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ARTICLE

Formic Acid as a Sustainable and Complementary Reductant: Approach to Fused Benzimidazoles by Molecular Iodine-Catalyzed Reductive Redox Cyclization of *o*-Nitro-*t*-Anilines

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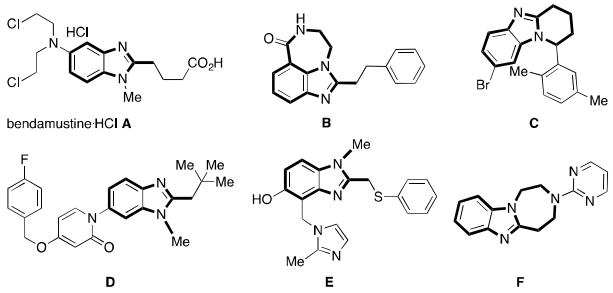
Molecular iodine was found to be an excellent catalyst for reductive redox cyclization of *o*-nitro-*t*-anilines **1** into fused tricyclic or 1,2-disubtituted benzimidazoles **2**. A range of functions such as halides (F, Cl, Br), methoxy, ester, trifluoromethyl, cyano, pyridine and even nitro groups were tolerated using formic acid as a clean, safe, user-friendly and complementary reductant. When iodine was used in stoichiometric amount (50 mol %), the methodology allowed direct synthesis of benzimidazole hydroiodides **2**·**HI** in high yields by simple precipitation from reaction mixture.

Fused tricyclic and 1,2-disubstituted benzimidazole heterocycles are of great interest in medicinal chemistry.[1] Representative recent examples include the anticancer agent bendamustine hydrochloride **A**,[2] poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor **B**,[3] modulators of tumour necrosis factor (TNF) activity **C**,[4] anti-obesity drug **D**,[5] anti-hepatitis B virus (HBV) agent **E**,[6] and histamine H_3 receptor ligand **F**.[7]



Scheme 1. Representative fused tricyclic or 1,2-disubstituted benzimidazoles.

Methods of synthesis of such important scaffolds can be roughly classified into two categories (Scheme 2). In the first category, the reactions proceed via non-redox cyclization (pathway 1) [8] of anilines **4** or amidines **5** or redox neutral condensation (pathway 2)[9] of *o*-phenylenediamines **6** with α,ω-dialdehydes **7** without external reductant or oxidant. This strategy requires usually several steps to obtain the starting materials, and harsh reaction conditions, thus limited in the substrate range. The second strategy needs a reductant or oxidant to promote the cyclization. When *o*-NH_2-*t*-anilines **3** were used as low oxidation state *o*-dinitrogen precursors, different oxidative[11-14] and dehydrogenative[10] cyclization conditions were developed, notably H_2O_2/acid,[11] oxone/HCO_2H,[12] CF_3CO_3H,[13] TEMPO (pathway 3).[14]. These pathways have some clear limitations, such as the availability of the starting materials **3**,[15] which are obtained by a 6-electron reduction of the parent nitroanilines **1**, and the formation of side-products directly linked to the oxidizing conditions. For examples, when H_2O_2 was used in hydrochloric or hydrobromic acid, halogenated fused benzimidazoles were obtained as the main products.[16]

In this context, an alternative method by $2e^-$ reductive redox cyclization of *o*-nitro-*t*-anilines **1**,[17] the parent compounds of *o*-NH_2-*t*-anilines **2** (pathway 4), would be more straightforward with better atom-, step- and redox- efficiencies. Indeed, in a single operation, a cascade of reaction occurs including: a reduction of the nitro group, an oxidation of the α-methylene group and a cyclization. Evidently, this $2e^-$ reductive redox cyclization of **1** is more advantageous than its $6e^-$ reductive cyclization of the corresponding *o*-nitroanilides **8** (pathway 5),[18] generally not practically available, which limits their application.[19]

For the cyclization of **1** via pathway 4, although the global reaction is a two-electron reduction, both oxidation and reduction processes occur in the same molecule, the nitro group is reduced partially by the methylene moiety of the *t*-amino group and two other electrons are furnished by an external reductant. An ideal or complementary reductant for this purpose should provide only two required electrons and should not act as a competitive reductant. Compared to reported $2e^-$ reductive redox cyclization conditions such as H_2/Pd,[20] CO/Pd,[21] Na_2SO_3,[22] $TiCl_3$,[23] or pyrolytic,[24] and photolytic[25] one, transfer hydrogenation provides a more beneficial and practical alternative.

