Base promoted peroxide systems for the efficient synthesis of nitroarenes and benzamides

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ABSTRACT

A useful and efficient approach for the synthesis of nitroarenes from several aromatic amines (including heterocycles) using peroxide and base has been developed. This oxidative reaction is very easy to handle and afforded the products in good yields. Formation of benzamides from benzylamine was also successfully carried out with this metal-free catalytic system in good to excellent yields.

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Introduction

Nitro compounds are considered as an 'ideal intermediates' for the synthesis of commercially important chemicals like dyes, perfumes, and pharmaceuticals [1–4]. There are numerous nitro containing drugs available in the market such as nitroxoline, oxamniquine, metronidazole, nitrofurantoin, chloramphenicol, and nitrofural (Fig. 1) [5–10]. Due to environmental concerns the preparation of nitro compounds in large scale by classical direct nitration method is not a benign choice as it requires very harsh conditions. Therefore, the direct oxidation of amines into nitro compounds draws the attention of researchers as it is a safer process than the classical method. Thus, several protocols have been developed for the oxidative transformation of aryl amines to nitroarenes (Fig. 2). Oxidants like H_2O_2 [11], m-CPBA [12], HOF-CAN [13], TBHP with KI [14], peracetic acid [15], peroxyfluoroacetic acid [16], sodium perborate with tungstophosphoric acid and cetyl-trimethylammonium bromide (CTAB) [17], TBHP with CrS-2 [18], TBHP with $Rh_2(cap)_4$ [19], and H_2O_2 with $CaWO_4$ [20], were employed for this transformation. However, most of the reported methods suffer from many shortcomings, such as uncontrolled
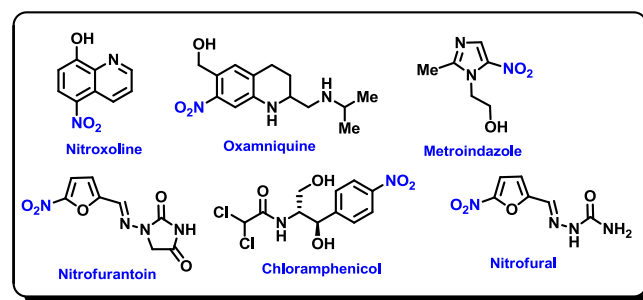

Fig. 1. Representative nitro containing biologically active molecules.

oxidation, use of harsh reaction conditions, poor yields, longer reaction times, and poor selectivity. In addition to this, oxidative method via H_2O_2 has been previously reported as environmental friendly and cheaper reagent, since its only byproduct is water. Due to the poor oxidizing nature of H_2O_2, it needs to be coupled with a catalyst or a reagent to carry out the oxidation by activating it to a reactive intermediate. Therefore, the development of mild and effective protocol is highly desirable in this area.

On the other hand, amides are another important chemical class, which are widely used as intermediates in various organic syntheses and also an important linkage in proteins and peptides. They are useful raw material for plastic industry, detergent,

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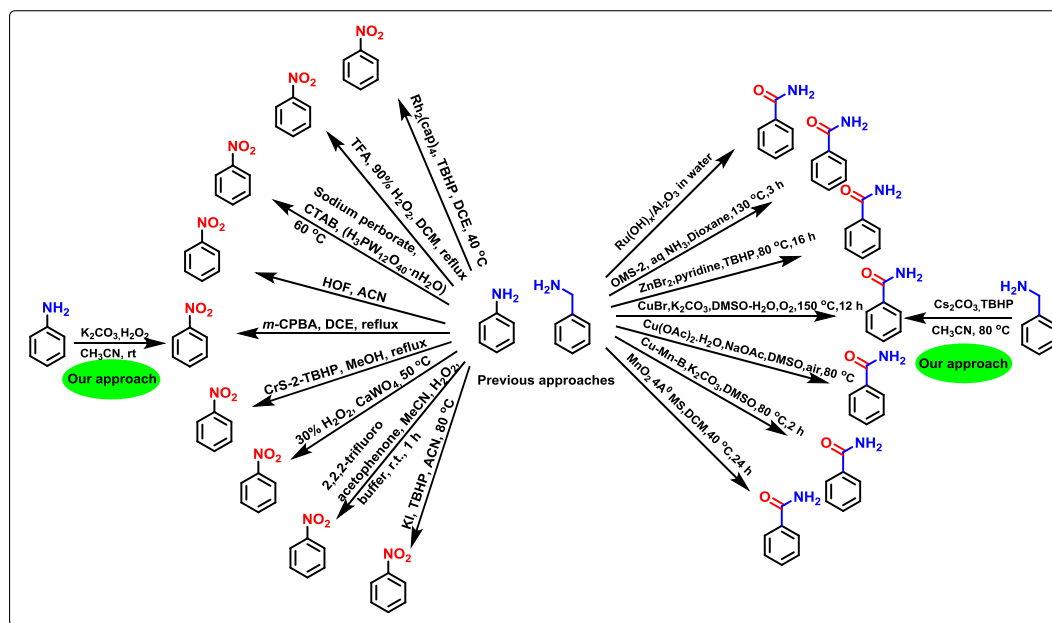   E-mail address: kv_sashidhara@cdri.res.in (K.V. Sashidhara).

