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Direct and catalytic synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines

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Abstract—We describe here a new synthesis of quinoxaline derivatives by a Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines.

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles and they constitute useful intermediates in organic synthesis.[1] They have been reported for their applications in dyes,[2] pharmaceuticals,[3,4] and have also been used as building blocks for the synthesis of organic semiconductors.[5,6] 2,3-Substituted quinoxalines can be prepared by condensation of aryl-1,2-diamines and α-functionalized ketones, usually α-dicarbonyl compounds or their equivalents.[7–10] To the best of our knowledge, epoxides have never been involved in quinoxaline synthesis, excepted in one report, using α-sulfonyl epoxides and leading to 2-phenyl quinoxalines in moderate yields.[11] In all cases, the reduced range of commercially available starting materials results in multi-step reactions.

We present here a new strategy to prepare differently substituted quinoxalines directly from simple epoxides and diaminoaryl compounds, in a oxidative coupling catalyzed by bismuth powder. The use of bismuth, non toxic[12] and commercially available, is an interesting feature of the process.

The reaction proceeds in DMSO under molecular oxygen in the presence of catalytic amounts of Bi(0) powder and of copper triflate or triflic acid as additives. The results obtained in the synthesis of quinoxaline derivatives are summarized in Table 1.

The synthesis of 2,3-disubstituted quinoxalines (Scheme 1) was achieved in yields of 53–70% using phenylene diamine and internal epoxides (entries 1–4). The oxidative coupling of 1,2-phenylene diamine and monosubstituted styrene oxide derivatives afforded 2-arylquinoxalines in 64–65% yields (entries 5 and 6).

The replacement of phenylene diamine by 2,3-diaminomaleonitrile or by 2,3-diaminopyridine (entries 7–9, respectively) led also to the expected heterocycles in 53–71% yields, according to Scheme 2.

Among this series, we prepared some quinoxalines bearing functional groups without observing any side reactions or yield decrease. These functional groups, e.g. chloride, nitrile or vinylic functions (entries 4, 6 and 7), allow further functionalization of the molecules.

The best results were obtained using 1.5 equiv. of the diamino compound. Several attempts with only 1 equiv. afforded lower yields. The change of 1,2-phenylene diamine by 2,3-diaminopyridine or 2,3-diaminomaleonitrile did not affect the reaction yield or the reaction conditions.

The isolated yields of this series of quinoxalines were in the range of 53 to 71%. Except for entries 3, 5 and 6, almost no by-products were formed, but some polymerization of the epoxide under the reaction conditions led to a partial mass-loss.

In the case of coupling with styrene oxides (entries 5 and 6) the formation of 2-aryl-1,2,3,4-tetra-

Keywords: quinoxaline; epoxides; heterocycles; bismuth; catalysis.

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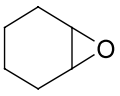
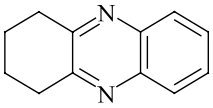
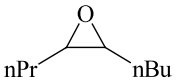
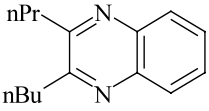
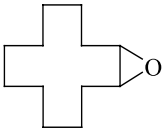
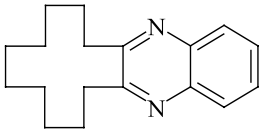
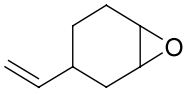
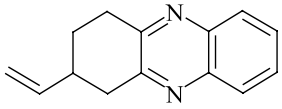
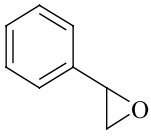
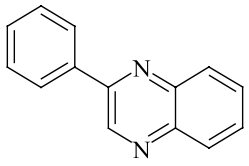
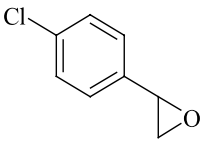
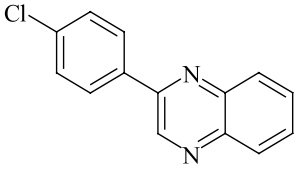
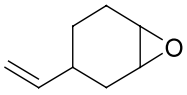
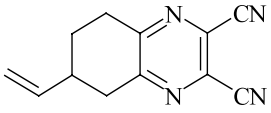
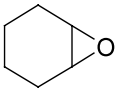
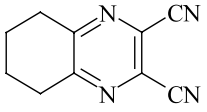
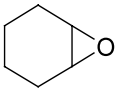
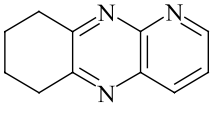
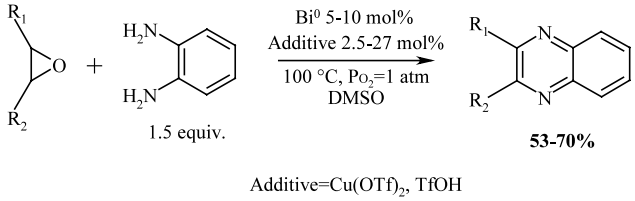
Table 1. Bi-catalyzed synthesis of quinoxaline derivatives from epoxides under O_2 (1 atm), in DMSO at 100°C

