Asian Journal of Chemistry; Vol. 27, No. 2 (2015), 419-424

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.16927

Synthesis of 1,5-Benzodiazepine Derivatives Using *p*-Toluenesulfonic Acid as Catalyst

SHASHA WANG, LIJUAN HU, SUYAN CHENG and LANZHI WANG*

College of Chemistry and Material Science, Hebei Normal University, Shijiazhuang 050024, P.R. China

*Corresponding author: E-mail: wanglanzhi@126.com

Received: 24 December 2013; *Accepted*: 25 April 2014; *Published online*: 10 January 2015; AJC-16588

A series of substituted ethyl 4-oxo-4-phenylbut-2-enoates were prepared and reacted with substituted o-phenylenediamine, undergone Michael addition reactions and cyclodehydration to provide novel 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2- carboxylate derivatives with excellent yields. The synthetic protocol fulfilled many green-chemical requirements by using simple catalyst *p*-toluenesulfonic acid as activator and ethanol as solvent at room temperature.

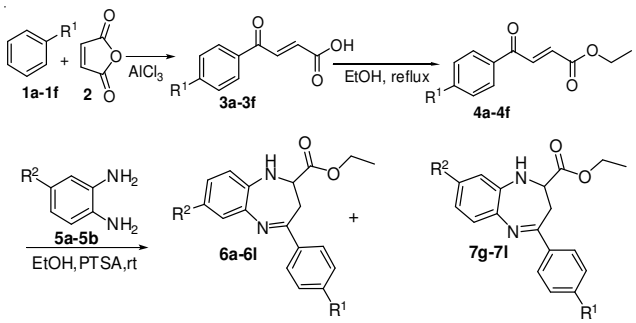
Keywords: Michael addition, 1,5-Benzodiazepine derivatives, *p*-Toluenesulfonic acid.

INTRODUCTION

Benzodiazepines and their polycyclic derivatives constitute an important class of heterocyclic compounds that possess a wide range of therapeutic, pharmacological and industrial properties[1,2]. Many members of the benzodiazepine family have wide applications in medicinal chemistry such as central nervous system agents, antibacterial, antiinflammatory, pesticides antianxiety, analgesic, antidepressive, hypnotic agents and insecticides[3-5]. More recently, the area of pharmacological applications of 1,5-benzodiazepines has been extended to antibiotics[6], anticancer[7] and antiviral[8]. Moreover, 1,5-benzodiazepines are also valuable precursors for the preparation of various fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furanobenzodiazepines[9].

A general way to construct the ring skeletons of 1,5-benzodiazepine is *via* reactions of *o*-phenylenediamines (*o*-PDA) with ketones, α,β-unsaturated carbonyl compounds, or β-haloketones[10] by using various of reagents and catalysts including BF_3-OEt_2[11], $NaBH_4$[12], MgO and $POCl_3$[13], Al_2O_3/P_2O_5 under microwave[14], AcOH under microwave[15], Yb-$(OTf)_3$[16]. These methods have their own merits but also suffer from the drawbacks with respect to toxic solvents, cost of reagents and reaction work-ups. Therefore, the search for a better reaction system for the synthesis of 1,5-benzodiazepines in terms of mild reaction conditions, economic viability and selectivity continues to attract the interest of synthetic organic chemists.

The reagent *p*-toluenesulfonic acid (PTSA) is commercially available and low-cost chemical reagent with stability. Recently, it is reported that *p*-toluenesulfonic acid has the prospect to be used as a substitute for conventional acidic catalytic materials due to the proven advantage, such as non-toxicity, ease of handling, commercially availability, inexpensiveness, air and water compatibility and strong organic acidic nature[17,18]. Herein, we report a simple, rapid and metal-free method for synthesis of new 4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-carboxylate derivatives by the condensation of substituted *o*-phenylenediamines with ethyl 4-oxo-4-phenylbut-2-enoate by using a catalytic amount of *p*-toluenesulfonic acid as efficient catalyst and ethanol as clean green solvent at room temperature (**Scheme-I**).



Scheme-I: Synthesis of 1,5-benzodiazepine derivatives

EXPERIMENTAL

General Information: All the solvents and chemicals were obtained commercially and were used as received. All compounds were identified. IR spectra were taken as KBr discs with a Bruker-TENSOR 27 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500 MHz and Mass spectra were recorded on U.S. PMG mass spectrometer. Elemental analyses were obtained on a Vario EL III CHNOS elemental analyzer.

Synthesis of 1,5-benzodiazepine derivatives: The starting materials ethyl 4-oxo-4-phenylbut-2-enoates (**4a-4f**) were prepared by the reported method[19].

A mixture of 4-methyl-*o*-phenylenediamine/4-bromo-*o*-phenylenediamine (2 mmol), 4-oxo-4-phenylbut-2-enoates (4 mmol) and *p*-toluenesulfonic acid (10 mol %) in 20 mL EtOH was stirred at room temperature for 6-7 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue was obtained. The crude products were purified by silica gel column chromatography to afford the corresponding products in high purity.

