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Note

An efficient synthesis of 1,5-benzodiazepines catalysed by $GaCl_3$ under solvent free conditions

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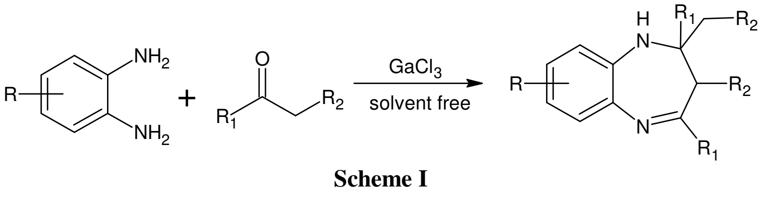
Various 1,5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones using catalytic amount of $GaCl_3$ (5 mol%) under solvent free conditions. This method is facile, efficient, environmentally benign and affords 1,5-benzodiazepines in excellent yield.

Keywords: *o*-Phenylenediamines, ketones, gallium(III) chloride, 1,5-benzodiazepines, solvent free

In mid 1950's Hoffmann-LaRoche announced the discovery of Librium® (chlorodiazepoxide) and Valium® (diazepam) which brought revolution in the research for more potent and efficient central nervous system (CNS) acting agents[1]. This led to the discovery of around two dozen new CNS acting agents with highly selective biological activities. These researches certainly triggered more intensive efforts in other related benzodiazepine scaffolds, more clearly 1,5-benzodiazepines. This scaffold is also one of the privileged structures of organic chemistry possessing a variety of biological activities like antianxiety, anticonvulsant, hypnotic, sedative, antidepressive[2]. This scaffold is also found use for synthesis of commercial dye and acrylic fibers[3]. In addition these molecules are also good synthons for the production of fused ring compounds like oxazino-, triazolo-, or furano-benzodiazepines[4]. Because of this unique position in synthetic as well as medicinal chemistry there have been intensive searches for their efficient and facile synthesis. One established method for the production of these molecules seems to be condensation of 1,2-diamines with α-methylene ketones. A variety of catalysts like $BF_3.OEt_2$ (Ref. 5), polyphosphoric acid-SiO_2 (Ref. 6), $NaBH_4$ (Ref. 7), MgO-$POCl_3$ (Ref. 8), Al_2O_3-P_2O_5 (Ref. 9), $YbCl_3$ (Ref. 10), $Yb(OTf)_3$ (Ref. 11), CAN (Ref. 12) and ionic liquids[13], *etc*. have been employed for the synthesis of 1,5-benzodiazepines. In spite of some good procedures available to chemist, many of these suffer from disadvantages like requirement of anhydrous conditions, use of strong acid or organic solvents, elevated temperature, prolonged reaction time, *etc*. Some of these catalysts break up into even more hazardous and non degradable toxic compounds during aqueous work-up. Therefore, search for a safe and mild protocol for synthesis of these important molecules is a subject of continued investigations[14].

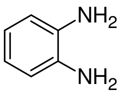
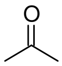
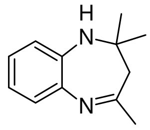
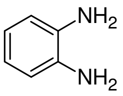
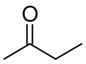
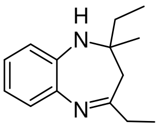
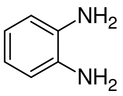
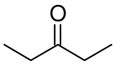
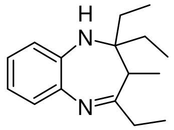
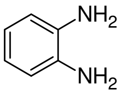
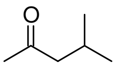
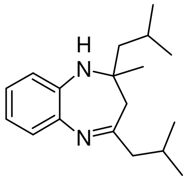
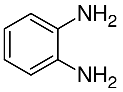
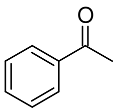
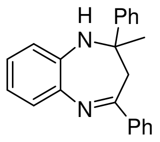
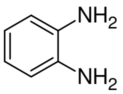
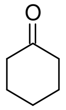
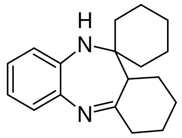
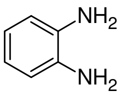
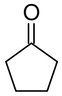
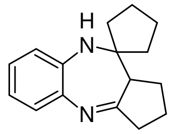
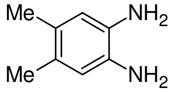
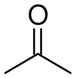
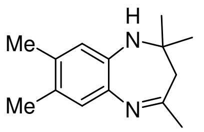
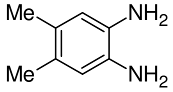
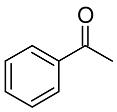
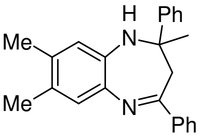
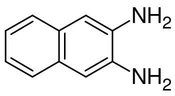
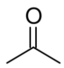
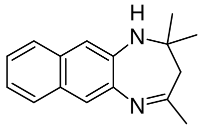
Though both indium and gallium are in the same group *i.e.* IIIA of the periodic table, indium and its salts have been studied extensively and are reviewed from time to time[15], in contrast gallium and its salts remained almost ignored. The comparable ionization potentials (Ga: FIP, 5.99 eV, E^o, $Ga^{+3}/Ga = -0.56$ V; In: FIP, 5.79 eV, E^o, $In^{+3}/In = -0.345$ V) indicate that they should have equally attractive properties. Very recently, the use of gallium is reported in some major reactions of organic chemistry like Reformatsky[16], Barbier[17], Grignard[18], bromination of aromatics[19a] and allylation of indoles[19b]. The application of gallium(III) halides are developing[20] at a very fast pace and have been reviewed recently[21]. In continuation[22] to the studies on the exploration of these important catalytic activities of gallium and its salts, this catalyst was employed for the synthesis of 1,5-benzodiazepines from *o*-phenylene diamine and α-methylene ketones.

