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Original synthesis of α-chloroketones in azaheterocyclic series using TDAE approach

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Abstract—We report herein an original and rapid synthesis of new α-chloroketones in azaheterocyclic series based on TDAE strategy from the reaction between 2-(trichloromethyl)quinoxaline and aromatic aldehydes. This reactivity has been generalized to a quinolinic trichloride.

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 from coming 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[5–7] (see Fig. 1).

α-Haloketones are synthetic intermediates frequently used in the synthesis of organic compounds. Moreover, their preparation generally proceeds via an acid or light initiation for addition of chlorine to ketones.[8] Other methods reported for the preparation of α-chloroketones use copper (II) chloride,[9] trichloroisocyanuric acid,[10] *N*-chlorosuccinimide,[11] sulfuryl chloride,[12] polymer-supported chlorine[13] or *p*-toluene-sulfonyl chloride in basic media.[14]

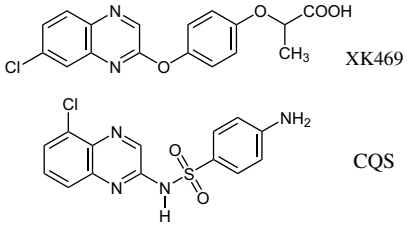
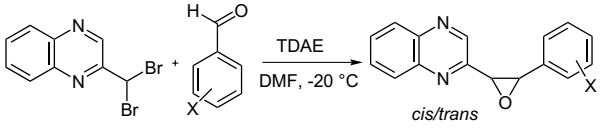


Figure 1. Structures of XK469 and CQS.

On the other hand, we have shown that from *o*- and *p*-nitrobenzyl chloride, Tetrakis(DimethylAmino)Ethylene (TDAE)[15] could generate a nitrobenzyl carbanion which is able to react with various electrophiles as aromatic aldehydes,[16] α-keto esters, diethyl ketomalonate and α-keto lactam derivatives.[17] Recently, we have reported that the reaction of 2-(dibromomethyl)quinoxaline with aromatic aldehydes in the presence of TDAE furnished a mixture of cis/trans isomers of oxiranes (Scheme 1).[18] The formation of these oxiranes may be explained by nucleophilic addition of α-bromo carbanion, formed by action of TDAE with 2-(dibromomethyl)quinoxaline, on carbonyl group of aldehydes followed by an intramolecular nucleophilic substitution.

In continuation of our program directed toward the study of single electron transfer reactions of bioreductive



Scheme 1. Reaction of 2-(dibromomethyl)quinoxaline with aromatic aldehydes.

Keywords: TDAE; 2-(Trichloromethyl)quinoxaline; α-Chloroketones; Aromatic aldehydes.
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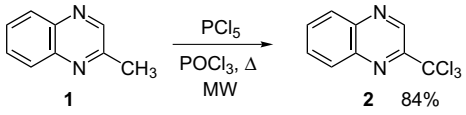
alkylating agents[19] and the preparation of new potentially bioactive compounds as anticancer agents, we report herein an original and efficient synthesis of new azaheterocyclic α-chloroketones based on TDAE strategy from the reaction between 2-(trichloromethyl)quinoxaline **2** and aromatic aldehydes **3a–d**. This reactivity has been generalized to other azaheterocyclic trichlorides.

The 2-(trichloromethyl)quinoxaline **2** was prepared by chlorination of 2-methylquinoxaline **1** using a microwave assisted reaction with a $PCl_5/POCl_3$ mixture in 84% yield[20] (Scheme 2).

