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Synthesis of quinoxalines by cyclization of α-arylimino oximes of α-dicarbonyl compounds

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Abstract

Heating the title compounds **1** at reflux in acetic anhydride yields quinoxalines **3** and **4** via a presumed aryliminoiminyl radical **5**, resulting from homolytic cleavage of the N–O bond in the intermediate ester **2**. The observed regioselectivity of the reaction is also rationalized by implicating such a radical.

Keywords: α-arylimino oximes; iminyl radical; quinoxalines; spirodienyl radical.

Quinoxaline derivatives are very useful compounds with well-known biological activity.[1,2] Of the routes available for the synthesis of quinoxalines, the cyclization of appropriately functionalized 1-*N*-4-aryl-1,4-diaza-1,3-dienes is the most promising in terms of regiochemistry and generality. However, the first of two early examples, which involved cyclization of α-arylimino phenylhydrazones of α-dicarbonyl compounds, employed extremely vigorous conditions and was plagued by low yields and other practical disadvantages.[3] The second, which dealt with the photocyclization of acetate and benzoate esters of the α-phenylimino oxime of benzil, was rather limited in scope and also suffered from low yields.[4] We recently reported an oxidative cyclization of benzil α-arylimino oximes **1** ($R^1 = R^2 = Ph$) to 2,3-diphenylquinoxaline 1-oxides as another representative example of this approach.[5]

As previously mentioned, what makes the cyclization of the diaza-dienes **1** to quinoxaline derivatives so promising is the expected regioselectivity in those cases where nonsymmetrical substrates are used. The lack of regioselectivity is the main drawback of the most widely used method for quinoxaline synthesis, namely the condensation of *o*-phenylenediamines with α-dicarbonyl compounds.[1,2]

Our investigations on the preparation of the title compounds initially involved the synthesis, isolation and thermal conversion of the oxime acetates **2** to the quinoxalines **3** (Scheme 1 and

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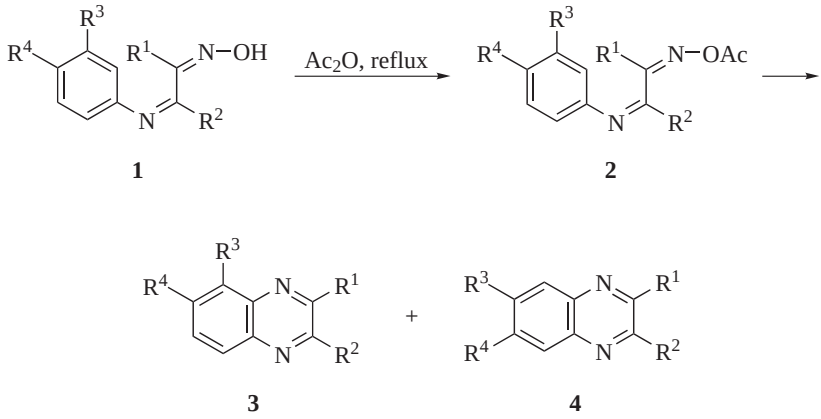


Scheme 1.

Table 1, entries 2–4 and 8). However, we soon realized that the one pot procedure described here, which employs the oximes **1** instead of their esters **2**, provided comparable or better yields of quinoxalines under especially mild conditions in only one step.[6]

When the starting α-arylimino oximes **1** originating from symmetrical diketones ($R^1 = R^2$)[5] and when the aryl group bore only a *para* substituent ($R^3 = H$), this substituent ended up naturally in the 6-position of the quinoxaline system (i.e. **3** = **4** in this case, Table 1, entries 2–4).

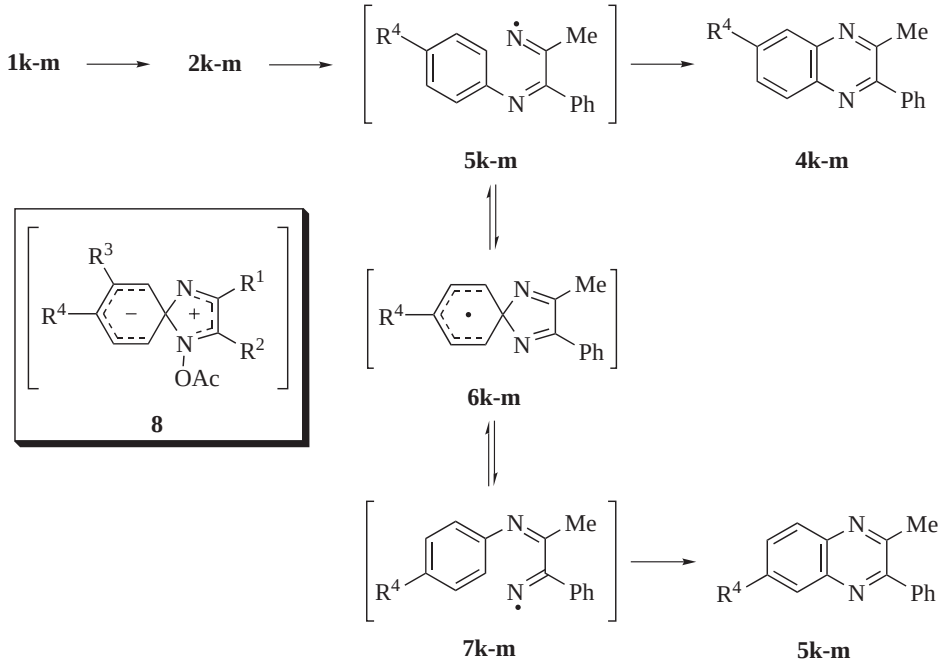
Interesting site selection was observed, however, when the *meta* substituted derivatives **1g–i** and **2h** were cyclized. Contrary to that normally expected on the basis of steric considerations, the regioisomers **3g–j**, resulting from attack at the position *ortho* to the R^3 subsituent, prevailed over regioisomers **4g–j** originating from attack at the *para* position. It is clear from the results shown in Table 1 (entries 7–9) that the ratio **3**/**4** is only slightly dependent on the substituent (in all of these cases $R^1 = R^2$).

