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Rapid and efficient synthesis of 2-substituted-tetrahydropyrido[3,4-*b*] quinoxalines using TDAE strategy

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ABSTRACT

We report herein an original and rapid synthesis of substituted 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline derivatives by TDAE strategy from 2,3-bis(bromomethyl)quinoxaline and *N*-(toluenesulfonyl)benzylimines.

The quinoxaline derivatives show very interesting biological properties,[1] such as antibacterial,[1b] antiviral,[2] anticancer,[3] antifungal, antihelmintic, antileishmanial,[4] anti-HIV,[4] insecticidal, and anti-inflammatory activites,[5] and their interest in medicinal chemistry is far from coming to an end.[6] Many drug candidates bearing quinoxaline core structures are in clinical trials in antiviral,[7] anticancer, antibacterial,[1d] and CNS (central nervous system) therapeutic areas. Among them, the XK469 ((±)-2-[4-(7-chloro-2-quinoxaliny)oxy]phenoxy propionic acid) (Fig. 1) was known as anti neoplastic quinoxaline topoisomerase II inhibitor and possesses antitumor activity especially against murine and human solid tumors.[8–10]

On the other hand, the tetra- and dihydropyrido[3,4-*b*]pyrazine derivatives exhibited interesting biological activity as anticancer agents.[11] In spite of the great interest that could represent combined structures presenting the quinoxaline and the tetrahydropyridine nucleus, few synthesis of tetra-hydropyrido[3,4-*b*] quinoxaline derivatives have been reported.[12]

Since 2003, we have shown that from *o*- and *p*-nitrobenzyl chloride, tetrakis(dimethylamino)ethylene (TDAE)[13] could generate a nitrobenzyl carbanion which is able to react with various electrophiles as aromatic aldehydes, α-ketoester, ketomalonate, α-ketolactam and sulfonimine derivatives.[14] In quinoxaline series, we have reported the reaction of 2-(dibromomethyl)quinoxaline with aromatic aldehydes in the presence of TDAE furnished a mixture of cis/trans isomers of oxiranes[14] and the synthesis of new α-chloroketones based on TDAE strategy from the reaction between 2-(trichloromethyl)-quinoxaline and aromatic aldehydes.[15]

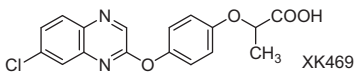

Figure 1. Structure of XK469.

In continuation of our program directed toward the study of single electron transfer reactions of bioreductive alkylating agents[16] and the preparation of new potentially bioactive compounds as anticancer agents,[17] we report herein an original and efficient synthesis of new substituted 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalines based on the TDAE strategy from the reaction between 2,3-bis(bromomethyl)quinoxaline and sulfonimine.

The reaction of 2,3-bis(bromomethyl)quinoxaline **1** with 3 equiv of sulfonimine **2a** in the presence of TDAE at −20 °C for 1 h, led to the 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline **3a**. The reaction of 2,3-bis(bromomethyl)quinoxaline **1** with sulfonimine **2a** was studied (Scheme 1) under various conditions (Table 1). The best yield in product **3a** (60%) is obtained using 1 equiv of TDAE in THF at −20 °C for 1 h.

We have generalized this reaction with other sulfonimines **2b–k** to prepare a new series of 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalines **3b–k**[18] in moderate to good yields (56–67%) as shown in Scheme 2 and reported in Table 2.

The formation of these pyrido[3,4-*b*]quinoxaline derivatives **3a–k** could be explained by two mechanisms, the first one would

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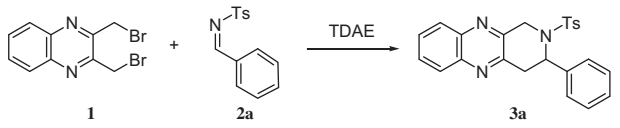
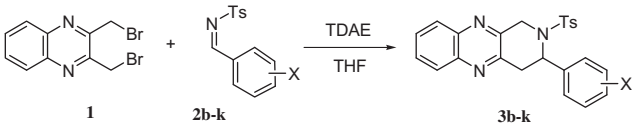


Scheme 1. Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with *N*-(toluenesulfonyl)benzylimine **2a**.

Table 1
Optimization of the reaction of 2,3-bis(bromomethyl)quinoxaline **1** with *N*-(toluenesulfonyl)benzylimine **2a** using TDAE strategy[a]

Entry	Solvent	Equiv of TDAE	Yield[b] (%)
1	THF	1.05	46[c]
2	THF	1.05	60
3	THF	1.5	29
4	DMF	1.05	41

[a] All the reactions are performed using 3 equiv of *N*-(toluenesulfonyl)benzylimine **2a**, 1 equiv of 2,3-bis(bromomethyl)quinoxaline **1** and 1 equiv of TDAE in anhydrous THF stirred at −20 °C for 1 h.
[b] All yields refer to chromatographically isolated pure products and are relative to 2,3-bis(bromomethyl)quinoxaline **1**.
[c] The reaction mixture was stirred at −20 °C for 1 h and then warmed up to room temperature for 0.5 h.



