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One-step Synthesis of 3,4-Dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones in an Ionic Liquid

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Summary. A novel class of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones was synthesized in very short reaction times with good yields in the presence of 3-butyl-1-methyl imidazolium bromide as a room temperature ionic liquid at 120°C. The ionic liquid can be recycled for subsequent reactions without any loss of efficiency.

Keywords. Orthoester; Cyclic β-diketone; Quinazoline; 2-Aminobenzimidazole; Ionic liquid.

Introduction

Bridgehead nitrogen heterocycles with a benzazole skeleton have received increasing attention due to their potential biological properties, and considerable efforts have been undertaken to exploit synthesis routes to these compounds [1, 2]. Environmental consciousness promotes significant efforts to find an alternative reaction medium in green chemistry. Ionic liquids (ILs) have been extensively tested as environmentally friendly solvents for a large variety of reactions [3–5].

In continuation of our effort to introduce new multi-component reactions [6] and feasible methods for the synthesis of 4*H*-pyrimido[2,1-*b*]benzazoles [7], herein we wish to report the utilization of 1-butyl-3-methylimidazolium bromide as an ionic liquid and efficient promoter for the synthesis of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones under classical heating conditions at 120°C. To the best of our knowledge, this is the first reported one-pot three-component synthesis of this important class of heterocyclic compounds from the easily available starting compounds.

This one-pot method involves the classical heating of a mixture of 2-aminobenzimidazole **1**, cyclic β-diketone **2**, and orthoester **3** without using any catalyst in the ionic liquid to give a family of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones **4** in relatively good yields (Scheme 1).

Results and Discussion

In an initial study, in order to examine the best solvent, different solvents and ionic liquids, such as tetramethylguanidinium triflouroacetate (*TMGT*), tetramethylguanidinium acetate (*TMGA*), tetrabutylammonium bromide (*TBAB*), tetrabutylammonium chloride (*TBAC*), methylimidazolium triflouroacetate (*MIT*), 1-butyl-3-methylimidazolium bromide ([*bmim*]Br), 1-butyl-3-methylimidazolium hexaflouroposphate ([*bmim*]PF_6), in this condensation reaction were applied (Table 1). In the course of this study it was found that 1-butyl-3-methylimidazolium bromide was the best suited ionic liquid for this reaction in terms of yield and easy work-up.

In order to improve the yields, we performed reactions using different quantities of reagents. The best result was obtained with an 1:1:1:1.1 mole ratio of 2-aminobenzimidazole, cyclic β-diketone, orthoester, and [*bmim*]Br. The yield of product was a trace at

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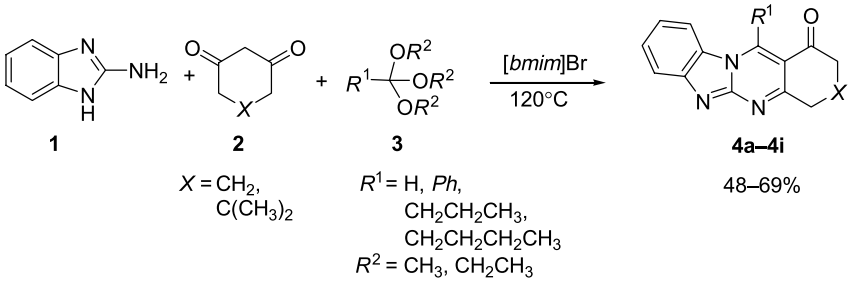


Scheme 1

Table 1. One-pot synthesis of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones under classical heating conditions at 120°C or reflux in different solvents[a]

Entry	Solvent	Time/min	Yield/%
1	–	30	trace
2	$CHCl_3$	30	trace
3	CH_3COOCH_3	30	trace
4	CH_3CH_2OH	30	trace
5	H_2O	30	10
6	*TMGT*	30	25
7	*TMGA*	30	30
8	*TBAB*	30	32
9	*TBAC*	30	30
10	*MIT*	30	24
11	[*bmim*]Br	30	58
12	[*bmim*]PF_6	30	51

[a] 2-aminobenzimidazole (1 mmol), dimedone (1 mmol), and triethylorthoformate (1 mmol)

120°C after 1 h in the absence of the ionic solvent. Obviously, [*bmim*]Br is an important component of the reaction.

