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tert-Butyl nitrite catalyzed synthesis of benzimidazoles from *o*-phenylenediamine and aldehydes at room temperature

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ABSTRACT

A simple and efficient method is demonstrated for the synthesis of benzimidazoles *via* cyclocondensation of *o*-phenylenediamine with aldehydes in the presence of catalytic amount of *tert*-butyl nitrite. All the reactions were carried out at room temperature while the desired products were obtained in good to excellent yields.

Introduction

Benzimidazole motifs are present in many drugs, bioactive molecules and natural products [1]. For instance, benzimidazole derivatives are active pharmacophores which display anti-viral, anti-microbial, anti-cancer, anti-ulcer and anti-inflammatory properties (Fig. 1) [1a,2]. On the other hand, benzimidazole derivatives are well-used in synthetic organic chemistry as building blocks and ligands [3]. Moreover, benzimidazole based materials and polymers displayed promising applications in different fields, including optical sensing, energy storage, LED, dyes, etc. [4]. Owing to their biological and chemical significance, the synthesis of benzimidazole derivatives has gained continuous interest in organic chemistry [5]. Synthesis of benzimidazoles has been typically achieved by the condensation of *o*-phenylenediamine with carbonyl compounds in the presence of different reagents and oxidants [5g,5m–r]. However, most of the reported methods uses metal catalysts [5k,l,p,q], stoichiometric amount of oxidants [5h], higher reaction temperature [5r], etc. In general, organocatalytic methods are attractive in organic synthesis due to their efficiency and selectivity [6].

tert-Butyl nitrite (TBN) is metal-free multi-tasking reagent extensively used in various organic transformations [7]. Besides diazotization and nitration, *tert*-butyl nitrite has been used as radical initiator, oxidant, etc. [8]. Over the last few years, our research work is focused on the chemistry of *N*-nitrosamines [9] and we have reported TBN mediated solvent-free synthesis of *N*-nitrosamines [9a], radical dimerization of thiobenzamide [9f], transamidation of secondary amides [9e], and nitration of *N*-alkyl anilines [9b]. Recently, we have reported the synthesis of benzotriazoles from *o*-phenylenediamine using *tert*-butyl nitrite [9g]. This method provides excellent yields of benzotriazoles under neutral conditions while several acid labile functional groups were found to be stable. In continuation of this work,

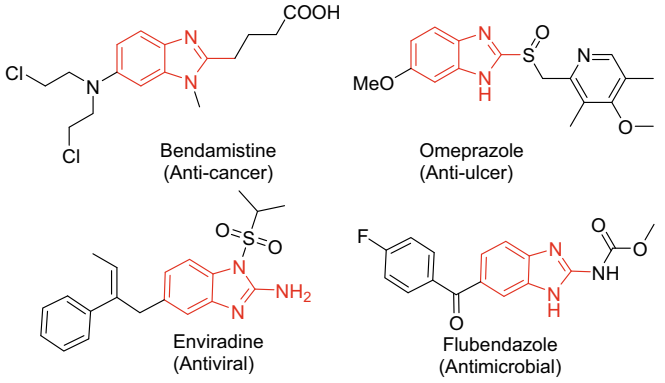

Fig. 1. Pharmacological activities of benzimidazole derivatives.

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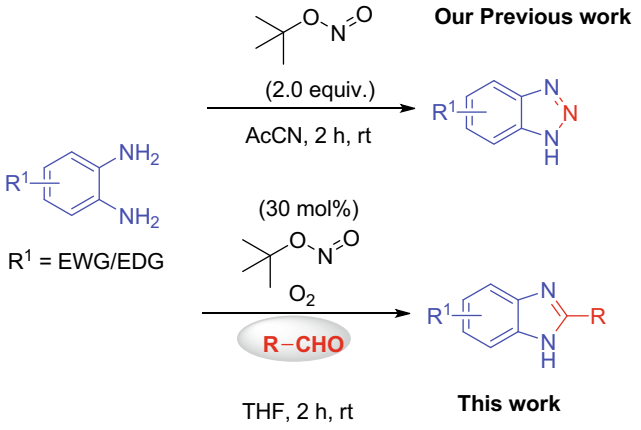
here we report TBN catalysed transformation of *o*-phenylenediamines into benzimidazoles in the presence of aldehydes at room temperature (Scheme 1).

