Asian Journal of Chemistry; Vol. 23, No. 4 (2011), 1611-1614

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis of 1,5-Benzodiazepines Catalyzed by Zinc Triflate in Solvent-Free Medium

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(*Received*: 19 June 2010; *Accepted*: 7 December 2010) AJC-9369

The *o*-phenylenediamines were smoothly reacted with different ketones to afford the corresponding 1,5-benzodiazepine derivatives in excellent yields. All the reactions were carried out in presence of air and moisture stable zinc triflate (10 % mol) catalyst in solvent-free medium at room temperature.

Key Words: Benzodiazepine, *o*-Phenylenediamines, Zinc triflate, Ketones.

INTRODUCTION

1,5-Benzodiazepines and their derivatives belong to a very important family of bioactive compounds. They are widely used as anticonvulsant, antiinflammatory, hypnotic, sedative, analgesic and antidepressive reagents[1-3]. Recently, these compounds has shown the activity of anticancer, antiviral (non-nucleoside inhibitors of HIV-1 reverse transcriptase), cardiovascular, antifungal and antibacterial. In addition, the 1,5-benzodiazepine derivatives are used as dyes for acrylic fibre in photography. The structural feature of benzodiazepines, could allow the diversity-oriented synthesis of small libraries of fused ring compounds such as triazolo, oxadiazolo, oxazino and furano benzo diazepines[4-6]. Owing to their broad spectrum of biological activity, these compounds have received a great deal of attention in connection with their synthesis. Generally, the 1,5-benzodiazepines are prepared by the condensation of *o*-phenylenediamines with ketones in presence of a catalyst. The catalysts reported in the literature are metal halides[7-9], metal triflates[10-13], metal oxides[14-17], organic acids and bases[18-26], heteropoly acids[27-29], molecular iodine, solid supported catalysts, polymer supported catalysts[30-33], ionic liquids, ultrasound and microwave promoted reactions[34-36]. Unfortunately, many of these methods suffer from one or other drawbacks, such as drastic reaction conditions, expensive reagents, prolonged reaction time, low yields and occurrence of several side reactions. Therefore, the search continues for better catalysts, for efficient synthesis of 1,5-benzodiazepines in terms of operational simplicity, reusability, economic viability and greater selectivity. In recent years, zinc triflate has received a considerable attention as a mild, high catalytic activity, low toxicity, moisture and air tolerant Lewis acid. This catalyst is commercially available and well known for various organic transformations[37-39]. Herein, we report a novel method for the synthesis of 1,5-benzodiazipines using a catalytic amount of zinc triflate in solvent-free medium.

EXPERIMENTAL

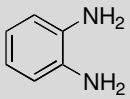
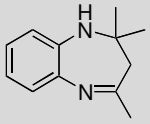
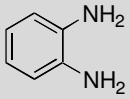
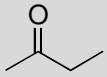
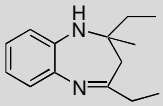
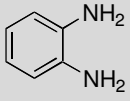
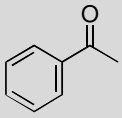
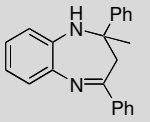
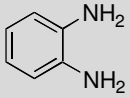
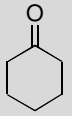
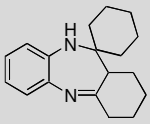
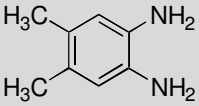
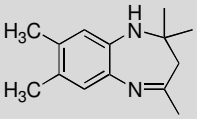
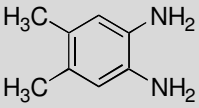
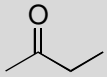
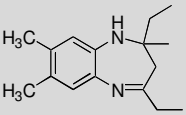
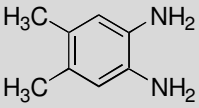
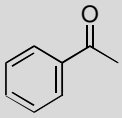
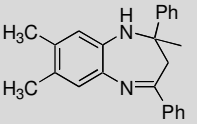
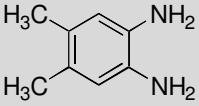
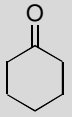
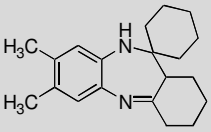
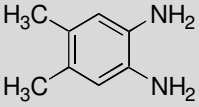
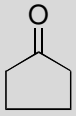
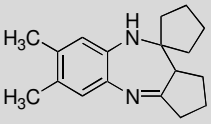
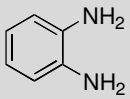
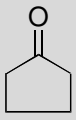
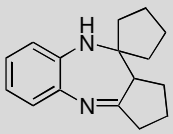
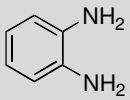
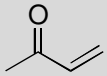
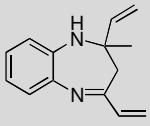
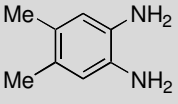
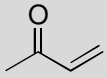
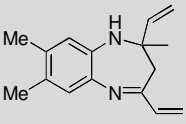
Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the synthesis of 1,5-benzodiazepines: To a stirred mixture of *o*-phenylenediamine (2 mmol) and ketone (6 mmol) was added the catalyst zinc triflate (0.2 mmol). The resulting reaction mixture was stirred appropriate time (Table-1). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the reaction mixture was diluted by adding ethyl acetate (20 mL) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography using 60-120 mesh. All the products were confirmed by their spectral data and compared with literature reports.

