Tetrahedron 66 (2010) 3405–3409

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Two isolated intermediates of the Tröger's base: synthesis and mechanism

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ARTICLE INFO

Article history:
Received 5 January 2010
Received in revised form
10 March 2010
Accepted 16 March 2010
Available online 20 March 2010

Keywords:
Tröger's base
Intermediates
Synthesis
Mechanism

ABSTRACT

By controlling the amount of catalyst 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride, two new intermediates of Tröger's bases (**11**, 1,6-dimethyl-3-(4-methylphenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate and **12**, 8-methyl-2,5-bis-(4-methylphenyl)-3,5,6,7-tetrahydropyrimido[5,6,1-*ij*]quinazoline-2-ium tetrafluoroborate) were simply obtained from the one-pot reaction of aromatic amine and formaldehyde in ionic liquid at ambient temperature. These results support the mechanism for Tröger's base formation supposed by Fernando Coelho and co-workers. However, the crystal structure of **12** and correlative quantum chemistry calculation results are not reconciled with their report.

1. Introduction

As a class of fascinating molecules,[1] Tröger's bases (TB, 1, Fig. 1) was first synthesized by Julius Tröger in 1887.[2] These relatively simple bicyclic molecules have geometrically rich V-shape, their dissymmetry was resulted from the impossibility of nitrogen inversion. TB chemistry has grown in importance over the years due to their applications in the fields of stereoselective catalysis,[3] recognition phenomena,[4] drug development,[5] bioorganic chemistry[6] and supra-molecular chemistry.[7]

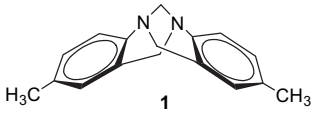

Figure 1. The structure of Tröger's base (**1**).

Generally, TB derivatives are synthesized by heating a mixture of aromatic amine and formaldehyde in absolute ethanol or DMSO in the presence of concentrated hydrochloric or trifluoroacetic acid (TFA).[4b,8–10]

The mechanism of the formation of the TB was firstly studied by Wagner.[11] In these works he assumed that there were four intermediates $[\mathbf{2}+\mathbf{H}]^+$ and **3**–**5** (Scheme 2) in the formation of TB. Intermediate **5** has been, however, questioned by Farrar,[12] who proposed compound **6** as the right structure (Fig. 2). Farrar isolated a byproduct identified as diazajulolidine **7** and thus he proposed **8** as an additional intermediate, which led to **7**.[12] Cooper and

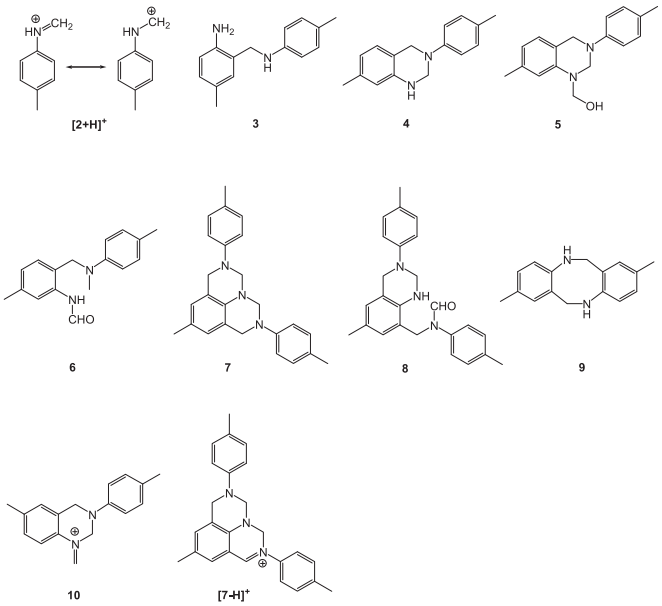

Figure 2. Intermediates ($[\mathbf{2}+\mathbf{H}]^+$, **3**–**5**,[11] **6**–**8**,[12] **9**,[13] $[\mathbf{7}-\mathbf{H}]^+$-**10**[14]) proposed previously.