7-Methyl-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6a): Yellow solid; m.p. 114-116 °C; IR (KBr, ν_{max}, cm^{-1}): 3340, 1725, 1604; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.284 (t, J = 7.50 Hz, 3H), 2.816 (dd, J_{BA} = 13 Hz, J_{XA} = 4 Hz, 1H), 3.377 (dd, J_{AB} = 13 Hz, J_{XB} = 11.25 Hz, 1H), 4.491 (dd, J_{AX} = 4 Hz, J_{BX} = 11.25 Hz, 1H), 4.204 (q, J = 7.50 Hz, 2H), 4.163 (s, 1H), 6.677 (d, 1H), 7.137-7.171 (m, 3H), 7.430 (d, 1H), 8.044-8.016 (m, 2H); MS[M + H^+]: 327; Anal. (%) calcd. for $C_{19}H_{19}N_2O_2F$: C 69.92, H 5.87, N 8.58; found C 69.82, H 5.48, N 8.56.

7-Methyl-4-(4-chlorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6b): Yellow solid; m.p. 114-116 °C; IR (KBr, ν_{max}, cm^{-1}): 3340, 1725, 1604; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.284 (t, J = 7.50 Hz, 3H), 2.806 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.382 (dd, J_{AB} = 13.50 Hz, J_{XB} = 10.50 Hz, 1H), 4.469 (dd, J_{AX} = 4 Hz, J_{BX} = 10.50 Hz, 1H), 4.219 (q, J = 7.50 Hz, 2H), 4.160 (s, 1H), 6.767 (d, 1H), 7.137-7.171 (m, 3H), 7.430 (d, 1H), 7.844-7.986 (m, 2H); MS[M + H^+]: 343; Anal. (%) calcd. for $C_{19}H_{19}N_2O_2Cl$: C 66.57, H 5.59, N 8.17; found C 66.52, H 5.48, N 8.46.

7-Methyl-4-(4-bromophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6c): Yellow solid; m.p. 110-112 °C; IR (KBr, ν_{max}, cm^{-1}): 3335, 1708, 1615; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.283 (t, J = 7 Hz, 3H), 2.804 (dd, J_{BA} = 13.75 Hz, J_{XA} = 4.50 Hz, 1H), 3.381 (dd, J_{AB} = 13.75 Hz, J_{XB} = 13.50 Hz, 1H), 4.474 (dd, J_{AX} = 4.50 Hz, J_{BX} = 13.50 Hz, 1H), 4.202 (q, J = 7 Hz, 2H), 4.273 (s, 1H), 6.770 (d, 1H), 7.140-7.191 (m, 3H), 7.450 (d, 1H), 7.944-8.034 (m, 2H); MS[M + H^+]: 387; Anal. (%) calcd. for $C_{19}H_{19}N_2O_2Br$: C 58.93, H 4.95, N 7.23; found C 58.52, H 4.48, N 7.46.

7-Methyl-4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6d): Yellow solid; m.p. 109-111 °C; IR (KBr, ν_{max}, cm^{-1}): 3324, 1719, 1643; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.292 (t, J = 7 Hz, 3H), 2.785 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.499 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.474 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.232 (q, J = 7 Hz, 2H), 4.220 (s, 1H), 6.831 (d, 1H), 7.140-7.191 (m, 3H), 7.450 (d, 1H), 7.944-8.031 (m, 2H); MS[M + H^+]: 309; Anal. (%) calcd. for $C_{19}H_{20}N_2O_2$: C 74, H 6.54, N 9.08; found C 74.52, H 6.48, N 9.26.

7-Methyl-4-(4-methyl phenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6e): Yellow solid; m.p. 102-104 °C; IR (KBr, ν_{max}, cm^{-1}): 3309, 1730, 1638; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.303 (t, J = 7 Hz, 3H), 2.011 (s, 3H), 2.756 (dd, J_{BA} = 13.50 Hz, J_{XA} = 3 Hz, 1H), 3.49 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1), 4.472 (dd, J_{AX} = 3 Hz, J_{BX} = 11 Hz, 1H), 4.232 (q, J = 7 Hz, 2H), 4.273 (s, 1H), 7.103 (d, 1H), 7.140-7.191 (m, 3H), 7.450 (d, 1H), 7.804-7.926 (m, 2H); MS[M + H^+]: 323; Anal. (%) calcd. for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found C 74.52, H 6.78, N 9.66.

