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Short communication

Ultrasound Assisted 1,4-diazabicyclo[2.2.2] Octaniumdiacetate Multicomponent Synthesis of Benzodiazepines: A Novel, Highly Efficient and Green Protocol

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Abstract

A simple and efficient method is presented for the synthesis of benzodiazepines through the multicomponent reaction of *o*-phenylenediamine, various aldehydes and 5,5-dimethylcyclohexane-1,3-dione (dimedone) in the presence of the acidic bis ionic liquid 1,4-diazabicyclo[2.2.2]octanium diacetate under ultrasound irradiation. The ionic liquid used is recoverable and reusable. This procedure is simple and environmentally friendly, and offers easy work-up, mild conditions and excellent yield in a short reaction time. All of the synthesized compounds were characterized by IR, ^{1}H NMR, mass spectrometry and elemental analysis.

Keywords: Dimedone, benzodiazepines, ionic liquid, green chemistry

1. Introduction

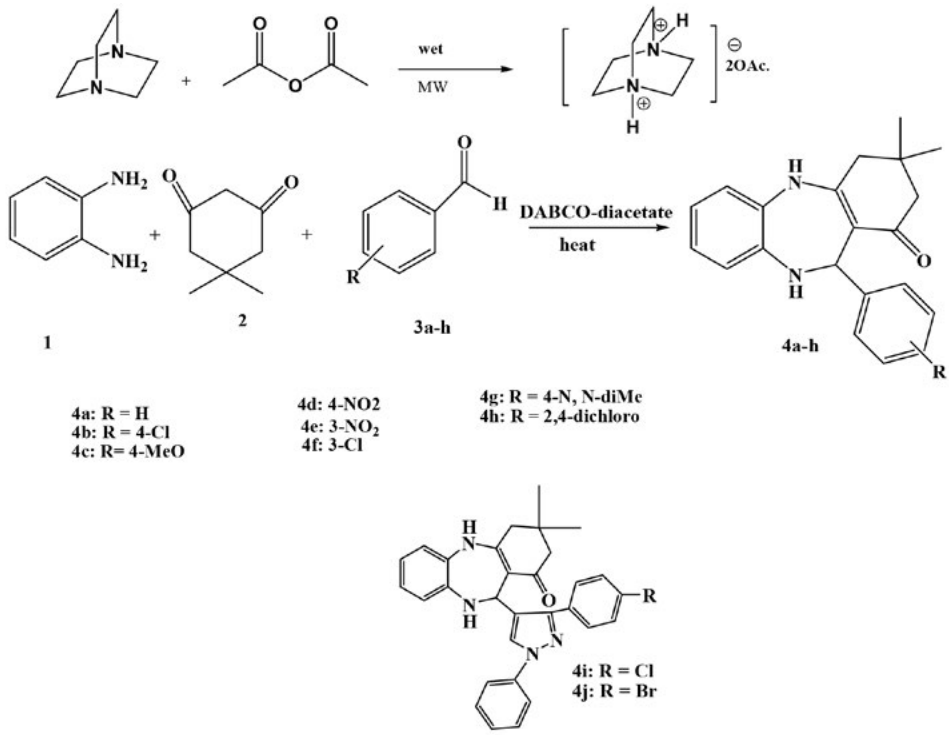
Benzodiazepine rings are important building blocks of heterocyclic and pharmaceutical compounds because they are anti-inflammatory, antidepressive, anticonvulsant, antiviral, antimicrobial, anti-HIV, antianxiety, anti-ulcerative, antitumor, analgesic, antihistaminic, anti-allergic, hypnotic and antipyretic.[1–7] Some benzodiazepines are used in industry as dyes.[8] Others are useful precursors for the synthesis of fused-ring compounds such as oxazino-, triazolo-, tetrazolo-, oxadiazolo- and furanobenzodiazepines.[9–12]

Benzodiazepines are generally synthesized by the reaction of β-haloketones with *o*-phenylenediamine,[13] condensation of α,β-unsaturated compounds with *o*-phenylenediamines[14] and condensation of ketones with *o*-phenylenediamine in the presence of ytterbium trichloride.[15] The disadvantages of previously reported procedures for the synthesis of benzodiazepines are their multistep reactions, anhydrous conditions, tedious work-up, long reaction times and generation of undesirable by-products.[16–18]

