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# An efficient synthesis of 2,3-diaryl (3*H*)-quinazolin-4-ones via imidoyl chlorides

Andrew Kalusa, Nicola Chessum, Keith Jones *

*Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK*

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ABSTRACT

A practical and efficient three step synthetic route to 2,3-diaryl (3*H*)-quinazolin-4-ones has been developed. The key step involves microwave-assisted condensation of an imidoyl chloride with an aryl amine. This methodology affords the products cleanly and in high yields.



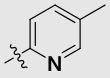
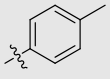
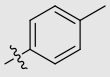
The quinazolinone moiety is a widely researched scaffold in medicinal chemistry. The quinazolinone core is found in a range of compounds exhibiting a broad spectrum of biological effects. These include kinase inhibition,[1] anticancer,[2] antimalarial,[3,4] diabetes and obesity.[5]

Over the years, the broad range of biological properties of 2,3-disubstituted (3*H*)-quinazolin-4-ones has prompted considerable synthetic efforts. Although a number of synthetic methodologies have been reported, accessing 2,3-diaryl (3*H*)-quinazolin-4-ones continues to be problematic owing to the limited nucleophilicity of aromatic amines.[6–12]

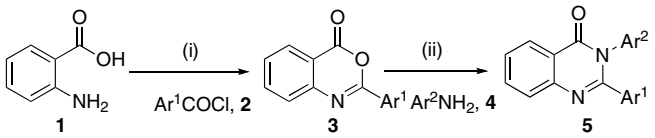
As part of our research programme, we needed to synthesise a series of 2,3-diaryl (3*H*)-quinazolin-4-one derivatives. The most commonly employed method for the synthesis of compounds with this substitution pattern involves condensation of benzoxazinone **3** with an amine **4** at high temperature[13,14] (Scheme 1).

Benzoxazinones **3** were synthesised by the reaction of anthranilic acid **1** with an acyl chloride **2** followed by dehydration. Subsequent microwave heating of benzoxazinones **3** with an aromatic amine **4** in DMF at 150 °C afforded the 2,3-disubstituted (3*H*)-quinazolin-4-one **5** in low yield (Scheme 1). The results are summarised in Table 1. The low yields obtained via this route were ascribed to poor nucleophilicity of the aryl amines.

**Table 1**
Synthesis of 2,3-diaryl (3*H*)-quinazolin-4-ones **5** from benzoxazinones **3**

| Entry | $Ar^1$ | $Ar^2$ | Yield[a] of 5 (%) | Product[b] |
|---|---|---|---|---|
| 1 |  |  | 4 | **5a** |
| 2 |  |  | 4 | **5b** |
| 3 |  |  | 7 | **5c** |
| 4 |  |  | 14 | **5d** |
| 5 |  |  | 12 | **5e** |
| 6 |  |  | 10 | **5f** |

[a] Isolated yield after flash chromatography and/or prep TLC.
[b] All compounds were characterised by $^1$H NMR, $^{13}$C NMR and HRMS.




**Scheme 1.** Reagents and conditions: (i) pyridine, rt or pyridine and then acetic anhydride, reflux, 40–60% (ii) DMF, 150 °C, microwave.

We also explored methodologies employing the diamide **9** as an intermediate following studies which were recently reported.[15,16] In this procedure, 2,3-dialkyl (3*H*)-quinazolin-4-ones were prepared by microwave-assisted cyclocondensation of diamides.

A series of diamides **9** was prepared by condensation of the appropriate amine with isatoic anhydride **6** followed by coupling of the resulting amine **7** with an acyl chloride **2** or carboxylic acid **8**. The isatoic anhydride **6** was prepared by reaction of anthranilic acid **1** with triphosgene in good yield.[17] The diamides **9** were converted to the corresponding 2,3-diaryl (3*H*)-quinazolin-4-ones by microwave heating in pyridine at 200 °C for 2 h (Scheme 2). The yields were low to moderate (Table 2).

* Corresponding author. Tel.: +44 208 722 4334; fax: +44 208 722 4047.
*E-mail address:* keith.jones@icr.ac.uk (K. Jones).