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doi:10.1016/j.tet.2010.03.057

Partridge[13] demonstrated that Tröger's bases could also be obtained via **9**. Coelho[14] and co-workers used direct infusion electrospray ionization mass and tandem mass spectrometric experiments (ESI-MS/MS) to monitor the formation of Tröger's base from different methylene source (formaldehyde or urotropine) and formaldehyde in neat TFA. When formaldehyde was used, three intermediates $[\mathbf{2}+\mathbf{H}]^+$ (*m*/*z* 120), $[\mathbf{4}-\mathbf{H}]^+$ (*m*/*z* 237), $[\mathbf{5}-\mathbf{H}]^+$ (*m*/*z* 267) were detected via analyzing the main fragment in ESI-MS/MS. When urotropine was used as methylene source, some new intermediates, such as $[\mathbf{4}-\mathbf{3H}]^+$ (*m*/*z* 237) and $[\mathbf{7}-\mathbf{H}]^+$ (*m*/*z* 368) were found (Fig. 2).

However, in all of these proposed intermediates, only **7**[12] and **9**[13] have been isolated. So, it is still significant to obtain new kind of intermediates to study the mechanism during the formation of TB derivatives.

2. Result and discussion

According to our previous experiments, the high active amine could afford the corresponding Tröger's base derivatives via a catalyst-free one-pot procedure.[15] So, there is no way to isolate any intermediates. *p*-Toluidine, an aromatic amine with lower activity was tested subsequently. Unfortunately, there was no reaction taking place in previous reaction conditions.

This problem was solved by using a suitable amount of catalyst 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride, which was synthesized in our lab.[16] Two new intermediates of TB (1,6-dimethyl-3-(4-methylphenyl)-1,4-dihydroquinzoli-3-ium tetrafluoroborate, Fig. 3) (**11**) and (8-methyl-2,5-bis-(4-methylphenyl)-3,5,6,7-tetrahydroprimido [5,6,1-*ij*]quinazoline-2-ium tetrafluoroborate, Fig. 3) (**12**) were obtained in ionic liquid 1-butylpyridiniumtetrafluoroborate ([BPY][BF_4]).

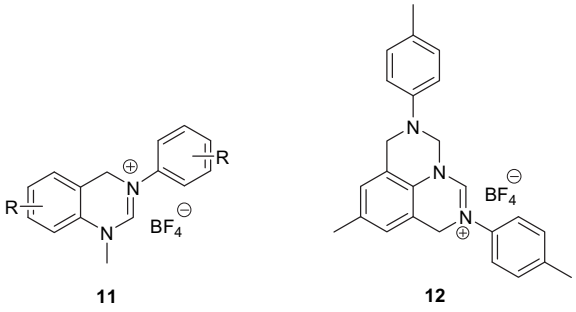
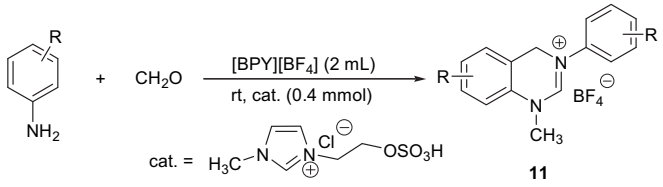


Figure 3. Two new intermediates of Tröger's bases.

Initially, a series of **11** was obtained under the suitable condition (Scheme 1 and Table 1), the X-ray diffraction of **11b** was shown in Figure 4. Subsequently, double amount of catalyst was added into the mixture of *p*-toluidine and formaldehyde, another intermediate **12** was isolated after 48 h in the yield of 60% (Scheme 2 and Fig. 5).

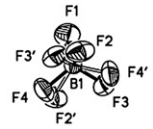


Scheme 1. The synthesis of **11**.

The results in Table 1 indicated that halogen is favourable in the reaction. That mentioned the formation of cation in this procedure. The lone pair electron of halogen can stabilize these cation intermediates and promote their resonance. The explanation will be put forward in the mechanism section.

Table 1
Synthesis of compound **11**

Compound	R	Time (h)	Yield (%)	Mp (°C)
11a	4-CH_3	20	75	194.3–195.5
11b	4-Cl	22	80	182.2–183.4
11c	4-Br	24	95	>300.0
11d	4-F	24	62	>300.0
11e	3-Cl-4-F	23	78	287.9–288.3
11f	3-Cl-4-CH_3	19	93	255.9–257.0



