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RESEARCH ARTICLE

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Combinatorial Synthesis of 3-Arylideneaminoquinazolin-4(1*H*)-one Derivatives Catalyzed by Iodine in Ionic Liquids

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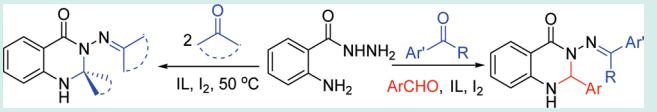
Supporting Information

ABSTRACT: A combinatorial synthesis of 3-arylideneaminoquinazolin-4(1*H*)-one derivatives is described by a reaction of 2-aminobenzohydrazides with two equivalents of aldehydes or ketones in ionic liquids catalyzed by iodine. Controlling the reaction temperature or reducing the activity of the substrates, respectively, the intermediate products of hydrazones were obtained first, and then they were applied to react with various aromatic aldehydes without being separated, resulting in structural diversification of quinazolinone derivatives.



KEYWORDS: quinazolin-4-(1*H*)-one, 2-aminobenzohydrazide, iodine, ionic liquid, synthesis

INTRODUCTION

Quinazolinones are an important class of molecules with physiological significance and pharmaceutical utility.[1] Especially for the 4(3*H*)-quinazolinone core, is well-known as a "privileged structure"[2] for drug design, which is defined as a class of molecules that are capable of binding to multiple receptors with high affinity.[3] The potential therapeutic applications of 4(3*H*)-quinazolinones include antiinflammatory,[4] antihypertensive,[5] anticancer,[6] antitumor,[7] and antibacterial activity.[8] They have recently also been evaluated as antagonists of various biological receptors, such as 5-HT_{5A} related diseases,[9] calcitonin gene-related peptide,[10] and vasopressin V3 receptors.[11] Among these 4(3*H*)-quinazolinones, aminoquinazolinones are bioactive molecules of particular importance, for example, 2-(arylamino)-4(3*H*)-quinazolinones (Figure 1, left) work as an inhibitor of the enzyme aldose reductase,[12] which prevents the onset of diabetic complications. Some 2-amino-4(3*H*)-quinazolinones (Figure 1, right) show antihypertensive activity[13] as well. It is reported that 2-aminobenzohydrazide reacts with aldehydes or ketones to provide 3-aminoquinazolinones.[14] However, these reported methods involve various disadvantages such as low yields, prolonged reaction times, and the use of metallic catalysts or toxic organic solvents. So development of a facile, metal-free catalyzed and green method to synthesis of 3-amonoquinazolinones appears desirable.

Over the past few years, molecular iodine (I_2) has emerged as a powerful catalyst for various organic transformations because of several advantages, such as its inexpensive, nontoxic, and ecofriendly nature.[15] In our previous paper,[16] we demonstrated that iodine was an effective catalyst to synthesis of quinazolinone derivatives from 2-aminobenzamides in ionic liquid. As a continuation of our research devoted to the development of new methods for the preparation of heterocycles in environmentally benign media,[17] we describe here the synthesis of 3-arylideneaminoquinazolin- 4(1*H*)-one derivatives in ionic liquids using iodine as catalyst.

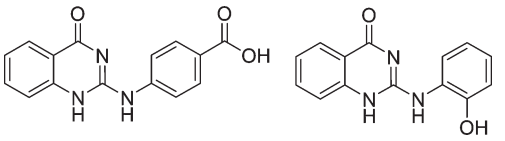
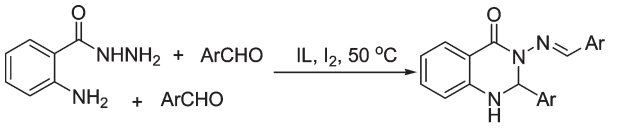


Figure 1. Interesting heterocycles.

Scheme 1. Reaction of 1 and Aldehyde in Ionic Liquid



1 **2** **3a-o**

RESULTS AND DISCUSSION

Treatment of 2-aminobenzohydrazide **1** with 2 equiv of aromatic aldehydes **2** in ionic liquid of [BMIm]Br in the presence of 5 mol % iodine at 50 °C resulted in the corresponding 3-(arylideneamino)-2,3-dihydro-2-arylquinazolin- 4(1*H*)-one derivatives **3a-o** in high yields (Scheme 1).

