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Transformation of 5,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles to 4-arylquinazolines

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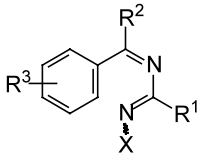
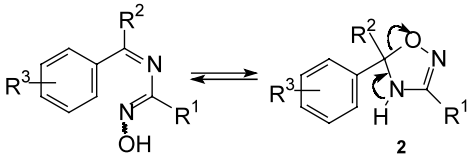
Abstract—The transformation of 5,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles to 4-arylquinazolines in boiling acetic anhydride via acyclic 1-acetyloxy-4-aryl-1,3-diaza-1,3-butadienes is described.

The discovery of the strong anticancer activity of some quinazoline derivatives[1] has caused increased interest in the synthesis of quinazolines.[2] A search through the review literature concerning quinazolines shows that only very little is known about synthesis of the system via the formation of the 1,8*a* bond.[3] For example, in Brown's monograph on quinazolines[4] this route was called 'unappealing' and only half a page was dedicated to it. The reason seems to be connected with the poor availability of the starting materials, namely 4-aryl-1,3-diaza-1,3-butadiene derivatives **1** suitable for quinazoline ring formation (Fig. 1).



1a X = H
1b X = OH
1c X = OAc

Figure 1.



Scheme 1.

Though compounds **1a** (X = H) are rather easily prepared by condensing benzamidines with aldehydes, on heating they unfortunately form 1,3,5-triazines[5] and not quinazolines. In contrast, some derivatives, e.g. **1b** (X = OH) or **1c** (X = OAc) are practically unknown. Until now we have found only one example of the synthesis of **1b** (R^1 = Ph, R^2 = R^3 = H, X = OH, 10% yield),[6] which involves the dehydration of benzaldoxime on molecular sieves in the presence of RuS_2 as a catalyst. The acetate **1c** of this compound remains unknown.

It is worth mentioning that quinolines[7] and quinoxalines[8] have been successfully obtained in high yields by heating easily available *O*-acetates of β,β-diphenyl-α,β-unsaturated ketoximes and α-arylimino-ketoximes in non-polar solvents, by formation of the respective 1,8*a*-bonds.

Looking for a convenient approach to **1c** (X = OAc) we noticed the formal tautomerism between **1b** and 5-aryl-4,5-dihydro-1,2,4-oxadiazoles **2** (Scheme 1).

We considered that **2** would react with acetic anhydride to yield the desired **1c** which on heating should be further transformed to quinazolines **3**.

Compounds **2** are reasonably easy to prepare.[9] We obtained several such 4,5-dihydro-1,2,4-oxadiazoles by the 1,3-dipolar cycloaddition reaction of arenenitrile *N*-oxides to benzophenone imines: R^1 = Ar, R^2 = Ph, R^3 = H[10] or R^1 = Ar, R^2 = *p*-MeC_6H_4, R^3 = Me[11] (Scheme 2). The *N*-oxides were prepared from areneoximoyl chlorides[12] using triethylamine.[13]

Heating **2** in an excess of boiling acetic anhydride for six hours followed by careful treatment of the resulting

Keywords: oxadiazoles; quinazolines; dipolar cycloaddition; transformation; electrocyclization; imines; nitrile oxides.

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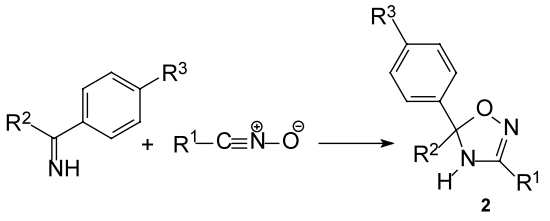
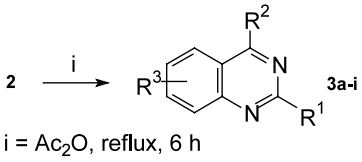


Scheme 2.



Scheme 3.

solution with water afforded solid products, which were collected and recrystallized from methanol (Scheme 3, Table 1).

MS and NMR analyses showed that compounds **2** in boiling acetic anhydride afford the expected quinazolines **3** with yields from low to satisfactory. In the case of **3f**–**3i** the position of the R^3 substituent was uncertain. X-Ray analysis of a single crystal of **3g** unequivocally proved that R^3 occupies position 7 of the quinazoline system (Fig. 2).[15] This indicates 1,8*a* bond formation via direct attack of the oxime nitrogen atom on one of the *ortho* positions of the benzene rings. Such a reaction can occur as a thermal electrocyclic disrotatory process. The intermediate 1,8*a*-dihydroquinazoline derivative can then thermally eliminate acetic acid to give the aromatic product (Scheme 4).

