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Synthesis of Key Intermediate of Rocaglamide *via* SmI_2 Catalyzed Intramolecular Reductive Coupling Reaction

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The compound of methyl 8b-hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8a-tetrahydrocyclopenta[b]-benzofuran-2-carboxylate (**3b**), can be obtained with moderate yields under optimum reaction conditions. During this optimization, intramolecular ketone-ester reductive coupling reactions promoted by SmI_2 have been studied. The synthetic procedure was successfully applied to the preparation of the key intermediate of the rocaglamide.

Keywords: Intramolecular reductive, Ketone-ester, SmI_2, Catalyzed.

INTRODUCTION

Carbon-carbon bond formation is the essence of organic synthesis and reductive couplings are amongst the most valuable methods for making carbon-carbon bonds[1]. Samarium diiodide (SmI_2) has been recognized as a most useful single-electron reductant in synthetic organic chemistry since its application was first reported by Kagan and co-workers[2,3]. Samarium diiodide (SmI_2) promoted intramolecular coupling reactions of ketone carbonyls with other functional groups to produce various carbocycles and heterocycles[4].

In these examples, the involvement of ketyl radicals has been often proposed as the key intermediates in these reactions. Similarly, ketone-ester coupling reactions would be expected to occur since such reactions are already known under the other electron transfer conditions[5]. In fact, the reaction of keto-ester substrates using SmI_2 as a reductant has been less explored[6].

Rocaglamide (Fig. 1) is a novel natural product which was isolated from *Aglaia elliptifolia* Merr. in 1982[7]. Featuring a cyclopenta[b]benzofuran core, is a class of natural product possessing diverse biological activity such as insecticidal, antifungal and antitumor activity[8]. We have reported the total synthesis of (±)-rocaglamide. The most critical step in synthesis of rocaglamide is to synthesize intermediate **3b**. In this work, we present an efficient and practical protocol, which synthesized intermediate **3b** by using SmI_2 as catalyst with moderate yield.

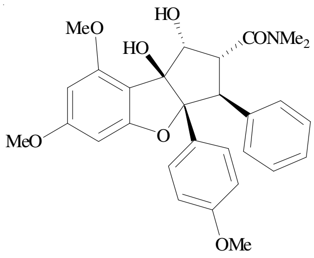


Fig. 1. Rocaglamide

EXPERIMENTAL

Melting points were measured with a XT-4 melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance DPX300 spectrometer with tetramethylsilane as the internal standard. IR spectra were determined on FTS-40 infrared spectrometer; Solvents used were purified and dried by standard procedures.

Synthesis of methyl 2-methoxymethylen-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo- 2, 3- dihydro benzo furan-2-yl]-3-phenylpropionate (2): Under a N_2 atmosphere, to a solution of 1 (3 g, 10 mmol) in THF (100 mL) was added a solution of Triton B (40 % in CH_3OH, 0.3 mL) and a solution of benzylidene malonate (2.4 g, 10.5 mmol). After stirring at 60 °C for 3 h, the solvent was removed *in vacuo*. To the residue was added a solution of HCl (1 × 25 mL) and this solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with brine (2 × 20 mL), dried with Na_2SO_4 and concentrated. The crude product was separated by silica-gel column chromatography (petroleum ether/EtOAc, 1:1) to afford diastereoisomers of **2a** (*trans*) and **2b** (*cis*) (**Scheme-I**).

2a, White solid, Yield: 16.3 %, m.p. 168-169 °C. ^{1}H NMR ($CDCl_3$): δ 3.29 (s, 3 H), 3.54 (s, 3 H), 3.67 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 4.21 (d, 1 H, J = 9.3 Hz), 4.47 (d, 1 H, J = 9.3 Hz), 5.97 (d, 1 H, J = 1.8 Hz), 6.27 (d, 1 H, J = 1.8 Hz), 6.63-6.67 (m, 2 H), 7.04-7.11(m, 3 H,), 7.17-7.21 (m, 2 H), 7.36-7.42 (m, 2 H).^{13}C NMR ($CDCl_3$): δ 194.5, 174.0, 169.8, 167.8, 167.6, 159.2, 159.1, 136.2, 130.2, 128.4, 127.4, 127.0, 126.9, 113.2, 104.3, 93.2, 92.7, 88.8, 55.9, 55.1, 53.4, 52.5, 52.1, 52.0. IR (KBr, ν_{max}, cm^{-1}): 2953, 2841, 1785, 1623, 1592, 1511, 1254, 1221, 1159, 1032, 927, 818, 698.