Results and discussion

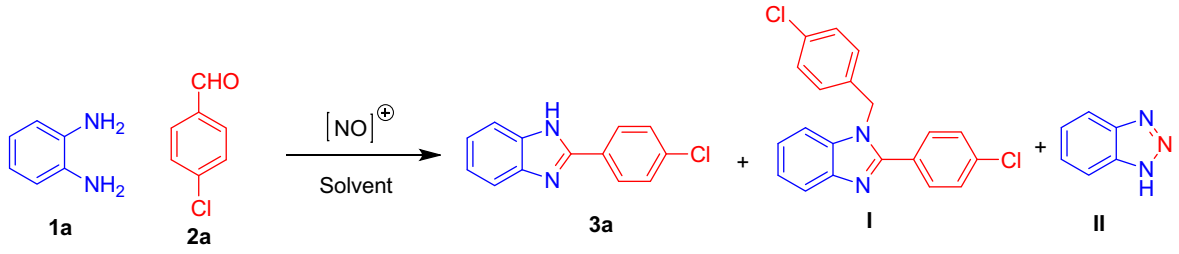
At the outset, *o*-phenylenediamine (**1a**) and 4-chlorobenzaldehyde (**2a**) was chosen as model substrates and subjected to the condensation in the presence of *tert*-butyl nitrite (TBN) at room temperature (Table 1). The reaction was performed with one equiv. of *tert*-butyl nitrite in different solvents including dichloromethane, acetonitrile, toluene, 1,4-dioxane, methanol, THF, DMF and DMSO (Table 1, entries 1–8). Among these solvents, the reaction proceeded well in THF by providing the desired product 2-(4-chlorophenyl) benzimidazole (**3a**) in 80% yield in 30 mins (Table 1, entry 6). On the other hand, other solvents provided a mixture of products containing 1,2-substituted benzimidazole (I) and benzotriazole (II) in considerable yields. Also, in some solvents (e.g. DCM, toluene, etc.) the starting materials were remaining unreacted. Nevertheless, only a minimum amount of these side products were obtained in THF while compared with other solvents. Hence, the optimization was carried out in THF by varying the amount of TBN. The formation of benzotriazole (II) was observed in high amount when the reaction with 2.0 equiv. of TBN (Table 1, entry 9). Therefore, the reaction was performed with catalytic amount of TBN (i.e. 50 mol% to 10 mol%) in THF.

Although a decrease in benzotriazole (II) formation was observed with catalytic amount of TBN, the yield of the desired product was also dropped significantly (Table 1, entries 10–12). It is also important to note that the **3a** was not observed in the absence of TBN (Table 1, entry 13). Considering the previous report on TBN mediated thiol oxidation [8d], we performed the condensation reaction with molecular oxygen (i.e. with oxygen balloon) in the presence of 50 mol% and 30 mol% of TBN (Table 1, entries 14 and 15). To our delight, the benzimidazole **3a**



Scheme 1. Synthesis of benzimidazoles.

Table1
Optimization study.[a]



S. No	'NO' Source	Mol%	Additives	Solvent	Time (hr)	Yield %[b]		
						3a	I	II
1	TBN	100	–	DCM[c]	0.5	26	24	20
2	TBN	100	–	CH_3CN	0.5	22	23	47
3	TBN	100	–	Tolune[c]	0.5	17	10	16
4	TBN	100	–	1-4 dioxane	0.5	46	20	15
5	TBN	100	–	MeOH	0.5	77	<5	14
6	TBN	100	–	THF	0.5	80	5	10
7	TBN	100	–	DMF	0.5	65	12	14
8	TBN	100	–	DMSO	0.5	62	12	17
9	TBN	200	–	THF	0.5	67	<10	21
10	TBN	50	–	THF[c]	0.5	65	<5	<5
11	TBN	30	–	THF[c]	0.5	59	<5	<5
12	TBN	10	–	THF[c]	1.0	40	<5	<5
13	TBN	00	–	THF[c]	2.0	<5	<5	nr
14	TBN	50	O_2	THF[c]	2.0	90	<5	<5
15	TBN	30	O_2	THF	2.0	90	<5	<5
16	$NOBF_4$	30	O_2	THF[c]	2.0	Trace	Trace	<10
17	Isoamyl Nitrite	30	O_2	THF	2.0	83	<5	<5
18	CF_3SO_3H	100	O_2	THF[c]	2.0	17	Trace	Trace

[a] Reaction conditions: Substrate **1a** & **2a** (1 mmol) and NO-source stirred in appropriate solvents (5 mL) at room temperature.
[b] Isolated yield.
[c] Imine was reminded in the reaction.

