TCT as a Rapid and Efficient Catalyst for the Synthesis of 1,5-Benzodiazepines

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Due to the remarkable importance of benzodiazepines and their biological and pharmacological activities this class of compounds has received a great deal of attention. They are widely used as anti-anxiety, anti-convulsant, anti-depressive and hypnotic agents.[1,2] 1,5-Benzodiazepines are employed as starting material for synthesis of fused ring benzodiazepine derivatives such as triazolo,[3] oxazino[4] or furano-benzodiazepines.[5] These compounds have also found commercial use in photography industry[6] and production of inflammatory agents.[7]

A number of ways have been reported in literatures for synthesis of 1,5-benzodiazepines that include condensation of *o*-phenylenediamine with α-β unsaturated compounds,[8] β-halo ketones[9] and ketones.[10] In this connection many reagents such as $BF_3{\cdot}OEt_2$,[11] $NaBH_4$,[12] PPA-SiO_2,[13] MgO-$POCl_3$,[14] $Yb(OTf)_3$,[15] Al_2O_3-P_2O_5,[16] SO_4^{2-}/ZrO_2,[17] I_2,[18] $InBr_3$,[19] $Ag_3PW_{12}O_{40}$,[20] $HClO_4/SiO_2$,[21] NBS,[22] Amberlyst-15,[23] and $Sc(OTf)_3$[24] have been used. However, many of these cited reagents are accomplished with some deficiency including long reaction times, use of expensive reagent, and occurrence of several side products, low yield, and harsh conditions. Therefore, the development of the new methods for synthesis of these compounds is desirable.

Recently considerable attention has been devoted to use of 2,4,6-trichloro-1,3,5-triazine (TCT) in organic synthesis.[25] In this paper, we report that 1,5-benzodiazepines can be rapidly, conveniently and efficiently synthesized using TCT (10 mol%) at room temperature in acetonitrile (Scheme 1).

We first examined the synthesis of 1,5-benzodiazepine from *o*-phenylenediamine and ketone in different solvents and found that acetonitrile was the best solvent when compared with DMF, DMSO, MeOH, CH_2Cl_2, $CHCl_3$ and toluene based on reaction time and yield. Then, the ability of *o*-phenylenediamines and different ketones as precursors in one-pot 1,5-benzodiazepines synthesis was considered and the results were summarized in Table 1. Cyclic ketone as well as acyclic ketones took part in this condensation reaction in good yields at room temperature. These reactions were carried out within 15-30 min. The reaction in the absence of TCT under similar conditions proceeded sluggishly.

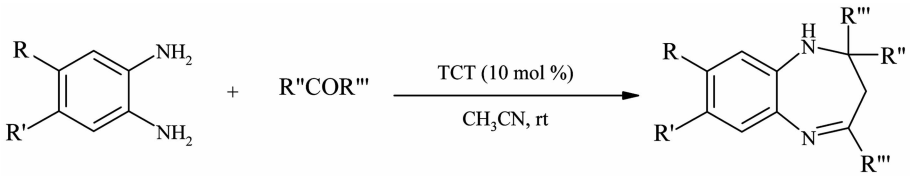
The proposed mechanism of this reaction has been shown in Scheme 2. The amine of *o*-phenylenediamine is first activated by TCT and then attacks the carbonyl group of the ketone, giving intermediate diimine. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form enamine which cyclized to afford the seven member ring.

1,5-Benzodiazepines were efficiently and conveniently synthesized from *o*-phenylenediamines and different ketones in the presence of catalytic amounts of TCT in acetonitrile at room temperature. Short reaction time, high yields, mild reaction conditions, use of inexpensive and stable catalyst are other advantages.

