SHORT PAPER

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Samarium diiodide mediated simultaneous reduction of nitro group and the azide group in *o*-nitrophenylazide: a new access to 2,3-dihydro-1*H*-1,5-benzodiazepines†

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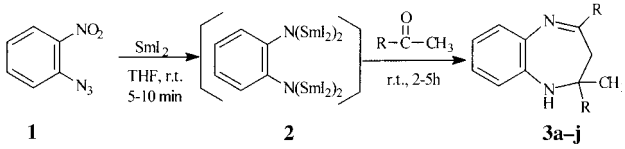
o-Nitrophenylazide was reduced by SmI_2 in anhydrous THF at room temperature to produce an active intermediate **2** (samarium amide), the 'living' double-anion *in situ* which reacted smoothly with ketones containing active methyl or methylene groups to afford 2,3-dihydro-1*H*-1,5-benzodiazepines in good yields under mild and neutral conditions.

2,3-Dihydro-1*H*-1,5-benzodiazepine derivatives have attracted interest due to their biological properties.[1] The methods for preparing these compounds using *o*-phenylenediamines as starting materials involved harsh conditions such as using acid or base catalysts, moderate to high thermal conditions and long reaction time.[2,3]

Applications of samarium diiodide as a mild, neutral, selective and versatile single-electron transfer reducing and coupling reagent in organic synthesis have grown significantly in the last two decades.[4] Both nitro compounds[5] and azide compounds[6] can be easily reduced by SmI_2 to the corresponding amines. However, little attention has been given to the intermediates derived from nitro or azide groups by SmI_2 treatment, which may lead to some reactions difficult to accomplish by other existing methodologies.[7] Recently, we have reported the samarium diiodide mediated simultaneous reduction of nitro groups and the S–S bond in bis(*o*-nitrophenyl) disulfides to produce active intermediates and their uses in the synthesis of some heterocycles containing nitrogen and sulfur.[8] In order to extend the application of SmI_2, we considered whether SmI_2 could mediated simultaneous reduction of nitro and azide groups in *o*-nitrophenylazide.

When *o*-nitrophenylazide **1** was added dropwise to a solution of SmI_2 in anhydrous THF at room temperature, the deep blue colour of the solution changed to a yellow colour within several minutes. The above phenomenon showed that the nitro group and the azide group could be simultaneously reduced by samarium diiodide, which resulted in the formation of an intermediate **2** (proposed to be samarium amide). When ketones containing active methyl groups were added to the solution of the intermediate **2**, the seven-membered heterocycles 2,3-dihydro-1*H*-1,5-benzodiazepines were obtained in good yields (Scheme 1).

The results are summarized in Table 1. Orlov[2b] reported that 2,3-dihydro-1*H*-1,5-benzodiazepines could be obtained from



Scheme 1

Table 1 Synthesis of 2,3-dihydro-1H-1,5-beznodiazepines mediated by SmI2

Entry	R	T (h)	Yield(%)[a]
3a	Et	2	78
3b	*n*-Pr	2	83
3c	*n*-Bu	4	85
3d	*n*-C_5H_{11}	4	75
3e	C_6H_5	1	88
3f	*p*-MeC_6H_4	1	87
3g	*p*-$MeOC_6H_4$	1	89
3h	*p*-ClC_6H_4	3	78
3i	*p*-BrC_6H_4	3	67
3j	*m*-$NO_2C_6H_4$	5	56

[a]Isolated yields based on *o*-nitrophenylazide.

o-phenylenediamine and aromatic ketones (*i.e.* **3e–j**) in the presence of acid medium under reflux conditions, however, the preparation of products **3a–d** using similar methods has not been reported. In our study, both aliphatic and aromatic ketones could react with the active intermediate **2** to give the desired products **3a–j** in satisfactory yields.

Although the detail mechanism of this reaction has not been clarified, the existence of the intermediate **2** might be explained by the following experimental phenomena. When MeOH (0.2 ml) was added to the solution of intermediate **2**, *o*-phenylenediamine was found, however, if ketones were added to the solution of *o*-phenylenediamine under the same conditions, no reaction took place and no products **3** could be detected. On the other hand, an attempt to synthesize products **3** *via* reduction of *o*-nitrophenylamine by SmI_2 followed by reacting with ketones under similar conditions failed. The two facts showed that the intermediate **2** derived from *o*-nitrophenylazide by SmI_2 treatment is a 'living' species *in situ* and more reactive than *o*-phenylenediamine.

