

Samarium(II) Iodide Promoted Novel Reductive Coupling Reactions of Ketones and Nitriles

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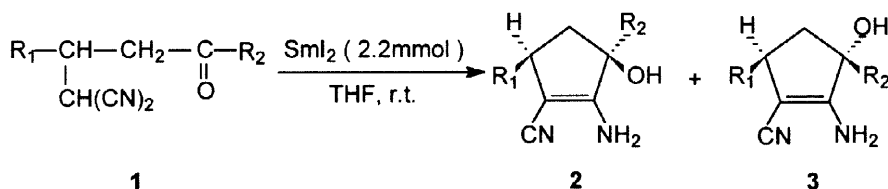
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Abstract: The intramolecular and intermolecular reductive coupling reaction of ketones-nitriles promoted by SmI₂ were studied. © 1998 Elsevier Science Ltd. All rights reserved.

Applications of samarium diiodide to organic synthesis have significantly grown in the last decade.¹ Pioneering work performed by Kagan with SmI₂ has served to outline the uses of this reagent in synthetic organic chemistry. Kagan's investigations have been followed by reports from other scientists, revealing that SmI₂ is an exceedingly reliable, mild, neutral, selective and versatile single electron transfer reagent for promoting reductive coupling reactions difficult to accomplish by other existing methodologies. For instance, Barbier reactions, Reformatsky reactions, pinacol couplings and ketone-olefin reductive couplings have been reported using SmI₂ as the reagent. However, little attention has been concerned on the reaction of nitriles with SmI₂. It is well known that carbonyl groups can easily be reduced by SmI₂. The cyano group, however, is more stable to SmI₂ than the carbonyl group and could not be coupled by this reagent. Soupe and Kagan reported that aromatic and aliphatic nitriles are inert in the presence of SmI₂.² Recently, we have reported a novel cyclodimerization of arylidenecyanoacetates promoted by SmI₂.³ Herein, we wish to describe our preliminary results on novel ketone-nitrile reductive couplings promoted by samarium diiodide in tetrahydrofuran.

When γ -ketonitriles **1** were treated with SmI₂ in dry THF at room temperature under a nitrogen atmosphere, the reductive cyclization products 2-amino-3-cyano-1,4-diaryl-2-cyclopenten-1-ols **2** were obtained along with their geometric isomers **3** (Scheme 1).



Scheme 1

Table 1 summarizes our results on the intramolecular cyclization of γ -ketonitriles. The reaction is highly chemoselective: only two isomers were obtained. The pinacol coupling products of ketones were not detected. The yield of product **3** is much higher than that of **2**. The structures and relative configuration of the products

have been established using spectroscopic data and by X-ray analysis. The X-ray diffraction studies on a single crystal of **2c**⁴ and **3c**⁵ indicate that the products **2** (1,4-*cis*) and **3** (1,4-*trans*) were diastereoisomers (**Fig. 1** and **Fig. 2**).

Table 1. The intramolecular reductive coupling of γ -ketonitriles

Entry	R ₁	R ₂	Reaction time (h)	Isolated Yield (%) ^{a,b}	
				2	3
a	C ₆ H ₅	C ₆ H ₅	2	23	49
b	4-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	1	30	54
c	4-ClC ₆ H ₄	C ₆ H ₅	2	25	55
d	3,4-OCH ₂ OC ₆ H ₃	C ₆ H ₅	2.5	21	48
e	2-ClC ₆ H ₄	C ₆ H ₅	1.5	23	53
f	C ₆ H ₅	4-CH ₃ C ₆ H ₄	2	27	47

a. Reaction is carried out at room temperature. b. 2.2 mmol SmI₂ and 1 mmol of **1** were used.

