Low-valent Titanium Induced Reductive Coupling of *o*-Nitrophenylazide with Benzoyl Substituted Ketene Dithioacetals: a Novel Synthesis of 4-Aryl-2-methylthio-3*H*-1,5-benzodiazepines

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Treated with the low-valent titanium derived from $TiCl_4$/Sm system, *o*-nitrophenylazide could produce the intermediate 2 *in situ*, which reacted with benzoyl substituted ketene dithioacetals to afford 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines in good yields under mild and neutral conditions.

Keywords Samarium, low-valent titanium, *o*-nitrophenylazide, benzoyl substituted ketene dithioacetals, 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines

Since its introduction by McMurry[1] and two other groups[2] in the 1970's, low-valent titanium has been extensively investigated as a versatile reagent in organic synthesis, especially with its exceptional ability to promote reductive coupling of many functional groups.[3-5] Our previous work has shown that $TiCl_4$/Sm system could effectively reduce nitro and azide compounds.[6] Nitro and azide compounds can also be reduced by low-valent titanium of other reagents.[7] However, they were only reduced to the corresponding amines and little attention has been paid to the reductive intermediates derived from nitro or azide groups, which might induce some reactions difficult to accomplish by other existing methodologies. Recently, our group reported the preparation of 2,3-dihydro-1*H*-1,5-benzodiazepines starting from *o*-nitrophenylazide induced by Sm/$TiCl_4$ system.[8] In order to extend the application of the Sm/$TiCl_4$ system, we studied the reaction of *o*-nitrophenylazide with benzoyl substituted ketene dithioacetals and obtained the desired products 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines induced by this system. Some of these 1,5-benzodiazepine compounds were reported to possess interesting biological properties.[9] 4-Aryl-2-methylthio-3*H*-1,5-benzodiazepines have been synthesized by the methylation of 1,5-benzodiazepin-2-thione[9,10] and by using *o*-phenylenediamine as starting materials.[11,12] However, the former afforded the desired products only in the impure state, while the later required high thermal condition and prolonged reaction time (refluxed in xylene for 24 h).

In our method reported here, *o*-nitrophenylazide (**1**) was treated with low-valent titanium for 5—10 min at room temperature, and the nitro and azide group were reduced simultaneously by the low-valent titanium reagent to form the intermediate (**2**) as a 'living' double-anion *in situ*.[8] Then benzoyl substituted ketene dithioacetals were added. The resulting mixture was stirred for 7—10 h at 60℃. Thus the desired products 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines (**4**) were obtained in good yields (Scheme 1).

The results and scope of this reaction are shown in Table 1. The reaction conditions are tolerant of alkoxyl group (Entries 3 and 8). Furthermore, aromatic halides showed remarkable selectivity to give 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines (**4**) without any dehalogenation product.

In conclusion, the main advantages of this new me-

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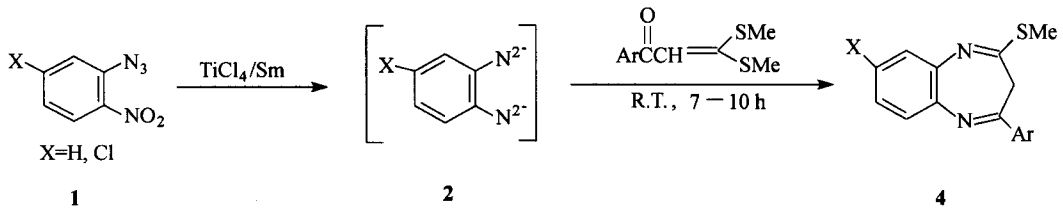
Scheme 1



1 2 4

Table 1 Preparation of 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines induced by $TiCl_4$/Sm

