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Original synthesis of oxiranes via TDAE methodology: reaction of 2,2-dibromomethylquinoxaline with aromatic aldehydes

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Abstract—We report herein the reaction of 2,2-dibromomethylquinoxaline **2** with aromatic aldehydes **3a**–**g** in the presence of TDAE. These reactions lead to a mixture of *cis*/*trans*-isomers of corresponding oxiranes **4a**–**g** in good yields. The stereoselectivity of the reaction was sensitive to steric hindrance.

The quinoxaline derivatives show very interesting biological properties (antibacterial,[1] antiviral, anticancer,[2] antifungal, antihelmintic, antileishmanial,[3] anti-HIV,[3] insecticidal) and their interest in medicinal chemistry is far to come to an end.[4] Many drug candidates bearing quinoxaline core structures are in clinical trials in antiviral,[1] anticancer, antibacterial,[2] and CNS (central nervous system) therapeutic areas. Among them, the XK469 and the chloroquinoxaline sulfonamide (CQS) were known as antineoplastic quinoxaline topoisomerase II inhibitors (Fig. 1).

The XK469 or (±)-2-[4-(7-chloro-2-quinoxaliny)oxy] phenoxy propionic acid, is an analog of the herbicide Assure® synthesized by DuPont Company, which possesses antitumor activity, especially against murine solid tumors and human xenografts.[5] CQS is a structural analog of sulfoquinoxaline, a compound used to control coccidiosis in poultry, rabbit, sheep, and cattle. CQS was selected for clinical development based on good activity against human tumor cells in the human tumor colony-forming assay[6] and subsequently has shown activity against murine and human solid tumors.[7] Moreover, oxiranes are versatile synthetic intermediates frequently used in the synthesis of organic compounds.[8] Their reactions generally involve cleavage of the strained oxirane ring and include a wide range of nucleophilic ring openings and acid- and base-induced isomerizations.[9]

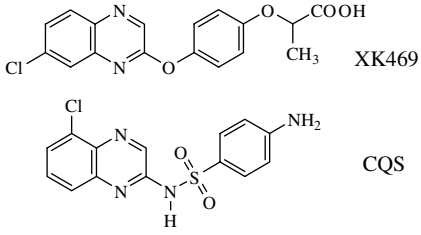

Figure 1. Structures of XK469 and CQS.

Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent which reacts with halogenated derivatives to generate an anion under mild conditions via a single electron transfer (SET).[10,11] In our research program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry, we have developed many reactions between halogenated derivatives and electrophile compounds such as aldehydes, ketones, α-keto-esters, α-ketolactams, and ketomalonates.[10–12]

The interest of quinoxaline derivatives in medicinal chemistry and the synthetic properties of oxiranes led us to investigate the reaction of *gem*-dihalogenated derivatives and electrophiles as aldehydes in the presence of TDAE. We report herein the reaction of 2,2-dibromomethylquinoxaline **2** with aromatic aldehydes **3a**–**g** in the presence of TDAE. These reactions lead to a mixture of *cis*/*trans*-isomers of corresponding oxiranes **4a**–**g**. 2,2-Dibromomethylquinoxaline **2** was synthesized in one step from 2-methylquinoxaline **1** by radical

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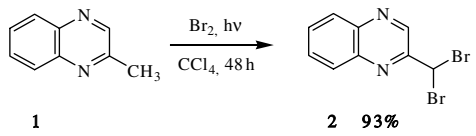


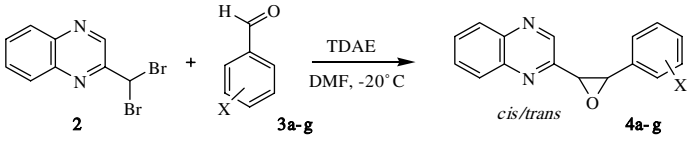
Scheme 1. Synthesis of 2,2-dibromomethylquinoxaline **2**.

bromination using bromine in refluxing carbon tetrachloride and light catalysis (Scheme 1). Contrary to previous work,[13] we have used an excess of bromine (2.5 equiv) to support the formation of dibromide **2**.

