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Eco-friendly synthesis of 1,4-benzodiazepine-2,5-diones in the ionic liquid [*bmim*]Br

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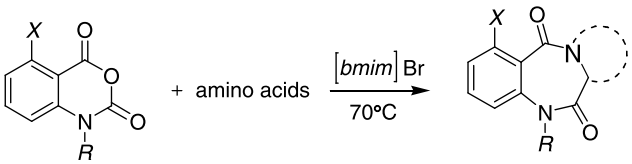
Abstract The green reaction of isatoic anhydrides with α-amino acids in presence of the ionic liquid 1-butyl-3-methylimidazolium bromide afforded 1,4-benzodiazepine-2,5-diones in excellent yields in absence of a catalyst. The reaction workup is simple and the ionic liquid was easily recovered from the reaction and reused. The methodology was quite general and a range of cyclic and acyclic α-amino acids were examined to produce 1,4-benzodiazepine-2,5-diones.

Keywords 1,4-Benzodiazepine-2,5-diones; α-Amino acids; Ionic liquid; Isatoic anhydride.

Introduction

A literature survey reveals the importance and valuable pharmacological properties of 1,4-benzodiazepine-2,5-diones (*BZD*s) in treatment of cancer, AIDS, hypertension, inflammation, pain, muscle relaxation, and depression. There has been a growing interest in ring systems, such as the pyrrole [2,1-*c*][1,4]benzodiazepines (*PBD*s) in the area of molecular recognition [1–7]. These molecules (*PBD*s) can be recognized and bind to specific sequences of *DNA*; therefore, they have been known to be potential antitumor and gene targeted drugs. Several methods have been reported for the synthesis of *BZD*s. However, the reported methods suffer from many limitations, such as requiring harsh reaction conditions, presence of strong acids as catalyst, volatile and unfriendly organic solvents, long reaction time, and low yields [7–16]. Due to the above reported synthesis limitations and as a part of our ongoing research program on the study of *BZD*s [4], and synthesis of heterocyclic compounds [17], we developed a simple synthesis route for producing the important class of 1,4-benzodiazepine-2,5-diones **3** by condensation of isatoic anhydrides **1** and α-amino acids **2** in presence of 1-butyl-3-methylimidazolium bromide ([*bmim*]Br) as ionic liquid (Scheme 1).

In this methodology, environmentally unfriendly organic solvents were replaced with environmentally friendly, ''greener'', ionic liquids (ILs). The reactions in environmentally friendly ILs have different thermodynamic and kinetic behaviors and higher selectivity or conversion have been demonstrated [18–21]. These useful materials not only dissolve many organic and inorganic substances, but they can also



1 **2** **3** (87–95%)

Scheme 1

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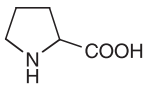
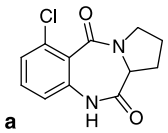
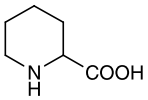
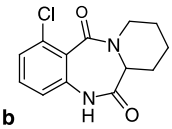
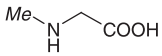
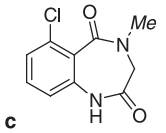
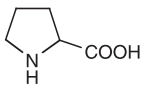
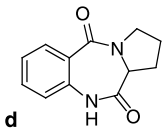
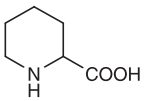
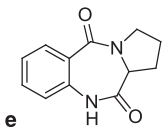
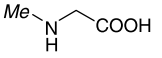
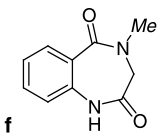
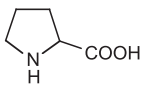
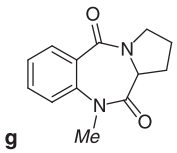
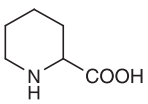
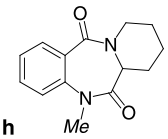
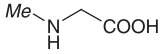
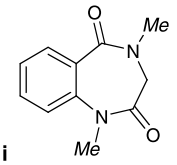
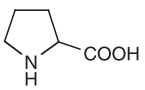
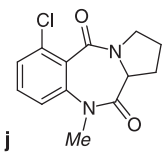
Table 1 Reactions of isatoic anhydrides **1** with α-amino acids **2** in the presence of [*bmin*]Br