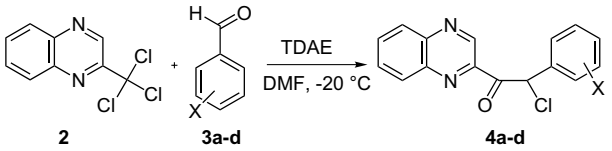
The reaction of 2-(trichloromethyl)quinoxaline **2** with 3 equiv of corresponding aromatic aldehydes **3a–d** in the presence of TDAE at −20 °C for 1 h, followed by 2 h at room temperature led to the unexpected α-chloroketone **4a–d** in moderate to good yields (27–69%) as shown in Scheme 3 and reported in Table 1.[21]

The poor yield (27%) observed with *p*-cyanobenzaldehyde may be explained, as in benzylic series,[22] by the possibility of cyano group to favor other competitive reactions. However, no new product could be isolated.

This TDAE strategy presents the advantage of forming highly functionalized and original α-chloroketones whose access is not easy by classical synthesis methods.[9–14] Moreover, only the formation of α-chloroketone was observed, contrary to the cathodic addition of benzylidene trichloride to aldehyde developed by Steiniger[23] where a mixture of α-chloro- and α-hydroxyketone has been obtained in lower yield. The correct structure of α-chloroketones **4a–d** has been determined by a 2D NMR analysis (HMBC sequence).



Scheme 2. Synthesis of 2-(trichloromethyl)quinoxaline **2**.



Scheme 3. Reaction of **2** with aromatic aldehyde **3a–d**.

Table 1. Reactions of 2-(trichloromethyl)quinoxaline **2** and aromatic aldehydes **3a–d** using TDAE[a]

Aromatic aldehyde	X	α-Chloroketone	Yield (%)[b]
3a	4-Cl	**4a**	60
3b	4-CF_3	**4b**	69
3c	4-CN	**4c**	27
3d	2-CH_3	**4d**	60

[a] All the reactions are performed using 3 equiv of aromatic aldehyde **3a–d**, 1 equiv of trichloride **2** and 1 equiv of TDAE in anhydrous DMF.

[b] % All yields refer to chromatographically isolated pure products and are relative to trichloride **2**.

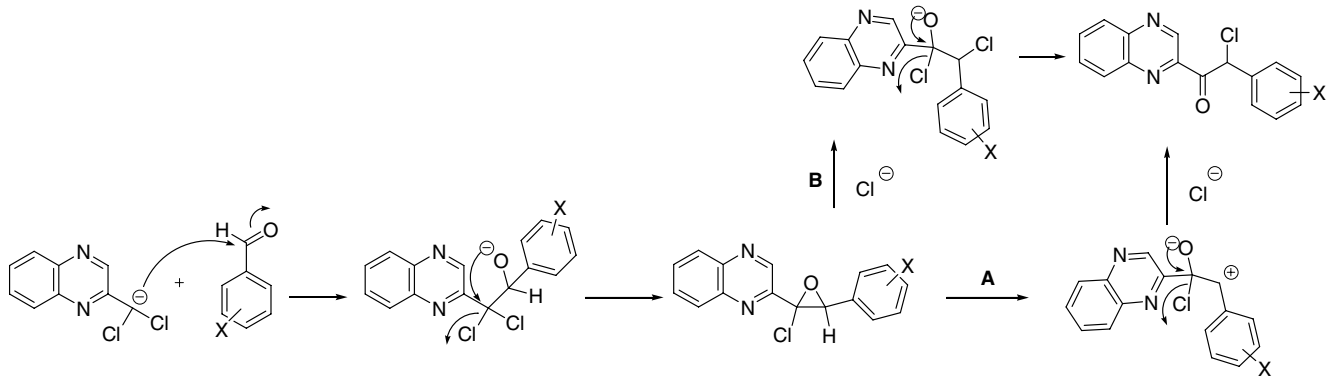
Pertaining to the original formation of α-chloroketones **4a–d**, we could consider the formation of a chloro-oxirane as intermediate according to the mechanism proposed for the formation of oxirane from 2-(dibromomethyl)quinoxaline (Scheme 4).[18] Chloro-oxiranes, and particularly aromatic chloro-oxiranes, are known for their strong instability (at room temperature or by SiO_2 action) leading to α-chloroketones, through an α-carbonyl carbocation (pathway **A**).[24] However, the NMR analyses of crude products, before purification on silicagel column, showing the NMR characteristics of α-chloroketones (**4a–d**) confirm that the purification should not be responsible for the rearrangement.