2b, White solid, Yield: 35 %, m.p. 169-170 °C. ^{1}H NMR ($CDCl_3$) δ: 3.17 (s, 3 H), 3.27 (s, 3 H), 3.65 (s, 3 H), 3.77 (s, 3 H), 3.86 (s, 3 H), 4.33 (d, 1H, *J* = 10.8 Hz), 4.53 (d, 1 H, *J* = 10.8 Hz), 5.78 (d, 1 H, *J* = 1.8 Hz), 6.27 (d, 1 H, *J* = 1.8 Hz), 6.82-6.85 (m, 2H), 7.05-7.13 (m, 3 H,), 7.31-7.34 (m, 2 H), 7.69-7.76 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ: 194.3, 174.0, 169.5, 167.6, 167.5, 159.6, 159.1, 135.4, 130.0, 127.7, 127.5, 127.3, 127.0, 113.4, 103.7, 92.8, 92.3, 88.5, 55.8, 55.7, 55.2, 54.1, 52.2, 52.1, 51.4. IR (KBr, ν_{max}, cm^{-1}): 2953, 1746, 1707, 1620, 1594, 1510, 1255, 1219, 1156, 1124, 841, 816, 698.

General procedure for the preparation of 3b using SmI_2 catalyzed reaction: (Scheme-I): To the reactant of metal samarium (0.90 g, 6 mmol) in a flame-dried, 100 mL, three-necked round-bottom flask equipped with a stir bar, septum and nitrogen inlet was added a solution of $C_2H_4I_2$ (1.69 g, 6 mmol) in THF (7 mL). After stirring for 1 h, the solution changed to blue and the reaction was continued for 1 h under ultrasound irradiation. Anhydrous benzene (10 mL) was then added and the reaction was continued for an additional 2 h. A solution of **2b** (1.56 g, 3 mmol) in benzene (20 mL) was added and the reaction was allowed to proceed for 10 h under ultrasound irradiation. The reaction was quenched with the addition of HCl (1mol/L, 20 mL) and the solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with brine (2 × 20 mL), dried with anhydrous Na_2SO_4 and concentrated. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 2:3) to afford diastereoisomers **3**.

White crystalline. m.p. 161-162 °C. Yield: 56.8 %. ^{1}H NMR ($CDCl_3$): δ 3.04 (s, 1 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.06 (d, 1H, *J* = 13.2 Hz), 4.24 (d, 1H, *J* = 13.2 Hz), 6.10 (d, 1 H, *J* = 1.8 Hz), 6.35 (d, 1H, *J* = 1.8 Hz), 6.66-6.70 (m, 2 H), 6.89-6.97 (m, 4 H), 7.08-7.12 (m, 3 H). ^{13}C NMR($CDCl_3$): δ 203.3, 167.2, 164.9, 161.0, 158.9, 158.6, 135.4, 129.1, 128.0, 127.9, 127.7, 127.1, 125.4, 113.2, 112.2, 106.1, 99.3, 92.9, 89.9, 88.5, 56.4, 55.7, 55.6, 55.1, 55.0, 52.9, 52.0, 51.5. IR (cm^{-1}): 3420, 2980, 1760, 1720, 1620, 1600, 1520, 1480, 1260, 1230, 1180, 1160, 1120, 1100, 1020, 820, 710.

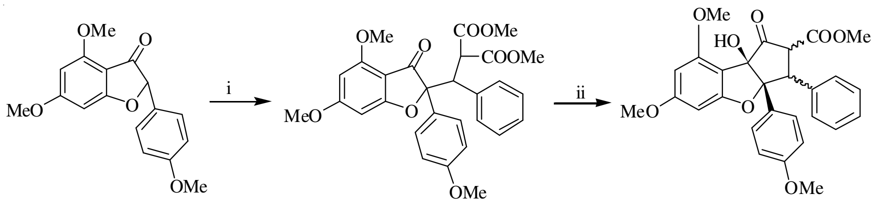
RESULTS AND DISCUSSION

Cyclic ketone constitute an important class of many biologically active natural products[9]. The aim of the research was to synthesize tricyclic ketone by a method involving less reaction time and promises better quality and yield of the product.