Multicomponent reactions (MCRs) are efficient tools in modern synthetic organic chemistry because they are fast, simple, offer high-atomic efficiency, are environmentally friendly and save time and energy.[19–23] On the other hand, ionic liquids are suitable compounds because they are non-flammable, non-volatile, soluble, exhibit polarity and are highly thermal and chemically stable.[24] MCRs combined with ionic liquid can assist in the synthesis of the benzodiazepines to reduce the cost of starting materials and decrease the generation of undesirable by-products. In continuation of our studies on the green synthesis of organic materials,[25–29] some derivatives of benzodiazepine were synthesized using the ionic liquid 1,4-diazabicyclo[2.2.2]octaniumdiacetate (DABCO-diacetate) under ultrasound irradiation in an MCR.

2. Results and Discussion

The MCR of benzaldehyde, 5,5-dimethylcyclohexane-1,3-dione (dimedone) and *o*-phenylendiamine is essentially a condensation reaction. The reaction rate can be increased either by activating the carbonyl group of aldehydes using acidic reagents or using a strong nucleophilic dimedone derivative in basic media. In the current study, we used the acidic bis ionic liquid DABCO-diacetate as green media for the synthesis of benzodiazepines in a condensation reaction of *o*-phenylenediamine, aldehydes and/or dimedone (Scheme 1).



Scheme 1. Multicomponent synthesis of benzodiazepines in the presence of DABCO-diacetate.

Initially, a sample reaction was carried out using 4-nitrobenzaldehyde (1mmol) **3d**, *o*-phenylenediamine **1** (1 mmol) and dimedone **2** (1 mmol) in DABCO-diacetate as an efficient catalyst for the synthesis of benzodiazepines **4a.** This protocol proceeded smoothly at room temperature to afford product **4a** in a fairly high yield. The reactions were also carried out using the neutral ionic liquids [BMIM]Br and [BMIM]BF_4 or in the absence of ionic liquids for purpose of comparison with our target reaction. It was interesting to note that the sample reaction did not proceed in the presence or absence of imidazolium ionic liquids, confirming the important role of DABCO-diacetate in the synthesis of benzodiazepines.

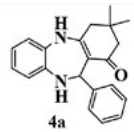
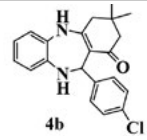
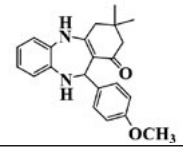
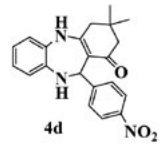
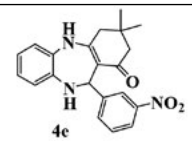
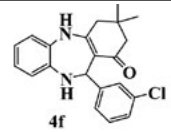
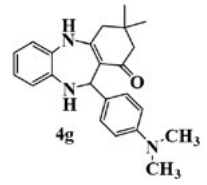
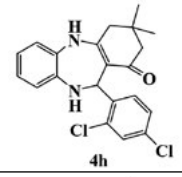
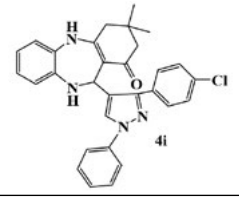
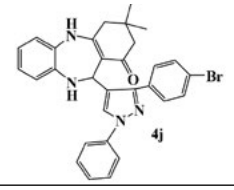
To optimize the amount of ionic liquid media required for this reaction, a sample reaction was carried out using different quantities of ionic liquid. The best results were obtained with 0.5 mmol of DABCO-diacetate per 1 mmol of substrate. For further investigation, the reaction between 4-nitrobenzaldehyde, *o*-phenylendiamine and dimedone was done in the presence of a catalytic amount of DABCO-diacetate at different temperatures. When the reaction was performed at room temperature, product **4a** formed smoothly at a low yield. To achieve better results, the temperature was increased to 90 °C and benzodiazepine **4a** was obtained at a yield of 82%. The results are summarized in Table 1.