The reaction of 2,2-dibromomethylquinoxaline **2** with 3 equiv of aromatic aldehydes in the presence of TDAE at −20 °C for 1 h, followed by 2 h at room temperature, led to a mixture of *cis*/*trans*-isomers of corresponding oxiranes **4a**–**g** in good yields, as shown in Scheme 2 and reported in Table 1.[14]

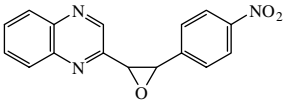
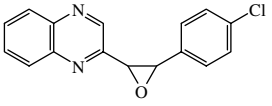
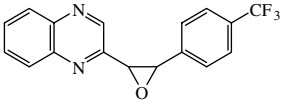
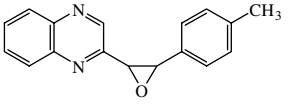
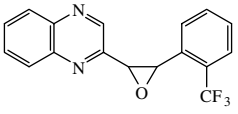
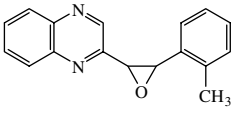
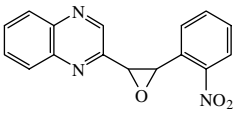
^{1}H NMR spectral studies reveal that oxiranes were identified as *trans*- or *cis*-isomers by their coupling constant. Two distinct doublets appeared in the region at 4.13–5.03 ppm with $J = 1.6$–1.9 Hz or $J = 4.2$–4.7 Hz each of the signal corresponding to one proton. The small value (1.6–1.8 Hz) of this coupling constant is consistent with a *trans*-isomer as reported in the literature data[15,16] and large value (4.3–4.5 Hz) indicates the *cis*-isomer of oxirane.

The formation of these oxiranes **4a**–**g** may be explained by nucleophilic addition of α-bromo carbanion, formed by action of TDAE with 2,2-dibromomethylquinoxaline **2**, on carbonyl group of aldehyde **3a**–**g** followed by an intramolecular nucleophilic substitution. The relative *cis*/*trans* percentage of oxirane isomers reported in Table 1 showed that the stereoselectivity of these reactions was sensitive to steric hindrance. The reactions with *ortho*-substituted aldehydes were most selective.

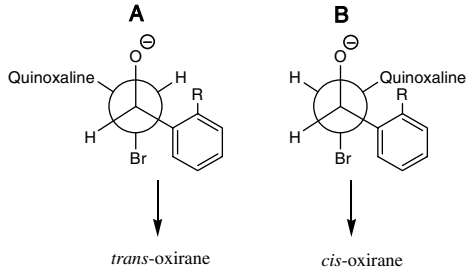


Scheme 2. Reactions of 2,2-dibromomethylquinoxaline **2** with aromatic aldehydes in the presence of TDAE.

Table 1. Reactions of 2,2-dibromomethylquinoxaline **2** and aldehydes using TDAE[a]

Aldehyde **3**	Oxirane **4**		*cis*/*trans*-Isomers (%)[b]	Yield (%)[c]
4-Nitrobenzaldehyde **3a**		**4a**	47/53	83
4-Chlorobenzaldehyde **3b**		**4b**	45/55	45
4-Trifluoromethylbenzaldehyde **3c**		**4c**	48/52	79
4-Methylbenzaldehyde **3d**		**4d**	50/50	38
2-Trifluoromethylbenzaldehyde **3e**		**4e**	20/80	48
2-Methylbenzaldehyde **3f**		**4f**	30/70	42
2-Nitrobenzaldehyde **3g**		**4g**	25/75	35

[a] All the reactions are performed using 3 equiv of aromatic aldehydes **3a**–**g**, 1 equiv of dibromide **2**, and 1 equiv of TDAE in anhydrous DMF.
[b] % Isomers determined on ^{1}H NMR measurements from the crude product.
[c] % Yield relative to dibromide **2**.



