

Indium (Zinc)—Copper-Mediated Barbier-Type Alkylation Reaction of Nitrones in Water: Synthesis of Amines and Hydroxylamines

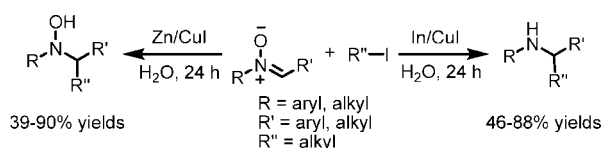
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ABSTRACT



An efficient method for the Barbier-type alkylation reaction of various nitrones (including chiral version) and alkyl halides in water is described. The amines and hydroxylamines can be obtained in good yields, depending on the judicious choice of the metal complexes used.

In recent years, there has been great interest in the development of organic reactions in aqueous media,¹ especially Barbier-type reactions in aqueous media.² The use of water as a solvent in organic synthesis has many advantages from both economical and environmental aspects.³ In conjunction with our interest in the development of new organic reactions in aqueous media for the functionalization of biomolecules,

our group has extensively studied the indium- or zinc-mediated allylation and alkylation reactions of carbonyl compounds and imines in aqueous media.^{2e–g,4} Most of the previously reported metal-mediated alkylation reactions were focused on the use of activated imines, such as sulfonimines, tosyl, aryl hydrazones, and glyoxylic oxime ethers, etc.⁵ However, due to the unstable nature of most imines, only limited imines could be employed in aqueous reactions. Successful cases usually employed methanol and water as

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cosolvent. To the best of our knowledge, the analogous metal-mediated alkylation reactions of more stable nitrones using alkyl halides in water have not been investigated. Herein, we report an efficient method for the alkylation of a wide variety of nitrones promoted by indium (zinc)-copper in aqueous media. The amines and hydroxylamines can be obtained depending on the judicious choice of the metal complexes used.

Initial studies were focused on the alkylation reaction of nitron **1a** and cyclohexyl iodide **2** under different reaction conditions. The results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions^a

		yield (%) ^b		
entry	conditions	3a	4a	
1	Sn/CuI	0	0	
2	Mg/CuI	0	0	
3	In/CuI	82	0	
4	In	6	0	
5	CuI	0	0	
6	In/CuBr	44	0	
7	In/CuCl	34	0	
8	In/AgI	61	0	
9	In/AgBr	40	0	
10	In/AgCl	29	0	
11	Fe/CuI	0	11	
12	Al/CuI	0	38	
13	Zn/CuI	0	90	
14	Zn	0	42	
15	Zn/CuBr	0	72	
16	Zn/CuCl	0	60	
17	Zn/AgI	0	79	
18	Zn/AgBr	0	60	
19	Zn/AgCl	0	58	

^a Reaction was carried out at rt for 1 day, using In or Zn (2 mmol), CuI (1 mmol), **1a** (0.5 mmol), cyclohexyl iodide (2 mmol), and water (10 mL).

^b Isolated yield.

As shown in Table 1, among the different metals investigated, indium and zinc (good reducing metals with high potential to mediate organic transformations via single-electron transfer process) were observed to be effective metals for the activation of the alkylation reaction of **1a** in water to obtain the corresponding amine **3a** and hydroxy-

Table 2. Alkylation Reactions of Nitrones in Water

entry	substrate	R''-I	product	yield (%) ^a
1	1a	cyclohexyl iodide	3a	82
2	1a	isobutyl iodide	3b	82
3	1a	cyclopentyl iodide	3c	74
4	1a	isopentyl iodide	3d	80 ^b
5	1b	isobutyl iodide	3e	62
6	1c	isobutyl iodide	3f	88
7	1d	isobutyl iodide	3g	78
8	1e	isobutyl iodide	3h	75
9	1f	isobutyl iodide	3i	81
10	1f	cyclopentyl iodide	3j	70
11	1g	isobutyl iodide	3k	55
12	1g	cyclohexyl iodide	3l	46
13	1h	isobutyl iodide	3m	72 ^c

^a Isolated yield. ^b Diastereomeric ratio: 54:46. ^c Diastereomeric ratio: 98:2.











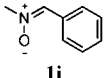


lamine **4a** in 82 and 90% yields, respectively (Table 1, entries 3 and 13). It was worth noting that without the use of CuI in In/CuI or Zn/CuI system, the reaction proceeded sluggishly to give the desired product in lower yield (Table 1, entries 4 and 14). In addition, the utilization of other copper salts instead of CuI produced the corresponding products in relatively low yields (Table 1, entries 6 and 7). Moreover, when silver salts were used, the desired product was obtained in lower yield as compared to the reactions carried out using copper iodide (Table 1, entries 8–10). It was also found that the use of metal such as indium is indispensable for the occurrence of this alkylation reaction (Table 1, entry 5). Interestingly, when Zn/CuI was used as reaction promoter,

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we found that the product was hydroxylamine **4a** rather than amine **3a**. Furthermore, it was observed that these reactions proceeded in lower yields in organic solvents than in water. For example, only 30 and 18% yields of amines were obtained using CH₃CN and MeOH as solvents for the In/CuI system, and 31 and 21% yields of the hydroxylamines were obtained using CH₃CN and MeOH as solvents for the Zn/CuI system.