Using the conversion of 2-aminobenzohydrazide **1** and furan-2-carbaldehyde **2a** as a model, several parameters were explored as shown in Table 1. The yield of **3a** was low at 50 °C in the absence of iodine (29%, Table 1, entry 1), and much greater in

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Table 1. Synthetic Results of 3a under Different Reaction Conditions[a]

entry	I_2 (mol %)	ionic liquid[b]	temp/°C	yield (%)[c]
1	0	[BMIm]Br	80	29
2	1	[BMIm]Br	50	72
3	**5**	**[BMIm]Br**	**50**	**91**
4	10	[BMIm]Br	50	90
5	5	[BMIm]Br	rt	47
6	5	[BMIm]Br	80	90
7	5	[BMIm]Br	100	89
8	5	[EMIm]Br	50	85
9	5	[PMIm]Br	50	86
10	5	[EMIm]BF_4	50	84
11	5	[PMIm]BF_4	50	85

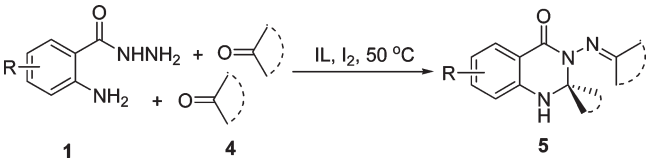
[a] Reaction condition: 2 mL of solvent, **1** (0.151 g, 1 mmol), **2a** (0.192 g, 2.0 mmol), and iodine (0.013 g, 0.05 mmol). [b] BMIm = 1-butyl-3-methylimidazolium; EMIm = 1-ethyl-3-methylimidazolium; PMIm = 1-methyl-3-propylimidazolium. [c] Isolated yields.

Table 2. Synthetic Results of 3a−o in Ionic Liquids[a]

entry	Ar	time (h)	products	yields (%)[b]
1	2-furyl	8	**3a**	91
2	2-thienyl	8	**3b**	88
3	C_6H_5	8	**3c**	83
4	2-BrC_6H_4	7	**3d**	82
5	2-ClC_6H_4	6	**3e**	92
6	3-ClC_6H_4	8	**3f**	90
7	2-FC_6H_4	6	**3g**	89
8	3,5-$(MeO)_2C_6H_3$	12	**3h**	86
9	2-$NO_2C_6H_4$	6	**3i**	89
10	4-$NO_2C_6H_4$	7	**3j**	84
11	4-ClC_6H_4	6	**3k**	84
12	2,4-$Cl_2C_6H_3$	6	**3l**	86
13	4-BrC_6H_4	8	**3m**	91
14	2-$CH_3OC_6H_4$	8	**3n**	90
15	4-$CH_3OC_6H_4$	7	**3o**	92

[a] Reaction condition: 2 mL [BMIm]Br, **1** (0.151 g, 1 mmol), **2** (2.0 mmol) and iodine (0.013 g, 0.05 mmol), 50 °C. [b] Isolated yields.

Scheme 2. Reaction of 1 and Ketone in Ionic Liquids



the presence of various quantities of the catalyst, reaching a maximum of 91% yield with 5 mol % iodine (Table 1, entries 2, 3, and 4). The yield of **3a** was also dependent on temperature (entries 5−7), proceeeding smoothly at 50 °C. Different imidazolium ionic liquid were also tested, and [BMIm]Br appeared to be the best medium for this transformation (entry 3 vs 8−11).

After reaction completion as monitored by TLC, products were isolated by simple filtration after the addition of a small amount of water to the cooled reaction mixture. Water in the filtrate was removed by distillation under reduced pressure, and the [BMIm]Br in the residue could be reused after being evaporated at 80 °C for 4 h in vacuum. Successive reuse of the recycled ionic liquid of [BMIm]Br in the model reaction gave high yields of **3a** (88%) even after the fourth cycle.