In other respects, the formation of the α-chloro-ketones could be explained with a second mechanism (pathway **B**) where the chloro-oxirane would be attacked by chloride anion, coming from $TDAECl_2$, leading to the corresponding α-chloroketones after expulsion of the second chlorine atom.

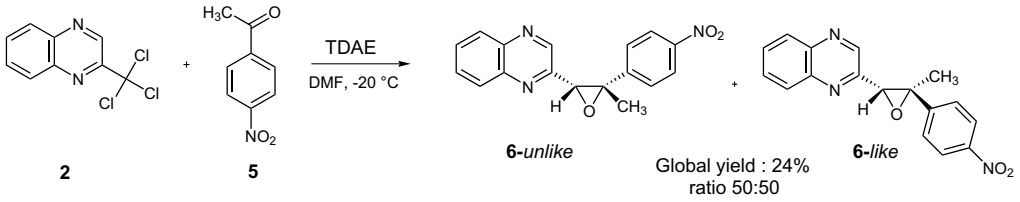
In order to develop this methodology to aromatic ketone as electrophile, we have investigated the reaction of 2-(trichloromethyl)quinoxaline **2** with 3 equiv of *p*-nitroacetophenone **5** in the presence of TDAE. According to the same procedure developed with aldehydes, this reaction led to the diastereomeric non-halogenated oxiranes **6** in 24% yield in the ratio 50:50 (Scheme 5).[25] The **6**-*like* and **6**-*unlike* diastereomers were separated, their configuration was deduced from the known γ-gauche effect, that is, the upfield shift of the ^{13}C NMR resonances of 1,2-*cis* substituents. This characterization relies on the ^{13}C NMR signal for CH_3 of *like*-stereoisomers (17 ppm) being more shielded than the analogous signal for the *unlike*-stereoisomers (25 ppm). The formation of these compounds could be explained by the low reactivity of ketones associated to the high reactivity of $-CCl_3$ group in the presence of TDAE, as shown by Carpenter,[26] leading to the formation of a $-CHCl_2$ group. The non-isolated 2-(dichloromethyl)-quinoxaline reacts with *p*-nitro-acetophenone to form oxirane **6** as shown with 2-(dibromomethyl)quinoxaline.[18]

Moreover, this original reactivity has been generalized to other azaheterocyclic compounds. So, we have prepared the 2-(trichloromethyl)-8-nitroquinoline **8** in 98% yield, according to the same chlorination procedure.[20] In the presence of TDAE and 3 equiv of aromatic aldehyde **3a** or **3e** and in the same experimental conditions, the trichloride **8** has furnished the corresponding α-chloroketones **9a** or **9e**, respectively, in 59 and 37% (Scheme 6).[27]

In conclusion, we have developed in this work an original and rapid synthesis of new α-chloroketones in azaheterocyclic series based on TDAE strategy from the reaction between 2-(trichloromethyl)quinoxaline and aromatic aldehydes. We have proposed an original

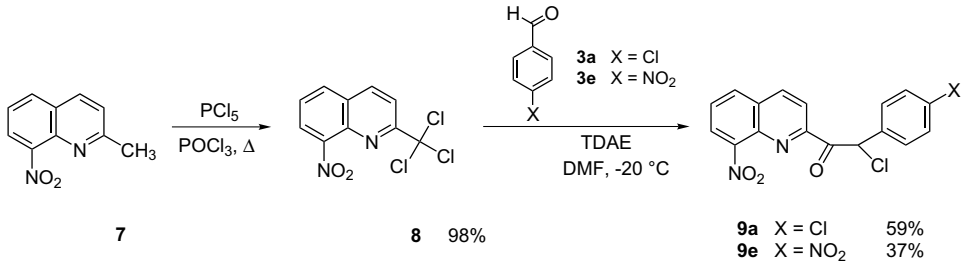


Scheme 4. Formation mechanism of α-chloroketone **4a**–**d**.



