Chinese Journal of Catalysis 36 (2015) 734–741

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/chnjc

Article

Efficient, environmentally benign, one-pot procedure for the synthesis of 1,5-benzodiazepine derivatives using *N*-methyl-2-pyrrolidonium hydrogen sulphate as an ionic liquid catalyst under solvent-free conditions

Hossein Naeimi *, Hossein Foroughi

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, 87317, Iran

ARTICLE INFO

Article history:
Received 22 December 2014
Accepted 23 January 2015
Published 20 May 2015

Keywords:
Ionic liquid
Benzodiazepine
Solvent-free conditions
Dimedone

ABSTRACT

A powerful and environmentally benign method has been developed for the one-pot synthesis of 4-substituted-1,5-benzodiazepines via the three-component reaction of a series of aldehydes with dimedone and *o*-phenylenediamine using [H-NMP][HSO_4] as a Brönsted acidic ionic liquid catalyst under solvent-free conditions. The key benefits of this new method over existing techniques include high yields, the use of a green catalyst, short reaction times and facile catalyst separation.

1. Introduction

Fused 1,5-benzodiazepines are a highly valuable class of organic compounds that posses a wide variety of interesting biological properties [1–7]. For example, 1,5-dibenzodiazepine derivatives have been reported to exhibit inhibitory activities towards hepatitis C virus (HCV) NS5B [8] and HIV-1 protease [9,10], as well as finding numerous applications in medicinal chemistry [11], where they have been used as anti-inflammatory [12], hypnotic [13], anticoagulant [14], antibacterial [15], antidepressant [16], antiepileptic [17,18] and analgesic [19] agents. Several methods have been reported for the synthesis of 1,5-benzodiazepine derivatives *via* the condensation of *o*-phenylenediamine and dimedone with various aldehydes or ketones in the presence of a wide variety of Brönsted acid catalysts, including acyl chlorides [8,9] oxalic acid in water [20], acetic acid in refluxing ethanol [21,22], HCl in ethanol [23], acetic acid in toluene [24] and H_2SO_4 in water [25]. Several other methods have also been developed for the synthesis of 1,5-benzodiazepine derivatives, such as the cycloaddition reaction of 2,2-dihydroxy-1-phenylethanone with an *o*-phenylenediamine derivative and dimedone [26], the hetero-Cope rearrangement and the condensation of a 2-formyl benzoic acid substrate with an *o*-phenylenediamine derivative and tetronic acid in water under microwave irradiation conditions [27].

A multi-component reaction (MCR) is a chemical transformation involving the combination of three or more different starting materials in a single one-pot procedure to give a complex product. MCRs are useful tools in organic synthesis because they can be used to generate complex molecular architectures in one pot from simple starting materials [28–31]. Research towards the development of MCRs has grown considerably during the last decade, and several environmentally

* Corresponding author. Tel: +98-315-5912388; Fax: +98-315-5912397; Email: naeimi@kashanu.ac.ir
DOI: 10.1016/S1872-2067(14)60304-1 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 36, No. 5, May 2015

friendly and high yielding MCRs have been reported for the production of a wide range of interesting organic compounds from readily available and commercially inexpensive starting materials [32,33].

As part of our ongoing research towards the application of catalysts in organic synthesis [28–33], we recently became interested in the use of catalysts in MCRs. Herein, we report the development of an efficient method for the synthesis of 4-substituted-1,5-benzodiazepines via the one-pot MCR of a series of aldehydes with *o*-phenylenediamine and dimedone (Scheme 1). This reaction provided facile access to the target molecules in high yields over short reaction times using [H-NMP][HSO_4] as an ionic liquid catalyst. Furthermore, this method is environmentally benign and robust, and involves easy separation and work-up procedures.

2. Experimental

2.1. General

All of the reagents used in the current study were purchased from Merck, Aldrich, CDH and Fluka and used without further purification.

Fourier transform infrared (FT-IR) spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer. Ultraviolet (UV-Vis) spectra were obtained in $CDCl_3$ on a Perkin-Elmer 550 S spectrophotometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) were recorded in DMSO and $CDCl_3$ solvents on a Bruker DRX-400 spectrometer using tetramethylsilane (TMS) as an internal reference. Elemental analyses (C, H, N) were conducted on a Carlo ERBA Model EA 1108 analyzer. Electrospray ionization mass spectroscopy (ESI-MS) experiments were performed on an Agilent Technology (HP) 5973 instrument at an ionization potential of 70 eV. Melting points (M.P) determined on a Thermo Scientific 9300 melting point apparatus. The purities of the substrates and reaction monitoring were accomplished by TLC on silica-gel PolyGram SILG/UV 254 plates (Merck).

2.2. Preparation of N-methyl-2-pyrrolidonium hydrogen sulfate [H-NMP][HSO_4] ionic liquid

1-Methyl-2-pyrolidone (0.2 mol) was charged into a 250-mL three-necked flask containing a magnetic stirrer. An equimolar amount of concentrated H_2SO_4 (98 wt%) was then added to the flask in a drop-wise manner, and the resulting mixture was heated at 80 °C for 12 h. The mixture was then cooled to ambient and washed three times with ether to remove any non-ionic residues before being dried under vacuum on a rotary evaporator at 25 °C to [H-NMP][HSO_4] as a clear, viscous ionic liquid. The pH of the resulting ionic liquid (10% *w*/*v*) was determined to be 1.2.

2.3. General procedure for the synthesis of 4-substituted-1,5-benzodiazepines (**3a–3o**)

Dimedone (1 mmol), *o*-phenylenediamine (1 mmol) and an aromatic aldehyde (1 mmol) were added to [H-NMP][HSO_4] (0.14 g) under solvent-free conditions, and the resulting mixture was stirred at 100 °C for the stipulated time. Upon completion of the reaction, as determined by TLC (1:1 – ethyl acetate:petroleum ether), the mixture was cooled to room temperature and washed by water before being filtered to remove the catalyst. The resulting oil was crystallized from a 6:5 (*v*/*v*) mixture of methanol and water to give a residue, which was purified by recrystallization from ethanol. The products were characterized by a comparison of their physical and spectral data with those of the authentic samples.

