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Samarium Diiodide Catalyzed Synthesis of 2,3-Dihydro-1*H*-benzo[*b*][1,4]-diazepine Derivatives

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Samarium diiodide (SmI_2) was found to be an efficient catalyst for the condensation of *o*-phenylenediamine and ketones to afford the corresponding 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepines in moderate to excellent yields under very mild and solvent-free conditions. The real active species here was suggested to be a Sm(III) intermediate formed *in situ* and the mechanism of the present reaction was proposed.

Keywords samarium diiodide, 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine, synthesis, catalysis

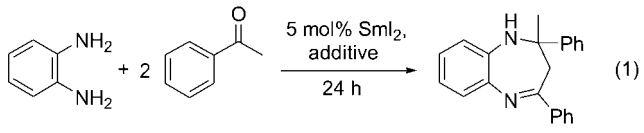
Introduction

Benzodiazepines and their derivatives are a class of pharmacologically important compounds widely used as anticonvulsant, analgesic, hypnotic, sedative and antidepressive agents.[1] In addition, 1*H*-benzo[*b*][1,4]-diazepines are also available starting materials for the synthesis of other fused ring benzodiazepine derivatives such as triazolo-, oxazino-, oxadiazolo- or furano- benzodiazepines.[2] Because of their wide range of pharmacological property and potential industrial and synthetic applications, the synthesis of 1*H*-benzo[*b*]-[1,4]-diazepine and its derivatives has recently attracted considerable attention. Several methods for the preparation of 1*H*-benzo[*b*][1,4]-diazepine derivatives have been reported in the literature, including condensation reactions of *o*-phenylenediamine with *α*,*β*-unsaturated carbonyl compounds,[3] *β*-haloketones[4] or ketones promoted by $BF_3 \cdot Et_2O$,[5] polyphosphoric acid,[6] SiO_2,[6] $MgO/POCl_3$,[7] $Yb(OTf)_3$[8] or superacid sulfated zirconia.[9] More recently, a stoichiometric amount of ionic liquid promoted[10] and microwave irradiated[11] preparation of 1*H*-benzo[*b*][1,4]-diazepine derivatives have also been presented. However, some of these processes owned limitations such as expensive reagents, inconvenient catalyst preparation, high catalyst loading, drastic reaction conditions and presence of side reactions.

Samarium diiodide (SmI_2) has been found to be not only a reducing agent[12] but also a Lewis acid-type precatalyst[13] widely used in various reactions. The application of SmI_2 in organic synthesis has attracted great attention due to its superiorities of low cost and simple preparation. As a part of our studies to explore the utility of SmI_2 catalyzed carbon-nitrogen bond forming reactions,[14] we have investigated the catalytic activity of SmI_2 in the condensation of *o*-phenylenediamine with ketones for the preparation of 1*H*-benzo[*b*][1,4]-diazepine derivatives. Herein, we wish to report our preliminary results.

Results and discussion

First, the condensation of acetophenone with *o*-phenylenediamine was tested in the presence of 5 mol% SmI_2 for 24 h under different conditions (Eq. 1). The results are summarized in Table 1. As shown in the table, the reaction with CH_3CN as solvent or without solvent both yielded the corresponding 2,3-dihydro-1*H*-benzo-[*b*][1,4]-diazepine in 90% yield in the presence of 4 Å molecular sieves (Entries 2 and 3). The same reaction without 4 Å molecular sieves gave lower yield (Entry 4). Increasing reaction temperature led to a decrease in the yield of the product (Entry 5). This may be because of the instability of *o*-phenylenediamine at relatively high temperature.



(1)

The condensation of *o*-phenylenediamine with other ketones was examined in the presence of 5 mol% SmI_2 and 4 Å molecular sieves at room temperature for 24 h under solvent-free condition (Eq. 2). A summary of this study was listed in Table 2. The reactions with aromatic and aliphatic ketones both afforded the corresponding 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepines in mode-

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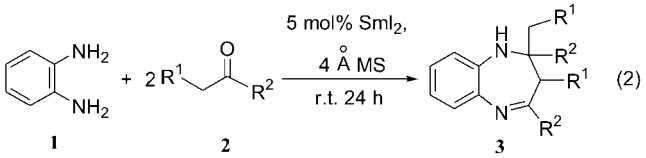
Table 1 SmI_2-catalyzed condensation of *o*-phenylenediamine with acetophenone[a]

Entry	Solvent	Additive	Temp./℃	Isolated yield/%
1[b]	—	MS	r.t.	trace
2	—	MS	r.t.	90
3	CH_3CN	MS	r.t.	91
4	CH_3CN	—	r.t.	73
5	CH_3CN	MS	80	71

[a] Typical reaction conditions: *o*-phenylenediamine/acetophenone 1∶2.1 (molar ratio), 5 mol% SmI_2 relative to *o*-phenylenediamine, 24 h, 4 Å MS (molecular sieves). [b] The reaction was carried out without catalyst.