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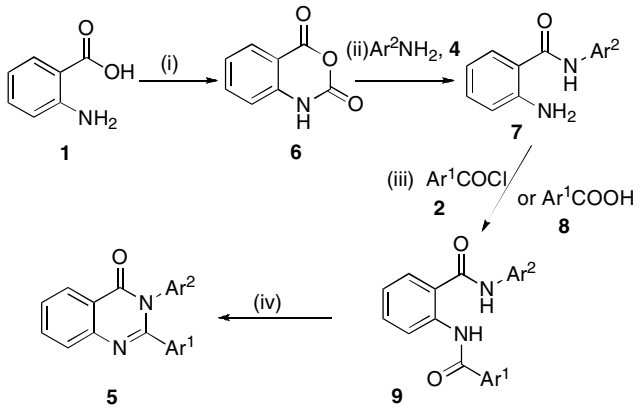



**Scheme 2.** Reagents and conditions: (i) triphosgene, THF, 0 °C to rt, 89%; (ii) dimethylacetamide, 110 °C, DMAP; (iii) triethylamine, $CHCl_3$, 40 °C or HATU, DIPEA, DMF, rt; (iv) pyridine, microwave, 200 °C, 2 h.

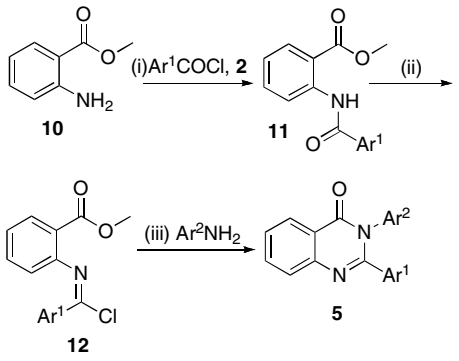
**Table 2**
Synthesis of 2,3-substituted (3*H*)-quinazolin-4-ones **5** from diamide **9**

| Entry | $Ar^1$ | $Ar^2$ | Yield[a] of 5 (%) | Product[b] |
|---|---|---|---|---|
| 1 |  |  | 23 | **5g** |
| 2 |  |  | 52 | **5h** |
| 3 |  |  | 35 | **5i** |
| 4 |  |  | 47 | **5j** |

[a] Isolated yield after flash chromatography.
[b] All compounds were characterised by $^1H$ NMR, $^{13}C$ NMR and HRMS.

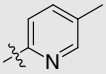
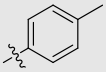
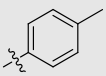
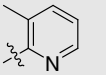
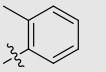
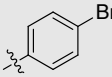
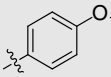
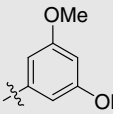
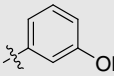
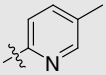
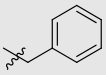
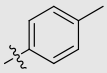
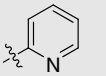
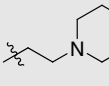
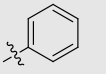
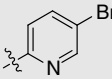
Although the second route involving dehydration of diamide **9** gave access to several 2,3-diaryl (3*H*)-quinazolin-4-ones **5**, a more efficient and general route was sought. We were attracted by recent work reported by a group at Albany Molecular Research.[18] They described a highly stereoselective synthesis of 2,3-disubstituted (3*H*)-quinazolin-4-ones involving reaction of an imidoyl chloride with a chiral amino acid. We envisaged that we could synthesise 2,3-diaryl (3*H*)-quinazolin-4-one derivatives by reacting an imidoyl chloride with aryl amines and subsequent ring closure.

The imidoyl chloride **12** was synthesised by acylation of methyl anthranilate **10** with an acyl chloride **2** under standard conditions.[19] The resulting amide **11** was subsequently treated with thionyl chloride to afford imidoyl chloride **12** in quantitative yield. The imidoyl chloride **12** can be stored under argon and remained stable for several days. The imidoyl chloride **12** was condensed with a series of amines **4** in pyridine under microwave heating at 200 °C to afford the desired 2,3-diaryl (3*H*)-quinazolin-4-ones (Scheme 3). The results are summarised in Table 3.




**Scheme 3.** Reagents and conditions: (i) $CHCl_3$, triethylamine, 40 °C, (ii) thionyl chloride, reflux, (iii) pyridine, microwave, 200 °C.