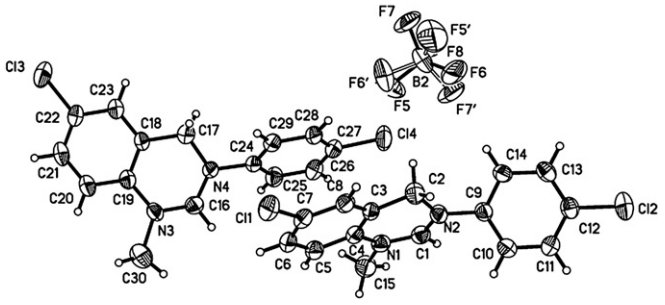
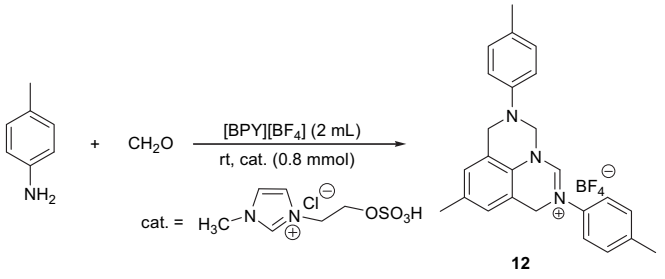


Figure 4. X-ray diffraction of **11b**.



Scheme 2. The synthesis of **12**.

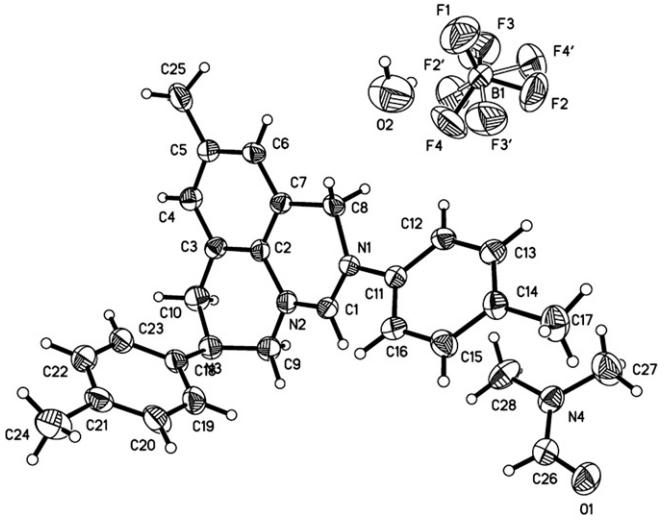


Figure 5. X-ray diffraction of **12**.

Interestingly, as shown in Figure 5, it is clearly that the X-ray diffraction of **12** is different from the structure of $[\mathbf{7}-\mathbf{H}]^+$ (*m*/*z* 368) supposed by Fernando[14] and co-workers (Scheme 2). Theoretically, both of these two structures ($[\mathbf{7}-\mathbf{H}]^+$ and **11**) are possible.

To further support our result, theoretic calculations about the stability of the two compounds were performed. The geometry structures of these two molecules on the potential energy surface were fully optimized using density functional theory with the Becke 3-parameter hybrid exchange[17] and Lee-Yang-Parr[18] correlation density functional (B3LYP) in conjunction with the 6–31 G (d) basis set. The optimized geometry structures of the two possible structure at the B3LYP/6-31 G (d) level are shown in Figure 6. It is clear that in the optimized geometrics of **12**, N–C–N$^+$ can form a stable conjugated system, whereas [**7**−**H**]$^+$ cannot.

Their total energies of [**7**−**H**]$^+$ and **12** are −1131.892157 and −1131.910257 hartree, respectively, which showed that the energy of **12** is 47.52 kJ/mol lower than that of [**7**−**H**]$^+$. Therefore, **12** is the more reasonable structure for the intermediate of TB.

On the basis of our experimental result, a reasonable mechanism for the formation of **12** was outlined in Scheme 3 and Scheme 4. It was considered that **10**, which was detected by Fernando[14] and co-workers by on-line ESI-MS/MS, was a key intermediate in the formation of **11**, **12** and TB. Both of **11** and **12** could give TB by relative resonance or reversible process.

