# Facile Method for the Combinatorial Synthesis of 2,2-Disubstituted Quinazolin-4(1*H*)-one Derivatives Catalyzed by Iodine in Ionic Liquids

Xiang-Shan Wang,* Ke Yang, Jie Zhou, and Shu-Jiang Tu

*School of Chemistry and Chemical Engineering, Xuzhou Normal University, The Key Laboratory of Biotechnology on Medical Plant, Xuzhou Jiangsu 221116, P. R. China*

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A mild and facile method for the combinatorial synthesis of quinazolin-4-(1*H*)-one derivatives, containing simple 2,2-disubstituted quinazolin-4-(1*H*)-ones, spirocyclic quinazolin-4-(1*H*)-ones, spiro-heterocyclic quinazolin-4-(1*H*)-ones, and dispirocyclic quinazolin-4-(1*H*)-ones, is described, which results in high yields by using ionic liquids as green media. The method involves the reaction of 2-aminobenzamides with various ketones catalyzed by iodine and provides new quinazolin-4-(1*H*)-one library for biomedical screening.

## 1. Introduction

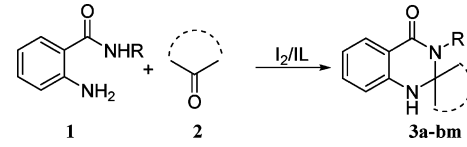
Room temperature ionic liquids (RTILs), especially those based on the 1-*N*-alkyl-3-methyl imidazolium cation, have shown great promise as attractive alternatives to conventional solvents.[1] The distinctive property of room temperature ionic liquids is that they have essentially no vapor pressure, which makes them optimal replacements for the volatile organic solvents traditionally used as industrial solvents. Another feature of ionic liquid is its ability to be reused many times. Because of these advantages, ionic liquids have made significant contributions to green chemistry and have been used widely as reaction medium in organic chemistry,[2] as well as in combinatorial chemistry.[3]

Quinazoline and its derivatives have recently been evaluated as antagonists of various biological receptors, such as 5-$HT_{5A}$ related diseases,[4] calcitonin gene-related peptide,[5] and vasopressin V3 receptors.[6] 2-Substituted quinazolines have also been tested for their potential activities, for example, antiinflammatory,[7] antihypertensive,[8] anticancer,[9] antitumor,[10] and antibacterial activity.[11] Hence, the synthesis of quinazoline derivatives is currently of great interest in organic synthesis. Previous methods reported for the synthesis of 2-arylquinazoline were based on 2-aminobenzamide with aromatic aldehyde catalyzed by $NH_4Cl$, $AlCl_3/ZnCl_2$, *p*-TSA, other Lewis acids, and asymmetric Bronsted acids[12] or one-pot condensation of isatoic anhydride and amines with aldehydes in organic solvent.[13] In addition, using 2-nitrobenzamide and aldehyde or ketone as reactants induced by low-valence titanium was also reported as a facile process to synthesize quinazoline derivatives in the literature.[14]

To the best of our knowledge, most of above-mentioned studies on the synthesis of quinazolines are focused on 2-monosubstituted ones using various aldehydes as reactants. Few examples has been given to obtain double substituents on the 2-position in quinazoline moieties from ketones. Furthermore, the known methods are described in organic solvent catalyzed by Alum or *p*-TSA.[15] These reported methods involve various disadvantages, such as low yields, prolonged reaction times, and the use of toxic organic reagents and catalysts. So, development of a facile and green method to synthesize 2,2-disubstituted quinazoline appears urgently necessary.