Scheme 2

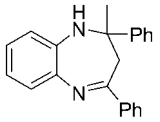
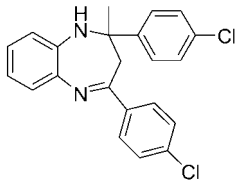
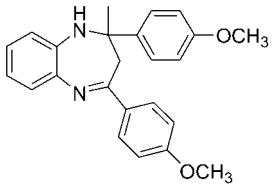
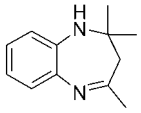
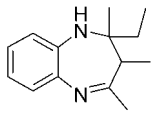
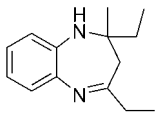
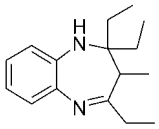


rate to excellent yields. Even for the aromatic ketone with substituent Cl on the aromatic ring, the reaction went smoothly and yielded the desired 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine in high yield (Entry 2). However, a relative lower yield was obtained for the reaction of aromatic ketone substituted by electron-donating group such as OCH_3 (Entry 3). It is probable that the high electron density of the aromatic ring of *p*-methoxyacetophenone is not in favor of the attacking of amine to carbonyl group. The dependence of the activity of aliphatic ketones on their steric hindrance was observed. The reaction of *o*-phenylenediamine with acetone gave the corresponding 2,3-dihydro-1*H*-benzo-[*b*][1,4]-diazepine almost quantitatively and with butanone in a 93% overall yield of a pair of diastereoisomers, while only 46% yield with 3-pentanone (Entries 4—6).

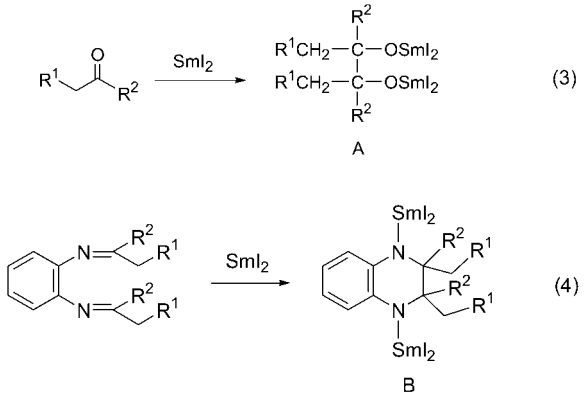
SmI_2 is generally regarded as a precatalyst in its catalyzed reactions because the color change of the reaction mixture from dark blue to yellow occurred in all the cases suggesting the formation of Sm(III) species *in situ*.[13,15] In the present reaction, the same color change was also observed after *o*-phenylenediamine, ketone and SmI_2 were mixed together for a while. Accordingly, it was suggested that the real Sm(III) species here might be the pinacol-Sm(III) complex A (Eq. 3) generated from the SmI_2-mediated ketone pinacol reduction[16] or the vicinal diamine-Sm(III) complex B (Eq. 4) formed by the analogous imine coupling reaction,[17] although the actual Sm(III) intermediate was not yet clear. Then, the active species of Sm(III) formed *in situ* promoted the formation of the intermediate diimine, and the following intramolecular aldol-type condensation of imines[18] occurred to afford the corresponding 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (Scheme 1).

In summary, we have demonstrated that samarium diiodide is an efficient catalyst for the condensation of *o*-phenylenediamine and ketones to afford the corresponding 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepines in moderate to excellent yields. The simplicity and cheapness of the catalyst, low catalyst loading and very mild and solvent-free reaction conditions make the present reaction an environment-friendly and practical method

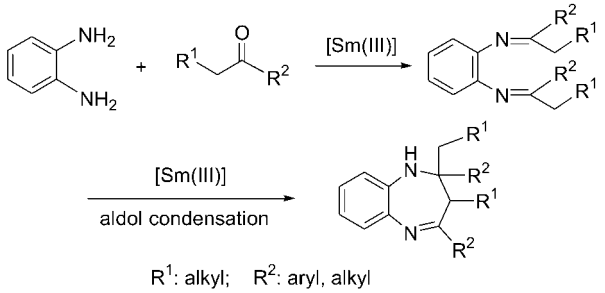
Table 2 SmI_2-catalyzed condensation of *o*-phenylenediamine with ketones[a]