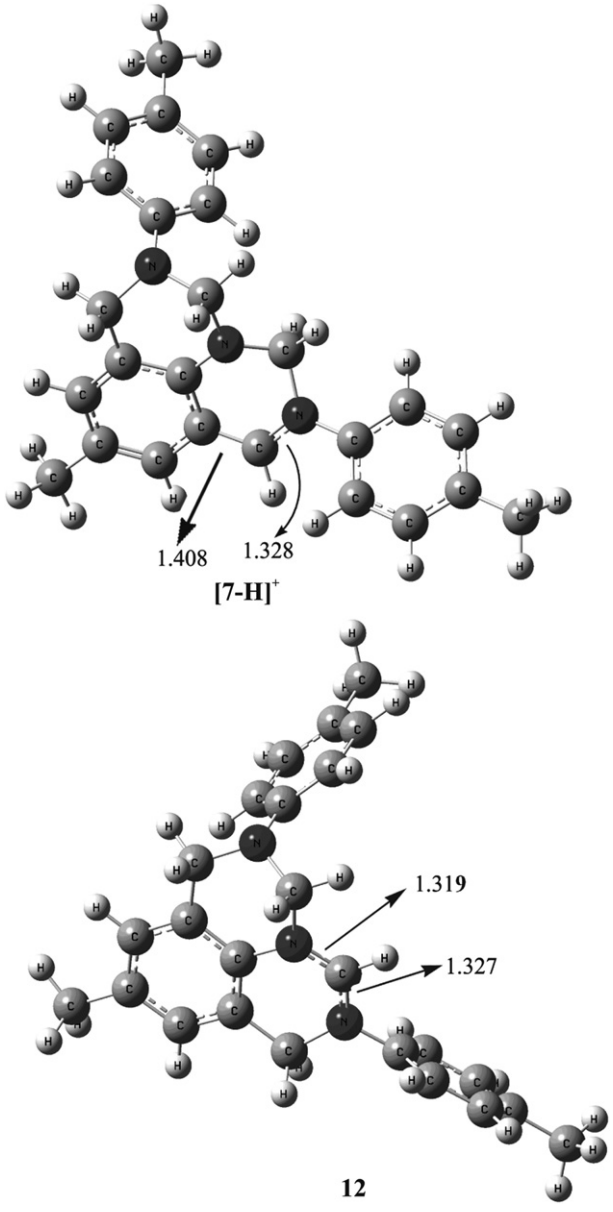
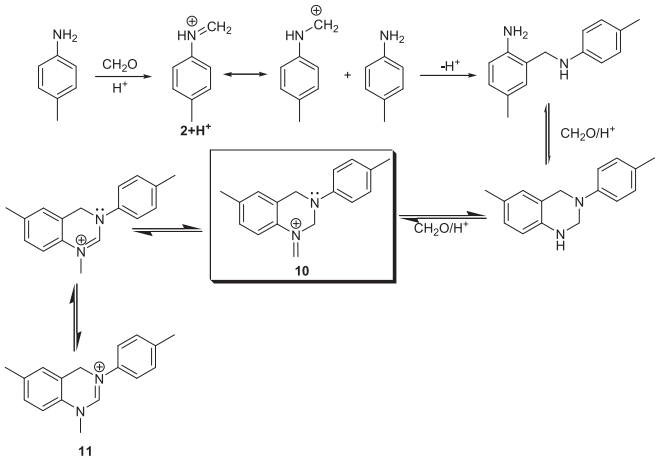
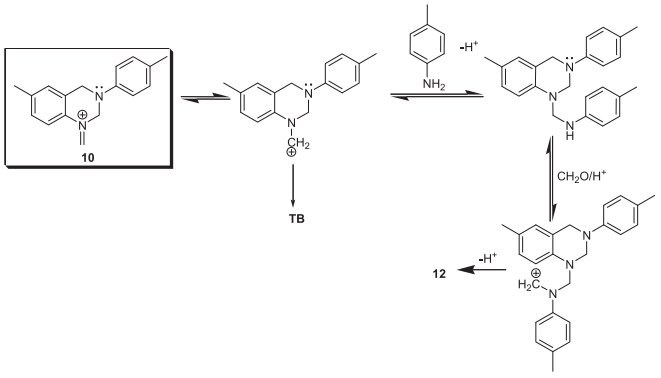


Figure 6. The optimized geometrics of [**7**−**H**]$^+$ and **12** at the B3LYP/6-31 G (d) level.



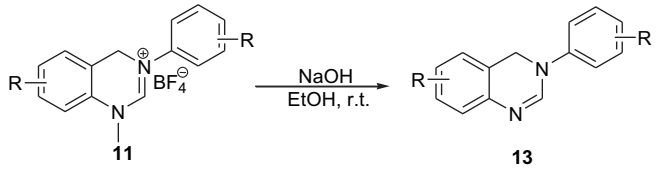
Scheme 3. A possible mechanism for the formation of **11**.



Scheme 4. A possible mechanism for the formation of **12** and **TB**.