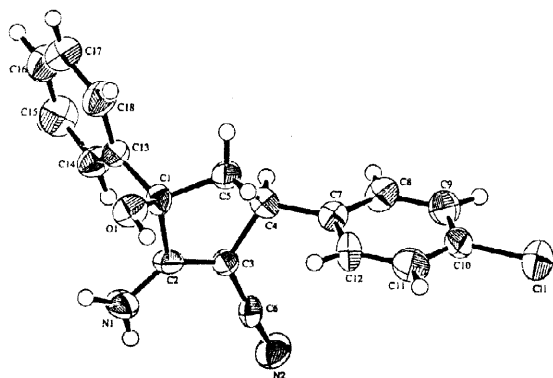


Fig. 1 ORTEP diagram of **2c**

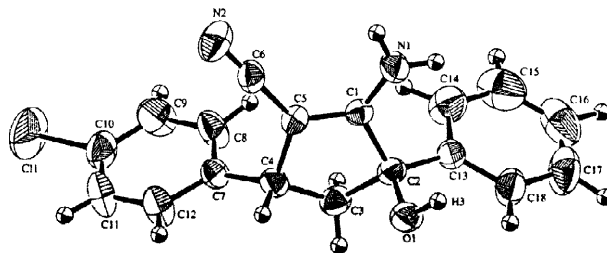
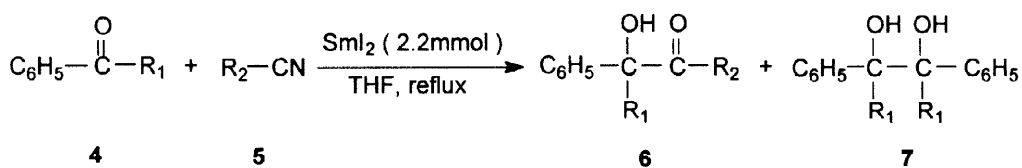


Fig. 2 ORTEP diagram of **3c**

In order to check the reactivity of SmI₂ to ketone-nitrile reductive couplings, we studied the intermolecular reaction of ketones or aldehydes **4** with nitriles **5** promoted by SmI₂, which affords α -ketols **6** and/or pinacols **7** (**Scheme 2**).



Scheme 2

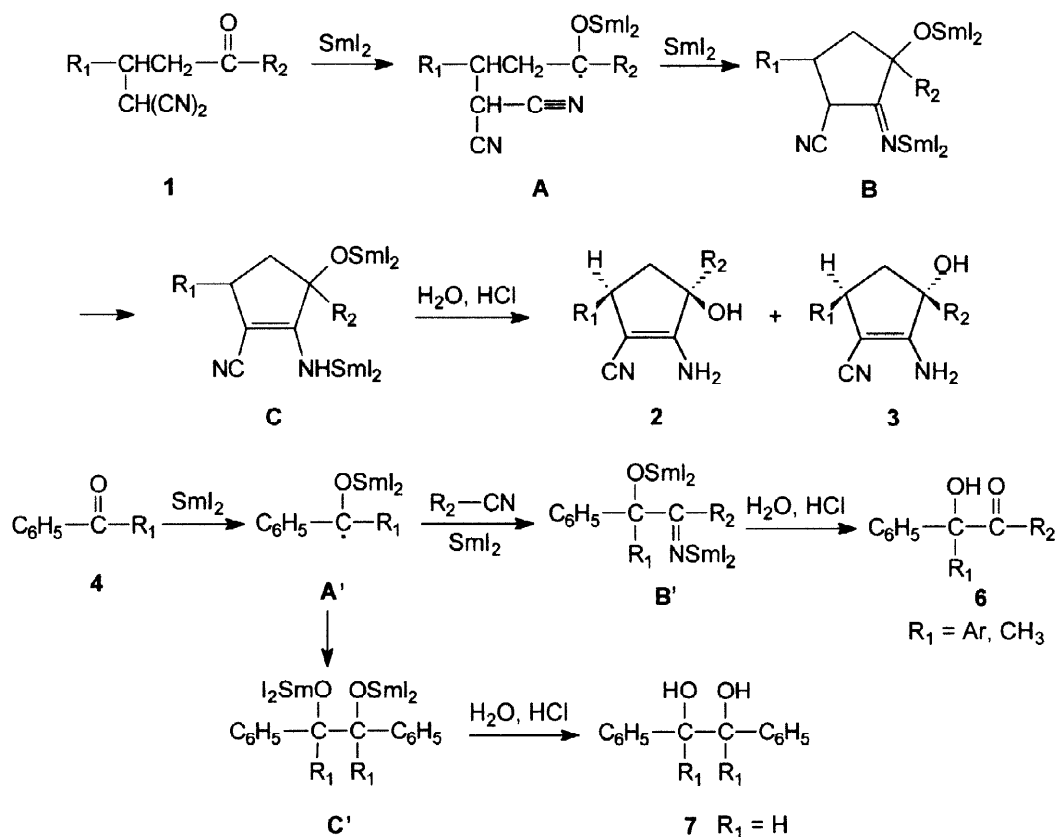
Table 2 summarizes our results on the ketone-nitrile reductive couplings. When benzophenone and aromatic nitriles were heated at reflux with SmI₂ under a nitrogen atmosphere, α -ketols **6** were obtained in good yields (**Entry 1-4**). If the reaction is carried out at room temperature, the reaction is slow and gives lower yield (**Entry 5**). On the other hand, treatment of aromatic aldehydes and nitriles with SmI₂ at room temperature, even if under reflux did not give α -ketols **6**, only pinacol coupling products were obtained in good yields (**Entry 6-7**). Treatment of acetophenone and benzonitrile with SmI₂, gave α -ketols **6** along with pinacol **7** (**Entry 8**).

