



# One-pot synthesis of hydrazine derivatives from aldehydes via radical addition reactions

Kim Ji Hye, Jang Doo Ok\*

Department of Chemistry, Yonsei University, Wonju 26493, Republic of Korea

## ARTICLE INFO

### Article history:

Received 27 April 2018

Revised 31 May 2018

Accepted 3 June 2018

Available online 4 June 2018

### Keywords:

One-pot  
Radical  
Aldehyde  
Hydrazine

## ABSTRACT

A one-pot procedure for the synthesis of hydrazine derivatives from aldehydes via radical addition reactions was developed. Lewis acids promoted both the condensation between aldehydes and benzhydrazide, and the alkyl radical addition to the C=O bond of hydrazones, affording moderate-to-high yields of hydrazine derivatives. The present process provides a tin-free radical, sustainable, and eco-friendly synthetic method.

© 2018 Elsevier Ltd. All rights reserved.

## Introduction

The hydrazine scaffold is a common skeleton in biologically active compounds.<sup>1</sup> Hydrazine derivatives are frequently employed as precursors of various heterocyclic compounds.<sup>2</sup> They also serve as protected amines, which are transformed to amines by *N-N* bond cleavage.<sup>3</sup> However, hydrazines, including structurally simple alkyl hydrazines are difficult to synthesize directly from hydrazine, affording low yields and complex mixtures of products.<sup>4</sup> One of the most reliable methods to prepare hydrazine derivatives is the nucleophilic addition to hydrazones.<sup>5</sup> However, strong nucleophiles such as organometallic compounds are required due to the intrinsically low reactivity of hydrazones. The use of organometallic reagents promotes the deprotonation of  $\alpha$ -hydrogens, thus, requires anhydrous conditions and often results in side reaction products.

These problems can be avoided by employing radical reactions. Radical species are neutral, and thus, are not affected by moisture. It has been shown that radical reactions can be performed in aqueous conditions.<sup>6</sup> Recently, we found that radical reactions proceed smoothly “on water” conditions with a significant solvent effect of water.<sup>7</sup> In addition, radical reactions provide several advantages over ionic reactions including high chemoselectivity and low tendency of rearrangement reactions.

It has been reported that radicals add to C=N bond of imine derivatives, including *N*-acyl hydrazones,<sup>8a-d</sup> *N,N*-dialkyl

hydrazones,<sup>8e-g</sup> *O*-benzyl oximes,<sup>8h-o</sup> *N*-tosyl imines,<sup>8p-s</sup> *N*-acyl imines,<sup>8t</sup> *N*-Boc-imines,<sup>8u</sup> and *N-tert*-butanesulfonyl imines.<sup>8v</sup> Some imine derivatives require Lewis acids to promote the radical addition reactions due their low reactivity.<sup>9</sup>

Generally, imine derivatives are prepared by the condensation of aldehydes with hydrazine derivatives in the presence of Lewis acids. Furthermore, radical additions to C=N bonds are more feasible than that to C=O bonds. Considering that Lewis acids are employed in both the preparation of imine derivatives and radical addition reactions, and the large reactivity difference between the C=N and C=O bonds towards radical addition reactions, a one-pot multi-component procedure was designed for the synthesis of hydrazines from aldehydes via radical addition reactions. One-pot multi-component reactions are sustainable and eco-friendly synthetic methods that form more than one bond in a single step and generate minimal waste.<sup>10</sup>

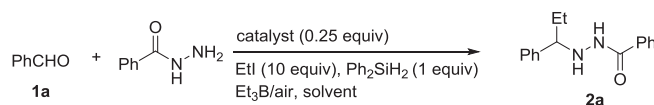
## Results and discussions

Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O is known to promote the condensation between aldehydes and hydrazine,<sup>11</sup> and a mixture of THF and (CH<sub>2</sub>Cl)<sub>2</sub> has been reported as the optimal solvent system for radical reactions.<sup>8a</sup> Bearing these facts in mind, we examined the one-pot radical addition reaction to hydrazones employing benzaldehyde, benzhydrazide, ethyl iodide, and diphenylsilane in the presence of Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O in THF:(CH<sub>2</sub>Cl)<sub>2</sub> (v/v, 1:1) at room temperature. A solution of triethylborane was added portion-wise to the reaction mixture to maintain chain conditions, affording the ethyl-added product **2a** in 40% yield (Table 1, entry 1). A variety of Lewis acids

\* Corresponding author.

E-mail address: [dojang@yonsei.ac.kr](mailto:dojang@yonsei.ac.kr) (D.O. Jang).

**Table 1**  
Screening of reaction conditions for the one-pot synthesis of **2a** from benzaldehyde **1a**.



Entry	Catalyst	Solvent	Et <sub>3</sub> B (equiv) <sup>a</sup>	Time (h)	Yield (%) <sup>b</sup>
1	Zn(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	3.5	28	40
2	ZnCl <sub>2</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	62
3	SnCl <sub>2</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	46
4	Mg(ClO <sub>4</sub> ) <sub>2</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	55
5	MgBr <sub>2</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	67
6	In(OTf) <sub>3</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	45
7	Sc(OTf) <sub>3</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	76
8	Yb(OTf) <sub>3</sub>	THF:(CH <sub>2</sub> Cl) <sub>2</sub> (v/v, 1:1)	2.5	20	78
9	Yb(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	4.5	36	64
10	Yb(OTf) <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	2.5	20	52
11	Yb(OTf) <sub>3</sub>	THF	2.5	20	50
12	Yb(OTf) <sub>3</sub>	MeOH	4.5	36	54

<sup>a</sup> 0.5 Equiv of triethylborane (1 M solution in THF) was added every 4 h.

