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Solid-phase synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines

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Abstract—The solid-phase synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines using an *N*-Fmoc-β-amino-2-nitrobenzenepropanoic acid scaffold is described. The resin-bound scaffold was reductively alkylated with aldehydes or ketones after Fmoc deprotection, followed by reduction of the nitro group with tin(II) chloride. Subsequent cyclization of the 1,3-diamine intermediates with aryl isothiocyanates in the presence of 1,3-diisopropylcarbodiimide (DIC) afforded the desired products in high purity with moderate to good yield after trifluoroacetic acid (TFA) cleavage.

Combinatorial chemistry has emerged as an important tool in drug discovery since 1991.[1] Solid-phase synthesis of small heterocycles is receiving considerable attention, since it is well suited to the rapid generation of diverse libraries of drug-like compounds.[2] Quinazoline derivatives are well known natural alkaloids, which are widely distributed in the plant and animal kingdoms.[3] Many biologically active molecules with a quinazoline or quinazolinone structure have been reported in the literature.[4] To date, a number of solid-phase methods for the preparation of quinazolinones and quinazolinediones have been developed,[5] but there are few reports on solid-phase synthesis of quinazolines and its 3,4-dihydro-derivatives.[6–8] In 1997, Wang and Hauske reported the first solid-phase synthesis of 3,4-dihydroquinazolines.[6] The synthesis was started with resin-supported cinnamyl iminophosphorane, which was then treated with an aryl isocyanate. The resulting carbodiimide underwent 1,2-addition with a secondary amine followed by an intramolecular Michael addition to give the desired products. In 2001, Zhang et al. developed another solid-phase approach for the preparation of 3,4-dihydroquinazolines using 4-bromomethyl-3-nitrobenzoic acid as the synthetic scaffold.[7] The resin-bound scaffold reacted with a primary amine followed by reduction of the nitro group to form a 1,3-diamine intermediate, which was subsequently cyclized with different reagents. Most recently, a solid-phase synthetic method for the preparation of 3,4-dihydroquinazoline derivatives was reported by Srivastava et al.[8] This synthesis also involves a 1,3-diamine key intermediate, which was derived from 2-nitrobenzaldehydes.

In this report, we describe the solid-phase synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines using β-amino-2-nitrobenzenepropanoic acid as the scaffold. β-Amino-2-nitrobenzenepropanoic acid has been used as a photolabile linker (ANP linker) in solid-phase synthesis.[9] Since the nitro group of the ANP linker can be readily reduced to an amino group to form a 1,3-diamine structure, we envisioned that it could be an ideal scaffold for the synthesis of 3,4-dihydroquinazolines.

Scheme 1 illustrates our strategy for the solid-phase synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines. *N*-Fmoc ([(9*H*-fluoren-9-ylmethoxy)carbonyl])-protected scaffold **2** was first tethered to rink amide resin **1** using 1,3-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) as the activating system. The Fmoc protecting group was removed with 20% piperidine/*N*,*N*-dimethylformamide (DMF). The amino group of resin-bound scaffold **3** was subsequently reductively alkylated with an aldehyde or ketone using a published procedure.[10] Depending on the nature of the alkylation reagents, the optimal condition for monoalkylation