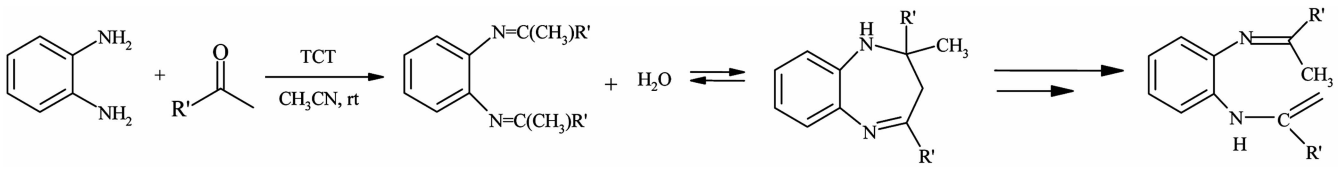
Experimental

Products were known and characterized by comparison of their spectral data (^{1}H NMR, ^{13}C NMR and IR) and melting points with those reported in the literature. Monitoring of the reaction was accomplished by TLC on SIL G/UV 254 sheets. All yields refer to isolated products.

General procedure for preparation of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (1). In a 25 mL round

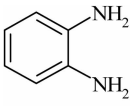
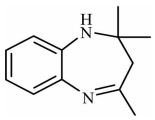
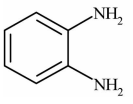
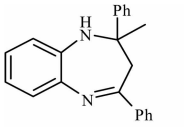
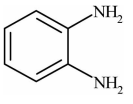
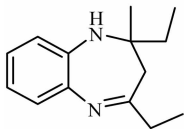
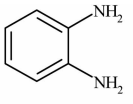
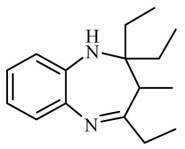
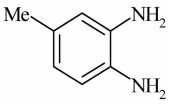
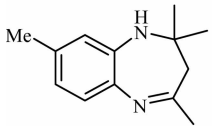
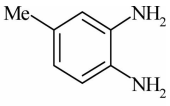
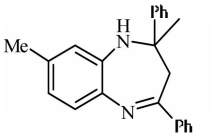
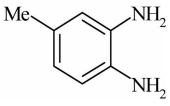
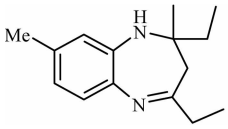
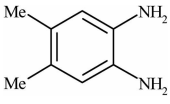
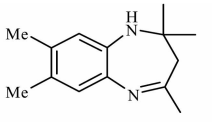
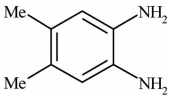
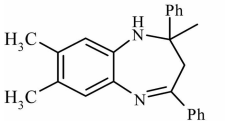


Scheme 1



Scheme 2

Table 1. Condensation of *o*-phenylenediamines with acetones in the presence of TCT at room temperature in acetonitrile

Entry	Phenylenediamine	Ketone	Product/Number	Time (min)	Yield (%)	Mp/°C (Reported)
1		CH_3COCH_3	 **1**	20	82	136-138 (135-137)[22]
2		CH_3COPh	 **2**	23	85	149-151 (150-152)[19]
3		$CH_3COC_2H_5$	 **3**	22	75	137-139 (137-139)[19]
4		$(CH_3CH_2)_2CO$	 **4**	25	75	143-145 (143-144)[19]
5		CH_3COCH_3	 **5**	15	84	128-129 (127-129)[20]
6		CH_3COPh	 **6**	17	88	90-92 (91-93)[20]
7		$CH_3COC_2H_5$	 **7**	18	78	117-119 (116-118)[20]
8		CH_3COCH_3	 **8**	15	79	113-115 (112-114)[19]
9		CH_3COPh	 **9**	17	78	115-116 (115-116)[19]

bottomed flask, *o*-phenylenediamine (1 mmol), acetone (2.5 mmol) and TCT (0.1 mmol) in acetonitrile (10 mL) were stirred magnetically at room temperature in 20 min. The progress of the reaction was followed by TLC (eluent: ethyl acetate/*n*-hexane 1:4). On completion, 10 mL of water was added into the reaction mixture and the organic layer was extracted with dichloromethane (3 × 10 mL). After drying the organic layer ($MgSO_4$), the solvent evaporated under reduced pressure. The product of compound 1 was obtained by plate chromatography using ethyl acetate and *n*-heptane (1:4 v/v) as an eluent in 82% yield. Solid: mp 136-138 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (6H, s), 2.25 (2H, s), 2.33 (3H, s), 3.45 (1H, br), 6.60-7.25 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.6, 140.5, 137.6, 126.5, 125.2, 121.9, 121.4, 67.5, 45.0, 30.2, 29.7; IR (KBr) 3289, 1637, 1597 cm^{-1}; m/z (EI) 188 (M^+).

