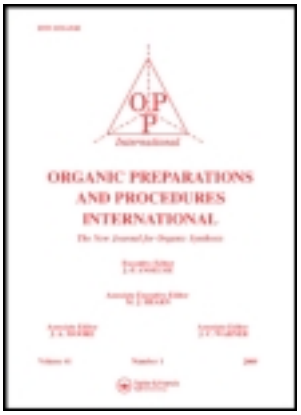

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An Expeditious Synthesis of Tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8(4H)-ones and Dihydro-1,2,4-triazolo[1,5-a]pyrimidines

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An Expeditious Synthesis of Tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones and Dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines

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There is currently great interest in solid-state reactions as they offer potential reduction in environmental contamination with the elimination of solvents.[1,2] One practical approach to achieve this goal is by grinding the solid reactants together using a mortar and pestle, a technique adopted for a number of reactions.[3,4] One-pot multi-component reactions (MCRs) have been exploited as a powerful tool for the assembly of large libraries of biologically active compounds.[5,6] Among heterocycles, quinazolinones and triazolo-pyrimidines have attracted a great deal of attention due to their therapeutic and pharmacological properties.[7,8] Drugs such as *fluconazole* and *itraconazole* are notable examples of antifungal molecules possessing the triazole nucleus. In view of the above and considering the fact that ionic liquids have been used as eco-friendly catalysts as well as solvents in organic synthesis,[9–13] it was thought worthwhile to utilize the catalytic potential of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) in the synthesis of tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones and dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines. Although different strategies have been employed for the synthesis of these compounds,[14–18] these methods suffer from drawbacks such as long reaction times, cumbersome isolation of the products and harsh reaction conditions. We now report a facile and efficient ionic liquid-catalyzed multi-component synthesis of tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones (**3**) and dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines (**4**) in excellent yields from 3-amino-1,2,4-triazole, aldehydes and dimedone (or ethyl acetoacetate), respectively, by simple grinding using a mortar and pestle at room temperature (*Scheme 1*).

In order to optimize the reaction conditions, test reactions of 3-amino-1,2,4-triazole (**1**), benzaldehyde (**2a**) and dimedone were carried out in the presence of various ionic liquid catalysts. While there was no observable product in the absence of the catalyst, the addition of various [Bmim] salts, brought about a dramatic change in the reaction profile, the best result being obtained using 15 mol% of [Bmim]BF_4 at room temperature in 12 min. Although it was also determined that heating at 70°C in the presence of 15 mol%

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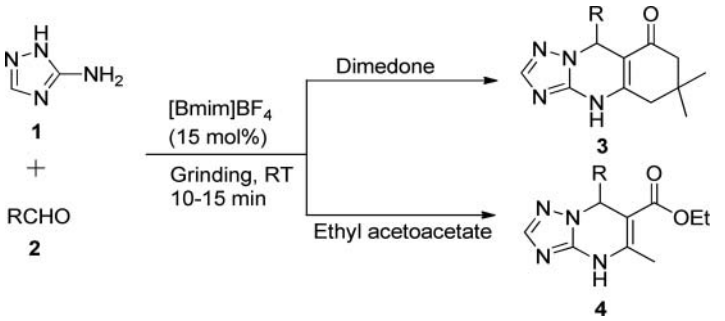

Scheme 1

of [Bmim]BF_4 led to the desired product in 92% yield in 12 min, grinding of the reactants at room temperature with 15 mol% of [Bmim]BF_4 is the better procedure.

The optimized set of conditions was used for the reaction of 3-amino-1,2,4-triazole (**1**), with aldehydes (**2**) and dimedone (ethyl acetoacetate) to afford a number of quinazolinones **3** and triazolo-pyrimidines **4** (Table 1). Aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents, including a heterocyclic aldehyde, underwent smooth coupling to afford the desired products **3a**-**n** and **4a-f** in excellent yields. Although the reaction of aliphatic aldehydes with dimedone did not occur (Table 1*, Entries 15, 16*), it worked well with ethyl acetoacetate, leading to relatively good yields (*Entries 23–25*). In an attempt to further broaden the scope of process, 1,3-indandione was treated with benzaldehyde and 3-amino-1,2,4-triazole (**1**). However, instead of the desired products, Knoevenagel-type products were obtained.