Over the past few years, molecular iodine ($I_2$) has emerged as a powerful catalyst for various organic transformations to afford the products in good to excellent yields. Because of several advantages, such as it being inexpensive, nontoxic, and eco-friendly, iodine has been used as a catalyst in the investigation of different organic reactions.[16] As a continuation of our research devoted to the development of new methods for the preparation of heterocycles in environmentally benign media and with iodine-catalyzed reactions,[17] we would like to synthesize these potential active compounds in ionic liquids using various ketones, including aliphatic, aromatic, cyclic, and heterocyclic ketones and cyclohexane-

**Scheme 1.** Reaction of **1** and Ketones in Ionic Liquid




**1** **2** **3a-bm**

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

| entry | temp./°C | ionic liquid[b] | $I_2$ (mol %) | time/h | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | 50 | [BMIm][$BF_4$] | 0 | 4 | 72 |
| 2 | rt | [BMIm][$BF_4$] | 5 | 4 | trace |
| 3 | 50 | [BMIm][$BF_4$] | 5 | 4 | 92 |
| 4 | 80 | [BMIm][$BF_4$] | 5 | 4 | 87 |
| 5 | 50 | [BMIm][$BF_4$] | 5 | 2 | 82 |
| 6 | 50 | [BMIm][$BF_4$] | 5 | 6 | 92 |
| 7 | 50 | [EMIm]Br | 5 | 4 | 84 |
| 8 | 50 | [PMIm]Br | 5 | 4 | 80 |
| 9 | 50 | [BMIm]Br | 5 | 4 | 83 |
| 10 | 50 | [EMIm][$BF_4$] | 5 | 4 | 90 |
| 11 | 50 | [PMIm][$BF_4$] | 5 | 4 | 90 |

[a] Reaction condition: 2 mL of solvent, 2-aminobenzamide (0.272 g, 2 mmol), acetone (0.122 g, 2.1 mmol), and iodine (0.026 g, 0.1 mmol). [b] BMIm = 1-butyl-3-methylimidazolium; EMIm = 1-ethyl-3-methylimidazolium; PMIm = 1-methyl-3-propylimidazolium. [c] Isolated yields.

* To whom correspondence should be addressed. E-mail: xswang1974@yahoo.com.

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**Table 2.** Synthetic Results of **3aa**−**cm** in Ionic Liquids[a]

