STUDY ON THE SYNTHESIS OF AMINOALCOHOL VIA REACTION BETWEEN ALDEHYDE AND IMINE BY SAMARIUM (II) IODIDE CATALYST

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Abstract: *Samarium (II) iodide (SmI_2) has become one of the common, effective catalysts for coupling reactions between carbonyl compounds to form 1,2-diol by initiating free radical formation. In this paper, we present the results of studying the role of SmI_2 catalyst on the aza-pinacol coupling reaction between aldehyde and imine under different mole ratios of SmI_2, temperature and solvent conditions. The results showed that, in the THF solvent, at -78 °C, with 2.0 mole equivalent of the SmI_2 catalyst, the reaction of pinacol coupling produces 1,2-aminoalcohols with efficiency of up to 91% yield and limited 1,2-diol by product.*

Keywords: Samarium (II) iodide; Aminoalcohol; Pinacol coupling; Imine.

1. INTRODUCTION

Samarium (II) iodide, first discovered and published by Kagan, has become one of the most widely used free radical catalysts in organic synthesis, especially in reactions involving both carbonyl compounds [1]. Due to the small redox-reduction potential ($E^0_{(Sm^{2+}/Sm^{3+})}$ = - 1,33 V) and maybe adjust the changes according to the reaction environment by adding water, alcohol or ligands such as: hexamethylphosphoramit (HMPA) hoặc 1,3-dimethyl-3,4,5,6-tetrahydro-2 (1H) – pyrimidinone (DMPU),… which can change the activity, selectivity as well as the product yield [2, 3]. Therefore, there are many publications on carbon-carbon coupling reaction between carbonyl compounds with imine compounds or derivatives (oximes, imine, iminium salts, hydrazone and nitrones) using samarium (II) iodide as a catalyst in organic synthesis as well as synthesis of bioactive molecules [4]. Aminoalcohols, product of the coupling reaction between aldehydes and imines, are a privileged structure found in biologically active natural products as well as important intermediates, chiral auxiliaries or metal ligand in catalytic asymmetric synthesis. However, one of the limitations of this catalyst in the coupling reaction is the formation of many by products due to the homocoupling reaction between aldehydes or between imines [5]. In this paper, we present some research results on the C-C cross coupling reaction between imine and aldehydes to form aminoalcohol corresponding in high yield and excellent selectivity.

2. EXPERIMENTAL

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and dry conditions. The reaction mixtures have been magnetically stirred with teflon stirring bars, and the temperatures were measured externally. All the reactions have been monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of *n*-pentane and ethyl acetate (EtOAc), with detection by UV light, or a $KMnO_4$ staining solution. Acros silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Infrared spectrum has been recorded with Spectrum Two, Perkin Elmer at Le Quy Don Technical University. The nuclear magnetic resonance (NMR) spectra have been recorded with Brucker Avance 500 MHz spectrometers at Vietnam National University. ^{1}H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using δ ($CDCl_3$) = 7.26 ppm as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using δ ($CDCl_3$) = 77.0 ppm as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (qt), multiplet (m) or br (broad).

General procedure for synthesis of aminoalcohol using catalyst SmI_2: A solution of samarium (II) iodide 0.1 M in anhydrous tetrahydrofuran (THF) (20 mL, 2 mmol) was cooled to -78^{o}C under a atmosphere nitrogen, and solution of imine mixture **2a-f** (1 mmol, 1.0 eq) and aldehydes **1a-f** (1.2 mmol, 1.2 eq) in anhydrous THF (10 mL) was carefully added. The reaction mixture was kept under magnetic stirring at -78^{o}C until the starting material disappeared (TLC monitoring). After addition of saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was filtered through a layer of Celite, extracted with ethyl acetate (3 x 10 mL) and then the organic phase was dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude product was purified by silica gel chromatography (eluent hexane/EtOAc: 10/1) and the reaction yield is calculated on the weight of **3a-f** product.