Spectral data for selected compounds

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a): Yellow solid: m.p. 136-137 ºC. IR (KBr, ν_{max}, cm^{-1}): 3341, 3059, 2928, 2860, 1650, 1600, 1556, 1417, 1378, 1254, 1189, 1017, 973, 746. ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 6H), 2.22 (s,

TABLE-1
$Zn(OTf)_2$ CATALYZED SYNTHESIS OF 1,5-BENZODIAZEPINES IN SOLVENT-FREE MEDIUM

S. No.	Diamine 1	Ketone 2	Product 3	Reaction time (h)	Yield (%)
a				2.5	93
b				3.0	91
c				2.5	93
d				3.0	89
e				2.0	95
f.				2.5	92
g				2.0	95
h				3.0	90
i				3.0	89
j				3.0	88
k				2.5	85
l				2.0	88

2H), 2.35 (s, 3H), 2.95 (brs, 1H, NH), 6.72-6.74 (m, 1H), 6.98 (m, 2H), 7.10-7.18 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 141.1, 138.4, 127.1, 125.6, 122.4, 121.9, 68.7, 45.6, 30.5, 30.3. EIMS m/z (%) 189 (m^+ 12), 188 (45), 173 (100), 132 (25), 104 (18), 92 (15), 77 (30), 65 (20), 51 (35).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3b): Yellow solid. m.p. 136-137 ºC. IR (KBr, ν_{max}, cm^{-1}): 3329, 3087, 2968, 2834, 1674, 1615, 1578, 1451, 1215, 1163, 1005, 956, 847, 734. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, *J* = 6.5 Hz), 1.25 (t, 3H, *J* = 6.5 Hz), 1.72 (q, 2H, *J* = 6.5 Hz), 2.18 (m, 2H), 2.36 (5, 3H), 2.69 (q, 2H, *J* = 6.5 Hz), 3.28 (brs, 1H, NH), 6.79-7.34 (m, 4H). ^{13}C NMR (50MHz, $CDCl_3$): δ 175.6, 140.8, 138.2, 127.2, 126.5, 125.3, 121.7, 70.6, 42.1, 35.6, 35.7, 26.8, 10.5, 8.9. EIMS: m/z (%): 216 (m^+ 20), 187 (10), 158 (30), 143 (22), 105 (100), 90 (25), 76 (15), 51 (12).

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3c): Yellow solid: m.p. 150-151 ºC. IR (KBr, ν_{max}, cm^{-1}): 3380, 3098, 2951, 2863, 1635, 1576, 1452, 1289, 1094, 963, 741. ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 2.94 (d, 1H, *J* = 12.0 Hz), 3.15 (d, 1H, *J* = 12.0 Hz), 3.42 (brs, 1H, NH), 6.54-7.00 (m, 3H), 7.16-7.32 (m, 7H), 7.55-7.65 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.6, 146.4, 140.2, 139.6, 138.3, 129.7, 128.5, 128.4, 128.3, 127.0, 127.5, 126.6, 125.8, 121.4, 121.8, 73.9, 43.0, 29.9. EIMS: m/z (%): 312 (m^+ 25), 235 (40), 158 (100), 143 (12), 105 (78), 90 (15), 76 (20), 51 (22).