Fig. 2. Previous protocols for the synthesis of nitro benzenes and benzamides and our present study.

lubricants, pharmaceuticals, etc [21]. The traditional method for the synthesis of amides usually involves the coupling reaction between carboxylic acid/activated carboxylic acid with ammonia [22]. But handling problem with ammonia makes it a tedious job. Besides this, rearrangement of ketoximes [23] and hydrolysis of nitriles were also reported [24]. Due to reaction complications, multiple reaction steps and formation of waste byproducts, these methods are usually avoided.

The oxidation of benzylamines into benzamides is less discussed but is the most efficient and atom economic route for the amide synthesis. For this purpose *in situ* RuO$_4$ is found to be effec-

tive catalyst [25] but it requires the protection of amine group with BOC. Heterogeneous ruthenium catalysts Ru(OH)$_x$/Al$_2$O$_3$ [26,27] and manganese oxide octahedral molecular sieves (OMS-2) [28] are reported for oxidation of benzylamines to corresponding amides. Other than these reports RuCl$_3$ [29], CuBr-K$_2$CO$_3$/air [30], ZnBr$_2$/TBHP or FeCl$_3$/TBHP [28], MnO$_2$ [31] etc. catalysts have also been employed. Recently, ligand free copper-manganese spinel oxide catalysed amidation reaction has been reported from benzylamine and aryl halides (Fig. 2) [32]. However, all these oxidations of benzyl amine are metal-catalyst based oxidation reactions. These metal catalysts are very expensive, produces unfavourable

Table 1
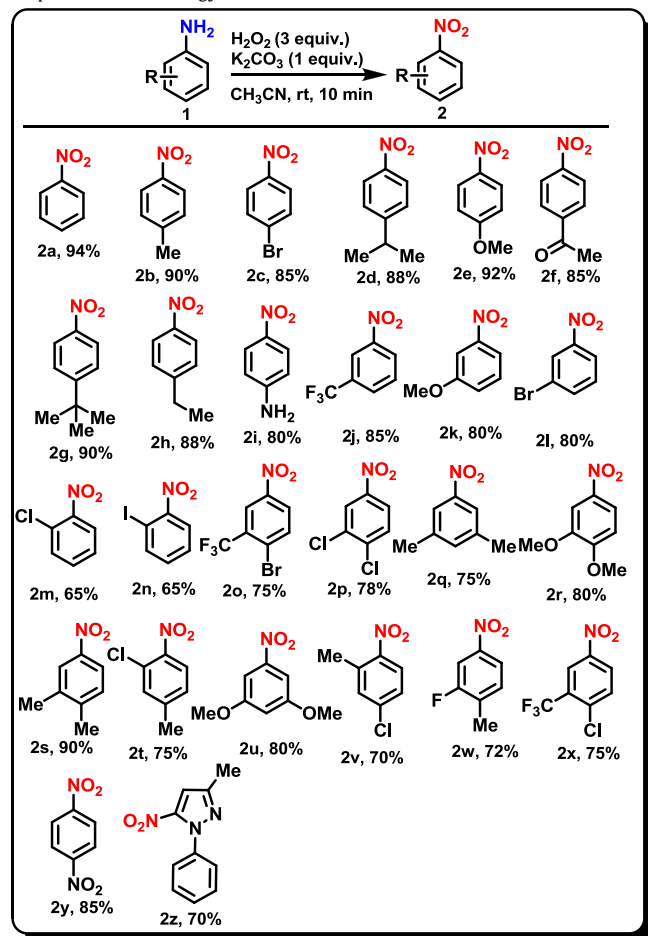Results of the optimization study for oxidation of aniline to nitro benzene.[a]
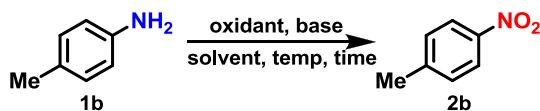
Entry	Oxidant (equiv)	Base (equiv)	Solvent	Temp (°C)	time (min/h)	yield (%)[b]
1[c]	TBHP (1.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	rt	12 h	ND
2[c]	TBHP (1.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	40	8 h	28
3[c]	TBHP (1.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	80	8 h	49
4[c]	TBHP (2.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	80	4 h	72
5	TBHP (3.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	80	4 h	89
6	TBHP (3.0)	Cs$_2$CO$_3$ (0.5)	CH$_3$CN	80	4 h	68
7	TBHP (3.0)	K$_2$CO$_3$ (1.0)	CH$_3$CN	80	4 h	70
8	TBHP (3.0)	Na$_2$CO$_3$ (1.0)	CH$_3$CN	80	4 h	65
9	TBHP (3.0)	–	CH$_3$CN	80	4 h	ND
10	–	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	80	4 h	ND
11	H$_2$O$_2$ (3.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	80	5 min	74
12	H$_2$O$_2$ (3.0)	Cs$_2$CO$_3$ (1.0)	CH$_3$CN	rt	15 min	84
13	**H$_2$O$_2$ (3.0)**	**K$_2$CO$_3$ (1.0)**	**CH$_3$CN**	**rt**	**10 min**	**90**
14	H$_2$O$_2$ (3.0)	Na$_2$CO$_3$ (1.0)	CH$_3$CN	rt	10 min	72
15	H$_2$O$_2$ (3.0)	K$_2$CO$_3$ (1.0)	DMSO	rt	10 min	87
16	H$_2$O$_2$ (3.0)	Cs$_2$CO$_3$ (1.0)	Toluene	rt	10 min	21
17	H$_2$O$_2$ (3.0)	Cs$_2$CO$_3$ (1.0)	DCE	rt	30 min	ND
18	H$_2$O$_2$ (3.0)	Cs$_2$CO$_3$ (1.0)	Ethanol	rt	30 min	ND

