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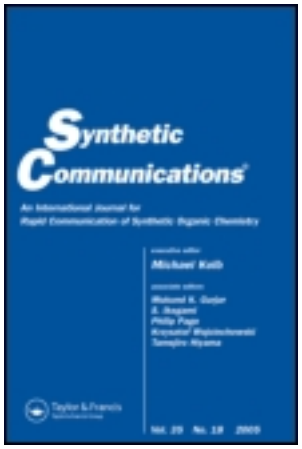

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Efficient Synthesis of Some New 2,3-Dimethylquinoxaline-1-oxides Using Bis(acetoxy)phenyl-λ ^{3}-iodane as an Oxidant

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EFFICIENT SYNTHESIS OF SOME NEW 2,3-DIMETHYLQUINOXALINE-1-OXIDES USING BIS(ACETOXY)PHENYL-λ^3-IODANE AS AN OXIDANT

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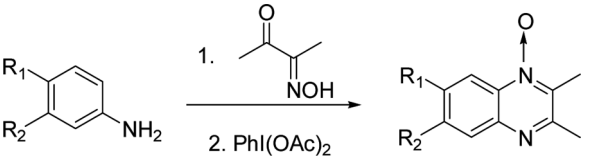
GRAPHICAL ABSTRACT



Abstract *A series of 2-(arylimino)-3-(hydroxyimino)butanes* ***3a–g****, easily accessed by the condensation of variously substituted anilines* ***1a–g*** *with biacetyl monoxime* ***2****, were efficiently cyclized to afford 2,3-dimethylquinoxaline-1-oxides* ***4a–g*** *using bis(acetoxy) phenyl-*λ^3*-iodane as an oxidant. This methodology utilizes a commercially available and environmental benign oxidant to achieve the title compounds in excellent yields under mild conditions.*

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Keywords 2-(Arylimino)-3-(hydroxyimino)butanes; bis(acetoxy)phenyl-λ^3-iodane; 2,3-dimethylquinoxaline-1-oxides

INTRODUCTION

Heterocycles are ubiquitous scaffolds in pharmacologically active compounds, agrochemicals, and natural products. Quinoxaline systems, in particular, constitute a privileged substructure and are present in a large number of compounds with diverse biological activities such as cytotoxic agents and CB2 receptor agonists.[1] The quinoxaline ring system represents the core skeleton of various antibiotics, for example, triostin A, quinomycin, levomycin, and actinoleutin. Interestingly, quinoxaline *N*-oxide and its derivatives also exhibit antileishmanial, antimalarial, anti-inflammatory, trypanocidal, anticancer, antituberculosis, and antimycobacterial

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activities.[2] Methyl-3-[(2-quinoxalinyl)methylene]carbazate-*N,N′*-dioxide, commercially known as carbadox,[3] has proven to be an efficient antibacterial and growth-promoting material. Penicillin derivatives of quinoxaline *N,N′*-dioxide carboxylic acids[4] exhibit remarkable activity against *Salmonella* and *Proteus* species.[5]

Because of the broad biological properties, a variety of approaches have been developed for the preparation of quinoxaline-*N*-oxides. The most common method for the synthesis of quinoxaline *N*-oxides involves the *N*-oxidation of quinoxaline by using different oxidizing reagents such as hydrogen peroxide, peracetic acid, peroxyformic acid, *m*-chloroperbenzoic acid, monoperphthalic acid, permaleic acid, and peroxy sulfuric acid in sulfuric acid.[6] Even though this strategy for synthesis of quinoxaline *N*-oxides has proven to be efficient and general, all of these synthetic routes share several drawbacks such as drastic reaction conditions, tedious workup, the use of toxic and corrosive reagents, long reaction times, and poor selectivity. For example, treatment of 2,3-diphenylquinoxaline with excess of aqueous H_2O_2 in acetic acid gives expected 1,4-dioxide along with *N,N′*-dibenzoyl-*o*-phenylenediamine.[7] Quinoxaline-*N*-oxides have been synthesized successfully by the reaction of benzofurazan-1-oxide with enones and amines.[8] Maroulis et al. also have reported the synthesis of some quinoxaline-*N*-oxides by the oxidative cyclization of benzil-α-arylimino oximes using lead tetraacetate (LTA).[9] This reaction was regioselective but the choice of reagent was inappropriate because of highly toxic nature of LTA. To overcome these difficulties, development of a convenient protocol for the synthesis of quinxaline-*N*-oxides is still of paramount importance.

