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### Unusual synthesis of azines and their oxidative degradation to carboxylic acid using iodobenzene diacetate

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#### ABSTRACT

Reaction of 3-hydrazonobutan-2-one oxime with aromatic aldehydes resulted in the formation of 1,2-bis(arylidene)hydrazine commonly referred as azine as an unexpected product, instead of expected product 3-(aryl)methylenehydrazonobutan-2-one oxime, which were subsequently oxidized to corresponding aromatic acids with an ecofriendly oxidizing agent iodobenzene diacetate. Azines and carboxylic acids were characterized by IR and NMR (<sup>1</sup>H, <sup>13</sup>C, HMBC, and HMQC) studies.

#### ARTICLE HISTORY

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#### **KEYWORDS**

3-Hydrazonobutan-2-one oxime; aromatic acid; azine; iodobenzene diacetate; oxidative degradation



#### Introduction

Azines also regarded as 2,3-diaza-1,3-butadiene derivatives contain two azomethine groups (C=N) which are linked by nitrogen–nitrogen bond. Azines as dipolarophiles are of fundamental importance as synthons in the synthesis of heterocyclic compounds<sup>[1,2]</sup> such as 1,3,4-thiadiazoles,<sup>[3]</sup> 1,3,4-oxadiazoles.<sup>[4]</sup> They undergo 1,3-cycloadditions to afford perhydro [1,2,4]triazolo[1,2-*a*][1,2,4] triazole-1,5-dithiones by crisscross cycloaddition.<sup>[5]</sup> Compounds possessing azine moiety are also of great significance as they exhibit diverse pharmacological activities, such as antitumor,<sup>[6]</sup> anticonvulsant,<sup>[7]</sup> antioxidant,<sup>[8]</sup> antimicrobial,<sup>[9]</sup> and allosteric modulators of metabotropic glutamate receptor subtype

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<sup>()</sup> Supplemental data [full experimental detail, NMR (<sup>1</sup>H, <sup>13</sup>C, HMBC, and HMQC) spectra] can be accessed on the publisher's website.

5 (mGluR5).<sup>[10]</sup> Recently azines have been reported as promising candidate for the development of the potential quorum sensing inhibitors which could be used in conjugation of known antibiotics to curb the pathogenesis of *Pseudomonas aeruginosa*.<sup>[11]</sup> In addition, they are also developed for use as fluorescence chemosensor,<sup>[12]</sup> optical sensors,<sup>[13]</sup> and conducting materials.<sup>[14]</sup>

Azines are usually prepared by reacting two equiv. of a carbonyl compound with 1 equiv. of hydrazine hydrate or hydrazine salt in ethanol under reflux using conventional heating,<sup>[15]</sup> however, ultrasound irradiation using BiCl<sub>3</sub> as catalyst,<sup>[16]</sup> grinding at room temperature,<sup>[17]</sup> microwave irradiation under solvent free conditions in the presence of CH<sub>3</sub>COONa/CaCl<sub>2</sub> have also been reported.<sup>[18]</sup> Transformation of semicarbazones/ thiosemicarbazones into azines under microwave irradiation has recently been described in literature.<sup>[19,20]</sup>

A perusal of the literature revealed that products of diversified nature may be achieved by the oxidation of azines depending upon the potential of oxidizing agent used (Scheme 1). For instance, oxidation of azines with 30% hydrogen peroxide in the presence of poly(bis-1,2-phenylene) diselenide as catalyst resulted into arene carboxylic acids,<sup>[21]</sup> whereas *m*-chloroperbenzoic acid in alkaline medium afforded mononitrones.<sup>[22]</sup> When cerium(IV) ammonium nitrate (CAN) was used as oxidizing agent cleavage of aromatic azines occurred leading into corresponding aldehydes.<sup>[23,24]</sup> Tribromoisocyanuric acid (TBCA) in the presence of wet SiO<sub>2</sub> also led to the regeneration of carbonyl compounds from azines.<sup>[25]</sup> Oxidative cyclization of azines to 2,5-disubstituted 1,3,4-oxadiazoles has been reported with lead tetraacetate.<sup>[26]</sup> Unfortunately, most of these methods involve toxic or expensive reagents, harsh reaction conditions, longer reaction times, high/below zero reaction temperatures and difficult workup procedures.



Scheme 1. Reported methods for oxidation of azines.

