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Alum-Catalyzed One-Pot Solventless Synthesis of 1,5-Benzodiazepines

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Alum [$KAl(SO_4)_2{\cdot}12H_2O$] was found to be an efficient, non-toxic, cheap, and environmentally benign catalyst for the synthesis of 1,5-benzodiazepines, in good to excellent yields, from the condensation of 1 mole of *o*-phenylenediamine with 2 moles of ketone under solvent-free conditions.

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Introduction

Benzodiazepines are a class of drugs possessing hypnotic,[1] anxiolytic, anticonvulsant, amnestic, and muscle relaxant properties. Different benzodiazepines are often used for the short-term relief of severe, disabling anxiety or insomnia. They serve as cholecystokinin A and B antagonists,[2] opioid receptor ligands,[3] platelet-activating factor antagonists,[4] HIV inhibitors,[5] as farnesyltransferase inhibitors,[6] and recently they have been reported to show anti-leukaemic and anti-platelet activity.[7] The synthesis of benzodiazepines has been achieved by catalysts such as Zn[L-proline]$_2$,[8] $YbCl_3$,[9] $SbCl_3$–Al_2O_3,[10] BF_3 etherate,[11] ionic liquids,[12] polystyrene supported sulfonic acid,[13] and on ultrasound irradiation.[14] However, these methods have one or more disadvantages such as high temperature, moisture sensitivity of the reagent used, prolonged reaction time, co-occurrence of side reactions, use of stoichiometric amount of catalyst, harsh reaction conditions, and complicated workup procedures. These facts provide the necessary impetus to develop better and safer procedures for the synthesis of benzodiazepines.

Alum is employed in organic synthesis as a mild and efficient Lewis acid.[15] It is also environmentally benign, non-polluting, non-toxic, inexpensive, and safe. In our endeavour to develop a greener protocol for the synthesis of pharmacologically active benzodiazepines in one step from the cyclocondensation of one equivalent of *o*-phenylenediamine with two equivalents of ketone, we explored the usage of alum as a Lewis acid for this purpose.

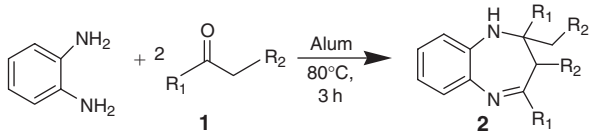
Results and Discussion

When a mixture of *o*-phenylenediamine (10 mmol), acetophenone **1a** (20 mmol), and crystalline alum (10 mol-%) was refluxed in acetonitrile (50 mL) with stirring for 4.5 h, the product was isolated in 40% yield by column chromatography over silica gel and was found to be 2-methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine as revealed by comparison of its spectroscopic and physical data with an authentic sample.[8,16] When pulverized alum was used under the same reaction conditions, the reaction was completed in 3 h (TLC), possibly because of an increase in the surface area. To obtain optimum concentration of alum for better yields, a set of experiments was performed employing different concentrations of alum for a reaction between 10 mmol of *o*-phenylenediamine and 20 mmol of acetophenone in acetonitrile for 3 h; the results are shown in Table 1. It is apparent from this table that just 2.5 mol-% of alum was enough to push the reaction to completion. It was desirable for acetonitrile, being toxic, to be removed in view of the development of a greener procedure. Towards this end, when a mixture of *o*-phenylenediamine (10 mmol), acetophenone **1a** (20 mmol) and pulverized alum (2.5 mol-%) was heated, without any solvent, in a round-bottom flask at 80°C, complete conversion into the desired product took 3 h as described in Scheme 1. To benefit in terms of time economy, the reaction was subjected

Table 1. Optimization of the amount of alum for the preparation of 1,5 diazepines

Entry	Mol-%	Amount alum [g]	Yield [%]
1	0	0	[A]
2	0.5	0.238	20
3	1.0	0.476	30
4	2.0	0.952	50
5	**2.5**	**1.119**	**95**
6	5.0	2.380	60
7	10.0	4.760	40

[A]No reaction.



R_1 = aryl or alkyl groups
R_2 = alkyl group

Scheme 1. Synthesis of 1,5-benzodiazepines.