Formic acid has emerged as a safe, user-friendly surrogate for hydrogen in the frame of synthetic chemistry and renewable energies.[26] Indeed, by applying formic acid as reductant, no

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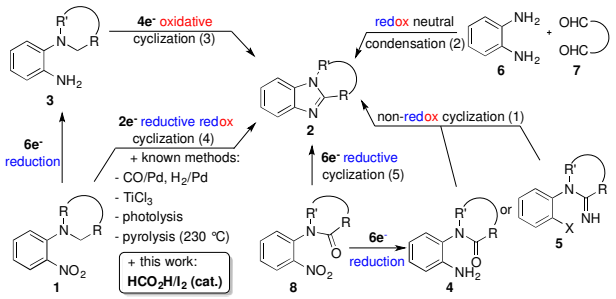
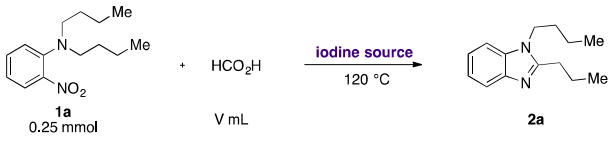
high-pressure vessels are necessary and the only by-product is gaseous CO_2 spontaneously removed from the reaction media. Compared to previous methods using H_2[20] or CO,[21] the manipulation of flammable and/or highly toxic gases is avoided.



Scheme 2. Cyclization methods of synthesis of fused tricyclic and 1,2-disubstituted benzimidazoles

Additionally, the use of readily available and inexpensive elements as reagents, building blocks and catalysts has drawn our attention because of its simplicity and feasibility for large-scale synthesis. In light of our interest in using molecular iodine as a versatile catalyst for redox transformations, we described here such a practical synthesis of diverse fused benzimidazoles[27] Compared to classical metal-catalyzed reduction with formic acid, this approach is even more attractive in the context where no expensive metal catalysts[28] and/or ligands[29] are required.

Table 1. Reaction condition screening

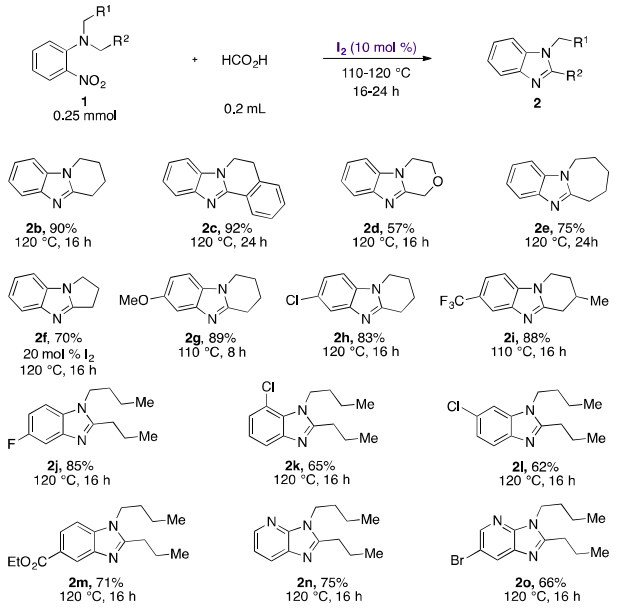


entry[a]	iodine source (mol %)	t (h)	V (mL)	conversion (%)[b]
1	KI (10)	12	0.2	43
2	NaI (10)	12	0.2	32
3	TBAI (10)	12	0.2	38
4	CuI (10)	12	0.2	27
5	I_2 (10)	12	0.2	70
6	I_2 (5)	12	0.2	48
7	-	12	0.2	trace
8	I_2 (10)	12	0.1	56
9	I_2 (10)	12	0.5	65
10	**I_2 (10)**	**24**	**0.2**	**>95 (85)**[c]
11	HI (20)[d]	24	0.2	>95
12	HI (20)[e]	24	0.2	>95
13	I_2 (10)	24	0[f]	trace

[a] Reaction conditions: **1a** (0.25 mmol), iodine source (10 mol %), HCO_2H (V mL) under an argon in a 17 mL test tube closed with a rubber septum unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated yield of **2a** by chromatography. [d] Aqueous 55% HI. [e] HI as **1a**·HI salt (20%) and **1a** (0.20 mmol, 80%) were used as starting material and catalyst. [f] HOAc (0.2 mL) was used in place of HCO_2H.

