Intramolecular cascade radical cyclizations promoted by samarium diiodide

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Abstract

Samarium diiodide promotes intramolecular cascade radical cyclizations of cyanamide radical precursors conveniently to afford polycyclic N-heterocycles in moderate to good yields.

Keywords: Cascade radical cyclizations, samarium diiodide, cyanamides, N-heterocycles

Introduction

Over the past several years, cascade radical cyclizations, in which the cyclized intermediate directly undergoes further cyclization, have received considerable synthetic attention because they have shown great utility as highly effective methods to construct polycyclic structures in one step.¹⁻⁴ Recently, some natural products have been efficiently synthesized on the basis of cascade radical cyclizations.⁵⁻⁷

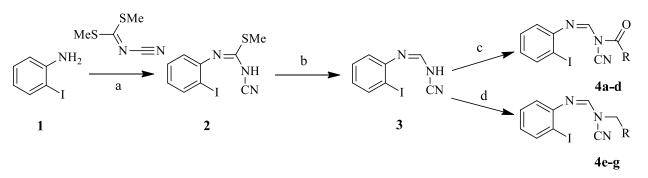
Samarium diiodide (SmI₂) has become an exceedingly powerful single electron transfer reagent for promoting reduction and has been applied to a multitude of important synthetic reactions, such as Barbier couplings, Reformatsky reactions, ketone-olefin reductive couplings and pinacol couplings, among which the SmI₂-promoted intramolecular cyclizations are particularly attractive.⁸⁻¹³

Recently, *N*-acylcyanamides were introduced as radical partners in tributyltin hydride mediated radical cascade cyclizations leading to polycyclic nitrogen heterocycles.¹⁴ We report here that SmI₂ can promote the radical cascade cyclizations of cyanamide precursors yielding polycyclic *N*-heterocycles.

Results and Discussion

Scheme 1 shows the synthesis of cyanamides 4. Condensation of 2-iodoaniline 1 with dimethyl cyanoimidodithiocarbonate¹⁵ in the presence of Cs_2CO_3 in DMF at 100 °C gave adduct 2. Raney-

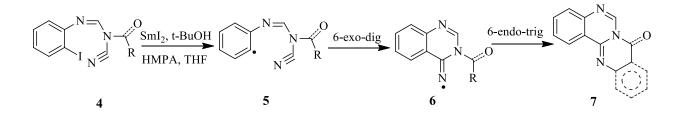
nickel desulfurization of 2 in ethanol under reflux afforded 3. Starting from 3, cyanamides 4 were prepared by two different synthetic routes. Acylation of 3 in the presence of Et_3N in CH_2Cl_2 afforded 4a-d. Substitution at the NH group of compound 3 was performed by reaction with alkyl bromides under basic conditions to yield 4e-g.



Reagents and conditions: (a) Cs_2CO_3 , DMF, 100°C; 41%; (b) Raney Ni, ethanol, reflux; 73%; (c) RCOCl, Et₃N, CH₂Cl₂; 52-71%; (d) RCH₂Br, Cs₂CO₃, DMF; 42-55%

Scheme 1. The synthetic routes to the cyanamides 4.

The cyano group is usually stable and cannot be reduced under radical conditions. Occasionally, cyano group shifts can be observed with nitriles.¹⁶⁻¹⁸ However, substrates **4** containing cyano groups formed the intermediate radicals and cyclized to afford **7** in moderate to good yields under radical conditions with SmI_2 (Scheme 2). The results are listed in Table 1.



Scheme 2. The intramolecular cascade radical cyclizations promoted by SmI₂.

The polycyclic formation can be explained by the putative mechanism presented in Scheme 2. The aryl radicals **5** generated from the precursors **4** underwent a 6-exo-dig cyclization into the nitriles to give the intermediate radicals **6**. The intermediates **6** further underwent a 6-endo-trig addition onto the unsaturated moiety and subsequent aromatization or reduction under the reaction conditions (SmI₂-HMPA) to yield the corresponding polycyclic compounds **7**.