Table 1
Isolated quinoxalines from α-arylimino oximes **1** and their corresponding esters **2**

Entry	Starting oxime (ester) **1** (**2**)	R^1	R^2	R^3	R^4	Quinoxaline yield (%)			
						3	**4**	Total **3**+**4**	Ratio **3**/**4**
1	**a**	Ph	Ph	H	H	57			
2	**b**	Ph	Ph	H	MeO	65 (64)[a]			
3	**c**	Ph	Ph	H	Me	63 (62)[a]			
4	**d**	Ph	Ph	H	Cl	53 (82)[a]			
5	**e**	Me	Ph	H	H	66			
6	**f**	Me	Me	H	H	16			
7	**g**	Ph	Ph	MeO	H	47	32	79	1.5
8	**h**	Ph	Ph	Me	H	51 (51)[a]	25 (22)[a]	76 (73)[a]	2.0 (2.3)[a]
9	**i**	Ph	Ph	Cl	H	48	26	74	1.8
10	**j**	Ph	Ph	Me	Me	47	29	76	1.6
11	**k**	Me	Ph	H	MeO	50 [16][b]	17 [6][b]	67 [22][b]	2.9 [2.7][b]
12	**l**	Me	Ph	H	Me	44	18	62	2.4
13	**m**	Me	Ph	H	Cl	36	18	54	2

[a] Starting from the corresponding ester **2** after reflux in xylene.
[b] After reflux in Ni(dust)/Ac_2O, AcOH.[9]

The slight preference for *ortho* substitution and the small substituent effect on the yields observed are in accord with homolytic aromatic substitution by iminyl radicals depicted in Scheme 2 (vide infra). The *ortho* substituted product is often dominant in intermolecular homolytic aromatic substitution reactions.[7]



Scheme 2.

When the starting diketone was unsymmetrical ($R^1 = Me$, $R^2 = Ph$), the corresponding α-arylimino oximes **1** (Table 1, entries 11–13, $R^3 = H$), although substituted exclusively in the *para* position of the arylimino group, yielded both regioisomers **3k–m** and **4k–m**.

We believe that cyclization of the α-arylimino oximes **1** to the corresponding quinoxalines, in acetic anhydride, proceeds, after an initial acetylation step, via the iminyl radical **5** and the spirodienyl one **6**. This is exemplified in Scheme 2, for $R^1 = Me$, $R^2 = Ph$ and $R^3 = H$. The degenerate rearrangement of radical **5** to the isomeric radical **7** via the spirodienyl radical **6** was not unexpected since a similar rearrangement was reported by McNab two decades ago.[8] This rearrangement explains the formation of both regioisomers **3** and **4** (Table 1, entries 11–13) and reflects the ability of radicals to attack *ipso* positions.[7]

In order to verify our proposition we performed the cyclization of **1k** with nickel powder in a mixture of acetic anhydride and acetic acid. These conditions were considered appropriate for the generation of iminyl radicals from ketoximes.[9] We obtained the same product distribution (Table 1, entry 11) but in substantially lower overall yield. The above result provided further evidence for the operation of the proposed mechanism and particularly for the intermediacy of the iminyl radical **5**.

Since the cyclization of a hetero-1,3,5-hexatriene to a five-membered ring is possible in principle, one has also to consider pericyclic or intramolecular nucleophilic addition routes to generate an intermediate, such as **8**.[10] Intermediate **8**, after acetate equilibration and reopening,

could lead to a regioisomer of the starting oxime ester **2** and ultimately to both regioisomers **3** and **4**. However, such a situation was not encountered recently in the closely analogous case of the electrocyclization of the carbonates of 1-hydroxy-1,4-diaza hexatrienes which resulted in only one of the two possible regioisomeric pyrazine products in good yields.[11]

In spite of the above evidence it is still possible that a portion of the reaction follows a non-radical route. The small difference observed in product distribution when the leaving group was changed from acetyloxy (**3h**/**4h** = 2.3) to *t*-butoyloxy (**3h**/**4h** = 1.4) and our failure to detect products resulting from the presumed decomposition of the acyloxy radicals might be suggestive to this effect.

In conclusion, the results now reported represent a simple, mild and straightforward method for the synthesis of quinoxaline derivatives via iminyl radicals by the use of easily available precursors and cheap reagents. It suffices to say that the lack of mild processes for the generation of iminyl radicals was considered the main reason for the scarce, until recently, published work on iminyl radicals.[12]

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6. Typical experimental procedure: A 1 mmol solution of the α-arylimino oxime **1** in 5 mL of acetic anhydride was heated at reflux. The progress of the reaction was monitored by TLC. At the early stages of the reaction the spot corresponding to the oxime **1** disappeared and a new spot appeared corresponding to the oxime acetyl ester **2**. The reflux was continued until the oxime ester **2** was fully consumed (usually 8–24 h). The solvent was removed in vacuo and the residue was column chromatographed (low pressure, silica gel, mixtures of petroleum ether/ethyl acetate of increasing polarity). All compounds were identified by the usual spectroscopic techniques and gave satisfactory elemental analyses. In particular, compounds **3k**–**m** and **4k**–**m** were identified by converting the former product to the corresponding mono *N*-oxides.
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