Table 2. The intermolecular reductive coupling of ketones with nitriles

Entry	R ₁	R ₂	Reaction time (h)	Yield (%) ^{a,b}	
				6	7
1	C ₆ H ₅	C ₆ H ₅	4	78 ^c	--
2	C ₆ H ₅	4-ClC ₆ H ₄	5	75 ^c	--
3	C ₆ H ₅	3-CH ₃ C ₆ H ₄	5	87 ^c	--
4	4-CH ₃ C ₆ H ₄	C ₆ H ₅	2.5	83 ^c	--
5	C ₆ H ₅	C ₆ H ₅	24	45 ^d	--
6	H	4-ClC ₆ H ₄	8	--	81 ^c
7	H	4-ClC ₆ H ₄	8	--	84 ^d
8	CH ₃	C ₆ H ₅	10	30 ^c	44 ^c

a. Yields of isolated products. b. 1 mmol of 4 and 1.2 mmol of 5 were used. c. Reaction is carried out under reflux. d. Reaction is carried out at room temperature.

The formation of cyclopentenes and α -ketols may be explained by the mechanism presented in **Scheme 3**.



In the intramolecular ketone-nitrile reaction, after the formation of ketyl anion (A), ring closure occurs via radical addition onto the nitrile group. Then the carbon-nitrogen double bond is transformed to form a carbon-carbon double bond due to the stabilization by the cyano group. In the intermolecular reaction, however, the

carbon-nitrogen double bond couldn't be transferred to form a carbon-carbon double bond in the absence of a cyano group, and α -ketols **6** are formed. On the other hand, the ketyl radical (A') from aromatic aldehydes has less of a handicap than that of benzophenone and the pinacol coupling reaction could proceed prior to the ketone-nitrile reaction.

Typical procedure: A solution of substrate **1** (1 mmol) in THF (3 ml) was added to SmI₂ (2.2 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred under these conditions until the reaction was completed. The reaction was quenched with dilute HCl (1M, 1 ml) and extracted with ether. After the usual work-up, the crude product was purified by preparative TLC (ethyl acetate : cyclohexane, 1 : 2) to give **2** and **3**.

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References and Notes

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- Crystal data for **2c**: C₁₈H₁₅ClN₂O; M = 310.78, colorless prismatic crystals, 0.20 x 0.20 x 0.30 mm, monoclinic, space group C2/c, a = 24.416(2), b = 12.215(4), c = 10.772(4) Å, β = 99.78(1), V = 3183(1) Å³, Z = 8, D_c = 1.305 gcm⁻³, F(000) = 1296.00, μ (M₀K_α) = 2.42 cm⁻¹. Intensity data were collected on Rigaku AFC7R diffractometer with graphite - monochromated M₀-K_α radiation (λ = 0.71069 Å) Using ω-2θ scan mode with 2θ_{max} = 50.0°. 2953 unique reflections were measured and 915 reflections with I > 3.00 σ (I) were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full - matrix least - squares technique to R = 0.044 and R_w = 0.047 for 915 observations and 200 parameters.
- Crystal data for **3c**: C₁₈H₁₅ClN₂O; M = 310.78, colorless prismatic crystals, 0.20 x 0.20 x 0.30 mm, orthorhombic, space group Pbcn, a = 13.307(5), b = 10.481(5), c = 23.350(6) Å, V = 3272(3) Å³, Z = 8, D_c = 1.262 gcm⁻³, F(000) = 1296.00, μ (M₀K_α) = 2.36 cm⁻¹. Intensity data were collected on Rigaku AFC7R diffractometer with graphite - monochromated M₀-K_α radiation (λ = 0.71069 Å) Using ω-2θ scan mode with 2θ_{max} = 50.0°. 3278 reflections were collected and 1426 reflections with I > 3.00 σ (I) were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full - matrix least - squares technique to R = 0.043 and R_w = 0.049 for 1426 observations and 259 parameters.