3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3a**). Yield: 75%; pale green solid, m.p. = 246–248 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 360 nm; IR (KBr, cm^{-1}): υ 3296, 3237, 3057, 2955, 1584, 1384, 1530, 1329, 1424, 1277; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.03 (s, 3H, CH_3–), 1.08 (s, 3H, CH_3), 2.11 (q, 2H, *J* = 16.0 Hz, CH_2), 2.56 (s, 2H, CH_2–C=O), 5.71 (s, 1H, N–H), 6.08 (s, 1H , C–H), 6.47–6.57 (m, 3H, Ar), 6.89 (d, 1H, *J* = 8.0 Hz, Ar), 6.95 (t, 1H, *J* = 8.0 Hz, Ar), 7.0–7.1 (m, 3H, Ar), 8.15 (d, 1H, *J* = 4.0 Hz, Ar), 8.69 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 27.95, 29.06, 32.21, 44.74, 50.05, 56.49, 110.68, 119.87, 120.44, 121.01, 122.98, 126.11, 127.7, 127.98, 131.49, 138.84, 145.1, 155.12, 192.52; ESI-MS (*m*/*z*, %): 318 (M^+, 26), 241 (100), 149 (52), 83 (45), 77 (34), 57 (85), 55 (62); Anal. Calcd. for $C_{21}H_{22}N_2O$: C 79.21, H 6.96, N 8.80; Found: C 79.24, H 6.98, N 8.84.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3b**). Yield: 81%; yellow solid, m.p. = 280–281 °C (decomp.); R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 348 nm; IR (KBr, cm^{-1}): υ 3355, 3279, 3181, 2955, 1591, 1381, 1511, 1339, 1425, 1275; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 0.99 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.14 (q, 2H, *J* = 16.0 Hz, CH_2), 2.53 (s, 2H, CH_2–C=O), 5.64 (s, 1H, N–H), 5.87 (s, 1H, C–H), 6.43 (d, 1H, *J* = 6.4 Hz, Ar), 6.55–6.61 (m, 2H, Ar), 6.9 (d, 1H, *J* = 6.4 Hz, Ar), 7.21 (d, 2H, *J* = 8.8 Hz, Ar), 7.84 (d, 2H, *J* = 8.8 Hz, Ar), 8.58 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.09, 28.80, 32.20, 44.82, 49.93, 56.63, 109.44, 120.52, 120.75, 121.09, 123.08, 123.43, 128.57, 131.39, 138.03, 146.05, 153.05, 155.05, 192.85; ESI-MS (*m*/*z*, %): 397 (M^+, 29), 241 (100), 149 (66), 83 (51), 77 (32), 57 (39), 55 (47); 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-2,3,4,5,10,11-hexahydro-11-[(2-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3c**). Yield: 80%; orange solid, m.p. = 230–232 °C (decomp.); R_f = 0.281 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max}= 346 nm; IR (KBr, cm^{-1}): υ 3378, 3303, 3069, 2957, 1591, 1381, 1528, 1332, 1473, 1279; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.01 (q, 2H, *J* = 16.0 Hz, CH_2), 2.58 (s, 2H, CH_2–C=O), 5.04 (s, 1H, N–H), 6.01 (s, 1H, C–H), 6.32 (d, 1H, *J* = 8.0 Hz, Ar), 6.58 (t, 1H, *J* = 8.0 Hz, Ar), 6.67 (t, 1H, *J* = 8.0 Hz, Ar), 6.79 (d, 1H, *J* = 8.0 Hz, Ar), 7.04 (d, 1H, *J* = 8.0 Hz, Ar), 7.14–7.2 (m, 2H, Ar), 7.74 (d, 1H, *J* = 8.0 Hz, Ar), 8.91 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.11, 28.82, 32.22, 44.87, 49.91, 56.62, 109.46, 120.53, 120.78, 121.07, 123.1, 123.46, 126.14, 128.56, 128.59, 131.38, 138.06, 146.03, 153.08, 155.08, 192.89; ESI-MS (*m*/*z*,