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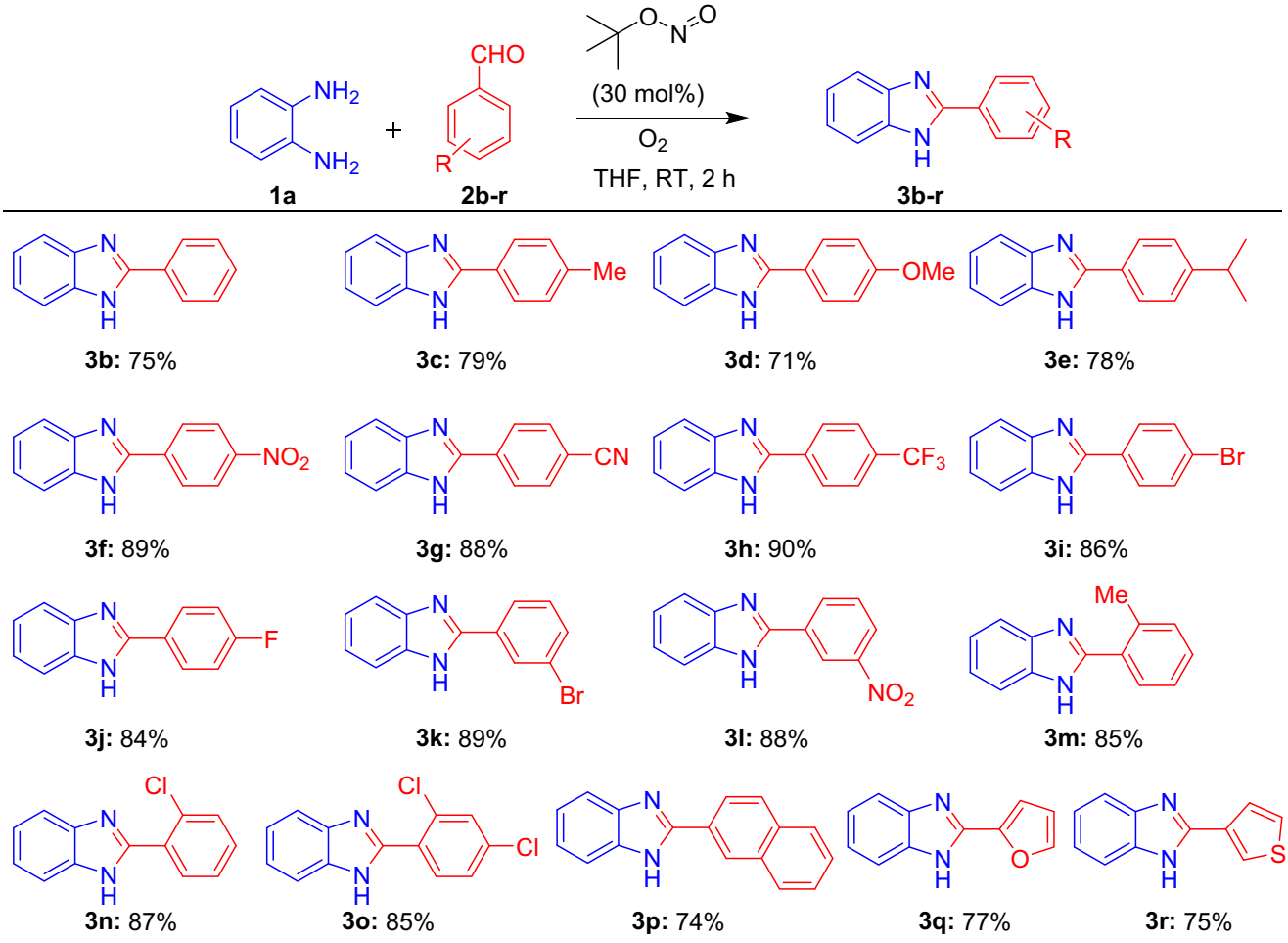
Table 2
Scope of aryl aldehydes.[a,b]



[a] Reaction conditions: Substrate **1a** & **2** (1 mmol) and TBN (30 mol%) in THF (5 mL) for 2 h at room temperature.
[b] Isolated yield.

was obtained in 90% yield under both the reaction conditions within 2 h at room temperature.