The investigation was initiated with *o*-phenylenediamine, acetone and $GaCl_3$ (1:2.1:0.1) under solvent free conditions and RT stirring (**Scheme I**). The reaction was carried out for 30 min and 1,5-benzodizepine was isolated in 94% yields (entry 1, **Table I**). Further, the catalyst quantity was optimized

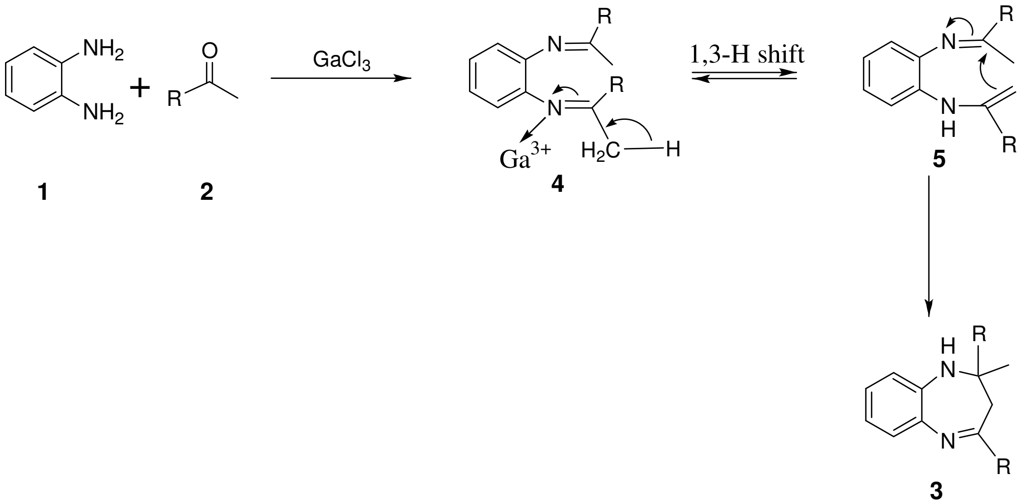


Scheme I

Table I — $GaCl_3$ mediated synthesis of 1,5-benzodiazepines

Entry	Diamine	Ketone	Benzodiazepine[a]	Time (min)	Yields (%)[b]
1				30	94[c] 68[d] 94[e] 94[f]
2				25	88
3				25	91
4				30	89
5				25	92
6				20	93
7				25	87
8				30	93
9				20	90
10				30	87

[a] All compounds were chracterised by spectral and physical data and comparison with those of authentic samples
[b] yields refers to pure isolated products; [c] using 5 mol% of $GaCl_3$; [d] using 2 mol% of $GaCl_3$; [e] using 10 mol% of $GaCl_3$; [f] using 20 mol% of $GaCl_3$



Scheme II

to 5 mol% of $GaCl_3$ and excellent results were achieved. Using less amount of catalyst, *i.e.* 2 mol%, resulted in the decrease of product yield (**Table I**). Increasing the amount of catalyst (*i.e.* 20 mol%) did not show any significant effect on the reaction rate as well as yields. However, this reaction did not yield the desired product in the absence of catalyst even after stirring for 20 hr. Similarly, other 1,5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones in 87-94% yields (**Table I**).