[a] All reactions were carried out using **1b** (0.1 g, 0.93 mmol), TBHP (70 wt% in H$_2$O), H$_2$O$_2$ (35 wt% in H$_2$O), solvent (4 mL) at indicated time.
[b] Isolated yields after purification.
[c] Unreacted starting material recovered too. ND = no product.

Table 2
Scope of the methodology for oxidative transformation of anilines to nitro benzenes.

Scheme 1. Scope of the methodology for oxidative transformation of *o*-phenylenediamines.

and an eco-friendly metal-free protocol for the oxidation of primary amines to their corresponding amides using Cs_2CO_3 in the presence of TBHP.

Results and discussion

Inspired from the literature reports, we planned to design an oxidant system which could efficiently oxidize anilines to nitrobenzenes under mild reaction conditions. The combination of peroxides in basic medium may increase its oxidizing power. Therefore, initially the reaction was performed by treating *p*-toluidine (**1b**) as model substrate with TBHP and Cs_2CO_3 using CH_3CN as solvent at room temperature for 12 h, under the present reaction condition, the reaction did not lead to the product formation (Table 1, entry 1). Therefore, we conducted same reaction at 40 °C for 8 h, which produced 28% of the product yield with unreacted starting material (Table 1, entry 2). This result prompted us to explore further for improving the yield of the product (**2b**). Then, the reaction was performed by increasing the temperature to 80 °C, the yield of the product was improved to 49% (Table 1, entry 3). Upon increasing the amount of TBHP to 2.0 and 3.0 equiv, resulted in the increased yield to 72% and 89%, respectively (Table 1, entries 4–5). Subsequently, reducing the amount of Cs_2CO_3 to 0.5 equiv, deprived the yield to 68%. Whereas, other bases like K_2CO_3 and Na_2CO_3 were unable to improve the yield (Table 1, entries 6–8). Consequently, evaluation of the reaction without base or TBHP failed to produce any product, which revealed that combination of these reagent is indispensable for this reaction (Table 1, entries 9–10). The next set of reaction was performed to investigate the role of oxidant by changing TBHP with H_2O_2. The reaction with

waste, and are difficult to use in large scale. To the best of our knowledge, only one protocol is available in the literature for oxidative amidation of benzylamines under metal free conditions with TBHP/I_2 [33]. Keeping the above mentioned drawbacks in our minds, herein, we report a metal free, mild base promoted oxidation of aromatic amines into nitroarenes using K_2CO_3 in the presence of H_2O_2 in acetonitrile (CH_3CN) at room temperature