The structures of products **4** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The mass spectra of these compounds displayed molecular ion peak at appropriate m/z values. The ^{1}H NMR spectrum of **4a** exhibited one sharp line readily recognized as arising from two methyl groups at $\delta =$ 1.19 ppm, along with two singlets ($\delta = 2.16$ and 2.58 ppm) for two methylene protons, and a multiplet ($\delta = 7.50$–8.38 ppm) for the aromatic protons. A sharp singlet was observed for the CH proton ($\delta =$ 9.07 ppm) in the pyrimidine ring. The ^{1}H NMR spectra of **4b**–**4i** are similar to those of **4a**, except for the X and R^1 groups, which exhibit characteristic signals with appropriate chemical shifts.

To explore the scope and limitations of this reaction, we extended it to various substituted orthoesters in the presence of 2-aminobenzimidazole and cyclic β-diketones. As indicated in Table 2, the reaction proceeds efficiently with all of them.

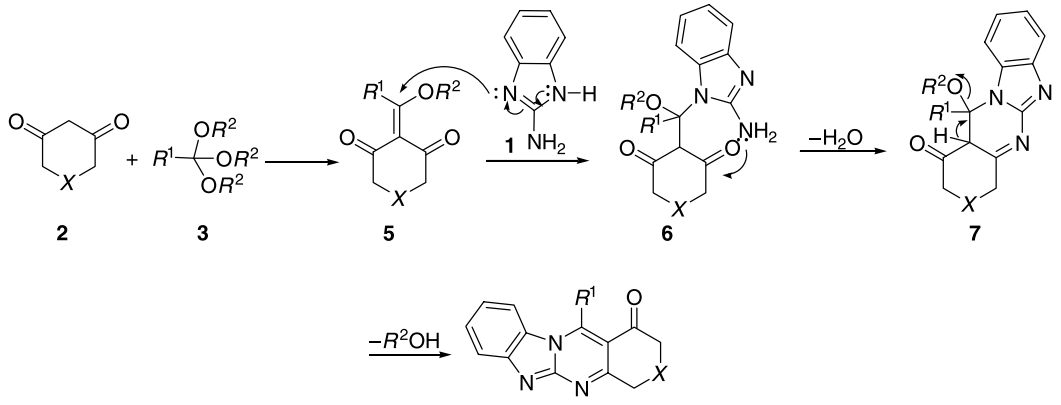
One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. We were able to separate [*bmim*]Br from the reaction medium easily by washing with water, evaporating the solvent under vacuum, and reuse it for subsequent reactions (Table 2, **4c**).

Although we could not isolate any intermediate, the reaction may involve the initial formation of intermediate **5** between 1,3-cyclohexanedione **2** and orthoester **3**, which undergoes reaction with 2-amino-

Table 2. One-pot synthesis of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones by the condensation of 2-aminobenzimidazole, cyclic β-diketone, and orthoester in [*bmim*]Br at 120°C

Product	X	R^1	R^2	Time/min	Yield/%
4a	$C(CH_3)_2$	H	CH_3	35	58
4b	CH_2	H	CH_3	30	59
4c	$C(CH_3)_2$	H	CH_2CH_3	35	48, 46, 47, 46[a]
4d	CH_2	H	CH_2CH_3	40	62
4e	$C(CH_3)_2$	*Ph*	CH_2CH_3	40	63
4f	CH_2	*Ph*	CH_2CH_3	45	64
4g	CH_2	$CH_2CH_2CH_3$	CH_3	40	62
4h	$C(CH_3)_2$	$CH_2CH_2CH_2CH_3$	CH_3	50	68
4i	CH_2	$CH_2CH_2CH_2CH_3$	CH_3	45	69

[a] The same[*bmim*]Br was used for each of the four runs



Scheme 2

benzimidazole **1** to produce **6**. Intramolecular condensation of **6** leads to **7**, which then yields **4** by the spontaneous elimination of alcohol (Scheme 2) [8].