7-Methyl-4-(4-ethylphenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6f): Yellow solid; m.p. 105-107 °C; IR (KBr, ν_{max}, cm^{-1}): 3312, 1730, 1641; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.259 (t, J = 7 Hz, 3H), 1.293 (t, 3H, J = 7 Hz), 2.715 (q, 2H, J = 7 Hz), 2.760 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.495 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.495 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.218 (q, J = 7 Hz, 2H), 4.270 (s, 1H), 7.103 (d, 1H), 7.140-7.191 (m, 3H), 7.450 (d, 1H), 7.804-7.926 (m, 2H); MS[M + H^+]: 336; Anal. (%) calcd. for $C_{20}H_{22}N_2O_3$: C 70.99, H 6.55, N 8.28; found C 70.92, H 6.58, N 8.34.

7-Bromo-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6g): Yellow solid; m.p. 101-103 °C; IR (KBr, ν_{max}, cm^{-1}): 3343, 1729, 1600; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.306 (t, J = 7 Hz, 3H), 2.816 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.457 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.502 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.242 (q, J = 7 Hz, 2H), 4.283 (s, 1H), 6.837 (d, 1H), 7.137-7.171 (m, 3H), 7.430 (d, 1H), 8.044-8.016 (m, 2H); MS[M + H^+]: 391; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2BrF$: C 55.26, H 4.12, N 7.16; found C 55.34, H 4.18, N 7.24.

7-Bromo-4-(4-chlorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6h): Yellow solid; m.p. 98-100 °C; IR (KBr, ν_{max}, cm^{-1}): 3366, 1730, 1605; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.301 (t, J = 7 Hz, 3H), 2.817 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.450 (dd, J_{AB} = 13.50 Hz, J_{XB} = 10.50 Hz, 1H), 4.491 (dd, J_{AX} = 4 Hz, J_{BX} = 10.50 Hz, 1H), 4.242 (q, J = 7 Hz, 2H), 4.318 (s, 1H), 6.833 (d, 1H), 7.152 (d, 1H), 7.467 (d, J_{gh} = 7 Hz, 3H), 7.963 (d, J_{hg} = 7 Hz, 2H); MS[M + H^+]: 407; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2BrCl$: C 53.03, H 3.96, N 6.87; found C 53.34, H 3.98, N 6.84.

7-Bromo-4-(4-bromophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6i): Yellow solid; m.p. 100-102 °C; IR (KBr, ν_{max}, cm^{-1}): 3344, 1729, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.306 (t, J = 7 Hz, 3H), 2.822 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.455 (dd, J_{AB} = 13.50 Hz, J_{XB} = 10.50 Hz, 1H), 4.489 (dd, J_{AX} = 4 Hz, J_{BX} = 10.50 Hz, 1H), 4.244 (q, J = 7 Hz, 2H), 4.273 (s, 1H), 6.835 (d, 1H), 7.154-7.175 (q, 1H), 7.478 (d, 1H), 7.610 (d, J_{gh} = 8.50 Hz, 2H), 7.905 (d, J_{hg} = 8.50 Hz, 2H); MS[M + H^+]: 451; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2Br_2$: C 47.82, H 3.57, N 6.20; found C 47.84, H 3.58, N 6.24.

7-Bromo-4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6j): Yellow solid; m.p. 92-94 °C; IR (KBr, ν_{max}, cm^{-1}): 3348, 1728, 160; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.306 (t, J = 7 Hz, 3H), 2.809 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.524 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.518 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.241 (q, J = 7 Hz, 2H), 4.293 (s, 1H), 6.840 (d, 1H), 7.134-7.156 (q, 1H), 7.445-7.490 (m, 4H), 8.011-8.031 (q, 2H); MS[M + H^+]: 373; Anal. (%) calcd. for $C_{18}H_{17}N_2O_2Br$: C 57.92, H 4.59, N 6.20; found C 47.84, H 3.58, N 6.24.

7-Bromo-4-(4-methylphenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6k): Yellow solid; m.p. 99-101 °C; IR (KBr, ν_{max}, cm^{-1}): 3344, 1727, 1603; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.308 (t, J = 7.10 Hz, 3H), 2.427 (s, 3H), 2.785 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.504 (dd, J_{AB} = 13.50 Hz, J_{XB}

= 11 Hz, 1H), 4.489 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.244 (q, *J* = 7.10 Hz, 2H), 4.273 (s, 1H), 6.840 (d, 1H), 7.147 (d, 1H), 7.290 (d, J_{gh} = 8 Hz, 2H), 7.477(s, 1H), 7.939 (d, J_{hg} = 8 Hz, 2H); MS[M + H^+]: 387; Anal. (%) calcd. for $C_{19}H_{19}N_2O_2Br$: C 58.93, H 4.95, N 7.23; found C 58.84, H 4.98, N 7.24.