In view of above observations and in continuation of our interest in the greener synthesis of a wide variety of heterocyclic scaffolds,<sup>[27-29]</sup> we herein report an unusual synthesis of azines from 3-hydrazonobutan-2-one oxime, followed by their oxidative cleavage to corresponding aromatic acids utilizing iodobenzene diacetate (IBD) as an oxidizing agent.

#### **Results and discussion**

The reaction of diacetyl monoxime 1 with hydrazine hydrate 2 in ethanol afforded an exclusive formation of 3-hydrazonobutan-2-one oxime 3 under refluxing condition. We envisaged that reaction of 3-hydrazonobutan-2-one oxime 3 with aromatic aldehydes (4a-f) in methanol at room temperature might afford the required 3-(aryl)methylenehydrazonobutan-2-one oxime derivatives 5 (Scheme 2). However, stirring a mixture of 3 and aromatic aldehydes 4a-f in methanol at room temperature resulted in an unexpected crystalline product in moderate yield together with a small amount of diacetyl monoxime 1 (Scheme 2). The unexpected product was unambiguously characterized as (1E,2E)-1,2-bis (4-chlorobenzylidene)hydrazine 6a by combined application of various spectroscopic techniques like IR, NMR (<sup>1</sup>H, <sup>13</sup>C, HMBC, and HMQC studies) (see Supporting information).<sup>[17,30]</sup> Typically, when two moles of aldehydes were treated with 3 the yields of respective azines 6a-f were improved.

IR spectrum of azine **6a**, as a representative example, displayed a strong absorption band at 1620 cm<sup>-1</sup> due to C=N function. <sup>1</sup>H NMR spectrum of **6a** revealed, in addition to expected aromatic signals, a characteristic singlet signal at  $\delta$  8.63 ppm corresponding to two protons of the azomethine (CH=N). In addition, the <sup>13</sup>C NMR spectrum of **6a** displayed a characteristic peak for two imine carbons at about  $\delta$  161.8 ppm. The signals at  $\delta$  130.0, 130.9, and 161.8 ppm were attributed to C-3/C-5, C-2/C-6, and CH=N, respectively, by performing a HMQC experiment. The long-range connectivities in the <sup>1</sup>H<sup>-13</sup>C HMBC display correlation of C-1 and C-2/C-6 with the singlet at  $\delta_{\rm H}$  8.63 ppm, which is assigned as the azomethine proton. Other correlations are seen from H-2/H-6 to imine carbon, C-4, C-2/C-6 and H-3/H-5 to C-1, C-3/C-5.



Scheme 2. Conversion of 3-hydrazonobutan-2-one oxime into azine and subsequent oxidative degradation into carboxylic acid.

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Formation of azines **6** suggests a cross reaction between 3-hydrazonobutan-2-one oxime **3** and aromatic aldehydes **4**. Further an experiment was accomplished with an objective to ascertain the cross reaction by treating acetone hydrazone with 4-chlorobenzaldehyde **4a** in methanol under similar conditions which led to the formation of corresponding azine **6a**.

The probable mechanism for the synthesis of azines **6** is shown in Scheme 3. Initially, the nucleophilic addition of terminal nitrogen of 3-hydrazonobutan-2-one oxime **3** to carbonyl carbon of aromatic aldehyde **4** and following the loss of water results in the formation of intermediate, 3-(aryl)methylenehydrazonobutan-2-one oxime **5**. In the next step, nucleophilic attack of methanol to the imine moiety of **5** takes place which in turn reacts with second equivalent of aldehyde to give the intermediate **9**. This intermediate can then undergo nucleophilic attack by methanol to afford intermediate, diacetyl mono-xime dimethyl acetal **10** after elimination of (2-benzylidenehydrazinyl) (phenyl) methanol **11**. Intermediate **11** undergoes dehydration to yield **6**.

Though Shang et al.<sup>[4]</sup> has reported bis(trifluoroacetoxy)iodobenzene (BTI) mediated oxidative cyclization of azines to 1,3,4-oxadiazoles, however, in the present study we planned to study the behavior of IBD toward azines since the reactivity of I(III) reagents is usually dependent on the nucleophilic ligands attached to the central iodine. Initially, the reaction of azine **6a** with 2.2 equiv. of IBD in different solvents, e.g., dichloromethane, acetic acid, acetic acid–dichloromethane under stirring condition did not proceed even after 12 h at room temperature. However, a change of solvent to THF in this reaction resulted in oxidative degradation of **6** to corresponding carboxylic acids **8** (Scheme 2) contrary to oxidative cyclization to oxadiazoles 7 by BTI.<sup>[4]</sup> The structure of the compound **8a** was established from various spectroscopic studies like IR and NMR (<sup>1</sup>H, <sup>13</sup>C, HMBC, and HMQC).

