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Structurally diversified products from the reactions of 2-aminobenzamides with 1,3-cyclohexanediones catalyzed by iodine

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ABSTRACT

Controlling the reaction temperature at 50 °C, 80 °C, and 110 °C, respectively, the iodine-catalyzed reaction of 2-aminobenzamides with 1,3-cyclohexanediones gave structurally diversified products. In the latter, it gave bis-quinazolin-4(3*H*)-ones unexpectedly, with 1,3-cyclohexanediones ring-opening.

Introduction

Quinazoline and its derivatives are an important class of heterocyclic compounds, which have attracted a considerable attention for their anti-cancer activity,[1] and have also been tested for their potential biological and pharmacological activities, for example anti-inflammatory,[2] anti-hypertensive,[3] anti-tumor,[4] and anti-bacterial activity.[5] Recently, they have also been evaluated as antagonists of various biological receptors, such as treating 5-HT_{5A} receptor related diseases,[6] antagonists of calcitonin gene-related peptide receptor,[7] vasopressin V3 receptor antagonists.[8] Hence, the synthesis of quinazoline derivatives is currently of great interest both in organic synthesis and medicinal chemistry.[9]

To our knowledge, only a few literature studies concern about the synthesis of bis-quinazoline derivatives.[10] As a novel member of this family, it contains two quinazoline moieties, may afford unique biological activities. In our previous study,[10a] we have described that quinazolin-4(3*H*)-one or bis-quinazolin-4(3*H*)-one derivatives were obtained in high yields, using 2-aminobenzamides and various kinds of aldehydes or ketones including 1,4-cyclohexanedione as reactants in ionic liquids catalyzed by iodine. As a continued study to the synthesis of the potential biological active molecules and with iodine-catalyzed reactions, herein, we would like to report the reaction of 2-aminobenzamide with 1,3-cyclohexanedione catalyzed by iodine. With the unexpected ring-opening of 1,3-cyclohexanedione, novel bis-quinazolin-4(3*H*)-one derivatives were obtained in moderate yields respectively.

Results and Discussions

Treatment of 2-aminobenzamide **1a** with an equivalent of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **2a** in toluene at 100 °C catalyzed by 5 mol % iodine, gave 2-(3-(1,2,3,4-tetrahydro-2-methyl-4-oxoquinazolin-2-yl)-2,2-dimethylpropyl)quinazolin-4(3*H*)-one **3a** in 42% yield unexpectedly (Scheme 1).

Subsequently, reaction conditions including reaction temperature, amount of iodine, and mole ratio, were optimized in our lab. The yield of **3a** was improved to 72% in toluene at reflux catalyzed by 10 mol % iodine, with a molar ratio of **1a** and **2a** being 2.1:1. Under the optimized reaction conditions, various kinds of 2-aminobenzamides **1** and 1,3-cyclohexanediones **2** were subjected to the reaction to give **3a**–**i** in moderate yields (65–75%, Scheme 2, Table 1). The structure of **3a** was confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 1.

According to the structure of the product and the literature,[12] we think that the dehydration, isomerization, cyclization, ring-opening of dimedone, second dehydration, and cyclization reactions may take place in a sequence. The proposed mechanism was outlined in Scheme 3.

In order to get more insight into the above-mentioned reaction, we lowered the reaction temperature to obtain the intermediates. To our delight, intermediate **5a** was isolated in 43% yield,[13] when the reaction temperature was controlled at 80 °C, with the molar ratio of **1a** and **2a** being 1.1:1 (Scheme 4). The structure of **5a**

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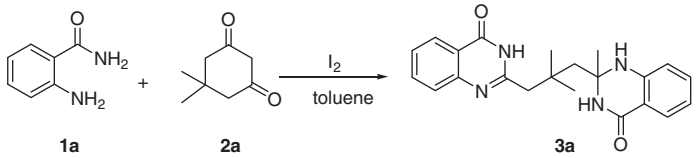
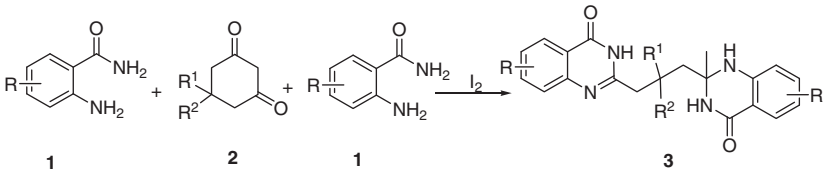


Scheme 1. The model reaction of **1a** and **2a**.