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[b,e][1,4]-diazepine (3d): Yellow solid: m.p. 135-136 ºC. IR (KBr, ν_{max}, cm^{-1}): 3290, 3078, 2942, 2864, 1640, 1600, 1456, 1373, 1289, 1056, 834, 741. ^{1}H NMR ($CDCl_3$): δ 1.22-1.84 (m, 16H), 2.35-2.70 (m, 3H), 4.50 (brs, 1H, NH), 6.64-7.35 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.5, 142.3, 138.4, 129.5, 126.3, 121.6, 121.3, 63.2, 52.4, 40.7, 39.1, 34.4, 33.6, 25.3, 24.5, 23.5, 21.3, 21.7. EIMS: m/z (%): 268 (m^+, 15), 186 (18), 104 (100), 89 (35), 75 (41), 50 (22).

2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (3e): Yellow solid: m.p. 112-113°C. IR (KBr, ν_{max}, cm^{-1}): 3291, 3078, 2863, 1635, 1596, 1247, 1197, 1021, 846, 739. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 6H), 2.18 (s, 3H), 2.21 (s, 3H), 2.22 (s, 2H), 2.35 (s, 3H), 2.82 (brs, 1H, NH), 6.53 (1, 1H), 6.40 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.4, 138.6, 135.3, 133.7, 129.6, 127.5, 122.4, 67.8, 45.6, 30.1, 30.6, 29.6, 19.2, 18.7. EIMS: m/z (%): 216 (m^+ 20), 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100).

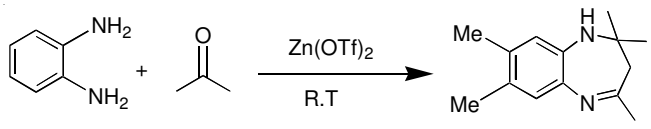
2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepines (3f): Yellow solid. m.p. 112-113 ºC. IR (KBr, ν_{max}, cm^{-1}): 3291, 3092, 2967, 2851, 1635, 1597, 1408, 1357, 1292, 1169, 1056, 952, 834, 742. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 6H), 2.18 (s, 3H), 2.21 (s, 3H), 2.22 (s, 2H), 2.33 (s, 3H), 2.85 (brs, 1H, NH), 6.40 (s, 1H), 6.55 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 138.6, 135.2, 133.4, 129.7, 127.5, 122.6, 67.9, 45.4, 30.6, 30.9, 29.7, 19.2, 18.5. EIMS: m/z (%): 216 (M^+ 20) , 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100).

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3g): Yellow solid: m.p. 116-117 ºC. IR (KBr, ν_{max}, cm^{-1}): 3289, 3089, 3042, 2851, 1635, 1609, 1568, 1462, 1255, 1061, 937, 732. ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H), 2.26 (s, 6H), 2.89 (d, 1H, *J* = 12.0 Hz), 3.12 (d, 1H, *J* =12.0 Hz), 3.46 (brs, 1H, NH), 6.59 (s, 1H), 7.12 (s, 1H), 7.16-7.16 (m, 6H), 7.50-7.60 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 147.4, 139.5, 137.4, 135.8, 134.3, 129.4, 129.1, 129.5, 128.3, 127.5, 126.9, 126.6, 125.4, 122.3, 73.1, 43.4, 29.5, 19.6, 18.4. EIMS: m/z (%): 340 (m^+ 15), 263 (35), 186 (100), 171 (20), 133 (18), 118 (12), 104 (21), 79 (15), 54 (12), 51 (10).

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo-[b]cyclopenta[e][1,4]-diazepine (3j): Yellow solid: m.p. 139-140 ºC. IR (KBr, ν_{max}, cm^{-1}): 3339, 3058, 2963, 2850, 1659, 1600, 1578, 1472, 1356, 1032, 756. ^{1}H NMR ($CDCl_3$): δ 1.35-1.90 (m, 12H), 2.38-2.62 (m, 3H), 4.30 (brs, 1H, NH), 6.72-7.35 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.1, 143.6, 139.1, 132.4, 126.5, 119.7, 118.2, 67.7, 54.7, 39.5, 38.3, 33.5, 28.2, 24.6, 24.1, 23.2. EIMS: m/z (%): 240 (m^+ 20), 172 (28), 104 (100), 89 (15), 75 (48), 50 (25).

