Catalytic Reduction of *ortho*- and *para*-Azidonitrobenzenes via *tert*-Butoxide Ion Mediated Electron Transfer

James Burnley, Giorgio Carbone, John E. Moses*

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK
Fax +44(115)9513533; E-mail: john.moses@nottingham.ac.uk

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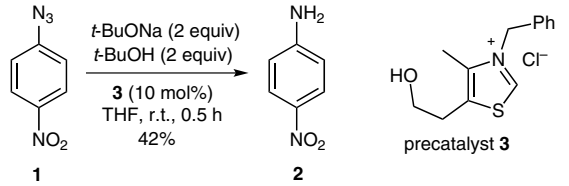
Abstract: The reduction of a range of substituted azidonitrobenzene derivatives to the corresponding aniline is described. The chemoselective reaction proceeds cleanly and in good yield, generating minimal waste products. The process involves a thiazolium salt derived species which is proposed as a radical anion relay, with *tert*-butoxide as the stoichiometric reductant.

Key words: azide, reduction, *tert*-butoxide, electron transfer, N-heterocyclic carbene

The organic azide is a versatile functional group demonstrating a wealth of diverse reactivity.[1] Despite some reservations about their safe handling and stability,[2] the recent advent of 'click chemistry'[3] has led to a huge revival in the use of organic azides, particularly in the areas of bioconjugation,[4] materials science,[5] and drug discovery.[6] Although their chemistry has been well studied in the most part,[1–7] much scope remains for future development of organic azides, particularly in radical-based reactions.[7] Building upon our interests in this field,[8] we report here a new method for the catalytic reduction of nitroaromatic azides to the corresponding nitroaniline.

The reduction of aromatic azides is a well-documented transformation and can be achieved using numerous methods,[2] including photocatalysis,[9] electrochemistry,[10] through catalytic hydrogenation,[11] and hydride-promoted reductions such as $LiAlH_4$,[12] $NaBH_4$,[13] tributyltin hydride,[14] and triethylsilane.[15] However, aside from the classic Staudinger reaction,[16] few methods offer the level of chemoselectivity that is desired in modern organic chemistry.

In the course of studying the chemistry of aromatic azides with N-heterocyclic carbene species, we made the serendipitous observation that in the presence of thiazolium salt **3**, the *tert*-butoxide ion apparently functions as a selective reducing agent for the azido group of *para*-azidonitrobenzene (**1**, Scheme 1). In our original reaction conditions, treatment of *para*-azidonitrobenzene (**1**) with two equivalents of sodium *tert*-butoxide, two equivalents of *tert*-butanol, and 10 mol% of the thiazolium salt in THF at room temperature over 30 minutes afforded aniline **2** in 42% isolated yield (Scheme 1). In order to rationalise the underpinning details of the reaction, a number of key experiments were subsequently performed.



Scheme 1 Original reaction conditions

A review of the literature revealed that nitrobenzene (**4**) reacts with the *tert*-butoxide ion in THF to produce the corresponding butoxynitrobenzene **7**. Details about the mechanism of this formal nucleophilic aromatic substitution reaction (S_NAr) were provided by Guthrie et al.,[17] who demonstrated that an electron-transfer process was in operation (Scheme 2). In the first instance, nucleophilic attack of the *tert*-butoxide ion onto the nitrobenzene **4** leads to the *para*-addition product **5**, which itself reacts with a second equivalent of *tert*-butoxide ion to give the corresponding dianion **6**.[18] The subsequent formation of the butoxynitrobenzene **7** occurs through a two electron-transfer process, with concomitant formation of two equivalents of the nitrobenzene radical anion **8** (Scheme 2).[19]

Whereas **8** is an electron sink in the overall transformation, the corresponding reaction with 1-azido-4-nitrobenzene (**1**) might proceed via the intermediate dianion **9** (cf. **6**) which, through the loss of nitrogen and double protonation, would, in principle, deliver the corresponding aniline **2** directly (Scheme 2). Indeed, this hypothesis was supported by the fact that *tert*-butoxide ion itself can serve as a single-electron donor.[17a]

A further investigation of this transformation involved the addition of two equivalents of sodium *tert*-butoxide and two equivalents of *tert*-butanol to the azide **1**, in a solution of THF at room temperature without the use of the thiazolium catalyst (0.5 h). The mildly exothermic reaction, which evolved a gas, immediately turned dark brown; analysis of the crude reaction mixture indicated that a small quantity of aniline **2** had indeed been formed, although the unreacted starting material **1** was predominant (Scheme 3).