Furthermore, the condensation reaction was carried out with other nitrosating agents such as nitrosonium tetrafluoroborate ($NOBF_4$) and isoamylnitrite in the presence of oxygen. The product **3a** was not observed with $NOBF_4$ while isoamyl nitrite gave the benzimidazole **3a** in 83% yield (Table 1, entry 16 and 17). In addition, to understand the involvement of acid in the reaction, we have attempted the reaction in the presence of CF_3SO_3H (instead of TBN) under oxygen atmosphere. However, the product **3a** was obtained only in 17% yield (Table 1, entry 18). Overall, the optimization study indicates that a catalytic amount of TBN (i.e. 30 mol %) in the presence of oxygen is sufficient for the efficient preparation of benzimidazoles from *o*-phenylenediamines and aryl aldehydes.

With optimized conditions in hand, the scope of different aryl aldehydes was investigated for the preparation of benzimidazoles (Table 2). Initially, *o*-phenelenediamine was subjected to the condensation reaction with un-substituted as well as electron donating groups substituted benzaldehydes in the presence of 30 mol% TBN. All these reactions underwent smoothly to provide the desired products **3b**-**3e** in 71–79% yield. On the other hand, condensation of *o*-phenelenediamine with electron withdrawing group functionalized benzaldehydes (e.g. 4-NO_2, 4-CN, 4-CF_3, 4-F and 4-Br) provided corresponding benzimidazoles in 84–90% yields under the optimized conditions (Table 2, 3f-3j). Furthermore, *meta*-substituted benzaldehydes (3-Br and 3-NO_2), sterically hindered *ortho*-substituted benzaldehydes (2-Me, 2-Cl and 2,4-di-Cl) as well as 2-naphthyl aldehyde also participated in the condensation reaction efficiently in the presence of TBN and provided the desired products in good to excellent yields (Table 2, 3k-3p). Overall, it was observed that the reaction proceeds smoothly irrespective of functional groups at the *ortho*, *para* and *meta*-positions of the aryl aldehydes. Similar to aryl aldehydes, to our delight heterocyclic aldehydes such as 2-furaldehyde and 3-thiophene aldehyde also gave the corresponding benzimidazoles **3q** and **3r** in 75–77% yields (Table 2, 3q-3r).

After exploring the scope of different aldehydes, a wide range of functionalized *o*-phenelenediamines was subjected to the condensation reaction with 4-chlorobenzaldehyde under optimized reaction conditions (Table 3). To our delight, *o*-phenylenediamines bearing electron donating groups (e.g. methyl, *tert*-butyl) and withdrawing groups (e.g. halogens, nitro, trifluoromethane, carbonyl, etc.) underwent cyclization smoothly. These reactions provided the corresponding benzimidazoles in 82–89% yields within 2 h at room temperature (Table 3, 4a-4g). In addition, *o*-phenelenediamines bearing di-substitutions (i.e. 4,5-di-Me, 3,5-di-Me, 3,4-di-Me and 4,5-di-Cl) also participated efficiently in the reaction to provide the desired benzimidazoles in 86–89% yields (Table 3,4h-4k).

