Monatshefte für Chemie 138, 1191–1194 (2007)
DOI 10.1007/s00706-007-0635-0
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Ionic Liquid Promoted Eco-friendly and Efficient Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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Received November 2, 2006; accepted (revised) November 28, 2006; published online June 11, 2007

Summary. 2,3-Dihydroquinazolin-4(1*H*)-ones were efficiently synthesised by the reaction of isatoic anhydride, a primary amine or ammonium acetate, and different aromatic aldehydes in 1-butyl-3-methylimidazolium tetrafluoroborate ([*bmim*]BF_4) without using any acidic catalyst. Also a bis-derivative of the title compound as a polyheterocyclic system was synthesised successfully in high yield.

Keywords. 2,3-Dihydroquinazolinone; Heterocycles; Green chemistry; Ionic liquid.

Introduction

Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems. Heterocycles are important, not only because of their abundance, but above all because of their chemical, biological, and technical significances. Heterocycles count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals, herbicides, and dyes. One of such systems are quinazolinones which have an important place in medicinal and biological chemistry [1]. Several quinazolinone derivatives have been synthesised as potential antimicrobial [1], anticancer [2], and antimalarial agents [3]. *Cohen et al.* were the first to report on the synthesis and diuretic activity of quinazolinone sulfonamides [4]. Metolazone is a 3-phenyl-substituted quinazolinone diuretic agent that has been used effectively in treatment of hypertension [5]. One of the main group of quinazolinones, are 2,3-dihydroquinazolin-4(1*H*)-ones, which have several biological activities indeed [6], and are also key intermediates for the synthesis of quinazolin-4(3*H*)-ones [7] as another member of this biologically important family [8]. Furthermore, a literature search shows that the study of polyheterocyclic systems based on a quinazolinone structural block has attracted interest owing to their potential useful biological activities [9].

In view of an increasing interest in developing environmentally benign reactions, atom-economic catalytic processes or reactions without using any catalyst and the use of green solvents are ideal processes in organic chemistry. There is a widespread interest in room temperature ionic liquids (ILs) as new, non-volatile solvents in both academia and industry research areas [10].

As a continuation of our research devoted to the development of the synthesis of quinazolinone derivatives [11], herein we report an efficient and green procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Results and Discussion

When a mixture of isatoic anhydride, a primary amine, and an aromatic aldehyde in 1-butyl-3-meth-

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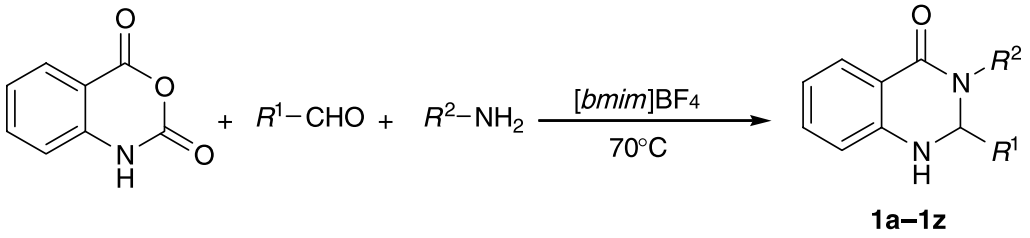

Scheme 1

ylimidazolium tetrafluoroborate ([*bmim*]BF_4) were stirred at 70°C without using any acidic catalyst, the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones **1** were obtained (Scheme 1). As shown in Table 1, the desired products were obtained in excellent yields. The reactions were completed smoothly within 1–2 h and the products were isolated by a simple work-up procedure. Despite other previously reported methods, heteroaromatic aldehydes and aromatic amines worked well under the reaction conditions (Table 1).

Table 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

Product[a]	R^1	R^2	Yield/%[b]	Time/h
1a	Me	*Ph*	90	1.5
1b	*Me*	4-ClC_6H_4	92	2
1c	*Me*	4-$CH_3OC_6H_4$	89	2
1d	*Et*	*Ph*	91	1.5
1e	*Et*	4-ClC_6H_4	87	2
1f	*Et*	4-$O_2NC_6H_4$	93	2
1g	*Et*	3-$O_2NC_6H_4$	85	2
1h	*Et*	4-$CH_3OC_6H_4$	83	1.5
1i	*Ph*	*Ph*	80	1.5
1j	*Ph*	4-$O_2NC_6H_4$	85	2
1k	*Ph*	3-$O_2NC_6H_4$	90	1
1l	4-ClC_6H_4	*Ph*	94	2
1m	*n-Pr*	4-$NO_2C_6H_4$	89	1.5
1n	*Et*	4-HOC_6H_4	91	1
1o	*n-Bu*	4-ClC_6H_4	89	1
1p	H	*Ph*	92	1.5
1q	H	4-ClC_6H_4	85	1
1r	H	2-$CH_3OC_6H_4$	90	1.5
1s	H	4-$CH_3C_6H_4$	92	2
1t	4-$CH_3C_6H_4$	2-Thiazolyl	82	2
1u	4-ClC_6H_4	2-Thiazolyl	80	2
1v	4-HOC_6H_4	2-Thiazolyl	85	2
1w	2,4-$Cl_2C_6H_3$	2-Thiazolyl	83	2
1x	3-$O_2NC_6H_4$	2-Thiazolyl	80	2
1y	4-$O_2NC_6H_4$	2-Thiazolyl	85	2
1z	1,4-C_6H_4	2-Thiazolyl	78	2.5