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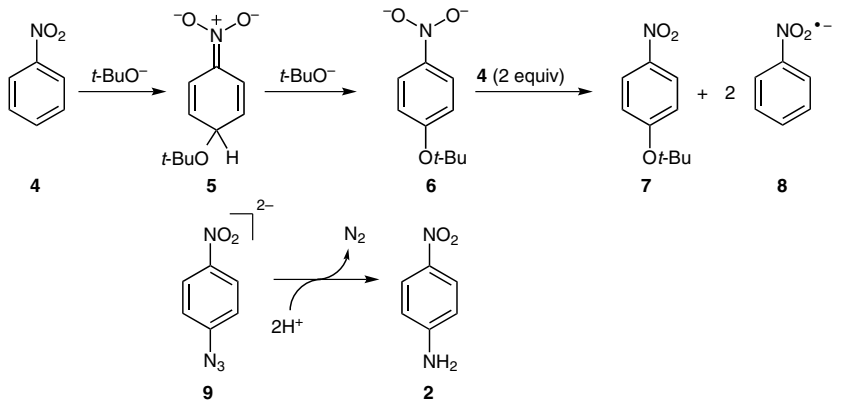
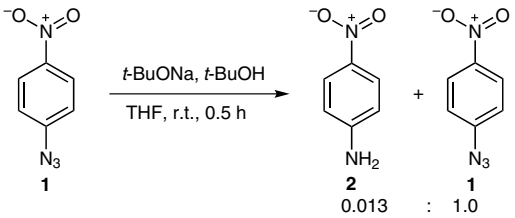


Scheme 2 Mechanism of the electron-transfer reaction of nitrobenzene (**4**) with *tert*-butoxide ion and proposed reduction of azidonitrobenzene **9** via electron transfer.



Scheme 3 Experiment performed using 2 equiv of both *tert*-butoxide and *tert*-butanol. The **2**/**1** ratio was determined by ^{1}H NMR spectroscopy of the crude mixture.

However, under strictly aprotic conditions, product **2** was not obtained at room temperature over a period of 30 minutes (Table 1, entries 1 and 2).

When the reaction was performed in the presence of two equivalents of *tert*-butanol, a low but detectable yield of the aniline **2** was observed; using just one equivalent of sodium *tert*-butoxide over a period of 30 minutes did not lead to any detectable product (Table 1, entries 3 and 4).

Prolonging the reaction period to 16 hours in the presence of both two equivalents of *tert*-butanol and sodium *tert*-butoxide, resulted in a dramatic increase in yield (84%) of aniline **2** (Table 1, entry 5). Under otherwise identical conditions except with only one equivalent of sodium *tert*-butoxide, the yield dropped significantly to 34% (Table 1, entry 6). Heating azide **1** in THF at 50 °C lead to the recovery of unreacted starting material (Table 1, entry 7); in the presence of two equivalents of *tert*-butanol and sodium *tert*-butoxide at 50 °C, a significant increase in the rate of formation of the aniline **2** over a period of 30 minutes was observed (78%, Table 1 entry 8, cf. entry 4).

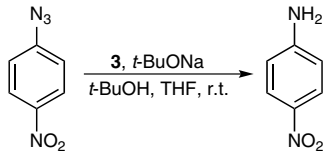
The function of the thiazolium salt was unclear since the azide reduction occurred, albeit sluggishly, in its absence. This led us to consider a possible catalytic role for the thiazolium salt, which would explain the increased rate at room temperature. In fact, it has been reported that certain thiazolium salts in combination with a suitable base can catalyse electron-transfer reduction processes.[20] Thus, when 10 mol% of thiazolium salt **3** was introduced to a reaction with two equivalents of both sodium *tert*-butoxide and *tert*-butanol, a significant increase in the yield (42%) of aniline **2** was observed after 30 minuts as compared to the control reaction (Table 1 entry 9, cf. entry 4). As previously observed, when only one equivalent of sodium *tert*-butoxide was used over 16 hours a low 28% yield of **2** was obtained (Table 1 entries 6 and 10). Increasing the reaction time to five hours the aniline product could be isolated in an excellent 88%, supporting the proposal of **3** in a catalytic role (Table 1, entry 11).