HMQC spectrum of **8a** shows signals for C-3/C-5 and C-2/C-6 at  $\delta$  129.6 and 132.3, respectively. In the <sup>1</sup>H–<sup>13</sup>C HMBC, C-1, and C-3/C-5 give correlation with H-3/H-5 protons. Carbons of carboxyl group, C-4 and C-2/C-6 correlate with H-2/H-6.

To demonstrate the scope of this oxidative degradation, several different substituted azines (6b-k) were treated with IBD at room temperature in THF and the respective arene carboxylic acids (8b-k) were obtained in good yields (Table 1). The azines (6g-k) required



Scheme 3. Proposed mechanism for formation of azines 6 from 3-hydrazonobutan-2-one oxime 3 and aromatic aldehydes 4.

	H <sub>3</sub> C N-NH <sub>2</sub> ArCHO	PhI(OAc) <sub>2</sub> (2.2 equiv)	0
	Ar N <sup>N</sup>	THF, rt, 4h	Ar <sup></sup> OH
	3 3h 6		8
6, 8	Ar	Yield (%) <sup>a</sup>	Yield (%) <sup>b</sup>
a	CI	90	79
b		80	75
C	CI	88	77
d	Br	90	80
e	H <sub>3</sub> CO	84	70
f	O <sub>2</sub> N	87	78
g	O <sub>2</sub> N	85 <sup>c</sup>	76
h	H <sub>3</sub> C	79 <sup>c</sup>	72
i	OCH3	85 <sup>c</sup>	70
j	CI	91 <sup>c</sup>	76
k	CI	85 <sup>c</sup>	77

<b>Table 1.</b> Substrate scope for oxidative degradation of azines $(0\mathbf{d} - \mathbf{K})$ into carboxylic acids $(0\mathbf{d} - \mathbf{K})$	(Od-K	-K
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<sup>a</sup>lsolated yield for product 6 obtained from 3-hydrazonobutan-2-one oxime except 6g-k.

<sup>b</sup>Yield of the isolated product 8.

'Isolated yield correspond to product 6g-k obtained from reaction of aldehyde and hydrazine hydrate.

for this purpose were prepared by the reaction of aromatic aldehydes **4** and hydrazine hydrate **2** using known procedure.<sup>[15]</sup> The identities of the known azines (**6b**-**k**) were established by comparison of their melting points with those reported earlier,<sup>[9,17,19]</sup> mixed mp and co-TLC with authentic samples which were synthesized by reacting aldehydes with hydrazine hydrate and the results are summarized in Table 1. The structure of carboxylic acids **8b**-**k** was confirmed on the basis of mixed mp and co-TLC with standard sample. The versatility of the present protocol was further confirmed by the fact that oxidative transformation of **6–8** was accomplished well on gram scale under the same conditions.



Scheme 4. Proposed mechanistic pathway for formation of arene carboxylic acids 8 through oxidative degradation of azines 6.

Reactions of hypervalent iodine reagents are usually rationalized as ligand exchange, oxidative addition, reductive elimination, and ligand coupling which resemble with the chemistry of transition metal derivatives. A plausible mechanism for the oxidative degradation of azine to carboxylic acid is outlined in Scheme 4. The electrophilic attack of IBD on azines 6 would result in generation of nitrogen-iodine(III) species A which would undergo reductive loss of iodobenzene along with elimination of acetic acid to afford intermediate B. Tautomerization of intermediate B would afford N,N'-diacylhydrazine C. Subsequent nucleophilic attack of water on intermediate C would result in the formation of desired product 8.

#### Conclusion

In summary, we have achieved an unusual synthesis of azines from 3-hydrazonobutan-2one oxime by cross reaction with aromatic aldehydes. The present protocol offers a novel and efficient route for the preparation of a large number of arene carboxylic acids through oxidative cleavage of crystalline azines using ecofriendly reagent IBD in a relatively short period of time. Arene carboxylic acids have industrial significance and are otherwise prepared by oxidation of carbonyl compounds.