Regarding the scope of the reaction and to check the efficacy and applicability of this catalyst the desired products could be successfully obtained from variously substituted diamines. Diamines with electron releasing (entry 8-9) and *o*-naphthylene diamine also reacted smoothly with ketones to afford products in excellent yields. Both aromatic and aliphatic ketones (acyclic and cyclic) reacted well with diamine to afford the corresponding 1,5-benzodizepines in excellent yields. In case of unsymmetrical ketones (**Table I**, entries 2, 4), cyclization occurred selectively from one side of the carbon chain and only less sterically hindered α-methylene was involved in the cyclization reaction to give the desired product. The reaction of cyclic ketones (**Table I**, entries 6, 7) with diamines gave fused-ring 1,5-benzodizepines. The reaction is presumed to proceed *via* the initial formation of diimine **4** from the reaction of *o*-phenylenediamine with two equivalent of ketone with the assistance of $GaCl_3$ (**Scheme II**, the proposed mechanism is purely probable/conjectural). $GaCl_3$ is an established water scavenger and seems to help both in the formation of imines and the cyclisation step. Diimine thus formed undergoes 1,3-hydrogen shift to produce enamine **5** which cyclizes to form the seven membered ring.

In summary, the present method employing $GaCl_3$ is mild, efficient and environmentally benign protocol for the synthesis of 1,5-benzodizepines under solvent free conditions. 1,5-benzodizepine derivatives are obtained in excellent yields with short reaction time. Operational simplicity, avoidance of organic solvents and anhydrous reaction conditions are the other attractive features which make this procedure superior to the existing procedures. Needless to say, during work-up no hazardous/unsafe products were formed in this new method being reported.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from commercial source and used as received. IR spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. ^1H NMR spectra were recorded on Varian Gemini 300 (300 MHz) spectrometer using TMS as internal standard. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel G (Merck). $GaCl_3$ was procured from Aldrich and ketones were obtained from SD Fine Chem Ltd. and used without further purification. All other chemicals and solvents used were obtained from commercial sources and used as received or dried using standard procedures.

General procedure for preparation of 1,5-benzodizepines

To a stirred mixture of *o*-phenylenediamine (1 mmol) and ketone (2.1 mmol) at RT was added $GaCl_3$ (0.05 mmol). Further, the reaction mixture was stirred for time given in **Table I**. After completion of reaction (monitored *via* TLC), the reaction mass was diluted with ethyl acetate (20 mL), washed with saturated $NaHCO_3$ solution (3×15 mL) and then with brine (3×10mL). The organic layer was dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave the crude product which was purified by recrystallization from ethyl acetate:hexane mixture.

Representative spectral data

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (entry 1): m.p. 133-134°C; IR (KBr): 3311, 2978, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29-7.11 (m, 4H), 3.05 (br s, 1H), 2.42 (s, 3H), 2.23 (s, 2H), 1.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 142.1, 138.4, 129.0, 127.3, 126.9, 123.8, 122.5, 70.1, 46.1, 32.7, 30.9; EIMS: *m/z* 188.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (entry 3): m.p. 144-146°C; IR (KBr): 3315, 2957, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-6.88 (m, 4H), 3.49 (br s, 1H), 2.87 (q, J = 6.7 Hz, 1H), 2.71-2.54 (m, 2H), 1.73-1.51 (m, 2H), 1.39-1.19 (m, 4H), 1.12-0.87 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 143.7, 139.6, 132.9, 128.6, 126.9, 126.4, 126.1, 120.5, 118.4, 70.7, 46.9, 35.4, 29.3; EIMS: *m/z* 244.

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (entry 5): m.p. 152-153°C; IR (KBr): 3316, 2967, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53-7.41 (m, 4H), 7.36-7.11 (m, 7H), 7.04-6.87 (m, 3H), 3.36 (br s, 1H), 3.21 (d, J = 12.5 Hz, 1H), 2.89 (d, J = 12.5 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 168.5, 147.8, 139.9, 139.3, 130.5, 128.8, 127.9, 126.2, 125.9, 124.8, 119.7, 72.8, 45.6, 30.5, 29.6; EIMS: *m/z* 312.

Acknowledgments

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References

1 Sternbach L H, *J Med Chem* 22, **1979**, 1.

2 In a majority of these researches molecular modifications/manipulations of all functional group transformations were carried out. In these researches, critical starting materials were aminobenzopheneones and alkyl aminobenzophenones; for one process for the production of aminobenzopheneones, see: Gopinath K W, Sandhu J S, Mago D & Sharma A K, *Brit Patent*, **1976**, 1460141; *Japan Kokai* 350; *Chem Abstr*, 37423, **1978**.

3 (a) Smalley R K, in *Comprehensive Organic Chemistry*, Vol 4, edited by Barton B and Ollis W D (Pergamon, Oxford) **1979**, p600; (b) Landquist J K, in *Comprehensive Organic Chemistry*, Vol 1, edited by Kartrizky A R and Reews C W, (Pergamon, Oxford) **1984**, p166.