Table 3
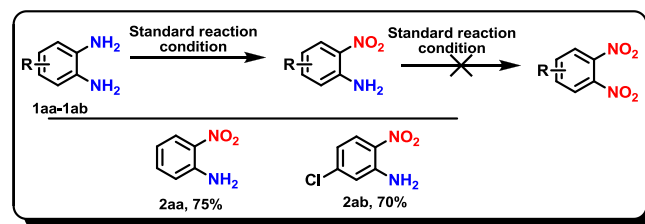Results of the optimization study for oxidation of benzylamine to benzamide.[a]

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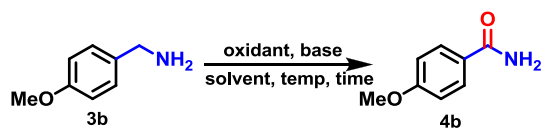
Entry	Oxidant (equiv)	Base (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	H_2O_2 (3.0)	K_2CO_3 (1.0)	CH_3CN	rt	12	ND
2[c]	H_2O_2 (3.0)	K_2CO_3 (1.0)	CH_3CN	40	8	32
3[c]	H_2O_2 (3.0)	Cs_2CO_3 (1.0)	CH_3CN	80	8	47
4	**TBHP (3.0)**	**Cs_2CO_3 (1.0)**	**CH_3CN**	**80**	**4**	**91**
5	TBHP (3.0)	Na_2CO_3 (1.0)	CH_3CN	80	4	73
6	TBHP (3.0)	–	CH_3CN	80	4	ND
7	–	Cs_2CO_3 (1.0)	CH_3CN	80	4	ND
8	TBHP (3.0)	Cs_2CO_3 (1.0)	DMF	80	4	88
9	TBHP (3.0)	Cs_2CO_3 (1.0)	DMSO	80	4	81
10	TBHP (3.0)	Cs_2CO_3 (1.0)	Toluene	80	4	ND

[a] All reactions were carried out using **3b** (0.1 g, 0.71 mmol), TBHP (70 wt% in H_2O), H_2O_2 (35 wt% in H_2O), solvent (4 mL) at indicated time.
[b] Isolated yields after purification.
[c] Unreacted starting material recovered too. ND = no product detected.

H_2O_2 was completed within 5 min providing **2b** in 74% yield (Table 1, entry 11). Therefore, the reaction was repeated at room temperature and it was found that within 15 min the reaction afforded **2b** in 84% yield (Table 1, entry 12). Encouraged from this result, in the next experiment K_2CO_3 was used as base instead of Cs_2CO_3. To our delight, the addition of K_2CO_3 in the stirring solution of **1b** in CH_3CN and H_2O_2, an exothermic reaction took place and within 10 min, the reaction mixture turned into a yellow solid providing **2b** in 90% yield (Table 1, entry 13). Afterwards, changing the base as Na_2CO_3 provided **2b** in low yield (Table 1, entry 14). Further, the role of the solvent was screened and it was observed that reaction furnished lower yield in DMSO and toluene, whereas DCE and ethanol failed to provide any product (Table 1, entries 15–18). Thus, the optimized condition that worked best in our hand was treating **1b** with 3.0 equiv of H_2O_2, 1.0 equiv of K_2CO_3 in CH_3-CN as the solvent at room temperature for 10 min. The scope of the protocol was tested with a variety of anilines (**1**) and it was gratifying to note that all the substrates afforded respective nitroarenes (**2**) in 65–94% yield (Table 2). The mono-substituted anilines (**1b-1n**) bearing substitution at *ortho, para* or *meta* position of the ring smoothly afforded corresponding nitrobenzenes (**2b-2n**).

It was observed that electron-rich anilines provided nitro benzenes with higher yields than corresponding halo analogues. Next, the scope of the methodology was tested with various di-substituted anilines, which adequately produced nitro analogues (**2o-2x**) with good to excellent yields 70–80%. The electronic and steric factor plays a crucial role in this reaction. It was observed that 2-halo anilines (**1m-1n**) provided the nitroarenes with comparatively low yield, which might be due to steric hindrances. Further, under the reaction conditions 4-nitroaniline successfully provided 1,4-dinitrobenzene with 85% yield, however the reaction failed with 2-nitroaniline. The conversion of 4-nitroaniline into 1,4-dinitro benzene (**2y**) is the quite remarkable. This methodology is equally applicable to heterocyclic systemsand this was demonstrated taking 5-amino-3-methyl-1-phenylpyrazole as an example, wherein the desired product (**2z**) was found in 70% yield. Interestingly, in case of *o*-phenylenediamines (**1aa-1ab**) the reaction yielded 2-nitro anilines (**2aa-2ab**). However, further oxidation to 1,2-dinitro benzene was not achieved (Scheme 1). This may be due to the strong electron-withdrawing effect of nitro group of 2-nitroaniline which prevents further oxidation.