RESULTS AND DISCUSSION

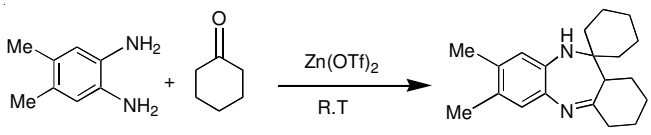
Initially a systematic study was carried out for evaluation of zinc triflate as a catalyst for the reaction of *o*-phenylenediamine with acetone under various reaction conditions. The reaction was not found in absence of catalyst even after stirring for 5 h. In the next reaction, *o*-phenylenediamine and acetone were stirred in presence of equivalent amounts of the catalyst Zn $(OTf)_2$. The reaction was completed within 2 h at room temperature in absence of solvent. The next reaction was carried out using the same reactants with 0.5 equivalent amounts of catalyst and the reaction was completed within 2.0 h at same reaction conditions. In another reaction, with the same reactants, was carried out using the catalyst 10 mol % and the reaction was completed within 2.5 h to give the corresponding product of 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodia zepine (**3a**) in 93 % yield. With these results we optimized the quantity of catalyst (10 mol %) for all the reactions (**Scheme-I**).



1 2 3

Scheme-I

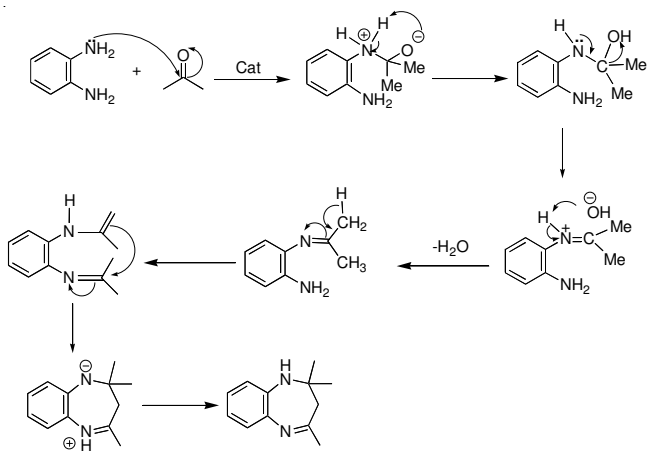
Encouraged by the above results, we turned our attention to various ketones with *o*-phenylenediamine and dimethyl *o*-phenylenediamine systems under similar reaction conditions. The reactions with *o*-phenylenediamine and ethyl methyl ketone (**3b**), acetophenone (**3c**), cyclohexene (**3d**), cyclopentane (**3i**) and acrylketone (**3k**) were reacted smoothly under similar reaction conditions to afford the corresponding derivatives in excellent yields (**Scheme-II**).



Scheme-II

In a similar manner, dimethyl *o*-phenylenediamine was treated with acetone to afford the corresponding derivative of 2,2,4-trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodi azephine (**3e**) in 95 % yield. The reaction was completed within 2 h of reaction time at room temperature. In continuation of this work, dimethyl *o*-phenylenediamine was reacted with ethyl methyl ketone (**3f**), acetophenone (**3g**), cyclohexanone (**3h**), cyclopentanone (**3i**) and acryl acetone (**3l**) successfully to obtain the corresponding derivatives with excellent yields in solvent-free conditions. The ketones were used as reactant as well as solvent for the reaction. In all the cases, reactions were carried out at room temperature by taking 1:3 molar ratios of *o*-phenyldiamine and ketone. All the products were characterized by their spectroscopic data. The scope and generalities of the above process are illustrated with respect to the reactions of different *o*-phenylenediamines and a wide range of ketones (Table-1).

The plausible reaction mechanism for the formation of 1,5-benzodiazepines involves an intermolecular imine and enamine cyclization promoted by zinc triflate as shown in the **Scheme-III**. The amino groups of *o*-phenylenediamine attack on carbonyl group of ketone to give the intermediate dimine. The dimine on further 1,3-hydrogen shift from methyl group, followed by the formation of isomeric enamine gives the cyclized seven membered ring.



Scheme-III: Mechanism

Conclusion

We have described a novel and efficient protocol for the synthesis of 1,5-benzodiazepines through the condensation of *o*-phenylenediamines and ketones using zinc triflate as a mild and moisture stable catalyst. This method is advantageous over existing methods in terms of operational simplicity and isolation of products.

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