Recently, ultrasound irradiation has been introduced as a useful, clean and mild protocol for organic synthesis. The well-known features of ultrasound-assisted reactions are formation of purer products at high yields, increased

Table 1. Optimization of reaction conditions.

entry	catalyst	Catalyst amount (mmol)	Reaction conditions	Time (min)	Yield (%)
1	–	–	Reflux in EtOH	720	–
2	[BMIM]Br	0.5	Stir, rt	720	11
3	[BMIM]BF_4	0.5	Stir,rt	720	7
4	DABCO-diacetate	0.5	Stir, rt	240	86
5	DABCO-diacetate	0.3	Stir, rt	90	81
6	DABCO-diacetate	0.7	Stir, rt	90	87
7	DABCO-diacetate	0.5	Heat, 90°C	60	89
8	DABCO-diacetate	0.5	Ultrasound, rt	8	98
9	DABCO-diacetate	0.5	Ultrasound, 40 °C	8	96
10	DABCO-diacetate	0.5	Ultrasound, 60 °C	6	97

Table 2. Synthesis scope of benzodiazepines **4a–j**.

entry	product	Heat, 90 °C		Ultrasound, rt		Mp (°C)	
		Time (min)	Yield (%) [a,b]	Time (min)	Yield (%) [a,b]	found	reported
1	 4a	75	82	10	95	248–250	251–252 [18]
2	 4b	60	84	8	97	238–240	239–240 [18]
3		60	85	8	96	198–200	203–205 [18]
4	 4d	60	89	8	98	271–273	274–275 [18]
5	 4e	75	88	10	95	262–264	–
6	 4f	75	89	10	96	248–250	–
7	 4g	90	85	12	93	231–232	232–233 [30]
8	 4h	90	83	15	94	198–200	203–205 [18]
9	 4i	90	81	17	94	209–210	–
10	 4j	60	82	6	95	245–247	–

[a] Isolated yield. [b] Products characterized by comparison of spectroscopic and physical data with those of samples synthesized using proposed procedures.

selectivity, enhanced reaction rates, easier experimental procedures and cleaner reactions. For these reasons, we were interested in the synthesis of benzodiazepines under ultrasound irradiation at various temperatures. The results are summarized in Table 1. Ultrasonic irradiation at room temperature was the best choice to shorten the reaction times and enhance productivity. The reaction scope was checked using various aromatic aldehydes for reaction with **1** and **2** under optimized conditions. The results are summarized in Table 2.

As shown in Table 2, the reaction under ultrasound irradiation at room temperature afforded products in shorter reaction times at higher yields. The structures of products **4a–j** were characterized by IR, ^{1}H NMR, mass spectroscopy, elemental analysis and by comparison of their melting points with those of available authentic samples.

A reasonable mechanism for the formation of benzodiazepines is shown in Scheme 2. Initially, DABCO-diacetate can increase the electrophilic character of the carbonyl species through its inherent Brønsted acidity under ultrasound irradiation. Because the ionic liquid can polarize the carbonyl group of aldehyde, the nucleophilic addition of dimedone **2** and subsequent dehydration led to intermediate **6**. The Michael addition reaction between **1** and **6** afforded intermediate **7,** followed by simple condensation of the amino group with carbonyl and dehydration, leading to product **4**.

3. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. The IR spectra were determined using a Shimadzu IR-470 spectrometer. The ^{1}H NMR spectra were recorded on a 400 MHz Bruker DRX-400 using $CDCl_3$ as the solvent and TMS as the internal standard. The chemicals were purchased from Merck and Fluka. Elemental analysis was done on a Carlo-Erba EA1110CNNO-S analyzer and the results agreed with the calculated values. All solvents used were dried and distilled according to standard procedures. For the ultrasound reactions, an Astra 3D ultrasound apparatus (9.5 dm^3, 45 kHz frequency, input power with heating at 305 W, 2 transducers) from Techno-Gaz was used.