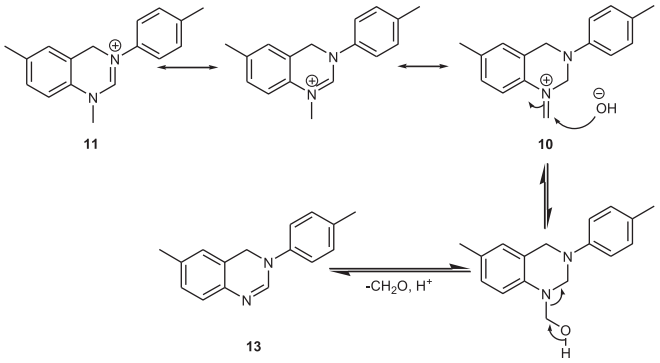
Actually, heating **11a** or **12** at 150 °C for 48 h with more formaldehyde (36–40%, aq 2.0 equiv) and catalyst (0.8 mmol) in ionic liquid [BPY][BF_4] (ca. 4 mL) yield the expected Tröger's base in 33% and 25% yield, respectively.

To further confirm this supposed mechanism, compound **11** was dealt with NaOH in EtOH—the reversible condition of its formation at room temperature. As expected, a new kind of compound 3-aryl-3,4-dihydroquinazolines was easily obtained (Scheme 5, 6 and Table 2). This interesting reaction showed the rationality of the mechanism outlined in Scheme 3 and Scheme 4.



Scheme 5. The synthesis of compound **13**.

3,4-Dihydroquinazoline is an effective substrate to form and stabilize an *N*-heterocyclic Carbene (NHC) tautomer in heterocycle/olefin coupling. For example, Ellman and co-workers[19] selected it to form a Rh–NHC complex to study Rh(I)-mediated heterocycle C–H activation reactions. However, the direct synthesis of 3-aryl-3,4-dihydroquinazolines is underdeveloped. Only three papers have ever reported the synthesis of some analogous framework.[20–22] The discovery may offer the most straightforward route to synthesize 3-aryl-3,4-dihydroquinazolines.



Scheme 6. A possible mechanism for the formation of **13**.

Table 2
Synthesis of compound **13**

Compound	R	Time (h)	Yield (%)	Mp (°C)
13a	4-CH_3	10	65	157.0–159.2
13b	4-Cl	12	75	181.2–183.8
13c	4-Br	12	85	189.3–192.1
13d	4-F	12	30	240.5–243.2
13e	3-Cl-4-F	12	80	170.2–172.6
13f	3-Cl-4-CH_3	9	85	187.4–188.9

3. Conclusion

In summary, by controlling the amount of catalysis 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride, two new intermediates of Tröger's bases (**11**, 1,6-dimethyl-3-(4-methylphenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate and **12**, 8-methyl-2,5-bis-(4-methylphenyl)-3,5,6,7-tetrahydropyrimido-[5,6,1-*ij*]quinazoline-2-ium tetrafluoroborate) were simply obtained from the one-pot reaction of aromatic amine and formaldehyde in ionic liquid at ambient temperature. These results support the mechanism for Tröger's base formation supposed by Coelho and co-workers. However, the crystal structure of **12** and correlative quantum chemistry calculation results are not reconciled with their report. Compound **11** can be easily transform into 3-aryl-3,4-dihydroquinazolines in mild condition. Moreover, these two types of new compounds, which have multi modifiable site can be used as active synthon to synthesize more interesting molecules.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without further purification. NMR spectra were measured in DMSO-d_6 or $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbance were reported in cm^{-1}. Mass spectra were recorded on Bruker TOFMS high resolution mass spectrometer.

The preparation of 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride was according to the reported method.[16]

4.2. General procedure for the synthesis of 11

A mixture of aromatic amine (2.0 mmol), formaldehyde (2.5 mmol) and 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride (0.4 mmol) was stirred in [BPY][BF_4] (2 mL) at room temperature. After 19–24 h reaction, water was added and the precipitate was collected and then purified from 95% EtOH–DMF (10:1) after washed with water three times. The analytical data for represent compound are shown below.

*4.2.1. 1,6-Dimethyl-3-(4-methylphenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11a**).* δ_H (400 MHz, DMSO-d_6) 8.84 (s, 1H, =CH), 7.55 (d, *J* 8.4 Hz, 2H, Ar–H), 7.41 (d, *J* 8.4 Hz, 2H, Ar–H), 7.30–7.32 (m, 2H, Ar–H), 7.14 (s, 1H, Ar–H), 5.26 (s, 2H, $-CH_2$), 3.62 (s, 3H, $-CH_3$), 2.39 (s, 3H, $-CH_3$), 2.34 (s, 3H, $-CH_3$); δ_C (100 MHz, DMSO-d_6) 151.6, 148.1, 144.0, 138.5, 137.7, 130.2, 129.4, 127.4, 125.6, 121.6, 118.6, 116.9, 65.9, 48.9, 37.8; MS [ESI] *m*/*z* for $[C_{17}H_{19}N_2-2]^+$ found 249.1597, requires 249.1543.

