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Hypervalent iodine oxidation of benzil-α-arylimino oximes: an efficient synthesis of 2,3-diphenylquinoxaline-1-oxides

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Abstract—A mild and efficient synthetic protocol for the oxidation of benzil-α-arylimino oximes **3** utilizing iodobenzene diacetate (IBD) as an oxidizing agent has been developed. Oximes **3**, obtained by the condensation of (*E*)-benzil monoxime **2** with various appropriately substituted anilines **1**, on treatment with iodobenzene diacetate in dichloromethane at room temperature underwent oxidative cyclization to afford 2,3-diphenylquinoxaline-1-oxide **4** in excellent yields.

Among various classes of heterocyclic compounds, quinoxalines constitute an important component of pharmacologically active compounds. The quinoxaline ring is a part of various antibiotics, for example, echinomycin, levomycin and actinoleutin,[1,2] which inhibit the growth of Gram positive bacteria and are active against various tumours.[3] In addition, quinoxaline derivatives, especially, quinoxaline-*N*-oxides are associated with a wide spectrum of biological activity ranging from antiinfective[4–6] and anticancer[7] to antimycobacterium tuberculosis[8] and angiotensin II receptor antagonists.[9] Moreover, quinoxaline-*N*-oxides are also of great synthetic utility since they permit functional group and structural modifications which are not easily accessible by other methods.[10,11]

A perusal of literature revealed that most common syntheses of quinoxaline-*N*-oxides involved oxidation of the parent heterocycle by oxidants such as Ac_2O–H_2O_2, *m*-chloroperbenzoic acid, monoperoxyphthalic acid, etc.[11] However, the versatility of this method is somewhat limited as the reaction lacks regioselectivity and results in the formation of mixtures of mono and di-*N*-oxides. Also, most of these reagents require carefully controlled reaction conditions as, though uncommon, explosions may occur. Recently, Maroulis et al.[12] reported an alternative synthesis of quinoxaline-*N*-oxides involving oxidative cyclization of benzil-α-arylimino oximes with lead tetraacetate (LTA). Though regioselectivity was achieved using this approach, the high toxicity associated with LTA makes its use rather undesirable. Keeping these observations in mind and in continuation of our efforts to explore the utility of iodine(III) reagents[13–15] in the synthesis of a wide variety of heterocyclic compounds possessing various biological activities, we herein report an efficient method for the synthesis of 2,3-diphenylquinoxaline-1-oxides **4** using iodobenzene diacetate (IBD) as the oxidant. The procedure is facile, regioselective and avoids the use of highly toxic and hazardous reagents.

The general method employed to prepare the title compounds **4a–i** is outlined in Scheme 1. The key intermediates, benzil-α-arylimino oximes **3** were prepared in varying yields by condensation of (*E*)-benzil monoxime **2** with appropriately substituted anilines **1** in aqueous ethanol according to the literature method.[12] Subsequently, oxidative intramolecular cyclization of oximes **3** with 1.1 equiv of IBD in dichloromethane at room temperature provided the desired 2,3-diphenylquinoxaline-1-oxides in 60–75% yields (Table 1).[16]

The known products **4a–f** were identified by comparison of mps with those reported in the literature. The structures of novel compounds **3g–i** and **4g–i** were confirmed from their spectral data[17] (IR, ^{1}H, ^{13}C NMR and HRMS) and elemental analysis. The IR spectrum of **3** revealed a characteristic absorption band for the =N–OH functional group at 3153 cm^{-1}. The ^{1}H NMR

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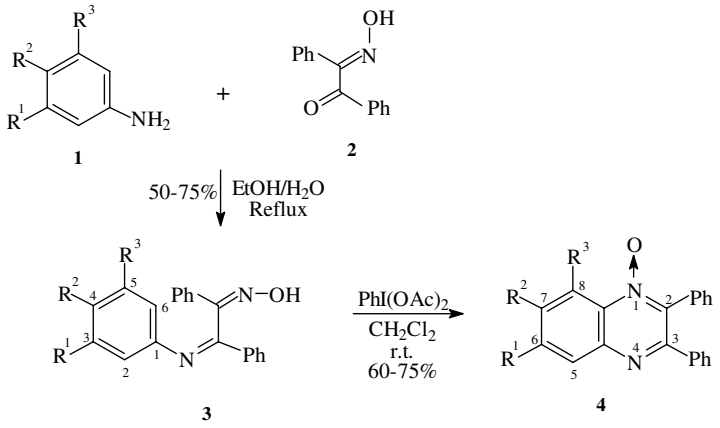

Scheme 1.

Table 1. Physical data of the 2,3-diphenylquinoxaline-1-oxides **4** prepared

Compound	R^1	R^2	R^3	Mp (°C)	Lit.[12] mp (°C)	Yield[a,b] (%)
4a	H	H	H	206–207	205–206	60 (48)
4b	H	CH_3	H	202–204	203–204.5	66 (64)
4c	CH_3	H	H	182–184	180–182	62 (51)
4d	H	OCH_3	H	225–226	227–228	65 (27)
4e	H	Cl	H	211–212	210–211	70 (66)
4f	Cl	H	H	156–158	156–157	60 (41)
4g	H	Br	H	200		75
4h	H	F	H	180		62
4i	H	F	Cl	152–154		70

[a] Isolated yield.
[b] Reported yield given in parentheses.

spectra of **3** displayed the oxime proton (=N–OH) as a broad singlet in the range δ 10.83–11.27. The disappearance of this singlet confirmed that benzil-α-arylimino oximes **3** has been converted into cyclic 2,3-diphenylquinoxaline-1-oxides **4**. Also, the IR spectrum of **4** showed the disappearance of the stretching =N–OH band.

