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PII:	\$0040-4039(18)30736-6
DOI:	https://doi.org/10.1016/j.tetlet.2018.06.007
Reference:	TETL 50045
To appear in:	Tetrahedron Letters

Received Date:27 April 2018Revised Date:31 May 2018Accepted Date:3 June 2018



Please cite this article as: Hye Kim, J., Ok Jang, D., One-pot synthesis of hydrazine derivatives from aldehydes via radical addition reactions, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.007

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Tetrahedron Letters

journal homepage: www.elsevier.com

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

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: One-pot Radical Aldehyde Hydrazine 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=N 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.

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ACCEPTED MANUSCRIPT Tetrahedron Letters

1. Introduction

The hydrazine scaffold is a common skeleton in biologically active compounds.¹ Hydrazine derivatives are frequently employed as precursors of various heterocyclic compounds.² They also serve as protected amines, which are transformed to amines by N-N bond cleavage.³ However, hydrazines, including structurally simple alkyl hydrazines are difficult to synthesize directly from hydrazine, affording low yields and complex mixtures of products.⁴ One of the most reliable methods to prepare hydrazine derivatives is the nucleophilic addition to hydrazones.⁵ 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 α -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.⁶ Recently, we found that radical reactions proceed smoothly "on water" conditions with a significant solvent effect of water.⁷ 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,^{8a-d} *N*,*N*-dialkyl hydrazones,^{8e-g} *O*-benzyl oximes,^{8h-o} *N*-tosyl imines,^{8p-s} *N*-acyl imines,^{8t} *N*-Boc-imines,^{8u} and *N*-tert-butanesulfinyl imines.^{8v} Some imine derivatives require Lewis acids to promote the radical addition reactions due their low reactivity.⁹

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 **Table 1**. Screening of reaction conditions for the one-not synthe 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.¹⁰

2. Results and discussions

 $Zn(ClO_4)_2.6H_2O$ is known to promote the condensation between aldehydes and hydrazine, 11 and a mixture of THF and (CH₂Cl)₂ has been reported as the optimal solvent system for radical reactions.¹² 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(ClO₄)₂.6H₂O in THF:(CH₂Cl)₂ (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 such as $ZnCl_2$, $SnCl_2$, $Mg(ClO_4)_2$, MgBr₂, In(OTf)₃, Sc(OTf)₃, and Yb(OTf)₃ were screened (entries 2-8). It was found that Sc(OTf)₃ and Yb(OTf)₃ 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)₃ and Yb(OTf)₃ have been previously used as efficient Lewis acid catalysts in organic reactions.¹³ Subsequently, various solvents were screened for the Yb(OTf)₃-catalyzed reaction such as CH₂Cl₂, THF, (CH₂Cl)₂, and MeOH (entries 9–12). Nevertheless, the combination of THF and (CH₂Cl)₂ (v/v, 1:1) turned out to be the best choice of the solvent.

	PhCHO ⁺ Ph 1a	NH2 H Etl (10 equiv), P Et ₃ B/air, solvent	quiv) ▶ h₂SiH₂ (1 equiv)	$\begin{array}{c} Ph \xrightarrow{Et} & H \\ Ph \xrightarrow{N} & N \\ H & O \\ \mathbf{2a} \end{array} $	
entry	catalyst	solvent	Et ₃ B (equiv) ^a	time (h)	yield (%) ^b
1	$Zn(ClO_4)_2.6H_2O$	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	3.5	28	40
2	ZnCl ₂	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	62
3	SnCl ₂	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	46
4	Mg(ClO ₄) ₂	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	55
5	MgBr ₂	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	67
6	In(OTf) ₃	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	45
7	Sc(OTf) ₃	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	76
8	Yb(OTf) ₃	THF:(CH ₂ Cl) ₂ (v/v, 1:1)	2.5	20	78
9	Yb(OTf) ₃	CH_2Cl_2	4.5	36	64
10	Yb(OTf) ₃	(CH ₂ Cl) ₂	2.5	20	52
11	Yb(OTf) ₃	THF	2.5	20	50
12	Yb(OTf) ₃	МеОН	4.5	36	54

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

^a0.5 equiv of triethylborane (1 M solution in THF) was added every 4 h. ^bIsolated yield

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).