*4.2.2. 1-Methyl-6-chloro-3-(4-chlorophenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11b**).* δ_H (400 MHz, DMSO-d_6) 8.94 (s, 1H, =CH), 7.69–7.73 (m, 4H, Ar–H), 7.56 (s, 1H, Ar–H), 7.46 (d, *J* 8.8 Hz, 2H, Ar–H), 5.30 (s, 2H, $-CH_2$), 3.64 (s, 3H, $-CH_3$); δ_C (100 MHz, DMSO-d_6) 152.7, 139.1, 133.2, 132.2, 130.6, 129.8, 129.0, 126.7, 123.8, 121.5, 117.5, 47.8, 37.7; MS [ESI] *m*/*z* for $[C_{15}H_{13}Cl_2N_2]^+$ found 291.0473, requires 291.0456.

Crystal data for **11b**. Empirical formula $C_{15}H_{13}BCl_2F_4N_2$, yellow, crystal dimension 0.37×0.16×0.15 mm, monoclinic, space group *P*2(1)/c, *a*=14.5133 (19) Å, *b*=16.628(3) Å, *c*=13.5067(16) Å, α=90.00°, β=90.171(2)°, γ=90.00°, *V*=3259.4(8) $Å^3$, *Mr*=378.98, *Z*=8, *Dc*=1.545 Mg/m^3, λ=0.71073 Å, μ (Mo K_α)=0.439 mm^{-1}, *F*(000)=1536.0, *S*=1.000, R_1=0.0511, wR_2=0.0719. Crystallographic data for the structures of **11b** reported in this letter have been deposited with the Cambridge Crystallographic Date Centre as supplementary publication No. CCDC-070729a.

*4.2.3. 1-Methyl-6-bromo-3-(4-bromophenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11c**).* δ_H (400 MHz, DMSO-d_6) 8.99 (s, 1H, =CH), 7.85 (d, *J* 8.4 Hz, 2H, Ar–H), 7.70 (d, *J* 8.8 Hz, 1H, Ar–H), 7.63 (d, *J* 8.8 Hz, 2H, Ar–H), 7.57 (s, 1H, Ar–H), 7.39 (d, *J* 8.8 Hz, 1H, Ar–H), 5.31 (s, 2H, $-CH_2$), 3.63 (s, 3H, $-CH_3$); δ_C (100 MHz, DMSO-d_6) 150.0, 139.7, 132.6, 132.0, 129.7, 128.9, 124.3, 124.0, 121.5, 120.8, 119.5, 48.0, 37.9; MS [ESI] *m*/*z* for $[C_{15}H_{13}Br_2N_2+H]^+$ found 381.9509, requires 381.9503.

*4.2.4. 1-Methyl-6-fluoro-3-(4-fluorophenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11d**).* δ_H (400 MHz, DMSO-d_6) 8.88 (s, 1H, =CH), 7.71–7.74 (m, 2H, Ar–H), 7.47–7.51 (m, 3H, Ar–H), 7.34–7.38 (m, 1H, Ar–H), 7.24 (d, *J* 8.8 Hz, 1H, Ar–H), 5.30 (s, 2H, $-CH_2$), 3.63 (s, 3H, $-CH_3$); δ_C (100 MHz, DMSO-d_6) 162.8, 162.2, 159.7, 152.4, 136.8, 128.2, 124.6, 121.9, 117.9, 116.8, 115.9, 114.2, 89.6, 48.4, 37.8; MS [ESI] *m*/*z* for $[C_{15}H_{13}F_2N_2-2H]^+$ found 257.0786, requires 257.0879.

*4.2.5. 1-Methyl-5-chloro-6-fluoro-3-(3-chloro-4-fluorophenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11e**).* δ_H (400 MHz, DMSO-d_6) 8.95 (s, 1H, =CH), 8.10–8.16 (m, 1H, Ar–H), 7.61–7.80 (m, 3H, Ar–H), 7.47–7.50 (m, 1H, Ar–H), 5.34 (s, 2H, $-CH_2$), 3.65 (s, 3H, $-CH_3$); δ_C (100 MHz, DMSO-d_6) 153.1, 152.6, 137.2, 128.9, 125.5, 123.8, 123.2, 120.6, 118.4, 117.8, 116.1, 115.5, 89.1, 47.9, 37.6; MS [ESI] *m*/*z* for $[C_{15}H_{11}Cl_2F_2N_2+H]^+$ found 328.0336, requires 328.0340.