We next examined the scope of the reaction with a range of functionalised azidonitrobenzenes. Gratifyingly, the *ortho*-substituted azidonitrobenzene **10** underwent reduction delivering an excellent 94% yield (Table 2, entry 2). However, both the *meta*-substituted azidonitrobenzene **11** and phenylazide **12** afforded no reduction products (Table 2, entries 3 and 4).[21] The reaction conditions were amenable to electron-withdrawing trifluoromethyl groups in both the *ortho* and *meta* positions. Although requiring longer reaction times (Table 2, entries 5–7), no appreciable loss in yield was observed. Finally, electron-donating methoxy groups were tolerated in both the *meta*- and *para*-nitro benzenes **16** and **17**, albeit resulting in slightly lower yields of the corresponding anilines (Table 2, entries 8 and 9). It was clear from the experiments that substrates displaying only *ortho*- and *para*-nitro substitution patterns with respect to the appended azide were suitable for reduction under these conditions. Finally, benzoyl group was tolerated in the *ortho* position as the *para*-nitroaniline **18** was isolated in 60% yield.

It was apparent from the experiments that at least two equivalents of sodium *tert*-butoxide and *tert*-butanol were required to effect full azide reduction, which was consistent with the observations of Guthrie,[17,18] and related studies on the electrochemical reduction of aromatic azides.[10] Furthermore, the substrate scope was limited to *ortho*- and *para*-nitroazidobenzenes suggesting that a reactive intermediate was involved that could perhaps be stabilised by a mesomeric effect.

A further indication of the reaction mechanism was revealed when $^3O_2$ was introduced into the system; completely shutting down the reduction pathway and leading to almost quantitative recovery of the starting material **1**.

Table 1 Optimisation of the Reduction of 1-Azido-4-nitrobenzene (**1**)

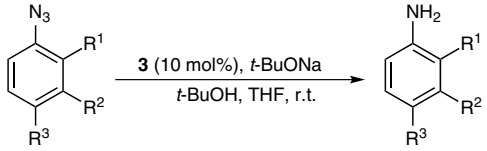


1 **2**

Entry	NaO*t*-Bu (equiv)	*t*-BuOH (equiv)	**3** (mol%)	Temp	Time (h)	Yield of **2** (%)[a]
1	–	–	–	r.t.	0.5	0.0
2	2.0	–	–	r.t.	0.5	0.0
3	1.0	2.0	–	r.t.	0.5	0.0
4	2.0	2.0	–	r.t.	0.5	1.4
5	2.0	2.0	–	r.t.	16	84
6	1.0	2.0	–	r.t.	16	34
7	–	–	–	r.t.	0.5	0.0
8	2.0	2.0	–	r.t.	0.5	78
9	2.0	2.0	**3** (0.10)	r.t.	0.5	42
10	1.0	2.0	**3** (0.10)	r.t.	16	28
11	2.0	2.0	**3** (0.10)	r.t.	5.0	88

[a] Reaction performed at 0.122 mmol scale of **8** in a 0.25 M solution.

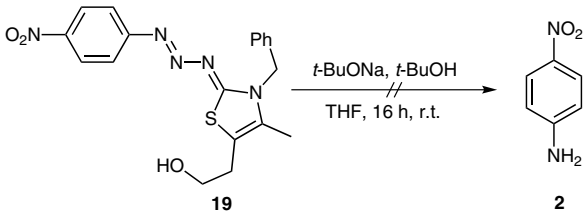
Table 2 Reduction of Azidonitrobenzenes



Entry	Compd	R^1	R^2	R^3	Time (h)	Yield (%)
1	**2**	H	H	NO_2	5	88
2	**10**	NO_2	H	H	5	94
3	**11**	H	NO_2	H	16	–
4	**12**	H	H	H	16	–
5	**13**	H	CF_3	NO_2	12	84
6	**14**	CF_3	H	NO_2	12	89
7	**15**	Cl	H	NO_2	12	86
8	**16**	NO_2	H	OMe	12	66
9	**17**	OMe	H	NO_2	12	72
10	**18**	Bz	H	NO_2	12	60