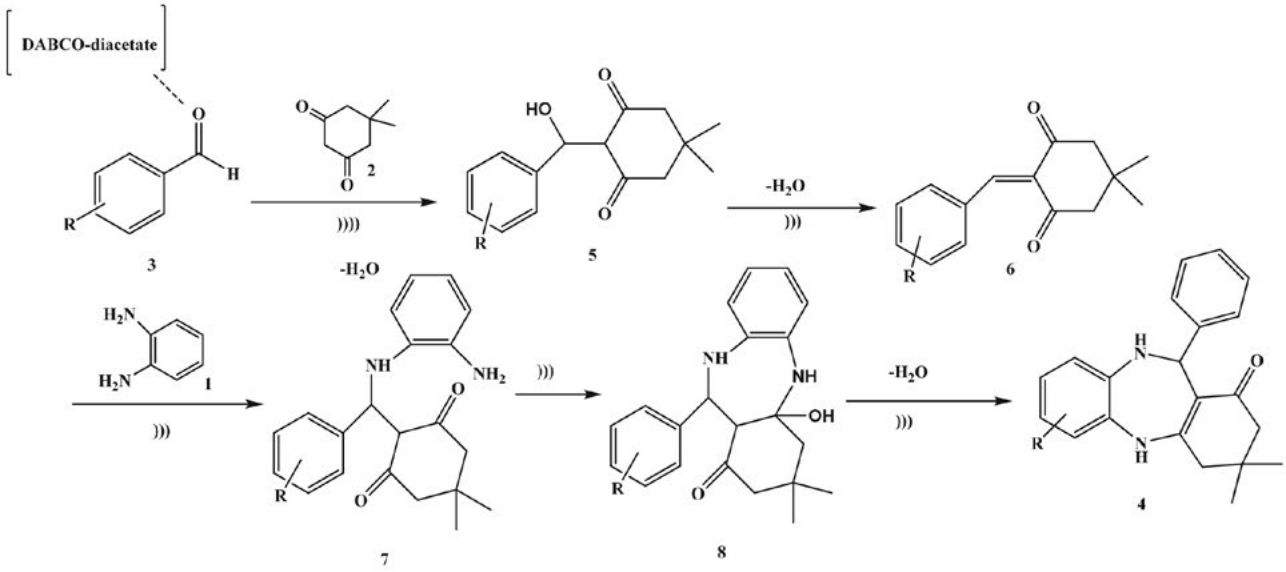
3. 1. Synthesis of DABCO-diacetate

This ionic liquid was synthesized as already described by Fekri et al.[27–29]

A mixture of 1,4-diaza-bicyclo[2.2.2]octane (10 mmol) and acetic acid (20 mmol) was irradiated using microwave (180 W) for 2 min at 100 °C three times. After completion of the reaction, the mixture was washed with diethyl ether (3×10 mL). The organic product was extracted from the liquid phase and evaporated under vacuum to produce the desired ionic liquid. The analytical data for DABCO-diAc is as follows: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 2H); 3.01 (s, 12H); 14.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.95; 44.54, 175.87 ppm.

3. 2. General Procedure for Synthesis of Benzodiazepines

A mixture of appropriate *o*-phenylendiamine (1 mmol), the corresponding aldehydes (1 mmol), dimedone and DABCO-diacetate (0.5 mmol) was placed into a Pyrex open vessel and irradiated in a water bath under silent conditions by ultrasound (45 kHz) at room temperature for the required reaction times as indicated in Table 2. Af-



Scheme 2. Plausible mechanistic method for synthesis of benzodiazepines.

ter completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in 20 mL of H_2O. The product was separated by filtration, recrystallized from EtOH and dried to afford the crystalline compounds **4a–j**. The ionic liquid was recovered for subsequent use. All synthesized compounds were characterized by their physical constant, IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

3,3-dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1H -dibenzo [b,e][1,4]diazepin-1-one *(4a)*: Off white solid; mp: 248–250 °C (reported 251–252 °C),[18] IR (KBr): ν 3473 (N-H stretch), 2987, 1727 (C=O stretch), 1606 (C=C aromatic), 1537, 1346, 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, CH_3), 2.2 (s, 2H, CH_2), 2.4 (s, 2H, CH_2), 5.05 (s, 1H, C-H), 6.73–6.87 (m, 5H, Ar), 7.09 (d, *J* = 8.2Hz, 2H, Ar), 7.37 (t, *J* = 7.8 Hz, 2H, Ar) ppm. HR-MS (m/z 334). Anal. calcd. for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 79.04; H, 7.86; N, 8.36.

11-(4-chlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one *(4b)*: Off white solid; mp: 238–240 °C (reported 239–240 °C),[18] IR (KBr): ν 3314 (N-H stretch), 3098, 2956, 1732 (C=O stretch), 1612 (C=C aromatic), 1476, 1343, 1098 (C-Cl stretch) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 6H, CH_3), 2.3 (s, 4H, CH_2), 5.05 (s, 1H, C-H), 6.68 (d, *J* = 8.4Hz, 2H, Ar), 6.87–6.93 (m, 2H, Ar), 7.15 (d, *J* = 8.0 Hz, 2H, Ar), 7.86 (d, *J* = 8.4 Hz, 2H, Ar) ppm. HR-MS (m/z 352). Anal. calcd. for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94. Found: C, 71.50; H, 6.06; N, 7.96.