In continuing our effort to develop practical and simple methods for the synthesis of bioactive nitrogen-containing molecules, we are particularly interested in using molecular iodine as well as its derivatives for redox transformations. We initiated our study with the reaction of *o*-(dibutylamino) nitrobenzene **1a** in formic acid in the presence of different iodide sources as catalysts (10 mol %) (Table 1, entries 1-5). Among these iodine sources (KI, NaI, TBAI, CuI, I_2), molecular iodine was shown to be the most efficient catalyst, leading to the desired benzimidazole in good conversion (entry 5, 70%) even when only a 5 mol % catalyst loading was used (entry 6, 48%). A background control experiment in the absence of any iodine source resulted in the formation of the expected product **2a** but only in a trace quantity (entry 7).

The reaction conditions were further optimized by varying the quantity of HCO_2H. Indeed, lowering (entry 8) or increasing (entry 9) the HCO_2H amount resulted in lower conversions, possibly due to the dilution effect for the latter case.[30] Finally, the reaction achieved almost total conversion after 24 h of heating (entry 10). The same catalytic activity was observed when aqueous HI was used as the iodine source (entry 11). HI salt of the starting nitroaniline **1a**·HI could also conveniently employed as a solid and water-free HI source (entry 12). When acetic was used in stead of formic acid, the desired benzimidazole was also formed but in a negligible quantity (entry 13). To confirm the redox catalytic role of I_2/HI couple, other non redox acids were also evaluated at the catalysts (HCl, trifluoroacetic acid, H_2SO_4, CH_3SO_3H...). In all these cases, **2a** was yielded only in trace quantities, suggesting redox activity of iodide is critical for the reaction.



Scheme 3. Scope of the formation of fused tricyclic and 1,2-disubstituted benzimidazoles.

Having developed a reliable protocol, we evaluated the reaction scope. We first tested a range of nitrobenzenes *o*-substituted by different secondary amines. Gratifyingly, all tested substrates underwent clean transformation into the desired fused benzimidazoles in moderate to excellent yields.

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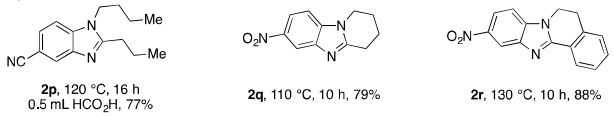
While the reactions with piperidine derivatives **1b**,**c** provided the corresponding products in high yields under similar conditions, the reactions with morpholine **1d** resulted in lower yield, possibly due to a complexation between the oxygen atom of the morpholine moiety and iodine. Azepane **1e** and pyrrolidine **1f** were less reactive than piperidine **1c**. In case of pyrrolidine **1f**, a higher molecular iodine catalyst loading (20%) was required to attain high yield (70% instead of 45%). The reaction displayed good functional group tolerance on the benzene ring, either electron donating (**2g**) or withdrawing (**2i**, **2m**) substituents reacted well under the optimized conditions. Halogens in different positions were also compatible (**2h**, **2j**-**l**), particularly bromide (**2o**). Furthermore, the reaction extensible to heteroaromatic nitro compounds (**2n**,**o**) is particularly interesting in view of obtaining fused polyaromatic heterocycles.

The substrate scope of reductive processes is often limited if other reducible substituents are present in the molecule. The important feature of the present methodology is the ability to tolerate such functional groups (ester **2m**, pyridine **2n**, bromopyridine **2o**, nitrile **2p**).

Interestingly, when dinitroanilines **1q**,**r** was submitted to the standard reaction conditions, only the *o*-nitro group reacted and cyclized to the expected nitrobenzimidazole, leaving the *p*-nitro untouched. This *p*-nitro group can act as a masked 5-amino group of the benzimidazole ring, readily released with a reductant for further functionalization into useful products (compounds **A** and **D**, Scheme 1).

In case of fused benzimdazole **2r**, we observed a formation of a pale yellow precipitate in non-negligible quantities (up to 18% as **2r**·**HI**) during the course of the reaction. ^{1}H, ^{13}C NMR and HRMS analyses associated with elemental microanalysis of this solid obtained by simple filtration showed that it was a hydroiodide salt **2r**·**HI**.



2p, 120 °C, 16 h
0.5 mL HCO_2H, 77%

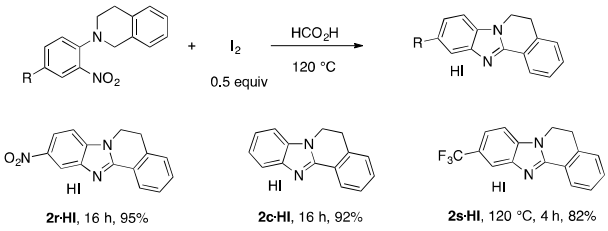
2q, 110 °C, 10 h, 79%

2r, 130 °C, 10 h, 88%

Scheme 4. Formation of fused tricyclic and 1,2-disubstituted benzimidazoles in the presence of reducible substituent.