1,2-diphenyl-2-anilinoethanol (3a): Prepared according to the general method: 20 mL SmI_2, *N.1*-diphenylmetanimine (181 mg, 1 mmol, 1.0 eq) and benzaldehyde (127 mg, 1.2 mmol, 1.2 eq). The product **3a** was isolated as Moon-colored solid (254.6 mg, 88% yield). R_f = 0.22 (hexane/EtOAc: 10/1). IR (cm^{-1})**:** $\upsilon_{\text{-NH}}$: 3588; υ_{OH}: 3308; $\upsilon_{\text{=C-H (aren)}}$: 3063, 3030; $\upsilon_{CH(sp3)}$: 2900, 2885, $\upsilon_{\text{=C-C (aren)}}$: 1603,1495; $\upsilon_{C\text{-}N}$: 1033. ^{1}H NMR (500 MHz. $CDCl_3$) δ (ppm): 7.28-7.05 (m, 15H, *aromatic*); 4.77 (d, *J* = 1.5Hz, 1H (CH-OH)); 4.63 (d, *J* = 2.4Hz,1H, (CH-NH)); 3.11 (s, 1H, NH); 2.46 (s, 1H, OH). ^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 139.9, 139.7, 128.14, 128.1, 127.9, 127.8, 127.1, 126.9, 79.0, 76.8.

2-Anilino-2-(4-methylphenyl)ethanol (3b): Prepared according to the general method: 20 mL SmI_2, *N.1*-diphenylmetanimine (181 mg. 1 mmol. 1.0 eq) and 4-metyl-benzaldehyhe (144 mg. 1.2 mmol. 1.2 eq). The product **3b** was isolated as yellow liquid (276.1 mg, 91% yield). R_f = 0.24. IR (cm^{-1})**:** $\upsilon_{\text{-NH}}$: 3518; υ_{OH}: 3398; $\upsilon_{\text{=C-H (aren)}}$:3051, 3025; $\upsilon_{CH(sp3)}$: 2921, $\upsilon_{\text{=C-C (aren)}}$: 1601,1501; $\upsilon_{C\text{-}N}$: 1045. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.10-6.87 (m, 11H, *aromatic*); 6.49-6.33 (m, 3H); 4.71-4.69 (dd, *J* = 13.0, 4.6 Hz,1H); 4.35-4.33 (dd, *J* = 11.5, 6.5 Hz, 1H); 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 147.35, 140.39, 137.69, 137.56, 129.30, 129.09, 129.06, 129.05, 127.90, 127.31, 117.93, 113.96, 64.77, 63.51, 21.15.

2-Anilino-2-(4-bromophenyl)ethanol (3c): Prepared according to the general method: 20 mL, SmI_2, *N.1*-diphenylmetanimine (181 mg. 1 mmol. 1.0 eq) và 4-bromo-benzaldehyhe (222 mg. 1.2 mmol. 1.2 eq.). The product **3c** was isolated as yellow liquid (271.5 mg, 85% yield). R_f = 0.25. IR (cm^{-1})**:** $\upsilon_{\text{-NH}}$: 3506; υ_{OH}: 3348; $\upsilon_{\text{=C-H (aren)}}$: 3031; $\upsilon_{CH(sp3)}$: 2902; $\upsilon_{\text{=C-C (aren)}}$: 1600.1502; $\upsilon_{C\text{-}N}$: 1085. ^{1}H NMR (500 MHz. $CDCl_3$) δ (ppm): 7.87-7.79 (m, 2H, *aromatic*); 7.45-7.21 (m, 9H, *aromatic*); 7.05-6.84 (m. 2H. *aromatic*); 5.12 (d, *J* = 5.5 Hz, 1H); 4.36 (dd, *J* = 8.5, 6.2 Hz, 1H); 3.94 (s, 1H); 3.35 (s, 1H). ^{13}C NMR (125MHz. $CDCl_3$) δ (ppm): 146.78, 140.16, 137.65, 131.88, 129.03, 128.74, 128.35, 128.01, 126.59, 121.85, 121.06, 116.14, 73.15, 60.05.