4 (a) Aversa M C, Ferlazzo A, Giannetto P & Kohnke F H, *Synthesis*, **1986**, 230; (b) Reddy K V V, Rao P S & Ashok D, *Synth Commun* 30, **2000**, 1825.

5 Haris R C & Straley J M, *US Patent* 1537737, **1968**; *Chem Abstr* 73, **1970**, 100054w.

6 Herbert J A L & Suschitzky H, *J Chem Soc, Perkin Trans 1,* **1974**, 2657.

7 Jung D I, Choi T W, Kim Y Y, Kim I S, Park Y M, Lee Y G & D H Jung, *Synth Commun,* 29, **1999**, 1941.

8 Morales H R, Bulbarela A & Contreas R, *Heterocycles* 24, **1986**, 135.

9 Balakrishana M S & Kaboudin B, *Tetrahedron Lett,* 42, **2001**, 1127.

10 Kaboudin B & Navaee K, *Heterocycles* 55, **2001**, 1443.

11 Wu J, Xu F, Zhou Z & Shen Q, *Synth Commun,* 36, **2006**, 457.

12 Yi W B & Cai C, *Synth Commun*, 37, **2007**, 3827.

13 Varala R, Enugala R, Nuvula S & Adapa S R, *Synlett,* **2006**, 1009.

14 Jarikote D V, Siddiqui S A, Rajagopal R, Daniel T, Lahoti R J & Srinivasan K V, *Tetrahedron Lett,* 44, **2003**, 1835.

15 (a) Nair V, Ros S, Jayan C N & Pillai B S, *Tetrahedron* 60, **2004**, 1959; (b) Podlech J & Maier T C, *Synthesis* **2003**, 633; (c) Ranu B C, *Eur J Org Chem* **2000**, 2347; (d) Chauhan K K & Frost C G, *J Chem Soc, Perkin Trans 1,* **2000**, 3015; (e) Li C-J, Chan T-H, *Tetrahedron,* 55, **1999**, 11149; (f) Cintas P, *Synlett*, **1995**, 1087.

16 Zhang X-L, Han Y, Tao W-T & Huang Y-Z, *J Chem Soc, Perkin Trans 1,* **1995**, 189.

17 (a) Wang Z, Yuan S & Li C-J, *Tetrahedron Lett*, 43, **2002**, 5097; (b) Han Y & Huang Y-Z, *Tetrahedron Lett,* 35, **1994**, 9433.

18 Tsuji T, Usuji S-I, Yorimitsu H, Shinokubo H, Matsubara S & Oshima K *Chem Lett,* **2002**, 2.

19 (a) Arisawa M, Suwa A, Ashikawa M & Yamaguchi M, *Arkivoc* (viii), **2003** 24; (b) Prajapati D, Gohain M & Gogoi B J, *Tetrahedron Lett*, 47, **2006**, 3535.

20 (a) Mikami S, Yorimitsu H & Oshima K, *Synlett,* **2002,** 1137; (b) Viswanathan G S & Li C-J, *Synlett*, **2002**, 1553; (c) Ryo A, Yoshio N & Masahiko Y, *Synthesis,* **2004**, 1307; (d) Mieko A, Chie M & Masahiko Y, *Syhthesis,* **2002**, 138; (e) Lee S I, Sim S H, Kim S M, Kim K & Chung Y K, *J Org Chem*, 71, **2006**, 7120; (f) Arisawa M, Akamatsu K & Yamaguchi M, *Org Lett*, 3, **2001**, 789; (g) Yoshioka S, Osita M, Tobisu M & Chatani N, *Org Lett*, 7, **2005**, 3697; (h) Huang Z-H, Zou J-P & Jiang W-Q, *Tetrahedron Lett*, 47, **2006**, 7965.

21 (a) Kellogg R M, *Chemtracts,* 16, **2003**, 78; (b) Yamaguchi M, Tsukagoshi T & Arisawa M, *Chemtracts,* 13, **2000**, 431; (c) Amemiya R & Yamaguchi M, *Eur J Org Chem,* **2005**, 5145; (d) Barman D C, *Synlett,* **2003**, 2440.

22 (a) Sharma U, Bora U, Boruah R C & Sandhu J S, *Tetrahedron Lett*, 43, **2002**, 143; (b) Gadhwal S, Baruah M & Sandhu J S, *Synlett*, **1999**, 1573; (c) Gohain M, Prajapati D, Gogoi B J & Sandhu J S, *Synlett*, **2004**, 1179; (d) Laskar D D, Gohain M, Prajapati D & Sandhu J S, *New J Chem,* 26, **2002**, 193.