First Example of $Cu(OTf)_2$-catalyzed Synthesis of Quinoxalines from α-Diazoketones and Aryl 1,2-Diamines

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α-Diazoketones undergo smooth coupling with aryl 1,2-diamines in the presence of 10 mol % of copper(II) triflate to provide the corresponding 2-alkyl- or 2-aryl-quinoxalines in excellent yields with high selectivity. $Rh_2(OAc)_4$ is also found to be an equally effective catalyst for this transformation. It is a new and alternative approach for the preparation of biologically well-defined quinoxaline derivatives.

Quinoxaline derivatives have received considerable interest from the pharmaceutical industry because of their interesting therapeutic properties such as antiviral, antibacterial, anti-inflammatory, anti-protozoaval, and as kinase inhibitors.[1] They have also been evaluated as anticancer, anthelmintic agents, antifungal and insecticidal agents.[2] In addition, quinoxaline nucleus is a part of several antibiotics such as echinomycin, levomycin, and actinomycin which are known to inhibit the growth of gram-positive bacteria and active against various transplantable tumors.[3] Besides this, they have found applications as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents.[4,5] Since they display a broad spectrum of biological properties, they are considered as privileged structures in combinatorial drug discovery. Drug formulations containing quinoxalines such as Lamprene are currently available (Figure 1). Consequently, a variety of methods have been developed for the synthesis of quinoxalines, which include condensation of aryl 1,2-diamines with 1,2-ketones, oxidative cyclization of α-hydroxy ketones with 1,2-diamines, cyclization–oxidation of phenacyl bromides with 1,2-diamines, oxidative coupling of epoxides with ene-1,2-diamines.[6–9] However, many of these methods suffer from several drawbacks such as the use of strong oxidizing agents, expensive metal catalysts, harsh reaction conditions, and also the yields are far from satisfactory. Therefore, the development of simple, convenient, and general approach would certainly be useful in generating combinatorial libraries for drug discovery.

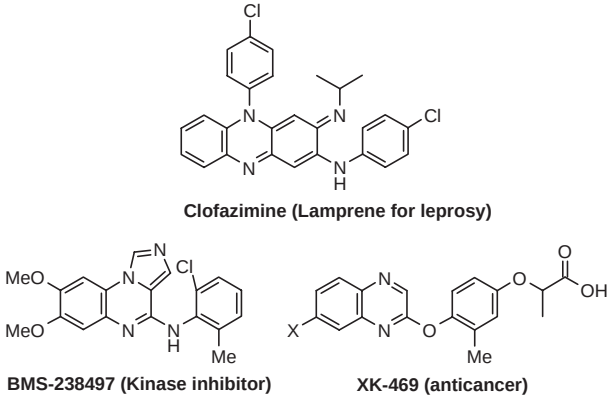


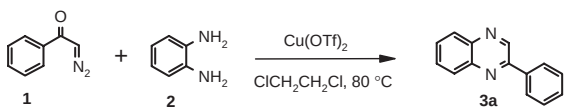
Figure 1. Structures of Lamprene, BMS-238497, and XK-469.

The ready availability, relative stability, and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base, and transition-metal catalytic conditions make them useful intermediates in organic synthesis.[10] Interestingly, α-diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H and X–H insertion reactions and cyclization reactions.[11] These reactions are chemoselective, which allow new carbon–carbon and carbon–hetero atom bond formation under mild conditions.[12] However, there have been no reports on the coupling of α-diazoketones with aryl 1,2-diamines to generate biologically potent quinoxaline derivatives.

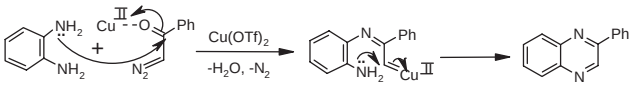
In this article, we report a novel method for the synthesis of quinoxalines via the coupling of aryl 1,2-amines and α-diazoketones using a catalytic amount of copper(II) triflate under mild reaction conditions. Accordingly, treatment of diazoacetophenone (**1**) with *o*-phenylenediamine (**2**) in the presence of 10 mol % of $Cu(OTf)_2$ in dichloroethane (DCE) at 80 °C afforded 2-phenylquinoxaline (**3a**) in 94% yield (Scheme 1).

