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Ultrasound enhanced synthesis of 1,5-benzodiazepinic heterocyclic rings

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Abstract—1,5-Benzodiazepines are synthesized by a reaction of *o*-phenylenediamines with a diketone or ketones series by ultrasound irradiation in presence of APTS. The condensation occurred in a mild condition with good to excellent yields.

Benzodiazepines are an important class of pharmacologically active compounds finding applications as anti-inflammatory, anti-convulsant, sedative and hypnotic agents.[1] In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer,[2] viral infection[3] and cardiovascular disorders.[4]

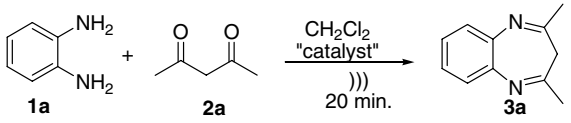
Because of this wide range of pharmacological and clinical activities, this class of compounds has attracted the attention of many organic synthetic chemists. Among the protocol to prepare 1,5-benzodiazepines we can cite the use of ionic liquids,[5] ceric ammonium nitrate,[6] $InBr_3$,[7] 'sulfated zirconia'[8] as catalyst or promoter of the reactions. Some solvent-free conditions have been employed too.[9] Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, expensive reagents, tedious work-up procedures and/or long reactions times.

It is well known that many organic reactions have been accelerated by ultrasound irradiation.[10,11] Compared with traditional methods, this technique is more convenient, easily controlled and can have a very high potential in green chemistry approach.[12] Recently, we have shown the synthesis of numerous useful organic compounds under ultrasound irradiation. For example, aryl acetylenes,[13] heterocycles[14] as well as in cross-coupling reactions.[15]

As a part of our growing interest in sonochemistry, with the aim to improve the synthesis of 1,5-benzodiazepines, we decided to undertake a systematic study of the preparation of these heterocyclic compounds under milder conditions.

We initially focussed our attention on the determination of the best experimental conditions for the reaction, electing *o*-phenylenediamine **1a** and 2,4-pentanedione **2a** as standard reagents (Scheme 1).

Attempts for the synthesis of 1,5-benzodiazepines under ultrasound irradiation were examined using silica as catalyst and the desired product (**3a**) was obtained in 67% yield. A variety of catalysts were examined. By using Amberlyst® 15 and DOWEX® (Table 1, entries 4 and 5) provided **3a** in 55% and 31% yield, respectively. Moreover, low yields were obtained in the absence of a catalyst (Table 1, entry 1) and other catalysts (Table 1, entries 6–9). The *p*-toluenesulfonic acid (APTS) showed the best activity and the product **3a** was obtained in 83%



Scheme 1. Standard reaction.

Keywords: 1,5-Benzodiazepines; Ultrasound irradiation; Condensation.
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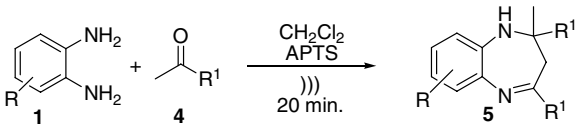
Table 1. Study of catalyst effect on reaction using **1a** and **2a** under ultrasound conditions

Entry	Catalyst	Yield[a] (%)
1	No catalyst	22
2	Silica	67
3	APTS	83
4	Amberlyst®	55
5	DOWEX®	31
6	K-10	38
7	$AlCl_3$	33
8	$MgCl_2$	37
9	$ZnCl_2$	29

[a] Isolated yield.

yield (Table 1, entry 3). The reaction was performed in different solvents such as ethyl acetate, CH_2Cl_2, dioxane and DME. Dichloromethane was found to be the best solvent in terms of yield and reaction time.

The reactions were carried out by taking a 1:1 mole ratio of **1a** and **2a** along with a catalytic amount of APTS (10 mol %) in a round bottom flask and this was located in the maximum energy area of a water bath of an ultrasonic cleaner. The reaction proceeds very well at room temperature giving good to excellent yields of 1,5-benzodiazepines derivates (**3**) and in all cases the reaction



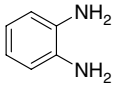
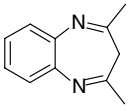
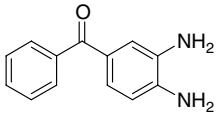
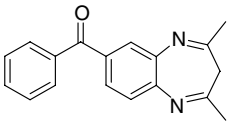
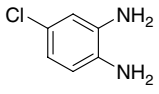
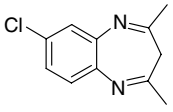
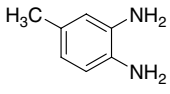
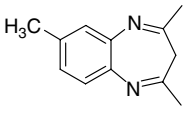
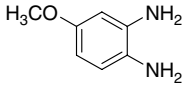
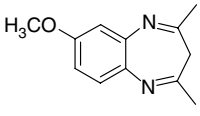
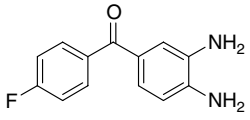
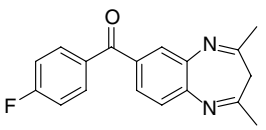
Scheme 2. Reaction between diamines **1** and ketones **4**.

is clean and completed within 15 min.[16] Representative results of the reaction are summarized in Table 2. It is clear that this is a general method that tolerates both electron-withdrawing and electron-donating groups in the diamine **1**.

To analysis the scope of reaction we tested ketones as carbonylic sources to afford the 1,5-benzodiazepines **5** (Scheme 2). As can be seen in Table 3, acetone **4a** reacted with four different diamine **1** (Table 3, entries 1–4) affording **5a–d** in good yields. The condensation of acetone **4a** with 5-methoxy-2-amino aniline **1e** (Table 3, entry 3) in the presence of APTS, gave two products (**5c** and **5c′**). When acetone **4a** was employed itself was used as solvent.

