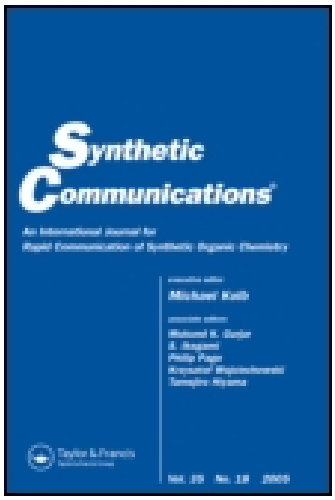

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DERIVATIVES OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE FROM o-NITROANILINES AND CHALCONES INDUCED BY LOW-VALENT TITANIUM

Yongmin Ma [a] & Yongmin Zhang [b]

[a] Department of Chemistry , Zhejiang University , XiXi Compus, Hangzhou, 310028, P. R. China

[b] Department of Chemistry , Zhejiang University , XiXi Compus, Hangzhou, 310028, P. R. China

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DERIVATIVES OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINE FROM *o*-NITROANILINES AND CHALCONES INDUCED BY LOW-VALENT TITANIUM

Yongmin Ma and Yongmin Zhang*

Department of Chemistry, Zhejiang University,
XiXi Compus, Hangzhou, 310028, P. R. China

ABSTRACT

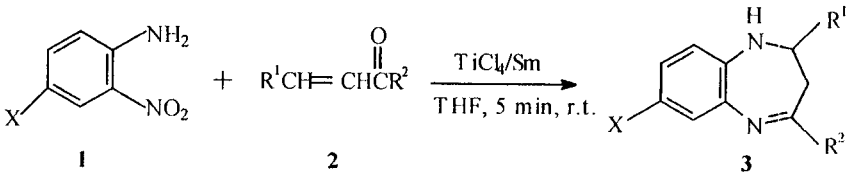
2,3-Dihydro-1H-1,5-benzodiazepines have been prepared in good yield by reaction of *o*-nitroanilines with chalcones induced by the $TiCl_4$-Sm-THF system under mild reaction conditions.

Low-valent titanium reagent has an exceedingly high ability in promoting reductive coupling of carbonyl compound and its attracting increasing interest in organic synthesis.[1] A lot of other functional groups can also be reduced.[2] Recently, we reported the reduction of sulfoxides to sulfides and reductive coupling of niltriles with nitro compounds using $TiCl_4$/Sm/THF system.[3]

*Corresponding author.

Mishriky described that 2,3-dihydro-1H-1,5-benzodiazepine was derived from *o*-phenylenediamine with chalcone by the effect of base catalysis when the components are reacted at 120°C.[4] Here, we wish to report that 2,3-dihydro-1H-1,5-benzodiazepine could be formed from *o*-nitroanilines and chalones promoted by $TiCl_4$/Sm in anhydrous THF under a neutral, room temperature condition, and the reaction is very quick. But, when a mixture of *o*-phenylenediamine and chalcone was stirred under similar condition, the reaction could not happen even at reflux temperature.

When *o*-nitroanilines **1** and chalcones **2** were treated with low-valent titanium, prepared from titanium tetrachloride and samarium powder in anhydrous tetrahydrofuran, the products 2,3-dihydro-1H-1,5-benzodiazepines **3** were obtained in good yields (Scheme 1). The results were summarized in Table 1.



Scheme 1.

Table 1. Cross-Coupling Reactions of *o*-Nitroanilines and Chalcones Induced by $TiCl_4$/Sm System

Entry	X	R^1	R^2	Yield (%)*
a	H	C_6H_5	C_6H_5	90
b	H	*p*-CH_3-C_6H_4	C_6H_5	92
c	H	*p*-CH_3O-C_6H_4	C_6H_5	92
d	H	3,4-OCH_2O-C_6H_4	C_6H_5	88
e	H	*p*-Cl-C_6H_4	C_6H_5	85
f	Cl	C_6H_5	C_6H_5	79
g	Cl	*p*-CH_3-C_6H_4	C_6H_5	84
h	Cl	*p*-CH_3O-C_6H_4	C_6H_5	88
i	Cl	3,4-OCH_2O-C_6H_4	C_6H_5	86
j	Cl	*p*-Cl-C_6H_4	C_6H_5	81
k	H	C_6H_5	C_6H_5CH=CH	72

*Isolated Yield.