The SmI₂-mediated reduction of aryl iodide results in a carbon radical which is intramolecularly trapped by a cyanamide, which in turn is trapped by an alkene or a phenyl ring. This methodology is useful in building polycyclic systems in a single step. Moreover, this new process has some methodological advantages since samarium salts are easily eliminated from products.

| Entry | Precursor | R | Product | Yield (%) ^a |
|-------|------------|--------------------|---|------------------------|
| 1 | 4 a | * | γ | 78 |
| 2 | 4b | H ₃ C* | о N N N СН ₃ 7b | 61 |
| 3 | 4c | H ₃ C * | O N N CH₃ N 7c | 65 |
| 4 | 4d | Br * | O N N N N Br 7d | 58 |
| 5 | 4e | * | 7e | 74 |
| 6 | 4f | H ₃ C * | N N CH ₃ N N 7f | 63 |
| 7 | 4g | * | N N N N N N 7g | 55 |

Table 1. The heterocyclic compounds 7 prepared by intramolecular cascade cyclizations with SmI₂

^aIsolated yield.

Conclusions

In summary, polycyclic *N*-heterocycles can be conveniently prepared *via* SmI₂-promoted intramolecular cascade radical cyclizations with cyanamides as radical precursors.

Experimental Section

General. Unless otherwise indicated, all reactions were carried out under a dry nitrogen atmosphere. DMF was freshly distilled from calcium hydride and THF was distilled from sodiumbenzophenone immediately prior to use. The other reagents were used directly without further purification. Melting points (mp) were obtained on a B-540 Büchi melting-point apparatus and are uncorrected. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) data were recorded on a DPX-400 instrument with CDCl₃ or DMSO- d_6 as solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are given in ppm and spin-spin coupling constants, *J*, are given in Hz. Mass spectra (MS) were recorded on a HP5989A mass spectrometer. Elemental analyses were carried out on a PE EA2400 CHN analyzer.

Synthesis of *N*-(2-iodophenyl)-*N*'-cyano-S-methylisothiourea (2). Dimethyl cyanodithioimidocarbonate (1.46 g, 10 mmol) was dissolved in DMF (20 mL). To the stirred solution were added 2-iodoaniline (2.19 g, 10 mmol) and K₂CO₃ (2.07 g, 15 mmol). The solution was kept at 100 °C for 8 h and then poured into ice water. A yellow precipitate formed immediately and was collected by filtration (0.32 g, 41%). Mp 178-180 °C; ¹H NMR (DMSO-*d*₆) δ : 10.35 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.36-7.48 (m, 2H), 7.14 (t, *J*₁ = 7.2 Hz, *J*₂ = 7.2 Hz, 1H), 2.63 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ : 161.3, 158.1, 139.2, 130.3, 128.5, 124.1, 116.1, 83.6, 13.3. ESI-MS: [M+1]⁺ m/z 318. Anal. calcd. for C₉H₈IN₃S: C, 34.08; H, 2.54; N, 13.25. Found: C, 34.17; H, 2.52; N, 13.23.

Synthesis of *N*-cyano-*N'*-(2-iodophenyl)formamidine (3). To a solution of compound 2 (1.2 g, 3.8 mmol) in absolute ethanol (25 mL) was added Raney Nickel 2800 (1.2 g). The mixture was heated to reflux for 6 h and quickly filtered while it was still hot. The filtrate was concentrated to half its volume and the product was crystallized. The solid was filtered and dried in a vacuum container to afford **3** (0.75 g, 73%) as a white solid. Mp 166-168 °C; ¹H NMR (CDCl₃) δ : 9.16 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.37 (s, 1H), 7.06-7.21 (m, 2H), 6.93 (t, $J_I = 7.2$ Hz, $J_2 = 7.2$ Hz, 1H); ¹³C NMR (CDCl₃) δ : 160.9, 157.3, 139.0, 129.1, 122.7, 118.6, 115.7, 84.2. ESI-MS: [M+1]⁺ m/z 272. Anal. calcd. for C₈H₆IN₃: C, 35.45; H, 2.23; N, 15.50. Found: C, 35.37; H, 2.25; N, 15.58.