The required cyclization precursors 2, methyl 2-methoxy-methylen-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropionate were easily prepared by Michael addition of benzylidene malonate to **1** under the presence of Bu_4N^+ OH^- afforded a couple of diastereoisomers of **2a** (*trans*) and **2b** (*cis*) (the ratio of 1 to 2.24) in good yields (**Scheme-I**). The structure of **2b** was confirmed by X-ray diffraction[10].

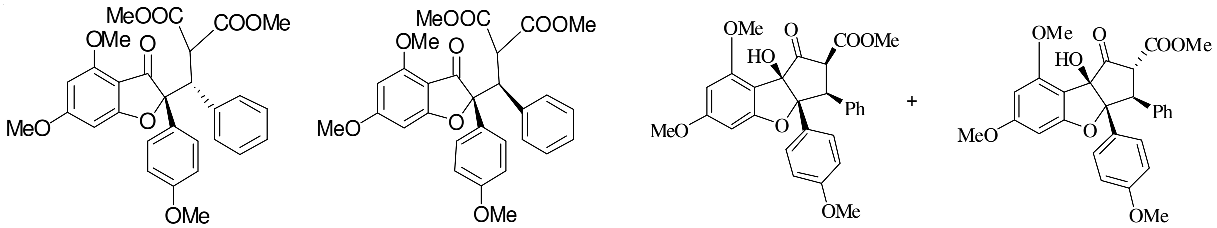
According to our initial scheme, the compound **3b** was prepared from **2b** *via* intramolecular keto-ester reductive coupling (**Scheme-I**). Reductive coupling of carbonyl compounds by Ti^{3+} and Zr^{3+} are well known[11,12]. In this reaction the Ti^{3+} and Zr^{3+} were used as the reductive agent, however no reaction took place by TLC monitoring, only crude materials were recovered. In this communication, we report that SmI_2 was the best reductive coupling system in all tested reagent. Through optimizing the solvent and other conditions, the coupling products **3b** were obtained in modest yield.

As shown in Table-1, the effect of reaction temperature and the influence of catalyst ratio for the reaction were studied



1 2 3

Reagents and conditions: (i) PhCH = $CHCO_2Me$, $Bu_4N^+OH^-$; (ii) SmI_2



2a 2b 3b

Scheme-I

for this reaction. Here, we obtained the optimal reaction conditions that were 6 mmol of 3 mmol of SmI_2 and **2b** in benzene at room temperature for 10 h under ultrasound irradiation (Table-1, Entry 2), the yield of **3b** to 56.8 %. Improve or reduce the catalyst ratio, the yield of **3b** will be increased (Table-1, Entries 1, 3-5). If we decreased the reaction temperature to -78 °C or increased reaction temperature to 50 °C and the desired product was obtained only in low yield (Table-1, entries 7, 6). No product was observed when MeOH, *t*-BuOH was introduced in reaction as Additve. (Table-1, Entries 8, 9); HMPA had much effect on reaction, it will cause the yield decline and the yield is trace.

With the optimal conditions identified, the synthesis of **3b** was carried out under several conditions. The effects of different reaction time and the use or not of ultrasound irradiation on the reaction were investigated and the results are shown in Table-2. The results indicated that ultrasound irradiation can accelerate the reaction. With ultrasound irradiation, when the reaction time was prolonged to 4-10 h, the reaction was relatively quick and high yield of product 3 was obtained (entries 6-9). When the reaction time was prolonged further to12 h under ultrasound irradiation, a tiny improvement of yield (56.9 %, entry 10) was obtained compared to that at 10 h (56.8 %, entry 9). When there is no ultrasound irradiation, the reaction was relatively slow and low yield of product was detected within 6, 12, 18 h (entries 1-3). When the reaction time was prolonged to 24, 32 h, without ultrasound irradiation, **3** could be obtained in 55.3 %, 56 % yield, respectively (entries 4, 5). The present new method for the synthesis of **3b** under ultrasound irradiation offers several advantages including faster reaction rates, fewer byproducts, as compared with the drawbacks of the classical method, which involves a long tedious process (24 h). In this way, the optimal reaction conditions were identified to be the catalytic system of SmI_2 in benzene under ultrasound irradiation for 10 h.