Entry	Isatoic anh. **1**		Amino acid **2**	Product **3**	Time/min	Yield/%[a]	Mp/°C reported [Ref.]	
	R	*X*						
1	H	Cl		 **a**	45	90	275–278	>250 [17]
2	H	Cl		 **b**	170	87	217–219	–
3	H	Cl		 **c**	160	89	223–225	230–232 [17]
4	H	H		 **d**	20	95 (94, 92, 93, 89)[b]	218–219	216–218 [13]
5	H	H		 **e**	95	88	183–188	–
6	H	H		 **f**	80	91	223–226	–
7	*Me*	H		 **g**	50	94	254–226	–
8	*Me*	H		 **h**	140	89	144–146	–
9	*Me*	H		 **i**	125	90	248–251	–
10	*Me*	Cl		 **j**	45	91	168–169	–

[a] Isolated yields; [b] Ionic liquid was used for five times

be readily recycled. Using room temperature and close to room temperature ionic liquids, in particular those based on the 1-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents [22–24].

Results and discussion

The reaction of isatoic anhydrides **1** with α-amino acids **2** in the presence of [*bmim*]*X* (*X* = Br, PF_6, BF_4), afforded 1,4-benodiazepine-2,5-diones (*BZD*s) **3** in high yields. The best results were obtained when [*bmim*]Br was used at 70°C for 45–170 min. The results are summarized in Table 1. The products were obtained in mild condition and no impurities were observed by TLC. Using simple work-up, the products were isolated and no further chromatographic purification was performed since no impurities were observed by NMR. It is worthy to note that no products were obtained when the reaction was run in the presence of conventional solvents such as methanol and *DMSO* instead of ionic IL. Therefore, it can be suggested that the IL plays a role as promotor besides the role of the media. In other words, the solvophobic properties of the IL are able to generate an internal pressure and promote the association of the reactants in a solvent cavity during the activation process and hence accelerate the reaction. This property of the ILs is very efficient for the preparation of the product **3** in which the entropy of reaction is decreased in the transition state. New and known *BZD*s **3** obtained by this method were completely characterized by IR, mass, ^{1}H, and ^{13}C NMR analyses.

Recovery and reusability of [*bmim*]Br was another advantage of using ILs as solvents. To check the reusability of the IL, a model reaction of isatoic anhydride and α-amino acids in [*bmim*]Br (entry 4, Table 1) was executed. The reaction was run at 70°C for 45 min, and after completing the reaction, the mixture was washed with water. Water was evaporated and the recycled IL was washed with diethyl ether for further purification and reused for the next reaction. Its activity did not show any significant decrease even after four runs.

In conclusion, we developed a simple, efficient, and green methodology for the synthesis of 1,4-benzodiazepine-2,5-diones using [*bmim*]Br. The simple experimental procedure and utilization of an inexpensive and reusable catalyst with excellent yields are the advantages of the present method.

Experimental

Typical procedure for the preparation of 1-chloro-7,8,9,10-tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12-(5H,6aH)-dione (**3b**, $C_{13}H_{13}ClN_2O_2$)

A mixture of 163 mg isatoic anhydride (**1b**) (1 mmol), 129 mg pipecolinic acid (**2b**) (1 mmol), and 219 mg [*bmim*]Br (1 mmol) was placed in a test tube and heated at 70°C. After 170 min, product **3b** was formed (TLC) (Table 1). The reaction mixture was cooled to room temperature, followed by addition of water. The precipitated residue was filtered off and was recrystallized for further purification from ethanol to afford the pure product. White powder; mp 217–219°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.78 (m, 6H), 1.98 (d, $^3J_{HH}$ = 13.2 Hz, 1H), 2.64 (t, $^3J_{HH}$ = 13.1 Hz, 1H), 4.28 (m, 1H), 7.05 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.29 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.41 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 10.44 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 23.3, 23.5, 40.6, 50.6 (N–CH), 119.9, 126.3, 126.5, 131.8, 133.1, 139.1, 165.9, 171.7 ppm; IR (KBr): $\bar{\nu}$ = 3477, 1706, 1639 cm^{-1}; MS (70 eV): *m*/*z* (%) = 265 (M^+, 36), 235 (75), 207 (26), 180 (55), 153 (41), 126 (55), 84 (100), 55 (55).