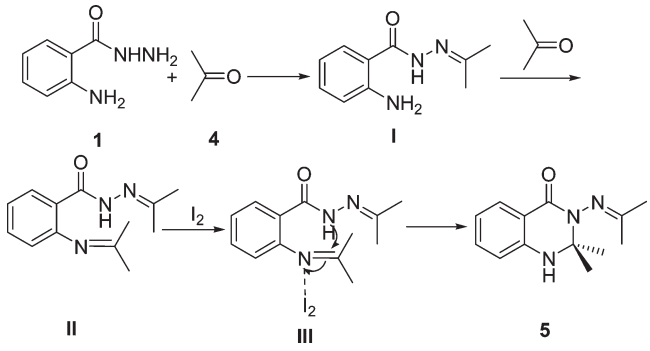
These optimized conditions were applied to the conversion of various kinds of aromatic aldehydes into the corresponding 3-(arylideneamino)-2,3-dihydro-2-arylquinazolin-4(1*H*)-one analogues. Reactions using aldehydes containing electron-withdrawing

Table 3. Synthetic Results of 5a−h in Ionic Liquids[a]

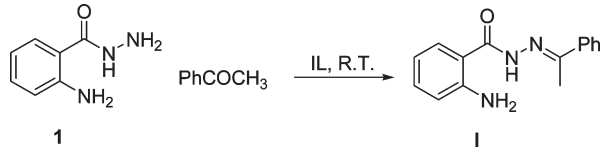
entry	R	ketone **4**	product	time (h)	yields (%)[b]
1	H	acetone	**5a**	10	78[c]
2	H	cyclopentanone	**5b**	12	82
3	H	cycloheptanone	**5c**	14	76
4	H	tetrahydropyran-4-one	**5d**	10	87
5	H	tetrahydrothiopyran-4-one	**5e**	10	86
6	4-Cl	tetrahydropyran-4-one	**5f**	8	87
7	4-Cl	tetrahydrothiopyran-4-one	**5g**	10	90
8	5-Br	tetrahydrothiopyran-4-one	**5h**	10	86

[a] Reaction condition: 2 mL [BMIm]Br, **1** (0.151 g, 1 mmol), **4** (2.0 mmol) and iodine (0.013 g, 0.05 mmol), 50 °C. [b] Isolated yields. [c] 95% Yield of **5a** was obtained if the amount of acetone was increased to 4 mmol.

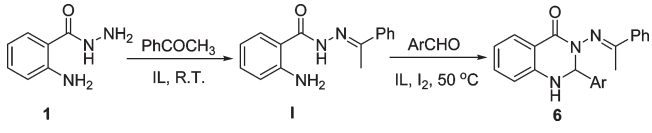
Scheme 3. Possible Mechanism for the Formation of Products 5



Scheme 4. Reaction of 1 and Acetophenone



Scheme 5. Separated Reaction of 1, Acetophenone, and 2



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Scheme 6. Separated Reaction of 1, 3-Nitrobenzaldehyde and 2

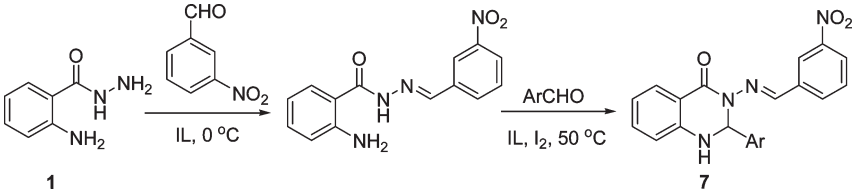

Table 4. Synthetic Results of 6a−i in Ionic Liquids[a]

entry	Ar	time (h)	products	yields (%)[b]
1	4-$CH_3C_6H_4$	8	**6a**	90
2	4-FC_6H_4	6	**6b**	92
3	2,4-$Cl_2C_6H_3$	4	**6c**	92
4	4-BrC_6H_4	6	**6d**	89
5	3-$NO_2C_6H_4$	4	**6e**	88
6	2-thienyl	6	**6f**	92
7	2-FC_6H_4	4	**6g**	90
8	C_6H_5	8	**6h**	93
9	3,4-$Me_2C_6H_3$	8	**6i**	87

[a] Reaction condition: 2 mL [BMIm]Br, **1** (0.151 g, 1 mmol), acetophenone (0.120 g, 1 mmol), r.t.; **2** (1 mmol) and iodine (0.013 g, 0.05 mmol), 50 °C. [b] Isolated yields.

groups (such as halide and nitro) or electron-donating groups (such as alkoxyl group) all proceeded smoothly within a few hours, giving **3a−o** with high yields (Table 2).