%): 363 (M^+, 26), 241 (100), 149 (55), 83 (36), 77 (42), 57 (49), 55 (62); Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56; Found: C 69.46, H 5.85, N 11.60.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-nitro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3d**). Yield: 78%; pale yellow solid, m.p. = 195–197 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max}= 348 nm; IR (KBr, cm^{-1}): υ 3375, 3328, 3049, 2959, 1589, 1383, 1529, 1345, 1431, 1277; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.05 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.14 (q, 2H, J = 16.0 Hz, CH_2), 2.58 (s, 2H, CH_2–C=O), 5.81 (s, 1H, N–H), 6.20 (s, 1H, C–H), 6.50 (d, 1H, J =5.2 Hz, Ar), 6.51-6.6 (m, 2H, Ar), 6.9 (d, 1H, J = 7.2 Hz, Ar), 7.29 (t, 1H, J = 8.0 Hz, Ar), 7.45 (d, 1H, J = 8.0 Hz, Ar), 7.81 (d, 1H, J = 9.2 Hz, Ar), 7.98 (s, 1H, Ar), 8.79 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.1, 28.81, 32.24, 44.86, 49.93, 56.64, 109.47, 120.56, 120.76, 121.06, 123.11, 123.47, 126.16, 128.49, 128.56, 131.39, 138.09, 146.05, 153.1, 155.09, 192.86; ESI-MS (*m/z*, %): 363 (M^+, 30), 241 (100), 149 (38), 83 (40), 77 (41), 57 (39), 55 (58); Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C 69.41, H 5.82, N 11.56; Found: C 69.45, H 5.86, N 11.57.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-chloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3e**). Yield: 85%; pale green solid, m.p. = 235–237 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max}= 344 nm; IR (KBr, cm^{-1}): υ 3301, 3238, 3054, 2956, 1587, 1381, 1532, 1329, 1426, 1278; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.0 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.11 (q, 2H, J = 16.0 Hz, CH_2), 2.52 (s, 2H, CH_2–C=O), 5.73 (s, 1H, N–H), 5.78 (s, 1H, C–H), 6.45 (d, 1H, J = 8.2 Hz, Ar), 6.55 (m, 2H, Ar), 6.88 (d, 1H, J = 8.2 Hz, Ar), 6.98 (d, 2H, J = 8.4 Hz, Ar), 7.01 (d, 1H, J = 8.4 Hz, Ar), 8.61 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.17, 28.69, 32.24, 44.84, 49.90, 56.43, 109.38, 120.62, 120.72, 121.05, 123.11, 123.28, 128.36, 131.45, 138.06, 146.08, 150.02, 152.06, 192.81; ESI-MS (*m/z*, %): 362 (M^+, 33), 354 ($M+2^+$, 11), 241 (100), 149 (57), 83 (35), 77 (28), 57 (68), 55 (53); Anal. Calcd. for $C_{21}H_{21}ClN_2O$: C 71.48, H 6.0, N 7.94; Found: C 71.53, H 6.5, N 7.98.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-chloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3f**). Yield: 78%; white solid, m.p. = 239–240 °C (decomp.); R_f = 0.281 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max}= 348 nm; IR (KBr, cm^{-1}): υ 3292, 3235, 3062, 2959, 1589, 1382, 1515, 1314, 1422, 1278; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.09 (q, 2H, J = 16.0 Hz, CH_2), 2.57 (s, 2H, CH_2–C=O), 5.07 (s, 1H, N–H), 6.01 (s, 1H, C–H), 6.33 (d, 1H, J = 7.2 Hz, Ar), 6.44–6.62 (m, 2H, Ar), 6.7 (d, 1H, J = 7.6 Hz, Ar), 6.82 (d, 1H, J = 7.6 Hz, Ar), 6.85–7.0 (m, 2H, Ar), 7.20 (d, J = 7.6 Hz, 1H, Ar), 8.77 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.17, 28.72, 32.26, 44.84, 49.88, 56.42, 109.32, 120.61, 120.66, 121.12, 123.13, 123.42, 126.11, 128.53, 128.62, 131.42, 138.04, 146.06, 149.55, 151.06, 192.82; ESI-MS (*m/z*, %): 352 (M^+, 36), 354 ($M+2^+$, 12), 241 (100), 149 (52), 83 (49), 77 (33), 57 (42), 55 (51); Anal. Calcd. for $C_{21}H_{21}ClN_2O$: C 71.48, H 6.0, N 7.94; Found: C 71.54, H 6.6, N 7.99.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(2,3-dichloro) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3g**). Yield: 82%; pale green solid, m.p. = 256–358 °C (decomp.); R_f = 0.281 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 348 nm; IR (KBr, cm^{-1}): υ 3379, 3301, 3060, 2958, 1589, 1380, 1532, 1332, 1423, 1289; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.12 (q, 2H, J = 16.0 Hz, CH_2), 2.56 (s, 2H, CH_2–C=O), 4.96 (s, 1H, N–H), 6.07 (s, 1H, C–H), 6.30 (d, 1H, J = 7.6 Hz, Ar), 6.53–6.60 (m, 2H, Ar), 6.62 (d, 1H, J = 7.2 Hz, Ar), 6.75 (t, 1H, J = 8.0 Hz, Ar), 6.91 (d, 1H, J = 7.6 Hz, Ar), 7.08 (d, 1H, J = 7.6 Hz, Ar), 8.64 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.14, 28.67, 32.23, 44.81, 49.92, 56.29, 109.10, 120.68, 121.08, 121.35, 123.65, 126.13, 126.84, 128.83, 131.71, 132.05, 132.57, 137.33, 143.52, 156.12, 192.90; ESI-MS (*m/z*, %): 386 (M^+, 24), 388 ($M+2^+$, 14), 390 ($M+4^+$, 4), 351 (52), 241 (100), 149 (25), 83 (34), 77 (24), 69 (52), 57 (43), 55 (54); Anal. Calcd. for $C_{21}H_{20}Cl_2N_2O$: C 65.12, H 5.20, N 7.23; Found: C 65.15, H 5.24, N 7.26.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(2,4-dichloro) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3h**). Yield: 83%; pale green solid, m.p. = 230–232 °C (decomp.); R_f = 0.281 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 347 nm; IR (KBr, cm^{-1}): υ 3303, 3241, 3055, 2957, 1590, 1382, 1533, 1330, 1468, 1278; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.11 (q, 2H, J = 16.0 Hz, CH_2), 2.57 (s, 2H, CH_2–C=O), 4.99 (s, 1H, N–H), 5.99 (s, 1H, C–H), 6.34 (d, 1H, J = 7.6 Hz, Ar), 6.56–6.63 (m, 2H, Ar), 6.65 (d, 1H, J = 8.4 Hz, Ar), 6.79 (d, 1H, J = 8.0 Hz, Ar), 6.92 (d, 1H, J = 7.2 Hz, Ar), 7.22 (s, 1H, Ar), 8.74 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.16, 28.69, 32.26, 44.78, 49.93, 56.31, 109.12, 120.72, 121.06, 121.37, 123.68, 126.15, 126.88, 128.87, 131.68, 132.04, 132.59, 137.38, 149.57, 156.18, 192.92; ESI-MS (*m/z*, %): 386 (M^+, 26), 388 ($M+2^+$, 16), 390 ($M+4^+$, 6), 241 (100), 149 (66), 83 (57), 77 (30), 57 (65), 55 (45); Anal. Calcd. for $C_{21}H_{20}Cl_2N_2O$: C 65.12, H 5.20, N 7.23; Found: C 65.16, H 5.25, N 7.28.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-chloro-3-nitro) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3i**). Yield: 77%; pale yellow solid, m.p. = 196–197 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-VIS: λ_{max} = 348 nm; IR (KBr, cm^{-1}): υ 3305, 3240, 3039, 2958, 1600, 1381, 1532, 1339, 1426, 1276; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.02 (s, 3H, CH_3), 1.07 (s, 3H, CH_3–), 2.13 (q, 2H, J = 16.0 Hz, CH_2), 2.54 (s, 2H, CH_2–C=O), 5.77 (s, 1H, N–H), 6.08 (s, 1H, C–H), 6.50 (d, 1H, J = 8.0 Hz, Ar), 6.59 (m, 2H, Ar), 6.91 (d, 1H, J = 8.0 Hz, Ar), 7.24–7.29 (m, 2H, Ar), 7.68 (s, 1H, Ar), 8.74 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.04, 28.75, 32.19, 44.69, 49.84, 56.02, 109.07, 120.75, 120.85, 121.18, 123.36, 123.63, 124.85, 131.21, 131.44, 132.66, 138.04, 146.18, 147.33, 155.94, 192.9; ESI-MS (*m/z*, %): 397 (M^+, 21), 399 ($M+2^+$, 4), 241 (100), 149 (47), 83 (47), 77 (27), 69 (81), 57 (91), 55 (67); Anal. Calcd. for $C_{21}H_{20}ClN_3O_3$: C 63.40, H 5.07, N 10.56; Found: C 63.46, H 5.13, N 10.64.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-methyl)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3j**). Yield: 76%; pale green solid, m.p. = 224–226 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 361 nm; IR (KBr, cm^{-1}): υ 3307, 3245, 3050, 2959, 1595, 1380, 1538, 1327, 1471, 1276; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.01 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.01 (q, 2H, J = 16.0 Hz, CH_2), 2.01 (s, 3H, Me), 2.52 (s, 2H, CH_2–C=O), 5.69 (s, 1H, N–H), 5.69 (s, 1H, C–H), 6.45 (d, 1H, J = 7.6 Hz, Ar), 6.5–6.6 (m, 2H, Ar), 6.81 (d, 2H, J = 7.6 Hz, Ar), 6.86 (d, 1H, J = 8.4 Hz, Ar), 6.92 (d, J = 7.6 Hz, 2H, Ar), 8.53 (s, 1H,