Scheme 2. The reaction of **1** and **2** in toluene.

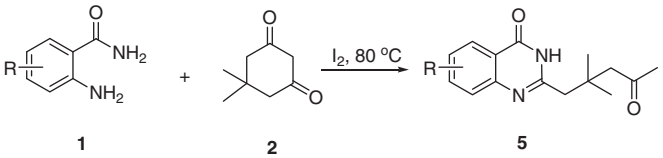
Table 1
Synthetic results of **3a–i** in toluene [a,11]

Products	R	R^1	R^2	Time (h)	Isolated yields (%)
3a	H	CH_3	CH_3	12	72
3b	4-Cl	CH_3	CH_3	15	68
3c	5-Cl	CH_3	CH_3	16	70
3d	5-CH_3	CH_3	CH_3	10	75
3e	H	H	CH_3	15	65
3f	5-CH_3	H	CH_3	12	73
3g	5-Br	H	CH_3	11	67
3h	4-Cl	H	CH_3	14	70
3i	5-CH_3	H	H	13	65

[a] Reaction condition: toluene (10.0 mL), **1** (2.1 mmol), **2** (1.0 mmol) and iodine (0.026 g, 0.01 mmol), 110 °C.

was agreed with the one[14] reported by Miyano and Lessel, respectively.

In our continued study, intermediate products **5** were obtained without further separation, then, they were treated with another equivalent of different 2-aminobenzamide directly at 110 °C (Scheme 5), giving structurally diversified bis-quinazolin-4(3*H*)-one derivatives **6a–g** in moderate yields (Table 2) as we expected.



5a: R = H, 43 %; **5b**: R = 5-CH_3, 58 %; **5c**: R = 5-Br, 62 %

Scheme 4. The synthetic route of products **5a–c**.

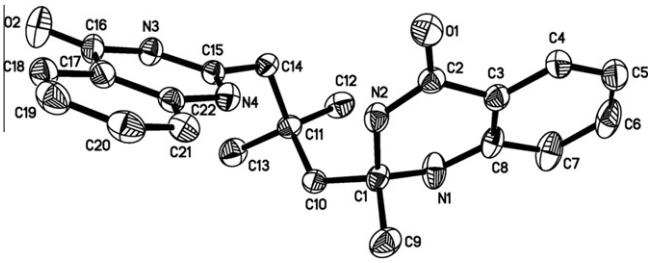
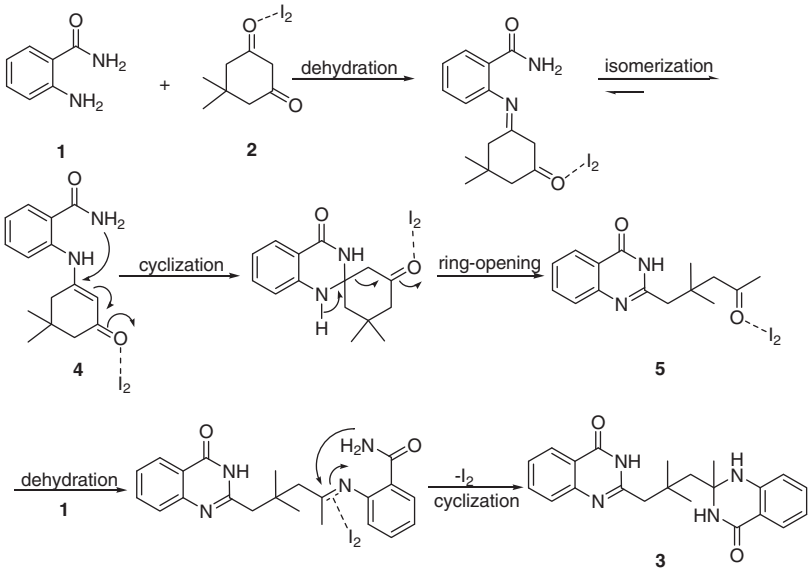
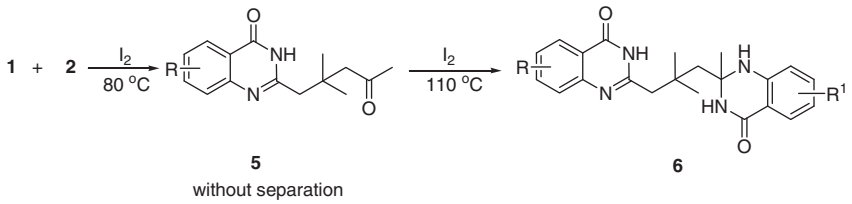