In conclusion, we introduced a three-component condensation reaction of 2-aminobenzimidazole, a cyclic β-diketone, and an orthoester for the fast synthesis of a novel family of 3,4-dihydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-one ring systems. The one-pot synthesis protocol in the absence of any catalyst makes it an interesting approach.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in *DMSO*-d_6. All the products are new compounds, which were characterized by IR, ^{1}H NMR, ^{13}C NMR (because of the low solubility of compounds **4b** and **4d** the ^{13}C NMR could not be obtained), and mass spectral data.

Typical Procedure for the Synthesis of 3,3-Dimethyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one ***4a***

A mixture of 0.140 g dimedone (1 mmol), 0.106 g trimethylorthoformate (1 mmol), and 0.150 g 2-aminobenzimidazole (1 mmol) was successively added to a screw-capped vial containing a magnetic stirring bar in 0.3 g [*bmim*]Br and was heated at 120°C in a preheated oil bath for 35 min. Then the reaction mixture was washed with cold H_2O and the solid residue was washed with $3 \times 10\,cm^3$ acetone to yield 0.153 g (58%) **4a** as a yellow powder.

3,3-Dimethyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4a** or **4c**, $C_{16}H_{15}N_3O$)

Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu} = 2971, 1682\,cm^{-1}$; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.19$ (s, CH_3), 2.59 (s, CH_2), 3.68 (s, CH_2), 7.50 (t, $J = 7.24$ Hz, CH arom), 7.64 (t, $J = 6.47$ Hz, CH arom), 7.93 (d, $J = 7.22$ Hz, CH arom), 8.38 (d, $J = 7.52$ Hz, CH arom), 9.19 (s, CH prymidine) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 28.54$, 32.92, 50.07, 56.14, 112.98, 117.37, 120.20, 123.04, 127.08, 128.52, 145.29, 153.17, 157.85, 194.79 ppm; MS (EI, 70 eV): m/z (%) = 265 (M^+, 100), 209 (50), 181 (20), 154 (30), 103 (30), 77 (10).

3,4-Dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4b** or **4d**, $C_{14}H_{11}N_3O$)

Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu} = 2936, 1687\,cm^{-1}$; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.84$–2.72 (m, $3CH_2$), 7.49 (t, $J = 7.83$ Hz, CH arom), 7.64 (t, $J = 7.55$ Hz, CH arom), 7.94 (d, $J = 7.98$ Hz, CH arom), 8.33 (d, $J = 8.49$ Hz, CH arom), 9.09 (s, CH prymidin) ppm; MS (EI, 70 eV): m/z (%) = 237 (M^+, 100), 209 (50), 181 (20), 154 (30), 103 (30), 77 (10).

3,3-Dimethyl-12-phenyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4e**, $C_{22}H_{19}N_3O$)

Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu} = 2958, 1670\,cm^{-1}$; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.22$ (s, $2CH_3$), 2.61 (s, CH_2), 3.75 (s, CH_2), 7.45–7.52 (m, C_6H_5 and CH arom), 7.63 (t, $J = 7.45$ Hz, CH arom), 7.92 (d, $J = 8.21$ Hz, CH arom), 8.79 (t, $J = 8.25$ Hz, CH arom) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 28.61$, 32.57, 39.12, 51.69, 112.87, 117.50, 119.99, 120.56, 122.79, 126.96, 127.99, 128.59, 129.09, 129.35, 140.30, 145.85, 149.87, 158.55, 163.65, 194.47 ppm; MS (EI, 70 eV): m/z (%) = 341 (M^+, 100), 285 (50), 256 (20), 133 (30).