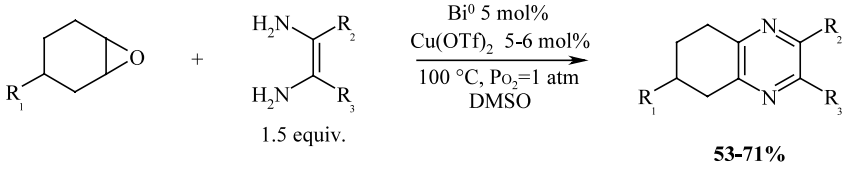
Entry	Epoxide	Catalyst mol% Additives mol% Time	Diamino compound	Product	Isolated yield (%)
1		Bi^0 5% $Cu(OTf)_2$ 6% 5 h	1,2-Phenylene diamine		**62**
2		Bi^0 10% TfOH 20% 8 h	1,2-Phenylene diamine		**70**
3		Bi^0 9% TfOH 27% 23 h	1,2-Phenylene diamine		**53**
4		Bi^0 5%, $Cu(OTf)_2$ 5% 3.6 h	1,2-Phenylene diamine		**68**
5		Bi^0 5% $Cu(OTf)_2$ 4% 3.6 h	1,2-Phenylene diamine		**64**
6		Bi^0 5% $Cu(OTf)_2$ 6% 6.6 h	1,2-Phenylene diamine		**65**
7		Bi^0 5%, $Cu(OTf)_2$ 6% 4 h	2,3-Diamino maleonitrile		**71**
8		Bi^0 6% $Cu(OTf)_2$ 5% 3.5 h	2,3-Diamino maleonitrile		**67**
9		Bi^0 5% $Cu(OTf)_2$ 5% 3.5 h	2,3-Diamino pyridine		**53**



Scheme 1. Synthesis of 2,3-susbstituted quinoxaline derivatives from epoxides and phenylene diamine.

hydroquinoxalines was observed (18–25%). These resulted from the nucleophilic addition of the diamine to the epoxide. On the other hand, in the case of cyclododecene oxide (entry 3), the formation of cyclododecanone, from the acid-catalyzed isomerization of the epoxide[13,14] was obtained in 12% yield.

No quinoxalines were obtained in the absence of Bi(0), DMSO or molecular oxygen. The use of $Bi(0)/O_2$/DMSO or $Bi(III)/O_2$/DMSO as the catalytic system in the



Scheme 2. Synthesis of tetrahydroquinoxaline derivatives from cyclohexene oxides and 1,2-enediamines.

oxidative ring opening of epoxides have already been reported.[15,16] The Bi(0)-catalyzed reaction did not take place in the absence of an additive.

Two different additives, $Cu(OTf)_2$ and TfOH, were used, according to the epoxide structure. For monosubstituted epoxides or for cyclohexene oxide, $Cu(OTf)_2$, used in 4–6 mol%, gave the best results. In contrast, for the other disubstituted epoxides, the use of a strong Brönsted acid such as TfOH, in 20–27 mol%, was the best compromise between yield of quinoxaline and acid-catalyzed epoxide polymerization.

For the mechanistic aspects of this new transformation, we propose a first oxidation of the epoxide to the corresponding α-hydroxyketone and its further oxidation to the α-diketone, in agreement with our recent results in this field.[17] This oxidation proceeds by oxidative ring opening of the oxirane by DMSO,[18] catalyzed by an acidic additive, leading to the corresponding α-hydroxyketone, or α-hydroxyaldehyde. In a second step, the ketol (or ketal) is oxidized to the α-diketone or to the α-ketoaldehyde intermediates by the $Bi(0)/O_2$ system, in a Bi(III)/Bi(0) redox process.[16] The in situ α-dicarbonyl compound obtained affords the corresponding quinoxaline after the double condensation/dehydratation with the 1,2-diamino derivatives.

The general procedure for 2,3-substituted quinoxaline synthesis can be described as follows: a mixture of bismuth(0) (0.25 mmol) and the additive (0.25 mmol) in DMSO (15 ml) is heated at 100°C under O_2 (1 atm). The epoxide (5 mmol) in DMSO (5 ml) is then introduced through a serum cap and the mixture is stirred at this temperature until complete consumption of the epoxide (monitored by GC). The diamino compound (7.5 mmol) in DMSO (2 ml) is then introduced and the mixture is kept until the reaction is completed. The reaction mixture is hydrolyzed with brine (50 ml), and extracted with diethyl ether (3×50 ml). The combined organic layers are dried over $MgSO_4$ and evaporated. The crude product is purified by column chromatography over silica gel with pentane and dichloromethane as the eluent. The products are identified by ^1H and ^{13}C NMR and mass spectroscopy, and compared with authentic samples or literature data.[19]

The procedure is identical for the synthesis of 2-arylquinoxalines, excepted that both the epoxide and the diamino compounds are introduced simultaneously.

In conclusion, a new synthesis of mono- and disubstituted quinoxalines has been achieved in one-pot reaction via the Bi-catalyzed condensation of epoxides and diamino derivatives. The process involves the in situ generation and trapping of the α-diketone or α-ketoaldehyde intermediates.

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19. Several of the obtained quinoxalines are known compounds to which the spectroscopic data were compared. For others, data for 2,3-cyano-5,6,7,8-tetrahydroquinoxaline (entry 8), for example, are: yellow powder, mp: 138.7–139.3°C. NMR (200 MHz, $CDCl_3$, 20°C, $\delta_{TMS}=0$ ppm) ^1H: 3.1–2.9 (4H, m), 2.0–1.8 (4H, m); ^{13}C: 158.5, 130.5, 113.2, 32.3, 21.6. MS: 184 (100%), 183 (67%), 169 (89%), 156 (20%), 144 (6%), 129 (6%), 77 (14%), 52 (14%), 41 (16%).