Compound **2**: Solid: mp 149-151 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.78 (3H, s), 2.92 (1H, d, J = 12.6 Hz), 3.12

(1H, d, J = 12.6 Hz), 3.40 (1H, br), 6.50-6.95 (3H, m), 7.10-7.30 (7H, m), 7.50-7.60 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.3, 146.3, 139.8, 139.2, 138.0, 129.6, 128.3, 128.0, 127.8, 126.9, 126.8, 126.1, 125.2, 121.2, 120.9, 73.4, 42.9, 29.7; IR (KBr) 3310, 1634, 1596 cm^{-1}; m/z (EI) 312 (M^+).

Compound **3**: Solid: mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (3H, t, J = 7.1 Hz), 1.24 (3H, t, J = 7.2 Hz), 1.68 (2H, q, J = 7.1 Hz), 2.10 (2H, m), 2.33 (3H, s), 2.67 (2H, q, J = 7.2 Hz), 3.23 (1H, br), 6.72-7.27 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.2, 140.6, 137.7, 126.8, 126.0, 125.1, 121.5, 70.3, 41.9, 35.4, 26.7, 10.5, 8.3; IR (KBr) 3320, 1637, 1595 cm^{-1}; m/z (EI) 216 (M^+).

Compound **4**: Solid: mp 143-145 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75-1.47 (13H, m), 1.60 (3H, s), 2.86 (3H, q, J = 7.0 Hz), 3.75 (1H, br), 6.65-7.40 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.6, 142.2, 138.7, 132.5, 126.5, 118.0, 117.3, 68.5, 46.0, 35.5, 28.2, 27.8, 12.0, 11.3, 7.6, 7.1; IR (KBr) 3320, 1637, 1595 cm^{-1}; m/z (EI) 244 (M^+).

Compound **6**: Solid: mp 90-92 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.80 (3H, s), 2.45 (3H, s), 3.05 (1H, d, J = 12.9 Hz), 3.15 (1H, d, J = 12.9 Hz), 3.45 (1H, br), 6.65-7.65 (13H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.1, 137.3, 134.1, 131.2, 130.7, 129.1, 128.6, 128.5, 128.4, 128.2, 127.3, 126.0, 125.5, 123.2, 113.3, 50.8, 45.8, 28.8, 20.8; IR (KBr) 3350, 1645, 1595 cm^{-1}; m/z (EI) 326 (M^+).

Compound **9**: Solid: mp 115-116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.75 (3H, s), 2.30 (6H, s), 2.95 (1H, d, J = 12.6 Hz), 3.15 (1H, d, J = 12.6 Hz), 3.50 (1H, br), 6.65 (1H, s), 7.20 (1H, s), 7.05-7.20 (6H, m), 7.55-7.65 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.5, 147.4, 139.3, 137.4, 135.5, 134.5, 129.3, 129.1, 128.9, 128.0, 127.5, 126.6, 126.3, 125.1, 122.0, 72.8, 42.8, 29.7, 19.0, 18.4; IR (KBr) 3320, 1637, 1595 cm^{-1}; m/z (EI) 342 (M^+).

Compound **14**: Solid: mp 136-138 °C ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24-1.85 (16H, m), 2.32-2.71 (3H, m), 4.46 (1H, br), 6.66-7.34 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.7, 142.5, 137.9, 129.4, 126.2, 121.2, 121.0, 62.9, 52.2, 40.2, 39.0, 34.2, 33.1, 25.1, 24.3, 23.0, 21.5, 21.3; IR (KBr) 3300, 1637, 1595 cm^{-1}; m/z (EI) 268 (M^+).

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