<sup>b</sup> Isolated yield.

such as ZnCl<sub>2</sub>, SnCl<sub>2</sub>, Mg(ClO<sub>4</sub>)<sub>2</sub>, MgBr<sub>2</sub>, In(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, and Yb(OTf)<sub>3</sub> were screened (entries 2–8). It was found that Sc(OTf)<sub>3</sub> and Yb(OTf)<sub>3</sub> catalyzed the reaction efficiently to give the ethyl-added product **2a** in 76% and 78% yields, respectively (Table 1, entries 7 and 8). Due to their high reactivity and inertness toward air and water, Sc(OTf)<sub>3</sub> and Yb(OTf)<sub>3</sub> have been previously used as efficient Lewis acid catalysts in organic reactions.<sup>12</sup> Subsequently, various solvents were screened for the Yb(OTf)<sub>3</sub>-catalyzed reaction such as CH<sub>2</sub>Cl<sub>2</sub>, THF, (CH<sub>2</sub>Cl)<sub>2</sub>, and MeOH (entries 9–12). Nevertheless, the combination of THF and (CH<sub>2</sub>Cl)<sub>2</sub> (v/v, 1:1) turned out to be the best choice of the solvent.

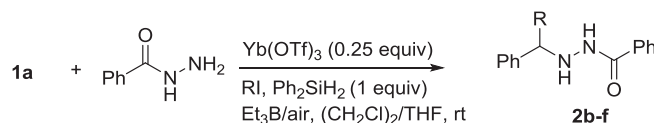
Under the optimized reaction conditions, the radical addition of various alkyl iodides was investigated. The results are presented in Table 2. The reaction with 10 equiv of isopropyl iodide afforded the isopropyl-added product **2b** in 59% yield (Table 2, entry 1). Upon increasing the amount of isopropyl iodide to 30 equiv, the yield of the addition product **2b** increased to 80% (entry 2). A similar tendency was observed in the reaction with cyclohexyl iodide. Thus, the reaction with 10 equiv of cyclohexyl iodide gave the corresponding addition product **2c** in 63% yield, while the reaction with 30 equiv afforded **2c** in 81% yield (entries 3 and 4, respectively). The lower yields of addition product using 10 equiv of alkyl iodides was attributed to the competition reaction between the alkyl radical and ethyl radical, which is produced from triethylborane. The

reaction with tertiary alkyl iodides took place smoothly to give the corresponding addition products in moderate-to-high yields (entries 5 and 6). The addition of a primary radical was examined using *n*-octyl iodide affording 64% isolated yield (entry 7).

Subsequently, the scope and limitations of the reaction with respect to the aldehyde substrate were investigated. Reactions using isopropyl iodide were performed with various aldehydes under the optimized reaction conditions. The results are summarized in Table 3. Aryl aldehydes bearing a halogen group such as fluorine and chlorine at the 4-position gave high yields of isopropyl-added products (Table 3, entries 1 and 4). Instead, halide substituents at the 2-position gave lower yields (entries 3, 6, and 7). The drop in the yield might be caused by the steric hindrance of the halide near the reaction site. Aryl aldehydes bearing a strong electron-donating or electron-withdrawing group showed a deteriorating effect on the outcome of the radical addition reaction to the C=N bond (entries 8 and 9). The aliphatic aldehyde cyclohexyl aldehyde gave the corresponding addition product in high yield, instead *n*-octyl aldehyde, which is an aliphatic aldehyde with a long chain, provided a lower yield (entries 11 and 12, respectively). The reaction with *tert*-butyl aldehyde did not proceed, possibly due to high steric hindrance.

A plausible mechanism for the synthesis of hydrazine derivatives from aldehydes via radical addition reactions is depicted in

**Table 2**  
Synthesis of hydrazine derivatives from **1a** with various alkyl iodides.



Entry	R (equiv)	Et <sub>3</sub> B (equiv) <sup>a</sup>	Time (h)	Product	Yield (%) <sup>b</sup>
1	<sup>i</sup> Pr (10)	3.5	28	<b>2b</b>	59
2	<sup>i</sup> Pr (30)	3.5	28	<b>2b</b>	80
3	<sup>h</sup> Hex (10)	2.5	20	<b>2c</b>	63
4	<sup>h</sup> Hex (30)	3.0	24	<b>2c</b>	81
5	<sup>t</sup> Bu (30)	3.5	28	<b>2d</b>	79
6	1-Ad (30)	3.0	24	<b>2e</b>	69
7	<i>n</i> -Oct (30)	3.0	24	<b>2f</b>	64

<sup>a</sup> 0.5 Equiv of triethylborane (1 M solution in THF) was added every 4 h.

<sup>b</sup> Isolated yield.

Download English Version:

<https://daneshyari.com/en/article/7828643>

Download Persian Version:

<https://daneshyari.com/article/7828643>

[Daneshyari.com](https://daneshyari.com)