N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 27.85, 29.16, 32.23, 44.71, 50.09, 55.07, 56.51, 110.69, 119.86, 120.47, 121.07, 122.96, 126.35, 127.58, 127.94, 131.53, 138.87, 145.11, 155.14, 192.56; ESI-MS (*m/z*, %): 332 (M^+, 43), 241 (100), 149 (55), 83 (39), 77 (41), 57 (77), 55 (46); Anal. Calcd. for $C_{22}H_{24}N_2O$: C 79.48, H 7.28, N 8.43; Found: C 79.53, H 7.35, N 8.49.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-methoxy) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3k**). Yield: 73%; pale cream solid, m.p. = 229–231 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 364 nm; IR (KBr, cm^{-1}): υ 3301, 3238, 3015, 2956, 1587, 1382, 1535, 1327, 1426, 1279; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10 (s, 3H, Me), 2.19 (s, 1H, C–H), 2.31 (q, 2H, *J* = 16.0 Hz, CH_2), 2.52 (s, 2H, CH_2–C=O), 5.7 (s, 1H, N–H), 6.45 (d, 1H, *J* = 7.6 Hz, Ar), 6.5–6.58 (m, 2H, Ar), 6.81 (d, 2H, *J* = 8.0 Hz, Ar), 6.87 (d, 1H, *J* = 8.4 Hz, Ar), 6.91(d, *J* = 8.0 Hz, 2H, Ar), 8.55(s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 27.82, 29.19, 32.23, 44.75, 50.04, 54.11, 56.42, 110.67, 111.46, 113.56, 119.93, 120.41, 121.05, 123.06, 128.89, 131.46, 138.89, 146.66, 155.21, 192.08; ESI-MS (*m/z*, %): 348 (M^+, 67), 241 (100), 149 (36), 83 (35), 77 (42), 57 (43), 55 (52); Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04; Found: C 75.86, H 6.97, N 8.07.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-methoxy) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3l**). Yield: 74%; pale cream solid, m.p. = 217–218 °C (decomp.); R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 361 nm; IR (KBr, cm^{-1}): υ 3369, 3306, 3063, 2955, 1599, 1384, 1534, 1327, 1425, 1236; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.07 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.12 (q, 2H, *J* = 16.0 Hz, CH_2), 2.57 (s, 2H, CH_2–C=O), 3.89 (s, 3H, Me), 5.0 (s, 1H, N–H), 5.95 (s, 1H, C–H), 6.28 (d, 1H, *J* = 7.6 Hz, Ar), 6.45–6.55 (m, 3H, Ar), 6.58 (d, 1H, *J* = 7.6 Hz, Ar), 6.75 (d, 1H, *J* = 8.4 Hz, Ar), 6.86 (d, *J* = 7.6 Hz, 1H, Ar), 6.94 (t, 1H, *J* = 8.0 Hz, Ar), 8.59 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 27.95, 29.08, 32.32, 44.77, 50.05, 54.79, 56.43, 110.75, 111.47, 113.56, 119.89, 120.06, 120.40, 121.05, 123.06, 128.85, 131.47, 138.86, 146.65, 155.26, 159.24, 192.65; EI-MASS (*m/z*, %): 348 (M^+, 42), 241 (100), 149 (52), 83 (61), 77 (27), 57 (85), 55 (72); Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04; Found: C 75.9, H 6.98, N 8.10.

3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-methoxy) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3m**). Yield: 76%; pale green solid, m.p. = 225–227 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max}= 364 nm; IR (KBr, cm^{-1}): υ 3326, 3278, 3050, 2954, 1586, 1382, 1538, 1332, 1497, 1274; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.12 (q, 2H, *J* = 16.0 Hz, CH_2), 2.52 (s, 2H, CH_2–C=O), 3.55 (s, 3H, Me), 5.64 (s, 1H, N–H), 5.72 (s, 1H, C–H), 6.44–6.48 (m, 2H, Ar), 6.53–6.57 (m, 2H, Ar), 6.60 (s, 1H, Ar), 6.62 (d, 1H, *J* = 8.0 Hz, Ar), 6.86 (d, 1H, *J* = 7.6 Hz, Ar), 6.91 (t, 1H, *J* = 8.0 Hz, Ar), 8.53 (s, 1H, N–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 27.81, 29.18, 32.21, 44.72, 50.02, 54.99, 56.41, 110.64, 111.44, 113.54, 119.91, 120.08, 120.43, 121.03, 123.03, 128.87, 131.44, 138.87, 146.63, 155.24, 159.25, 192.60; ESI-MS (*m/z*, %): 348 (M^+, 72), 241 (100), 149 (45), 83 (31), 77 (37), 69 (34), 57 (35), 55 (42); Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C 75.83, H 6.94, N 8.04; Found: C 75.86, H 6.97, N 8.07.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(2-hydroxy) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3n**). Yield: 71%; pale cream solid, m.p. = 201–202 °C; R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-vis: λ_{max} = 360 nm; IR (KBr, cm^{-1}): υ 3622, 3302, 3238, 3100, 2957, 1599, 1384, 1528, 1328,1424,1276; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.13 (q, 2H, *J* = 16.0 Hz, CH_2), 2.56 (s, 2H, CH_2–C=O), 5.18 (s, 1H, N–H), 5.93 (s, 1H, C–H), 6.35 (t, 2H, *J* = 7.2 Hz, Ar), 6.38 (d, 1H, *J* = 6.8 Hz, Ar), 6.50–6.55 (m, 3H, Ar), 6.66 (d, 1H, *J* = 8.0 Hz, Ar), 6.76 (t, 1H, *J* = 7.2 Hz, Ar), 6.86 (d, *J* = 7.2 Hz, 1H, Ar), 8.53 (s, 1H, N–H), 9.35 (s, 1H, O–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.04, 29.05, 32.22, 44.71, 50.11, 56.39, 110.89, 113.22, 115.08, 118.65, 119.77, 120.43, 120.96, 122.97, 128.71, 131.47, 138.95, 146.62, 155.07, 157.26, 192.55; EI-MASS (*m/z*, %): 348 (M^+, 23), 241 (100), 149 (47), 83 (35), 77 (46), 57 (40), 55 (48); Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.38; Found: C 75.47, H 6.68, N 8.43.