| entry | R | 2 | time (h) | products | yields (%)[b] |
|---|---|---|---|---|---|
| 1 | H | acetone | 4 | **3aa** | 92 |
| 2 | H | butan-2-one | 5 | **3ab** | 96 |
| 3 | H | pentan-2-one | 4 | **3ac** | 95 |
| 4 | H | 3-methylbutan-2-one | 6 | **3ad** | 90 |
| 5 | H | hexan-2-one | 4 | **3ae** | 95 |
| 6 | H | hexan-3-one | 6 | **3af** | 98 |
| 7 | H | 4-methylpentan-2-one | 5 | **3ag** | 93 |
| 8 | 4-$MeOC_6H_4(CH_2)_2$ | acetone | 6 | **3ah** | 90 |
| 9 | 4-$FC_6H_4$ | acetone | 4 | **3ai** | 90 |
| 10 | Ph | acetone | 4 | **3aj** | 90 |
| 11 | H | acetophenone | 8 | **3ak** | 89 |
| 12 | H | 4′-nitroacetophenone | 6 | **3al** | 88 |
| 13 | H | 3′-chloroacetophenone | 7 | **3am** | 90 |
| 14 | H | 4′-chloroacetophenone | 6 | **3an** | 89 |
| 15 | H | 4′-methylacetophenone | 8 | **3ao** | 86 |
| 16 | H | 4′-fluoroacetophenone | 5 | **3ap** | 90 |
| 17 | H | 3′-bromoacetophenone | 6 | **3aq** | 87 |
| 18 | H | 4′-bromoacetophenone | 8 | **3ar** | 86 |
| 19 | Ph | 4′-nitroacetophenone | 6 | **3as** | 92 |
| 20 | H | 1-(3-chlorophenyl)propan-1-one | 8 | **3at** | 92 |
| 21 | H | cyclopentanone | 6 | **3au** | 89 |
| 22 | H | cyclohexanone | 6 | **3av** | 94 |
| 23 | H | cycloheptanone | 6 | **3aw** | 90 |
| 24 | H | cyclooctanone | 5 | **3ax** | 92 |
| 25 | H | cyclododecanone | 5 | **3ay** | 82 |
| 26 | 4-$FC_6H_4$ | cyclohexanone | 7 | **3az** | 93 |
| 27 | 4-$MeC_6H_4$ | cyclohexanone | 8 | **3ba** | 93 |
| 28 | Ph | cyclohexanone | 8 | **3bb** | 90 |
| 29 | 4-$MeOC_6H_4$ | cyclohexanone | 7 | **3bc** | 88 |
| 30 | H | 2,3-dihydroinden-1-one | 8 | **3bd** | 82 |
| 31 | H | 1*H*-inden-2(3*H*)-one | 6 | **3be** | 92 |
| 32 | H | naphthalen-1-one | 10 | **3bf** | 78 |
| 33 | Ph | 1*H*-inden-2(3*H*)-one | 6 | **3bg** | 89 |
| 34 | 4-$MeOC_6H_4$ | 1*H*-inden-2(3*H*)-one | 6 | **3bh** | 93 |
| 35 | $C_6H_5CH_2$ | 1*H*-inden-2(3*H*)-one | 6 | **3bi** | 93 |
| 36 | 4-$MeOC_6H_4CH_2$ | 1*H*-inden-2(3*H*)-one | 7 | **3bj** | 90 |
| 37 | H | tetrahydropyran-4-one | 6 | **3bk** | 90 |
| 38 | H | chroman-4-one | 8 | **3bl** | 82 |
| 39 | Ph | tetrahydropyran-4-one | 6 | **3bm** | 88 |
| 40 | 4-$MeC_6H_4$ | tetrahydropyran-4-one | 6 | **3bn** | 91 |
| 41 | 4-$MeOC_6H_4$ | tetrahydropyran-4-one | 6 | **3bo** | 92 |
| 42 | 4-$FC_6H_4$ | tetrahydropyran-4-one | 6 | **3bp** | 89 |
| 43 | $C_6H_5CH_2$ | tetrahydropyran-4-one | 4 | **3bq** | 93 |
| 44 | 4-$MeOC_6H_4CH_2$ | tetrahydropyran-4-one | 4 | **3br** | 93 |
| 45 | H | tetrahydrothiopyran-4-one | 4 | **3bs** | 87 |
| 46 | H | thiochroman-4-one | 9 | **3bt** | 84 |
| 47 | Ph | tetrahydrothiopyran-4-one | 6 | **3bu** | 85 |
| 48 | 4-$MeC_6H_4$ | tetrahydrothiopyran-4-one | 6 | **3bv** | 87 |
| 49 | 4-$MeOC_6H_4$ | tetrahydrothiopyran-4-one | 6 | **3bw** | 82 |
| 50 | $C_6H_5CH_2$ | tetrahydrothiopyran-4-one | 5 | **3bx** | 90 |
| 51 | 4-$FC_6H_4$ | tetrahydrothiopyran-4-one | 5 | **3by** | 83 |
| 52 | 4-$MeOC_6H_4CH_2$ | tetrahydrothiopyran-4-one | 5 | **3bz** | 92 |
| 53 | Naphthalen-2-yl | tetrahydrothiopyran-4-one | 9 | **3ca** | 80 |
| 54 | H | 1-benzylpiperidin-4-one | 6 | **3cb** | 93 |
| 55 | H | ethyl 4-oxopiperidine-1-carboxylate | 6 | **3cc** | 88 |
| 56 | H | *t*-butyl 4-oxopiperidine-1-carboxylate | 6 | **3cd** | 89 |
| 57 | 4-$MeOC_6H_4$ | *t*-butyl 4-oxopiperidine-1-carboxylate | 8 | **3ce** | 83 |
| 58 | 4-$MeC_6H_4$ | *t*-butyl 4-oxopiperidine-1-carboxylate | 8 | **3cf** | 81 |
| 59 | Ph | *t*-butyl 4-oxopiperidine-1-carboxylate | 8 | **3cg** | 84 |
| 60 | 4-$FC_6H_4$ | *t*-butyl 4-oxopiperidine-1-carboxylate | 8 | **3ch** | 82 |
| 61 | $C_6H_5CH_2$ | *t*-butyl 4-oxopiperidine-1-carboxylate | 6 | **3ci** | 92 |
| 62 | 4-$MeOC_6H_4CH_2$ | *t*-butyl 4-oxopiperidine-1-carboxylate | 6 | **3cj** | 92 |
| 63 | 4-$MeOC_6H_4$ | ethyl 4-oxopiperidine-1-carboxylate | 8 | **3ck** | 79 |
| 64 | 4-$MeC_6H_4$ | ethyl 4-oxopiperidine-1-carboxylate | 8 | **3cl** | 88 |
| 65 | 4-$FC_6H_4$ | ethyl 4-oxopiperidine-1-carboxylate | 8 | **3cm** | 76 |

