Pergamon

Tetrahedron Letters 43 (2002) 1867–1869

TETRAHEDRON LETTERS

Samarium diiodide promoted synthesis of *N*,*N*′-disubstituted amidines

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Received 6 November 2001; revised 8 January 2002; accepted 18 January 2002

Abstract—An efficient one-step preparation of an *N*,*N*′-disubstituted amidine by the direct nucleophilic addition of an amine to the parent nitrile using catalytic amounts of SmI_2 under relatively mild conditions is developed. Alkyl, benzyl and aryl amidines are prepared in moderate to good yields from the corresponding nitriles. © 2002 Elsevier Science Ltd. All rights reserved.

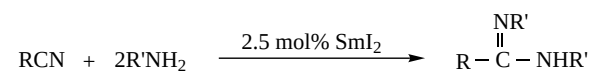
Amidines are very important compounds widely used as antibiotics, diuretics, antiphlogistic drugs, anthelmintics and wide-spectrum acaricides.[1,2] They are also valuable synthons for the preparation of azacyclic compounds.[3] As a result of their importance, several methods for their preparation are reported in detail in the literature. These include condensation reactions of amines with amides,[2] nitriles,[4,5] carboxylic acids,[6] or orthoformates[7] in the presence of condensation agents such as $POCl_3$, P_2O_5, PCl_3 or catalysts such as $AlCl_3$, Cu_2O, HOAc, and the Beckmann-type rearrangement of ketoximes.[8] In recent years, rare earth metal triflates have been found to be effective Lewis acids for promoting the amination of nitriles affording amidines in good yields.[9]

SmI_2 has been found to be a mild and versatile reducing or coupling agent for a variety of reactions. More recently, the use of SmI_2 as a precatalyst in organic synthesis, for reactions such as aldol reactions, Michael additions, Diels–Alder reactions and ring opening reactions, has received great attention.[10] As a part of our studies to explore the utility of SmI_2-catalyzed carbon–nitrogen bond forming reactions, we have investigated the catalytic activity of SmI_2 in the condensation of amines with nitriles for the preparation of *N*,*N*′-disubstituted amidines (Scheme 1). Herein, we wish to report our preliminary results.

The reaction was carried out at 55 or 80°C for 1 or 2 days, using the nitrile and amine in the presence of 2.5 mol% (relative to the nitrile) of SmI_2. The results are summarized in Table 1.[11]

As shown in Table 1, alkyl, benzyl, phenyl and heteroaryl nitriles can react with amines to give the corresponding amidines in moderate to good yields. The condensation occurs smoothly starting from different primary amines (Table 1, entries 1, 4 and 8). However, no amidine is obtained when *i*-$C_3H_7NH_2$ is used as the reagent (Table 1, entry 3). The mole ratio of nitrile to amine is a key factor in the condensation reaction. For example, the reaction of acetonitrile with *n*-butylamine gives *N*,*N*′-di-*n*-butyl-acetamidine in 58% yield at 80°C after 24 h in the case of a 1:2 nitrile:amine mole ratio, while 86% yield is obtained from a 1:3 mole ratio. When the mole ratio is increased beyond 1:4, the yield does not increase any further (entries 4, 6 and 7). The effect of reaction temperature was investigated with the same reaction. It was observed that lower temperatures lead to lower yields (entries 5 and 6).

It was noticed that the yield of amidine increases to a maximum at first and then gradually decreases as time passes (Table 2). The reason might be due to the formation of a by-product. Further examination shows *s*-triazine, the main by-product, is formed by the cyclotrimerization of the nitrile besides the desired amidine and its yield increases slowly and continuously as the reaction time progresses. It seems that the amidine already formed can be transformed into *s*-tri-



Scheme 1.

Keywords: samarium diiodide; synthesis; catalysis; *N*,*N*′-disubstituted amidine.

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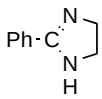
PII: S0040-4039(02)00129-6

Table 1. SmI_2-catalyzed preparation of *N*,*N*′-disubstituted amidines

Entry	R	R′	Product	Mole ratio (RCN:R′NH_2)	Temp. (°C)	Time (h)	Isolated yield (%)[a]
1	CH_3	*n*-C_3H_7	**3a**	1:2	55	24	59
2	CH_3	*n*-C_3H_7	**3a**	1:3	55	24	78
3	CH_3	*i*-C_3H_7	**3b**	1:2	55	24	0
4	CH_3	*n*-C_4H_9	**3c**	1:2	80	24	58
5	CH_3	*n*-C_4H_9	**3c**	1:3	55	24	18
6	CH_3	*n*-C_4H_9	**3c**	1:3	80	24	86
7	CH_3	*n*-C_4H_9	**3c**	1:4	80	24	86
8	CH_3	*n*-C_6H_{13}	**3d**	1:2	80	24	54(35[b])
9	Ph	*n*-C_3H_7	**3e**	1:3	55	24	58
10	Ph	*n*-C_4H_9	**3f**	1:3	80	24	59
11	4-Py	*n*-C_3H_7	**3g**	1:3	55	48	52
12	$PhCH_2$	*n*-C_3H_7	**3h**	1:3	55	24	45
13	Ph	-CH_2	 **3i**	1:1.5	80	24	35

[a] The reaction was carried out in an open system.
[b] The reaction was carried out in a closed system.

azine still further. In order to confirm this inference, some supplementary experiments with an *N*,*N*′-disubstituted amidine were tried. The *N*,*N*′-disubstituted amidine alone cannot be transformed into *s*-triazine no matter whether SmI_2 is used or not. However, *s*-triazine is obtained in the presence of the corresponding nitrile and a catalytic amount of SmI_2. For example, the reaction of *N*,*N*′-di-*n*-butyl-benzamidine with benzonitrile in a 1:2 mole ratio at 80°C for 24 h gave 2,4,6-triphenyl-*s*-triazine in 27% yield in the presence of 7.5 mol% (relative to the amidine) SmI_2, while no *s*-triazine was detected without SmI_2. According to these experiments, the course of the reaction can be thought to occur as shown in Scheme 2.