It is worthwhile to mention that when the reaction is carried out on a large scale, using 40 mmol of benzaldehyde, 40 mmol of dimedone, 40 mmol of 3-amino-1,2,4-triazole and 6.0 mmol of [Bmim]BF_4, the corresponding product **3a** is obtained in the same yield (92%) as on the small-scale reaction. During initial grinding of the reactants, complete melting of the mixture occurs suggesting the release of heat. The generation of heat may be due to the occurrence of 'hot spots'.[19] The formation of a liquid phase (called eutectic mixture) prior to the reaction, results in uniform distribution of the reactants and brings the reacting species into greater contact than does a solvent.[4] This explains the shorter reaction time and better yields under solvent-free conditions. The recovered catalyst may be reused four times without any noticeable decrease in its activity and in yields.

Experimental Section

All the chemicals including ionic liquids were procured from Aldrich (USA) and E. Merck (Germany) and used as received. IR spectra were recorded as KBr pellets on a Jasco FT/IR-5300 spectrophotometer. ^1H and ^{13}C NMR spectra were carried out in DMSO-d_6 and $CDCl_3$ on a Jeol AL300 FTNMR spectrometer at 300 MHz and 75 MHz, respectively; chemical shifts are given in δ, relative to TMS as an internal standard. Elemental analysis (C, H, N) was performed using CHN Analyzer Model CE-440. Melting points were measured in open

Table 1
Synthesis of Tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin8(4*H*)-ones (**3**) and of Dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines (**4**)

Entry	Product	R	Time (min)	Yield[a] (%)	mp. (°C)	
					Found	*lit.*
1	**3a**	C_6H_5	11	92	249–251	248–250[15]
2	**3b**	4-MeC_6H_4	13	87	278–280	280–282[14]
3	**3c**	3-$NO_2C_6H_4$	12	82	290–293	290–292[14]
4	**3d**	4-BrC_6H_4	13	90	287–288	284–288[15]
5	**3e**	4-ClC_6H_4	15	85	283–285	285–288[14]
6	**3f**	3-BrC_6H_4	12	82	280–282	—
7	**3g**	3-ClC_6H_4	13	83	291–292	—
8	**3h**	4-$MeOC_6H_4$	10	80	231–233	230–233[14]
9	**3i**	4-$NO_2C_6H_4$	11	85	>300	>300[15]
10	**3j**	4-FC_6H_4	14	81	279–281	—
11	**3k**	3,4,5-$(MeO)_3C_6H_2$	13	86	250–253	—
12	**3l**	4-$Me_2NC_6H_4$	15	89	285–287	290–293[16]
13	**3m**	2,4-$Cl_2C_6H_3$	13	84	>300	>300[16]
14	**3n**	2-Thienyl	12	89	254–257	—
15	**3o**	Et	20	0	—	—
16	**3p**	H	20	0	—	—
17	**4a**	C_6H_5	12	80	190–192	190–192[18]
18	**4b**	4-$MeOC_6H_4$	11	84	220–223	—
19	**4c**	4-MeC_6H_4	12	81	246–248	—
20	**4d**	4-BrC_6H_4	13	80	221–225	—
21	**4e**	4-$NO_2C_6H_4$	15	75	263–264	—
22	**4f**	4-FC_6H_4	14	77	218–220	—
23	**4g**	H	13	73	194–197	196–198[18]
24	**4h**	Me	13	71	151–153	150–152[18]
25	**4i**	Et	12	72	148–150	—

[a]Isolated yields based on 3-amino-1,2,4-triazole.

capillaries and are uncorrected. All the products were characterized based on their mp, IR, ^{1}H NMR and ^{13}C NMR. The data of the unknown products are given below in Table 2.