11-(4-methoxyphenyl)-3,3-dimethyl-2,3,4,5,10, 11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one *(4c):* Off white solid; mp: 198–200 °C (reported 203–205 °C),[18] IR (KBr): ν 3232 (N-H stretch), 3018, 2983, 1743 (C=O stretch), 1609 (C=C stretch), 1465, 1328, 1248 (C-O stretch), 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 6H, CH_3), 1.92 (s, 4H, CH_2), 3.82 (s, 3H, OCH_3), 5.12 (s, 1H, N-H), 7.29–7.34 (m, 2H, Ar), 7.66–7.70 (m, 3H, Ar), 8.27 (d, *J* = 8.4Hz, 1H, Ar), 8.53 (d, *J* = 8.0Hz, 1H, Ar), 8.87 (t, *J* = 1.6 Hz, 1H, Ar) ppm. HR-MS (m/z 348). Anal. calcd. for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.80; H, 6.98; N, 8.06.

3,3-dimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one *(4d)*: White solid; mp: 271–273 °C (reported 274–275 °C),[18] IR (KBr): ν 3214 (N-H stretch), 3098, 2956, 1731 (C=O stretch), 1609 (C=C aromatic), 1567 (NO_2 stretch), 1445, 1324 (NO_2 stretch), 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 6H, CH_3), 1.89 (s, 4H, CH_2), 5.08 (s, 1H, N-H), 6.87 (d, *J* = 8.2Hz, 2H, Ar), 7.11 (t, *J* = 7.5 Hz, 1H, Ar), 7.23–7.32 (m, 3H, Ar), 7.67 (d, *J* = 8.2Hz, 2H, Ar) ppm. HR-MS (m/z 379). Anal. calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.40; H, 5.88; N, 11.56.

3,3-dimethyl-11-(3-nitrophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one *(4e)*: Off white solid; mp: 262–264 °C, IR (KBr): ν 3314 (N-H stretch), 2987, 1742 (C=O stretch), 1600 (C=C aromatic), 1543 (NO_2 stretch), 1456, 1387 (NO_2 stretch), 1243 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (s, 6H, CH_3), 2.17 (s, 4H, CH_2), 5.09 (s, 1H, N-H), 7.16 (s, 1H, Ar), 7.32 (d, *J* = 8.6 Hz, 2H, Ar), 7.73 (d, *J* = 8.1Hz, 1H, Ar), 8.05–8.17 (m, 3H, Ar), 8.43 (d, *J* = 7.8Hz, 1H, N-H) ppm. HR-MS (m/z 379). Anal. calcd. for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.45; H, 5.85; N, 11.59.

3,3-dimethyl-11-(3-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one *(4f)*: White solid; mp: 248–250 °C, IR (KBr): ν 3231 (N-H), 3089, 2987, 1738 (C=O stretch), 1604 (C=C stretch), 1565, 1450, 1242, 1123 (C-Cl stretch) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 6H, CH_3), 2.1 (s, 4H, CH_2), 5.10 (s, 1H, C-H), 7.53 (t, *J* = 7.6Hz, 2H, Ar), 7.66 (d, *J* = 7.6 Hz, 2H, Ar), 8.08–8.12 (m, 1H, Ar), 8.15–8.17 (m, 2H, Ar), 8.20–8.23 (m, 1H) ppm. HR-MS (m/z 352). Anal. calcd. for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94. Found: C, 71.51; H, 6.03; N, 7.96.

11-(4-(dimethylamino)phenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo [b,e] [1,4] diazepin-1-one *(4g)*: White solid; mp: 231–232 °C (reported 232–233 °C),[30] IR (KBr): ν 3423 (N-H stretch), 2956, 1735 (C=O stretch), 1601 (C=C stretch), 1463, 1360, 1228, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 6H, CH_3), 2.07 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 2.56 (s, 6H, N $(CH_3)_2$), 5.04 (s, 1H, C-H), 7.01–7.03 (m, 2H, Ar), 7.55–7.57 (m, 2H, Ar), 7.73 (dd, *J* = 3.2Hz, *J* = 5.6Hz, 1H, Ar), 7.85 (d, *J* = 8.4 Hz, 2H, Ar) ppm. HR-MS (m/z 361). Anal. calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.62. Found: C, 76.46; H, 7.53; N, 11.66.

