

Cu(I) Mediated Deamination of N-Boc Aryl Hydrazines and Its Mechanistical Implications

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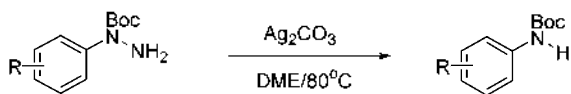
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Aryl amines are important structural motive in synthetic chemistry as they are frequently encountered in a number of natural products, pharmaceuticals and medicinal chemicals.¹ They are also embedded in a variety of polymeric materials utilizing their unique electro- and photochemical properties.² We have recently reported that N-Boc aryl hydrazines undergo Ag⁻¹ mediated deamination reactions to produce the corresponding N-Boc aryl amines in good to excellent chemical yields (Scheme 1).³



Scheme 1. Ag⁺ Mediated Deamination of N-Boc Aryl Hydrazines.

Particularly attractive is the mildness of the reaction conditions, tolerating an array of sensitive, otherwise incompatible, functional groups. Conventionally, N-Boc aryl hydrazines can be either reductively deaminated with Zn(0) in boiling acetic acid⁴ or treated with an acid to remove the Boc group prior to the subsequent reductive cleavage of the N-N bond.⁵ We have recently found that Cu⁺¹ can also catalyze the deamination reactions in the presence of a base. Herein, we wish to present the details of the Cu⁻¹ mediated deamination reaction as well as its mechanistical feature.

As is the case with Ag⁺¹, the basicity of the counter ion of the copper(I) salt plays a key role. While deamination occurs

with copper(I) acetate, albeit low in conversion, no reactions were observed with copper (I) halides in the absence of a base. The deamination does not go to completion with less than stoichiometric amount of either CuCl or NaOH. The deamination reaction proceeded most efficiently in anhydrous DME (Table 1).

Using the conditions in entry 5, we studied deamination reactions of other aryl hydrazides bearing various functional groups (Table 2).⁶

The aryl hydrazides with electron donating groups (entries 2, 4) undergo faster deaminations than those with electron withdrawing groups (entries 3, 5, 6, 7). Notable is that C-N bond cleavages were observed in entries 3, 5, 6, 7 and 8, where the products are nitrobenzene, benzonitrile, methyl benzoate, acetophenone and biphenyl, respectively. Due to their high volatility, the isolated yields of C-N bond cleavage products were not correctly measured except in entry 8, in which we isolated biphenyl in 13% yield. Crude NMR and TLC analyses indicate that the presence of electron withdrawing group facilitates the formation of C-N cleavage product.

The mechanism of the C-N bond cleavage is proposed in Scheme 2 as we obtained nitrobenzene from N-Boc 4-nitrophenyl hydrazine when heated with NaOH alone in DME. No deaminated product was produced.

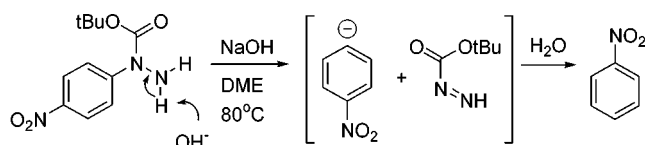
The proposed mechanism in Scheme 2 may not operate in the C-N bond cleavage reactions of the aryl hydrazides with electron donating group, due in part to the instability of the

Table 1. Deaminations in Various Solvents

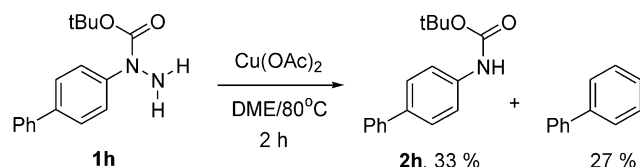
Entry	Solvent	Time (h)	Yield
1	benzene	24	52%
2	toluene	24	41%
3	THF	24	48%
4	CH ₂ Cl ₂	24	51%
5	DME	6	95%
6	EtOAc	24	67%
7	MeCN	24	72%
8	DMF	24	42%
9	DMSO	24	49%
10	MeOH	11	85%

Table 2. Deaminations of Various Other Aryl Hydrazides

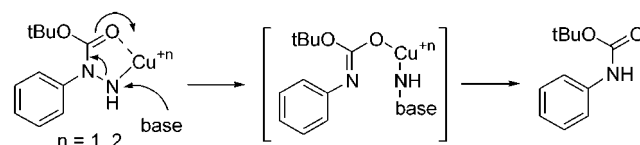
Entry	R	Time (h)	Yield (%)
1	H	6	95 (2a)
2	Me	10	80 (2b)
3	NO ₂	60	55 (2c)
4	MeO	4	81 (2d)
5	CN	48	73 (2e)
6	CO ₂ Me	80	71 (2f)
7	COMe	72	72 (2g)
8	Ph	11	77 (2h)



Scheme 2. Proposed Mechanism for the C-N Bond Cleavage.



Scheme 3. Cu(II) Mediated N-N and C-N Cleavage Reaction.



Scheme 4. Proposed Mechanism for the Deamination.

resulting aryl anions. In fact, the C-N bond cleavage reaction of N-Boc 4-biphenyl hydrazine was extremely slow under the above base-only conditions. Nevertheless, the C-N cleavage did occur to provide biphenyl in 25% yield after 24 h when two fold excess of NaOH was used. No deaminated product was detected in this case either.

From the control experiment using Cu^{+2} in lieu of Cu^{+1} , we isolated both deaminated product **2h** and biphenyl from N-Boc 4-biphenyl hydrazine, upon heating at 80 °C in DME (Scheme 3). Therefore, the deamination reaction would not be a reduction-oxidation process, but rather a Lewis acid promoted, base catalyzed elimination of NH_2 group.

Mechanistically, the deamination process may proceed through the pathway involving initial complexation with copper ion, followed by either ionic or radical cleavage pathway (Scheme 4).

The result in Scheme 3 further indicates that copper cation would facilitate the C-N bond cleavage reaction. The copper ion is presumed to stabilize the negative charge on the aryl

group via formation of aryl-cation complex.

In summary, we have found that copper cation can mediate the deamination reactions of N-Boc aryl hydrazines to produce N-Boc aryl amines in the presence of a base. The reaction is believed to proceed through the formation of copper chelate and subsequent elimination of NH_2 group. The accompanying C-N bond cleavage may also be viewed as an elimination of aryl anion with or without the aid of copper cation, depending on the substrate.

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6. Representative procedure: A mixture of N-Boc phenyl hydrazine (**1a**, 50 mg, 0.24 mmol), CuCl (24 mg) and NaOH (10 mg) in 2 mL of anhydrous DME was heated at 80 °C for 1h. Upon cooling to rt, the reaction mixture was partitioned into CH_2Cl_2 and H_2O . The separated organic layer was dried over MgSO_4 , concentrated in vacuo and purified by column chromatography (hexanes/ EtOAc : 15/1) to give 44 mg of N-Boc phenylamine **2a** as a white solid in 95% yield.