Ketones, including acetone, cyclic, and heterocyclic examples, also reacted smoothly with 2-aminobenzohydrazides under these conditions. These desired reactions generated the interesting spirocyclic quinazolin-4-(1*H*)-one derivatives in high yields, as shown in Scheme 2 and Table 3.

Consistent with previous suggestions in the literature,[18] we suggest that iodine catalyzes the reaction as a mild Lewis acid. The proposed mechanism was shown in Scheme 3 using acetone as reactant. The hydrazone **I** and Schiff base **II** are formed by condensation with acetone. Intramolecular attack on the iodine-activated intermediate **III** then forms the final quinazolin-4-(1*H*)-one derivatives **5**.

In partial support of this scheme, (*E*)-2-amino-*N*′-(1-phenylethylidene) benzohydrazide **I** was isolated in high yield (95%) upon reaction of acetophenone in place of acetone (in the absence of iodine) for 3 h (Scheme 4).

The clean isolation of intermediate hydrazide allowed us to introduce carbonyl components sequentially. Reaction of 2-aminobenzohydrazide with acetophenone at room temperature was followed by the addition of an equivalent of aromatic aldehyde in the presence of 5 mol % of iodine. In this way, a series of 3-(1-phenylethylideneamino)-2,3-dihydro-2-arylquinazolin-4(1*H*)-one derivatives **6** was obtained in high yields at 50 °C (Scheme 5, Table 4).

The sequential reaction could also be performed with 3-nitrobenzaldehyde if the first step was performed at 0 °C for 2 h to provide the intermediate hydrazone. Subsequent reaction with a second aromatic aldehyde at 50 °C gave 3-(3-nitrobenzylideneamino)-2,3-dihydro-2-arylquinazolin-4(1*H*)-one derivatives **7** in high yields (Scheme 6, Table 5). Other aldehydes we tested in the first step gave mixtures.

Table 5. Synthetic Results of 7a−j in Ionic Liquids[a]

entry	Ar	products	time (h)	yields (%)[b]
1	2-Furyl	**7a**	2.5	82
2	2-ClC_6H_4	**7b**	2.5	84
3	4-MeC_6H_4	**7c**	2	84
4	2-$CH_3OC_6H_4$	**7d**	2.5	86
5	2,3-$(CH_3O)_2C_6H_3$	**7e**	3	91
6	3-ClC_6H_4	**7f**	3	90
7	3-BrC_6H_4	**7g**	3	92
8	4-$NO_2C_6H_4$	**7h**	2	89
9	4-$CH_3OC_6H_4$	**7i**	3	88
10	PhCH═CH—	**7j**	3	85

[a] Reaction condition: 2 mL [BMIm]Br, **1** (0.151 g, 1 mmol), 3-nitrobenzaldehyde (0.151 g, 1 mmol), 0 °C; **2** (1 mmol), and iodine (0.013 g, 0.05 mmol), 50 °C. [b] Isolated yields.

CONCLUSION

In summary, an effective method has been developed for the combinatorial synthesis of 3-arylideneaminoquinazolin-4(1*H*)-ones. These reactions include 2-aminobenzohydrazides with two equivalents of aldehydes or ketones in ionic liquids catalyzed by iodine. The advantages of this procedure include mild reaction conditions, high yields, one-pot operational simplicity, and the use of environmentally benign conditions.

ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures, spectral data and copy figures of compounds **3a−o**, **5a−h**, **6a−i**, and **7a−j**, ORTEP images, simplified crystal data, and crystallographic information files (CIF) of **3a**, **5c**, **6i**, and **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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