2-Anilino-2-(4-methoxyphenyl)ethanol (3d): Prepared according to the general method: 20 mL, diphenylmetanimine (181 mg, 1 mmol, 1.0 eq) và 4-methoxybenzandehyde (220 mg, 1.2 mmol. 1.2 eq). The product **3d** was isolated as yellow liquid (309.3 mg, 84% yield). R_f = 0.25. IR (cm-1): υ-NH: 3545; υOH: 3398; υ=C-H (aren):3051, 3025; υCH(sp^3): 2920; υ=C-C (aren): 1601,1501; υC-N : 1045. 1H NMR (500 MHz, CDCl3) δ (ppm): 7.41 – 7.25 (m, 7H); 7.11 – 6.97 (m, 2H); 6.95 – 6.87 (m, 5H); 6.82 – 6.79 (m, 2H); 5.88 (d, *J* = 7,0 Hz, 1H); 5.06 – 5.01 (m, 1H); 4.77 (d, *J* = 7,3 Hz, 1H); 3.83 (d, *J* = 4,4 Hz, 1H); 3.67 (s, 2H). 13C NMR (125MHz. CDCl3) δ (ppm): 160.12, 148.24, 138.67, 136.27, 129.59, 129.34, 128.71, 127.85, 127.61, 120.02, 117.03, 115.62, 76.18, 61.15, 54.37.

1.2 -diphenyl-2-(*tert*-butylsulfinyl)imino ethanol (3e): Prepared according to the general method: 20 mL, *N*-benzylidene-*tert*-butylsulfinylimine (209 mg, 1 mmol, 1.0 eq.) và benzaldehyde (127 mg, 1.2 mmol, 1.2 eq.). The product **3e** was isolated as yellow liquid (253.6 mg, 80% yield). R_f = 0.21. IR (cm^{-1})**:** $\upsilon_{\text{-NH}}$: 3533; υ_{OH}: 3356; $\upsilon_{\text{=C-H (aren)}}$: 3032; $\upsilon_{CH(sp^3)}$: 2925,

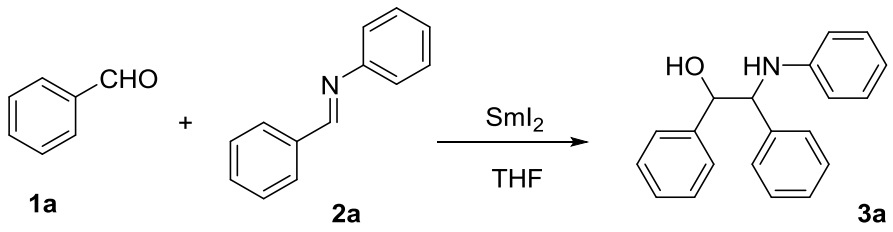
2902; $\upsilon_{=C-C\ (aren)}$: 1601,1546; υ_{C-N}: 1050. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 – 7.39 (m, 2H *aromatic*); 7.36 – 7.28 (m, 8H *aromatic*); 5.23 (dd, *J* = 6.6, 1.0 Hz, 1H); 4.55 (dd, *J* = 8.5, 6.1Hz, 1H); 4.29 (d, *J* = 5.8 Hz, 1H); 3.74 (d, *J* = 4.6 Hz, 1H); 1.46 (s, 9H). ^{13}C NMR (125MHz. $CDCl_3$) δ (ppm): 143.12, 140.58, 129.43, 129.24, 128.37, 128.14, 127.95, 126.87, 76.47, 65.03, 60.18, 23.17.

1-phenyl-2-(ethoxycarbonyl)-2-(*tert*-butylsulfinyl) imino ethanol (3f): Prepared according to the general method: 20 mL, ethyl-2-((*tert* -butylsulfinyl)imino)acetate (201 mg, 1 mmol, 1.0 eq) và benzaldehyde (127 mg, 1.2 mmol, 1.2 eq). The product **3f** was isolated as yellow liquid (260.1 mg, 83% yield). R_f = 0.20. IR (cm^{-1})**:** υ_{-NH}: 3517; υ_{OH}: 3301; $\upsilon_{=C-H\ (aren)}$: 3022; $\upsilon_{CH(sp3)}$: 2935, 2906; $\upsilon_{=C-C\ (aren)}$: 1603, 1501; υ_{C-N}: 1040. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 – 7.36 (m, 5H *aromatic*); 5.23 (d, *J* = 6,8 Hz, 1H); 4.85-4.84 (dd, *J* = 8,3; 5,7 Hz, 1H); 4.37 – 4.23 (m, 4H); 1.34 – 1.28 (m, 10H). ^{13}C NMR (125MHz, $CDCl_3$) δ (ppm): 171.25, 141.11, 128.67, 128.32, 127.89, 72.33, 62.09, 61.48, 58.76, 23.12, 15.02.