7-Bromo-4-(4-ethylphenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (6l): Yellow solid; m.p. 91-93 °C; IR (KBr, ν_{max}, cm^{-1}): 3345, 1727, 1603; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.307 (t, *J* = 7.10 Hz, 3H), 1.271 (t, *J* = 7.70 Hz, 3H), 2.723 (t, *J* = 7.70 Hz, 2H), 2.785 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.512 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11.50 Hz, 1H), 4.507 (dd, J_{AX} = 4 Hz, J_{BX} = 11.50 Hz, 1H), 4.240 (q, *J* = 7.10 Hz, 2H), 4.270 (s, 1H), 6.842 (d, 1H), 7.134-7.155 (q, 1H), 7.315 (d, J_{gh} = 8 Hz, 2H), 7.468 (s, 1H), 7.962 (d, J_{hg} = 8 Hz, 2H); MS[M + H^+]: 401; Anal. (%) calcd. for $C_{19}H_{19}N_2O_3Br$: C 56.99, H 4.75, N 6.95; found C 56.84, H 4.98, N 6.94.

8-Bromo-4-(4-fluorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7g): Yellow solid; m.p. 123-125 °C; IR (KBr, ν_{max}, cm^{-1}): 3362, 1717, 1600; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.313 (t, *J* = 7 Hz, 3H), 2.821 (dd, J_{BA} = 13.75 Hz, J_{XA} = 3.75 Hz, 1H), 3.472 (dd, J_{AB} = 13.75 Hz, J_{XB} = 11 Hz, 1H), 4.481 (dd, J_{AX} = 3.75 Hz, J_{BX} = 11 Hz, 1H), 4.251 (q, *J* = 7 Hz, 2H), 4.352 (s, 1H), 7.103-7.163 (m, 5H), 8.006-8.035 (q, 2H); MS[M + H^+]: 391; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2BrF$: C 55.26, H 4.12, N 7.16; found C 55.34, H 4.18, N 7.24.

8-Bromo-4-(4-chlorophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7h): Yellow solid; m.p. 115-117 °C; IR (KBr, ν_{max}, cm^{-1}): 3369, 1733, 1621; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.316 (t, *J* = 6.60 Hz, 3H), 2.821 (dd, J_{BA} = 13.75 Hz, J_{XA} = 3.75 Hz, 1H), 3.472 (dd, J_{AB} = 13.75 Hz, J_{XB} = 11 Hz, 1H), 4.481 (dd, J_{AX} = 3.75 Hz, J_{BX} = 11 Hz, 1H), 4.251 (q, *J* = 6.60 Hz, 2H), 4.352 (s, 1H), 7.113-7.165 (t, 3H), 7.439 (d, J_{gh} = 7.50 Hz, 2H), 7.961 (d, J_{hg} = 7.50 Hz, 2H); MS[M + H^+]: 407; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2BrCl$: C 53.03, H 3.96, N 6.87; found C 53.34, H 3.98, N 6.84.

8-Bromo-4-(4-bromophenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7i): Yellow solid; m.p. 118-120 °C; IR (KBr, ν_{max}, cm^{-1}): 3370, 1732, 1621; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.315 (t, *J* = 7.20 Hz, 3H), 2.818 (dd, J_{BA} = 13.50 Hz, J_{XA} = 3.75 Hz, 1H), 3.461 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.468 (dd, J_{AX} = 3.75 Hz, J_{BX} = 11 Hz, 1H), 4.256 (q, *J* = 7.20 Hz, 2H), 4.280 (s, 1H), 7.109-7.120 (m, 2H), 7.159 (d, 1H), 7.599 (d, J_{gh} = 8.75 Hz, 2H), 7.889 (d, J_{hg} = 8.75 Hz, 2H); MS[M + H^+]: 451; Anal. (%) calcd. for $C_{18}H_{16}N_2O_2Br_2$: C 47.82, H 3.57, N 6.20; found C 47.84, H 3.58, N 6.24.

8-Bromo-4-phenyl-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7j): Yellow solid; m.p. 116-118 °C; IR (KBr, ν_{max}, cm^{-1}): 3362, 1734, 1607; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.313 (t, *J* = 7.20 Hz, 3H), 2.812 (dd, J_{BA} = 13.50 Hz, J_{XA} = 4 Hz, 1H), 3.533 (dd, J_{AB} = 13.50 Hz, JXB = 11 Hz, 1H), 4.505 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.251 (q, *J* = 7.20 Hz, 2H), 4.358 (s, 1H), 7.101-7.118 (m, 2H), 7.168 (d, 1H), 7.470-7.485 (m, 3H), 8.005-8.024 (q, 2H); MS[M + H^+]: 373; Anal. (%) calcd. for $C_{18}H_{17}N_2O_2Br$: C 57.92, H 4.59, N 6.20; found C 47.84, H 3.58, N 6.24.