7,8,9,10-Tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12(5H,6aH)-dione (**3e**, $C_{13}H_{14}N_2O_2$)

White powder; mp 183–188°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59–1.76 (m, 5H), 2.25 (d, $^3J_{HH}$ = 13.5 Hz, 1H), 3.01 (m, 1H), 4.18 (m, 1H), 4.55 (d, $^3J_{HH}$ = 13.7 Hz, 1H), 6.99 (d, $^3J_{HH}$ = 7.99 Hz, 1H), 7.28 (t, $^3J_{HH}$ = 8.6 Hz, 1H), 7.47 (t, $^3J_{HH}$ = 7.46 Hz, 1H), 7.95 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 8.49 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 22.8, 23.2, 40.4, 51.1, 120.4, 125.1, 127.6, 131.2, 132.1, 135.9, 168.6, 170.2 ppm; IR (KBr): $\bar{\nu}$ = 3415, 1678, 1647 cm^{-1}; MS (70 eV): *m*/*z* (%) = 230 (M^+, 76), 201 (95), 173 (43), 146 (85), 119 (66), 84 (100), 55 (52).

4-Methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3f**, $C_{10}H_{10}N_2O_2$)

White powder; mp 223–226°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31 (s, 3H), 3.92 (s, 2H), 7.023 (d, $^3J_{HH}$ = 8.02 Hz, 1H), 7.29 (t, $^3J_{HH}$ = 7.61 Hz, 1H), 7.49 (t, $^3J_{HH}$ = 7.65 Hz, 1H), 7.98 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 8.61 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.5 (N–CH_3), 52.5 (CH_2), 120.5, 125.3, 126.6, 131.7, 132.5, 135.6, 167.2, 170.2 ppm; IR (KBr): $\bar{\nu}$ = 3211, 1697, 1636 cm^{-1}; MS (70 eV): *m*/*z* (%) = 190 (M^+, 70), 161 (75), 119 (83), 90 (70), 63 (39), 44 (100).

10-Methyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]-diazepine-5,11-(10H,11aH)-dione (**3g**, $C_{13}H_{14}N_2O_2$)

White powder; mp 254–258°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02–2.13 (m, 3H), 2.75 (m, 1H), 3.41 (s, 3H), 3.57 (m, 1H), 3.83 (m, 1H), 4.06 (d, $^3J_{HH}$ = 5.46 Hz, 1H), 7.22 (d, $^3J_{HH}$ = 8.14 Hz, 1H), 7.31 (t, $^3J_{HH}$ = 7.37 Hz, 1H), 7.53 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 22.2, 34.0, 44.7, 55.1, 119.6, 123.5, 127.7, 128.1, 130.0, 138.6, 163.2, 167.9 ppm;

IR (KBr): $\bar{\nu} = 1664$, 1631 cm^{-1}; MS (70 eV): m/z (%) = 230 (M^+, 55), 201 (20), 161 (61), 133 (71), 105 (83), 70 (100), 41 (61).

5-Methyl-7,8,9,10-tetrahydrobenzo[e]pyrido[1,2-a][1,4]-diazepine-6,12-(5H,6aH)dione (**3h**, $C_{14}H_{16}N_2O_2$)
White powder; mp 144–146°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$–1.73 (m, 3H), 1.83–1.87 (m, 1H), 1.98–2.02 (m, 1H), 2.19–2.23 (m, 1H), 2.94–2.98 (m, 1H), 3.38 (s, 3H), 4.17–4.20 (m, 1H), 4.52 (d, $^3J_{HH} = 13.61$ Hz, 1H), 7.18 (d, $^3J_{HH} = 8.20$ Hz, 1H), 7.28 (t, $^3J_{HH} = 7.08$ Hz, 1H), 7.50 (t, $^3J_{HH} = 7.97$ Hz, 1H), 7.84 (d, $^3J_{HH} = 7.47$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.2$, 23.2, 23.4, 34.5, 34.7, 51.1, 120.6, 125.5, 129.5, 130.2, 131.8, 140.9, 168.54, 170.32 ppm; IR (KBr): $\bar{\nu} = 1673$, 1634 cm^{-1}; MS (70 eV): m/z (%) = 245 (M^+, 30), 161 (29), 133 (29), 104 (38), 84 (100), 55 (24).