The combined results strongly suggest that a radical process with *tert*-butoxide ion as the single-electron reductant is in operation.[17a]

The rate-enhancing role of the thiazolium salt **3** is uncertain. It has been shown that certain N-heterocyclic carbenes react with aromatic azides to form a variety of derivatised triazenes,[22] and it was considered whether such an intermediate was involved in the reduction process. Thus, the triazene **19** was synthesised from azidonitrobenzene **1** upon reaction of the thiazolium salt **3** and NaH (81% yield), and subjected to the optimised reaction conditions. Even after prolonged reaction times of up to 16 hours, the triazene **19** was shown to be stable with no observed degradation or conversion into aniline **2** (Scheme 4).



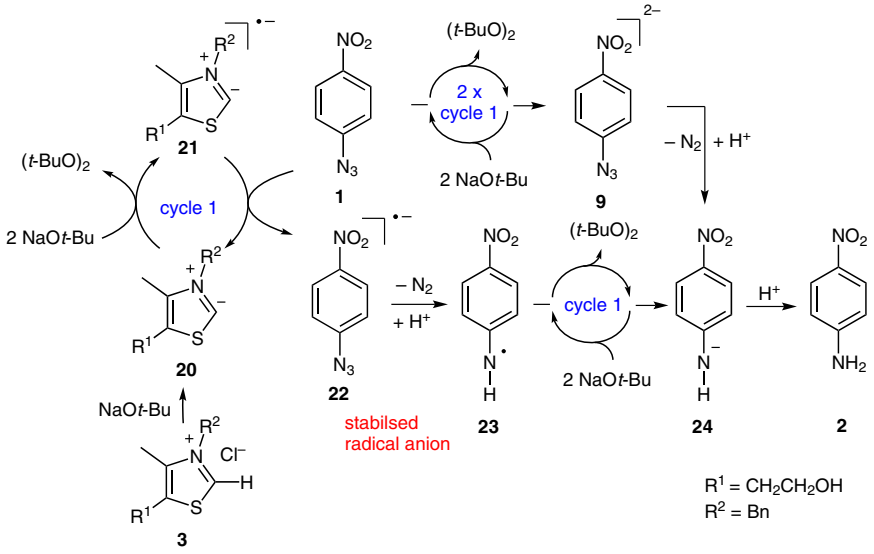
19 **2**

Scheme 4 Triazene **19** was shown to be stable to the reduction conditions and ruled out as a plausible intermediate.

Based upon the current experimental evidence we propose a general mechanism to explain the transformation. Thus, deprotonation the thiazolium salt **3** to the corresponding thiazolium ylide **20** (or carbene) occurs. However, rather than **20** operating as the expected nucleophilic catalyst,[23] we speculate that it facilitates the electron transfer from the *tert*-butoxide ion to the azidonitrobenzene **1**, perhaps as a radical anion carrier.

Thus, the thiazolium ylide **20** enters into a catalytic cycle (Scheme 5, cycle 1) where it acts as a radical anion relay **21**, from sodium *tert*-butoxide to the azidonitrobenzene **1** (Scheme 5). The stabilised radical anion **22** can then extrude nitrogen and undergo protonation to deliver the aminyl radical species **23**, which is consistent with the observations of Liu et al.[24] The aminyl intermediate **23** is then free to undergo a further radical addition via the same radical anion relay process (Scheme 5, cycle 1) to generate the anionic species **24**. Finally, a second protonation event delivers the aniline **2**, along with two mol of *tert*-butylperoxide per mol of azide (Scheme 5). This mechanism is consistent with the substrate requirement for *ortho*- or *para*-nitroazidobenzene, since such substitution patterns would stabilise the intermediate radical species. Alternatively, the anion **9** could also, in principle, be formed prior to the extrusion of nitrogen.

