Base-oxidant promoted metal-free *N*-demethylation of arylamines

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Abstract. A metal-free oxidative *N*-demethylation of arylamines with triethylamine as a base and *tert*-butyl hydroperoxide (TBHP) as oxidant is reported in this paper. The reaction is general, practical, inexpensive, non-toxic, and the method followed is environmentally benign, with moderate to good yields.

Keywords. *N*, *N*-dialkylaniline; *N*-dealkylation; Triethylamine; *tert*-butyl hydroperoxide; metal-free.

1. Introduction

Reinventing organic transformations with less expensive and environmentally benign methods which have been otherwise successfully catalyzed by transition metal complexes is attracting the attention of chemists.¹ Many tertiary *N*-methylamines find place as part of natural products, pharmaceuticals, etc.² Several new and important pharmaceutical compounds can be obtained by the oxidative *N*-dealkylation or modification of the *N*-methylamine group of alkyl and aryl tertiary amines present in alkaloids and drugs.^{2c,d} Moreover, many tertiary *N*-methylamines are known to have profound pharmacological properties which have applications as psycho-active agents, anticancer agents, in DNA alkylation damage repair, cancer metastatic chemoprevention and also for drug metabolism.³ In classical methods, enzymatic processes are mostly responsible for this conversion in which metal complexes⁴ and various oxidases or peroxidases, like horseradish peroxidase, lipogenase, cytochrome P-450, bleomycin, methemoglobin, amine oxidase, and hydrogen peroxide with either dioxygen or peroxide as oxidant have been employed.⁵ This reaction involves two alternative mechanisms, one is a formal hydroxylation of a C–H bond on the carbon adjacent to the heteroatom (HAT, hydrogen atom transfer), and the other is a one-electron oxidation of the heteroatom itself (SET, single electron transfer).⁶ A copper catalyzed oxidative demethylation of *N*, *N*-dimethyl anilines in the presence of TBHP has been reported.⁷ Alternatively a plethora of expensive and less environmentally benign strategies

have been reported on *N*-dealkylation of alkyl and aryl amines.⁵ Hence there is intense interest to look for an efficient *N*-dealkylation of aryl amines under mild conditions.

We have been engaged in iron-catalyzed reactions and green technologies and recently reported the use of iron(III) chloride for the C–H functionalization of *N*, *N*-dialkylanilines resulting in the construction of C–C and C–O bonds.⁸ As a part of our interest on *N*, *N*-dialkylanilines and their derivatives, we strived to develop a metal-free oxidative *N*-demethylation of arylamines with triethylamine as a base and *tert*-butyl hydroperoxide (TBHP) as oxidant (Scheme 1). This is a generic, metal-free, practical, inexpensive, non-toxic and environmentally benign method.

2. Experimental

2.1 Materials and Methods

All commercially available chemicals were used as received. Triethylamine and *tert*-butyl hydroperoxide (TBHP) were purchased from Sigma Aldrich. Thin-layer chromatography plates were visualized by exposure to UV light/iodine and/or by immersion in an acidic staining solution of phosphomolybdic acid followed by heating on a hot plate. ¹H NMR spectra were obtained on 300, 400 and 500 MHz, and ¹³C NMR spectra 75, 100 and 125 MHz, spectrometers with tetramethylsilane and chloroform-d₁, respectively, as the internal standard. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ¹H NMR and δ = 77.0 for ¹³C NMR). Data for ¹H NMR are reported as follows: chemical shift

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Scheme 1. Oxidative *N*-demethylation of arylamines.

(multiplicity, coupling constant, number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet).

2.2 General synthetic procedures

2.2a Preparation of *N, N*-dialkyl anilines from aniline: 4-Ethyl aniline (8.252 mmol) was dissolved in 50 mL of glacial acetic acid under inert N_2 condition. Paraformaldehyde (80.871 mmol) was added and the contents were stirred for 15 min. Sodium cyanoborohydride (38.785 mmol) was added as the next step and it was stirred overnight at room temperature. The reaction mixture was poured in the saturated Sodium hydroxide solution, which contained crushed ice. Ethyl acetate was added later and the upper layer was collected which contained the compound and was further subjected to solvent evaporation.

2.2b Procedure for *N*-demethylation from *N, N*-dialkyl anilines: A round-bottom flask was charged with *N, N*-dialkyl aniline dissolved in toluene solution, under N_2 condition. TBHP was added drop wise and reaction was stirred for 2 min. Triethyl amine was added thereafter, and then the contents of the reaction were stirred for 3 h at 110°C under inert N_2 condition. The reaction mixture was washed 2–3 times with H_2O and ethyl acetate. The upper organic layer was separated and dried over sodium sulphate and then subjected to rotavapour. The crude mixture was purified by column chromatography on silica gel (60–120).

3. Results and Discussion

Our initial efforts on controlled demethylation of *tert*-anilines involved the optimization of various parameters such as base, oxidant and the solvent, etc., and *N, N*-dimethyl aniline was chosen for the purpose. Among various polar (1, 4-Dioxane, DMF, DCM, MeOH and H_2O), semi-polar (THF, CH_3CN , etc.) and hydrocarbon solvents (Benzene, *o*-, *m*-, *p*- Xylenes and Toluene) tested (Table 1, entries 16–22), CH_3OH , DCM and H_2O failed to effect this conversion. Hydrocarbon

Table 1. Optimization reaction conditions^a.