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In conclusion, the low-valent titanium, prepared by $TiCl_4$/Sm system, induced the reactions of *o*-nitrophenylamines and chalcones has been studied. Further studies on other chemical transformation of this low-valent reagent are now in progress.

EXPERIMENTAL

Tetrahydrofuran 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 a Perkin-Elmer 683 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR spectra were determined on a Brucker AC 300 and Brucker AC 80 spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in ppm downfield from internal standard tetramethylsilane. Mass spectra were recorded on HP5989B Mass spectrometer. Elemental analyses were carried out on an EA 1110 instrument.

General Procedure for the Synthesis of 2,3-Dihydro-1H-1,5-benzodiazepines 3a–k: $TiCl_4$ (0.22 ml, 2 mmol) was added dropwise using syringe to a stirred suspension of Sm powder (0.45 g, 2 mmol) in freshly distilled dry THF (20 ml) at room temperature under a N_2 atmosphere. After the completion of addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of *o*-nitroanilines compounds **1a–k** (1 mmol) and chalcones compound **2a–k** (1 mmol) in anhydrous THF (3 ml) was added. The mixture was stirred at room temperature under N_2 atmosphere. After the reaction completed, the reaction mixture was quenched with 0.1 N HCl (5 ml) and extracted with diethyl ether (3×15 ml). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15 ml) and a saturated solution of NaCl (15 ml) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1: 8) as eluent.

2,3-Dihydro-2,4-diphenyl-1H-1,5-benzodiazepine (3a): mp 126–128°C (lit.,[5,6] 129–129.5°C). ν_{max} (cm^{-1}): 3360, 1620. δ_H (ppm) 3.00 (2H, d, J = 3.2 Hz, CH_2), 3.70 (1H, br s, NH), 5.05 (1H, dd, J = 4.8, 4.6 Hz, CH), 7.15–8.10 (14H, m, ArH).

2,3-Dihydro-2-(4′-methylphenyl)-4-phenyl-1H-1,5-benzodiazepine (3b): mp 125–127°C. ν_{max} (cm^{-1}): 3380, 1610. δ_H (ppm) 2.20 (3H, s, CH_3), 2.98 (2H, d, J = 3.7 Hz, CH_2), 3.47 (1H, br s, NH), 4.85 (1H, dd, J = 4.6, 4.4 Hz, CH), 6.92–7.94 (13H, m, ArH). *m/z*: 312 (M^+, 13.67), 297 (9.82), 221 (40.86),

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195 (26.87), 194 (100), 118 (8.20), 77 (40.93). Anal. Calcd. For $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.25; H, 6.42; N: 8.90.

2,3-Dihydro-2-(4′-methoxyphenyl)-4-phenyl-1H-1,5-benzodiazepine (3c): mp 143–145°C. (lit.[5,6] 146–147°C). ν_{max} (cm^{-1}): 3360, 1615. δ_H (ppm) 3.04 (2H, d, J = 3.8 Hz, CH_2), 3.60 (3H, s, OCH_3), 3.75 (1H, br s, NH), 5.00 (1H, dd, J = 4.7, 4.6 Hz, CH), 6.60–7.80 (13H, m, ArH).

2,3-Dihydro-2-(3′,4′-methylenedioxyphenyl)-4-phenyl-1H-1,5-benzodiazepine (3d): mp 148–150°C. ν_{max} (cm^{-1}): 3360, 1610. δ_H (ppm) 3.08 (2H, d, J = 3.3 Hz, CH_2), 3.50 (1H, br s, NH), 4.90 (1H, dd, J = 4.8, 4.8 Hz, CH), 5.72 (2H, s, OCH_2O), 6.65–7.83 (12H, m, ArH). *m/z*: 342 (28.49), 327 (15.87), 265 (30.43), 195 (48.61), 194 (100), 148 (33.34), 77 (47.55). Anal. Calcd. For $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.43; H, 5.38; N, 8.10.

2,3-Dihydro-2-(4′-chlorophenyl)-4-phenyl-1H-1,5-benzodiazepine (3e): mp 140–142°C. (lit.[5] 144–145°C). ν_{max} (cm^{-1}): 3385, 1620. δ_H (ppm) 2.96 (2H, d, J = 3.0 Hz, CH_2), 3.45 (1H, br s, NH), 5.00 (1H, dd, J = 4.5, 4.4 Hz, CH), 6.80–7.80 (13H, m, ArH).