Scheme 3. Stereoselectivity of the oxirane formation.

Intramolecular substitution proceeds by a S_N2 mechanism. Two conformations are possible for the transition state as shown in Scheme 3.

However, the one that predominates is often determined by an eclipsing effect. In conformation **A**, the *ortho*-substituted benzene ring is placed between a hydrogen and a bromine atom, while in conformation **B**, it is between quinoxaline ring and bromine atom. This means that **A** is more stable, and most of the intramolecular substitution should occur from this conformation. These effects become larger while increasing size of the substituents.

We have shown in this work that 2,2-dibromomethylquinoxaline **2** formed an α-bromo carbanion using TDAE methodology. Moreover, this anion reacted on carbonyl group of aldehyde **3a**–**g** to give oxirane derivatives in good yields. The stereoselectivity of the reaction was sensitive to steric hindrance.

Acknowledgment

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14. General procedure for the reaction of 2,2-dibromomethylquinoxaline **2** and aldehydes using TDAE. Into a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet were added, under nitrogen at −20 °C, 7 mL of anhydrous DMF solution of **2** (0.3 g, 1 mmol) and aldehyde **3a**–**g** (3 mmol). The solution was stirred and maintained at this temperature for 30 min and then TDAE (0.3 g, 1.5 mmol) was added dropwise (via a syringe). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to room temperature for 2 h. After this time TLC analysis (dichloromethane) clearly showed that **2** was totally consumed. The orange-red turbid solution was filtered (to remove the octamethyloxamidinium dibromide) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with toluene (3×40 mL), the combined organic layers were washed with H_2O (3×40 mL), and dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as crude product. Purification by silica gel chromatography (dichloromethane) gave the corresponding mixture of *cis*/*trans*-isomer oxiranes **4a**–**g** as solids. New products: **4a** *cis*-isomer; ^1H NMR ($CDCl_3$) δ 4.64 (d, $J = 4.4$ Hz, 1H); 4.73 (d, $J = 4.4$ Hz, 1H); 7.51 (d, $J = 8.6$ Hz, 2H); 7.73 (m, 2H); 7.97 (m, 2H); 8.03 (d, $J = 8.6$ Hz, 2H); 8.68 (s, 1H). ^{13}C NMR ($CDCl_3$) 58.9; 59.1; 123.4 (2CH); 127.6 (2CH); 128.8; 129.3; 130.2; 130.6; 140.4; 141.5; 142.0; 142.7; 147.6; 148.7. *trans*-Isomer; ^1H NMR ($CDCl_3$) δ 4.28 (d, $J = 1.6$ Hz, 1H); 4.40 (d, $J = 1.6$ Hz, 1H); 7.58 (d, $J = 8.7$ Hz, 2H); 7.82 (m, 2H); 8.11 (m, 2H); 8.28 (d, $J = 8.7$ Hz, 2H); 8.89 (s, 1H). ^{13}C NMR ($CDCl_3$) 60.5; 62.2; 124.0 (2CH); 126.6 (2CH); 129.2; 129.5; 130.5; 130.8; 141.8; 142.2; 142.8; 143.2; 148.2; 150.1. Anal. Calcd for $C_{16}H_{11}N_3O_3$ (293.28): C, 65.53; H, 3.78; N, 14.33. Found: C, 65.59; H, 3.66; N, 14.33. Compound **4b** *cis*-isomer; ^1H NMR ($CDCl_3$) δ 4.56 (d, $J = 4.4$ Hz, 1H); 4.65 (d, $J = 4.4$ Hz, 1H); 7.15 (d, $J = 8.7$ Hz, 2H); 7.25 (d, $J = 8.7$ Hz, 2H); 7.75 (m, 2H); 8.03 (m, 2H); 8.62 (s, 1H). ^{13}C NMR ($CDCl_3$) 59.0; 59.3; 128.1 (2CH); 128.6 (2CH); 128.8; 129.4; 130.0; 130.4; 131.7; 134.1; 141.6; 142.0; 143.0; 149.6. *trans*-Isomer; ^1H NMR ($CDCl_3$) δ 4.23 (d, $J = 1.8$ Hz, 1H); 4.25 (d, $J = 1.8$ Hz, 1H); 7.36 (m, 4H); 7.79 (m, 2H); 8.11 (m, 2H); 8.86 (s, 1H). ^{13}C NMR ($CDCl_3$) 61.2; 61.9; 127.1 (2CH); 128.9 (2CH); 129.1; 129.4; 130.1;130.6; 134.5; 134.7; 141.8; 142.2; 142.6; 150.9. Anal. Calcd for $C_{16}H_{11}ClN_2O$ (282.72): C, 67.97; H, 3.92; N, 9.91. Found: C, 67.91; H, 3.95; N, 9.63. Compound **4c**