3. RESULTS AND DISCUSSION

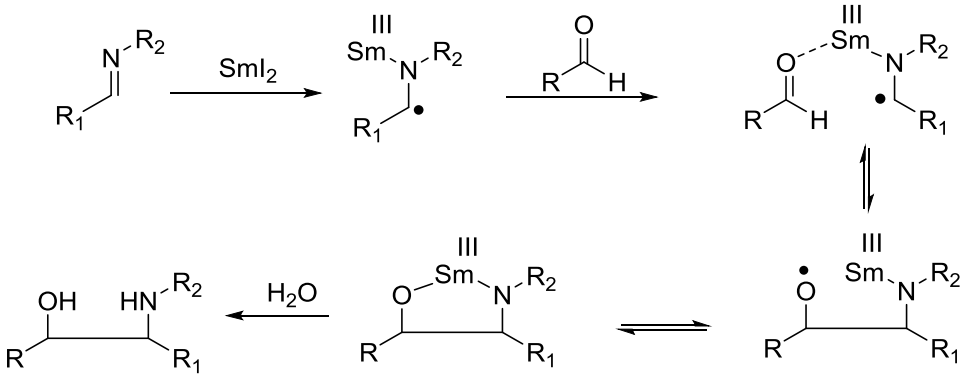
3.1. Influence of catalyst concentration on reaction yield

Firstly, the pinacol coupling reaction was investigated between *N*,1-diphenylmetanimine **2a** and benzaldehyde **1a** using SmI_2 catalyst at the molar ratio SmI_2 : imine **2a** of 1: 1, in anhydrous THF solvent. After 6 hours stirring at -30 °C, the desired product **3a** was obtained as Moon-colored solid in 41% yield (Scheme 1).



Scheme 1. *Synthesis of 1,2-diphenyl-2-anilinoethanol.*

The reaction mechanism was shown in scheme 2: initially, radical intermediate was formed by attack of SmI_2 on double bond of imine, secondly, as a role of Lewis acid, SmI_2 in this radical intermediate was coordinated with pair electron on oxygen of aldehyde to give a transition state of Sm (III) where imine free radical subsequently attacks on carbonyl compound to create C-C bond in five-membered ring complex. Finally, hydrolysis of this ring complex affords the desired product 1,2-aminoalcohol (scheme 2) [6].



Scheme 2. *The reaction mechanism between imine and aldehydes using catalyst SmI_2.*

Through the mechanism of the reaction, it was found that the selectivity and reaction yield was significantly affected by the catalyst concentration. The reaction was stirred in THF at -30 °C, at molar ratio of SmI_2 : imine **2a** of 1:1, 2: 1, 3: 1, 4: 1, 5: 1, respectively. The results show that with SmI_2/imine **2a** of 2: 1 reaction yield reached the highest of 58%. Increasing catalyst ratio SmI_2 compared with imine **2a** led to decrease of reaction yield which can be explained by increasing the concentration of free radicals, so these radicals can react each other to form homocoupling byproducts (table 1).

Table 1. *Influence of catalyst ratio on the reaction yield.*

SmI_2/imine **2a**	1:1	2:1	3:1	4:1	5:1
Yield **3a**	41%	**58%**	54%	51%	46%

3.2. Effect of temperature on the aminoalcohol yield

Continuously, studies address the effect of temperature on the reaction conversion. The coupling reaction was carried out in THF using molar ratio SmI_2 : imine **2a** of 2:1 in the temperature range of -78 °C to -30 °C. After stirred 6 hours, the results showed that increasing the temperature effects negatively to the reaction yield. The intermediate complex was stable at low temperature, so homogenous catalyst could require the reaction temperature of down to -78 °C, and thus, at this temperature the highest reaction yield was up to 88% (table 2).

Table 2. *Effect of temperature on pinacol coupling reaction yield.*

Temperature	-30 °C	-40 °C	-50 °C	-60 °C	-78 °C
Yield **3a**	58%	62%	70%	76%	**88%**

3.3. Effect of the solvent on the aminoalcohol yield

To optimize the reaction yield, the effect of different solvent on the rate of reaction using a homogenous catalyst SmI2 should also be seriously taken into consideration. We therefore decided to investigate the effect of solvent such as hexane, toluene, CH_2Cl_2, ethanol, THF and under solvent-free conditions on the reaction yield with the molar ratio of SmI_2 with imine **2a** is 2: 1, stirred for 6 hours, at -78 °C. The results showed that the solvent directly affected the resulting aminoalcohol's conversion **3a**. The reaction could afford the desired product in low yield in protic solvents as well as in the absence of the use of solvents. In non-polar aprotic solvents, the reaction could strong accelerate and could afford aminoalcohol from moderate to very good yields up to 88% with THF solvent (table 3).