Furthermore, a further screening of the solvents revealed that decreasing the polarity of the solvent had a positive effect on the reaction yield. The use of highly polar solvents caused low yields along with several byproducts (Table-3, entries 3-9) and benzene displayed as the best choice to promote the transformation with 56.8 % yield (Table-3, entry 2). Using cyclohexane take place of benzene, the yield of compound **3** will be reduced to 12.5 %. The cause may be that dissolving ability of substance **2b** in cyclohexane is weaker than benzene (Table-3, entry 1). Obviously, the solvent plays a crucial role in the process of the reaction.

Conclusion

In summary, we have developed a simple and efficient intramolecular reductive coupling reaction of ketones with esters using samarium(II) iodide as catalyst. The influences of the various conditions on the yield are studied. We obtained the optimal reaction conditions that were 6 mmol SmI_2 and 3 mmol of compound **2b** were used in benzene solvent (30 mL) at room temperature under ultrasound irradiation 10 h. Hence, it will be useful to explore the area of samarium(II) iodide catalyst in the synthesis of industrially important chemicals.

TABLE-1
OPTIMIZATION FOR THE REACTION OF **2b** OF CATALYST RATIO

Entry	SmI_2 (mmol)	2b (mmol)	Temp (°C)	Additve	3b Yield^a (%)
1	9.0	3.0	r.t.	none	52.0
2	6.0	3.0	r.t	none	56.8
3	3.0	3.0	r.t	none	26.9
4	1.5	3.0	r.t	none	22.5
5	1.0	3.0	r.t	none	20.2
6	6.0	3.0	50	none	33.3
7	6.0	3.0	-78	none	11.3
8	6.0	3.0	r.t	MeOH	No reaction
9	6.0	3.0	r.t	*t*-BuOH	No reaction
10	6.0	3.0	r.t	HMPA	Trace

[a]Isolated yields, [b]Reaction was carried out at room temperature; r.t. = Room temperature

TABLE-2
OPTIMIZATION FOR THE REACTION OF **2b** OF TIME

Entry	Solvent	Volume (mL)	Time (h)	3b Yield ^{a} (%)	Reaction conditions
1	Benzene	30	6	6.5	Room temperature stir
2	Benzene	30	12	25.2	Room temperature stir
3	Benzene	30	18	36.3	Room temperature stir
4	Benzene	30	24	55.3	Room temperature stir
5	Benzene	30	32	56.0	Room temperature stir
6	Benzene	30	4	15.0	Ultrasound irradiation
7	Benzene	30	6	18.1	Ultrasound irradiation
8	Benzene	30	8	36.3	Ultrasound irradiation
9	Benzene	30	10	56.8	Ultrasound irradiation
10	Benzene	30	12	56.9	Ultrasound irradiation

[a]Isolated yields, [b]2 mmol SmI_2 and **1** mmol of **1** were used in benzene solvent (30 mL)

TABLE-3
EFFECTS OF DIFFERENTSOLVENTS ON THE **2b** YIELD OF PRODUCT

Entry	Solvent	Volume (ml)	Time (h)	3b Yield[a b] (%)
1	Cyclohexane	30	10	12.5
2	Benzene	30	10	56.8
3	Toluene	30	10	46.0
4	1,2-Dichloroethane	30	10	21.6
5	THF	30	10	14.1
6	1,4-Dioxane	30	10	12.6
7	DMF	30	10	10.2
8	CH_3CN	30	10	5.2
9	H_2O	30	10	No reaction

[a]Isolated yields, [b]Reaction was carried out at room temperature, 6 mmol SmI_2 and 3 mmol of **2** were used in benzene solvent (30 mL) under Ultrasound irradiation 10 h

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