[a] Reaction condition: 2 mL of [BMIm][$BF_4$], **1** (2 mmol), **2** (2.1 mmol), and iodine (0.1 mmol), 50 °C. [b] Isolated yields.

1,4-dione as reactants to react with 2-aminobenzamides to build 2,2-disubstituted quinazolin-4-(1*H*)-one derivatives catalyzed by iodine. Such variations may contribute to the bioactivity differences and enrich the compound library for biomedical screening.

## 2. Results and Discussion

Treatment of 2-aminobenzamides **1** and ketones **2** in ionic liquid of [BMIm]$BF_4$ in the presence of 5 mol % iodine at 50 °C resulted in the corresponding 2,2-disubstituted quinazolin-4-(1*H*)-one derivatives**3aa-cm** in high yields (Scheme 1).

Using the conversion of 2-aminobenzamide and acetone as a model reaction, different reaction temperatures were tested to optimize the conditions first. A summary of the optimization experiment is listed in Table 1. In our initial study, the reaction of 2-aminobenzamide and acetone was carried out in the absence of iodine at 50 °C, with moderate yield of **3aa** being obtained (72%, Table 1, entry 1). However, the other ketones we tested, in Table 2, gave poor yields, so a small amount of iodine (10 mol %) was added to enhance the rate of conversion. To our delight, the yield of **3aa** increased distinctly (92%), as expected. The reaction temperature also played an important role in this reaction. It turned out that only trace amount of product was detected by TLC at room temperature, (Table 1, entry 2), while the reaction went smoothly at 50 °C to produce a high yield. To find the optimum reaction time, the reaction was carried out in ionic liquid [BMIm][$BF_4$] for 2, 4, and 6 h (Table 1, entries 5, 3, and 6, respectively), resulting in the isolation of **3aa** in 82%, 92%, and 92% yield, correspondingly. Thus, reaction conditions of 50 °C and 4 h were identified as the optimum. Moreover, different ionic liquids were further studied. As shown in Table 1, different groups on the methylimidazolium, anions were chosen as media for this reaction, and [BMIm][$BF_4$] appeared to be the best media for this reaction.

After reaction completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. A small amount of water was added to the mixture, and the product was isolated by filtration. Water in the filtrate was removed by distillation under reduced pressure, and [BMIm][$BF_4$] in the residue could be reused after being evaporated at 80 °C for 4 h in vacuum. Investigations using 2-aminobenzamide and acetone as model substrates showed with with the successive reuse of the recycled ionic liquid of [BMIm][$BF_4$], even in the fourth cycle, the yield of the product **3aa** is fairly high (85%).

