Rapid in situ generation of benzene diazonium ions under basic aqueous conditions from bench-stable triazabutadienes

Jie He, Flora W. Kimani, John C. Jewett*

Table of Contents

General Procedures .......................................................... 2
Synthesis .......................................................................... 2
Degradation test in aqueous buffers ........................................... 5
NOESY Experiments .......................................................... 12
References ....................................................................... 16
NMR spectra .................................................................... 17
**General Procedures**

All reactions were performed under an argon atmosphere, with the flasks oven dried and cooled in a vacuum oven prior to use. All compounds and solvents were commercially obtained and used as received. $^1$H and $^{13}$C NMR data was acquired on Bruker AVIII-400, DRX-500 or DRX-600 and referenced with residual solvent peaks; CDCl$_3$ 7.26 ppm and 77.0 ppm; DMSO-$d_6$ 2.49 ppm and 39.5 ppm; MeOD 4.87 ppm and 49.0 ppm; D$_2$O 4.80 ppm. Coupling constants are expressed in hertz and abbreviations for multiplicities given as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets, and m = multiplet where applicable. Mass spectral analysis was performed on a Bruker ICR ESI.

**Synthesis**

Compounds 1 and 3 were synthesized according to our previously published methods.$^1$ The general synthetic route of compounds 2 and 4 is summarized in Scheme S1.

**Scheme S1.** Synthetic route of compounds 2 and 4.

3-(1-(tert-butyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate (S2a)

*Tert*-butylamine (1.46 g, 20 mmol) was dissolved in 5 mL methanol in round bottom flask and with stirring 2.94 mL (20 mmol) of glyoxal solution in water (40% w/w) was added. After a few minutes, a yellow sticky solid formed to which 2.14 g (40 mmol) of ammonium chloride and 3.2 mL formaldehyde (37% wt in water)
were added and the resulting mixture was diluted with 40 mL methanol. The mixture was then refluxed for 1 h before 2.8 mL of phosphoric acid (85% wt in water) was added dropwise. The reaction was stirred at reflux overnight. Solvent was removed under vacuum and residue was poured into 30 g ice. The aqueous mixture was neutralized with 40% KOH to pH 9 and extracted with dichloromethane. The organic layer was separated, dried and concentrated to give crude product, which was then dissolved in 20 mL toluene and 1.4 equiv. of 1,3-propane sultone and the reaction mixture was refluxed for 16 h. An off-white precipitate was observed and on cooling, was isolated as the product (67%). $^1$H NMR (500 MHz, DMSO-d$_6$) δ 9.27 (1H, t, $J = 1.7$ Hz), 8.01 (1H, t, $J = 1.9$ Hz), 7.86 (1H, t, $J = 1.8$ Hz), 4.28 (2H, t, $J = 7.1$ Hz), 2.46 – 2.38 (2H, m), 2.18 – 2.06 (2H, m), 1.59 (9H, s). $^{13}$C NMR (125 MHz, DMSO-d6) δ 135.1, 123.1, 120.6, 59.8, 48.5, 48.1, 29.5, 26.7. HRMS C$_{10}$H$_{16}$N$_2$O$_3$S [M+H$^+$]: calculated: 247.11109, measured: 247.1111.

3-(1-(4-bromo-2,6-dimethylphenyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate (S2b)

4-bromo-2,6-dimethylaniline (4 g, 20 mmol) was dissolved in 5 mL methanol in round bottom flask and with stirring 2.94 mL (20 mmol) of glyoxal solution in water (40% w/w) was added. After a few minutes, a yellow sticky solid formed to which 2.14 g (40 mmol) of ammonium chloride and 3.2 mL formaldehyde (37% wt in water) were added and the resulting mixture was diluted with 40 mL methanol. The mixture was then refluxed for 1 h before 2.8 mL of phosphoric acid (85% wt in water) was added dropwise. The reaction was stirred at reflux overnight. Solvent was removed under vacuum and residue was poured into 30 g ice. The aqueous mixture was neutralized with 40% KOH to pH 9 and extracted with dichloromethane. The organic layer was separated, dried and concentrated to give compound S1b as light brown solid (50%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 7.69 (1H, dd, $J = 1.2$, 1.0 Hz), 7.53 – 7.48 (2H, m), 7.24 (1H, t, $J = 1.3$ Hz), 7.14 (1H, dd, $J = 1.2$, 1.0 Hz), 1.97 (6H, t, $J = 0.7$ Hz).

To a round bottom flask, S1b (2.5 g, 9.96 mmol) and 1,3-propane sultone (1.8 g, 14.9 mmol) were added which was followed by the addition of 100 mL toluene. The mixture was then brought to reflux overnight. After cooling down to room temperature, precipitate was filtered and washed with ether to give white solid
(54%). Product was used for the next step without further purification. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.41 (1H, t, $J = 1.6$ Hz), 8.13 (1H, dd, $J = 2.0, 1.5$ Hz), 7.95 (1H, t, $J = 1.8$ Hz), 7.62 (2H, t, $J = 0.7$), 4.44 (2H, t, $J = 7.0$ Hz), 2.46 (2H, t, $J = 7.0$ Hz), 2.22 (2H, quint, $J = 7.0$ Hz), 2.08 (6H, s).