11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5, 10,11-hexahydro-1H-dibenzo[b,e][1,4] diazepin-1-one *(4h)* : Off white solid; mp: 198–200 °C (reported 203–205 °C),[18] IR (KBr): ν 3312 (N-H stretch), 3109, 2987, 1743 (C=O stretch), 1457, 1358, 1192 (C-Cl stretch) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (br s, 6H, CH_3), 1.85 (d, *J* = 7.2Hz, 2H, CH_2), 2.47 (d, *J* = 28.7Hz, 2H, CH_2), 5.30 (s, 1H, C-H), 7.09–7.14 (m, 1H, Ar), 7.17–7.19 (m, 1H, Ar), 7.20–7.22 (m, 1H, Ar), 7.23–7.29 (m, 2H, Ar), 7.53–7.55 (m, 1H, Ar), 7.75–7.79 (m, 1H, Ar) ppm. HR-MS (m/z 386). Anal. calcd. for $C_{21}H_{20}Cl_2N_2O$: C, 65.12; H, 5.20; N, 7.23. Found: C, 65.10; H, 5.23; N, 7.23.

11-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e] [1,4]diazepin-1-one *(4i)* White solid; mp: 209–210 °C, IR (KBr): ν 3652 (N-H stretch), 2956, 1733 (C=O stretch), 1608 (C=C stretch), 1460, 1375, 1259, 1097 (C-Cl stretch) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 6H, CH_3),

2.20 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 5.05 (s, 1H, C-H), 6.71–6.82 (m, 3H, Ar), 7.01 (s, 3H, Ar), 7.35–7.41 (m, 1H, Ar), 7.44 (s, 1H, Ar), 7.54–7.56 (m, 2H, Ar), 7.71–7.78 (m, 2H, Ar), 7.87 (d, *J* = 8.8 Hz, 2H, Ar) ppm. HR-MS (m/z 494). Anal. calcd. for $C_{30}H_{27}ClN_4O$: C, 72.79; H, 5.50; N, 11.32. Found: C, 72.75; H, 5.536; N, 11.33.

11-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one ***(4j)*** White solid; mp: 245–247 °C, IR (KBr): ν 3431 (N-H stretch), 2956, 1733 (C=O stretch), 1593 (C=C stretch), 1460, 1375, 1093 (C-Br stretch) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 6H, CH_3), 2.30 (s, 4H, CH_2), 5.05 (s, 1H, C-H), 7.01 (s, 2H, Ar), 7.39 (t, *J* = 7.2 Hz, 2H, Ar), 7.50–7.51 (m, 2H, Ar), 7.52–7.53 (m, 2H, Ar), 7.55–7.57 (m, 1H, Ar), 7.70–7.72 (m, 2H, Ar), 7.83 (d, *J* = 8.0 Hz, 3H, Ar) ppm. HR-MS (m/z 538). Anal. calcd. for $C_{30}H_{27}BrN_4O$: C, 66.79; H, 5.04; N, 10.39. Found: C, 66.76; H, 5.00; N, 10.38.

4. Conclusion

In conclusion, DABCO-diacetate was used under ultrasound irradiation as a mild and efficient protocol for synthesis of diazepines. This method can be very useful for synthesis because it offers a high yield and decreased reaction time. DABCO-diacetate is inexpensive, non-toxic and easy to handle, and can act as green media. Its simple work-up procedure, short reaction time and high yield of the product are additional advantages of this protocol.

5. Acknowledgement

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Povzetek

V prispevku je predstavljena enostavna in učinkovita metoda priprave benzodiazepinov v večkomponentni reakciji *o*-fenilendiamina, različnih aldehidov in 5,5-dimetilcikloheksan-1,3-diona (dimedona) v prisotnosti kisle bis ionske tekočine 1,4-diazabiciklo[2.2.2]oktanijevega diacetata, z uporabo ultrazvoka. Uporabljeno ionsko tekočino lahko regeneriramo in ponovno uporabimo. Metoda je enostavna in okolju prijazna, omogoča enostavno izolacijo, mile reakcijske pogoje in odličen izkoristek v kratkem reakcijskem času. Vse pripravljene spojine so bile okarakterizirane z IR, ^{1}H NMR in masno spektrometrijo ter elementno analizo.