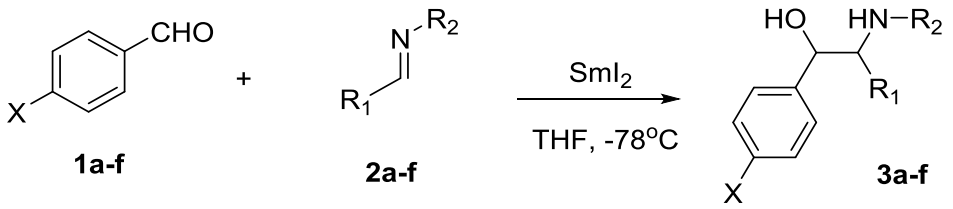
Table 3. *Yield of the solvent on the efficiency of the coupling pinacol.*

Solvent	Hexane	Toluene	CH_2Cl_2	THF	ethanol	Free solvent
Yield **3a**	41%	47%	69%	**88%**	30%	27%

Finally, the study was then extended to the pinacol coupling reaction of different imines with benzaldehyde derivatives in presence of SmI_2 as a catalyst. The reaction carried out for 6h at -78 °C in THF at the molar ration SmI_2: imine of 2: 1. Experimental results shown that the nature of benzaldehyde derivatives exhibited a significant effect on the reaction yield. The coupling reaction of imine with aldehyde could afford 91% yield after 6h stirring in THF. The presence of an electron-donating group in the benzaldehyde led to a significant enhancement in the reaction rate, with from 85-91% yield being achieved (table 4). In addition, the coupling reaction between

tert- butylsulfinyl imines with benzaldehyde in the optimal condition reaction give the desired products in very good yields (80-83%).

Table 4. *The result was a synthesis of some aminoalcohol using catalyst* SmI_2.



Entry	X	R_1	R_2	Yield
a	H	Ph	Ph	88 %
b	CH_3	Ph	Ph	**91** %
c	OCH_3	Ph	Ph	85 %
d	Br	Ph	Ph	84 %
e	H	Ph	*t*BuS(O)	80 %
f	H	CO_2Et	*t*BuS(O)	83%

4. CONCLUSION

In summary, we have reported a new efficient procedure to synthesis of aminoalcohol by cross-coupling reaction. Using SmI_2 as a catalyst, the methodology was efficient and compatible for versatile imines, benzaldehyde derivatives as starting materials. We have found that the optimal condition of this reaction is at -78°C, in anhydrous THF as a solvent and at molar ration of SmI_2 : imine of 2:1, desired products were obtained from moderate to high yield up to 91%. It was evident that this modified pathways, especially in asymmetric synthesis, could be streamlined to better yield and better stereoselectivity for this reaction in the future.

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TÓM TẮT

NGHIÊN CỨU PHƯƠNG PHÁP ĐIỀU CHẾ AMINOANCOL BẰNG PHẢN ỨNG GHÉP NỐI GIỮA ANDEHIT VỚI IMIN TRÊN XÚC TÁC SAMARI (II) IODUA

Samari (II) iodua (SmI_2) là một trong những chất xúc tác phổ biến, hiệu quả cho các phản ứng ghép nối giữa các hợp chất cacbonyl để tạo thành 1,2-diol qua cơ chế gốc tự do. Trong bài báo này, chúng tôi trình bày kết quả nghiên cứu ứng dụng xúc tác SmI_2 với phản ứng aza-pinacol ghép đôi giữa andehit và imin trong các điều kiện khác nhau. Kết quả cho thấy, trong dung môi THF, ở -78 °C, với 2 đương lượng chất xúc tác SmI_2, sản phẩm 1,2-aminoancol được tạo thành với hiệu suất lên đến 91% và độ chọn lọc cao do hạn chế tạo thành sản phẩm phụ 1,2- diol.

Từ khoá: Samari (II) iodua; Aminoancol; Phản ứng pinacol; Imin.

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