12-Phenyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4f**, $C_{20}H_{15}N_3O$)

Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu} = 2965, 1686, 1616\,cm^{-1}$; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.33$ (m, CH_2), 2.66 (t, $J = 6.88$ Hz, CH_2), 3.81 (t, $J = 5.59$ Hz, CH_2), 7.44–7.56 (m, C_6H_5 and CH arom), 7.62 (t, $J = 7.46$ Hz, CH arom), 7.91 (d, $J = 8.12$ Hz, CH arom), 8.34 (d, $J = 8.35$ Hz, CH arom) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 21.13$, 29.23, 32.05, 38.83, 114.68, 118.02, 120.90, 123.72, 127.80, 128.90, 129.56, 130.05, 130.31, 141.35, 146.69, 150.51,

161.45, 165.01, 195.19 ppm; MS (EI, 70 eV): m/z (%) = 313 (M^+, 100), 312 (90), 285 (75), 256 (10).

12-Propyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4g**, $C_{17}H_{17}N_3O$)
Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu}$ = 2955, 1682, 1618 cm^{-1}; ^1H NMR (300 MHz, *DMSO*-d_6): δ = 1.00 (t, J = 7.30 Hz, CH_3), 1.68–1.76 (m, CH_2), 2.24–2.26 (m, CH_2), 2.65–2.67 (m, CH_2), 2.74–2.2.76 (m, CH_2), 3.21 (t, J = 6.83 Hz, CH_2), 7.43 (t, J = 6.81 Hz, CH arom), 7.59 (t, J = 7.64 Hz, CH arom), 7.87 (d, J = 7.89 Hz, CH arom), 8.29 (d, J = 7.89 Hz, CH arom) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 27.51, 29.08, 32.64, 39.62, 50.65, 52.61, 108.37, 126.68, 127.39, 128.57, 145.17, 152.35, 152.59, 193.04 ppm; MS (EI, 70 eV): m/z (%) = 280 ($M^+ + 1$, 100), 251 (90), 222 (20).

12-Butyl-3,3-dimethyl-3,4-dihydrobenzimidazo[2,1-b] quinazolin-1(2H)-one (**4h**, $C_{20}H_{23}N_3O$)
Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu}$ = 3128, 1683, 1618, 1583 cm^{-1}; ^1H NMR (300 MHz, *DMSO*-d_6): δ = 0.93 (t, J = 7.33 Hz, CH_3), 1.18 (s, $2CH_3$), 1.38–1.45 (m, CH_2), 1.61–1.71 (m, CH_2), 2.59 (s, CH_2), 3.22–3.47 (m, $2CH_2$), 7.45 (t, J = 7.31 Hz, CH arom), 7.60 (t, J = 7.71 Hz, CH arom), 7.87 (d, J = 8.09 Hz, CH arom), 8.33 (d, J = 8.32 Hz, CH arom) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 14.35, 22.64, 28.36, 30.36, 32.03, 38.02, 41.17, 52.15, 112.42, 117.49, 119.83, 122.41, 126.80, 128.63, 145.54, 149.94, 158.56, 168.18, 195.83 ppm; MS (EI, 70 eV): m/z (%) = 322 ($M^+ + 1$, 35), 279 (100), 249 (20), 208 (15), 133 (25).

12-Butyl-3,4-dihydrobenzimidazo[2,1-b]quinazolin-1(2H)-one (**4i**, $C_{18}H_{19}N_3O$)
Yellow powder; mp > 280°C; IR (KBr): $\bar{\nu}$ = 3128, 1619, 1578, 1402 cm^{-1}; ^1H NMR (300 MHz, *DMSO*-d_6): δ = 0.94 (t, J = 6.66 Hz, CH_3), 1.40–2.66 (m, $4CH_2$), 3.19–3.73 (m, $2CH_2$), 7.55-7.60 (m, 2CH arom), 8.00 (d, J = 6.45 Hz, CH arom), 8.26 (d, J = 8.24 Hz, CH arom) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): δ = 14.35, 20.07, 22.68, 28.49, 30.32, 38.21, 38.59, 113.31, 117.16, 119.84, 122.38, 126.73, 128.66, 145.52, 149.64, 160.27, 168.50, 195.74 ppm; MS (EI, 70 eV): m/z (%) = 294 (M^+, 10), 273 (10), 251 (75), 133 (100).

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