3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-[(3-hydroxy) phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3o**). Yield: 75%; pale green solid, m.p. = 287–289 °C (decomp.); R_f = 0.125 (1:1 – ethyl acetate/*n*-hexane); UV-VIS: λ_{max}= 348 nm; IR (KBr, cm^{-1}): υ 3447, 3307, 3048, 2927, 1585, 1386, 1519, 1332, 1425, 1275; ^{1}H NMR (DMSO+$CDCl_3$, 400 MHz): δ 1.03 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.11 (q, 2H, *J* = 16.0 Hz, CH_2), 2.54 (s, 2H, CH_2–C=O), 5.60 (s, 1H, N–H), 5.94 (s, 1H, C–H), 6.37 (d, 1H, *J* = 7.6 Hz, Ar), 6.48–6.57 (m, 5H, Ar), 6.82 (t, 1H, *J* = 7.6 Hz, Ar), 6.89 (d, 1H, *J* = 7.6 Hz, Ar), 8.64 (s, 1H, N–H), 8.90 (s, 1H, O–H); ^{13}C NMR (DMSO+$CDCl_3$, 100 MHz): δ 28.02, 29.09, 32.20, 44.74, 50.07, 56.36, 110.86, 113.19, 115.05, 118.60, 119.75, 120.39, 120.98, 122.94, 128.74, 131.43, 138.93, 146.59, 155.04, 157.21, 192.50; ESI-MS (*m/z*, %): 334 (M^+, 34), 241 (100), 149 (61), 83 (57), 77 (25), 69(84), 57 (90), 55 (72); Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.38; Found: C 75.46, H 6.66, N 8.42.

3. Results and discussion

3.1. Catalytic performance

Ionic liquids (ILs) have been successfully used as solvents and catalyst in a wide variety of different reactions [34–36], and have the potential to be used in numerous other applications in organic synthesis. In a continuation of our recent work towards the development of Lewis and Brönsted acid catalyzed synthetic methodologies [37–40], we became interested in the use of ILs as catalysts for MCRs. The ^{1}H NMR spectrum of the IL [H-NMP][HSO_4] is shown in Fig. 1. This material was synthesized according to literature procedures and evaluated as a catalyst in the MCR of X and Y with Z [41–43]. The peak in the ^{1}H NMR spectrum of [H-NMP][HSO_4] at 2.41 ppm was assigned to the three protons of the methyl group belonging to the NMP moiety, and the peaks at 1.61, 2.05, and 3.10 ppm were attributed to six protons of the pyrrolidinium ring.

A general method has been developed in this study for the synthesis of 4-substituted-1,5-benzodiazepines and related heterocycles via the condensation reaction of an aromatic aldehyde with *o*-phenylenediamine and dimedone, followed by the Knoevenagel cyclization of the resulting adduct (shown in Scheme 1).

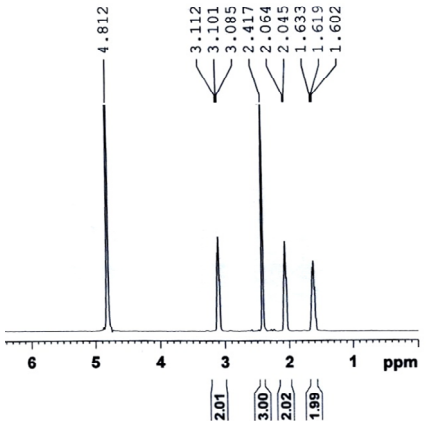
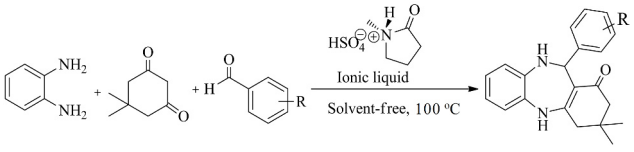


Fig. 1. ^{1}H NMR spectrum of [H-NMP][HSO_4] in D_2O.

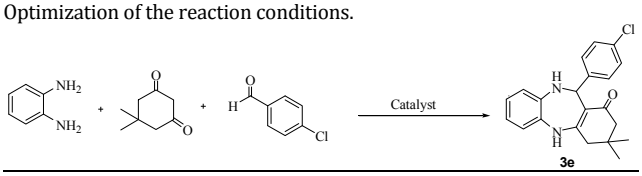


Scheme 1. Synthesis of 4-substituted-1,5-benzodiazepines under solvent-free conditions.

To highlight the advantages of this newly developed method, we have compared the results of the current study with those reported in literature for the same transformation using different conditions [20–25] (Table 1). The reaction of dimedone with *o*-phenylenediamine and benzaldehyde to give 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[phenyl]-1H-dibenzo [b,e][1,4]diazepin-1-one was selected as a model reaction to compare the different methods. The methods themselves were compared on the basis of the catalyst, reaction conditions, reaction time and percentage yield of the product. The results of this comparison revealed that our newly developed method is more efficient, faster and simpler than some of the existing methods.

When the reaction was carried out under solvent-free conditions at 60 °C, the product was isolated in 55% yield (Table 2, entry 9). Furthermore, when the reaction was conducted in the presence of 0.14 g of the [H-NMP][HSO_4] catalyst at 100 °C, the desired product **3e** was isolated in a 85% yield (Table 2, entry 11). These experiments therefore demonstrate that [H-NMP][HSO_4] works well as a catalyst for this transformation.

Table 2
Optimization of the reaction conditions.

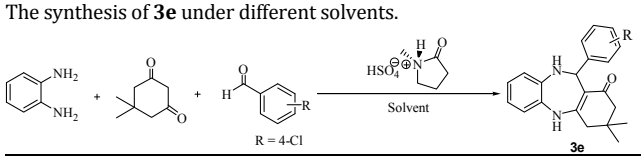


Entry	Catalyst	Time (min)	Temp. (°C)	Isolated yield (%)
1	$MeSO_3H$	50	Reflux [b]	65
2	CF_3COOH	40	Reflux	60
3	CuI	16	Reflux	55
4	Fe_3O_4	16	Reflux	55
5	MgO	13	Reflux	25
6	ZnO	16	Reflux	50
7	ZnS	14	Reflux	55
8	None	40	Reflux	40
9	Ionic liquid [a]	20	60	55
10	Ionic liquid	20	80	75
11	Ionic liquid	15	100	85
12	Ionic liquid	15	120	85

Reaction conditions: catalyst 10 mol%, *o*-phenylenediamine 1 mmol, dimedone 1 mmol, *p*-Cl-benzaldehyde 1 mmol. [a] *N*-methyl-2-pyrrolidiniume hydrogen sulfate [H-NMP][HSO_4] (0.14 g). [b] Reflux in EtOH.

The results of the optimization experiments indicated that the MCR was being catalyzed much more effectively by [H-NMP][HSO_4] that any of the other catalysts tested, because the desired product was obtained in much higher yields over shorter reaction times when the reaction was conducted in the presence of this IL catalyst (Table 2, entries 1–12).