In conclusion, we have developed a novel catalytic reduction of azidonitrobenzenes to the corresponding nitroanilines using sodium *tert*-butoxide as the reductant. The transformation is chemospecific for the azide functional group over the reductively sensitive nitro group, and is complementary to other known methodologies. A speculative mechanism based upon our preliminary studies has been proposed, however, further experimentation will be required in order to fully delineate the exact processes be-



Scheme 5 A suggested mechanism to explain the catalytic reduction of **1** to aniline **2** by *tert*-butoxide ion

hind the transformation. Studies are currently under way in our laboratories to fully elucidate the role of the catalyst in this process.

General Procedure for the Reduction of Azidonitrobenzenes (Table 2)

The thiazolium salt **3** (3.30 mg, 0.0122 mmol) was added to a solution of 1-azido-4-nitrobenzene (0.122 mmol) and *t*-BuOH (18.0 mg, 0.244 mmol) in degassed THF (0.50 mL) under argon at r.t. The resulting suspension was stirred for 5 min, and then NaO*t*-Bu (23.4 mg, 0.244 mmol) was added in one portion, and the mixture was stirred (Table 2). Water (2 mL) was added, and the products were extracted with EtOAc (2 × 2 mL), the combined organic phase was dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved by passing the resulting residue through a short pad of silica (eluting with 50% light PE–EtOAc) unless otherwise stated.

Analytical Data for 4-Nitroaniline (2)[25]

Yellow solid (15.0 mg, 88%), R_f = 0.3 (PE–EtOAc = 70:30); mp 145–148 °C (lit.[25] 146–147 °C). FTIR ($CHCl_3$): ν_{max} = 3509 (NH_2), 3417 (NH_2), 1624, 1600, 1505 (NO_2), 1335, 1311 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.96–7.92 (m, 2 H), 6.70 (br s, 2 H, NH_2), 6.62–6.58 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.7 (C), 135.6 (C), 126.4 (2 × CH), 112.4 (2 × CH). ESI-HRMS: *m/z* calcd for $C_6H_6N_2NaO_2$ $[M + Na]^+$: 161.0321; found: 161.0322.

Synthesis of Triazene 19

1-Azido-4-nitrobenzene (**1**, 50.0 mg, 0.305 mmol) and the thiazolium salt **3** (82.0 mg, 0.305 mmol) were dissolved in THF (1 mL), and the corresponding mixture was cooled to –78 °C. NaH (30.5 mg, 60% w/w mineral oil, 0.761 mmol) was added to the mixture in one portion. The reaction mixture was allowed to warm to r.t., at which point a bright red colour appeared. The reaction was stirred at r.t. until complete (TLC, 5 h). The reaction mixture was then poured onto sat. NH_4Cl solution (5 mL) and the products extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over anhyd $MgSO_4$, filtered, and the solvents were removed in vacuo. The resulting residue was finally subjected to flash column chromatography (eluting with EtOAc) to deliver the product as a bright red solid.

Analytical Data for Triazene 19

Yield 98.0 mg (81%); R_f = 0.2 (EtOAc). FTIR ($CHCl_3$): ν_{max} = 3108 (OH), 1520 (NO_2), 1428 (N=N), 1327, 1134, 1106 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.28 (d, *J* = 8.9 Hz, 2 H), 7.64 (d, *J* = 8.9 Hz, 2 H), 7.41–7.37 (m, 2 H), 7.33–7.30 (m, 1 H), 7.26–7.24 (m, 2 H), 5.42 (s, 2 H), 4.93 (t, *J* = 5.7 Hz, 1 H), 3.59 (app q, *J* = 5.7 Hz, 2 H), 2.76 (t, *J* = 5.7 Hz, 2 H), 2.16 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.8 (C), 155.6 (C), 145.4 (C), 135.8 (C), 133.1 (C), 128.9 (CH), 127.7 (CH), 126.5 (CH), 125.0 (CH), 121.7 (CH), 116.5 (C), 60.5 (CH_2), 48.6 (CH_2), 29.7 (CH_2), 11.2 (CH_3). ESI-HRMS: *m/z* calcd for $C_{19}H_{20}N_5O_3S$ $[M + H]^+$: 398.1281; found: 398.1291. Anal. Calcd for $C_{19}H_{19}N_5NaO_3S$ $[M + Na]^+$: 420.1101; found: 420.1122.

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Supporting Information

Full experimental procedures and characterisation for compounds listed in Table 2 and for compound **19** in this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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