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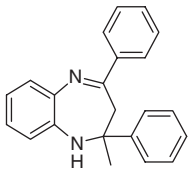
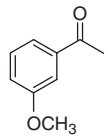
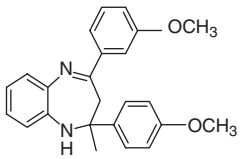
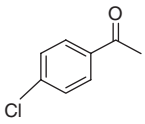
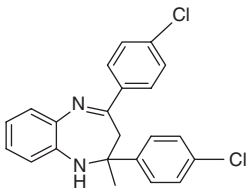
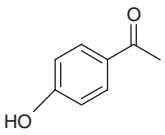
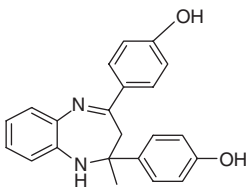
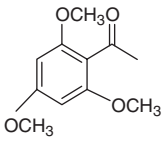
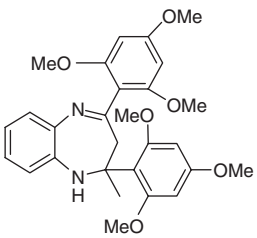
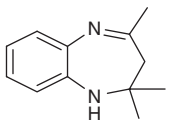
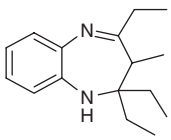
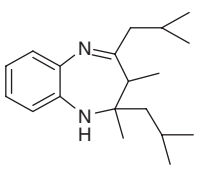
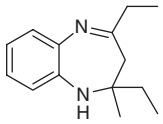
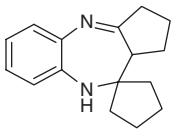
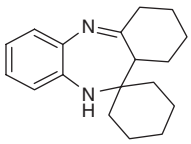
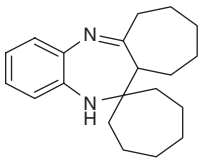
Table 2. Alum-catalyzed formation of 1,5-benzodiazepines
Yields are isolated yields. Melting points are uncorrected

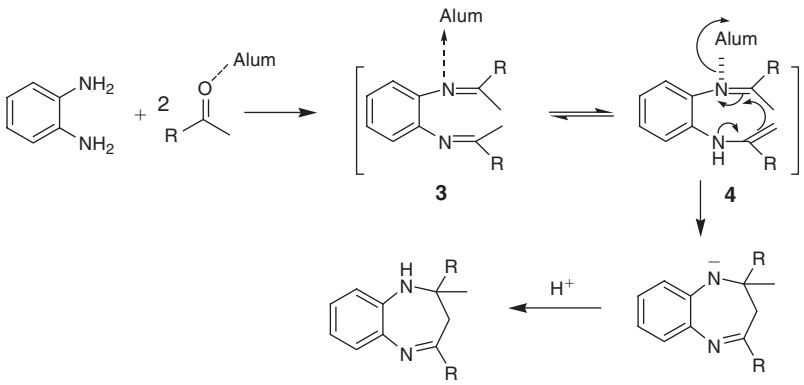
Entry	Ketone **1**	Product **2**	Time [h]	Yield [%]	Obs. mp [°C] (lit.)[8,16]
1	C_6H_5COMe **1a**	 **2a**	3.0	95	152–153 (150–152)
2	 **1b**	 **2b**	3.0	93	A
3	 **1c**	 **2c**	3.5	92	162–163 (160–163)
4	 **1d**	 **2d**	5.0	82	140–141 (137–139)
5	 **1e**	 **2e**	5.0	82	A
6	MeCOMe **1f**	 **2f**	3.5	90	136–137 (137–139)
7	EtCOEt **1g**	 **2g**	3.5	88	142–143 (145)
8	Pr^iCOMe **1h**	 **2h**	3.5	87	117–119 (118–120)

(*Continued*)

Table 2. (Continued)

Entry	Ketone **1**	Product **2**	Time [h]	Yield [%]	Obs. mp [°C] (lit.)[8,16]
9	EtCOMe **1i**	 **2i**	3.5	88	140–142 (139–141)
10	Cyclopentanone **1j**	 **2j**	4.0	85	136–137 (137–138)
11	Cyclohexanone **1k**	 **2k**	4.5	84	135–136 (137)
12	Cycloheptanone **1l**	 **2l**	5.0	82	134–136 (135)

[A]Oil.



Scheme 2. Proposed mechanism of the reaction.

to microwave irradiation (240 W) under solvent-free conditions for 3 min with a pause after every 30 s; the yield of the product dropped from 95 to 50%. Some decomposition to unidentified tarry material was also observed.

A range of substrates such as substituted acetophenones, dialkyl ketones, and cycloketones underwent reaction under similar conditions, and the results are depicted in Table 2. The present method thus provides a green alternative for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamine and ketones having hydrogens at the α-position, in the presence of non-toxic, mild, non-polluting, and environmentally benign alum.

Mechanism

The most probable mechanism seems to be alum-catalyzed formation of bis-imines **3** followed by tautomerism to the enamine **4**. The push by the NH lone pair of electrons of the enamine and the pull caused by chelation of alum to the imine N atom facilitates the cyclization to a seven-membered ring as described in Scheme 2.

Experimental

Melting points were measured in open capillaries on a Perfit melting point apparatus and are uncorrected. IR spectra on KBr disks were recorded on a Bruker-4800 infrared spectrometer. NMR and electron-impact mass spectrometry (EI-MS) spectra were recorded on Bruker AC-400 (400 and 100 MHz) and JEOL D-300 mass spectrometers, respectively. Elemental analyses were carried out with a Heraeus CHN rapid analyzer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million from tetramethylsilane (TMS) as internal standard. All experiments were performed in oven-dried glass apparatus. The alum

(Qualigens Fine Chemicals) used was a commercial reagent. SISCO silica was used as an adsorbent for TLC (0.5-mm thick plates). The visualization of spots was effected by exposure to iodine vapour and 5% 2,4-dinitrophenyl hydrazine in ethanol containing a few drops of conc. H_2SO_4. Column chromatography was performed over silica gel (60–120 mesh) with graded solvent systems of ethyl acetate/*n*-hexane. The solvents were dried before use as per established procedures.

