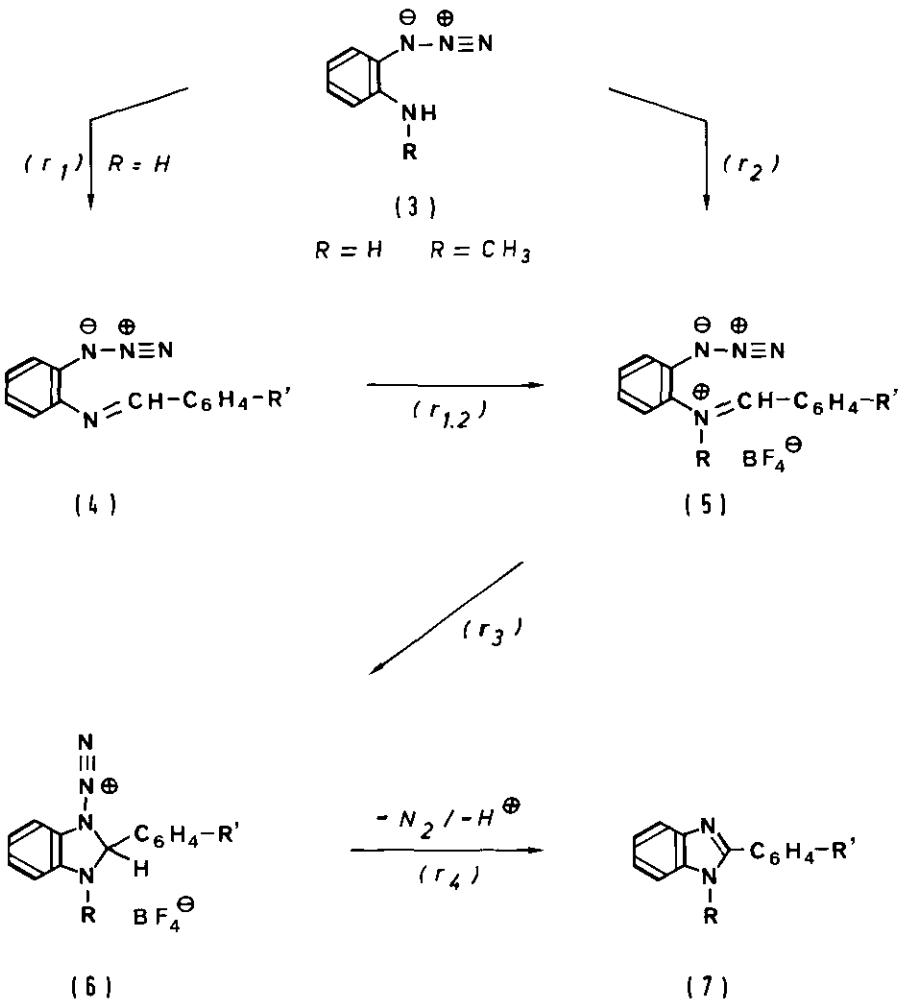

Table 2: 1-Methyl-2-(4'-R'-aryl)benzimidazoles (7.2, R = CH_3) via condensation of 2-azido-N-methylaniline (3.2, R = CH_3) with aromatic aldehydes and cyclisation in the presence of tetrafluoroboric acid

The tetrafluoroborate of 2-azido-N-methylaniline (3.2, R = CH_3) was refluxed in absolute 1,2-dichloroethane for 6 h with equimolar amounts of aromatic aldehydes and catalytic amounts of triethylamine at a water separator. The reaction mixture was worked up under basic and acidic conditions. The isolated 1-methyl-2-aryl-benzimidazoles (7.2) were purified by recristallization from n-hexane/benzene and identified by comparison with the authentic materials [5,6].

(7.2a) R' = NO_2 yield 63 % mp = 214 - 215 °C
(7.2b) R' = Cl yield 52 % mp = 112 - 113 °C
(7.2c) R' = CH_3 yield 62 % mp = 126 - 127 °C
(7.2d) R' = CH_3O yield 54 % mp = 117 - 118 °C

The alternative reaction pathways ($r_{1.2}$) and (r_2) independently confirm the formation of the phenylogous azido-iminium-salts (5.2, R = CH_3) as precursors for the generation of cyclic N-diazonium ions (6.2) through intramolecular addition of the azido group to the polarized CN-double bond. The subsequent reactions of the reactive intermediates (6.2) - N_2-elimination and deprotonation - proceed spontaneously and do not exhibit significant dependence on the substituents. The coplanar arrangement of the terminal azido- and iminium-groups at the benzenoid ring system seems to be an essential structural feature for the formation of cyclic N-diazonium ions [7]. Acyclic α,ω-azido-iminium-salts (1, E^1 = iminium-group) without this steric requirement cannot be cyclized under the same reaction conditions.

The formation of benzimidazoles through thermolysis (140-145 °C) of 2-azido-N-benzylidene-anilines has been reported by Krbechek and Takimoto [4] as well as by Hall and Kamm [8]. In this case the experimental conditions establish the generation of nitrenes. These reactive intermediates can be precluded for our investigations because the reaction of 2-azido-N-(4'-R'-benzylidene)anilines (4) does not occur in the range of 90 - 120 °C, without mediation of a strong acid (tetrafluoroboric acid) or a reactive electrophile (methyl trifluoromethanesulfonate or triethyloxoniumtetrafluoroborate) [9].

ACKNOWLEDGMENT

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