cis-isomer; ^{1}H NMR ($CDCl_3$) δ 4.63 (d, $J = 4.4$ Hz, 1H); 4.70 (d, $J = 4.4$ Hz, 1H); 7.46 (m, 4H); 7.74 (m, 2H); 8.02 (m, 2H); 8.66 (s, 1H). ^{13}C NMR ($CDCl_3$) 59.1; 59.4; 123.5; 125.3 (2CH); 126.8; 127.1 (2CH); 129.0; 129.4; 130.1; 130.5; 137.5; 141.5; 142.0; 142.8; 149.8. *trans*-Isomer; ^{1}H NMR ($CDCl_3$) δ 4.27 (d, $J = 1.7$ Hz, 1H); 4.35 (d, $J = 1.7$ Hz, 1H); 7.55 (d, $J = 8.7$ Hz, 2H); 7.66 (d, $J = 8.7$ Hz, 2H); 7.81 (m, 2H); 8.12 (m, 2H); 8.88 (s, 1H). ^{13}C NMR ($CDCl_3$) 61.0; 62.0; 123.7; 125.7 (2CH); 126.1 (2CH); 126.6; 129.1; 129.4; 130.3; 130.7; 139.9; 141.8; 142.2; 142.7; 150.6. Anal. Calcd for $C_{17}H_{11}F_3N_2O$ (316.28): C, 64.56; H, 3.51; N, 8.86. Found: C, 65.13; H, 3.77; N, 8.25. Compound **4d** *cis*-isomer; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H); 4.57 (d, $J = 4.2$ Hz, 1H); 4.62 (d, $J = 4.2$ Hz, 1H); 6.98 (d, $J = 8.7$ Hz, 2H); 7.19 (d, $J = 8.7$ Hz, 2H); 7.71 (m, 2H); 8.01 (m, 2H); 8.60 (s, 1H). ^{13}C NMR ($CDCl_3$) 21.1; 59.2; 60.0; 126.6 (2CH); 128.9; 129.0 (2CH); 129.3; 129.8; 130.0; 130.1; 137.9; 141.6; 141.9; 143.2; 150.3. *trans*-Isomer; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H); 4.22 (d, $J = 1.8$ Hz, 1H); 4.28 (d, $J = 1.8$ Hz, 1H); 7.25 (m, 4H); 7.79 (m, 2H); 8.11 (m, 2H); 8.87 (s, 1H). ^{13}C NMR ($CDCl_3$) 21.2; 61.8; 62.1; 125.7 (2CH); 129.1; 129.3; 129.4 (2CH); 130.0; 130.5; 132.9; 138.7; 141.8; 142.3; 142.5; 151.4. Anal. Calcd for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.34; H, 5.59; N, 10.56. Compound **4e** *cis*-isomer; ^{1}H NMR ($CDCl_3$) δ 4.74 (d, $J = 4.5$ Hz, 1H); 4.80 (d, $J = 4.5$ Hz, 1H); 7.30 (m, 1H); 7.47 (m, 2H); 7.71 (m, 2H); 7.79 (m, 1H); 8.00 (m, 2H); 8.52 (s, 1H). ^{13}C NMR ($CDCl_3$) 58.2; 59.5; 124.0; 125.8; 128.4; 128.6; 129.1; 129.2; 129.5; 129.9; 130.2; 131.5; 131.6; 141.7; 141.9; 142.6; 149.3. *trans*-Isomer; ^{1}H NMR ($CDCl_3$) δ 4.13 (d, $J = 1.6$ Hz, 1H); 4.61 (d, $J = 1.6$ Hz, 