Entry	Oxidant	Base	Solvent	% of Yield ^b
1	TBHP	$(C_2H_5)_3N$	Toluene	71
2	H_2O_2	$(C_2H_5)_3N$	Toluene	–
3	DDQ	$(C_2H_5)_3N$	Toluene	–
4	Benzyl peroxide	$(C_2H_5)_3N$	Toluene	Trace
5	$K_2S_2O_8$	$(C_2H_5)_3N$	Toluene	–
6	atm O_2	$(C_2H_5)_3N$	Toluene	13
7	TBHP	NaOH	Toluene	54
8	TBHP	NaH	Toluene	58
9	TBHP	Na_2CO_3	Toluene	69
10	TBHP	K_3PO_4	Toluene	70
11	TBHP	KOAc	Toluene	56
12	TBHP	Na ^t -OBu	Toluene	69
13	TBHP	Pyridine	Toluene	–
14	TBHP	Imidazole	Toluene	–
15	TBHP	DIPEA	Toluene	68
16	TBHP	$(C_2H_5)_3N$	MeOH	–
17	TBHP	$(C_2H_5)_3N$	THF	26
18	TBHP	$(C_2H_5)_3N$	DCM	–
19	TBHP	$(C_2H_5)_3N$	DMF	14
20	TBHP	$(C_2H_5)_3N$	CH_3CN	22
21	TBHP	$(C_2H_5)_3N$	DiOxane	22
22	TBHP	$(C_2H_5)_3N$	H_2O	–

solvents produced good yields and toluene was the best. The next most suitable solvent was THF.

Then we turned our attention on the strength of base and investigated the reaction output with sodium carbonate, sodium hydroxide, potassium phosphate, sodium hydride, potassium acetate, pyridine, imidazole, Dipea, sodium *tert*-butoxide and triethylamine. (Table 1, entries 1, 7–15) Triethyl amine was found to be the most efficient, followed by potassium phosphate. To optimize the reaction time, we conducted the reaction under refluxing toluene and realized that reflux for 3 h was enough for a fruitful conversion. Oxidants, DDQ and H_2O_2 failed to produce the desired product even on continued reflux for long hours (30 h). In the case of benzoyl peroxide, a trace amount of product was formed after stirring for a longer period of time. The reaction outcome was the same under dioxxygen or atmospheric conditions (Table 1, entries 1–6) in the presence of TBHP. However the reaction did not proceed in the absence of TBHP. It is noteworthy to mention that the oxidant TBHP and base triethylamine are essential for demethylation reaction. The product yield did not change significantly on the increase of the quantity of TBHP or triethylamine from 2 to 4 equiv. indicating that 2 equiv. of the reagents are optimum for a successful reaction. In the absence of base, the desired product did not form, though the starting material was consumed completely. From the above

investigations it was concluded that the optimized condition for the demethylation reaction is to reflux a mixture of the *tert*-aniline in toluene in the presence of 2 equiv. each of triethylamine and TBHP for 3 h.

Under the optimized conditions, the substrate scope for the selective *N*-demethylation of *N*, *N*-dialkyl anilines was investigated and the results are shown in Table 2. Methyl groups were removed chemoselectively in the presence of other substitutions like *N*-allyl, *N*-benzyl, and *N*-ethyl anilines (Entries 17–19).

When *N*, *N*-diethylaniline was used as a substrate, trace amount of *N*-deethylation product was obtained and most of the starting material remained unreacted (Entry 20). This may be due to the steric effect. *Para*- and *meta*- substituted *N*, *N*-dimethylanilines converted into the corresponding *N*-demethylation products in

moderate to good yields. The oxidative *N*-demethylation of aromatic amines with electron-withdrawing group such as fluoro, chloro, bromo, iodo and trifluoromethyl on the ring gave moderate yields under the reaction conditions (Entries 7–11). It is noteworthy that strong electron withdrawing CN or Nitro at the para position severely passivated the oxidative *N*-demethylation (Entries 14 and 15) and produced no product even on prolonged reaction times, and the starting material was recovered almost completely.

Our efforts to extend this methodology to 1-methylmorpholine, 9-methyl-9H-carbazole were in vain. *N*-methyl aniline as a substrate was also found to be resistant (Scheme 2). To have an insight on the reaction mechanism, we conducted the reaction under the optimized conditions in the presence of the radical

Table 2. Substrate scope.

Entry	Substrate	Time (h)	product	% of yield	Entry	Substrate	Time (h)	product	% of yield
1		3		71	11		3		45
2		3		88	12		3		81
3		3		83	13		3		85
4		3		77	14		12		00
5		3		76	15		12		00
6		3		78	16		3		53
7		3		65	17		6		43
8		3		63	18		6		40
9		3		60	19		5		48
10		3		59	20		12		trace

Scheme 2. *N*-demethylation of other alkyl and aryl compounds.

Scheme 3. Control experiment.

trapper, TEMPO⁹ (Scheme 3). The yield of the demethylated product was not affected, indicating that the reaction may not proceed through a radical intermediate. The exact mechanism for the product formation is not clear at the present stage. However the results from control experiments and related literature^{7,10} indicate that hydrogen atom transfer (HAT), rather than single electron transfer (SET) may be involved.

4. Conclusions

A promising protocol for metal-free oxidative *N*-demethylation of arylamines with triethylamine as a base and *tert*-butyl hydroperoxide (TBHP) as oxidant was developed. The reaction is general, practical, inexpensive, non-toxic, and follows an environmentally benign method, with moderate to good yields.

Supplementary Information (SI)

All the spectra are available at www.ias.ac.in/chemsci.

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