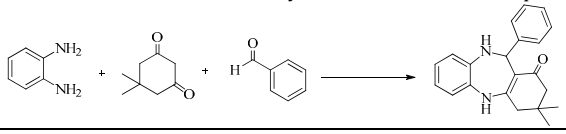
Table 3
The synthesis of **3e** under different solvents.



Entry	Solvent	Time (min)	Temp. (°C)	Isolated yield (%)
1	*n*-Hexane	16	Reflux	10
2	CH_2Cl_2	17	Reflux	30
3	H_2O	18	Reflux	40
4	CH_3CN	16	Reflux	20
5	MeOH	14	Reflux	45
6	EtOH	20	Reflux	50
7	None	15	100	85

Reaction conditions: [H-NMP][HSO_4] (0.14 g), *o*-phenylenediamine 1 mmol, dimedone 1 mmol, *p*-Cl-benzaldehyde 1 mmol.

Table 1
Comparison of the current method with several literature methods for the synthesis of 1,5-benzodiazepines.



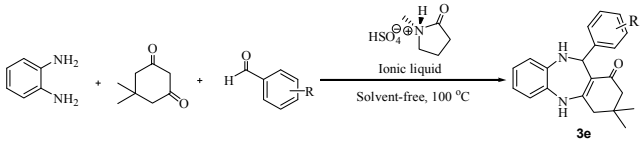
Entry	Catalyst	Reaction conditions	Time (min)	Yield (%)	[Ref.]
1	Oxalic acid (40 mol %)	Water, Reflux at 100 °C	120	84	20
2	Acetic acid (excess)	Ethanol, Reflux, 2 steps reaction	100	65	21
3	HCl	Ethanol, Reflux	150	60	23
4	Acetic acid (excess)	*i*-PrOH, Reflux at 120 °C	70	62	24
5	*p*-Toluenesulfonic acid and acetic acid	2 Steps reaction, Reflux	360	55	25
6 *	[H-NMP][HSO_4]	Solvent free, 100 °C	18	75	—

* Present study.

This method is complementary to the classical methods used for the synthesis of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-11-[(4-chloro)phenyl]-1H-dibenzo[b,e][1,4]diazepin-1-one (**3e**). The performance of the reaction was also evaluated using a variety of different solvents, including *n*-hexane, CH_2Cl_2, water, CH_3CN, MeOH and EtOH under refluxing conditions. The results of these experiments revealed that the use of a solvent led to a significant reduction in the yield of the desired product **3e** in all cases compared with the yield obtained under solvent-free conditions (Table 3, entries 1–7).

The effect of the catalyst loading was also investigated under solvent-free conditions (Table 4). The results of these experiments revealed that the optimum loading of the IL catalyst was 0.14 g, which gave the desired product **3e** in 85% yield

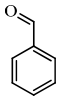
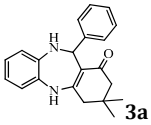
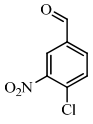
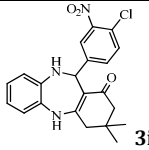
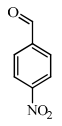
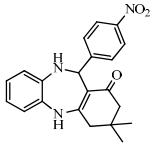
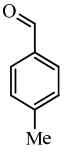
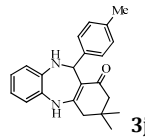
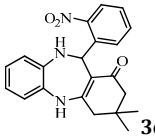
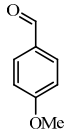
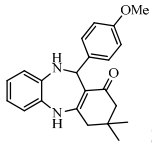
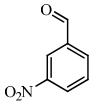
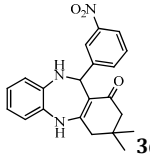
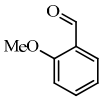
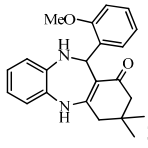
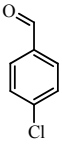
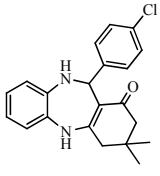
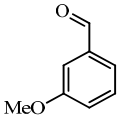
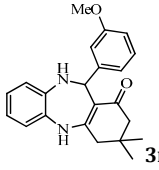
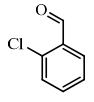
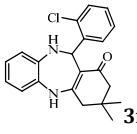
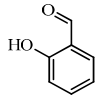
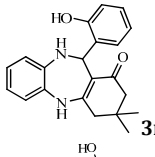
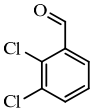
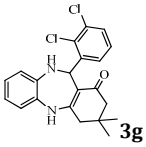
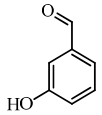
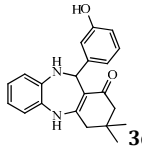
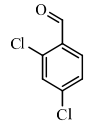
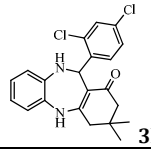
Table 4
The effect of the loading of the catalyst on the synthesis of **3e**.



Entry	Catalyst loading (g)	Time (min)	Isolated yield (%)
1	0.06	20	45
2	0.10	20	55
3	0.14	15	85
4	0.18	15	85
5	0.22	15	82

Reaction conditions: [H-NMP][HSO_4] as catalyst, *o*-phenylenediamine 1 mmol, dimedone 1 mmol, *p*-Cl-benzaldehyde 1 mmol, 100 °C.

Table 5
Synthesis of 4-substituted-1,5-benzodiazepine **3a–3o** in the presence of the [H-NMP][HSO_4] catalyst under solvent-free conditions.

Entry	Aldehyde	Product	Time (min)	Isolated yield (%)	m.p. (°C)	Entry	Aldehyde	Product	Time (min)	Isolated yield (%)	m.p. (°C)
1		 **3a**	18	75	246–248	9		 **3i**	14	84	196–197
2		 **3b**	14	81	280–281*	10		 **3j**	17	76	224–226
3		 **3c**	14	80	230–232*	11		 **3k**	18	73	229–231
4		 **3d**	15	78	195–197	12		 **3l**	18	74	217–218*
5		 **3e**	15	85	235–237	13		 **3m**	16	76	225–227
6		 **3f**	17	78	239–240*	14		 **3n**	19	71	201–202
7		 **3g**	15	82	256–258*	15		 **3o**	17	75	287–289*
8		 **3h**	13	83	230–232*						

Reaction conditions: *o*-phenylenediamine (1 mmol), aldehyde (1 mmol), dimedone (1 mmol) and [H-NMP][HSO_4] (0.14 g). * Decomposition point.

(Table 4, entry 3). Increasing or decreasing the loading of the catalyst did not lead to any further improvements in the yield of the reaction or a decrease in the reaction time.