8-Bromo-4-(4-methylphenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7k): Yellow solid; m.p. 108-110 °C; IR (KBr, ν_{max}, cm^{-1}): 3367, 1730, 1604; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.317 (t, *J* = 7.20 Hz, 3H), 2.419 (s, 3H), 2.781 (dd, J_{BA} = 12.50 Hz, J_{XA} = 4 Hz, 1H), 3.512 (dd, J_{AB} = 12.50 Hz, J_{XB} = 11 Hz, 1H), 4.487 (dd, J_{AX} = 4 Hz, J_{BX} = 11 Hz, 1H), 4.252 (q, *J* = 7.20 Hz, 2H), 4.323 (s, 1H), 7.103-7.114 (m, 2H), 7.152 (s, 1H), 7.277 (d, J_{gh} = 8 Hz, 2H), 7.918 (d, J_{hg} = 8 Hz, 2H); MS[M + H^+]: 387; Anal. (%) calcd. for $C_{19}H_{19}N_2O_2Br$: C 58.93, H 4.95, N 7.23; found C 58.84, H 4.98, N 7.24.

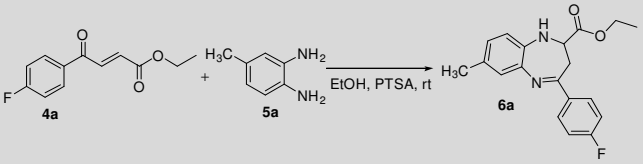
8-Bromo-4-(4-ethylphenyl)-2,3-dihydro-1,5-benzodiazepine-2-carboxylate (7*l*): Yellow solid; m.p. 106-108 °C; IR (KBr, ν_{max}, cm^{-1}): 3373, 1738, 1604; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.317 (t, *J* = 7.20 Hz, 3H), 1.276 (t, *J* = 7.50 Hz, 3H), 2.716 (t, *J* = 7.50 Hz, 2H), 2.782 (dd, J_{BA} = 13.50 Hz, J_{XA} = 3.75 Hz, 1H), 3.523 (dd, J_{AB} = 13.50 Hz, J_{XB} = 11 Hz, 1H), 4.491 (dd, J_{AX} = 3.75 Hz, J_{BX} = 11 Hz, 1H), 4.252 (q, *J* = 7.20 Hz, 2H), 4.323 (s, 1H), 7.104-7.117 (m, 2H), 7.154 (s, 1H), 7.305 (d, J_{gh} = 8 Hz, 2H), 7.943 (d, J_{hg} = 8 Hz, 2H); MS[M + H^+]: 401; Anal. (%) calcd. for $C_{19}H_{19}N_2O_3Br$: C 56.99, H 4.75, N 6.95; found C 56.84, H 4.98, N 6.94.

RESULTS AND DISCUSSION

The synthesis began with the preparation of substituted ethyl 4-oxo-4-phenylbut-2-enoates. Thus, Friedel-Crafts acylation took between substituted benzenes **1a-1f** and maleic anhydride (**2**), provided substituted 4-oxo-4-phenylbut-2- enoic acids (**3a-3f**) in good yield by reaction with $AlCl_3$. Next, **3a-3f** in ethanol with sulfuric acid gave **4a-4f** by esterification. The key step for synthesis target compounds 1,5-benzodiazepines was the Michael addition reactions between **4a-4f** and substituted *o*-phenylenediamines (**5a-5b**).

In order to identify the optimal reaction conditions for synthesis target compounds, the reaction of ethyl 4-(4-fluorophenyl)-4-oxobut-2-enoate (**4a**) and 4-methyl-*o*-PDA (**5a**) were chosen as a model reaction and the research results were shown in Table-1.

TABLE-1
SYNTHESIS OF 1,5-BENZODIAZEPINE **6a**



Entry	Catalyst (10 mol %)[a]	T(°C) [b]	Solvent[c]	Time (h)	Yield (%)[d]
1	PTSA	rt	H_2O	9	50
2	PTSA	rt	EtOH	6	90
3	PTSA	rt	CH_2Cl_2	7	90
4	PTSA	rt	CH_3CN	6.5	85
5	PTSA	rt	Toluene	7	84
6	PTSA	0	EtOH	5.5	80
7	PTSA	78	EtOH	4	70
8	HCl	rt	EtOH	5.5	75
9	$AlCl_3$	rt	EtOH	6	72
10	$FeCl_3$	rt	EtOH	7	70
11	Catalyst-free	rt	EtOH	10	41
12	PTSA (5 mol %)	rt	EtOH	5	88
13	PTSA (15 mol %)	rt	EtOH	5	90

Reaction conditions & reagents: [a]**4a** (4 mmol), **5a** (2 mmol) in EtOH, rt with *p*-toluenesulfonic acid (PTSA) (10 mol, 5 mol or 15 mol %), HCl (10 mol %), $AlCl_3$ (10 mol %), $FeCl_3$(10 mol %) or catalyst-free (10 mol %); [b]**4a** (4 mmol), **5a** (2 mmol) in EtOH, PTSA (10 mol %) at rt, 0 or 78 °C; [c]**4a** (4 mmol), **5a** (2 mmol), PTSA(10 mol %), at rt, 0 or 78 °C, in H_2O, CH_2Cl_2, CH_3CN, Toluene; [d]Yields of isolated products

Firstly, several solvents such as water, ethanol, dichloromethane, acetonitrile and toluene as reaction media were tested at room temperature (entries 1-5). It was evident that high yield was obtained when the reaction was performed in ethanol or dichloromethane (entries 2 and 3), whereas acetonitrile and toluene afforded moderate yields (entries 4 and 5). And, the reaction was sluggish in H_2O probably due to the poor solubility of both the catalyst and the substrates. Finally, ethanol was selected as the suitable solvent owing to the best efficiency (6 h, 90 %) for the reaction and green chemistry requirements.