In recent years, hypervalent iodine compounds, referred as λ^3-iodanes, are gaining the attention of a number of organic chemists because of their mild and highly selective oxidizing properties. These reagents have emerged as reagents of choice for various synthetically useful transformations. The reactivity pattern of λ^3-iodane reagents closely resembles with those of organometallic compounds such as salts of Pd, Pt, Hg(II), Ni(IV), Pb(IV), and Tl(III) as oxidizing agents. λ^3-Iodane reagents are commercially available and they do not have undesirable toxic, hazardous, and harmful effects. Inspired from applications of hypervalent iodine reagents and in continuation of our previous work on the synthesis of 2,3-diphenylquinoxaline-1-oxides,[10] we report herein the synthesis of 2-(arylimino)-3-(hydroxyimino)butanes **3** and their oxidation to some new 2,3-dimethylquinoxaline-1-oxides **4** using bis(acetoxy)phenyl-λ^3-iodane.

RESULTS AND DISCUSSION

The synthetic approach, illustrated in Scheme 1, starts from the appropriately substituted anilines (**1a–g**), which condensed with biacetyl monoxime (**2**) in toluene to furnish the key intermediates, 2-(arylimino)-3-(hydroxyimino)butanes (**3a–g**) in 70–80% yield. Subsequently, synthesis of the title compounds, 2,3-dimethylquinoxaline-1-oxides (**4a–g**), was achieved by intramolecular cyclization of 2-(arylimino)-3-(hydroxyimino)-butanes (**3a–g**) using bis(acetoxy)phenyl-λ^3-iodane as an oxidant in dichloromethane at room temperature (Scheme 1).

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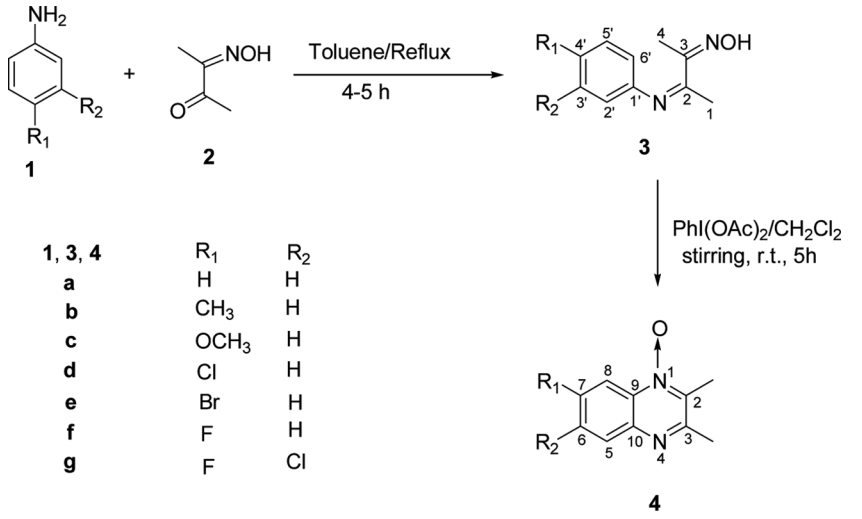

1, 3, 4	R_1	R_2
a	H	H
b	CH_3	H
c	OCH_3	H
d	Cl	H
e	Br	H
f	F	H
g	F	Cl

Scheme 1. Synthesis of 2,3-dimethylquinoxaline-1-oxides.