By using the optimized reaction conditions (In/CuI or Zn/CuI), we further explored this reaction for various nitrones and alkyl iodides in water. The results are summarized in Table 2 and Table 3.

Table 3. Alkylation Reactions of Nitrones in Water

$ \begin{array}{c} \text{O}^- \\ \\ \text{R}-\text{N}^+-\text{C}=\text{R}' \\ \text{1a-h} \end{array} + \text{R}''-\text{I} \xrightarrow[\text{H}_2\text{O, rt, 24 h}]{\text{Zn/CuI}} \begin{array}{c} \text{OH} \\ \\ \text{R}-\text{N}-\text{C}-\text{R}' \\ \\ \text{R}'' \\ \text{4a-l} \end{array} $				
entry	substrate	R''-I	product	yield (%) ^a
1	1a		4a	68
2	1a		4b	90
3	1a		4c	88
4	1a		4d	83
5	1a		4e	49 ^b
6	1c		4f	54
7	1d		4g	78
8	1e		4h	64
9	1f		4i	80
10	1f		4j	61
11	 1i		4k	48
12	1h		4l	39 ^c

^a Isolated yield. ^b Diastereomeric ratio: 55:45. ^c Diastereomeric ratio: 88:12.

As shown in Table 2, In/CuI efficiently mediated the alkylation reactions of various nitrones in water at ambient temperature to afford the corresponding alkylated amines in moderate to good yields. It is noted that when alkyl substituted nitron **1b** was used, the reaction also proceeded efficiently with isopropyl iodide to furnish the desired product in good yield (Table 2, entry 5). It was gratifying to find that the alkylation reaction using In/CuI worked efficiently for chiral nitron **1h** and afforded the desired product in good yield and high diastereoselectivity (98:2 *dr*, Table 2, entry 13). This provides a potentially efficient method for the synthesis of chiral amines. No desired product was obtained

when primary iodides such as *n*-butyl iodide was used in the reaction.

As shown in Table 3, Zn/CuI also efficiently mediated the alkylation reactions of various nitrones in aqueous media at ambient temperature. The corresponding alkylated hydroxylamines were obtained in moderate to good yields. The reaction proceeded more efficiently for the substrate **1a** and cyclohexyl iodide yielding the product in 90% (Table 3, entry 2). Interestingly, this alkylation reaction could proceed smoothly using butyl iodide to afford the product in moderate yield (Table 3, entry 1). It was also found that a moderate yield of the desired product was obtained when **1i** and chiral nitron **1h** were used as substrates (Table 3, entries 11 and 12). The structures of products **4f** (see Supporting Information for details) and **4i** (Figure 1) were further confirmed by a single crystal X-ray diffraction analysis.⁶

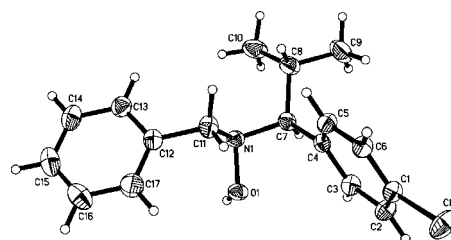
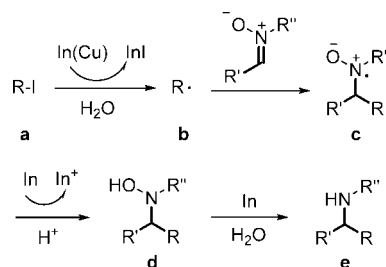


Figure 1. ORTEP diagram of the single-crystal X-ray structure of compound **4i**.

A plausible reaction mechanism was proposed to account for the alkylation reaction (Scheme 1). The reaction was

Scheme 1. Proposed Reaction Mechanism



initiated by a single-electron transfer (SET) from indium–copper to alkyl iodide **a** to generate an alkyl radical **b**. This radical **b** attacked the nitron to furnish a radical intermediate **c**. Subsequent indium-promoted reduction followed by the quenching of water afforded hydroxylamine **d**. Finally, **d** was further reduced via indium-mediated SET process to give the desired amine **e**.⁷

(6) Crystallographic data (including structure factors) for compounds **4f** and **4i** (CCDC 703861 and 703862) reported in this paper have been deposited with the Cambridge Crystallographic Data Center. See Supporting Information for details.

In summary, we have developed an efficient method for the Barbier-type alkylation reaction of different nitrones and alkyl halides in water. This finding sheds light on the fact that the alkylation reaction in the presence of In/CuI or Zn/CuI allows easy construction of a large library of amines or hydroxylamines. The mild reaction conditions, moderate to good yields, and the simplicity of the reaction procedure make this method attractive for scale-up purposes. Efforts to apply this method for the synthesis of complex molecules as well as expanding it to the intramolecular version are currently in progress.

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Supporting Information Available: Additional experiment procedures, spectra data for all the compounds, and two CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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