This result provided the incentive for further study of reactions with other α-diazocarbonyl compounds. Interestingly, various α-diazoketones reacted smoothly with several aryl 1,2-diamines to give the corresponding 2-alkyl- or 2-aryl-quinoxalines derivatives as the products of nitrogen insertion. Both aromatic and aliphatic diazoketones participated well in this conversion (Table 1). In all cases, the reactions proceeded efficiently in the presence of 10 mol % of $Cu(OTf)_2$ at 80 °C in dichloroethane and the products were obtained in high to excellent yields. No side product arising from a Wolff rearrangement was observed under these reaction conditions. Other side products such as α-keto-*O*-triflates (the products of OTf insertion) arising from $Cu(OTf)_2$, were not detected under these conditions. The effects of various copper salts such as $Cu(OAc)_2$, $Cu(BF_4)_2$, and $Cu(acac)_2$ were tested for this conversion.

Of these catalysts, $Cu(OTf)_2$ was found to be the most effective. As solvent, dichloroethane gave the best conversion. Alternatively, 5 mol % of $Rh_2(OAc)_4$ was found to be an equally effective catalyst for this transformation. Other Lewis acids such as $Yb(OTf)_3$, $Sm(OTf)_3$, and $In(OTf)_3$ failed to give the desired products. Similarly, Brønsted acids such as Montmorillonite K10 and heteropoly acids also did not give the expected product. The reaction may proceed via an initial formation of imine followed by N–H insertion, which would result in the formation of

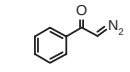
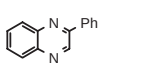
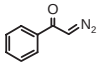
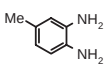
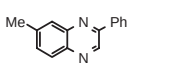
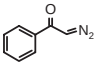
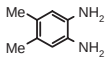
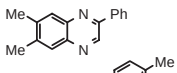
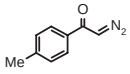
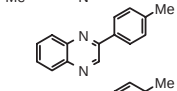
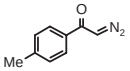
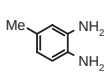
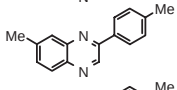
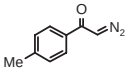
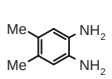
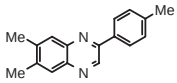
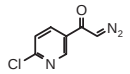
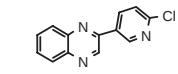
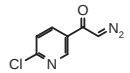
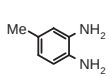
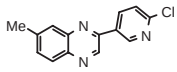
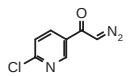
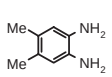
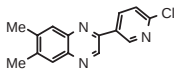
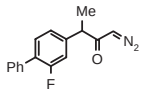
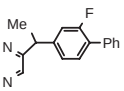
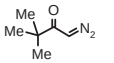
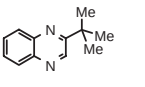
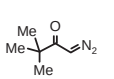
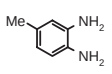
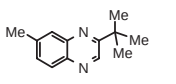
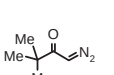
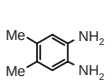
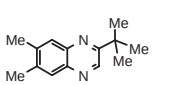


Scheme 1. Preparation of 2-phenylquinoxaline (**3a**).



Scheme 2.

Table 1. $Cu(OTf)_2$-catalyzed coupling of α-diazoketones with 1,2-diamines

Entry	α-Diazoketone	Diamine	Product[a]	Time/h	Yield/%[b]
A				2.0	94
B				2.5	92
C				3.0	90
D				2.5	91
E				3.0	94
F				2.5	90
G				2.0	90
H				2.5	89
I				3.0	90
J				2.0	88
K				2.5	88
L				3.0	90
M				2.5	92
N				2.0	93
O				2.5	91
P				3.0	89

[a]All products were characterized NMR, IR, and mass spectrometry. [b]Yield refers to pure products after chromatography.

the 2-phenylquinoxaline (Scheme 2).

The structures of the products were established by ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectrometry (HRMS). The scope and generality of this procedure is illustrated with respect to various α-diazoketones and aryl 1,2-diamines and the results are presented in Table 1.[12]

In summary, we have developed a novel method for the synthesis of 2-alkyl- or 2-aryl-quinoxalines via the coupling of α-diazoketones with aryl 1,2-diamines. In addition to its simplicity and mild reaction conditions, this method provides high yields of products with high selectivity making it a useful and attractive strategy for the preparation of biologically relevant 2-alkyl- or 2-aryl-quinoxalines in a single-step operation.

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12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett.

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