Figure 1. Crystal structure of product **3a**.



Scheme 3. The possible mechanism for the formation of product **3**.



Scheme 5. The crisscross reaction of **2** with two different equivalents of **1**.

Table 2
Synthetic results of **6a–g** in toluene [a,15]

Entry	R	R^1	Products	Isolated yields (%)
1	H	5-Br	**6a**	63
2	H	3-CH_3	**6b**	65
3	H	4-Cl	**6c**	70
4	H	5-Cl	**6d**	74
5	H	5-CH_3	**6e**	65
6	5-CH_3	4-Cl	**6f**	76
7	5-CH_3	5-Cl	**6g**	70

[a] Reaction condition: toluene (10.0 mL), **1** (1.1 mmol), dimedone (0.140 g, 1.0 mmol), and iodine (0.026 g, 0.01 mmol), 80 °C; then **1** (1.0 mmol), 110 °C.

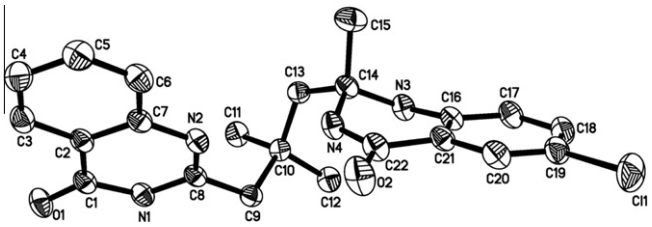


Figure 2. Crystal structure of product **6d**.

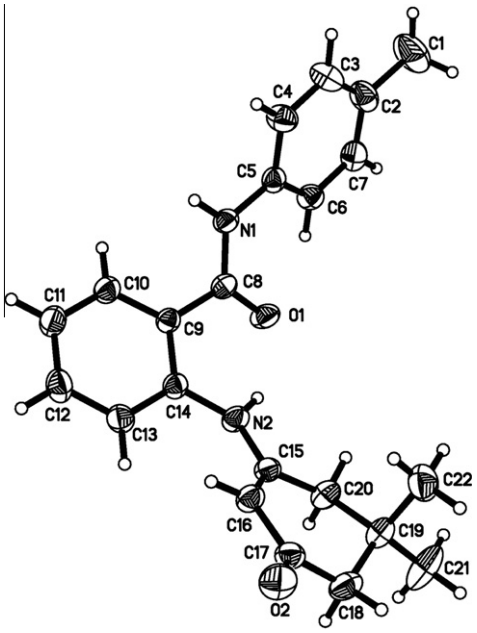
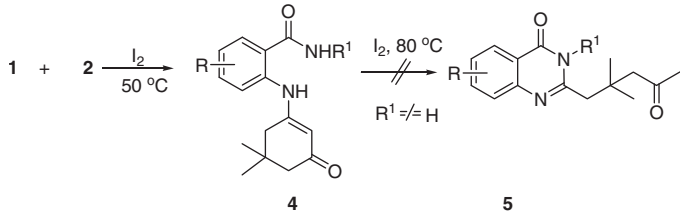


Figure 3. Crystal structure of intermediate **4f**.

