SYNTHESIS OF 3,4-DIHYDROQUINAZOLINES VIA CYCLIC N-DIAZONIUM IONS [1]

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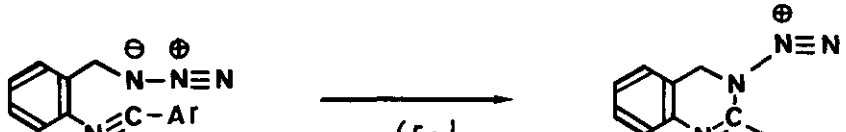
The condensation of 2-azidomethylanilines with aromatic aldehydes leads to the formation of the corresponding azomethines. Treatment with tetrafluoroboric acid results in the generation of phenylogous azidomethyl-iminium salts giving rise to the formation of 2-aryl-3,4-dihydroquinazolines. Cyclic N-diazonium ions are involved as reactive intermediates and synthetic precursors for the annelation of the 6-membered nitrogen heterocycle.

The intermolecular alkylation of organic azides to reactive N-diazonium ions has been accomplished only in a few cases using powerful precursors for carbenium ions [3-6]. BERGMANN [7] was successful in achieving the intramolecular N-alkylation of the azido-function through an activated nitrilium group.

Reaction of 2-azidomethylphenyldiazonium tetrafluoroborate with alkyl- and arylnitriles leads to the generation of the phenylogous azidomethyl-nitrilium salts (1). Subsequent cyclization (r_1) to 6-membered N-diazonium ions (2) and N_2-elimination with deprotonation result in the formation of the heteroaromatic quinazolines.



(1) (2)

In connection with studies concerning the formation of cyclic N-diazonium ions it should be evaluated whether the intramolecular N-alkylation (r_2) of an azido-function through an iminium group has synthetic prospects. Via this route the phenylogous azidomethyl-iminium salts (3) might be convertible into cyclic N-diazonium ions (4).

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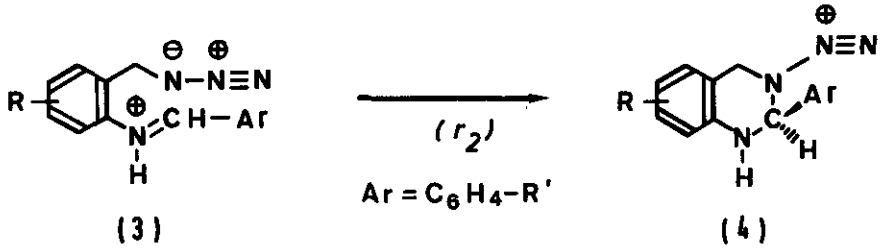


The precursors (3) of the cyclic N-diazonium ions were prepared via condensation of 2-azidomethylanilines [8,9] with substituted aromatic aldehydes and protonation of the corresponding azomethines with etheral tetrafluoroboric acid. The resulting iminium salts (3) spontaneously lose nitrogen - heating the tetrafluoroborates in acetonitrile or benzonitrile - and are apparently convertible into stable 3,4-dihydroquinazolines (5) with a conjugated amidine system [10-13]. The ^{1}H-NMR spectra show a singlet at τ = 5.28-5.32, which has to be attributed to the cyclic methylene group [12]. The constitution has been chemically confirmed through dehydrogenation (r_3) with manganese dioxide; via this route the heteroaromatic 2-arylquinazolines (6) are obtainable with respectable yield [10,15,16].

Table 1: 2-(4'-R'-Aryl)-3,4-dihydroquinazolines (5, R = H) via cyclization of 2-azidomethyl-N-(4'-R'-benzylidene)anilines (3) in the presence of tetrafluoroboric acid

2-Azidomethyl-N-(4'-R'-benzylidene)aniline (3 mmol), dissolved in 20 ml of anhydrous acetonitrile (Method A) or in 10 ml of anhydrous benzonitrile (Method B) were treated with 3 mmol tetrafluoroboric acid diethyl ether-complex for 5 min at room temperature. The resulting tetrafluoroborates (3a) - (3c) were heated until nitrogen evolution ceased. After hydrolysis with diluted hydrochloric acid, extraction with dichloromethane and cooling the cyclization products (5a) - (5c) were isolated by filtration and purified by recrystallisation.

(5a, R = H, R' = NO_2): Method A (30 min/70 °C): yield 60 %, mp = 140-142 °C (ethanol/water = 1:1).

(5b, R = H, R' = Cl): Method B (60 min/95 °C): yield 74 %, mp = 169-170 °C (ethanol/water = 1:1).

(5c, R = H, R' = CH_3): Method B (60 min/120 °C): yield 53 %, mp = 148-150 °C (cyclohexane/benzene = 6:1).