1H); 7.48 (m, 1H); 7.65 (m, 2H); 7.79 (m, 3H); 8.13 (m, 2H); 8.87 (s, 1H). ^{13}C NMR ($CDCl_3$) 61.1; 62.0; 124.0; 127.1; 129.4; 129.7; 129.8; 130.3; 130.6; 130.8; 130.9; 131.7; 132.9; 140.9; 141.8; 143.3; 144.1. Anal. Calcd for $C_{17}H_{11}F_3N_2O$ (316.28): C, 64.56; H, 3.51; N, 8.86. Found: C, 64.40; H, 3.72; N, 8.49. Compound **4f** *cis*-isomer;^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H); 4.55 (d, $J = 4.4$ Hz, 1H); 4.70 (d, $J = 4.4$ Hz, 1H); 6.92 (m, 1H); 7.10 (m, 2H); 7.56 (m, 1H); 7.71 (m, 2H); 8.00 (m, 2H); 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$) 18.7; 58.7; 59.5; 125.6; 127.1; 128.2; 128.8; 129.3; 129.7 (2CH); 130.1; 131.3; 136.0; 141.5; 141.9; 142.8; 150.2. *trans*-Isomer; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H); 4.18 (d, $J = 1.9$ Hz, 1H); 4.37 (d, $J = 1.9$ Hz, 1H); 7.22 (m, 3H); 7.39 (m, 1H); 7.80 (m, 2H); 8.12 (m, 2H); 8.90 (s, 1H). ^{13}C NMR ($CDCl_3$) 18.9; 60.2; 61.0; 124.2; 126.3; 128.3; 129.2; 129.4; 130.0; 130.1; 130.5; 134.3; 136.2; 141.9; 142.3; 142.6; 151.5. Anal. Calcd for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 78.23; H, 5.49; N, 10.56. Compound **4g** *cis*-isomer; ^{1}H NMR ($CDCl_3$) δ 4.84 (d, $J = 4.7$ Hz, 1H); 5.03 (d, $J = 4.7$ Hz, 1H); 7.35 (m, 1H); 7.70 (m, 2H); 7.80 (m, 3H); 7.97 (m, 2H); 8.54 (s, 1H). ^{13}C NMR ($CDCl_3$) 58.9; 59.3; 124.5; 127.6; 129.1; 129.2; 129.3; 130.0; 130.3; 132.3; 133.7; 141.6; 141.9; 142.6; 148.0; 149.1. *trans*-Isomer; ^{1}H NMR ($CDCl_3$) δ 4.17 (d, $J = 1.9$ Hz, 1H); 4.93 (d, $J = 1.9$ Hz, 1H); 7.56 (m, 1H); 7.80 (m, 4H); 8.15 (m, 2H); 8.24 (m, 1H); 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$) 59.7; 61.0; 124.9; 127.1; 129.2; 129.3; 129.4; 130.2; 130.6; 133.0; 134.5; 142.0; 142.3; 142.8; 147.6; 150.3. Anal. Calcd for $C_{16}H_{11}N_3O_3$ (293.28): C, 65.53; H, 3.78; N, 14.33. Found: C, 65.68; H, 3.48; N, 13.92.

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