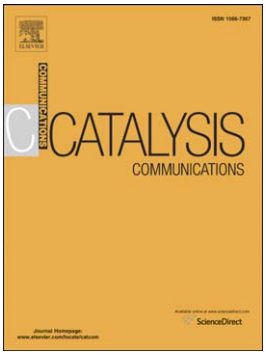

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ZnO-Loaded Mesoporous Silica (KIT-6) as an Efficient Solid Catalyst for Production of Various Substituted Quinoxalines

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Abstract

Conventional homogeneous and microporous heterogeneous catalysts for quinoxalines production from diamines and diketones usually suffer from difficult separation or harsh reaction conditions. Here, we demonstrate the production of various substituted quinoxalines using ZnO nanoparticle-loaded, highly ordered, mesoporous silica KIT-6 materials as solid catalysts in room temperature. The results show that the KIT-6-130-10Zn sample (aged at 130 °C and containing 10 wt% ZnO) effectively produces quinoxalines up to the maximum of 99%. We propose that the enhanced performance of the ZnO-loaded KIT-6 materials resulted from the homogeneous distribution of ZnO nanoparticles, along with the KIT-6's high specific surface area and large pore sizes.

Keywords: mesoporous materials, ZnO, *o*-phenylene-diamines, 1,2-diketones, quinoxalines

1. Introduction

Quinoxaline derivatives, a type of nitrogen containing heterocyclic compounds, are particularly attractive due to their vast exhibited biological activities that includes antibacterial, antidiabetic, antiviral, and other pharmacological activities [1-4]. Synthetic quinoxaline ring moiety can be classified as a type of antibiotics that also includes echinomycin, leromycin, and actinomycin, which have been found to be active against various transplantable tumors and inhibit Gram-positive bacterial growth [5]. As a nitrogen-containing heterocyclic compound, Quinoxalinone and its derivatives have been widely used in dyes [6], efficient electroluminescent materials [7], organic semiconductors [8], building blocks for the synthesis of anion receptors [9], cavitands [10], dehydroannulenes [11], and DNA cleaving agents [12].

Of the numerous substituted quinoxalines synthesis reported, the condensation of an aryl 1,2-diamine with 1,2-dicarbonyl compounds in refluxing solvents, such as ethanol or acetic acid, is one of the most common [13]. Catalytic systems involving various metal precursors, acids, and zeolites have been reported as improved methods [14]. In addition, other well-known methods also include microwave-assisted [15] and solid phase synthesis [16], with chemicals such as molecular iodine [17], KOH [18], $Ga(OTf)_3$ [19], ionic liquid [20], $ZrCl_4$ [21], and K10 clayzic [22]. Although increased reaction efficiencies were reported in these pioneering studies, homogeneous catalysts were mainly the catalyst employed. Additionally, several of the reported methods endure disadvantages that commonly includes high required amounts of reagent precursors, dependence on strong oxidizing reagents, expensive and rare catalysts, long reaction durations, occasion of side reactions, severe reaction environments, and difficult product separation from reaction mixture. For this reason, the breakthrough

of mild and facile synthesis with stable, recyclable, and ecofriendly heterogeneous catalysts for quinoxalines synthesis is important and very much in demand.

Recently, heterogeneous catalysts applied for organic synthesis [23-30] have been acknowledged as considerably important due to their ease of processing, superior reaction rates, higher selectivity, and easy work-up. Of the available solid catalysts, ZnO is well known to be highly active, recyclable, non-toxic, and abundant for several organic transformations [31-33]. In continuation of our interest in various heterogeneous nanoporous catalysts application, herein we want to explore the use of ZnO nanoparticles loaded mesoporous silica (namely ZnO-KIT-6) for the production of quinoxalines with methanol as the solvent, and *o*-phenylenediamines and diverse ketones as the reactants. Excellent product yields with high selectivity could be achieved with short reaction times (10-60 min) while being conducted under mild and convenient conditions.