[a] The products **1a**–**1n** were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures [11c]
[b] Isolated yield based on isatoic anhydride

According to the importance of the thiazole moiety in biological and medicinal chemistry [12], 2-amino thiazole was also used in the reaction, and several new 3-(2-thiazolyl)-2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones (Table 1, **1t**–**1y**) were obtained successfully. Along with the importance of bis-heterocyclic systems and their potential biological activities [13], we were interested to synthesize a bis-3-(2-thiazolyl)-2-substituted-2,3-dihydroquinazolin-4(1*H*)-one (Table 1, **1z**) through a pseudo-five-component reaction using a dialdehyde substrate. It is worth noting that in this compound two thiazole and two quinazolinone moieties were gathered together and this could be interesting in the view of medicinal chemistry. Conducting similar reactions in conventional organic solvents such as ethanol, acetonitrile, and chloroform under reflux conditions after 12 h gave only negligible amounts of the desired product. It is also worth to mention that the synthesis of 2,3-dihydroquinazolinones by this method in organic solvents has been reported to need an acidic catalyst [11].

In conclusion, a simple and green method for the synthesis of a novel class of quinazolinone family is introduced. The IL [*bmim*]BF_4 is an efficient and green medium for the synthesis of 2,3-dihydroquinazolinones. The method offers several advantages, such as omitting any toxic solvent or catalyst, simple work-up procedure without using any chromatographic method, and improving the yields. Starting materials are inexpensive and commercially available. We believe that many biologically active derivatives could be synthesised by this multi-component reaction with high atomic economy.

Experimental

Melting points were obtained in open capillary tubes and were measured on an electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. Elemental analysis was performed for the novel compounds **1o**–**1y** using a Heracus CHNO-Rapid analyzer; their

results agreed favorably with the calculated values. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

General Procedure for the Synthesis of 2,3-Dihydroquinazolin-4(1H)-ones

A mixture of 0.163 g isatoic anhydride (1 mmol), aromatic aldehyde (1 mmol), and amine or ammonium acetate (1 mmol) was added to 0.2 g [*bmim*]BF_4 and stirred at 70°C for an appropriate period of time (Table 1). After completion of the reaction, which was indicated by TLC (eluent: *n*-hexane/ethyl acetate = 2/1) H_2O was added, and the mixture was cooled to room temperature. The precipitated product was filtered off and finally recrystallized from ethanol.

2,2′-(1,4-Phenylen)bis-3-(2-thiazolyl)-2,3-dihydroquinazolin-4(1*H*)-one **1z** was synthesized by a similar procedure except that 2 mole equivalents of isatoic anhydride and 2-aminothiazole were reacted with 1 equivalent of terephthaldialdehyde.

Products (except **1o** and **1s**–**1y**) are known compounds and their physical data, IR, and ^{1}H NMR spectra were essentially identical with those of authentic samples. Other products, which are new, were characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy, MS, and elemental analysis.

3-Butyl-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**1o**, $C_{18}H_{19}ClN_2O$)

Mp 141–143°C; IR (KBr): $\bar{\nu}$ = 3302, 2935, 2866, 1629, 1488, 1413, 1370, 1322 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 0.84 (t, J = 6.9 Hz, CH_3), 1.257 (m, CH_2), 1.47 (m, CH_2), 2.73 (m, CH), 3.88 (m, CH), 5.85 (s, CH), 6.6–7.64 (m, 9Ar-H + NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 14.12, 19.98, 30.03, 44.59, 69.68, 114.77, 115.48, 117.72, 127.89, 128.43, 128.94, 133.35, 133.64, 140.69, 146.44, 162.59 ppm; MS: m/z (%) = 315 (M^+ + 1, 50), 314 (M^+, 10), 242 (25), 203 (100), 147 (45), 41 (20).

2,3-Dihydro-2-p-tolylquinazolin-4(1H)-one (**1s**, $C_{15}H_{14}N_2O$)

Mp 232–234°C; IR (KBr): $\bar{\nu}$ = 3312, 3194, 3061, 1662, 1610, 1509, 1485, 1438, 1386 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.28 (s, CH_3), 5.7 (s, CH), 6.63–7.61 (m, 8Ar-H), 8.25 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 21.18, 66.81, 114.85, 115.43, 117.52, 127.25, 127.78, 129.26, 133.72, 138.17, 139.09, 148.37, 164.11 ppm; MS: m/z (%) = 239 (M^+ + 1, 75), 238 (M^+, 55), 237 (100), 147 (80), 120 (75), 65 (25).