Entry	Ar	X	Time (h)	Product	Yield (%)[a]
1	C_6H_5	H	10	**4a**	85
2	4-MeC_6H_4	H	10	**4b**	80
3	4-$MeOC_6H_4$	H	10	**4c**	79
4	4-ClC_6H_4	H	8	**4d**	84
5	4-BrC_6H_4	H	8	**4e**	78
6	C_6H_5	Cl	7	**4f**	82
7	4-MeC_6H_4	Cl	7	**4g**	83
8	4-$MeOC_6H_4$	Cl	7	**4h**	80
9	4-ClC_6H_4	Cl	7	**4i**	84
10	4-BrC_6H_4	Cl	7	**4j**	82
11	3-BrC_6H_4	Cl	8	**4k**	78

[a] Isolated yields based on **1**.

thod are mild reaction conditions, reduced reaction time, absence of by-products and better yields than the previous methods. Therefore, the present new method will show its utility in organic synthesis.

Experimental

General

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. Melting points were uncorrected. Infrared spectra were recorded on a Bruker Vecter 22 spectrometer in KBr with absorptions reported in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC-80 spectrometer using $CDCl_3$ as the solvent. Chemical shifts were expressed in ppm downfield from internal standard tetramethylsilane. Mass spectra were recorded on a HP5989B MS spectrometer.

General procedure for the synthesis of 4-aryl-2-methylthio-3H-1,5-benzodiazepines (**4**):

A dry 50 mL flask was charged with Sm powder (0.45 g, 3 mmol), $TiCl_4$ (0.25 mL, 2.2 mmol) and THF (20 mL). The mixture was refluxed for 2 h under nitrogen, then cooled to room temperature. When black slurry was formed, a solution of *o*-nitrophenylazide (**1**) (1 mmol) in anhydrous THF (2 mL) was added to the reaction mixture, and stirred for about 5—10 min at room temperature. Then benzoyl substituted ketene dithioacetal (1 mmol) in anhydrous THF (2 mL) was added slowly. After stirring at 60℃ for a given time (Table 1, the reaction was monitored by TLC), the black reaction mixture was quenched with dilute HCl (0.5 mol/L, 2 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extract was washed with brine (10 mL), then dried over with anhydrous $MgSO_4$ and concentrated. The residue was purified on silica gel chromatography by using ethyl acetate/cyclohexane (1:4) as the eluent to afford 4-aryl-2-methylthio-3*H*-1,5-benzodiazepine derivatives.

4a m.p. 80—83℃ (MeOH), (lit.[11] 81—82℃); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.18—8.16 (m, 9H), 3.42 (s, 2H), 2.47 (s, 3H); IR (KBr) ν: 1583, 1564, 1540 cm^{-1}.

4b m.p. 110—112℃ (MeOH), (lit.[11] 110—111℃); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.18—7.97 (m, 8H), 3.37 (s, 2H), 2.48 (s, 3H), 2.42 (s, 3H); IR (KBr) ν: 1585, 1563, 1535 cm^{-1}.

4c m.p. 61—62℃ (MeOH), (lit.[11] 58—61℃); ^1H NMR ($CDCl_3$, 80 MHz) δ: 6.96—8.08 (m, 8H), 3.88 (s, 3H), 3.28 (s, 2H), 2.42 (s, 3H); IR (KBr) ν: 1586, 1566, 1536 cm^{-1}.

4d m.p. 81—82℃ (MeOH), (lit.[11] 82.5—83.5℃); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.20—8.03 (m, 8H), 3.36 (s, 2H), 2.48 (s, 3H); IR (KBr) ν: 1584, 1566, 1542 cm^{-1}.

4e m.p. 113—115℃ (MeOH); ^1H NMR ($CDCl_3$, 80 MHz) δ: 7.22—8.00 (m, 8H), 3.36 (s, 2H), 2.45 (s, 3H); IR (KBr) ν: 1586, 1566, 1540 cm^{-1}; MS (70 eV) *m/z* (%): 345 (M^+, 100), 330

(16), 298 (21), 273 (38); Anal. calcd for $C_{16}H_{13}BrN_2S$: C 55.65, H 3.77, N 8.12; found C 55.60, H 3.74, N 8.10.