#### **Experimental**

Melting points are taken in open glass capillaries in an electrical apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 1800 FTIR spectrophotometer using neat technique. Analytical TLC was performed using Merck Kieselgel 60 F254 silica gel plates. Visualization was performed by UV light (254 nm). <sup>1</sup>H and <sup>13</sup>C NMR spectra for analytical purpose were recorded in THF-d<sub>8</sub> operating at 400 and 101 MHz, respectively, and chemical shifts were recorded in ppm ( $\delta$ ) downfield from internal standard

tetramethylsilane ( $\delta$  0.00 ppm). 2D-Correlation spectra, ( ${}^{1}H{-}{}^{13}C$ ) gs-HMQC, ( ${}^{1}H{-}{}^{13}C$ ) gs-HMBC, and ( ${}^{1}H{-}{}^{15}N$ ) gs-HMBC, of compounds were acquired in a spectrometer operating at 9.4 Tesla, 400.13 MHz for  ${}^{1}H$ , 100.62 MHz for  ${}^{13}C$ , and 40.56 for  ${}^{15}N$  with a 5-mm inverse-detection H–X probe equipped with a z-gradient coil, at 300 K and processed using standard NMR software and in nonphase-sensitive mode. Diacetyl monoxime **1**, hydrazine hydrate **2**, aromatic aldehydes **4**, IBD, methanol, ethanol, and THF were commercially available.

#### Unusual synthesis of 1,2-bis(4-chlorobenzylidene)hydrazine 6a

3-Hydrazonobutan-2-one oxime **3** (460 mg, 4 mmol) was dissolved in 25 mL of methanol and 2 equiv. of 4-chlorobenzaldehyde **4a** (8 mmol) was added to it. The reaction mixture was allowed to stir for 3 h. Progress of reaction was monitored by TLC. A solid appeared during stirring. Solid thus obtained on completion of reaction was filtered, washed with ethanol and recrystallized from ethanol to afford 1,2-bis(4-chlorobenzylidene)hydrazine. The mother liquor containing diacetyl monoxime and azine was slightly concentrated and the products were separated by fractional crystallization.

**6a**: Yellow crystals; mp 208–209 °C (lit<sup>[17,19]</sup> mp 209–211 °C); yield: 90%; IR (cm<sup>-1</sup>): 1620 (CH=N stretching); <sup>1</sup>H NMR (400 MHz, THF- $d_8$ , δ): 7.48 (d, 4H, J = 8.1 Hz, Ph-3,5-H), 7.87 (d, 4H, J = 8.7 Hz, Ph-2,6H), 8.63 (s, 2H, CH=N); <sup>13</sup>C NMR (101 MHz, THF- $d_8$ , δ): 130.0 (×4, C-3, C-5), 130.9 (×4, C-2, C-6), 134.4 (×2, C-1), 137.9 (×2, C-4), 161.8 (×2, CH=N). Anal. calc. for C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 60.67; H, 3.64; N, 10.11; found: C, 60.31; H, 3.27; N, 10.36.

#### General procedure for synthesis of azines 6g-k

To a solution of aromatic aldehyde 4 (1 mmol) in ethanol (10 mL) containing conc. HCl (1–2 drops) was added hydrazine hydrate 2 (0.5 mmol) dropwise. The reaction mixture was stirred and then refluxed for 1 h. Upon completion of reaction (TLC analysis) the solvent was reduced. The precipitate was filtered, washed with cold water and recrystallized from ethanol to afford azines.

# Procedure for oxidative degradation of 1,2-bis(4-chlorobenzylidene)hydrazine into 4-chlorobenzoic acid 8a

To a stirred suspension (or) solution of 1,2-bis(4-chlorobenzylidene)hydrazine (6a) (1 mmol) in THF (15 mL) was added IBD (2.2 mmol) in small portions over a period of 5 min at room temperature. The reaction mixture was allowed to stir for about 4 h. Some fine crystals appeared on stirring. Crystals were filtered and mother liquor was concentrated to get more crystals.

**8a**: White crystals; mp 240–242 °C (lit<sup>[31]</sup> mp 242–243 °C); yield: 79%; <sup>1</sup>H NMR (400 MHz, THF- $d_8$ ,  $\delta$ ): 7.45 (m, 2H, Ph-3,5-H), 7.99 (m, 2H, Ph-2,6-H), 11.52 (sbr, 1H, OH); <sup>13</sup>C NMR (101 MHz, THF- $d_8$ ,  $\delta$ ): 129.6 (C-3,5), 130.8 (C-1), 132.3 (C-2,6), 139.7 (C-4), 166.9 (COOH).

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