General Procedure for the Synthesis of Tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8 (4H)-ones (3) and Dihydro-1,2,4-triazolo[1,5-a]pyrimidines (4)

A mixture of 3-amino-1,2,4-triazole (3.36 g, 40 mmol), aldehyde (40 mmol), dimedone (5.60 g, 40 mmol)/ethyl acetoacetate (5.20 g, 40 mmol) and 6 mmol of [Bmim]BF_4 (1.36 g) was ground in an *agate* mortar and pestle set for the appropriate time (Table 1). Upon completion of the reaction (as indicated on TLC), cold water (40 mL) was added to the

Table 2
IR, ^{1}H NMR, ^{13}C NMR Data and Combustion Analyses

Cmpd	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)	Combustion Analyses (Found)		
				C	H	N
3f	3451, 2963, 1645, 1577, 1546, 1522	0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.12–2.56 (m, 4H, CH_2), 6.25 (s, 1H, CH), 7.16–7.65 (m, 5H, Ar, CH), 11.34 (br s, 1H, NH)[a]	26.89, 28.30, 32.12, 49.76, 57.44, 104.89, 124.42, 127.18, 130.23, 132.10, 135.84, 144.50, 146.18, 150.29, 155.45, 193.46[a]	54.70 (54.53)	4.59 (4.61)	15.01 (14.89)
3g	3451, 2955, 1645, 1577, 1549, 1525	0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.13–2.56 (m, 4H, CH_2), 6.22 (s, 1H, CH), 7.12–7.76 (m, 5H, Ar, CH), 11.21 (br s, 1H, NH)[a]	26.92, 28.39, 32.27, 49.75, 57.49, 104.94, 125.62, 127.08, 130.33, 133.10, 136.48, 144.51, 146.78, 150.27, 155.28, 193.06[a]	62.10 (61.96)	5.21 (5.14)	17.04 (16.92)
3j	3451, 2955, 1648, 1577, 1486, 1420, 1367	0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.11–2.54 (m, 4H, CH_2), 6.22 (s, 1H, CH), 6.96–7.29 (m, 4H, Ar), 7.69 (s, 1H, CH), 11.16 (br s, 1H, NH)[a]	27.58, 28.95, 39.67, 50.27, 57.88, 105.59, 128.65, 130.13, 132.76, 142.12, 143.21, 150.61, 150.86, 193.44[a]	65.37 (65.25)	5.49 (5.38)	17.94 (17.82)
3k	3451, 2960, 1652, 1577, 1510, 1363	1.12 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.35–2.41 (m, 4H, CH_2), 3.75 (s, 6H, OCH_3), 3.81 (s, 3H, OCH_3), 6.34 (s, 1H, CH), 7.25 (m, 2H, Ar), 7.68 (s, 1H, CH), 11.63 (br, s, 1H, NH)[a]	27.33, 28.49, 32.62, 50.33, 55.49, 57.83, 60.81, 106.27, 114.06, 128.58, 134.29, 147.16, 150.34, 150.66, 157.29, 193.43[a]	62.49 (62.37)	6.29 (6.21)	14.57 (14.43)
3n	3451, 2963, 1648, 1577, 1540, 1453, 1363	1.10 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.27–2.45 (m, 4H, CH_2), 6.63 (s, 1H, CH), 6.85–7.11 (m, 3H, Ar), 7.25 (s, 1H, CH), 11.68 (br, s, 1H, NH)[a]	27.39, 28.86, 32.67, 50.24, 57.85, 105.69, 123.47, 124.53, 126.33, 143.64, 147.33, 150.50, 159.55, 193.44[a]	59.98; (59.81)	5.37 (5.41)	18.65 (18.57)

(Continued on next page)