General procedure for synthesis of cyanamides (4a-d)

To a solution of compound **3** (0.54 g, 0.2 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.4 mmol). The appropriate acyl chloride (0.3 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the mixture at 0 °C. The mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated NaHCO₃ solution and then extracted with CH_2Cl_2 . The organic layer was washed with water, brine and dried over Na₂SO₄. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by silica gel flash chromatography to give **4a-d**.

N-Cyano-*N*-[(2-iodophenylimino)methyl]benzamide (4a). White solid, yield 71%; ¹H NMR (CDCl₃) δ : 8.13 (s, 1H), 7.61-7.82 (m, 6H), 7.11–7.42 (m, 3H); ¹³C NMR (CDCl₃) δ : 169.6, 161.5, 158.3, 139.2, 135.3, 133.1, 130.1, 129.3, 128.7, 128.1, 124.3, 116.2, 83.6. ESI-MS: [M+1] ⁺ m/z 376. Anal. calcd. for C₁₅H₁₀IN₃O: C, 48.02; H, 2.69; N, 11.20. Found: C, 48.08; H, 2.67; N, 11.23.

N-Cyano-*N*-[(2-iodophenylimino)methyl]-4-methylbenzamide (4b). Off-white solid, yield 52%; ¹H NMR (CDCl₃) δ : 8.09 (s, 1H), 7.12–7.81 (m, 8H), 2.38 (s, 3H); ¹³C NMR (CDCl₃) δ : 169.4, 161.5, 158.3, 142.0, 139.2, 131.8, 130.1, 129.8, 128.7, 128.0, 124.3, 116.2, 83.7, 24.2. ESI-MS: [M+1] ⁺ m/z 390. Anal. calcd. for C₁₆H₁₂IN₃O: C, 49.38; H, 3.11; N, 10.80. Found: C, 49.45; H, 3.14; N, 10.85.

N-Cyano-*N*-[(2-iodophenylimino)methyl]-3-methylbenzamide (4c). Off-white solid, yield 64%; ¹H NMR (CDCl₃) δ : 8.10 (s, 1H), 7.13–7.79 (m, 8H), 2.36 (s, 3H); ¹³C NMR (CDCl₃) δ : 169.5, 161.5, 158.2, 139.1, 138.7, 133.9, 132.2, 129.6, 129.1, 128.8, 128.5, 124.7, 124.3, 116.1, 83.6, 24.0. ESI-MS: [M+1] ⁺ m/z 390. Anal. calcd. for C₁₆H₁₂IN₃O: C, 49.38; H, 3.11; N, 10.80. Found: C, 49.45; H, 3.13; N, 10.85.

3-Bromo-*N***-cyano-***N***-[(2-iodophenylimino)methyl]benzamide (4d).** Pale white solid, yield 58%; ¹H NMR (CDCl₃) δ: 8.25 (s, 1H), 7.47-7.93 (m, 6H), 7.12–7.36 (m, 2H); ¹³C NMR (CDCl₃) δ: 169.6, 161.6, 158.2, 139.1, 136.2, 134.9, 131.1, 129.6, 129.4, 128.8, 126.2, 124.3, 123.5, 116.3, 83.6. ESI-MS: [M+1]⁺ m/z 455. Anal. calcd. for C₁₅H₉BrIN₃O: C, 39.68; H, 2.00; N, 9.25. Found: C, 39.62; H, 2.01; N, 9.15.

General procedure for synthesis of cyanamides (4e-g)

To a solution of compound **3** (0.54 g, 0.2 mmol) in DMF (10 mL) was added Cs_2CO_3 (0.4 mmol). Alkyl bromide (0.22 mmol) was added dropwise to the mixture. The mixture was stirred for 8 h at 50 °C. After filtration, the filtrate was concentrated and the residue was purified by silica gel flash chromatography to give **4e-g**.