2. Materials and Methods

2.1 Chemicals

Triblock copolymer Pluronic™ P123 ($EO_{20}PO_{70}EO_{20}$, M = 5800), n-butanol, and tetraethyl orthosilicate (TEOS) were obtained from Aldrich to be used as the template, co-solvent, and silica source, respectively. Zinc nitrate hydrate ($Zn(NO_3)_2{\cdot}6H_2O$) was purchased from Wako and used as the zinc source. All chemicals and solvents used for this study were acquired from either Aldrich or AVRA and used without further purification. Column chromatographic separations were carried out on silica gel with a 60-120 mesh size.

2.2 Synthesis of KIT-6 with varying pore diameters

Pluronic P123 (4 g) was dissolved and stirred at 35°C for 3h in HCl solution (0.532M, 151 mL) for a typical synthesis of highly ordered 3D mesoporous KIT-6

silica. Then, n-butanol (4.0 g) was added immediately with continuous stirring, and stirred for another hour. Subsequently, TEOS (8.6 g) was added, and continuously stirred for 24 h at 35 °C. Following the hydrothermal treatment, the solution was poured into a polypropylene bottle and left stationary in an oven for 24h at 100 °C . Without washing, the white coloured product was filtered and dried inside an oven set for various temperatures to control KIT-6's pore diameter. By varying the aging temperature (100, 130, and 150 °C), various KIT-6 samples were prepared and denoted as KIT-6-T, where the synthesis temperature is represented by T. The final as-synthesized products were calcined in air at 540 °C.

2.3 Synthesis of KIT-6 supported zinc oxide

Zinc oxide nanoparticles were immobilized in the KIT-6 mesopores by a wet impregnation method. The desired amount of zinc source and the synthesized KIT-6 (1 g) were added to ethanol (25 mL) in a typical preparation. The mixture was then stirred at 50 °C for 24 h and dried overnight at 100 °C to remove any remaining ethanol. Finally, the sample was heated at 300 °C for 5 h in air. Samples of KIT-6 with varying pore diameters and amounts of zinc oxide were hereby prepared, and denoted as KIT-6-T-X, where X represents the zinc oxide weight percentage.

2.4 Characterization

Rigaku diffractometer with Cu Kα (λ = 0.154 nm) radiation was used to collect powder X-ray diffraction patterns (XRD) of KIT-6 with varying pore diameters and amounts of immobilized zinc oxide. Low-angle diffractograms were collected for the 2θ range of 0.7–10^{o} and high-angle ones in the range of 10–80^{o}. A Bellsorp-mini II analyser was used to collected nitrogen adsorption and desorption isotherms at -196 °C. All samples were degassed at 100 °C for 24 h prior to nitrogen adsorption measurements. The Brunauer-Emmett-Teller (BET) method and the

Barrett-Joyner-Halenda (BJH) method were used to calculate the specific surface areas and pore size distributions (obtained from the nitrogen isotherms adsorption branch), respectively. Sample morphology was observed by using a Hitachi S-4800 high-resolution field emission SEM (HR-FESEM) with a 15 kV acceleration voltage, whereas a 20 kV acceleration voltage was used for elemental mapping and energy dispersive spectroscopy (EDS) analysis. A JEOL JEM-2100F TEM with a 200 kV accelerating voltage was used to obtain High-resolution TEM (HRTEM) images. HRTEM sample preparation involved 2–5 min of sonication in ethanol and copper grid deposition.

2.5 Typical procedure for catalytic reaction

The ZnO-KIT-6 catalyst (10 mg) was added to a methanol solution (4 mL) of diamine (1 mmol) and 1,2-diketone (1 mmol), and stirred for various durations at room temperature. After the reaction has been completed, as indicated by thin-layer chromatography (TLC, using ethyl acetate/*n*-hexane 1/9), all products were characterized by spectral (infrared (IR), nuclear magnetic resonance (NMR)) data and also by melting point. The spectral data for two typical quinoxalines are given below. **Compound 3a: 2,3-Diphenylquinoxaline:** Off white solid; Mp: 126-127^{o}C; yield 98%; IR (KBr): ν_{max} 3055, 1965, 1540, 1440, 1350, 1060, 980, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.18 (dd, *J*=6.10, 3.42 Hz, 2 H), 7.78 (dd, *J*=6.34, 3.41 Hz, 2 H), 7.51 - 7.53 (m, 4 H), 7.32 - 7.35 (m, 6 H) ppm. **Compound 3e: 2,3,2',3'-Tetraphenyl-[6,6']biquinoxalinyl:** yellow solid; Mp: 309-311^{o}C (lit.,[22] >295^{o}C); yield 95%; Rf; 0.53, IR (KBr): ν_{max} 3055, 1615, 1480, 1345, 1060, 770, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.17 (d, *J*=1.71 Hz, 2 H), 8.10 (d, *J*=9.02 Hz, 2 H), 7.71 (dd, *J*=8.78, 1.71 Hz, 2 H), 7.51 (d, *J*=6.83 Hz, 8 H), 7.29 - 7.41 (m, 12 H) ppm.