Table 3
Synthetic results of **4a–l** in toluene [a,16]

Entry	R	R^1	Products	Time (h)	Isolated yields (%)
1	H	H	**4a**	6	90
2	H	Ph	**4b**	8	92
3	H	4-$MeOC_6H_4CH_2$	**4c**	8	87
4	H	3-Cl-4-FC_6H_3	**4d**	10	84
5	H	4-FC_6H_4	**4e**	10	88
6	H	4-MeC_6H_4	**4f**	8	90
7	H	2-Furylmethyl	**4g**	8	93
8	H	4-*i*-PrC_6H_4	**4h**	8	91
9	H	4-*n*-BuC_6H_4	**4i**	6	87
10	5-Me	H	**4j**	6	90
11	5-Cl	H	**4k**	10	86
12	5-Br	H	**4l**	10	86

[a] Reaction condition: toluene (10 mL), **1** (2.1 mmol), dimedone (0.280 g, 2.0 mmol), and iodine (0.026 g, 0.01 mmol), 50 °C.



Scheme 6. The reaction of **1** and **2** at 50 °C.

One of the products **6d** was also confirmed by X-ray diffraction analysis and its crystal structure is shown in Figure 2.

It is very interesting that intermediates **4a–l** were obtained in high yields (Table 3), when the reaction temperature was further lowered to 50 °C catalyzed by 5 mol % iodine. In addition, it was found that **4** with substituent on the nitrogen atom of amide could not be further converted into **5**. Perhaps, a high steric effect hindered the subsequent cyclization and ring-opening reactions. Therefore, the reaction was held at the stage of enamine (Scheme 6). The structure of **4f** was additionally confirmed by X-ray diffraction analysis and its crystal structure is shown in Figure 3.

Conclusion

In summary, the interesting and iodine-catalyzed reaction of 2-aminobenzamides with 1,3-cyclohexanediones is described in this Letter. Controlling the reaction temperature, it gives structurally diversified products, respectively, and produces novel and unexpected bis-quinazolinone derivatives at 110 °C finally.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.042.