N-Benzyl-*N*-cyano-*N'*-(2-iodophenyl)formamidine (4e). White solid, yield 55%; ¹H NMR (CDCl₃) δ : 7.91 (s, 1H), 7.08–7.83 (m, 9H), 4.11 (s, 2H); ¹³C NMR (CDCl₃) δ : 161.1, 158.2, 141.2, 139.2, 130.1, 129.3, 128.7, 127.2, 126.5, 124.3, 116.1, 83.7, 53.2. ESI-MS: [M+1]⁺ m/z 362. Anal. calcd. for C₁₅H₁₂IN₃: C, 49.88; H, 3.35; N, 11.63. Found: C, 49.81; H, 3.28; N, 11.35.

N-Cyano-*N'*-(2-iodophenyl)-*N*-(3-methylbenzyl)formamidine (4f). White solid, yield 47%; ¹H NMR (CDCl₃) δ : 7.91 (s, 1H), 7.11–7.84 (m, 8H), 4.11 (s, 2H), 2.38 (s, 3H); ¹³C NMR (CDCl₃) δ : 161.1, 158.2, 141.1, 139.1, 138.4, 130.1, 129.2, 128.8, 128.5, 127.2, 124.4, 124.3, 116.1, 83.6, 53.3, 24.4. ESI-MS: [M+1]⁺ m/z 376. Anal. calcd. for C₁₆H₁₄IN₃: C, 51.22; H, 3.76; N, 11.20. Found: C, 51.13; H, 3.73; N, 11.15.

N-Allyl-*N*-cyano-*N'*-(2-iodophenyl)formamidine (4g). White solid, yield 42%; ¹H NMR (CDCl₃) δ : 7.91 (s, 1H), 7.31-7.84 (m, 4H), 5.76 (m, 1H), 5.18 (dd, $J_I = 16.4$ Hz, $J_2 = 10.4$ Hz, 1H), 5.03 (dd, $J_I = 10.4$ Hz, $J_2 = 1.2$ Hz, 1H), 3.38–3.44 (m, 2H); ¹³C NMR (CDCl₃) δ : 161.0, 158.1, 139.1, 135.1, 129.3, 128.8, 124.3, 116.7, 116.2, 83.7, 50.3. ESI-MS: [M+1] ⁺ m/z 312. Anal. calcd. for C₁₁H₁₀IN₃: C, 42.46; H, 3.24; N, 13.51. Found: C, 42.52; H, 3.22; N, 13.48.

Typical procedure for the SmI₂-promoted cyclization reactions

A solution of *t*-butanol (155 mg, 2.1 mmol) in THF (1 mL) and cyanamide **4** (0.7 mmol) were added to a solution of HMPA (1.75 g, 10.0 mmol) and SmI_2 (0.1 M in THF, 21 mL, 2.1 mmol) at room temperature. The reaction mixture was subjected to TLC analysis until the reaction was completed. The reaction was quenched with 0.1 M HCl and extracted with ether. The ether layer

was washed with saturated $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel flash chromatography afforded the cyclization products **7**.

8H-Quinazolino[**4**,**3**-*b*]**quinazolin-8-one** (**7a**). Yellow white solid; mp 194-196 °C (lit.¹⁹ 197 °C; lit.²⁰ 198 °C); ¹H NMR (DMSO-*d*₆) δ: 9.33 (s, 1H), 8.86 (d, *J* = 7.8 Hz, 1H), 7.59–8.71(m, 6H), 7.52 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ: 160.2, 148.4, 145.5, 144.3, 138.4, 137.1, 134.2, 130.0, 129.2, 128.6, 128.3, 128.0, 126.4, 122.7, 119.1. ESI-MS: [M+1]⁺ m/z 248.