The structures of all the newly synthesized compounds **3c–g** and **4a–g** were characterized on the basis of infrared (IR), NMR (^{1}H and ^{13}C) spectral data, and elemental analyses. The known compounds **3a** and **3b** were identified by the comparison of their ^{1}H NMR with those reported in the literature.[11] The IR spectra of compounds **3c–g** displayed characteristic absorption bands ranging from 3117 to 3142 cm^{-1} (= N-OH). The ^{1}H NMR spectra of **3c–g** displayed two singlets of three proton intensity each at δ 2.02–2.05 ppm and δ 2.18–2.21 ppm corresponding to C_1 and C_4 methyl groups, respectively. It may be noted that methyl adjacent to hydroxyl imino group (= N-OH) is more deshielded than the other methyl group adjacent to =N-Ar due to high electronegativity associated with oxygen. One broad singlet of one proton intensity has also been observed at δ 7.95–8.25 ppm due to the hydroxy imino (=N-OH) group. The IR spectrum of **4a–g** showed the disappearance of the absorption band in the range 3117–3142 cm^{-1} (=N-OH), indicating the conversion of **3** to **4**. The ^{1}H NMR spectra of **4a–g** exhibited signals at δ 2.69–2.71 ppm and δ 2.74–2.77 ppm corresponding to C_3-CH_3 and C_2-CH_3, respectively. Protons in the aromatic region resonated in the range δ 7.36–8.75 ppm confirmed formation of quinoxaline nucleus. Further, disappearance of broad singlet at δ 7.95–8.25 ppm (=N-OH) also confirmed the oxidation of 2-(arylimino)-3-(hydroxyimino)butanes (**3**) to 2,3-dimethylquinoxaline-1-oxides (**4**). The ^{13}C NMR spectra of **3c–g** and **4a–g** are given in the experimental part.

A plausible mechanism for the conversion of **3** to **4** is outlined in Scheme 2. It is assumed that generation of a new I(III) intermediate (**5**) in the initial step takes place by the electrophilic attack of bis(acetoxy)phenyl-λ^3-iodane on the 2-aryliminoximes (**3**). This is followed by reductive elimination of iodobenzene and acetic acid to give 2-nitroso-3 (phenylimino)butan-2-ylacetate (**6**), which undergoes entropy-favored electrophilic cyclization to afford intermediate **7**. Loss of another mole of acetic acid and spontaneous aromatization leads to the formation of 2,3-dimethylquinoxaline-1-oxide (**4**).

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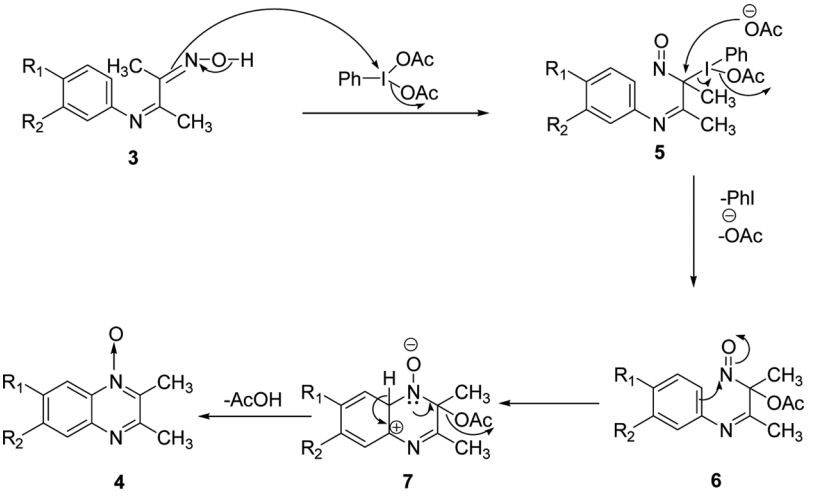

Scheme 2. Plausible mechanism for the formation of 2,3-dimethylquinoxaline-1-oxides.