4f m.p. 92—93℃ (MeOH); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 7.22—7.79 (m, 8H), 3.36 (s, 2H), 2.46 (s, 3H); IR (KBr) ν: 1600, 1563, 1539 cm^{-1}; MS (70 eV) *m/z* (%): 302 (M^+ + 2, 37), 301 (M^+ + 1, 21), 300 (M^+, 100), 285 (15), 267 (19), 253 (22), 228 (38). Anal. calcd for $C_{16}H_{13}ClN_2S$: C 64.11, H 4.33, N 9.32; found C 64.03, H 4.31, N 9.27.

4g m.p. 92—94℃ (MeOH); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 8.02 (d, J = 8.6 Hz, 2H), 7.20—7.51 (m, 5H), 3.38 (s, 2H), 2.46 (s, 3H), 2.44 (s, 3H); IR (KBr) ν: 1600, 1563, 1540 cm^{-1}; MS (70 eV) *m/z* (%): 316 (M^+ + 2, 42.1), 315 (M^+ + 1, 46.3), 314 (M^+, 100), 299 (10.7), 281 (12.7), 267 (23.2), 252 (11.4); Anal. calcd for $C_{17}H_{15}ClN_2S$: C 63.86, H 4.77, N 8.90; found C 63.85, H 4.76, N 8.85.

4h m.p. 94—96℃ (MeOH); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 8.08 (d, J = 8.6 Hz, 2H), 6.92—7.49 (m, 5H), 3.66 (s, 3H), 3.37 (s, 2H), 2.44 (s, 3H); IR (KBr) ν: 1592, 1564, 1536 cm^{-1}; MS (70 eV) *m/z* (%): 332 (M^+ + 2, 42.61), 331 (M^+ + 1, 47.05), 330 (M^+, 100.0), 315 (12.38), 297 (10.56), 283 (18.93), 268 (7.00), 258 (9.24), 240 (10.06), 133 (17.14); Anal. calcd for $C_{17}H_{15}ClN_2OS$: C 61.72, H 4.54, N 8.47; found C 61.69, H 4.50, N 8.43.

4i m.p. 139—141℃ (MeOH); (lit.[12] 139—140℃); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 8.04 (s, 2H), 7.22—7.51 (m, 5 H), 3.36 (s, 2 H), 2.45 (s, 3 H); IR (KBr) ν: 1600, 1566, 1533 cm^{-1}.

4j m.p. 98—100℃ (MeOH); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 8.00 (s, 2H), 7.22—7.65 (m, 5H), 3.37 (s, 2H), 2.46 (s, 3H); IR (KBr) ν: 1590, 1566, 1540 cm^{-1}; MS (70 eV) *m/z* (%): 382 (M^+ + 3, 29.70), 381 (M^+ + 2, 22.81), 380 (M^+ + 1, 100), 379 (M^+, 23.74), 365 (10.95), 347 (9.19), 333 (9.74), 308 (31.80), 284 (9.44), 266 (22.31), 252 (51.67); Anal. calcd for $C_{16}H_{12}BrClN_2S$: C 50.59, H 3.16, N 7.38; found C 50.57, H 3.15, N 7.35.

4k m.p. 78—82℃ (MeOH); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 7.22—8.24 (m, 7H), 3.35 (s, 2H), 2.47 (s, 3H); IR (KBr) ν: 1600, 1566, 1536 cm^{-1}; MS (70 eV) *m/z* (%): 382 (M^+ + 3, 34.24), 381 (M^+ + 2, 50.25), 380 (M^+ + 1, 100), 379 (M^+, 75.19), 365 (4.79), 347 (5.49), 333 (3.68), 308 (5.56), 252 (20.98), 75 (13.35); Anal. calcd for $C_{16}H_{12}BrClN_2S$: C 50.59, H 3.16, N 7.38; found C 50.56, H 3.13, N 7.36.

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