With the optimized conditions in hand, we proceeded to investigate the scope and limitations of our newly developed method using a variety of different aldehydes (Table 5). The results of these reactions revealed that aldehydes bearing an electron-donating (e.g., CH_3 or CH_3O) or electron-withdrawing (e.g., NO_2 or Cl) group were well tolerated under the optimized conditions, with the corresponding 4-substituted-1,5-benzodiazepine products **3a–3o** being formed in good to high yields. Aliphatic aldehydes reacted smoothly to give the corresponding 4-substituted-1,5-benzodiazepines, albeit in lower yields (20%–25%) than the aromatic aldehydes (71%–85%).

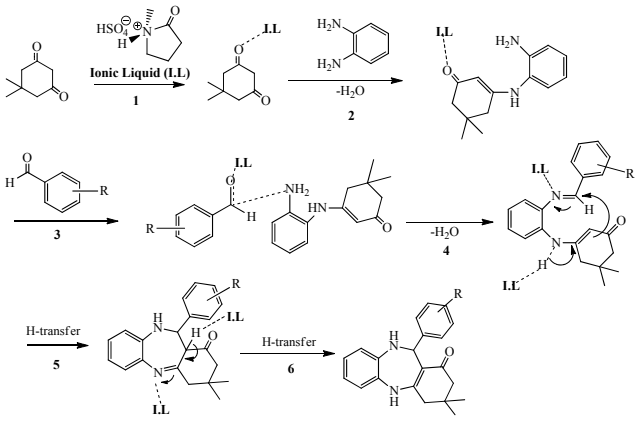
The structures of the resulting products were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and ESI-MS analyses. The FT-IR spectrum of **3i**, as a representative example, contained broad peaks at 3305 and 3240 cm^{-1}, which were attributed to the stretching vibrations of amine protons (2 NH groups). Furthermore, the bands at 3039 and 2958 cm^{-1} were attributed to the stretching vibrations of the CH, CH_2, and CH_3 groups in the molecules, whereas the strong bands at 1600 and 1381 cm^{-1} were attributed the stretching vibrations of carbonyl groups (C=O stretching). The FT-IR spectrum of **3i** also contained strong bands at 1532 and 1339 cm^{-1}, which indicated the presence of C–N stretching. The band at 1426 cm^{-1} in the FT-IR spectrum of **3i** was characteristic of a C=C stretching vibration, and the strong band at 1276 cm^{-1} confirmed the presence of C-O bond stretching. ^{1}H NMR analysis of compound **3i** revealed two singlets for the *gem*-dimethyl groups at δ = 1.02 and 1.07 ppm, as well as an AB quartet for the CH_2 protons at δ = 2.13 ppm with a coupling constant (J) of 16.0 Hz. The ^{1}H NMR spectrum of **3i** also contained a signal at δ = 2.54 ppm for the CH_2-C=O protons, as well as a signal at δ = 5.77 ppm for the NH proton. A signal was also observed at δ = 6.08 ppm for a CH proton, as well as signals corresponding to the aromatic protons at δ = 6.50–7.68 ppm and an NH proton at δ = 8.74 ppm. Furthermore, ^{13}C NMR analysis of **3i** revealed the presence of 21 distinct carbons, which was in agreement with the proposed structure. Finally, ESI-MS analysis of **3i** revealed the presence of a molecular ion peak with the expected *m/z* value [43].

3.2. Proposed reaction mechanism

Based on the results of the current study, we have proposed a mechanism for which is shown in Scheme 2. The proposed mechanism is based on sequential Michael addition and Knoevenagel cyclization reactions.

One molecule of dimedone (**1**) would undergo an initial Michael addition reaction with activated *o*-phenylenediamine (**2**) to provide enamine intermediate. The enamine intermediate would then react with the activated aromatic aldehyde (**3**) to give the corresponding imine, which would undergo an intramolecular cyclodehydration reaction to give the 4-substituted-1,5-benzodiazepines (**4–6**).

3.3. Catalyst recovery



Scheme 2. Proposed reaction mechanism for the IL-catalyzed formation of 4-substituted-1,5-benzodiazepine from *o*-phenylenediamine, dimedone and aldehyde.

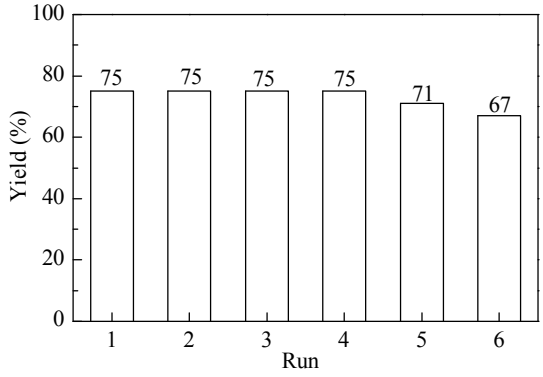


Fig. 2. Reusability of the catalyst.

The reusability of the catalyst was studied using the reaction of *o*-phenylenediamine with dimedone and benzaldehyde for the synthesis of 1,5-benzodiazepine **3a**. Upon completion of the reaction, the reaction mixture was washed three or four times with water, and the catalyst was separated by filtration. The [H-NMP][HSO_4] catalyst was then dried at 100 °C for 5 h before being reused in the next reaction. Pleasingly, the catalyst could be reused up to seven times with only a slight decrease in its activity, as shown in Fig. 2.

4. Conclusions

In summary, we have developed an efficient, nontoxic and inexpensive method for the synthesis of 4-substituted-1,5-benzodiazepine derivatives using [H-NMP][HSO_4] as a catalyst under solvent-free conditions. Most notably, the products were obtained in high yields over short reaction times. This newly developed method therefore represents a simple and efficient three-component procedure for the synthesis of 4-substituted-1,5-benzodiazepine from aldehydes, *o*-phenylenediamine and dimedone using a simple reusable IL catalyst.

Acknowledgments

The authors are grateful to University of Kashan for supporting this work by Grant No: 159148/55.