A radical mechanism recently proposed by Maroulis et al.[8] for the formation of quinoxalines from α-(*N*-arylimino)oxime acetates seems not to operate in this reaction. In the syntheses of quinolines and quinoxalines phenolic radical scavengers affect neither the composition nor yields of the products.[16] Also a reaction-path including a *spiro* intermediate formed as a result of an *ipso* attack of the oxime nitrogen atom on the benzene ring (Scheme 5) can be ruled out since we

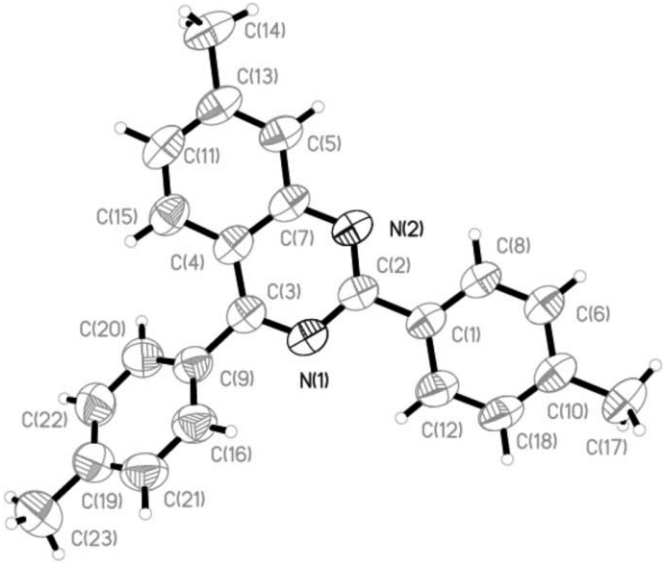
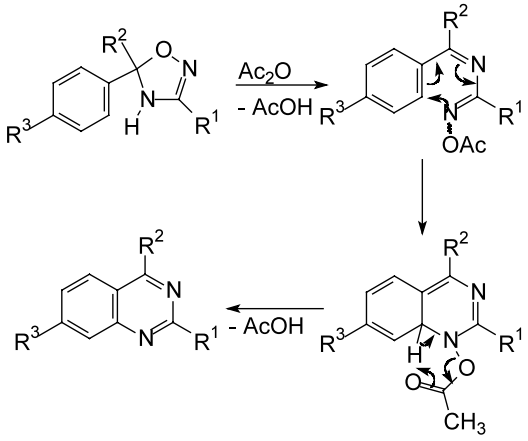


Figure 2. Crystal structure of **3g**. Displacement ellipsoids are drawn at the 50% probability level.



Scheme 4.

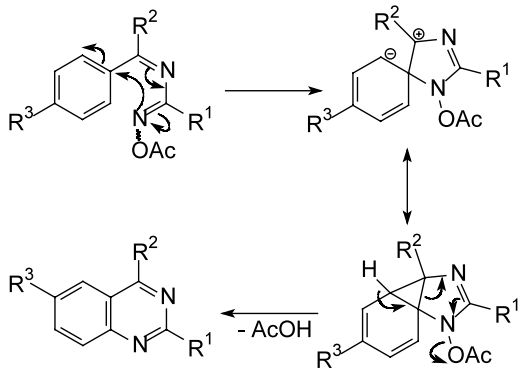
have not found 6-substituted quinazolines in the product mixtures.

To conclude, our results show that readily available 5,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles transform in

Table 1. Yields and melting points of quinazolines obtained by heating 5,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles in boiling acetic anhydride

Compound	R^1	R^2	R^3	Yield (%)	Mp (°C)
3a	Ph	Ph	H	64	120–121[a]
3b	4-MeC_6H_4	Ph	H	66	164–166
3c	3-$NO_2C_6H_4$	Ph	H	79	181–183
3d	3-ClC_6H_4	Ph	H	45	116–118
3e	4-BrC_6H_4	Ph	H	81	191–194
3f	Ph	4-MeC_6H_4	Me	33	119–121
3g	4-MeC_6H_4	4-MeC_6H_4	Me	78	153–155
3h	3-ClC_6H_4	4-MeC_6H_4	Me	30	152–154
3i	4-ClC_6H_4	4-MeC_6H_4	Me	80	147–148

[a] 119–120°C.[14]



Scheme 5.

boiling acetic anhydride into 4-arylquinazolines via 4,4-diaryl-1,3-diaza-1,3-butadiene derivatives, which undergo thermal electrocyclization to form the 1,8*a*-bond of the quinazoline system.

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13. Procedure: Triethylamine (0.01 mol) in chloroform (10 ml) was dropped into the oximoyl chloride (obtained from 0.01 mol of a respective benzaldoxime)[9] in chloroform (30 ml) at 0°C followed by addition of the imine (0.01 mol) solution in chloroform (15 ml). The resulting solution was stirred for 1 h at 0°C and then overnight at ambient temperature. The mixture was extracted with dilute aqueous hydrochloric acid, then with water, dried over anhydrous magnesium sulfate and evaporated to dryness. The solid residues were recrystallized from methanol.
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15. Crystallographic data for **3g** has been deposited with Cambridge Crystallographic Data Centre as the supplementary publication number CCDC 187507. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
16. Suwiński, J., unpublished results.