1,4-Dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3i**, $C_{11}H_{12}N_2O_2$)
White powder; mp 248–251°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.09$ (s, 3H), 2.28 (s, 3H), 3.69 (d, $^3J_{HH} = 14.77$ Hz, 1H), 4.03 (d, $^3J_{HH} = 14.9$ Hz, 1H), 7.30 (t, $^3J_{HH} = 7.16$ Hz, 1H), 7.40 (d, $^3J_{HH} = 7.97$ Hz, 1H), 7.39 (t, $^3J_{HH} = 7.39$ Hz, 1H), 7.68 (d, $^3J_{HH} = 7.54$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 35.2$, 52.3, 57.6, 121.3, 125.0, 128.3, 129.9, 131.8, 140.8, 166.3, 168.4 ppm; IR (KBr): $\bar{\nu} = 1676$, 1642 cm^{-1}; MS (70 eV): m/z (%) = 205 (M^+, 98), 175 (76), 161 (40), 133 (52), 105 (100), 77 (43), 42 (90).

6-Chloro-10-methyl-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a]-[1,4]diazepine-5,11 (10H,11aH)-dione (**3j**, $C_{13}H_{13}ClN_2O_2$)
White powder; mp 168–169°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.05$–2.08 (m, 3H), 2.71 (m, 1H), 3.38 (s, 3H), 3.54–3.58 (m, 1H), 3.88 (m, 1H), 4.09–4.12 (m, 1H), 7.14 (d, $^3J_{HH} =$ 7.0 Hz, 1H), 7.37–7.42 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.4$, 26.5, 36.0, 45.8, 57.4 (NCH_3), 120.2, 128.1, 128.8, 131.0, 133.7, 141.9, 162.0, 170.4 ppm; IR (KBr): $\bar{\nu} = 1682$, 1649 cm^{-1}; MS (70 eV): m/z (%) = 265 (M^+, 75), 195 (33), 180 (29), 167 (55), 139 (41), 112 (14), 70 (100), 41 (30).

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References

1. Cho NS, Song Y, Parkanyi C (1989) J Heterocycl Chem 26:1807
2. Thurston DE, Bose DS (1994) Chem Rev 94:433
3. Tucker HD, Lecount J (1996) In: Katritzky AR, Scriven EF (eds) Comprehensive Heterocyclic Chemistry, vol 9. Pergmon Press, New York, p 151
4. Jadidi K, Aryan R, Mehrdad M, Lugger T, Hahn FE, Ng SW (2004) J Mol Struc 692:37
5. Baraldi PG, Balboni G, Cacciari B, Guiotto A, Manfredini S, Romagnoli R, Spalluto G, Thurston DE, Howard PW, Bianchi N, Rutigliano C, Mischiati C, Gambari R (1999) J Med Chem 42:5131
6. Jones GB, Davey CL, Jenkins TC, Kamal A, Kneale GG, Neidle S, Webster GD, Thurston DE (1990) Anti-cancer Drug Des 5:249
7. Mohiuddin G, Keddy PS, Ahmed K, Ratnam CV (1986) Heterocycles 24:3489
8. Wright WB (1976) US Pat 3947408; (1976) Chem Abstr 85:46771
9. Mori M, Kiura M, Uozumi Y, Ban Y (1985) Tetrahedron Lett 26:5947
10. Keating TA, Armstrong RW (1996) J Org Chem 61:8935
11. Mohiuddin G, Neddy PSN, Ahmed K, Ratanam CV (1985) Indian J Chem 24B:905
12. Akssira M, Boumzebra M, Kasmi H, Dahdouh A (1993) Synth Commun 23:2265
13. Akssira M, Boumzebra M, Kasmi H, Dahdouh A (1994) Tetrahedron 50:9051
14. Kamal A, Reddy BSN, Reddy GSK (1999) Synlett:1251
15. Kamal A, Laxman E, Arifuddin M (2000) Tetrahedron Lett 41:7743
16. Fabienne HE, WO 2000 069835
17. Jadidi K, Gharemanzadeh R, Mehrdad M, Darabi HR, Khavasi HR, Asgari D (2008) Ultrason Sonochem 15:124
18. Holbrey JD, Seddon KR (1999) Clean Products Processes 1:223
19. Elare MJ, Seddon KR (2000) Pure Appl Chem 72:1391
20. Welton T (1999) Chem Rev 99:2071
21. Wasserschied P, Kiem M (2000) Angew Chem Int Ed 39:3772
22. Olivier-Bourbigou H, Magna L (2002) J Mol Catal A 182:419
23. Wilks JS (2004) J Mol Catal A 214:11
24. Jain N, Kumar A, Chauhan S, Chauhan SMS (2005) Tetrahedron 61:1015