The effect of temperature was studied by carrying out the model reactions at different temperatures (0 °C, rt and 78 °C) in the presence of catalyst *p*-toluenesulfonic acid in ethanol. It was observed that the reaction was smoothly completed in ethanol at room temperature with excellent yield (90 %) (entry 2). When the reaction was refluxed at 78 °C, the reaction time is markedly reduced, while the results were unsatisfactory with the low yield (70 %). And, the yield of product **6a** was moderate (80 %) when the temperature was lowered to 0 °C. Therefore the optimum temperature was room temperature.

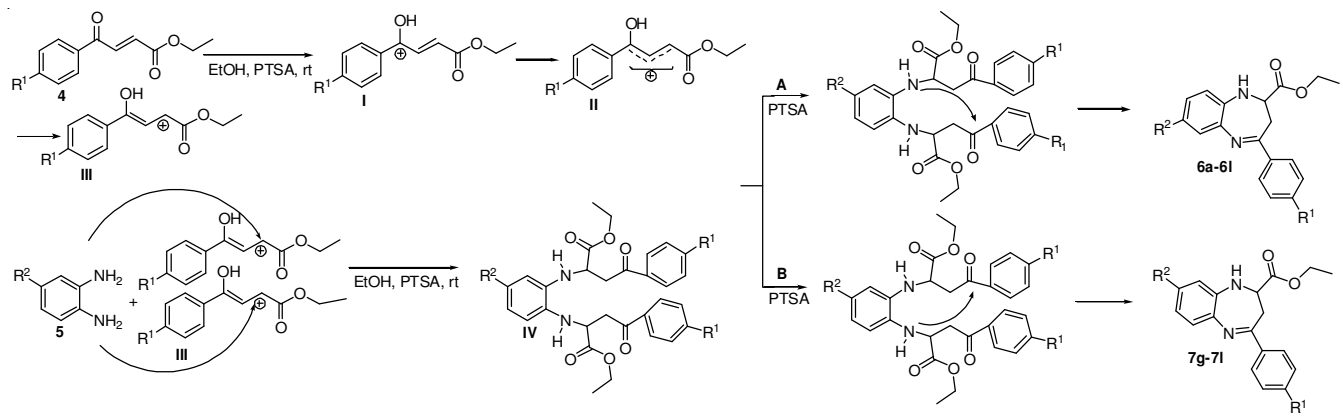
Our next studies focused on the effect of different acids such as Lewis acids, organic acid and mineral acid on the acid-catalyzed condensation of compounds **4a** and **5a**. It was found that only a low yield of product was obtained when the reaction was conducted in the absence of catalyst, even after 10 h (Table-1, entry 11). This result suggested that a catalyst played a critical role in this reaction. Among the acids examined, it turned out that *p*-toluenesulfonic acid was an optimal catalyst with excellent yield (Table-1, entry 2). In contrast, HCl, $AlCl_3$, $FeCl_3$ did not afford the desired product in good yields (entry 8 to 10).

Once we found *p*-toluenesulfonic acid was the best catalyst for this reaction, the quantity of the catalyst *p*-toluene-sulfonic acid was studied under the optimal condition (Table-1, entries 12-13). Results showed that decreasing the catalyst quantity to 5 mol %, the desired product **6a** was obtained in lower yield (88 %), while increasing of the catalyst quantity to 15 mol % has no significant effect on reaction rate and isolated yield of product (90 %). Therefore, the use of just 10 mol % is sufficient for this reaction.

Encouraged by the efficiency of the reaction protocol above, the scope of the reaction was examined. Firstly, various ethyl 4-oxo-4-phenylbut-2-enoates (**4**) were investigated to be reacted with 4-methyl-*o*-phenylenediamine/4-bromo-*o*-phenylenediamine under optimal conditions. In most cases, the reaction proceeded smoothly to give target products in good to excellent yields under mild conditions. And, reactions gave better yields when reactant compound **4** possessing electron-withdrawing groups generally than containing electron-donating groups. In addition, regioselectivities were discovered when *o*-phenylenediamines with -CH_3 and -Br groups, the products of substrates substituted by -CH_3 groups were selective, only one target product **6a-6f** was obtained (Table-2, entries 1-6), but -Br groups offered a mixture of corresponding isomers compounds **6g-l** and **7g-l** (Table-2, entries 7-12). And the structure of these regioisomers was confirmed by IR, ^{1}H NMR, MS and elemental analysis. The methyl and bromine both are *ortho*- and *para*- directing groups, but methyl is an electron-donating group, can activate benzene ring and bromine is an electron-withdrawing group, can passivate benzene ring. Therefore, on the whole, methyl can better activate the amine of unsymmetrical *o*-phenylenediamines at their *para*-position, give only one high selectivity target product compund **6a-6f**, conversely 4-bromobenzene-1,2-diamine generate almost the same amount mixture of regioisomers compounds **6g-6l** and **7g-7l** correspondingly.