A plausible mechanism for the transformation of **3** to **4** is outlined in Scheme 2. Initial electrophilic attack of IBD on the oxime **3** gives an I(III) intermediate **5**, which undergoes reductive loss of iodobenzene along with elimination of acetic acid to afford nitroso derivative **6**. Cyclization of **6** via an entropy favoured electrophilic process gives intermediate **7**, which loses a second mole of acetic acid to yield quinoxaline-*N*-oxide **4**.

In summary, the reported oxidative cyclization offers an interesting entry to 2,3-diphenylquinoxaline-1-oxides. $PhI(OAc)_2$ is a valuable substitute for $Pb(OAc)_4$ in oxidation reactions. This is a useful modification as it has advantages of milder and safer reaction conditions and higher yields.

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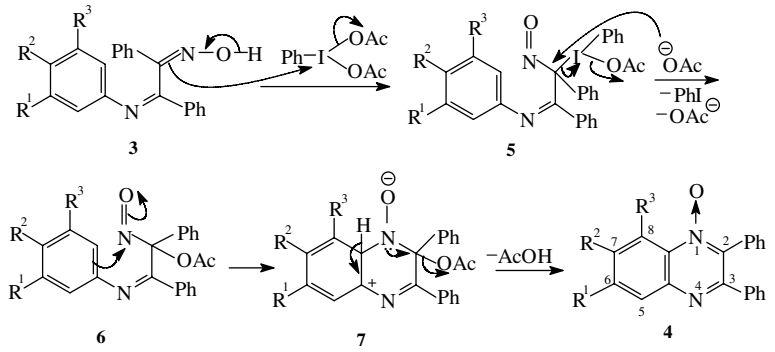

Scheme 2.

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16. General procedure: To a stirred suspension (or) solution of **3** (1.0 mmol) in dichloromethane (20 ml) was added IBD (0.354 g, 1.1 mmol) in small portions over a period of 5 min at room temperature. The reaction mixture was allowed to stir until the colour of solution became red. The progress of reaction was monitored by TLC. When all the starting material had been consumed, excess dichloromethane was distilled off in vacuo to give a gummy residue containing the product and iodobenzene. The product **4** was isolated by column chromatography on silica gel [100–200 mesh] (iodobenzene was removed with petroleum ether and the product was eluted with petroleum ether–chloroform of increasing polarity). Quinoxaline-1-oxides **4** were recrystallized from aqueous ethanol.
17. The IR spectra of the compounds were recorded on a Buck Scientific IR M-500 spectrophotometer using KBr pellets (ν_{max} in cm^{-1}), ^1H and ^{13}C NMR spectra on a Bruker instrument at 300 and 75 MHz, respectively; chemical shifts are expressed in δ-scale downfield from TMS as an internal standard. Compound **4g**. IR (cm^{-1}): 3099, 1600, 1569, 1473, 1345; ^1H NMR ($CDCl_3$): 7.16–7.37 (m, 10H, Ar), 7.82–7.86 (dd, 1H, $J = 9.0$ Hz, $J = 2.1$ Hz, 6-H), 8.00–8.03 (d, 1H, $J = 8.7$ Hz, 5-H), 8.73–8.74 (d, 1H, $J = 2.1$ Hz, 8-H); ^{13}C NMR: 122.17, 124.50, 126.31, 127.97, 128.16, 128.46, 129.01, 129.32, 129.66, 130.24, 130.75, 131.29, 131.60, 131.90, 135.32, 136.61, 137.43, 140.75, 142.46, 156.50. The accurate mass measurement of the lower isotopic ion is 377.0289 ($C_{20}H_{13}BrN_2O$ requires 377.0289).
Compound **4h**. IR (cm^{-1}): 2924, 1617, 1490, 1417, 1348, 1229; ^1H NMR ($CDCl_3$): 7.26–7.38 (m, 10H, Ar), 7.58–7.64 (dt, 1H, $J_{H-F} = 9.0$ Hz, $J_o = 5$ Hz, $J_m = 2.7$ Hz, 6-H), 8.19–8.23 (dd, 1H, $J_{H-F} = 9.3$ Hz, $J_o = 5.4$ Hz, 5-H), 8.28–8.32 (dd, 1H, $J_{H-F} = 9.0$ Hz, $J_m = 2.7$ Hz, 8-H); ^{13}C NMR: 104.44, 104.81, 121.69, 122.03, 128.16, 128.44, 129.21, 129.60, 129.70, 130.35, 130.78, 132.35, 132.47, 136.78, 137.46, 140.69, 140.80, 155.63, 161.46, 164.83. Mass (m/z): 316.1009 (M^+) ($C_{20}H_{13}FN_2O$ requires 316.1011).
Compound **4i**. IR (cm^{-1}): 2924, 1608, 1471, 1342; ^1H NMR ($CDCl_3$): 7.19–7.33 (m, 10H, Ar), 8.23–8.26 (d, 1H, $J = 7.2$ Hz, 5-H), 8.29–8.32 (d, 1H, $J = 9.0$ Hz, 6-H); ^{13}C NMR: 105.66, 106.02, 126.20, 127.46, 127.75, 128.18, 128.33, 128.49, 128.76, 128.96, 129.40, 129.64, 129.76, 130.06, 130.26, 130.35, 130.68, 131.52, 135.31, 137.31, 140.82, 156.76, 156.82, 160.16. The accurate mass measurement of the lower isotopic ion is 350.0608 ($C_{20}H_{12}ClFN_2O$ requires 350.0622).