*4.2.6. 1-Methyl-5-chloro-6-methyl-3-(3-chloro-4-methylphenyl)-1,4-dihydroquinazolin-3-ium tetrafluoroborate (**11f**).* δ_H (400 MHz, $CDCl_3$) 8.48 (s, 1H, =CH), 7.52–7.54 (m, 2H, Ar–H), 7.46–7.48 (m, 1H, Ar–H), 7.37 (d, *J* 8.4 Hz, 1H, Ar–H), 7.08 (d, *J* 8.0 Hz, 1H, Ar–H), 5.20 (s, 2H, $-CH_2$), 3.78 (s, 3H, $-CH_3$), 2.45 (s, 3H, $-CH_3$), 2.43 (s, 3H, $-CH_3$); δ_C (100 MHz, $CDCl_3$) 151.9, 139.3, 136.5, 135.9, 134.0, 132.1, 131.4, 122.8, 120.9, 117.9, 114.1, 47.5, 46.9, 38.2, 19.4; MS [ESI] *m*/*z* for $[C_{17}H_{17}Cl_2N_2]^+$ found 320.0874, requires 320.0847.

4.3. The procedure for the synthesis of 12

A mixture of *p*-toluidine (2.0 mmol), formaldehyde (2.5 mmol) and 1-methyl-3-(2-(sulfooxy)ethyl)-1*H*-imidazol-3-ium chloride (0.8 mmol) was stirred in [BPY][BF_4] (2 mL) at room temperature

for 48 h. The following procedure was same as the preparation of **11**, **12** was obtained in 60% yield.

*4.3.1. 8-Methylphenyl-3,5,6,7-tetrahydropyrimido[5,6,1-ij]quinazoline-2-ium tetrafluoroborate (**12**).* δ_H (400 MHz, DMSO-d_6) 8.95 (s, 1H, =CH), 7.52 (d, *J* 8.4 Hz, 2H, Ar–H), 7.42 (d, *J* 8.4 Hz, 2H, Ar–H), 7.16 (s, 1H, Ar–H), 7.09 (d, *J* 8.8 Hz, 2H, Ar–H), 7.05 (d, *J* 8.8 Hz, 2H, Ar–H), 6.95 (s, 1H, Ar–H), 5.56 (s, 2H, $-CH_2$), 5.21 (s, 2H, $-CH_2$), 4.76 (s, 2H, $-CH_2$), 2.38 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$), 2.19 (s, 3H, $-CH_3$); MS [ESI] *m*/*z* for $[C_{25}H_{26}N_3+H]^+$ found 369.2235, requires 369.2205.

Crystal data for **12**. Empirical formula $C_{56}H_{68}B_2F_8N_8O_3$, colourless, crystal dimension 0.50×0.44×0.42 mm, monoclinic, space group *C*2/c, *a*=19.1132(19) Å, *b*=10.1581(10) Å, *c*=28.007(2) Å, α=90.00°, β=91.069(2)°, γ=90.00°, *V*=5436.7(9) Å^3, *Mr*=1074.80, *Z*=4, *Dc*=1.313 Mg/m^3, λ=0.71073 Å, μ (Mo K_α)=0.100 mm^{-1}, *F*(000)=2264.0, *S*=1.018, R_1=0.0626, wR_2=0.2198. Crystallographic data for the structures of **12** reported in this letter have been deposited with the Cambridge Crystallographic Date Centre as supplementary publication No. CCDC-080319f.

4.4. The preparation of TB form 11a and 12

Heating **11a** or **12** at 150 °C for 48 h with more formaldehyde (36–40%, aq 2.0 equiv) and catalyst (0.8 mmol) in ionic liquid [BPY][BF_4] (ca. 4 mL) yield the expected Tröger's base in 33% and 25% yield, respectively.

4.5. The procedure for the synthesis of 13

Added NaOH (0.2 mmol) in the anhydrous ethanol (5 mL) solution of **11** (2.0 mmol), then stirred the mixture at room temperature. After 9–12 h reaction, collected and purified the precipitate from anhydrous EtOH to afford **13**.