2,3-Dihydro-2,4-diphenyl-7-chloro-1H-1,5-benzodiazepine (3f): mp 94–96°C. ν_{max} (cm^{-1}): 3380, 1620. δ_H (ppm) 2.95 (2H, d, J = 2.9 Hz, CH_2), 3.70 (1H, br s, NH), 4.80 (1H, dd, J = 4.5, 4.3 Hz, CH), 6.87–7.65 (13H, m, ArH). *m/z*: 332 (M^+, 30.54), 317 (16.20), 255 (20.76), 230 (34.30), 229 (26.27), 228 (100), 104 (16.41), 77 (35.16). Anal. Calcd. For $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42. Found: C, 76.04; H, 5.09; N, 8.34.

2,3-Dihydro-2-(4′-methylphenyl)-4-phenyl-7-chloro-1H-1,5-benzodiazepine (3g): mp 136–138°C. ν_{max} (cm^{-1}): 3380, 1610. δ_H (ppm) 2.22 (3H, s, CH_3), 3.10 (2H, d, J = 3.9 Hz, CH_2), 3.60 (1H, br s, NH), 4.80 (1H, dd, J = 4.7, 4.4 Hz, CH), 6.84–7.92 (12H, m, ArH). *m/z*: 346 (M^+, 13.84), 331 (10.03), 269 (7.16), 230 (34.96), 229 (21.26), 228 (100), 118 (9.20), 77 (32.28). Anal. Calcd. For $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08. Found: C, 75.93; H, 5.51; N, 7.93.

2,3-Dihydro-2-(4′-methoxyphenyl)-4-phenyl-7-chloro-1H-1,5-benzodiazepine (3h): mp 134–136°C. ν_{max} (cm^{-1}): 3320, 1620. δ_H (ppm) 3.05 (2H, d, J = 4.2 Hz, CH_2), 3.60 (1H, br s, NH), 3.63 (3H, s, OCH_3), 4.85 (1H, dd, J = 4.6, 4.3 Hz, CH), 6.83–7.88 (12H, m, ArH). *m/z*: 362 (M^+, 8.93), 347 (9.04), 285 (11.00), 230 (34.92), 229 (23.76), 228 (100), 134 (25.45), 77 (25.55). Anal. Calcd. For $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.29; H, 5.24; N, 7.53.

2,3-Dihydro-2-(3′,4′-methylenedioxyphenyl)-4-phenyl-7-chloro-1H-1,5-benzodiazepine (3i): mp 135–137°C. ν_{max} (cm^{-1}): 3380, 1620. δ_H (ppm) 2.98 (2H, d, J = 4.0 Hz, CH_2), 3.55 (1H, br s, NH), 4.75 (1H, dd, J = 4.3, 4.0 Hz, CH), 5.72 (2H, s, OCH_2O), 6.78–7.89 (11H, m, ArH). *m/z*: 376 (M^+, 11.13), 361 (8.26), 299 (14.33), 230 (35.15), 229 (41.72), 228 (100), 148 (20.06), 77

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(18.14). Anal. Calcd. For $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 69.81; H, 4.58; N, 7.26.

2,3-Dihydro-2-(4′-chlorophenyl)-4-phenyl-7-chloro-1H-1,5-benzodiazepine (3j): mp 108–110°C. ν_{max} (cm^{-1}): 3360, 1610. δ_H (ppm) 3.15 (2H, d, J = 3.4 Hz, CH_2), 3.70 (1H, br s, NH), 4.88 (1H, dd, J = 4.3, 4.3 Hz, CH), 6.84–7.96 (12H, m, ArH). *m/z*: 366 (M^+, 23.60), 351 (11.62), 289 (14.61). 230 (35.36), 229 (30.66), 228 (100), 138 (14.37), 77 (44.84). Anal. Calcd. For $C_{21}H_{16}Cl_2N_2$: C, 68.68; H, 4.39; N, 7.63. Found: C, 68.49; H, 4.34; N, 7.41.

2,3-Dihydro-2-phenyl-4-(2-phenylethenyl)-1H-1,5-benzodiazepine (3k): mp 134–136°C. (lit.[5,6] 136–137°C). ν_{max} (cm^{-1}): 3390, 1610. δ_H (ppm) 3.00 (2H, d, J = 4.0 Hz, CH_2), 3.55 (1H, br s, NH), 4.90 (1H, dd, J = 4.8, 4.2 Hz, CH), 6.55–7.45 (16H, m, ArH and CH=CH).

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