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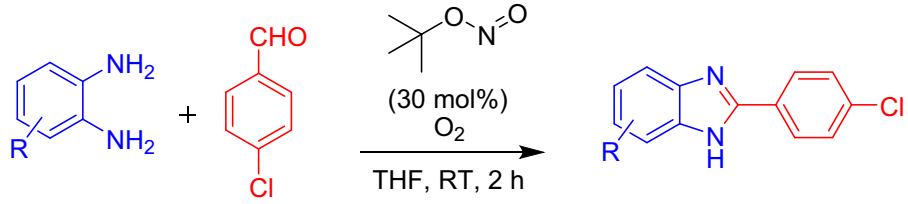
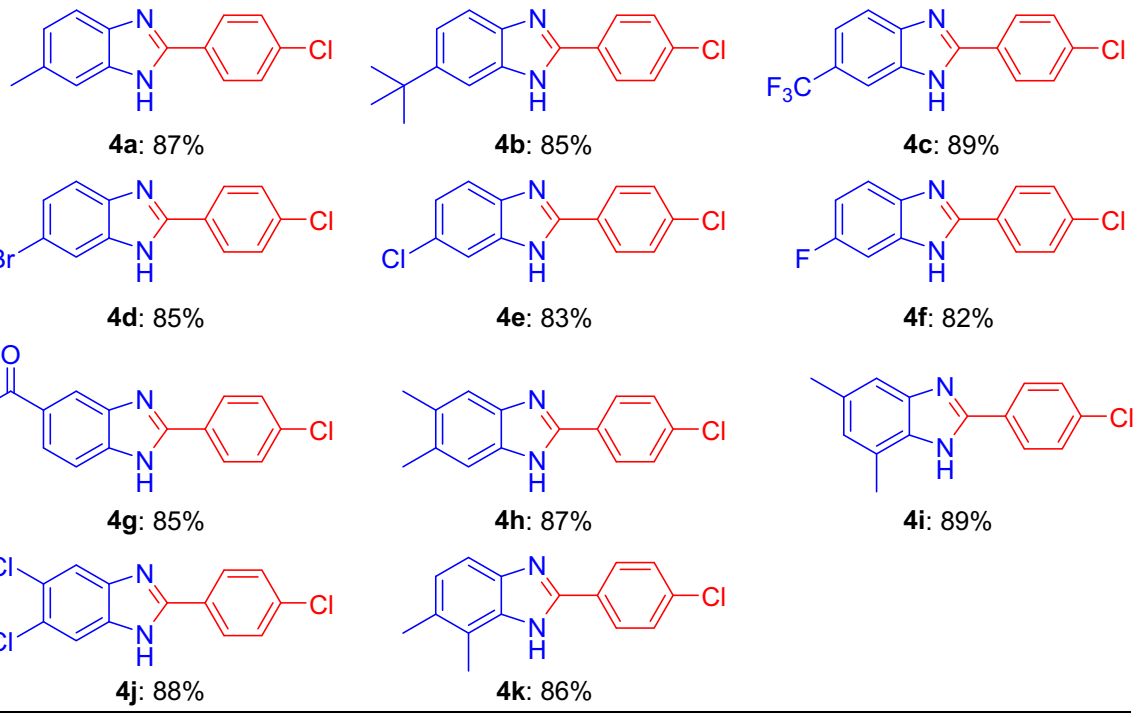
Table 3
Scope of *o*-phenelenediamines.[a,b]

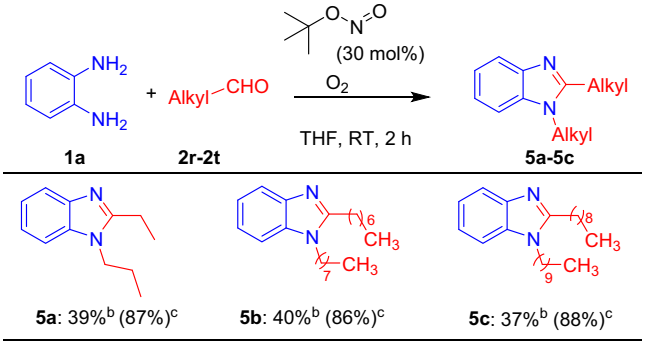


1b-1l 2a 4a-4k



[a] Reaction conditions: Substrate **1b-1 l** & **2a** (1 mmol) and TBN (30 mol%) in THF (5 mL) for 2 h at room temperature.
[b] Isolated yield.

Table 4
Scope of aliphatic aldehydes.[a,b]



5a: 39%[b] (87%)[c] **5b**: 40%[b] (86%)[c] **5c**: 37%[b] (88%)[c]

[c]The reaction was carried out with 2.0 equiv. of aldehyde.
[a] Reaction conditions: Substrate **1a** (1 mmol) & aldehyde **2r-2 t** (1 mmol) and TBN (30 mol%) in THF (5 mL) for 2 h at room temperature.
[b] Isolated yield.