EXPERIMENTAL

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. Infrared spectra were recorded on IR M-500 spectrophotometer (Buck Scientific Inc, Norwalk, CT) in KBr pellets (ν^{max} in cm^{-1}). ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Bruker instrument (Billerica, MA) by using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ in parts per million (ppm). Coupling constants (J) are given in hertz (Hz). Elemental analysis was performed at CDRI and the compounds gave satisfactory results (within ±0.05 of the calculated values).

Commercially available variously substituted anilines (**1**) and biacetyl monoxime (**2**) were used without further purification.

General Procedure for the Synthesis of 2-(Arylimino)-3-(hydroxyimino)butane 3

A solution of biacetyl monoxime **1** (10.1 g, 0.1 mol) and an appropriately substituted aniline **2** (0.1 mol) in toluene (20 ml) was refluxed for 4–5 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). On completion of the reaction, excess solvent was distilled off in a vaccum. The solid thus obtained was recrystallized from ethanol to give **3**.

2-(4-Methoxyphenylimino)-3-(Hydroxyimino)butane (3c)

Yield 82%; mp 143–144 °C; ^1H NMR ($CDCl_3$) δ: 2.05 (s, 3H, $-CH_3$), 2.21 (s, 3H, $-CH_3$), 3.83 (s, 3H, $-OCH_3$), 6.72 (d, 2H, $J = 8.7$ Hz, Ph-3, 5-H), 6.94 (d, 2H, $J = 8.7$ Hz, Ph-2, 6-H), 8.13 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 9.30, 15.54, 55.48, 114.25, 120.62, 143.68, 156.34, 159.04, 164.45; IR (cm^{-1}): 3117 (OH), 3086 (C-H),

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1612, 1504. Anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.11; H, 6.86; N, 13.55.

General Procedure for the Synthesis of 2,3-Dimethylquinoxaline-1-oxide 4

Bis(acetoxy)phenyl-λ^3-iodane (0.354 g, 0.0011 mol) was added to a solution of **3** (0.001 mol) in dichloromethane (20 ml) in small portions over a period of 5 min at room temperature. The reaction mixture was allowed to stir for 5 h at room temperature. The progress of the reaction was monitored by TLC. When all the starting material had been consumed, excess solvent was distilled off in vacuo to give a gummy residue containing the product and iodobenzene. The residue was triturated with petroleum ether to remove iodobenzene, and a solid was obtained that was recrystallized from aqueous ethanol to give **4**.

7-Methoxy-2,3-dimethylquinoxaline-1-oxide (4c)

Yield 72%; mp 128–132 °C; ^{1}H NMR ($CDCl_3$) δ: 2.71 (s, 3H, 3-CH_3), 2.74 (s, 3H, 2-CH_3), 4.00 (s, 3H, 7-OCH_3), 7.38 (dd, 1H, $J_o = 9.0$ Hz, $J_m = 2.4$ Hz, 6-H), 7.89 (s, 1H, 5-H), 7.92 (s, 1H, 8-H); ^{13}C NMR ($CDCl_3$) δ: 13.99, 23.43, 56.10, 97.27, 123.24, 130.37, 136.31, 139.55, 151.72, 160.75; IR (cm^{-1}): 3048 (C-H), 1612, 1498. Anal. calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.74; H, 5.94; N, 13.70.

Complete experimental details and ^{1}H and ^{13}C NMR spectra are given in the Supporting Information, available online.

CONCLUSION

In conclusion, we have developed an efficient and ecofriendly method for the synthesis of some new 2,3-dimethylquinoxaline-1-oxides from 2-(arylimino)-3-(hydroxyimino)butanes using bis(acetoxy)phenyl-λ^3-iodane as an oxidant.

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