Facile Synthesis of Amidines *via* the Intermolecular Reductive Coupling of Nitriles with Nitro Compounds Induced by Samarium(II) Iodide†

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Longhu Zhou‡ and Yongmin Zhang*

Department of Chemistry, Hangzhou University, Hangzhou, 310028, PR China

The intermolecular reductive coupling of nitriles with nitro compounds induced by Sml₂ was studied; amidine derivatives are prepared in good yields under neutral and mild conditions.

Applications of samarium diiodide in organic synthesis have grown significantly in the last decade. Pioneering work performed by Kagan² 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 any other existing methodologies. For instance, Barbier reactions, Reformatsky reactions, pinacol couplings and ketone–olefin reductive couplings have been reported using SmI₂ as a reagent substitute. The reactivity of SmI₂ towards various nitrogen compounds including nitro compounds, azo compounds, hydrazones, to some symbols in situation of arylidenecyanoacetates promoted by SmI₂.

Amidines are the nitrogen analogues of carboxylic acids and this unit is part of several compounds of biological interest. They can be prepared by reacting aromatic amines with nitriles under intensive reaction conditions, such as high temperatures and long reaction times, using sodium or lithium

Nitro groups are known to be easily reduced by SmI₂. The cyano group, however, is more stable to SmI₂ than the nitro group and could not be coupled by this reagent. Souppe and Kagan^{3b} reported that aromatic and aliphatic nitriles are inert in the presence of SmI₂, but *m*- or *p*-nitrobenzonitrile could be selectively reduced to the corresponding cyanoanilines in almost quantitative yields. We considered that the intermediate derived from a more active nitro group by SmI₂ treatment could perhaps attack the more stable cyano group, which does not react with SmI₂. Therefore, we have studied the behavior of the cyano group and the nitro group when reacted with SmI₂ in tetrahydrofuran (THF) at room temperature.

When aromatic nitro compounds 1 and nitriles 2 were treated with SmI_2 in dry THF, the intermolecular reductive cross coupling products, amidines 3 were found (Scheme 1).

Table 1 summarizes our results on the reaction of nitro compounds and nitriles with SmI₂. Aromatic nitro compounds reacted with aromatic or aliphatic nitriles to pro-

Scheme 1

Table 1 Intermolecular reaction of nitro compounds with nitriles induced by SmI₂^a

Entry	R ¹	R^2	<i>t</i> /h	Yield (%) ^b
а	C ₆ H ₅	C ₆ H ₅	2	69
b	p-CH ₃ C ₆ H ₄	C_6H_5	4	67
С	o-CH ₃ C ₆ H ₄	C_6H_5	1	62
d	C ₆ H ₅	$C_6H_5CH_2$	1	57
е	p-CH ₃ C ₆ H ₄	$C_6H_5CH_2$	4	67
f	p-CIC ₆ H ₄	$C_6H_5CH_2$	4	59
g	p -CIC $_6$ H $_4$	p-CIC ₆ H₄	2	70
ň	p-CH ₃ C ₆ H ₄	p-CIC ₆ H₄	2	82
i	C ₆ H ₅	p -CIC $_6$ H $_4$	2	87
i	p-CIC ₆ H ₄	C ₆ H ₅	1	78
k	p -CIC $_6$ H $_4$	m- $CH3C6H4$	4	74
1	p-CH ₃ C ₆ H ₄	m -CH $_3$ C $_6$ H $_4$	3	71
m	C ₆ H ₅	m -CH $_3$ C $_6$ H $_4$	1	72
n	CH ₃	C ₆ H ₅	2	0^c
0	CH ₃	C ₆ H ₅ CH ₂	2	0°

^a1 equiv. nitro compounds, 1.2 equiv. nitriles and 6 equiv. Sml₂ were used. ^bIsolated yield. ^cThe reaction was studied under below 0, at 25 °C and under refluxing conditions.

duce amidines in good yields. However, aliphatic nitro compounds failed to react with aromatic or aliphatic nitriles to give similar amidines as products under the same conditions, at low temperature or under refluxing conditions. Amidines 3 are not derived from the reaction of the nitriles with amines produced by the reduction of nitro compounds, since treatment of nitriles with amines under the same reaction conditions did not lead to a reaction taking place and no amidines could be detected.