Table 2
IR, ^{1}H NMR, ^{13}C NMR Data and Combustion Analyses *(Continued)*

Cmpd	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)	Combustion Analyses (Found)		
				C	H	N
4b	3255, 3097, 2988, 2905, 1695, 1253	1.11 (t, 3H, CH_3, J = 7.2 Hz), 2.56 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.02 (q, 2H, CH_2, J = 7.2 Hz), 6.37 (s, 1H, CH), 6.81–7.60 (m, 5H, Ar), 11.00 (br s,1H, NH)[b]	14.09, 19.07, 55.21, 59.80, 60.04, 99.04, 113.87, 128.49, 133.65, 145.52, 147.23, 148.65, 159.44, 165.69[b]	61.13 (60.96)	5.77 (5.70)	17.82 (17.69)
4c	3260,3097, 2988, 2900, 1699, 1253	1.12 (t, 3H, CH_3, J = 7.2 Hz), 2.29 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.02 (q, 2H, CH_2, J = 7.2 Hz), 6.37 (s, 1H, CH), 7.09–7.59 (m, 5H, Ar), 10.13 (br s,1H, NH)[b]	14.09, 19.07, 22.07, 59.80, 60.04, 99.04, 113.87, 128.49, 133.65, 145.52, 147.23, 148.65, 159.44, 165.69[b]	64.41 (64.27)	6.08 (6.12)	18.78 (18.69)
4d	3255, 3095, 2900, 2905, 1695, 1260	1.15 (t, 3H, CH_3, J = 7.2 Hz), 2.58 (s, 3H, CH_3), 4.06 (q, 2H, CH_2, J = 7.2 Hz), 6.37 (s, 1H, CH), 7.42–7.96 (m, 5H, Ar), 11.13 (br s,1H, NH)[b]	14.09, 19.07, 59.80, 60.04, 99.04, 100.92, 113.87, 128.49, 133.65, 145.52, 147.23, 148.65, 165.69[b]	49.60 (49.43)	4.16 (4.10)	15.43 (15.50)
4e	3255, 3097, 2988, 2905, 1705, 1253	1.17 (t, 3H, CH_3, J = 7.2 Hz), 2.62 (s, 3H, CH_3), 4.05 (q, 2H, CH_2, J = 7.2 Hz), 6.52 (s, 1H, CH), 7.26–8.20 (m, 5H, Ar), 11.43 (br s,1H, NH)[b]	14.10, 19.34, 59.71, 60.43, 97.82, 113.36, 123.91, 128.36, 146.74, 147.31, 147.79, 148.99, 165.11[b]	54.71 (54.56)	4.59 (4.51)	21.27 (21.12)
4f	3255, 3097, 2988, 2905, 1702, 1253	1.11 (t, 3H, CH_3, J = 7.2 Hz), 2.58 (s, 3H, CH_3), 4.04 (q, 2H, CH_2, J = 7.2 Hz), 6.41 (s, 1H, CH), 6.96–7.61 (m, 5H, Ar), 11.16 (br s,1H, NH)[b]	14.07, 19.16, 59.69, 60.14, 98.71, 115.35, 115.64, 129.01, 129.12, 145.95, 147.26, 148.76, 165.49[b]	59.60 (59.42)	5.00 (5.09)	18.53 (18.66)

(Continued on next page)

Table 2
IR, ^{1}H NMR, ^{13}C NMR Data and Combustion Analyses *(Continued)*

Cmpd	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)	Combustion Analyses (Found)		
				C	H	N
4i	3260, 3085, 2980, 2905, 1705, 1255	0.70 (t, 3H, CH_3, J = 7.2 Hz), 1.25–2.02 (m, 5H, CH_3 & CH_2), 2.49 (s, 3H, CH_3), 4.20 (q, 2H, CH_2, J = 7.2 Hz), 5.54 (s, 1H, CH), 7.65 (s, 1H, Ar), 10.60 (br s,1H, NH)[b]	7.90, 14.32, 19.17, 28.55, 57.24, 60.04, 97.28, 113.78, 146.91, 148.53, 165.96[b]	55.92 (55.83)	6.83 (6.71)	23.71 (23.64)

[a]In DMSO-d_6; [b]In $CDCl_3$.

reaction mixture and the precipitate formed was collected. With dimedone, the product **3** was purified further by washing with acetone, whereas in the case of ethyl acetoacetate, the product **4** was purified by recrystallization from ethanol. The ionic liquid may be recovered by the evaporation of water under vacuum, followed by washing with diethyl ether and drying in an oven at 90°C and reused four times.

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