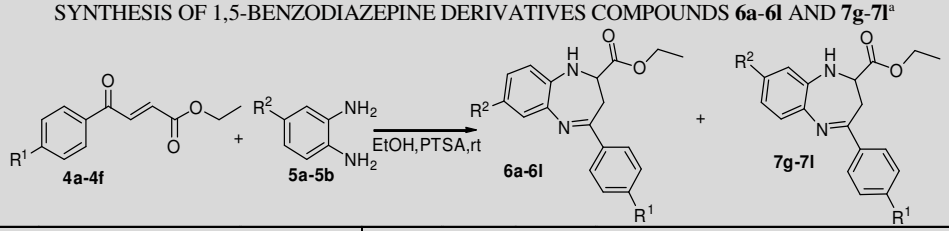
Mechanism: Based on the above results and characterization data of all products, a plausible mechanism was proposed for the synthesis of 1,5-benzodiazepines (**6a-6l**) and (**7g-7l**) from ethyl 4-oxo-4-phenylbut-2-enoates (**4**) and *o*-phenylenediamines (**5**) (**Scheme-II**).

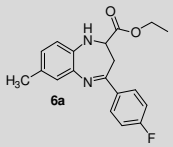
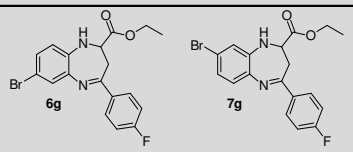
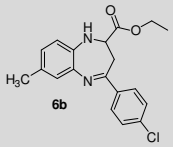
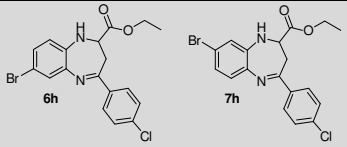
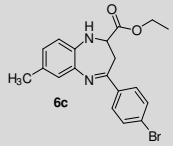
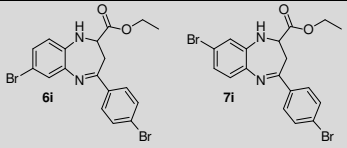
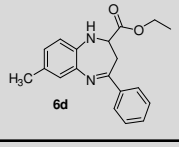
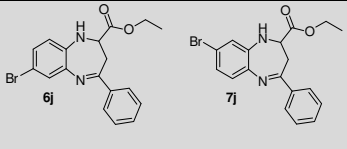
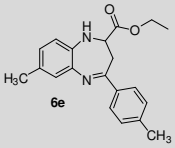
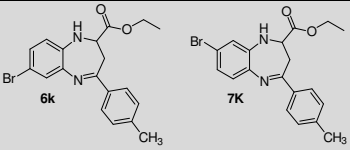
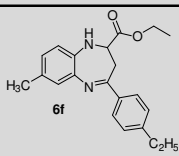
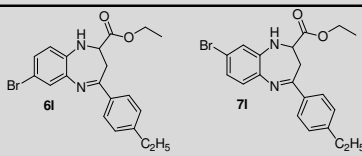
Firstly, *p*-toluenesulfonic acid activated the carbonyl of **4** to form its corresponding enolate form **I**, thereby **I** underwent the intramolecular hydrogen shift and gave more stable conjugated form **III**. Secondly, compound **5** took nucleophilic addition reactions to two conjugated form **III** under the optimal conditions and yielded the intermediate **IV**. Thereby, intermediate **IV** took intramolecular nucleophilic addition reaction between amino group and activated carbonyl group under acidic conditions. Due to the charge density of the two amino groups was differed, **IV** with regioselectivity gave two cyclization dehydration routes (A and B) to afford seven-membered ring **6** and **7** respectively. The structures of two regioisomers **6** and **7** were finally proved by ^{1}H NMR, MS, IR and element analysis. And, all hydrogen atoms of **6** and **7** were numbered sequentially with letters in ^{1}H NMR spectra, displayed in the Fig. 1.



