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A catalytic and *tert*-butoxide ion-mediated amidation of aldehydes with *para*-nitro azides†

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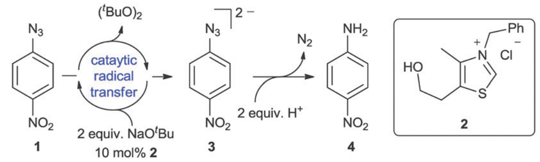
We report here a new catalytic reaction in which, *para*-nitro azides are acylated by aldehydes to produce amides and molecular nitrogen in a single step. The transformation is believed to proceed *via* an electron transfer process mediated by the *tert*-butoxide ion, and catalysed by a thiazolium salt derived species.



Scheme 1 A proposed mechanism to explain the catalytic reduction of **1** to aniline **4** by the *tert*-butoxide ion.

Amide bond forming reactions are among the most executed in organic chemistry, forming key linkages in peptides, proteins, synthetic polymers and drugs.[1] Traditional approaches to amide synthesis involving the coupling of activated carboxylic acid derivatives (anhydrides and acyl chlorides) with nucleophilic amines are expensive, wasteful and often produce toxic by-products necessitating lengthy purification.[2] The demand for sustainable and greener[3] approaches to amide synthesis has stimulated intense activity in the development of new and creative catalytic methods.[1d]

Straightforward and desirable methods involving the direct coupling of carboxylic acids and amines with certain boronic acid catalysts have been reported.[4] Other strategies generally involve either the catalytic or oxidative acylation of an amine, or occur by a suitable combination of complementary reaction partners following a unique pathway. For example, the generation of activated carboxylates from functionalised aldehydes by *N*-heterocyclic carbene (NHC) catalysts with a co-catalyst, followed by their conversion to amides has been shown to work with a variety of amines.[5] Oxidative processes utilising NHC's[6] and metal based catalysts have been used for amide formation from aldehydes with stoichiometric oxidants.[7] The ruthenium catalysed conversion of alcohols and primary amines with loss of H_2 developed by Milstein *et al.*[8] represents an example of an atom economic and green approach to amide synthesis, whereas the oxidative coupling of α-bromo nitroalkanes with amines offers a quite different pathway.[9]

The formation of amides by the intermolecular coupling of thioacids and electron poor anilines that require no activating or coupling reagents has been investigated.[10,11] The mechanism is believed to involve the nucleophilic attack of the thioacetate onto the azide *N*-3 followed by formation of a cyclic thiatriazoline intermediate, which collapses to give the amide, nitrogen gas and elemental sulfur.[11] In seeking to further develop the theme of this chemistry, we were intrigued by the possibility of using aldehydes directly in a redox azido-amidation type-process, thus broadening the range of available substrates and eliminating the sulfur by-product.

In recent studies, we observed that in the presence of the thiazolium salt (**2**), the *tert*-butoxide ion selectively reduces the azide group of 1-azido-4-nitrobenzene (**1**) (Scheme 1).[12] The reaction is believed to proceed by an electron transfer process *via* the dianion **3**, followed by concomitant loss of nitrogen gas to give aniline **4**.

We now report the *tert*-butoxide ion mediated amidation of aldehydes[13] with *para*-nitro azides, catalysed by a thiazolium salt derived catalyst. This clean transformation allows the synthesis of *para*-nitro aromatic amides in one step with high atom economy, and driven by loss of environmentally benign nitrogen gas.[14]

For the reaction development we opted to use the electron deficient 1-azido-4-nitrobenzene (**1**), with benzaldehyde (**5**) as the acyl donor. Using previously optimised conditions for the azide-reduction as a starting point (2 equiv. *tert*-BuONa, THF, rt),[12] a number of preliminary reactions were performed (Table 1).

Thus, treatment of the azide **1** and aldehyde **5** in THF with *tert*-BuONa at room temperature immediately resulted in the evolution of a gas and, complete conversion of the starting material **1**. After chromatography, the corresponding target

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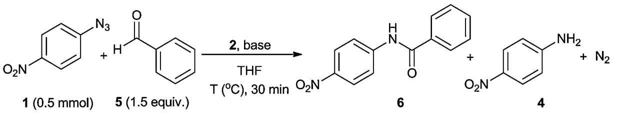
† Electronic supplementary information (ESI) available: Full experimental procedures and characterisation with ^1H and ^{13}C NMRs and schemes referenced in the text. See DOI: 10.1039/c3cc40452h