Table 2. Yield of amidine **3e** and *s*-triazine at different reaction times[a]

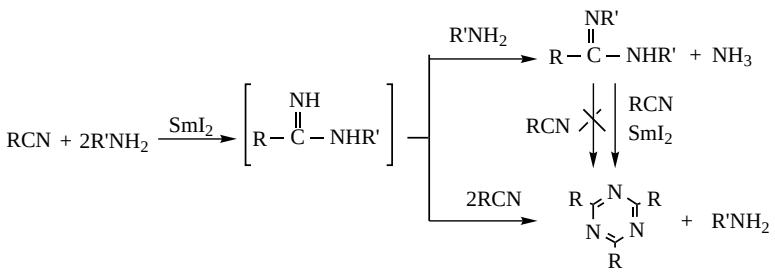
Entry	Time (h)	Isolated yield (%)	
		Amidine	*s*-Triazine
1	8	59	12
2	12	71	14
3	15	76	15
4	18	62	17
5	24	58	22

[a] Reaction conditions: 1:3 PhCN: *n*-$C_3H_7NH_2$, 2.5 mol% SmI_2 relative to PhCN, 55°C, open system.

According to Scheme 2, the reaction carried out in an open system should favor the formation of the amidine because of the smooth escape of NH_3. On the contrary, the reaction should be in favor of the formation of *s*-triazine in a closed system. The comparable experimental data for the reaction of PhCN with *n*-$C_6H_{13}NH_2$ obtained from the two different systems, respectively, support our hypothesis (Table 1, entry 8).

The color change of the reaction mixture from dark blue to light brown or white obviously indicates that the real active species for this reaction is the Sm(III) ion rather than the Sm(II) ion, although the true mechanism and actual Sm(III) intermediates are not yet clear.

In summary, SmI_2 has been found to be an efficient catalyst under mild reaction conditions and with good yields for the condensation of nitriles with amines to form *N*,*N*′-disubstituted amidines. This methodology gives us the chance to make better use of SmI_2 in organic synthesis.



Scheme 2.

Acknowledgements

The authors would like to thank the National Science Foundation of China (29872031), State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences for financial support.

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11. Spectral data: **3a**: elemental analysis: calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.49; H, 13.01; N, 19.49%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.94$ (m, 6H), 1.56 (m, 4H), 1.89 (s, 3H), 3.08 (m, 4H). MS (EI): m/z 142 (M^+). Compound **3c**: elemental analysis: calcd for $C_{10}H_{22}N_2$: C, 70.52; H, 13.02; N, 16.45. Found: C, 70.33; H, 12.85; N, 16.76%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.93$ (t, $J=7.2$ Hz, 6H), 1.37 (m, 4H), 1.54 (m, 4H), 1.92 (s, 3H), 3.14 (t, $J=7.6$ Hz, 4H). MS (EI): m/z 170 (M^+). Compound **3d**: elemental analysis: calcd for $C_{14}H_{30}N_2$: C, 74.26; H, 13.36; N, 12.38. Found: C, 73.82; H, 13.49; N, 12.71%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.89$ (m, 6H), 1.30 (m, 12H), 1.52 (m, 4H), 1.86 (s, 3H), 3.11 (m, 4H). MS (EI): m/z 226 (M^+). Compound **3e**: elemental analysis: calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.06; H, 9.76; N, 14.07%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.88$ (m, 6H), 1.54 (m, 4H), 3.13 (m, 4H), 7.36–7.54 (m, 5H). MS (EI): m/z 204 (M^+). Compound **3f**: elemental analysis: calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.20; H, 10.29; N, 12.27%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ (m, 6H), 1.31 (m, 4H), 1.50 (m, 4H), 3.16 (m, 4H), 7.35–7.44 (m, 5H). MS (EI): m/z 232 (M^+). Compound **3g**: elemental analysis: calcd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 69.67; H, 9.37; N, 20.96%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.91$ (m, 6H), 1.58 (m, 4H), 3.07 (m, 4H), 7.29–7.50 (m, 2H), 8.74 (m, 2H). MS (EI): m/z 205 (M^+). Compound **3h**: elemental analysis: calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.90; H, 10.22; N, 12.88%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 6H), 1.51 (m, 4H), 3.14 (m, 4H), 3.59 (s, 2H), 7.20–7.39 (m, 5H). MS (EI): m/z 218 (M^+). Compound **3i**: elemental analysis: calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.17. Found: C, 73.94; H, 6.87; N, 19.37%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.83$ (s, 4H), 6.05 (s, 1H), 7.38–7.94 (m, 5H). MS (EI): m/z 146 (M^+).