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

1a		O ↓ NHa	Yb(OTf) ₃ (0.25 equiv)		
	+	Ph N N	RI, Ph_2SiH_2 (1 equiv) Et ₃ B/air, (CH ₂ CI) ₂ /THF, rt	H O 2b-f	

R

entry	R (equiv)	Et ₃ B (equiv) ^a	time (h)	product	yield (%) ^b
1	^{<i>i</i>} Pr (10)	3.5	28	2b	59
2	^{<i>i</i>} Pr (30)	3.5	28	2b	80
3	^c Hex (10)	2.5	20	2c	63
4	^c Hex (30)	3.0	24	2c	81
5	^t Bu (30)	3.5	28	2d	79
6	1-Ad (30)	3.0	24	2e	69
7	<i>n</i> -Oct (30)	3.0	24	2f	64

 $^{\rm a}0.5$ equiv of triethylborane (1 M solution in THF) was added every 4 h. $^{\rm b}Isolated$ yield.

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.

Table 3. Synthesis of hydrazine derivatives from various aldehydes via isopropyl radical addition

O II	, Ŭ	NHa	Yb(OTf) ₃ (0.25	5 equiv)		
R H ⁺ Ph N ^{/,11/2} H H 1b-n			⁷ PrI (30 equiv), Ph ₂ SiH ₂ (1 equiv) R ² Et ₃ B/air, (CH ₂ CI) ₂ /THF, rt			NH 0 3a-I
entry	R		Et ₃ B (equiv) ^a	time (h)	product	yield (%) ^b
1	4-F-C ₆ H ₄	1b	3.5	28	3a	82
2	$3\text{-}\text{F-}\text{C}_6\text{H}_4$	1c	3.0	24	3b	76

3	$2\text{-}\text{F-}\text{C}_6\text{H}_4$	1d	3.5	28	3c	70
4	4-Cl-C ₆ H ₄	1e	3.5	28	3d	84
5	3-Cl-C ₆ H ₄	1f	3.0	24	3e	73
6	2-Cl-C ₆ H ₄	1g	3.5	28	3f	71
7	2-Br-C ₆ H ₄	1h	4.0	32	3g	68
8	4-NO ₂ - C ₆ H ₄	1i	3.5	28	3h	60
9	4-MeO- C ₆ H ₄	1j	4.0	32	3 i	56
10	4-Et-C ₆ H ₄	1k	3.5	28	3ј	71
11	^c Hex	11	2.5	20	3k	81
12	"Oct	1m	3.0	24	31	60
13	'Bu	1n	3.0	24	-	NR

^a0.5 equiv of triethylborane (1 M solution in THF) was added every 4 h. ^bIsolated yield.

A plausible mechanism for the synthesis of hydrazine derivatives from aldehydes via radical addition reactions is depicted in Scheme 1. Yb(OTf)₃ promotes the condensation of the aldehyde with benzhydrazide, producing a hydrazone. The ethyl radical that is formed by the reaction of Et₃B with O₂ reacts with the alkyl halide to generate an alkyl radical. This radical then adds to the C=N bond of the hydrazone to form a radical intermediate. The radical addition reaction is also assisted by Yb(OTf)₃. The radical intermediate abstracts a hydrogen from Ph₂SiH₂ to give the final product.



Scheme 1. Plausible mechanism of the one-pot procedure for the synthesis of hydrazines from aldehydes via radical addition reactions

3. Conclusions

We have developed a one-pot procedure for the synthesis of hydrazine derivatives from aldehydes via a radical addition reaction. Lewis acids promoted the condensation between various aldehydes and benzhydrazide, and the alkyl radical addition to the C=N bond of hydrazones. The present process is a tin-free radical reaction using non-toxic diphenylsilane as the radical chain carrier and hydrogen source, providing a sustainable and eco-friendly synthetic method.

Typical experimental procedure for the synthesis of hydrazine derivatives: A solution of triethylborane (0.25 mL, 0.25 mmol, 1 M solution in THF) was added to a solution of aldehyde (0.50 mmol), benzhydrazide (0.50 mmol, 78 mg), diphenylsilane (0.50 mmol, 0.09 mL), and alkyl halide (15 mmol) in the presence of Yb(OTf)₃ (0.125 mmol, 77.5 mg) in (ClCH₂)₂/THF (v/v, 1:1) (5 mL) at room temperature. Further triethylborane (0.25 mL, 1 M solution in THF) was added every 4 h and air was injected

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through a needle fixed directly above the solution until the entire starting material was consumed (as monitored by TLC). When the reaction was complete, the mixture was treated with saturated aqueous NaHCO₃ (5 mL). The aqueous phase was extracted with CH_2Cl_2 twice, and the organic layer was washed with brine and dried over MgSO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Highlights

- A one-pot procedure for the synthesis of hydrazine derivatives.
- Acception