Table 1 Optimisation of the reaction conditions and control experiments



Entry	**2** (equiv.)	Base (equiv.)	T (°C)	**6** yield[a] (%)	**4** yield[a] (%)
1	—	NaO^{t}Bu (2.0)	rt	56	39
2	—	KO^{t}Bu (2.0)	rt	51	36
3	1.0	NaO^{t}Bu (3.0)	rt	30	62
4	—	NaO^{t}Bu (2.0)	−25	0	0
5	1.0	NaO^{t}Bu (3.0)	−25	80	0
6	0.1	NaO^{t}Bu (2.0)	−25	81	0
7	0.1[b]	NaO^{t}Bu (2.0)	−25	83	0

[a] Isolated yield after chromatography. [b] **2** added after stirring a mixture of **1** and **5** at −25 °C in the presence of *tert*-BuONa.

amide **6** was isolated in 56% yield along with *para*-nitroaniline (**4**) (39%) (Table 1, entry 1). Similar results were achieved when the potassium salt of *tert*-butoxide ion was employed; giving amide **6** (51%) and aniline **4** (36%) (Table 1, entry 2). However, when the same reaction was carried out in the presence of 1 equiv. of the thiazolium salt **2**, the yield of the amide **6** decreased (30%) whereas the aniline **4** was isolated in higher yield (62%) (Table 1, entry 3).

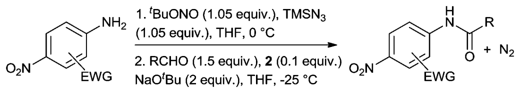
When a solution of **1** and **5** was treated with *tert*-BuONa (2 equiv.) at −25 °C without catalyst, unreacted starting materials were recovered (Table 1, entry 4). In contrast, the addition of **2** (1 equiv.) to the reaction mixture at −25 °C followed by *tert*-BuONa (3 equiv.) gave the target amide **6** in 80% yield with no observed aniline **4** (Table 1, entry 5). A reduced loading of **2** (0.1 equiv.) resulted in a similar yield of the amide **6** (81%) (Table 1, entry 6).

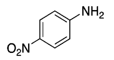
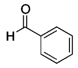
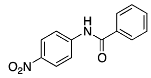
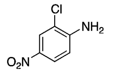
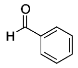
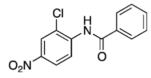
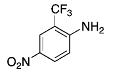
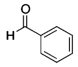
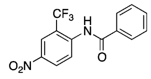
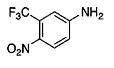
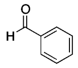
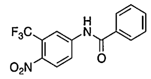
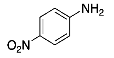
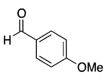
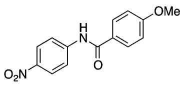
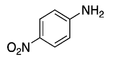
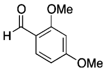
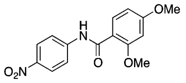
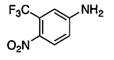
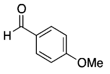
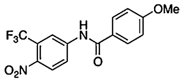
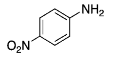
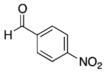
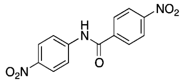
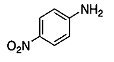
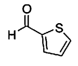
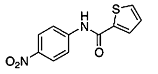
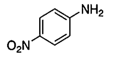
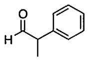
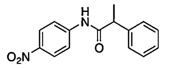
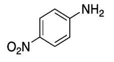
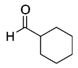
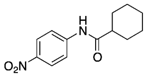
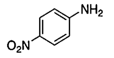
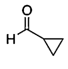
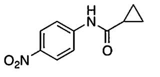
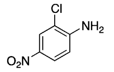
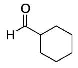
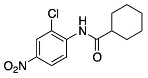
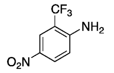
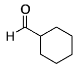
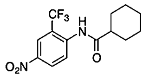
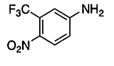
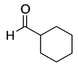
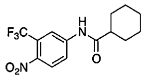
Stirring a mixture (30 min) of the azide **1**, the aldehyde **5** and *tert*-BuONa (2 equiv.) at −25 °C; no reaction was observed (TLC) until the addition of **2** (0.1 equiv.), then after a further 30 min, the amide **6** was isolated in 83% yield (Table 1, entry 7).

We next investigated the one pot diazotisation–azidation–amidation reaction, since this would negate the isolation of the azide substrate.[15] This proved viable; the diazotisation/azidation of *para*-nitroaniline **4** with *tert*-BuONO/TMSN$_3$ at 0 °C in THF,[16] followed by catalytic amidation at −25 °C provided the amide **6** in an excellent 94% yield (Table 2, entry 1). The scope of the tandem reaction was next investigated with a number of electron deficient anilines and several aldehydes (Table 2, entries 1–15). Both *ortho*- and *meta*-substituents on the *para*-nitroaromatic azide were well tolerated with benzaldehyde (**5**) (Table 2, entries 2–4). The reaction worked well when electron deficient anilines were coupled with electron rich aromatic aldehydes, including *ortho*- and *para*-substitution on the aromatic aldehyde (Table 2, entries 5–7).