Furthermore, we have investigated condensation of *o*-phenelenediamine with aliphatic aldehydes such as propanal, octanal and decanal under optimized conditions (Table 4). Interestingly, these aldehydes provided 1,2-disubstituted benzimidazoles as a major product in 37–40% yields (Table 4, **5a**-**5c**). It might be due to high reactivity of alkyl aldehydes over aryl aldehydes. Further, the reaction was carried out with 2.0 equiv. of aliphatic aldehydes which provided the 1,2-disubstituted benzimidazoles **5a**-**5c** in 86–88% yields.

A plausible mechanism for the reaction is depicted in Scheme 2. In the first step, *o*-phenylenediamine will react with benzaldehyde to form the imine intermediate (**A**). *tert*-Butyl nitrite (TBN) facilitates the formation of cyclic *N*-nitroso intermediate (**B**) from imine (**A**) *via N*-nitrosation [10]. The intermediate (**B**) delivers the desired product **C** (i.e. benzimidazole) and nitrous acid (HNO_2) in the presence of oxygen. In the case of formation of 1,2-disubstituted product, the intermediate (**B**) will react with another equivalent of aldehyde to form intermediate (**D**) which undergoes rearrangement [11] to generate 1,2-disubstituted product (**E**) and nitrous acid (HNO_2). Further nitrous acid reacts with *tert*-butanol to provide the *tert*-butyl nitrite (TBN) [12] to resume the catalytic cycle.

Conclusions

In conclusion, an efficient catalytic method for the preparation of benzimidazoles from *o*-phenylenediamine and aldehydes in the presence of *tert*-butyl nitrite is demonstrated. All the reactions were carried out at room temperature in the presence of oxygen as an oxidant. This current methodology showed a broad substrate scope while the desired products were obtained in good to excellent yields.

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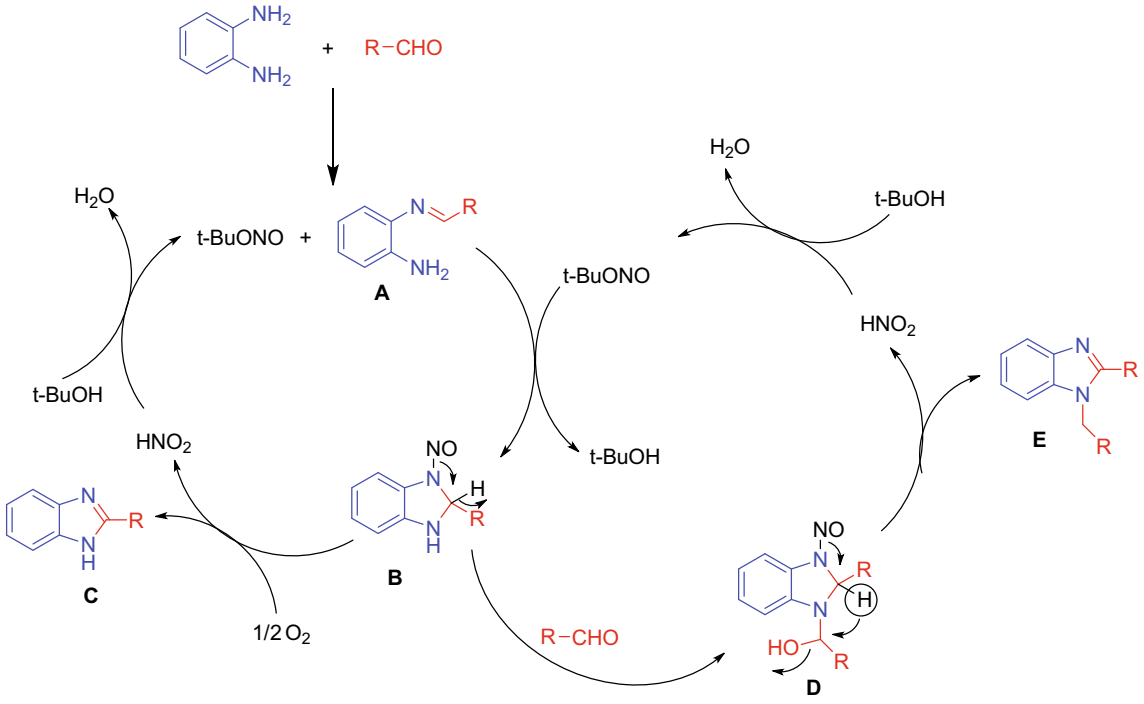

Scheme 2. Proposed mechanism of the reaction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151735.

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