General Procedure for the Synthesis of Substituted Benzodiazepines

A mixture of *o*-phenylenediamine (1.08 g, 10 mmol), ketone (20 mmol), and pulverized alum (1.19 g, 2.5 mol-%) was heated in round-bottom flask at 80°C until completion of reaction (3.0–5.0 h) as revealed by TLC. The reaction mixture was diluted with ethyl acetate (70 mL) and filtered. The filtrate was washed with brine (2×25 mL), dried over anhydrous Na_2SO_4, the ethyl acetate was distilled off under reduced pressure, and the residue was directly charged on a small silica gel column (ethyl acetate/*n*-hexane) to afford pure the benzodiazepines (82–95%).

Physical and Spectroscopic Data for Selected Products

*2-Methyl-2,4-diphenyl-2,3-dihydro-1*H-*1,5-benzodiazepine* ***2a***

Yellow crystals. δ_H ($CDCl_3$, 400 MHz) 7.60–7.55 (m, 4H), 7.0–6.55 (m, 3H), 3.40 (br s, 1H), 3.20 (d, 1H, *J* 12.8), 2.90 (d, 1H, *J* 12.8), 1.85 (s, 3H). δ_C ($CDCl_3$, 100 MHz) 29.7, 42.9, 73.3, 78.5, 121.2, 121.4, 121.6, 125.2, 126.1, 126.8, 126.9, 127.8, 127.9, 128.1, 128.5, 129.5, 137.9, 139.5, 139.9, 142.5, 147.5, 167.5. ν_{max}(KBr)/cm^{-1} 3325, 1636, 1598. Calc. for $C_{22}H_{20}N_2$ (312.4166): C 84.6, H 6. 5, N 9.0. Found: C 84.5, H 6.5, N 8.6%. *m*/*z* 312 (M^+).

*2-Methyl-2,4-di(4-hydroxyphenyl)-2,3-dihydro-1*H-*1,5-benzodiazepine* ***2d***

Yellow solid. δ_H ($CDCl_3$, 400 MHz) 7.45–6.95 (m, 12H), 4.20 (br s, 1H), 2.8 (s, 2H), 1.65 (s, 3H). ν_{max}(KBr)/cm^{-1} 3345, 1635, 1510. Calc. for $C_{22}H_{20}N_2O_2$ (344.4154): C 76.7, H 5.9, N 8.1. Found: C 76.8, H 5.8, N 8.2%. *m*/*z* 344 (M^+).

*2-Methyl-2,4-di(2,4,6-trimethoxyphenyl)-2,3-dihydro-1*H-*1,5-benzodiazepine* ***2e***

Viscous oil. δ_H ($CDCl_3$, 400 MHz) 7.35–6.20 (m, 8H), 3.55–3.15 (m, 9H), 4.10 (br s, 1H), 2.60 (s, 2H), 1.50 (s, 3H). ν_{max}(KBr)/cm^{-1} 3320, 2960, 1495. Calc. for $C_{28}H_{33}N_2O_6$ (492.5751): C 68.3, H 6.5, N 5.7. Found: C 68.3, H 6. 6, N 5.5%. *m*/*z* 492 (M^+).

*2,4-Diethyl-2-methyl-2,3-dihydro-1*H-*1,5-benzodiazepine* ***2i***

Yellow solid. δ_H ($CDCl_3$, 400 MHz) 7.30–6.75 (m, 4H), 3.20 (br s, 1H), 2.65 (q, 2H, *J* 7.0), 2.30 (s, 3H), 2.15 (m, 2H), 1.75 (q, 2H, *J* 6.9), 1.20 (t, 3H, *J* 7.0), 1.00 (t, 3H, *J* 6.9). δ_C ($CDCl_3$, 100 MHz) 35.6, 35.7, 42.1, 70.5, 121.9, 125.4, 126.0, 127.0, 137.8, 140.8, 175.5. ν_{max}(KBr)/cm^{-1} 3330, 1638, 1605. Calc. for $C_{14}H_{20}N_2$ (216.3087): C 77.7, H 9.3, N 13.0. Found: C 77.7, H 9.4, N 13.0%. *m*/*z* 216 (M^+).

*Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[e][1,4]diazepine* ***2l***

Pale yellow solid. δ_H ($CDCl_3$, 400 MHz) 7.35–6.60 (m, 4H), 3.62 (br s, 1H), 2.90–2.35 (m, 3H), 1.95–0.95 (m, 20H). δ_C ($CDCl_3$, 100 MHz) 22.5, 23.2, 26.4, 28.5, 28.7, 29.5, 29.8, 30.1, 38.6, 40.9, 54.5, 72.4, 121.2, 121.5, 125.6, 127.7, 137.5, 139.7, 179.2. ν_{max}(KBr)/cm^{-1} 3325, 1630, 1600. Calc. for $C_{20}H_{28}N_2$ (296.4580): C 81.0, H 9.5, N 9.4. Found: C 81.1, H 9.5, N 9.5%. *m*/*z* 296 (M^+).

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