Although the detailed mechanism of the above reaction has not yet been clarified, amidine formation can be explained by the putative mechanism presented in Scheme 2.

$$ArNO_2 \xrightarrow{2 \text{ Sml}_2} ArNO \xrightarrow{Sml_2} Ar\mathring{N} - OSml_2 \xrightarrow{RCN} Ar - \mathring{N} - \overset{OSml_2}{\underset{R}{\longrightarrow}} \bullet \xrightarrow{Sml_2} \stackrel{Sml_2}{\underset{R}{\longrightarrow}} \bullet$$

$$\begin{array}{c|c} \operatorname{OSml_2} & \operatorname{Sml_2} \\ \operatorname{Ar-N-C=N-Sml_2} & \xrightarrow{2 \operatorname{Sml_2}} & \operatorname{Ar-N-C=N-Sml_2} & \xrightarrow{H_2O} & \operatorname{ArN-C-R} \\ \operatorname{I}_{2 \operatorname{SmOSml_2}} & \operatorname{R} & \operatorname{R} \end{array}$$

Scheme 2

In conclusion, with high yields, mild and neutral conditions as well as a straightforward procedure, we think that the present work provides a useful method for the preparation of amidines. Further studies to develop other new uses for SmI_2 are now in progress in our laboratory.

Experimental

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer in KBr with

^{*}To receive any correspondence.

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[‡]Permanent address: Department of Chemistry, Xuzhou Normal University, Jiangsu, 221009, China.

absorptions in cm⁻¹. ¹H NMR spectra were determined on a JEOL PMX 60 SI spectrometer as CDCl₃ solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a Finnigan MAT GC-MS spectrometer. Microanalyses were carried out on a Carlo-Erba 1106 instrument.

General procedure for the synthesis of Amidines 3.—A solution of nitro compound 1 (1 mmol) and nitrile 2 (1.2 mmol) in anhydrous THF (3 ml) was added dropwise to a solution of SmI₂ (6 mmol) in THF (40 ml) at room temperature under a dry nitrogen atmosphere and the reaction stirred under N2. At completion, the reaction mixture was poured into 10% K₂CO₃ (50 ml) and extracted with diethyl ether $(3 \times 30 \text{ ml})$. The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 ml) and a saturated solution of NaCl (15 ml), and dried over anhydrous Na₂SO₄. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:3) as eluent.

N-Phenylbenzamidine **3a**. mp 115–117 °C (lit., 11 112 °C). ν /cm⁻¹ 3500, 3380, 1630, 1600, 1580, 1490, 1450, 1380, 1240, 1170, 1080, 1020, 835, 770, 750, 700. $\delta_{\rm H}$ 5.30 (2 H, br s, NH, C=NH), 6.87–7.83 (10 H, m, ArH).

4-Methyl-*N*-phenylbenzamidine **3b**. mp 99–100 °C (lit., ¹² 100.5–101 °C) *v*/cm⁻¹ 3470, 3310, 1640, 1610, 1580, 1510, 1380, 1235, 860, 790. $\delta_{\rm H}$ 2.30 (3 H, s, CH₃), 5.23 (2 H, br s, NH, C=NH), 6.70–7.95 (9 H, m, ArH).

N-(2-methylphenyl)benzamidine 3c. mp 102–104 °C (lit., ¹² 105 °C). ν/cm^{-1} 3470, 3320, 1640, 1575, 1490, 1390, 1240, 740, 720. δ_{H} 2.15 (3 H, s, CH₃), 4.90 (2 H, br s, NH, C=NH), 6.68-7.90 (9 H, m, ArH). MS: m/z 211 (M + 1, 45), 210 (M⁺, 100), 107 (78), 106 (88), 104 (88), 91 (36), 77 (86), 76 (22). Anal. Calc. for C₁₄H₁₄N₂: C, 79.97, H, 6.71, N, 13.32; Found: C, 79.81, H, 6.83, N, 13.40%. *N*-Phenylphenylacetamidine **3d**. mp 128–130 °C (lit., ¹² 127–130 °C).

 ν/cm^{-1} 3470, 3320, 1650, 1610, 1490, 1400, 1070, 860, 790. δ_{H} 3.63 (2 H, s, CH₂), 4.80 (2 H, br s, NH, C=NH), 6.80-7.73 (10 H, m,

N-(p-Tolylphenyl)phenylacetamidine 3e. mp 118–119 °C (lit., 12 119 °C). ν/cm^{-1} 3480, 3320, 1650, 1510, 1390, 1290, 1250, 850, 740, 700. $\delta_{\rm H}$ 2.27 (3 H, s, CH₃), 3.60 (2 H, s, CH₂), 4.73 (2 H, br s, NH, C=NH), 6.70-7.55 (9 H, m, ArH).

N-(*p*-Chlorophenyl)phenylacetamidine **3f**. mp 114–116 °C (lit., 13 114–116 °C). $\nu/\rm cm^{-1}$ 3450, 3320, 1650, 1590, 1490, 1430, 1400, 1300, 1230, 1090, 835, 750, 720, 700. $\delta_{\rm H}$ 3.57 (2 H, s, CH₂), 4.70 (2 H, br s, NH, C=NH), 6.67-7.50 (9 H, m, ArH).