Entry	Ketone	Product	Isolated yield/%
1	Acetophenone	 **3a**	90
2	*p*-Chloroacetophenone	 **3b**	86
3	*p*-Methoxyacetophenone	 **3c**	71
4	Acetone	 **3d**	99
5	Butanone	 **3e**  **3e'**	93[b] **3e**∶**3e'** =45∶55
6	3-Pentanone	 **3f**	46 (53[c])

[a] Typical reaction conditions: *o*-phenylenediamine/ketone 1∶2.1 (molar ratio), 5 mol% SmI_2 relative to *o*-phenylenediamine, r.t., 24 h, 4 Å MS (molecular sieves). [b] The overall yield of a pair of diastereoisomers (**3e**＋**3e'**). [c] *o*-Phenylenediamine and ketone reacted at room temperature for 4 h, followed by the addition of SmI_2.



Scheme 1



for the preparation of 1*H*-benzo[*b*][1,4]-diazepine derivatives.

Experimental

General remarks

All the manipulations were conducted under dry Ar atmosphere with flame-dried glassware. SmI_2 was synthesized by stirring a mixture of metal Sm and I_2 in a THF solution at room temperature for several hours.[19] Ketones were distilled prior to use. *o*-Phenylenediamine was recrystallized from hot water containing sodium hydrosulfite and treated with decolorizing charcoal. ^{1}H NMR spectra were obtained on a Varian INOVA-400 spectrometer using TMS as internal reference. Elemental analyses were determined on a Carlo Erba EA1110-CHNS-O analyzer. Mass spectra were recorded on a Micromass GCT instrument.

Typical procedure

A mixture of *o*-phenylenediamine (1 mmol) and ketone (2.1 mmol) was stirred in the presence of SmI_2 (0.05 mmol) and 4 Å molecular sieves at room temperature for 24 h. Then CH_2Cl_2 was added, followed by filtration to remove the insoluble substance and molecular sieves. The filtrate was concentrated *in vacuo* and purified by SiO_2 gel column chromatography using ethyl acetate/petroleum ether as eluent to afford 2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine. New compounds were fully characterized by ^{1}HNMR, MS and elemental analysis.

2-Methyl-2,4-di(4-chlorophenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (3b): Yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54—6.84 (m, 12H, PhH), 3.46 (br s, 1H, NH), 3.10 (d, J=13.2 Hz, 1H, CH**H**), 2.91 (d, J=13.2 Hz, 1H, CH**H**), 1.75 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 146.2, 140.3, 138.1, 136.6, 133.5, 129.0, 128.8, 128.7, 127.5, 127.1, 122.5, 122.0, 74.0, 43.4, 30.2; EI-MS *m/z* (%): 380 (M^+−H, 15), 365 (20), 269 (13), 230 (35), 228 (100). Anal. calcd for $C_{22}H_{18}N_2Cl_2$: C 69.30, H 4.76, N 7.35; found C 69.19, H 4.97, N 7.35.

2-Methyl-2,4-di(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (3c): Yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51—6.77 (m, 12H, PhH), 3.88 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.01—2.95 (m, 2H, CH_2), 1.76 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.0, 140.5, 138.5, 129.3, 128.6, 127.0, 126.4, 122.3, 122.0, 114.0, 113.8, 73.9, 55.8, 43.3, 30.2; EI-MS *m/z* (%): 372 (M^+, 24), 357 (31), 265 (14), 224 (100), 209 (25). Anal. calcd for $C_{24}H_{24}N_2O_2$: C 77.39, H 6.50, N 7.52; found C 77.23, H 6.68, N 7.13.

2,2,4-Trimethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine[6] **(3d)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17—6.73 (m, 4H, PhH), 3.01 (br s, 1H, NH), 2.40 (s, 3H, CH_3), 2.25 (s, 2H, CH_2), 1.35 (s, 6H, $CH_3\times2$).

2-Ethyl-2,3,4-trimethyl-2,3-dihydro-1*H*-benzo[*b*]-[1,4]-diazepine[8] **(3e)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.02—6.69 (m, 4H, PhH), 3.76 (br s, 1H, NH), 2.75—2.68 (m, 1H, CH), 2.16 (s, 3H, CH_3), 1.87—1.00 (m, 8H), 0.92 (t, J=8.4 Hz, 3H, CH_3).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine[8] **(3e')**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37—6.70 (m, 4H, PhH), 2.79 (br s, 1H, NH), 2.70—2.59 (m, 2H, CH_2), 2.20 (q, J=12.8 Hz, 2H, CH_2), 1.73—0.94 (m, 11H).