3. Results and discussion

3.1 Catalyst characterization

KIT-6 type mesoporous silica was successfully synthesized with Pluronic™ P123 as the structure-directing agent. The KIT-6 pore size could be controlled from 7.7 to 11.3 nm by aging the as-synthesized samples at different temperatures (from 100 to 150 °C, respectively), as summarized in **Table 1**. As the pore size increased, however, the corresponding specific surface area decreased. These samples of KIT-6-T (where T represents aging at 100, 130, or 150 °C) were then used as the host materials for further encapsulation of ZnO nanoparticles because of their suitable pore size (7.7 to 11.3 nm), pore volume (1.05 to 1.35 cm^3g^{-1}), and specific surface area (717 to 542 m^2g^{-1}).

Various amounts of ZnO nanoparticles from 5 to 30 wt% could be successfully encapsulated in the synthesized KIT-6-T samples (with the ZnO loaded samples denoted as KIT-6-T-X, where X represents the Zn weight percent). The synthesized ZnO-loaded KIT-6 samples were further characterized by nitrogen adsorption-desorption isotherms, scanning electron microscopy (SEM) with elemental mapping, and transmission electron microscopy (TEM). As shown in **Fig. 1(a)**, the KIT-6-130 samples with different ZnO loading all exhibit similar isotherms, *i.e.* type IV with a hysteresis, for the typical KIT-6 mesoporous architecture. The nitrogen adsorption/desorption isotherms of all samples are shown in **Fig. S1**. As shown in **Table 1**, both the specific surface area and the pore volume of all three KIT-6-T hosts decreased but their pore sizes retained similar values as the loading amount of ZnO was increased.

The corresponding small-angle X-ray diffraction (XRD) patterns showed well defined peaks assignable to a typical *Ia-3d* mesostructure, which indicated the

maintenance of the ordered mesostructure even after the encapsulation of the ZnO nanoparticles, as shown in **Fig. S2**. The SEM element mapping for KIT-6-130-10Zn in **Fig. 1(b)** clearly shows the homogeneous distribution of Zn element over the entire area. The bright-field TEM image and the high-angle annular dark field – scanning TEM (HAADF-STEM) image of the same sample confirmed the ordered mesostructure (**Fig. 1(c)**) and the formation of uniform ZnO particles (**Fig. 1(d)**). Other TEM images are also shown in the **Fig. S3**. These results indicate that ZnO nanoparticles with an average particle size of around 9 nm were indeed formed inside the KIT-6-T mesopores with the wet impregnation method described in the experimental section.

3.2 Catalytic reaction

To optimize the reaction conditions for producing quinoxalines, *o*-phenylenediamine **1** (OPDA, 1 mmol) and 1,2-diketone **2** (1 mmol) were employed as the reactants, and methanol as the solvent in room temperature (**Scheme 1**). We then screened all the samples and found that KIT-6-130-10Zn (10 mg) exhibited the best catalytic performance. Therefore, we used KIT-6-130-10Zn as the catalyst (hereafter denoted as ZnO-KIT-6). The reaction was also carried out in the absence of ZnO-KIT-6 solid catalyst, and no product formed under the same reaction conditions. In addition, bare KIT-6-130 sample (no ZnO) was also tested, but the quinoxaline yield was also low (less than 10%).