Scheme 2. Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with substituted *N*-(toluenesulfonyl)benzylimine **2b**–**k**.

occur by a nucleophilic addition of carbanion formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline, on the imine group of sulfonimine **2a–k** followed by an intramolecular nucleophilic substitution with the second bromomethyl group. The second pathway would envisage the formation of the biradical of 2,3-bis(bromomethyl)quinoxaline which reacts with imine as suggested by Nishiyama in benzene series.[19]

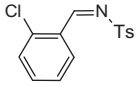
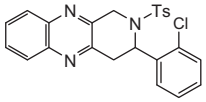
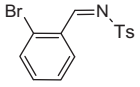
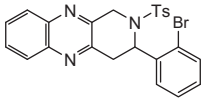
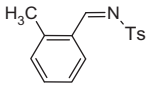
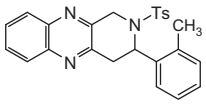
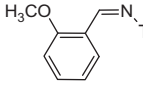
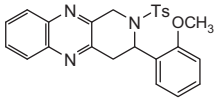
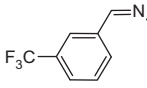
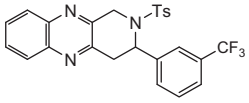
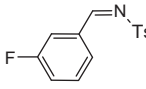
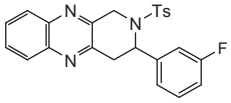
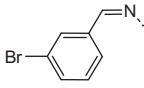
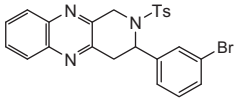
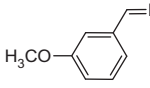
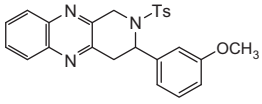
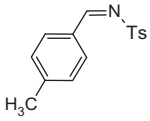
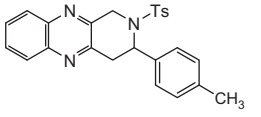
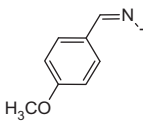
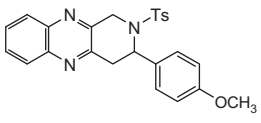
In the absence of intermediates or by-products in this reaction and in order to clarify this mechanism, we envisage the reaction of 2,3-bis(bromomethyl)quinoxaline **1** with another kind of unsaturated compound such as benzaldehyde **4** under the optimal conditions (Scheme 3).

This reaction has not furnished the expected 3-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline, but traces of 2-[3-(bromomethyl)quinoxalin-2-yl]-1-phenylethanol **5** have been identified. The formation of this product may be explained by an ionic addition of carbanion, formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline, on the carbonyl group of benzaldehyde. However, the alcoholate intermediate is not enough nucleophile to cyclize by an intramolecular nucleophilic substitution explaining the absence of the formation of 3-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline.

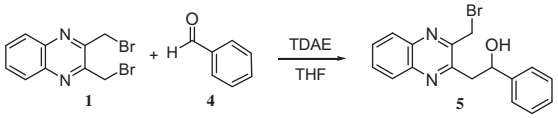
These results with benzaldehyde would seem to confirm an ionic pathway for the formation of these pyrido[3,4-*b*] quinoxaline derivatives **3a–k**.

In conclusion, we have developed in this work the synthesis of new substituted pyrido[3,4-*b*]quinoxalines by an easy, original, and mild procedure using TDAE methodology from 2,3-bis(bromomethyl)quinoxaline **1** and sulfonimines **2a–k**. The anti-plasmodial and cytotoxic activities of all synthesized compounds are under active investigation.

Table 2
Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with substituted *N*-(toluenesulfonyl)benzylimine **2b–k** using TDAE strategy[a]

	Sulfonimine	Product	Yield[b] (%)
1		**3b** 	59
2		**3c** 	65
3		**3d** 	56
4		**3e** 	66
5		**3f** 	61
6		**3g** 	58
7		**3h** 	64
8		**3i** 	63
9		**3j** 	67
10		**3k** 	64

[a] All the reactions are performed using 3 equiv of substituted *N*-(toluenesulfonyl)benzylimines **2b–k**, 1 equiv of 2,3-bis(bromomethyl)quinoxaline **1** and 1 equiv of TDAE in anhydrous THF stirred at −20 °C for 1 h.
[b] All yields refer to chromatographically isolated pure products and are relative to 2,3-bis(bromomethyl)quinoxaline **1**.



Scheme 3. Reaction of **1** with benzaldehyde **4**.

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