*4.5.1. 3,4-Dihydro-6-methyl-3-p-tolylquinazoline (**13a**).* δ_H (400 MHz, DMSO-d_6) 7.49 (s, 1H, =CH), 7.02 (d, *J* 8.8 Hz, 1H, Ar–H), 6.93 (d, *J* 8.8 Hz, 1H, Ar–H), 6.91 (s, 1H, Ar–H), 6.89 (d, *J* 8.4 Hz, 2H, Ar–H), 6.13 (d, *J* 8.4 Hz, 2H, Ar–H), 4.92 (s, 2H, $-CH_2$), 2.35 (s, 3H, $-CH_3$), 2.32 (s, 3H, $-CH_3$); MS [ESI] *m*/*z* for $[C_{16}H_{16}N_2]^+$ found 236.1301, requires 236.1313.

*4.5.2. 6-Chloro-3-(4-chlorophenyl)-3,4-dihydroquinazoline (**13b**).* δ_H (400 MHz, DMSO-d_6) 7.48 (s, 1H, =CH), 7.12(s, 1H, Ar–H), 6.88 (s, 1H, Ar–H), 6.80 (d, 1H, Ar–H), 6.75 (d, *J* 8.8 Hz, 2H, Ar–H), 6.41 (d, *J* 8.8 Hz, 2H, Ar–H), 4.92 (s, 2H, $-CH_2$); MS [ESI] *m*/*z* for $[C_{14}H_{10}C_{l2}N_2]^+$ found 276.0201, requires 276.0221.

*4.5.3. 6-Bromo-3-(4-chlorophenyl)-3,4-dihydroquinazoline (**13c**).* δ_H (400 MHz, DMSO-d_6) 7.86 (d, *J* 8.8 Hz, 2H, Ar–H), 7.53 (d, *J* 8.4 Hz, 2H, Ar–H), 7.51 (s, 1H, =CH), 7.20 (s, 1H, Ar–H), 7.18 (d, *J* 8.4 Hz, 1H, Ar–H), 7.05 (d, *J* 8.4 Hz, 1H, Ar–H), 4.95 (s, 2H, $-CH_2$); MS [ESI] *m*/*z* for $[C_{14}H_{10}Br_2N_2]^+$ found 363.9201, requires 363.9211.

*4.5.4. 6-Fluoro-3-(4-chlorophenyl)-3,4-dihydroquinazoline (**13d**).* δ_H (400 MHz, DMSO-d_6) 7.49 (s, 1H, =CH), 7.12 (d, *J* 8.4 Hz, 1H, Ar–H), 6.82 (s, 1H, Ar–H), 6.72 (d, *J* 8.8 Hz, 1H, Ar–H), 6.75 (d, *J* 8.4 Hz, 2H, Ar–H), 6.41 (d, *J* 8.4 Hz, 2H, Ar–H), 4.91 (s, 2H, $-CH_2$); MS [ESI] *m*/*z* for $[C_{14}H_{10}F_2N_2]^+$ found 244.0803, requires 244.0812.

*4.5.5. 7-Chloro-3-(3-chloro-4-fluorophenyl)-6-fluoro-3,4-dihydroquinazoline (**13e**).* δ_H (400 MHz, DMSO-d_6) 7.38 (s, 1H, =CH), 7.21–7.26 (m, 2H, Ar–H), 7.10–7.04 (m, 3H, Ar–H), 4.93 (s, 2H, $-CH_2$); MS [ESI] *m*/*z* for $[C_{16}H_8Cl_2F_2N_2]^+$ found 312.0021, requires 312.0033.

*4.5.6. 7-Chloro-3-(3-chloro-4-methylphenyl)-3,4-dihydro-6-methylquinazoline (**13f**).* δ_H (400 MHz, DMSO-d_6) 7.47 (s, 1H, =CH), 7.27–7.25 (m, 2H, Ar–H), 7.19 (s, 1H, Ar–H), 7.14 (s, 1H, Ar–H), 6.84 (s, 1H, Ar–H), 4.92 (s, 2H, $-CH_2$), 2.37 (s, 3H, $-CH_3$), 2.33 (s, 3H, $-CH_3$); MS [ESI] *m*/*z* for $[C_{16}H_{14}Cl_2N_2]^+$ found 304.0521, requires 304.0534.

Acknowledgements

We are grateful to the 'National Natural Sciences Foundation of China' (No. 20772103), 'Natural Sciences Foundation of Xuzhou Normal University' (No. 09XLA17), and the 'Qin Lan Project in Jiangsu Province' (No. QL200607, 08QLT001) for financial support.

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