2 **5**

Scheme 5. Reaction of **2** with *p*-nitroacetophenone **3a**–**d**.



7 **8** 98%

Scheme 6. Generalization of the reactivity in quinolinic series.

mechanism via a chloro-oxirane as intermediate for the formation of an α-chloroketone. This reactivity has been generalized to another azaheterocyclic nucleus with success. Moreover, an original reactivity has been observed with *p*-nitroacetophenone, as electrophile, leading to a diastereomeric mixture of non-halogenated oxiranes. Attempts to further develop the methodology and increase its scope are currently underway in our laboratory.

Acknowledgements

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21. General procedure for the reaction of 2-(trichloromethyl)-quinoxaline **2** and aromatic aldehydes **3a**–**d**, using TDAE. Into a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet was added, under nitrogen at −20 °C, 10 mL of anhydrous DMF solution of 2-(trichloromethyl)-quinoxaline **2** (0.45 g, 1.5 mmol) and aromatic aldehydes **3a**–**d** (4.5 mmol, 3 equiv). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.3 g, 1.5 mmol). 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 compound **2** was totally consumed. The orange–red turbid solution was filtered (to remove the octamethyl-oxamidinium dichloride) and hydrolyzed with 80 ml of H_2O. The aqueous solution was extracted with chloroform (3 × 40 mL) and the combined organic layers were washed with H_2O (3 × 40 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange oil as crude product. Purification by silica gel chromatography (dichloromethane) and recrystallization from ethanol gave the corresponding α-chloroketone derivatives. New products: Compound **4a**; beige solid; mp 110 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (s, 1H); 7.32 (d, $J = 8.7$ Hz, 2H); 7.58 (d, $J = 8.7$ Hz, 2H); 7.91 (m, 2H); 8.19 (m, 2H); 9.51 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 59.0 (CH); 129.1 (2 × CH); 129.6 (CH); 130.3 (2 × CH); 130.4 (CH); 131.2 (CH); 133.0 (C); 133.8 (C); 135.2 (C); 140.6 (C); 143.8 (CH); 144.1 (C); 144.2 (C); 191.7 (C). Anal. Calcd for $C_{16}H_{10}Cl_2N_2O$: C, 60.59; H, 3.18; N, 8.83. Found: C, 60.48; H, 3.20; N, 8.72. Compound **4b**; orange solid; mp 99 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (s, 1H); 7.62 (d, $J = 8.3$ Hz, 2H); 7.78 (d, $J = 8.3$ Hz, 2H); 7.93 (m, 2H); 8.19 (m, 2H); 9.53 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 58.8 (CH); 123.7 (C); 125.9 (2 × CH); 129.4 (2 × CH); 129.6 (CH); 130.4 (CH); 131.3 (CH); 131.4 (C); 133.1 (CH); 139.3 (C); 140.6 (C); 143.8 (CH); 144.1 (C); 144.3 (C); 191.6 (C). Anal. Calcd for $C_{17}H_{10}ClF_3N_2O$: C, 58.22; H, 2.87; N, 7.99. Found: C, 58.18; H, 2.86; N, 7.87. Compound **4c**; beige solid; mp 144 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.22 (s, 1H); 7.64 (d, $J = 8.5$ Hz, 2H); 7.77 (d, $J = 8.5$ Hz, 2H); 7.93 (m, 2H); 8.19 (m, 2H); 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 58.5 (CH); 