To extend the possibility of producing various kinds of quinoxalines, different substituted OPDA **1** and 1,2-diketones **2** were also used with the ZnO-KIT-6 catalyst for 10 to 60 min at room temperature to achieve the maximum corresponding quinoxalines yield. As shown in **Table 2**, several types of substituted OPDA, such as chloro, nitro, dichloro, cyclohexyl, and *bis*-OPDA, were used as reactants to obtain

the corresponding quinoxalines **3**. Substituted diamines **1** and various aromatic diketones **2** such as benzyl and furyl were used to produce various kinds of quinoxalines (**Table 2**, **entry 3a-l**). In addition, the ZnO-KIT-6 catalyst also provided a good yield when 3,3□-diamino benzidine was used (**Table 2**, **entry 3e & j**). Finally, aliphatic diamines such as cyclohexyldiamine (**Table 2, entry 3k & l**) also worked well in the presence of this catalyst with good yields.

We propose that the ZnO-KIT-6 catalyst can act as a Lewis acid catalyst, and the possible formation mechanism of quinoxalines **3** is proposed in **Scheme 2**. During the reaction, the di-ketone is activated, and the intermediate **A** is formed with the ZnO-KIT-6. Finally, the intermediate **A** is further reacted with the diketone, which is thus condensed to become the final product **3**. These results reveal that the ZnO-KIT-6 catalyst is a very efficient catalyst for producing various kinds of quinoxalines with excellent yields.

4. Conclusion

We have synthesized ZnO-loaded KIT-6 mesoporous silica as an efficient catalyst for producing various kinds of quinoxalines using various aromatic diamines and 1,2-diketones as reactants. The catalyst is proved to be very active and affords a high yield of quinoxalines with short reaction durations. We propose that the ZnO-KIT-6 catalyst can also be used in various acid-catalyzed multi-component reactions (MCRs) and can create a platform for the development of various pharmaceutical products.

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Figures and Table Caption.

Figure 1. (a) Nitrogen adsorption-desorption isotherms of KIT-6-130 with different ZnO loadings. (b) SEM elemental mapping and (c) a bright field TEM image for the KIT-6-130-10Zn sample.

Scheme 1. Chemical equation representing the production of quinoxalines **3** from the raw materials, diamines **1** and 1,2-diketones **2**, using the synthesized ZnO-KIT-6 catalyst.

Scheme 2 Proposed mechanism for the production of quinoxalines using ZnO-KIT-6 as the catalyst.

Table 1 Summary of porous properties of all samples. Samples are denoted as KIT-6-T-X, where T refers to the aging temperature and X refers to the weight percent of Zn.

Table 2. Production of various kinds of quinoxalines **3** with the maximum yields obtained using ZnO-KIT-6 as the catalyst and the diamines **1** and 1,2-diketones **2** raw materials as reactants.