4-Chloro-*N*-(4-chlorophenyl)benzamidine **3g**. mp 177–179 °C (lit., ¹⁴ 179 °C). ν /cm⁻¹ 3530, 3430, 1650, 1590, 1495, 1410, 1380, 1240, 1005 (1005) (10 1085, 1010, 860, 840, 790. δ_H 5.17 (2 H, br s, NH, C=NH), 6.80-7.73 (8 H, m, ArH).

4-Chloro-*N*-(4-methylphenyl)benzamidine **3h**. mp 129–131 °C. cm⁻¹ 3500, 3360, 1640, 1565, 1510, 1380, 1240, 1110, 1090, 1010, 840, 795. $\delta_{\rm H}$ 2.30 (3 H, s, CH₃), 5.07 (2 H, br s, NH, C=NH), 6.70-8.00 (8 H, m, ArH). MS m/z: 246 (M + 2, 32), 245 (M + 1, 21), 244 (M⁺, 100), 229 (15), 138 (88), 111 (44), 107 (94), 91 (36). Anal. Calc. for C₁₄H₁₂ClN₂: C, 69.00, H, 4.96, N, 1.49; Found: C, 69.30, H, 4.81, N, 1.59%.

4-Chloro-*N*-phenylbenzamidine **3i**. mp 107-109 °C (lit., ¹⁵ 106-110 °C). ν /cm⁻¹ 3480, 3350, 1640, 1600, 1565, 1500, 1440, 1380, 3480, 3350, 1640, 1600, 1565, 1500, 1440, 1380, 1230, 1180, 1090, 1010, 840, 825, 760. $\delta_{\rm H}$ 5.10 (2 H, br s, NH, C=NH), 6.80-7.90 (9 H, m, ArH).

N-(4-Chlorophenyl)benzamidine 3j. mp 114–116 °C (lit., 16 112– 115 °C). v/cm⁻¹ 3500, 3380, 1630, 1610, 1575, 1490, 1450, 1380, 1240, 1100, 1010, 860, 755, 700. $\delta_{\rm H}$ 5.00 (2 H, br s, NH, C=NH), 6.70-8.00 (9 H, m, ArH).

3-Methyl-N-(4-chlorophenyl)benzamidine 3k. mp 98–100 °C. ν/cm^{-1} 3490, 3340, 1630, 1590, 1495, 1380, 1250, 1100, 1010, 855, 810, 790, 760, 720. $\delta_{\rm H}$ 2.33 (3 H, s, CH₃), 4.90 (2 H, br s, NH, C=NH), 6.68-7.80 (8 H, m, ArH). MS m/z: 246 (M + 2, 32), 245 $(M + 1, 35), 244 (M^+, 100), 229 (9), 127 (97), 118 (60), 111 (35),$ 91 (58). Anal. Calc. for $C_{14}H_{12}ClN_2$: C, 69.00, H, 4.96, N, 11.49; Found: C, 69.23, H, 5.12, N, 11.37%.

3-Methyl-*N*-(4-methylphenyl)benzamidine **3l**. mp 88–90 °C. 3490, 3300, 1650, 1580, 1510, 1380, 1240, 1100, 1020, 920,

860, 790, 710. $\delta_{\rm H}$ 2.26 (3 H, s, CH₃), 2.33 (3 H, s, CH₃), 5.00 (2 H, br s, NH, C=NH), 6.75–7.85 (8 H, m, ArH). MS m/z: 225 (M + 1, 27), 224 (M⁺, 94), 209 (11), 133 (9), 118 (30), 107 (100), 106 (75), 91 (66), 77 (23). Anal. Calc. for C₁₅H₁₆N₂: C, 80.32, H, 7.19, N, 12.49; Found: C, 80.54, H, 7.03, N, 12.52%.

3-Methyl-*N*-phenylbenzamidine **3m**. mp 104–106 °C. ν /cm⁻¹ 3460, 3320, 1640, 1590, 1490, 1390, 1240, 1170, 1020, 840, 800, 770, 720, 695. $\delta_{\rm H}$ 2.37 (3 H, s, CH₃), 5.20 (2 H, br s, NH, C=NH), 6.90–7.80 (9 H, m, ArH). MS m/z: 211 (M + 1, 19), 210 (M⁺, 100), 195 (10), 194 (29), 118 (33), 93 (92), 91 (42), 77 (8). Anal. Calc. for C₁₄H₁₄N₂: C, 79.97, H, 6.71, N, 13.32; Found: C, 79.86, H, 6.87, N, 13.38%.

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