2,3-Dihydro-3-(thiazol-2-yl)-2-p-tolylquinazolin-4(1H)-one (**1t**, $C_{18}H_{15}N_3OS$)

Mp 197–198°C; IR (KBr): $\bar{\nu}$ = 3408, 3048, 1635, 1505, 1451, 1392 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.17 (s, CH_3), 6.73–7.77 (m, 10Ar-H), 7.37 (d, J = 3.27 Hz, CH), 8.14 (d, J = 3.27 Hz, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 20.98, 68.37, 114.23, 115.98, 116.14, 118.65, 126.07, 128.60, 129.46, 135.48, 137.41, 137.76, 137.92, 147.04, 158.06, 161.3 ppm; MS: m/z (%) = 322 (M^+ + 1, 100), 238 (50), 222 (80), 165 (7), 91 (8).

2-(4-Chlorophenyl)-2,3-dihydro-3-(thiazol-2-yl) quinazolin-4(1H)-one (**1u**, $C_{17}H_{12}ClN_3OS$)

Mp 175–176°C; IR (KBr): $\bar{\nu}$ = 3360, 3333, 3078, 1624, 1613, 1508, 1433 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.76–7.78 (m, 10Ar-H + CH), 8.18 (d, J = 3.72 Hz, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 67.99, 114.18, 116.09, 116.31, 118.92, 128.06, 128.68, 129, 133.33, 135.65, 137.77, 139.41, 146.76, 157.96, 161.1 ppm; MS: m/z (%) = 342 (M^+ + 1, 60), 259 (34), 242 (100), 152 (25), 77 (20).

2,3-Dihydro-2-(4-hydroxyphenyl)-3-(thiazol-2-yl) quinazolin-4(1H)-one (**1v**, $C_{17}H_{13}N_3O_2S$)

Mp 263°C (dec); IR (KBr): $\bar{\nu}$ = 3346, 1638, 1614, 1511, 1453 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.61–7.77 (m, 10Ar-H), 7.27 (d, J = 3.18 Hz, CH), 8.07 (d, J = 3.2 Hz, NH), 9.47 (s, OH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 68.32, 114.18, 115.56, 115.94, 116.04, 118.52, 127.44, 128.61, 130.63, 135.45, 137.75, 147.12, 157.72, 158.1, 161.32 ppm; MS: m/z (%) = 324 (M^+ + 1, 80), 239 (80), 224 (100), 120 (25), 77 (20).

2-(2,4-Dichlorophenyl)-2,3-dihydro-3-(thiazol-2-yl)quinazolin-4(1H)-one (**1w**, $C_{17}H_{11}Cl_2N_3O_2S$)

Mp 226–228°C; IR (KBr): $\bar{\nu}$ = 3420, 3088, 2925, 1656, 1614, 1586, 1503, 1457 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.82–7.88 (m, 9Ar-H), 7.68 (s, CH), 7.98 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 66.43, 113.55, 116.34, 116.52, 119.15, 127.13, 127.97, 128.60, 130.29, 133.05, 134.38, 135.75, 136.33, 137.84, 145.51, 157.11, 161.28 ppm; MS: m/z (%) = 376 (M^+, 25), 291 (100), 276 (80), 186 (20), 77 (25).

2,3-Dihydro-2-(4-nitrophenyl)-3-(thiazol-2-yl) quinazolin-4(1H)-one (**1x**, $C_{17}H_{12}N_4O_3S$)

Mp 185–187°C; IR (KBr): $\bar{\nu}$ = 3328, 3104, 1639, 1614, 1510, 1445, 1390 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.77–8.16 (m, 10Ar-H + CH), 8.26 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 68.04, 114.16, 116.16, 116.47, 119.21, 124.22, 127.54, 128.77, 135.74, 137.77, 146.46, 147.7, 147.75, 157.87, 160.98 ppm; MS: m/z (%) = 353 (M^+ + 1, 55), 352 (M^+, 10), 268 (100), 254 (80), 207 (30), 77 (20).

2,3-Dihydro-2-(3-nitrophenyl)-3-(thiazol-2-yl) quinazolin-4(1H)-one (**1y**, $C_{17}H_{12}N_4O_3S$)

Mp 165–167°C; IR (KBr): $\bar{\nu}$ = 3362, 3079, 2962, 1639, 1529, 1507, 1445, 1390 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.77–8.19 (m, 10Ar-H), 7.51 (d, J = 3.24 Hz, CH), 8.31 (d, J = 3.24 Hz, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 67.82, 114.12, 116.22, 116.55, 119.21, 121.16, 123.72, 128.75, 130.71, 132.41, 135.79, 137.81, 142.73, 146.48, 148.37, 157.88, 160.97 ppm; MS: m/z (%) = 353 (M^+ + 1, 83), 268 (95), 253 (100), 207 (30), 77 (20).

Acknowledgement

Financial support by the Research Council of Shahid Beheshti University is gratefully acknowledged.

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