Figure 1

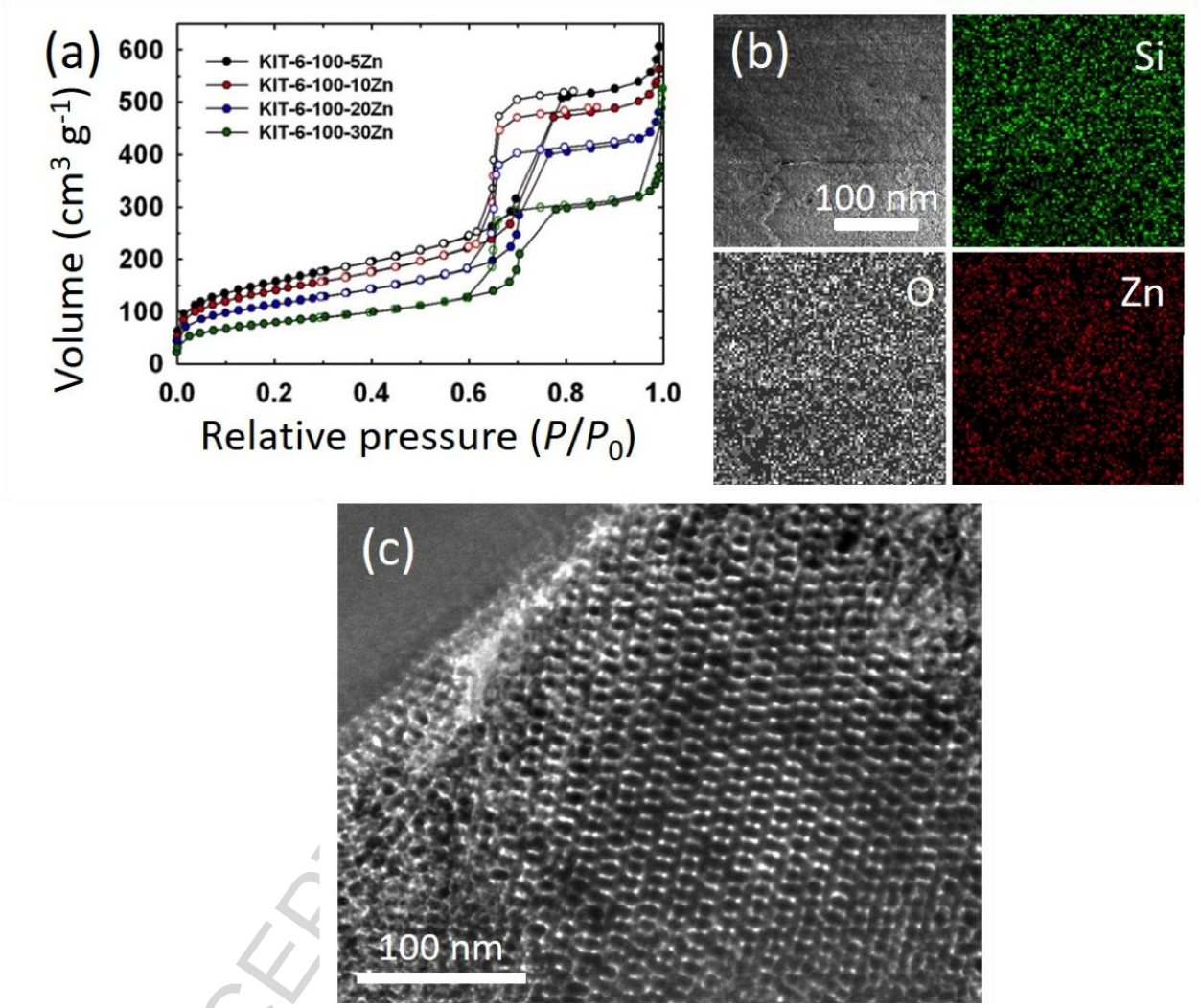
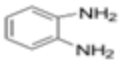
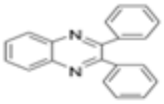
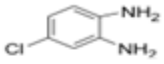
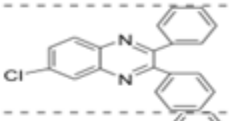
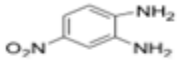
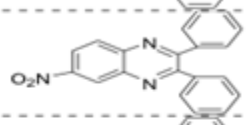
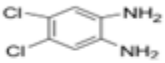
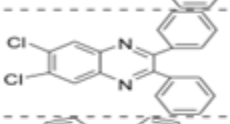
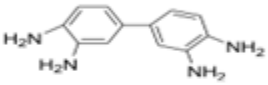
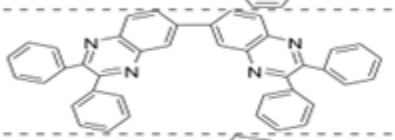
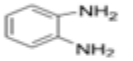
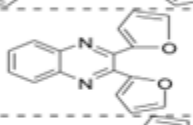
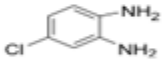
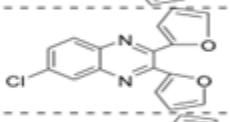
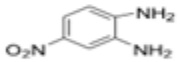
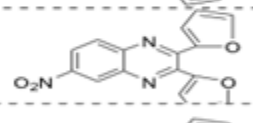
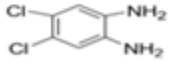
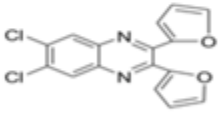
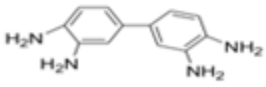
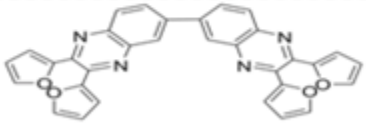
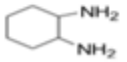
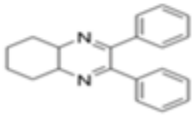
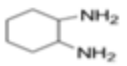
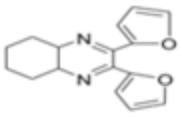