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11. *General procedure for the synthesis of **3**:* A dry 50 mL flask was charged with 2-aminobenzamides **1** (2.1 mmol), 1,3-cyclohexanedione **2** (1.0 mmol), iodine (0.026 g, 0.01 mmol) and toluene (10.0 mL). The mixture was stirred at reflux until the reactant was consumed. After the completion of the reaction monitored by TLC, toluene was recovered by distillation under reduced pressure, and the residue was purified by silica column chromatography using ethyl acetate and petroleum ether (1:3) as the eluent to give **3**. 2-(2,2-Dimethyl-3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propyl)quinazolin-4(3*H*)-one (**3a**): mp 250–252 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 1.10 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.74–1.84 (m, 2H, CH_2), 2.67–2.77 (m, 2H, CH_2), 6.59–6.65 (m, 2H, ArH), 6.89 (s, 1H, NH), 7.19–7.23 (m, 1H, ArH), 7.47–7.51 (m, 1H, ArH), 7.57–7.63 (m, 2H, ArH), 7.79–7.83 (m, 1H, ArH), 8.11 (d, J = 8.0 Hz, 1H, ArH), 8.26 (s, 1H, NH), 12.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_C 28.9, 31.2, 35.0, 45.6, 48.6, 69.7, 113.2, 114.0, 116.0, 120.6, 125.7, 126.1, 126.6, 127.1, 133.3, 134.4, 146.7, 148.2, 156.0, 161.6, 162.6. IR (KBr): 3374, 3139, 3036, 2969, 2928, 2780, 1600, 1567, 1518, 1501, 1470, 1436, 1387, 1275, 1248, 1224, 1196, 1145, 1132, 1072, 894, 788, 765 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{22}H_{24}N_4O_2Na$ [M+Na]$^+$ 399.1797, found 399.1846.
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13. *General procedure for the synthesis of **5**:* A dry 50 mL flask was charged with 2-aminobenzamides **1** (1.1 mmol), dimedone (0.140 g, 1.0 mmol), iodine (0.026 g, 0.01 mmol) and toluene (10.0 mL). The mixture was stirred at 50 °C until the reactant was consumed. After the completion of the reaction monitored by TLC, toluene was recovered by distillation under reduced pressure, and the residue was purified by silica column chromatography using ethyl acetate and petroleum ether (1:3) as the eluent to give products **5**. 2-(2,2-Dimethyl-4-oxopentyl) quinazolin-4(3*H*)-one (**5a**): mp 157–158 °C (Lit.[14b]: 158–160 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 1.06 (s, 6H, 2CH_3), 2.11 (s, 3H, CH_3), 2.04 (s, 2H, CH_2), 2.64 (s, 2H, CH_2), 7.45–7.49 (m, 1H, ArH), 7.59 (d, J = 8.0 Hz, 1H, ArH), 7.76–7.80 (m, 1H, ArH), 8.09 (d, J = 7.6 Hz, 1H, ArH), 12.08 (s, 1H, NH). IR (KBr): 3166, 3038, 3003, 2950, 2919, 2881, 1714, 1684, 1617, 1470, 1419, 1399, 1366, 1337, 1262, 1252, 1162, 964, 908, 772 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{15}H_{17}N_2O_2$ [M−H]$^-$ 257.1282, found 257.1288.
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15. *General procedure for the synthesis of **6**:* A dry 50 mL flask was charged with 2-aminobenzamide **1** (1.1 mmol), dimedone (0.140 g, 1.0 mmol), iodine (0.026 g, 0.01 mmol) and toluene (10.0 mL). The mixture was stirred at 80 °C until the reactant was consumed. Then, another equivalent of 2-aminobenzamide was added to the mixture, and refluxed for a few hours. After the completion of the reaction monitored by TLC, toluene was recovered by distillation under reduced pressure, and the residue was purified by silica column chromatography using ethyl acetate and petroleum ether (1:2) as the eluent to give products **6**. 2-(3-(6-Chloro-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)-2,2-dimethylpropyl)quinazolin-4(3*H*)-one (**6d**): mp 258–262 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 1.09 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.76–1.86 (m, 2H, CH_2), 2.74–2.79 (m, 2H, CH_2), 6.67 (d, J = 8.4 Hz, 1H, ArH), 7.10 (s, 1H, NH), 7.24 (d, J = 8.0 Hz, 1H, ArH), 7.47–7.50 (m, 2H, ArH), 7.59–7.61 (m, 1H, ArH), 7.79–7.82 (m, 1H, ArH), 8.10 (d, J = 7.6 Hz, 1H, ArH), 8.45 (s, 1H, NH), 12.18 (s, 1H, NH). IR (KBr): 3286, 3209, 3128, 3043, 2974, 2927, 1687, 1651, 1613, 1516, 1487, 1472, 1452, 1425, 1359, 1336, 1251, 1219, 1196, 1148, 1136, 1125, 1074, 1012, 971, 919, 901, 824, 787, 771 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{22}H_{23}ClN_4NaO_2$ [M+H]$^+$ 411.1588, found 411.1602.
16. *General procedure for the synthesis of **4**:* A dry 50 mL flask was charged with 2-aminobenzamides **1** (2.1 mmol), dimedone (0.280 g, 2.0 mmol), iodine (0.026 g, 0.01 mmol) and toluene (10.0 mL). The mixture was stirred at 50 °C until the reactant was consumed. After the completion of the reaction monitored by TLC, toluene was recovered by distillation under reduced pressure, and the residue was purified by recrystallization in EtOH to give products **4**. 2-((5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)amino)-*N*-(*p*-tolyl)-benzamide (**4f**): mp 212–214 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 0.96 (s, 6H, 2CH_3), 1.99 (s, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.33 (s, 2H, CH_2), 5.15 (s, 1H, CH), 7.14 (d, J = 8.4 Hz, 2H, ArH), 7.31–7.39 (m, 2H, ArH), 7.53–7.57 (m, 3H, ArH), 7.69 (d, J = 7.6 Hz, 1H, ArH), 8.89 (s, 1H, NH), 10.26 (s, 1H, NH). IR (KBr): 3275, 3187, 3133, 2951, 2888, 1651, 1623, 1597, 1487, 1442, 1403, 1369, 1319, 1232, 1210, 1167, 1147, 1119, 1083, 952, 894, 818, 759 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{22}H_{24}N_2O_2Na$ [M+Na]$^+$ 371.1735, found 371.1761.