The structure of products **3** were confirmed by IR, ^1H NMR, MS and elemental analysis. The IR spectra of **3a–j** exhibited a sharp band at ~3350 cm^{-1} (–NH stretching) and a middle strong absorption band at ~1650 cm^{-1} (C=N). The ^1H NMR spectra of products **3a-d** derived from aliphatic ketones and *o*-nitrophenylazide showed a two-proton singlet at δ_H ~2.10 which is due to the methylene group (CH_2) on the position 3 of heterocycles **3**. As for aromatic ketones, the ^1H NMR spectra of the corresponding products **3e–j** showed a two-proton singlet at δ_H ~2.80 on the same position. Mass spectra of the product **3a–j** showed that the cyclic 1,5-benzodiazepine ions and benzimidazole ions derived from the fragmentation and

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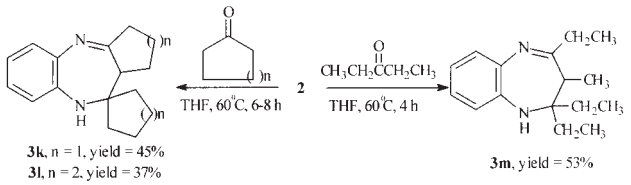
skeletal rearrangement of the molecular ions were the main spectral features.



Scheme 2

Herbert *et al.*[3b] reported that 1,5-benzodiazepine-2-spirocycloalkenes could be obtained from *o*-phenylenediamine and cyclic ketones in the presence of boron trifluoride-ether complex. In our study, ketones containing active methylene groups such as cyclopentanone, cylcohexanone, 3-pentanone (entries **3k–m**) have been tested to react with the intermediate **2** under mild and neutral conditions and afforded the corresponding products **3k–m** in low to moderate yields.

In conclusion, a series of 2,3-dihydro-1*H*-1,5-benzodiazepines were synthesized *via* the active intermediate **2** (samarium amide). We think that the present study provides a new, simple and versatile method for the synthesis of 2,3-dihydro-1*H*-1,5-bezodiazepine derivatives without resorting to acid or base catalysts.

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points were uncorrected. Infrared spectra were recorded on an IR-408 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC–80 spectrometer as $CDCl_3$ solutions. *J* values are in Hz. Chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane. Mass spectra were recorded on a HP 5989B MS spectrometer. Microanalysis was carried out on a Carlo-Erba 1106 instrument.

General procedure: a solution of *o*-nitrophenylazide **1** (1 mmol) in anhydrous THF (1 ml) was added dropwise to a solution of SmI_2 (8 mmol) in THF (30 ml) at room temperature under a dry nitrogen atmosphere. The mixture was stirred for 5-10 minutes and became yellow gradually. Then ketones (2.2 mmol) in THF (1 ml) were added to the mixture. After stirring for a given time (Table 1 and Scheme 2, the reaction was monitored by TLC), the reaction was quenched with dilute hydrochloric acid (0.1mol/l, 1 ml). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 ml), saturated brine (15 ml), and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative thick layer chromatography using ethyl acetate and cyclohexane (1:5) as eluant.

3a, *2,4-Diethyl-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine*: m.p. 96–98°C ν_{max}: 3342(NH), 2967, 2830, 1465, 1370(CH_3, CH_2), 1640(C=N)cm^{-1}. δ_H: 7.07–6.36(4H, m, ArH), 3.26(1H, br s, NH), 2.40(2H, t, *J*=6.5Hz, CH_2), 2.14(2H, s, CH_2), 1.60–0.95(11H, m, alkyl-H). *m/z*(%): 216(M^+, 13.4), 201(15.7), 187(100), 174(29.7), 148(36.7), 134(25.8). Anal. $C_{14}H_{20}N_2$. Calcd. C, 77.73; H, 9.32; N, 12.95. Found C, 77.91; H, 9.23; N, 12.86%.

3b, *2,3-Dihydro-2-methyl-2,4-dipropyl-1*H*-1,5-benzodiazepine*: m.p. 85–87°C. ν_{max}: 3350(NH), 2982, 2850, 1470, 1380(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.05–6.43(4H, m, ArH), 2.90(1H, br s, NH), 2.40(2H, t, *J*=6.5Hz, CH_2), 2.03(2H, s, CH_2), 1.85–0.85(15H, m, alkyl-H). *m/z*(%): 244(M^+, 11.2), 229(5.5), 201(66.4), 71(80.7), 57(100), 43(90.6). Anal. $C_{16}H_{24}N_2$. Calcd. C, 78.64; H, 9.90; N, 11.46. Found C, 78.47; H, 10.03; N, 11.50%.

3c, *2,4-Dibutyl-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine*: 66–68°C. ν_{max}: 3350(NH), 2967, 2850, 1458, 1380(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.23–6.46(4H, m, ArH), 3.02(1H, br s, NH), 2.44(2H, t, *J*=6.5Hz, CH_2), 2.06(2H, s, CH_2), 1.75–0.75(19H, m, alkyl-H). *m/z*(%): 272(M^+, 13.4), 215(100), 174(29.7), 132(30.7). Anal. $C_{18}H_{28}N_2$. Calcd. C, 79.36; H, 10.36; N, 10.28. Found C, 79.44; H, 10.23; N, 10.33%.