Encouraged by these promising results, we tried to apply the optimized reaction conditions for aliphatic amines as well. However, the aliphatic amines were not able to provide the nitro derivative. Further, to explore the synthetic utility of the protocol, we then carried out the reaction with benzylamines. Initialy, 4-methoxybenzylamine **3b** was treated under optimized reaction condition [H_2O_2 (3.0 equiv), K_2CO_3 (1.0 equiv) as base at room temperature], but even after 12 h the reaction was incomplete. Therefore, the reaction temperature was increased to 40 °C, analysis after 8 h revealed the formation of a product in minor amount with most of the starting material was unconsumed. The reaction furnished a white solid with 32% isolated yield which was spectrally characterized as 4-methoxybenzamide (**4b**) instead of 1-methoxy-4-(nitromethyl)benzene (Table 3, entry 2). The literature survey supported our observation that benzylic carbon is suceptable towards oxidation and could oxidize in the presence of H_2O_2 as oxidant to provide benzamide as sole product.

Most of the literature reported the use of either hazardous reagents or metal-catalyst as an oxidant. Taking this challenge, we then further optimized the reaction condition.

Therefore, the reaction was repeated by treating **3b** with Cs_2CO_3 as base and increasing the reaction temperature to 80 °C for 6 h, and this resulted in the formation of **4b** in 47% yield (Table 3, entry 3). The replacement of oxidant H_2O_2 with TBHP resulted in the completion of the reaction in 4 h to afford **4b** with 91% yield

(Table 3, entry 4). Further changing Na_2CO_3 as base did not improve the yield (Table 3, entry 5). The role of TBHP and Cs_2CO_3- in this reaction were also evaluated. It was found that absence of either of them in the reaction failed to furnish any product and in the both cases starting material was recovered (3, entries 6–7). Moreover, changing the solvent with DMF, DMSO provided **4b** with lower yield, while the reaction in toluene failed to afford any product (Table 3, entries 8–10). To evaluate the role of atmospheric air as an co-oxidant in the reaction, the reaction was performed under both nitrogen and oxygen atmosphere. Under nitrogen atmosphere, the reaction afforded **4b** in <5%, whereas under oxygen atmosphere, the reaction was complete in 1 h to afford **4b** in 88% yield. As there was no remarkable difference between the yield of **4b** under oxygen atmosphere and in open air, we continued the reaction in the open flask.

Table 4
Scope of the methodology for oxidative transformation of benzylamines to benzamides.

entry	benzylamine	product	yield [%]
1	3a	4a	90
2	MeO — 3b	MeO — 4b	92
3	Me — 3c	Me — 4c	88
4	MeO, OMe 3d	MeO, OMe 4d	92
5	MeO, MeO, OMe 3e	MeO, MeO, OMe 4e	90
6	Cl 3f	Cl 4f	75
7	F — 3g	F — 4g	85
8	F$_3$C 3h	F$_3$C 4h	85
9	F 3i	F 4i	75
10	I 3j	I 4j	80

With the optimized reaction conditions in hand, the general applicability was further evaluated with diverse benzylamine derivatives resulting in good to excellent yields (75–92%) of the products (Table 4, entries 1–10). The suitability of this strategy was also assessed for gram scale transformation. Thus, the oxidation of p-toluidine **1b** and 4-methoxybenzylamine **3b** under the respective standardized conditions for 2 g scale was performed and the reaction provided 4-methyl nitrobenzene **2b** in 85% yield and 4-methoxybenzamide **4b** in 88% isolated yield. Thus, it was also confirmed that the protocol can be successfully utilised on gram scale level. It was observed that, while performing the reaction at higher scale, addition of peroxide was exothermic and therefore slow addition of the same in portions was preferred.

Conclusion

In summary, we have established an easy and efficient transition-metal-free protocol for oxidation of aromatic amines to nitroarenes and benzyl amines to benzamides under mild reaction conditions. In both cases, the desired product was obtained in high to excellent yields. Remarkably, this methodology is environmentally friendly, cost effective, metal free and operationally simple. Multigram synthesis of nitrobenzenes and benzamide derivatives can easily be accomplished with the aid of this base promoted peroxide system.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151076.

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