Scheme-II: Plausible mechanism for synthesis of compounds **6a-6l** and **7g-7l**

TABLE-2
SYNTHESIS OF 1,5-BENZODIAZEPINE DERIVATIVES COMPOUNDS **6a-6l** AND **7g-7l**[a]



Entry	R^1	R^2	Product	Yield (%)[b]	Entry	R^1	R^2	Product	Yield (%)[b]
1	F	CH_3		90	7	F	Br		94 **6g:7g** = 1.5:1
2	Cl	CH_3		91	8	Cl	Br		93 **6h:7h** = 1.4:1
3	Br	CH_3		93	9	Br	Br		96 **6i:7i** = 1.7:1
4	H	CH_3		90	10	H	Br		92 **6j:7j** = 1.3:1
5	CH_3	CH_3		88	11	CH_3	Br		88 **6k:7k** = 1.5:1
6	C_2H_5	CH_3		87	12	C_2H_5	Br		89 **6l:7l** = 1.4:1

[a]Reaction conditions: Substrate **4** (4 mmol) and substrate **5** (2 mmol), EtOH, *p*-toluenesulfonic acid (PTSA) (10 mol %), rt; [b] Yields of isolated products

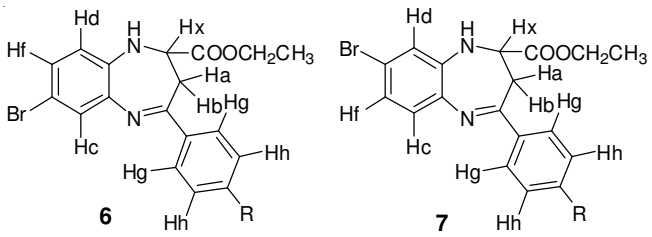


Fig. 1 Hydrogen atoms of compounds **6** and **7** numbered with letters

Conclusion

A convenient, economic and efficient preparation method for novel 1,5-benzodiazepines was successfully developed and various substituted 4-phenyl-2,3-dihydro-1,5- benzodiazepine-2-carboxylate can be obtained from Michael addition reactions with good to excellent yields (96-87 %). This method is in green nature due to solvent (ethanol) and catalyst (*p*-toluenesulfonic acid) at room temperature.

ACKNOWLEDGEMENTS

The authors are grateful for financial support from the National Natural Science Foundation of China (21276064), the Natural Science Foundation of Hebei Education Department (2008320) and the Science Foundation of Hebei Normal University (2011Y04).

REFERENCES

1. J.K. Landquist, eds.: A.R. Katritzky and C.W. Rees, Comprehensive Heterocyclic Chemistry, Pergamon, Oxford, Vol. 1, pp. 166-170 (1984).
2. H. Schutz, Benzodiazepines. Springer, Heidelberg (1982).
3. M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M.E. Marongiu, *Eur. J. Med. Chem*., **36**, 935 (2001).
4. G. Semple, H. Ryder, D.A. Kendrick, M. Szelke, M. Ohta, M. Satoh, A. Nishida, S. Akuzawa and K. Miyata, *Bioorg. Med. Chem. Lett*., **6**, 55 (1996).
5. T. Hussenether, H. Hübner, P. Gmeiner and R. Troschütz, *Bioorg. Med. Chem. Lett*., **12**, 2625 (2004).
6. (a) J. Knabe, H.P. Büch and S. Bender, *Arch. Pharm*., **328**, 59 (1995); (b) R.N. Brogden, R.C. Heel, T.M. Speight and G.S. Avery, *Drugs*, **20**, 161 (1980).
7. (a) K.S. Atwal, J.L. Bergey, A. Hedberg and S. Moreland, *J. Med. Chem*., **30**, 635 (1987); (b) Z. Khabnadideh, Z. Rezaei, A. Khalafi-Nezhad, R. Bahrinajafi, R. Mohamadi and A.A. Farrokhroz, *Bioorg. Med. Chem. Lett*., **13**, 2863 (2003).
8. M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M.E. Marongiu, *Eur. J. Med. Chem*., **36**, 935 (2001).
9. A. Chimirri, S. Grasso, R. Ottanà, G. Romeo and M. Zappalà, *J. Heterocycl. Chem*., **27**, 371 (1990).
10. X.Q. Pan, J.P. Zou, Z. Huang and W. Zhang, *Tetrahedron Lett*., **49**, 5302 (2008).
11. J.A.L. Herbert and H.J. Suschitzky, *Chem. Soc. Perkin Trans. I*, 2657 (1974).
12. R. Contreras, H. R. Morales and A. Bulbarela, *Heterocycles*, **24**, 135 (1986).
13. M.S. Balakrishna and B. Kaboudin, *Tetrahedron Lett*., **42**, 1127 (2001).
14. B. Kaboudin and K. Navaee, *Heterocycles*, **55**, 1443 (2001).
15. M. Pozarentzi, J. Stephanidou-Stephanatou and C.A. Tsoleridis, *Tetrahedron Lett*., **43**, 1755 (2002).
16. M. Curini, F. Epifano, M.C. Marcotullio and O. Rosati, *Tetrahedron Lett*., **42**, 3193 (2001).
17. L.F. Xiao, C.G. Xia and J. Chen, *Tetrahedron Lett*., **48**, 7218 (2007).
18. T. Li, Y. Souma and Q. Xu, *Catal. Today*, **111**, 288 (2006).
19. L.Z. Wang, Z.X. Hua and S.S. Wang, *Chinese J. Org. Chem*. (In press).