11-Methyl-8*H***-quinazolino[4,3-***b***]quinazolin-8-one (7b). Yellow white solid; mp 186–188 °C; ¹H NMR (DMSO-***d***₆) \delta: 9.35 (s, 1H), 8.76 (d,** *J* **= 7.8 Hz, 1H), 7.47-7.89(m, 6H), 2.48 (s, 3H); ¹³C NMR (DMSO-***d***₆) \delta: 160.1, 148.4, 145.4, 144.3, 140.5, 138.2, 134.2, 130.1, 128.9, 128.6, 128.3, 128.0, 127.7, 121.4, 119.0, 21.3. HRMS m/z calcd. for C₁₆H₁₁N₃O (M⁺) 261.0902, found 261.0909. Anal. calcd. for C₁₆H₁₁N₃O: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.32; H, 4.12; N, 15.93.**

10-Methyl-8*H***-quinazolino[4,3-***b***]quinazolin-8-one (7c).** Yellow white solid; mp 201-203 °C (lit. ²⁰ 211 °C); ¹H NMR (DMSO-*d*₆) δ: 9.35 (s, 1H), 8.78 (d, *J* = 7.8 Hz, 1H), 8.36 (s, 1H), 7.55-7.93(m, 5H), 2.48 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ: 160.2, 148.3, 145.5, 141.6, 138.4, 137.0, 136.8, 134.2, 130.2, 129.2, 128.6, 128.1, 126.4, 122.6, 119.0, 21.4. ESI-MS: [M+1] ⁺ m/z 262.

10-Bromo-8*H***-quinazolino[4,3-***b***]quinazolin-8-one (7d). Yellow solid; mp 211-212 °C (lit.²⁰ 229 °C); ¹H NMR (DMSO-***d***₆) \delta: 9.36 (s, 1H), 8.77 (d,** *J* **= 8.0 Hz, 1H), 8.51 (s, 1H), 7.64-8.07(m, 5H); ¹³C NMR (DMSO-***d***₆) \delta: 160.2, 148.4, 145.5, 143.8, 138.9, 138.4, 134.2, 133.1, 130.0, 129.2, 128.6, 126.4, 123.7, 124.4, 119.0. ESI-MS: [M+1] + m/z 326.**

8*H***-Quinazolino**[**4**,**3**-*b*]**quinazoline** (**7***e*). Yellow solid; mp 167-169 °C; ¹H NMR (DMSO-*d*₆) δ : 8.12 (s, 1H), 7.38-7.75 (m, 8H), 4.09 (s, 2H); ¹³C NMR (DMSO-*d*₆) δ : 153.7, 142.2, 139.3, 135.3, 134.2, 132.6, 130.0, 129.2, 128.6, 128.3, 128.0, 126.3, 125.8, 119.1, 49.7. HRMS m/z calcd. for C₁₅H₁₁N₃ (M⁺) 233.0953, found 233.0958. Anal. calcd. for C₁₅H₁₁N₃: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.14; H, 4.71; N, 17.86.

10-Methyl-8*H***-quinazolino[4,3-***b***]quinazoline (7f). Yellow solid; mp 154-156 °C; ¹H NMR (DMSO-***d***₆) \delta: 8.12 (s, 1H), 7.11-7.73(m, 7H), 4.09 (s, 2H), 2.37 (s, 3H); ¹³C NMR (DMSO-***d***₆) \delta: 153.7, 140.4, 139.5, 136.7, 135.3, 134.2, 132.6, 131.8, 129.1, 128.6, 128.0, 126.2, 125.8, 119.0, 49.9, 21.8. HRMS m/z calcd. for C₁₆H₁₃N₃ (M⁺) 247.1109, found 247.1116. Anal. calcd. for C₁₆H₁₃N₃: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.82; H, 5.35; N, 17.13.**

3,4-Dihydro-2*H***-pyrimido[1,2-***c***]quinazoline (7g).** Brown oil; ¹H NMR (DMSO-*d*₆) δ: 7.93(s, 1H), 7.28-7.61(m, 4H), 4.84(t, 2H), 3.62(t, 2H), 1.98(m,2H); ¹³C NMR (DMSO-*d*₆) δ: 142.9, 140.6, 138.3, 131.7, 129.2, 126.2, 123.7, 120.1, 45.3, 37.9, 18.4. HRMS m/z calcd. for C₁₁H₁₁N₃ (M⁺) 185.0953, found 185.0961. Anal. calcd. for C₁₁H₁₁N₃: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.51; H, 6.07; N, 22.88.

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