3-((Z)-3-(tert-butyl)-2-((E)-phenyltriaz-2-en-1-ylidene)-2,3-dihydro-1H-imidazol-1-yl)propane-1-sulfonate (2)

To a solution of $S2a$ (211 mg, 0.86 mmol) in 10 mL THF, azidobenzene (102 mg, 0.86 mmol) was added in THF solution (1 M). The mixture was stirred for 5 min in an ice bath. Then potassium tert-butoxide (192 mg, 1.72 mmol) was added in one portion. The mixture was slowly allowed to warm up to room temperature and stirred overnight. Reaction mixture was filtered through a plug of celite and solvent was removed under vacuum to give the product as yellow solid (25%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.35 – 7.30 (4H, m), 7.09 (1H, d, $J = 2.7$ Hz), 7.08 (1H, m), 6.96 (1H, d, $J = 2.6$ Hz), 4.24 (2H, t, $J = 6.7$ Hz), 2.40 – 2.36 (2H, m), 2.04 – 2.01 (2H, m), 1.63 (9H, s). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 152.6, 150.8, 128.8, 124.5, 120.1, 117.1, 112.9, 57.5, 48.4, 47.8, 28.2, 26.0. HRMS C$_{16}$H$_{22}$N$_5$O$_3$S [M-H$^-$]: calculated: 364.14434, measured: 364.14481.

3-((E)-3-(4-bromo-2,6-dimethylphenyl)-2-((E)-phenyltriaz-2-en-1-ylidene)-2,3-dihydro-1H-imidazol-1-yl)propane-1-sulfonate (4)

To a solution of $S2b$ (200 mg, 0.54 mmol) in 10 mL THF, azidobenzene (102 mg, 0.86 mmol) was added in THF solution (1 M). The mixture was stirred for 5 min in an ice bath. Then potassium tert-butoxide (192 mg, 1.72 mmol) was added in one portion. The mixture was slowly allowed to warm up to room temperature and stirred overnight. Reaction mixture was filtered through a plug of celite and solvent was removed under vacuum to give the product as yellow solid (53%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.47 (2H, s), 7.32 (1H, d, $J = 2.5$ Hz), 7.09 (2H, dd, $J = 8.3, 7.2$ Hz), 7.02 – 6.97 (1H, m), 6.87 (1H, d, $J = 2.5$ Hz), 6.51 – 6.38 (2H, m), 4.06 (2H, t, $J = 7.1$ Hz), 2.50 – 2.47 (2H, m), 2.07 – 2.05 (2H, m), 1.97 (6H, s). $^{13}$C NMR
Degradation test in aqueous buffers

All the tests were done in triplicate experiments. Empty NMR tubes were charged with different triazabutadienes (10 µmol), to which 0.5 mL aqueous buffers (pre-mixed with 10% D$_2$O) were added to initial the reaction. For pH 6, 7, 8 and 9, 0.1 M sodium phosphate buffers were used. For pH 10 and 11, 0.1 M borate buffers were used. $^1$H NMR experiments at pH 6 to 9 were taken at 2, 4, 8, 16, 32 and 64 (if necessary) minutes (Figure S1 to S5); experiments at pH 10 (Figure S6) were taken at 0.5, 18 and 72 hours; experiments at pH 11 (Figure S7) were taken at 1, 24, 96 hours. Characteristic peaks of each compound were followed (in both starting materials and products) to calculate the remaining concentrations of starting materials. For the comparison experiment of compound 1 and compound 4, an empty NMR tube was charged with 10 µmol of each compound and the rest procedure was the same as described above (Figure S5).
Figure S1. Degradation curves of compound 1 at different pH values. For pH 7, see ref 1.
Figure S2. Degradation curves of compound 2 at different pH values.
Figure S3. Degradation curves of compound 3 at different pH values.
Figure S4. Comparison of compounds 2 and 3 at pH 10

Figure S5. Comparison of compounds 2 and 3 at pH 11
**Figure S6.** Degradation curves of compound 4 at pH 6.

**Figure S7.** Degradation curves of compound 4 at pH 7.
Figure S8. Comparison of compounds 1 and 4 at pH 6 and 7
NOESY Experiments

Triazabutadienes were dissolved in DMSO-\textit{d}_6. NMR spectra were collected at 25 °C using a Bruker DRX-600 spectrometer at 600.13 MHz equipped with a 5 mm Nalorac H-C-N Z-axis gradient probe. NOESY spectra in TPPI quadrature detection mode were recorded with 512 real data points in the t1 dimension and 4k real data points in t2 dimension. NOESY experiments mixing time was set to 600 ms. The spectrum width was 7 ppm centered at 4.5 ppm. The number of scans was 8 and the relaxation delay was 1 s. The chemical shifts were referenced to DMSO solvent peak (2.49 ppm). Data were processed using XWINNMR and analyzed with the software MestReNova. Cross peaks of interest were integrated according to their peak volume on NOESY spectrum. All values were normalized by concentration difference (peaks from different molecules). NOE cross peaks of interest (Figure S8² to S11) are shown below (integration values are shown in blue numbers).
Figure S9. NOESY spectrum of 1
Figure S10. NOESY spectrum of 2
Figure S11. NOESY spectrum of 3
Figure S12. NOESY spectrum of 4

References:

NMR spectra

Spectrum 1. $^1$H NMR of Compound 1
Spectrum 2. $^1$H NMR of Compound 2
Spectrum 3. $^1$H NMR of Compound 3
Spectrum 4. $^1$H NMR of Compound 4
Spectrum 5. $^{13}$C NMR of compound 1
Spectrum 6. $^{13}$C NMR of Compound 2
Spectrum 7. $^{13}$C NMR of Compound 3
Spectrum 8. $^{13}$C NMR of Compound 4