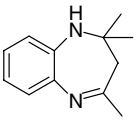
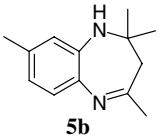
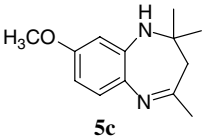
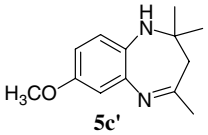
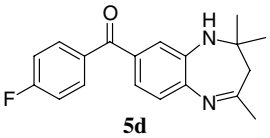
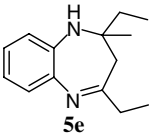
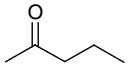
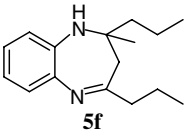
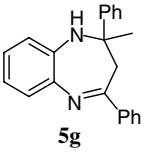
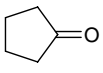
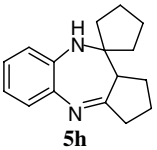
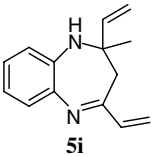
2-Butanone (**4b**) and 2-pentanone (**4c**) reacted with **1a** leading to **5e** and **5f** (Table 3, entries 5 and 6) in 83% and 81% yield, respectively. Acetophenone (**4d**),

Table 2. Reactions between diamines **1** and 2,4-pentanedione **2a**

Entry	Diamine (**1**)	Product (**3**)	Yield[a] (%)
1	 **1a**	 **3a**	83
2	 **1b**	 **3b**	79
3	 **1c**	 **3c**	87
4	 **1d**	 **3d**	77
5	 **1e**	 **3e**	87
6	 **1f**	 **3f**	82

[a] Isolated yield.

Table 3. Reactions between diamines **1** and ketones **4**

Entry	Diamine (**1**)	Ketone (**4**)	Product (**3**)	Yield[a] (%)
1	**1a**	 **4a**	 **5a**	85
2	**1d**	**4a**	 **5b**	78
3	**1e**	**4a**	 **5c** and  **5c'**	77[b]
4	**1f**	**4a**	 **5d**	78
5	**1a**	 **4b**	 **5e**	83
6	**1a**	 **4c**	 **5f**	81
7	**1a**	 **4d**	 **5g**	nr
8	**1a**	 **4e**	 **5h**	nr
9	**1a**	 **4f**	 **5i**	nr

[a] Isolated yield.
[b] Diastereoisomers not separated.

cyclopentanone (**4e**) and methyl vinyl ketone (**4f**) (Table 3, entries 7–9) were also used, but no reaction was observed.

In summary, we have shown that 1,5-benzodiazepinic heterocyclic can be efficiently prepared using ultrasound irradiation as a tool for creating diverse compound libraries. Considering the easiness of the preparation of initial reactants, convenient synthesis, and isolation of products and good chemical yields of the described transformations, this route provides a new valuable entry to 1,5-benzodiazepines. The obtained compounds represent valuable starting points for the development of compounds of biological interest. The limitations and the scope of this methodology are under investigation and will be reported in due course.

Acknowledgements

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16. *General experimental procedure*: A suspension of *o*-phenylenediamine (**1a**) (0.108 g, 1.0 mmol), carbonyl compound (**2** or **4**) (1.1 mmol) and APTS (10 mol %) in 5 mL of CH_2Cl_2 was irradiated in a water bath of an ultrasonic cleaner for 20 min. Then, the reaction was concentrated under vacuum. Purification by silica gel chromatography (eluting with hexane–ethyl acetate, 8:2–6:4) yielded 1,5-benzodiazepines (Tables 2 and 3).
Compound **3a**: Yield: 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.37–7.33 (m, 2H), 7.23–7.18 (m, 2H), 2.8 (s, 2H), 2.33 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 157.9; 140.4; 127.6; 125.0; 43.3; 2727. MS: *m*/*z* (%) 173 (14); 172 (100); 171 (41); 157 (15); 77 (10).
Compound **3f**: Yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.86 (t, $J = 6$ Hz, 2H), 7.75 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 7.14 (t, $J = 8.2$ Hz, 2H), 2.87 (s, 2H), 2.38 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 194.2; 159.6; 158.9; 143.2; 139.3; 133.6; 132.3; 130.1; 127.6; 125.6; 115.4; 115.1; 43.5; 27.6. MS: *m*/*z* (%) 295 (12); 294 (65); 199 (100); 123 (25).
Compound **5a**: Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.14–7.12 (m, 1H), 6.99 (m, 2H), 6.74–6.73 (m, 1H), 2.94 (br s, 1H), 2.36 (s, 3H), 2.22 (s, 2H), 1.34 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 172.6; 141.0; 138.2; 127.1; 125.8; 122.3; 121.9; 68.6; 45.3; 30.7; 30.1. MS: *m*/*z* (%) 189 (8); 188 (49); 173 (100); 92 (13).
Compound **5b**: Yield: 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 6.86 (d, $J = 4.1$ Hz 2H), 6.58 (t, $J = 4.5$ Hz 1H), 2.38 (s, 3H), 2.26 (s, 3H), 2.14 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 171.5; 140.6; 137.4; 134.2; 125.0; 124.4; 120.2; 69.3; 45.1; 30.5; 29.8; 18.4. MS: *m*/*z* (%) 2002 (22); 187 (100); 172 (5); 146 (39); 77 (10).