First of all, these optimized conditions were applied for the conversion of various kinds of aliphatic ketones and 2-aminobenzamides **1** into the corresponding 2,2-disubstituted quinazolin-4-(1*H*)-one analogues (Table 2, entries 1−10). Among these analogues, ketones containing higher hindrance, such as 3-methylbutan-2-one and 4-methylpentan-2-one (Table 2, entries 4 and 7), also gave satisfactory results. Even to inactive aromatic ketones, the reactions proceeded smoothly within a few hours and resulted in good to high yields (Table 2, entries 11−20). Subsequently, the substrate of chain ketones was extended to cyclic ones; for example, cyclopentanone, cyclohexanone, 3,4-dihydronaphthalen-1(2*H*)-one, 2,3-dihydroinden-1-one, and 1*H*-inden-2(3*H*)-one were also chosen to react with 2-aminobenzamides. The desired reactions were found to generate the interesting spirocyclic quinazolin-4-(1*H*)-one derivatives in high yields (Table 2, entries 21−36).

In our continued study, it was also found that spiro-heterocyclic quinazolin-4-(1*H*)-one derivatives were obtained easily in high yields (Table 2, entries 37−65) under the same reaction conditions, when the cyclic ketones were replaced by heterocyclic ketones. These heterocyclic ketones included tetrahydropyran-4-one, tetrahydrothiopyran-4-one, piperidin-4-one, chroman-4-one and thiochroman-4-one. The structures of **3ad**, **3aw**, and **3bs** were further confirmed by X-ray diffraction analysis, and their crystal structures are shown in Figures 1−3, respectively.

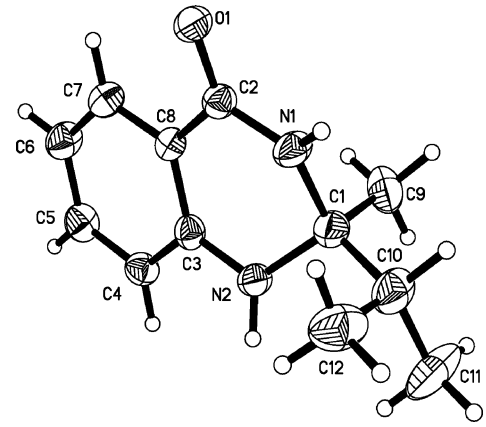



**Figure 1.** Crystal structure of the product **3ad**.

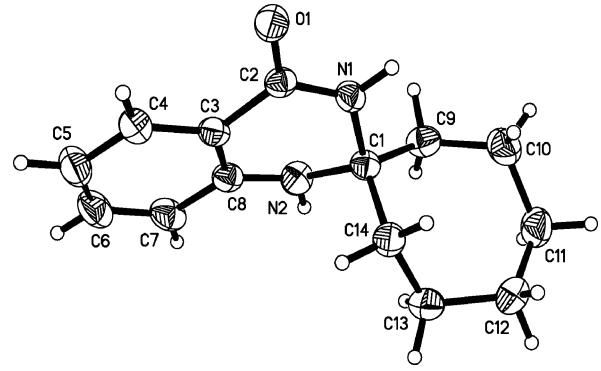



**Figure 2.** Crystal structure of the product **3aw**.

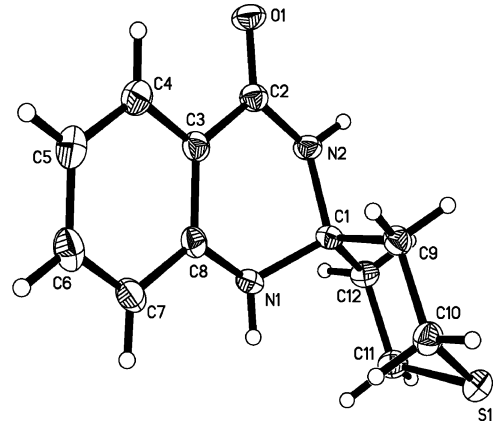
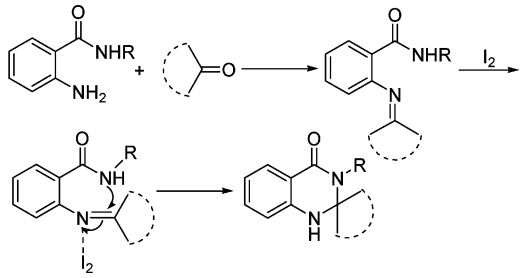