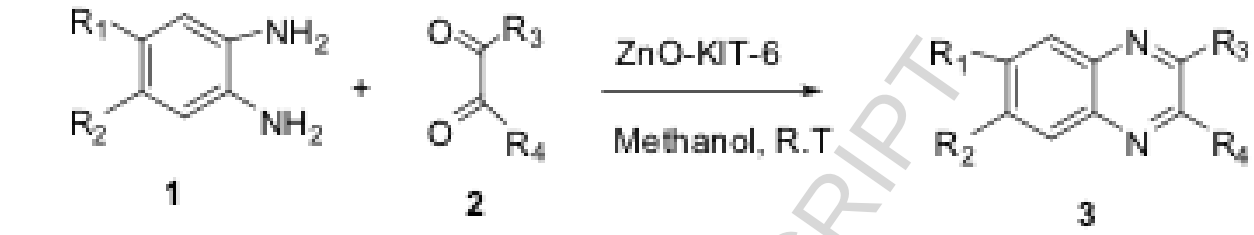
Table 1

Sample names	Surface area ($m^2 g^{-1}$)	Pore volume ($cm^3 g^{-1}$)	Pore size (nm)
KIT-6-100	717	1.05	7.7
KIT-6-100-5Zn	547	0.86	7.1
KIT-6-100-10Zn	490	0.81	7.1
KIT-6-100-20Zn	398	0.71	7.1
KIT-6-100-30Zn	275	0.54	7.1
KIT-6-130	614	1.21	9.1
KIT-6-130-5Zn	531	1.22	9.3
KIT-6-130-10Zn	485	1.14	9.3
KIT-6-130-20Zn	400	0.97	9.3
KIT-6-130-30Zn	275	0.67	9.3
KIT-6-150	542	1.35	11.3
KIT-6-150-5Zn	453	1.39	10.6
KIT-6-150-10Zn	410	1.26	10.6
KIT-6-150-20Zn	368	1.15	10.6
KIT-6-150-30Zn	334	1.05	10.6

Table 2

Entry	Substituted OPDA	Quinoxalines	Time (min)	Yield (%)
3a			10	98
3b			10	99
3c			25	88
3d			10	98
3e			30	95
3f			60	95
3g			20	93
3h			60	90
3i			30	93
3j			45	88
3k			60	82
3l			60	83

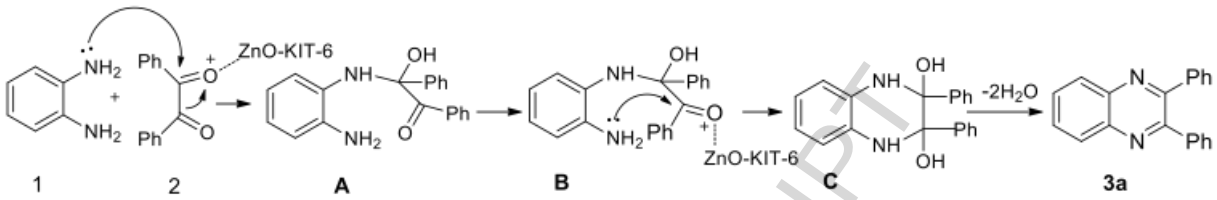
Scheme 1



1 2 3

$R_1 = R_2$ = H,Cl, NO_2, $R_3 = R_4$ = Ph,Furil

Scheme 2



Highlights

Highly ordered mesoporous KIT-6 materials are synthesized.

ZnO nanoparticles are uniformly formed in the KIT-6.

An efficient production of various substituted quinoxalines is demonstrated.

KIT-6-130-10Zn sample exhibits the most efficient catalytic ability.

Various quinoxalines with yields of 82 to 99% are produced.