On the basis of these observations, we undertook an experiment to fully transformed *o*-nitro-*t*-anilines **1c**, **1r-1s** directly into **2c**, **2r-2s** hydroiodide salts (Scheme 5). To achieve this goal, **1c**, **1r-1s** were heated with I_2 (50 mol %) under the standard conditions. In all cases tested, we were able to obtain the corresponding salts **2c**·**HI, 2r**·**HI-2s**·**HI** in high yields and purities by simple dilution of the reaction mixture with diethyl ether to induce their crystallization from the reaction mixture. Overall, this approach provided a convenient method to synthesize benzimidazoles as their iodide salts using I_2 as both catalyst and iodide source, avoiding the use of volatile, more expensive and extremely corrosive HI as a traditional reagent for this purpose.

To gain a better insight into the reaction mechanism, we initially carried out some control experiments. When *N*-butyl-*o*-nitroaniline, *p*-piperidinonitrobenzene or nitrobenzene was used, the reaction resulted in total recovery of unchanged starting substrates, suggesting that (i) *t*-aniline scaffold is necessary; (ii) the nitro group must be in the *o*-position to the *t*-amino group; (iii) the first step would not be the reduction of the nitro group by formic acid.

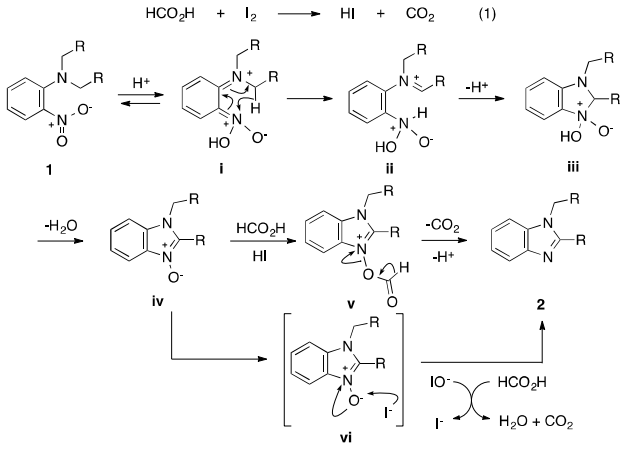


2r·HI, 16 h, 95% **2c·HI**, 16 h, 92% **2s·HI**, 120 °C, 4 h, 82%

Scheme 5. Direct formation of iodide salts.

Based on these observations, we proposed a plausible mechanism shown in Scheme 6. It was assumed that HI, generated *in situ* from the reaction between iodine and formic acid (eq. 1),[31] which acts as both strong Brønsted acid and reductant, was the active catalytic species.

We suggested the involvement of the corresponding benzimidazole *N*-oxide **iv**.[32] The first step of this sequence began with a protonation of **1** leading to **i**. With a conjugating structure, **i** underwent an intramolecular hydride transfer from the α-methylene of the amino moiety to the nitro group to provide iminium **ii**. Subsequent cyclization of **ii** into **iii** followed by a dehydration would provide **iv**. It should be noted that the formation of **iv** is easier when the α-methylene group is more acidic (tetrahydroisoquinolines **1c**, **1r** and **1s**), and is observable in an unachieved reaction mixture. An alternative mechanism of formation of **iv** involving a sequence of elimination/addition may also be envisaged. Deoxygenation of **iv** leading to benzimidazole **2** could proceed via formate **v** and subsequent fragmentation. It is possible that unstable formyl iodide, generated *in situ* from formic acid and hydroiodic acid or iodide, is the active formylating agent for the formation of *N*-formate **v**. The formation of this intermediate is possible thank to exceptionally strong nucleophilicity of iodide even in acidic media.



Scheme 6. Proposed mechanism for the formation of benzimidazole **2**

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Alternatively, iodide can act as direct reductant by removing the oxygen atom of **iv** via **vi** with the formation of hypoiodide, which could be regenerated by reaction with formic acid. In both cases, the catalytic role could be understood in view of the unique redox and nucleophilic properties of I_2/HI.

Conclusions

In summary, we have demonstrated that *N*-substituted and fused benzimidazole heterocycles could be conveniently synthesized via reductive cyclization of *o*-nitro-*t*-anilines with formic acid as reductant. More importantly, we have described the first example of molecular iodine-catalyzed reduction using formic acid as hydrogen source. It is anticipated that this study will set the stage for a variety of other catalytic unbalanced redox condensation processes involving an external redox reagent with better atom-, step- and redox- efficiencies.

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