When an electron deficient aromatic aldehyde was used, the yield of amide dropped significantly (38%) (Table 2, entry 8). The heteroaromatic thiophene-2-carbaldehyde was tolerated, giving the corresponding amide isolated in good yield (82%) (Table 2, entry 9). When aliphatic aldehydes were employed; high yields were consistently obtained (78–94% yield, entries 10–15).

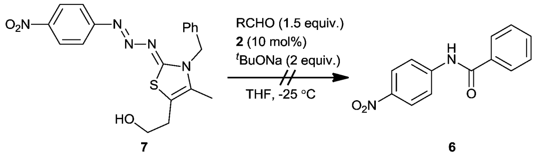
Table 2 Reaction of *para*-nitro aromatic azides with various aldehydes



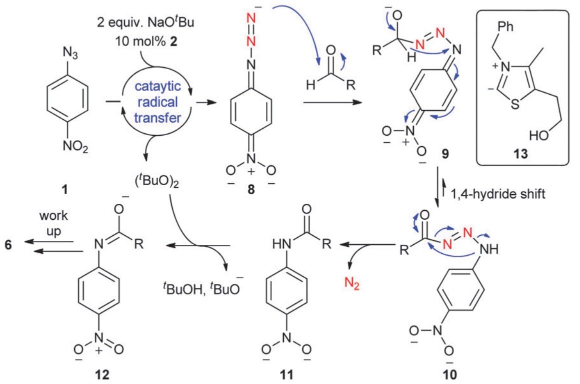
Entry	Aniline	Aldehyde	Amide	Yield[a] (%)
1				94
2				85
3				77
4				84
5				91
6				79
7				89
8				38
9				82
10				94
11				88
12				78
13				92
14				83
15				87

[a] Isolated yield after chromatography.

The reaction raises a number of interesting questions with regard to the mechanism. During the 1980's, Guthrie and co-workers published a number of detailed papers on the reaction mechanism between the *tert*-butoxide ion and nitrobenzene, involving SET processes.[17] Indeed, the function of *tert*-butoxide ion as an electron transfer agent is well documented.[18]



Scheme 2 Subjecting the triazene **7** to the preferred amidation conditions did not lead to the formation of **6**.



Scheme 3 A plausible amidation mechanism from **1** (R = Ph).

When the amidation reaction of the azide **1** and benzaldehyde (**5**) was attempted under an atmosphere of oxygen or in the presence of the radical trap TEMPO,[19] no reaction was observed with complete recovery of the azide **1**. These results, which are consistent with our earlier findings[12] provide support for a radical based mechanism in the amidation process (see Scheme S1, ESI†).

The relative nitrogen connectivity between the starting azide and the corresponding amide was determined by performing experiments with ^{15}N-labelled 1-azido-4-nitrobenzene. The reaction proceeded with retention of ^{15}N directly attached to the aromatic ring (see Scheme S2, ESI†).

The role of the thiazolium salt **2** is uncertain and warrants further investigation. However, preliminary mechanistic studies with the thiazolium derived triazene **7**[12,20] demonstrated that such species are stable to the amidation conditions (Scheme 2).

Based upon the available experimental data, we present a working mechanistic hypothesis. Thus, electron transfer from the *tert*-butoxide ion gives the dianion **8**, a process that we tentatively propose is catalysed by a thiazolium anion relay derived from **2** (**13**).[12] Whereas protonation and loss of nitrogen from **8** would deliver the corresponding aniline (Scheme 1), interception of the intermediate **8** by an aldehyde would deliver intermediate **9.**[14] A subsequent 1,4-hydride shift leads to intermediate **10** that is poised to extrude nitrogen gas and deliver the dianion **11**. Next, in a manner consistent with the observations of Guthrie,[17] we speculate that the loss of two electrons from **11** occurs *via* SET, with concomitant formation of two equivalents of the *tert*-butoxide anion from di-*tert*-butylperoxide. Overall imidate **12**, *tert*-butanol and *tert*-butoxide are generated which, upon protic work-up delivers the corresponding amide **6** and *tert*-butanol (Scheme 3).

In summary, we have documented a new and straightforward synthetic method for the catalytic synthesis of substituted *para*-nitroaromatic amides, based upon an azido-amidation mechanism. This method offers an orthogonal approach to current methodology and, in particular, the method works particularly well with electron deficient anilines, thus complementing existing methodologies involving activated carboxylic acid derivatives. Studies are currently ongoing to unravel the mechanistic details of the reaction.

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Notes and references

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