References

[1] Shorter E. Benzodiazepines. A Historical Dictionary of Psychiatry. New York: Oxford University Press, 2005. 41
[2] Bremner J B, Samosorn S. In: Newkome G R ed. Comprehensive Heterocyclic Chemistry III. Amsterdam: Elsevier, 2008
[3] Riemann D, Perlis M L. *Sleep Med Rev*, 2009, 13: 205
[4] Cortes E C, Cornejo A L, Garcia-Mellado de Cortes O. *J Heterocycl Chem*, 2007, 44: 183
[5] Makaron L, Moran C A, Namjoshi O, Rallapalli S, Cook J M, Rowlett J K. *Pharmacol Biochem Behav*, 2013, 104: 62
[6] Allison C, Pratt J A. *Pharmacol Therapeut*, 2003, 98: 171
[7] Hawkins E J, Malte C A, Imel Z E, Saxon A J, Kivlahan D R. *Drug Alcohol Depend*, 2012, 124: 154
[8] McGowan D, Nyanguile O, Cummings M D, Vendeville S, Vandyck K, Van-den Broeck W, Boutton C W, De Bondt H, Quirynen L, Amssoms K, Bonfanti J F, Last S, Rombauts K, Tahri A, Hu L L, Delouvroy F, Vermeiren K, Vandercruyssen G, Van der Helm L, Cleiren E, Mostmans W, Lory P, Pille G, Van Emelen K, Fanning G, Pauwels F, Lin T I, Simmen K, Raboisson P. *Bioorg Med Chem Lett*, 2009, 19: 2492
[9] Schimer J, Cigler P, Vesely J, Grantz-Saskova K, Lepsik M, Brynda J, Rezacova P, Kozisek M, Cisarova I, Oberwinkler H, Kraeusslich H G, Konvalinka J. *J Med Chem*, 2012, 55: 10130
[10] Fader L D, Bethell R, Bonneau P, Boes M, Bousquet Y, Cordingley M G, Coulombe R, Deroy P, Faucher A M, Gagnon A, Goudreau N, Grand-Maitre C, Guse I, Hucke O, Kawai S H, Lacoste J E, Landry S, Lemke C T, Malenfant E, Mason S, Morin S, O'Meara J, Simoneau B, Titolo S, Yoakim C. *Bioorg Med Chem Lett*, 2011, 21: 398
[11] Leggio L, Kenna G A, Swift R M. *Prog Neuro-Psychopharm Biol Psych*, 2008, 32: 1106
[12] Kodomari M, Noguchi T, Aoyama T. *Synth Commun*, 2004, 34: 1783
[13] Maiti G, Kayal U, Karmakar R, Bhattacharya R N. *Tetrahedron Lett*, 2012, 53: 1460
[14] Yi W B, Cai C. *J Fluorine Chem*, 2009, 130: 1054
[15] Xu J X, Zuo G, Chan W L. *Heteroatom Chem*, 2001, 12: 636
[16] Uchida H, Suzuki T, Mamo D C, Mulsant B H, Kikuchi T, Takeuchi H, Tomita M, Watanabe K, Yagi G, Kashima H. *J Anxiety Disord*, 2009, 23: 477
[17] Leonard B E. *Human Psychopharmacol*, 1999, 14: 125
[18] Holbrook A M, Crowther R, Lotter A, Cheng C, King D. *Can Med Assoc J*, 2000, 162: 225
[19] Pan X Q, Zou J P, Huang Z H; Zhang W. *Tetrahedron Lett*, 2008, 49: 5302
[20] Sangshetti J N, Chouthe R S, Jadhav M R, Sakle N S, Chabukswar A, Gonjari I, Darandale S, Shinde D B. *Arab J Chem*, 2013, doi:10.1016/j.arabjc.2013.04.004
[21] Cortes E C, Banos M A, Garcia-Mellado De Cortes O. *J Heterocycl Chem*, 2004, 41: 277
[22] Gurkovskii A L, Tonkikh N N, Petrova M V, Strakov A Y. *Chem Heterocycl Compd*, 1999, 35: 625
[23] Strakov A Y, Petrova M V, Tonkikh N N, Gurkovskii A I, Popelis Y, Kreishman G P, Belyakov S V. *Chem Heterocycl Compd*, 1997, 33: 321
[24] Tolpygin I E, Mikhailenko N V, Bumber A A, Shepelenko E N, Revinsky U V, Dubonosov A D, Bren V A, Minkin V I. *Russ J Gen Chem*, 2012, 82: 1243
[25] Tonkikh N N, Strakovs A Y, Rizhanova K V, Petrova M V. *Chem Heterocycl Compd*, 2004, 40: 949
[26] Jiang B, Li Q Y, Zhang H, Tu S J, Pindi S, Li G G. *Org Lett*, 2012, 14: 700
[27] Wang S L, Cheng C, Wu F Y, Jiang B, Shi F, Tu S J, Rajale T, Li G G. *Tetrahedron*, 2011, 67: 4485
[28] Zhu J P, Bienayme H. Multicomponent Reactions. Weinheim: Wiley-VCH, 2005
[29] Kumaravel K, Vasuki G. *Curr Org Chem*, 2009, 13: 1820
[30] Tietze L F, Bell H P, Brasche G. Domino Reactions in Organic Synthesis. Weinheim: Wiley-VCH, 2006
[31] Terrett N K. Combinatorial Chemistry. New York: Oxford University Press, 1998
[32] Chanda A, Fokin V V. *Chem Rev*, 2009, 109: 725
[33] Pirrung M C, Das Sarma K. *J Am Chem Soc*, 2004, 126: 444
[34] Dupont J, de Souza R F, Suarez P A Z. *Chem Rev*, 2002, 102: 3667
[35] Itoh H, Naka K, Chujo Y. *J Am Chem Soc*, 2004: 126: 3026
[36] Yue C B, Fang D, Liu L, Yi T F. *J Mol Liq*, 2011, 163: 99
[37] Naeimi H, Nazifi Z S. *C R Chim*, 2014, 17: 41
[38] Naeimi H, Nazifi Z S. *J Ind Eng Chem*, 2014, 20: 1043
[39] Shaterian H R, Ranjbar M. *J Mol Liq*, 2011, 160: 40
[40] Liu W W, Cheng L Y, Zhang Y M, Wang H P, Yu M F. *J Mol Liq*, 2008, 140: 68
[41] Tong X L, Li Y D. *ChemSusChem*, 2010, 3: 350
[42] Xie C X, Li H L, Li L, Yu S, Liu F S. *J Hazard Mater*, 2008, 151: 847
[43] Arellano M del R, Martinez R, Cortes E. *J Heterocycl Chem*, 1982, 19: 321

Graphical Abstract

Chin. J. Catal., 2015, 36: 734–741 doi: 10.1016/S1872-2067(14)60304-1

Efficient, environmentally benign, one-pot procedure for the synthesis of 1,5-benzodiazepine derivatives using *N*-methyl-2-pyrrolidonium hydrogen sulphate as an ionic liquid catalyst under solvent-free conditions

Hossein Naeimi*, Hossein Foroughi
University of Kashan, Iran

A simple and efficient procedure has been developed for the synthesis of 1,5-benzodiazepines via the three-component coupling of a series of aldehydes with *o*-phenylenediamine and dimedone using [H-NMP][HSO_4] as a catalyst under solvent-free conditions.