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The Reductive Addition Reaction of Substituted 2-Chloromethyl-1, 3, 4-oxadiazole to Aldehydes and Ketones Promoted by Samarium Diiodide

Xiao Liang XU[1], Wei Min ZHU[1], Yong Min ZHANG[1,2]*

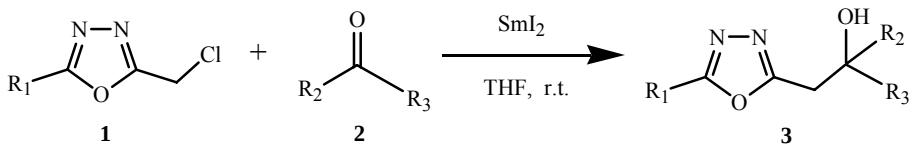
[1] Department of Chemistry, Zhejiang University, Xixi Campus, Hangzhou 310028
[2] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032

Abstract: 1-(β-Hydroxyalkyl)-1,3,4-oxadiazole derivatives were synthesized *via* reductive addition reactions of 2-chloromethyl-1,3,4-oxadiazole with carbonyl compounds under mild conditions promoted by SmI_2.

Keywords: Reductive addition, samarium diiodide, 1-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives, synthesize.

The metal mediated carbon-carbon bond formation between alkyl halides and carbonyl compounds, the barbier-type reaction, is a fundamental reaction in organic chemistry[1]. Such a reaction has played the key role in synthesizing numerous important biological and abiological compounds. SmI_2, the Kagan's reagent, has found the most widespread application to promote the inter- and intramolecular Barbier-type reactions[2]. A large variety of organic halides such as, primary and secondary alkyl halides, allylic and benzylic halides, 1-iodoalkynes, α-heterosubstituted alkyl halides can be used as substrates in this transformation[2e]. In contrast, the α-heterocyclic substituted alkyl halides have remained unexplored. To the best of our knowledge, no literature reported the synthesis of 1-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives by using SmI_2 as a reagent. Herein, we wish to describe a novel Barbier-type reaction of 2-chloromethyl-1,3,4-oxadiazole[3] with carbonyl compounds promoted by SmI_2 (**Scheme 1**).

Scheme 1



1 **2** **3**

* E-mail: yongminzhang@css.zju.edu.cn

When substrates **1** and carbonyl compounds **2** were added to a solution of 2.2 equiv. of SmI_2 in THF at room temperature under a nitrogen atmosphere, the deep blue color of SmI_2 changed to a yellow color immediately. TLC showed that the reductive coupling reaction was complete within a few minutes and afforded 1-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives smoothly in good to excellent yields upon subsequent protonation. 1,3,4-Oxadiazole ring is associated with many types of biological properties such as anti-inflammatory, hypoglycemic, antifungal and antibacterialactivities[4].

To investigate the ability of SmI_2 to promote these Barbier-type reactions, different experiments were performed. **Table 1** summarizes our results. All the reactions were completed at room temperature within 5 minutes. The reactions proceeded in good to excellent yields for the aliphatic aldehydes and ketones. However, when acetophenone or benzaldehyde used as substrates, which are more easily reduced to pinacol by samarium diiodide than aliphatic aldehydes and ketones, they only gave complex mixtures. When 0.5 mL HMPA or 2 mmol MeOH were added to the reaction system, the yields of the products were relatively lower.

Table 1 Babier-type reaction of 2-chloromethyl-1, 3, 4-oxadiazole with carbonyl compounds promoted by SmI_2

Entry	R_1	R_2, R_3	Product	Yield(%)[a, b]
1	C_6H_5	CH_3, CH_3	**3a**	93, 87[c], 65[d]
2	C_6H_5	H, $(CH_3)_2CH$	**3b**	89
3	C_6H_5	CH_3, $(CH_3)_2CHCH_2$	**3c**	93
4	C_6H_5	cyclohexanone	**3d**	89
5	C_6H_5	cyclopentanone	**3e**	85
6	4-$CH_3OC_6H_4$	CH_3, CH_3CH_2	**3f**	91
7	4-$CH_3OC_6H_4$	CH_3, $CH_3(CH_2)_2$	**3g**	82
8	4-$CH_3OC_6H_4$	H, $(CH_3)_2CHCH_2$	**3h**	74
9	4-$CH_3OC_6H_4$	cyclohexanone	**3i**	87
10	4-$CH_3OC_6H_4$	CH_3, $CH_3(CH_2)_4$	**3j**	88

a) All compounds were fully characterized by ^1H NMR, MS, EA and IR. b) Yields refer to % of isolated products based on substrate **1**. c) 0.5 mL HMPA was added. d) 2 mmol MeOH was added.

Although the mechanism of the above reaction has not been studied, for the initial formation of a radical species and its further reduction to an organosamarium species by the second equivalent of samarium diiodide the requirement of at least two molar equivalents of samarium diiodide would be suggested.

In conclusion, the present procedure is an efficient method for the synthesis of 1-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives. With its simplicity and milder reaction conditions, this procedure may provide a practical synthetic method of 1-(β-hydroxy-alkyl)-1,3,4-oxadiazole derivatives.

Acknowledgment

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5. *General procedure for the preparation of 1-(β-hydroxyalkyl)-1,3,4-oxadiazole derivatives (**3**):* A solution of 2-chloromethyl-1,3,4-oxadiazole (1 mmol) with aldehydes or ketones (1.2 mmol) in dry THF (3 mL) was added to the solution of SmI_2 (2.2 mmol) in THF (20 mL) at room temperature under a nitrogen atmosphere. The deep blue color of the solution immediately changed to yellow. After being stirred for 5 minutes (**Table 1**, the reaction was monitored by TLC), the reaction mixture was quenched with 0.1 mol/L hydrochloric acid (5 mL) and extracted with ether (3×15 mL). The organic phase was successively washed with brine (15 mL), water (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products, which were purified by preparative TLC using ethyl acetate and cyclohexane (1:2) as eluant.
6. All of the products obtained in this study were characterized (^{1}H NMR, MS, IR, EA). For example, product **3a**: m.p. 80-82°C; IR (KBr) ν (cm^{-1}): 3312, 2939, 2867, 1623, 1571, 1436, 1249, 724; ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): 8.04-8.07 (2H, m), 7.51-7.57 (3H, m), 3.13 (2H, s), 2.95 (1H, brs), 1.44 (6H, s); MS (70 *e*V) *m/z* (%): 219 (M^++1, 2.93), 203 (7.93), 160 (100), 131 (2.21), 118 (20.32), 77 (39.39); Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04, H 6.47, N 12.84; Found C 66.17, H 6.51, N 12.73.

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