**Figure 3.** Crystal structure of the product **3bs**.

According to the literature,[18] it is believed that iodine catalyzes the reaction as a mild Lewis acid. The proposed mechanism is shown in Scheme 2. The Schiff base is formed by the reaction of 2-aminobenzamide and ketone first; then the intramolecular amino group immediately attacks iodine-activated Schiff base to form final quinazolin-4-(1*H*)-one derivatives.

To obtain dispirocyclic compounds containing quinazolin-4-(1*H*)-one derivatives, the cyclohexane-1,4-dione was used to react with two molecules of 2-aminobenzamides (Scheme 3), with 1″,3″-dihydrospiro[1′,3′-dihydrospiro[cyclo hexane-1,2′-quinazolin]-4′-one-4,2″-quinazolin]-4″-one derivatives

**Scheme 2.** Possible Mechanism for the Formation of Products **3**



**Scheme 3.** Reaction of **1** and Cyclohexane-1,4-dione in Ionic Liquid

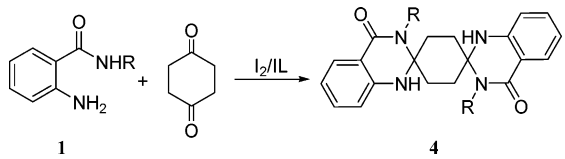


**Table 3.** Synthetic Results of **4aa**−**ah** in Ionic Liquids[a]

| entry | R | products | time (h) | yields (%)[b] |
|---|---|---|---|---|
| 1 | H | **4aa** | 4 | 96 |
| 2 | $C_6H_5CH_2$ | **4ab** | 4 | 95 |
| 3 | Ph | **4ac** | 6 | 90 |
| 4 | 4-$MeOC_6H_4CH_2$ | **4ad** | 5 | 93 |
| 5 | 4-$MeOC_6H_4(CH_2)_2$ | **4ae** | 5 | 96 |
| 6 | $C_6H_5(CH_2)_2$ | **4af** | 5 | 96 |
| 7 | 4-$MeC_6H_4$ | **4ag** | 8 | 87 |
| 8 | 4-$FC_6H_4$ | **4ah** | 8 | 84 |

[a] Reaction condition: 2 mL of [BMIm][$BF_4$], **1** (2 mmol), cyclohexane-1,4-dione (1.05 mmol), and iodine (0.05 mmol), 50 °C. [b] Isolated yields.

being obtained in high yields (Table 3). All the compounds were characterized by $^1$H NMR, $^{13}$C NMR, IR, and HRMS.

## 3. Conclusion

In summary, a mild, facile and environmentally benign method is developed for the combinatorial synthesis of quinazolin-4-(1*H*)-one derivatives in high yields catalyzed by iodine in ionic liquids. The advantages of this procedure include its mild reaction conditions, high yields, one-pot method, operational simplicity, and environmental benignity. Meanwhile, this method provides new compounds containing quinazolinone moiety for biomedical screening.

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**Supporting Information Available.** Crystallographic data for the structures of **3ad**, **3aw**, and **3bs** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications CCDC-758992, CCDC-758993, and CCDC-758994, respectively. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-(0) 1223−336033 or e-mail: deposit@ccdc.cam.ac.uk). Representative experimental procedures and spectral data of compounds **3aa**−**cm** and **4aa**−**ah**. This material is available free of charge via the Internet at http://pubs.acs.org.

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