**Table 3**
Synthesis of 2,3-diaryl quinazolin-4-ones 5 from imidoyl chloride **12**

| Entry | $Ar^1$ | $Ar^2$ | Yield[a] of 5 (%) | Product[b] |
|---|---|---|---|---|
| 1 |  |  | 85 | **5c** |
| 2 |  |  | 87 | **5d** |
| 3 |  |  | 83 | **5e** |
| 4 |  |  | 88 | **5g** |
| 5 |  |  | 85 | **5i** |
| 6 |  |  | 79 | **5k** |
| 7 |  |  | 77 | **5l** |
| 8 |  |  | 68 | **5m** |
| 9 |  |  | 74 | **5n** |
| 10 |  |  | 87 | **5o** |
| 11 |  |  | 64 | **5p** |
| 12 |  |  | 66 | **5q** |
| 13 |  |  | 51 | **5r** |
| 14 |  |  | 80 | **5s** |
| 15 |  |  | 40 | **5t** |
| 16 |  |  | 75 | **5v** |

[a] Isolated yield after flash chromatography.
[b] Characterised by $^1H$ NMR, $^{13}C$ NMR and HRMS.

As shown in Table 3, both aromatic and heteroaromatic amines underwent cyclocondensation with imidoyl chlorides **12** in good to excellent yields. Anilines carrying electron-withdrawing groups gave good yields (entry 6). Weakly nucleophilic aminopyridines also reacted successfully (entry 10) even when sterically hindered (entry 4). 5-Bromo-2-aminopyridine (Table 3, entry 15) gave only a moderate yield, possibly due to the presence of an electron-withdrawing bromine in the 5 position. The presence of a methyl group *ortho* to the amino group did not affect cyclocondensation (Table 3, entries 4 and 5). In contrast to the microwave reaction, conventional heating of the imidoyl chloride **12** with an aromatic amine under reflux for 24 h gave the corresponding 2,3-diaryl (3*H*)-quinazolin-4-ones in low yields along with side products. This new method offers a considerable improvement in yields in comparison to the previous two routes discussed. For example, compounds **5c** and **5e** were obtained in 85% and 83% yields, respectively, from the corresponding imidoyl chloride. Using the previously reported routes, yields of only 7% and 12%, respectively, were obtained.

In summary, we have developed a practical and efficient route to 2,3-diaryl (3*H*)-quinazolin-4-ones. The key step is the cyclocondensation of imidoyl chloride **12** with an aryl amine using microwave conditions.[19] This procedure was used to synthesise a series of 2,3-diaryl substituted (3*H*)-quinazolin-4-ones for biological screening in our research programme.

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19. *General procedure for synthesis of imidoyl chloride* **12**: Thionyl chloride (5 mL) was added to methyl 2-(picolinamido)benzoate (0.36 g, 1.4 mmol), and the resulting mixture was heated at 70 °C for 24 h. The excess thionyl chloride was removed under reduced pressure, and the crude product was dried under high vacuum at 70 °C for 30 min to afford a pale yellow solid in quantitative yield. *General procedure for synthesis of 2,3-diarylsubstituted quinazolin-4-ones*: Pyridine (1.5 mL) was added to imidoyl chloride **12** (0.328 g, 1.19 mmol) and *p*-toluidine (0.191 g, 1.78 mmol), and the resulting mixture was heated at 200 °C in a Biotage Initiator Sixty$^{TM}$ microwave for 30 min. The excess pyridine was removed under reduced pressure, and the residue was purified by flash chromatography (silica; DCM–ether; 1:1) to afford 2-(pyridin-2-yl)-3-*p*-tolylquinazolin-4(3*H*)-one **5e** (0.31 g, 83%), as a white solid: mp 206–207 °C; $\delta_H$ (500 MHz; $CDCl_3$); 2.31 (3H, s, methyl C–H), 7.07–7.11 (4H, m, aryl C–H), 7.21 (1H, dd, $J$ = 7.8, 4.8 Hz, aryl C–H), 7.52 (1H, d, $J$ = 7.8 Hz, aryl C–H), 7.59 (1H, t, $J$ = 7.8 Hz, aryl C–H), 7.67 (1H, m, aryl C–H), 7.85 (1H, m, aryl C–H), 7.90 (1H, d, $J$ = 7.9 Hz, aryl C–H), 8.41 (1H, d, $J$ = 7.9 Hz, aryl C–H), 8.46 (1H, d, $J$ = 4.8 Hz, aryl C–H); $\delta_C$ (125 MHz; $CDCl_3$) 21.1($CH_3$), 121.5, 123.8, 124.4, 127.3, 127.7, 127.8, 128.7, 129.5, 134.6, 134.7, 136.5, 138.3, 147.1, 148.8, 153.1, 153.4, 162.1 (C=O); LCMS (ESI): $R_t$ = 4.14 min: $m/z$ 314.12 ([M+H]$^+$, 100%); HRMS found 314.1278, $C_{20}H_{16}N_3O$ [M+H]$^+$ requires 314.1288.