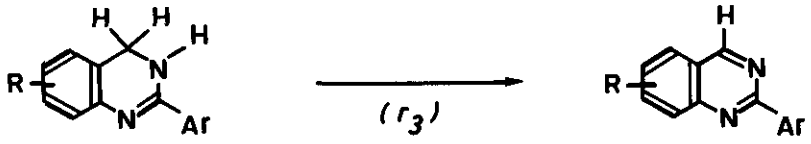


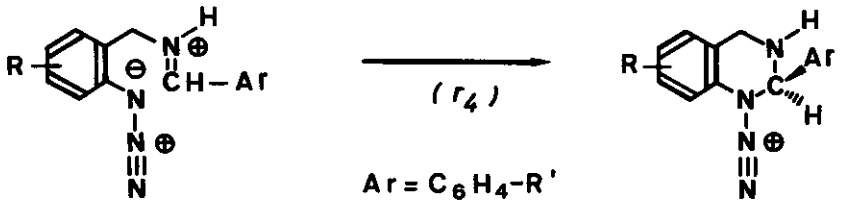
Table 2: 2-(4'-R'-Aryl)quinazolines (6) via dehydrogenation of 2-(4'-R'-Aryl)-3,4-dihydroquinazolines (5) with manganese dioxide

2-(4'-R'-Aryl)-3,4-dihydroquinazoline (5) (1-2 mmol) were treated with 1.5-3.5 g of manganese dioxide and heated at reflux in 40-50 ml of anhydrous benzene over an 1 hr-period. The boiling suspension was filtered to remove inorganic material. The organic filtrate was concentrated and the precipitated solid isolated and recrystallized.

(6a, R = H, R' = NO_2): yield 60 %, mp = 221-222 °C (benzene)
(6b, R = H, R' = Cl): yield 78 %, mp = 137-138 °C (ethanol)
(6c, R = H, R' = CH_3): yield 88 %, mp = 95-96 °C (ethanol/water).

The reaction temperature (cf. table 1) is significantly dependent on the substituent (R' = NO_2, Cl, CH_3) at the 4'-position of the benzylidene group. The substituent at the 4-position (R = NO_2, CH_3O) of the aryl moiety also reveals a considerable effect on the tendency of cyclization. The intramolecular addition (r_2) of the azido group to the cationic CN-double bond is apparently enhanced through an electron attracting group (R or R' = NO_2), because the electrophilic reactivity of the iminium group is remarkable increased.

In the same manner the cyclization of the phenylogous azido-methyliminium salts (7) via isomeric N-diazonium ions (8) can be accomplished under more drastic conditions, presumable because of the diminished reactivity of the nuclear azido group.



(7) (8)

The experimental results can be rationalized by two conclusions. The arrangement of both functional groups - the terminal azido and imino group - at an aromatic system seems to be an essential requirement for the formation of cyclic N-diazonium ions through ring closure. On the other hand, the cyclization reaction is decisively influenced through the electrophilic reactivity of the iminium group, which can be determined via substituents R or R' at p-position to the nitrogen or carbon atom of the functional group.

The reported reaction sequence represents a successful application of N-diazonium ions for the annelation of nitrogen heterocycles. Elimination of nitrogen can be regarded as a simple and general method for the introduction of a cyclic CN-double bond.

The two-step procedure - ring closure (r_2) of the azidomethyl-iminium salts and dehydrogenation (r_3) of the 3,4-dihydroquinazolines - has some advantages compared with the direct cyclization (r_1) of the azido-nitrilium salts to the corresponding heteroaromatic 2-arylquinazolines.

A C K N O W L E D G M E N T

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R e f e r e n c e s and N o t e s

1) N_2-Eliminations under the Influence of Electrophiles, Part 14.- Part 13: Reference 2.- 2) R. Kreher and U. Bergmann, Heterocycles 14, 1725 (1980).- 3) W. Pritzkow and G. Pohl, J. Prakt. Chem. 20, 132 (1963).- 4) N. Wiberg and K.H. Schmid, Angew. Chem. 76, 381 (1964).- 5a) A. Schmidt, Chem. Ber. 99, 2976 (1966).- 5b) R.Volgnandt and A. Schmidt, Z. Naturforsch. 30b, 295 (1975).- 6) R. Kreher and K. Goth, Z. Naturforsch. 31b, 217 (1976). Introduction and notes [5-7]: N-diazonium ions.- 7) R. Kreher and U. Bergmann, Tetrahedron Lett. 1976, 4259.- 8) R. Kreher and U. Bergmann, Z. Naturforsch. 31b, 222 (1976).- 9a) U. Bergmann, Part from the dissertation, Technische Hochschule Darmstadt 1980.- 9b) U. Bergmann, Diploma thesis, Technische Hochschule Darmstadt 1975.- 10) W.L.F. Armarego, 'Advances in Heterocyclic Chemistry' (Ed.: A.R. Katritzky) Vol. 1, p.282, Academic Press, New York - London 1963 (Review).- 11) W.L.F. Armarego, J. Chem. Soc. 1961, 2697.- The remarkable stability of 3,4-dihydroquinazolines compared with the 1,4-dihydroisomers was deduced from synthetic investigations. The structure of the 1,4-dihydroquinazolines must be stabilized by substitution of the heteroatom at 1-position with alkyl groups; cf. Reference 12,13.- 12) R.F. Smith, P.C. Briggs, R.A. Kent, J.A. Albright and E.J. Walsh, J. Heterocycl. Chem. 2, 157 (1965).- 13) S.C. Pakrashi and A.K. Chakravarty, J. Org. Chem. 37, 3143 (1972).- 14) A.J. Fatiadi, Synthesis 1976, 65 and 133.- 15) M. Lora-Tamayo, R. Madroñero and G.G. Muñoz, Chem. Ber. 94, 208 (1961).- 16) R.C. Elderfield, T.A. Williamson, W.J. Gensler and C.B. Kremer, J. Org. Chem. 12, 405 and 415 (1947).- 3,4-Dihydroquinazolines can be oxidized to quinazolines with alkaline potassium ferricyanide; cf. K. Schofield, J. Chem. Soc. 1952, 1927.-

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