113.0 (C); 118.1 (C); 129.7 (CH); 129.8 (2 × CH); 130.3 (CH); 131.4 (CH); 132.6 (2 × CH); 133.2 (CH); 140.4 (C); 140.6 (C); 143.8 (CH); 143.9 (C); 144.3 (C); 191.2 (C). Anal. Calcd for $C_{17}H_{10}ClN_3O$: C, 66.35; H, 3.28; N, 13.65. Found: C, 65.42; H, 3.55; N, 13.47. Compound **4d**; green solid; mp 128 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.76 (s, 3H); 7.18 (m, 3H); 7.38 (m, 2H); 7.86 (m, 2H); 8.12 (m, 2H); 9.53 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5 (CH_3); 58.4 (CH); 126.9 (CH); 128.4 (CH); 129.2 (CH); 129.6 (CH); 130.3 (CH); 131.0 (CH); 131.1 (CH); 132.7 (CH); 134.0 (C); 136.7 (C); 140.7 (C); 143.7 (CH); 144.2 (C); 144.8 (C); 192.7 (C). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.82; H, 4.42; N, 9.34.
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25. Compound **6**-*like*; pink solid, mp 186 °C (ethanol), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65 (s, 3H); 4.25 (s, 1H); 7.67 (d, $J = 8.8$ Hz, 2H); 7.83 (m, 2H); 8.11 (m, 2H); 8.27 (d, $J = 8.8$ Hz, 2H); 8.99 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.0 (CH_3); 63.1 (C); 66.0 (CH); 123.8 (2 × CH); 126.4 (2 × CH); 129.0 (CH); 129.5 (CH); 130.3 (CH); 130.7 (CH); 141.7 (C); 142.3 (C); 143.2 (CH); 147.6 (C); 148.2 (C); 149.8 (C). Compound **6**-*unlike*; pink solid, mp 157 °C (ethanol), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.92 (s, 3H); 4.56 (s, 1H); 7.49 (d, $J = 8.8$ Hz, 2H); 7.74 (m, 2H); 7.98 (m, 2H); 8.03 (d, $J = 8.8$ Hz, 2H); 8.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.0 (CH_3); 64.7 (CH); 65.9 (C); 123.6 (2 × CH); 127.8 (2 × CH); 128.7 (CH); 129.4 (CH); 130.1 (CH); 130.5 (CH); 141.4 (C); 141.9 (C); 142.4 (CH); 144.5 (C); 147.4 (C); 149.8 (C). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 65.65; H, 4.23; N, 13.51.
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27. Compound **9a**; beige solid; mp 190 °C (ethanol), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (s, 1H); 7.30 (d, $J = 8.5$ Hz, 2H); 7.56 (d, $J = 8.5$ Hz, 2H); 7.76 (m, 1H); 8.13 (m, 2H); 8.29 (d, $J = 8.7$ Hz, 1H); 8.42 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 60.4 (CH); 120.8 (CH); 124.7 (CH); 128.0 (CH); 129.1 (2 × CH); 130.2 (C); 130.5 (2 × CH); 131.8 (CH); 134.0 (C); 135.1 (C); 137.9 (CH); 147.5 (C); 148.4 (C); 151.9 (C); 191.5 (C). Anal. Calcd for $C_{17}H_{10}Cl_2N_2O_3$: C, 56.53; H, 2.79; N, 7.76. Found: C, 56.45; H, 2.71; N, 7.52. Compound **9e**; orange solid; mp 151 °C (ethanol), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25 (s, 1H); 7.81 (d, $J = 8.9$ Hz, 2H); 8.14 (m, 3H); 8.18 (d, $J = 8.9$ Hz, 2H); 8.30 (d, $J = 8.6$ Hz, 1H); 8.45 (d, $J = 8.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 59.8 (CH); 120.8 (CH); 124.1 (2 × CH); 124.9 (CH); 128.3 (CH); 130.1 (2 × CH); 130.3 (C); 131.9 (CH); 138.2 (CH); 142.5 (C); 147.9 (C); 148.1 (C); 148.3 (C); 151.5 (C); 191.0 (C). Anal. Calcd for $C_{17}H_{10}ClN_3O_5$: C, 54.93; H, 2.71; N, 11.30. Found: C, 54.92; H, 2.84; N, 11.62.