3d, *2,3-Dihydro-2-methyl-2,4-dipentyl-1*H*-1,5-benzodiazepine*: m.p. 62–64°C. ν_{max}: 3350(NH), 2983, 2830, 1466, 1365(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.10-6.40(4H, m, ArH), 2.85(1H, br s, NH), 2.40(2H, t, *J*=6.5Hz, CH_2), 2.03(2H, s, CH_2), 1.85–0.83(23H, m, alkyl-H). *m/z*(%): 300(M^+, 8.8), 229(62.8), 173(21.5), 119(98.5), 117(100). Anal. $C_{20}H_{32}N_2$. Calcd. C, 79.94; H, 10.73; N, 9.32. Found C, 79.76; H, 10.85; N, 9.39%.

3e, *2,3-Dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-benzodiazepine*: m.p. 100–102°C (lit.,[2b] 103°C). ν_{max}: 3334(NH), 2960, 2825, 1460, 1372(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.83-6.73(14H, m, ArH), 3.42(1H, br s, NH), 2.87(2H, s, CH_2), 1.58(3H, s, CH_3).

3f, *2,3-Dihydro-2-methyl-2,4-di(4′-methylphenyl)-1*H*-1,5-benzodiazepine*: m.p. 96–98°C (lit.,[2b] 98°C). ν_{max}: 3332(NH), 2974, 2835, 1465, 1380(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.89–6.85(12H, m, ArH), 3.52(1H, br s, NH), 2.87(2H, s, CH_2), 2.37(3H, s, CH_3), 2.28(3H, s, CH_3), 1.58(3H, s, CH_3).

3g, *2,3-Dihydro-2-methyl-2,4-di(4′-methoxylphenyl)-1*H*-1,5-benzodiazepine*: m.p. 114–116°C(lit.,[2b] 117°C). ν_{max}: 3330(NH), 2968, 2845, 1465, 1370(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.78–6.48(12H, m, ArH), 3.65(3H, s, OCH_3), 3.55(3H, s, OCH_3), 3.35(1H, br s, NH), 2.75(2H, s, CH_2), 1.55(3H, s, CH_3).

3h, *2,4-Di(4′-chlorophenyl)-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine*: m.p. 141–143°C(lit.,[2b] 143-144°C). ν_{max}: 3335(NH), 2983, 2842, 1472, 1368(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.23–6.46(4H, m, ArH), 3.02(1H, br s, NH), 2.44(2H, t, *J*=6.5Hz, CH_2), 2.06(2H, s, CH_2), 1.75–0.75(19H, m, alkyl-H).

3i, *2,4-Di(4′-bromophenyl)-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine*: m.p. 141–143°C(lit.,[2b] 141–142°C). ν_{max}: 3350(NH), 2960, 2830, 1465, 1372(CH_3, CH_2), 1645(C=N)cm^{-1}. δ_H: 7.73–6.65(12H, m, ArH), 3.40(1H, br s, NH), 2.81(2H, s, CH_2), 1.58(3H, s, CH_3).

3j, *2,3-Dihydro-2-methyl-2,4-di(3′-nitrophenyl)-1*H*-1,5-benzodiazepine*: m.p. 149–151°C (lit.,[2b] 151–153°C). ν_{max}: 3350(NH), 2970, 2835, 1475, 1366(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 8.23–6.69(12H, m, ArH), 3.52(1H, br s, NH), 2.92(2H, s, CH_2), 1.55(3H, s, CH_3).

3k, *2,3-Dihydro-2,2-tetramethylene-3,4-trimethylene-1*H*-1,5-benzodiazepine*: m.p. 127–129°C (lit.,[3b] 130°C). ν_{max}: 3350(NH), 2963, 2830, 1455, 1370(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.10–6.28(4H, m, ArH), 2.85(1H, br s, NH), 2.50–2.21(3H, m, CH_2 and CH), 1.80–1.48(12H, m, alkyl-H).

3l, *2,3-Dihydro-2,2-pentamethylene-3,4-tetramethylene-1*H*-1,5-benzodiazepine*: m.p. 145–147°C(lit.,[3b] 148?). ν_{max}: 3350(NH), 2960, 2825, 1465, 1365(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.28-6.36(4H, m, ArH), 3.32(1H, br s, NH), 2.57–2.05(3H, m, CH_2 and CH), 1.86–1.32(16H, m, alkyl-H).

3m, *2,2,4-Triethyl-2,3-dihydro-3-methyl-1*H*-1,5-benzodiazepine*: m.p. 114–117°C. ν_{max}: 3350(NH), 2965, 2835, 1470, 1383(CH_3, CH_2), 1650(C=N)cm^{-1}. δ_H: 7.40–6.37(4H, m, ArH), 3.50(1H, br s, NH), 2.80–2.13(3H, m, CH_2 and CH), 1.67–0.75(16H, m, alkyl-H). *m/z*(%): 244(M^+, 13.4), 215(100), 174(29.7), 132(30.7). Anal. $C_{16}H_{24}N_2$. Calcd. C, 78.64; H, 9.90; N, 11.46. Found C, 78.52; H, 9.81; N, 11.26%.

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