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-benzo[*b*]-[1,4]-diazepine[8] **(3f)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40—6.68 (m, 4H, PhH), 3.67 (brs, 1H, NH), 2.69—2.60 (m, 1H, CH), 2.37 (s, 3H, CH_3), 1.68—0.89 (m, 13H).

References

1 (a) Schutz, H. *Benzodiazepines*, Springer, Heidelberg, **1982**.
(b) Smalley, R. K. In *Comprehensive Organic Chemistry*, Vol. 4, Eds.: Barton, D.; Ollis, W. D., Pergamon, Oxford, **1979**, p. 600.
(c) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*, Vol. 1, Eds.: Katritzky, A. R.; Rees, C. W., Pergamon, Oxford, **1984**, pp. 166, 170.
(d) Randall, L. O.; Kappel, B. In *Benzodiazepines*, Eds.: Garattini, S.; Mussini, E.; Randall, L. O., Raven Press, New York, **1973**, p. 27.

2 (a) Essaber, M.; Baouid, A.; Hasnaoui, A.; Benharref, A.; Lavergne, J.-P. *Synth. Commun.* **1998**, *28*, 4097.
(b) El-Sayed, A. M.; Abdel-Ghany, H.; El-Saghier, A. M. M. *Synth. Commun.* **1999**, *29*, 3561.
(c) Xu, J. X.; Wu, H. T.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 84.
(d) Zhang, X. Y.; Xu, J. X.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 404.

(e) Reddy, K. V. V.; Rao, P. S.; Ashok, D. *Synth. Commun*. **2000**, *30*, 1825.
3 Stahlofen, P.; Ried, W. *Chem. Ber*. **1957**, *90*, 815.
4 Ried, W.; Torinus, E. *Chem. Ber*. **1959**, *92*, 2902.
5 Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2657.
6 Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun*. **1999**, *29*, 1941.
7 Balakrishna, M. S.; Kaboudin, B. *Tetrahedron Lett*. **2001**, *42*, 1127.
8 Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett*. **2001**, *42*, 3193.
9 Reddy, B. M.; Sreekanth, P. M. *Tetrahedron Lett*. **2003**, *44*, 4447.
10 Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett*. **2003**, *44*, 1835.
11 (a) Pozarentzi, M.; Stephanatou, J. S.; Tsoleridis, C. A. *Tetrahedron Lett*. **2002**, *43*, 1755.
(b) Kaboudin, B.; Navaee, K. *Heterocycles* **2001**, *55*, 1443.
12 (a) Molander, G. A. *Chem. Rev*. **1992**, *92*, 29.
(b) Imamoto, T. *Lanthanides in Organic Synthesis*, Academic Press, New York, **1994**.
(c) Molander, G. A.; Harris, C. R. *Chem. Rev*. **1996**, *96*, 307.
13 (a) Collin, J.; Giuseppone, N.; van de Weghe, P. *Coord. Chem. Rev*. **1998**, *178—180*, 117.
(b) Xu, F.; Zhu, X.; Shen, Q. *Chin. J. Org. Chem*. **2004**, *24*, 872 (in Chinese).
14 (a) Xu, F.; Sun, J.; Shen, Q. *Tetrahedron Lett*. **2002**, *43*, 1867.
(b) Xu, F.; Sun, J.; Yan, H.; Shen, Q. *Synth. Commun*. **2000**, *30*, 1017.
(c) Xu, F.; Zhu, X.; Shen, Q.; Lu, J.; Li, J. *Chin. J. Chem*. **2002**, *11*, 1334.
(d) Xu, F.; Luo, Y.; Deng, M.; Shen, Q. *Eur. J. Org. Chem*. **2003**, 4728.
15 Evans, W. J. *Polyhedron* **1987**, *6*, 803.
16 (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett*. **1983**, *24*, 765.
(b) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem*. **1983**, *250*, 227.
17 (a) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun*. **1990**, *20*, 981.
(b) Lebrun, A.; Rantze, E.; Namy, J.-L.; Kagan, H. B. *New J. Chem*. **1995**, *19*, 699.
18 Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett*. **1996**, *37*, 7291.
19 Imamoto, T.; Ono, M. *Chem. Lett*. **1987**, 501.

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