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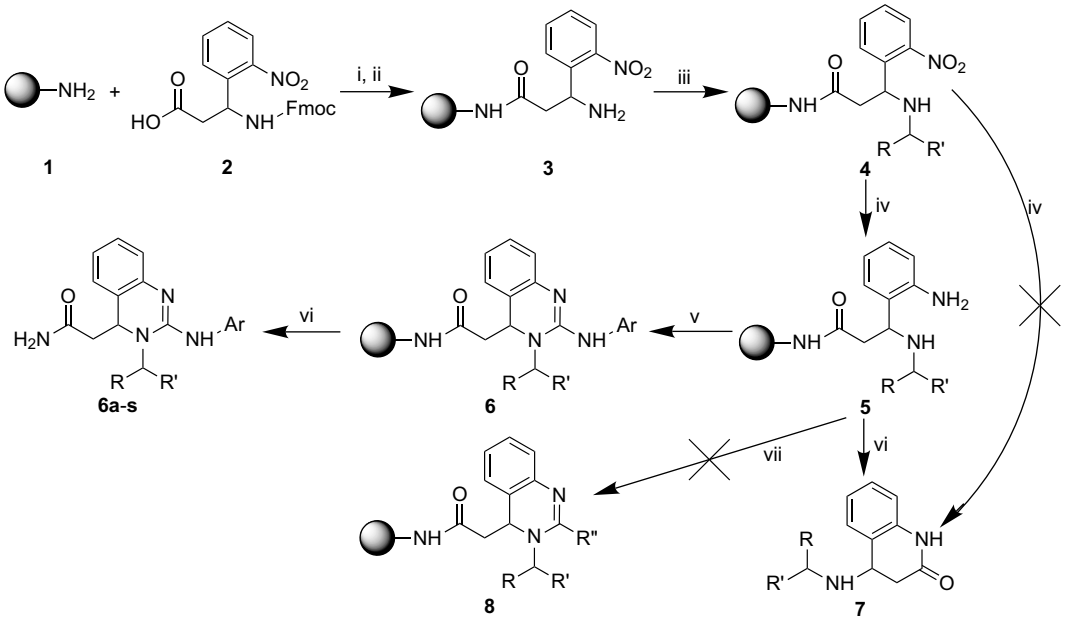


Scheme 1. Synthetic route for 3-alkyl-2-arylamino-3,4-dihydroquinazolines. Reagents and conditions: **1**, rink amide resin; (i) 2 equiv of *N*-Fmoc-β-amino-2-nitrobenzenepropanoic acid, 2 equiv of DIC, and 2 equiv of HOBt in DMF, rt, overnight; (ii) 20% piperidine/DMF, rt, 30 min; (iii) RCOR′ and $NaCNBH_3$ in $CH(OCH_3)_3$, rt; (iv) 2 M of $SnCl_2 \cdot H_2O$ in DMF, rt, 16 h; (v) 1 M of ArNCS and 1 M of DIC in DMF, rt, overnight; (vi) 95% TFA/H_2O, rt, 2 h; (vii) 6 equiv of R″CHO and 3 equiv of DDQ in DMF, rt, 5 h.

varies: (1) For unhindered aliphatic aldehydes (e.g., propionaldehyde), 20 equiv of aldehydes and 20 equiv of $NaCNBH_3$ in trimethyl *ortho*-formate (TMOF) were used. (2) For slightly hindered aliphatic aldehydes (e.g., isobutylaldehyde), 20 equiv of aldehydes and 20 equiv of $NaCNBH_3$ in TMOF were used in the presence of 1% methanol (MeOH) as the proton source. (3) For bulky aliphatic aldehydes (e.g., trimethylacetaldehyde), aliphatic ketones (e.g., cyclohexanone), and aromatic aldehydes (e.g., benzaldehyde), 10 equiv of alkylation reagents and 10 equiv of $NaCNBH_3$ were used in the presence of 1% acetic acid (HOAc) as the proton source. All of the aldehydes or ketones were incubated with the resin-bound scaffold **3** in TMOF for 30 min prior to the addition of $NaCNBH_3$ and the proton source to allow the imine formation. The reduction with $NaCNBH_3$ was carried out at room temperature for 30 min. For monoalkylation 20 aliphatic aldehydes, 5 simple aliphatic ketones, and 30 aromatic aldehydes were successfully evaluated.

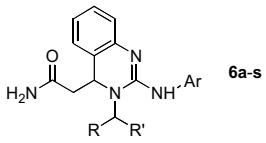
The nitro group of intermediate **4** was efficiently reduced with tin(II) chloride to afford resin-supported 1,3-diamine **5**. A major concern in this step is the possible concurrent formation of the six-membered lactam **7** resulting in cleavage of the intermediate from the resin. This problem was observed in the solid-phase synthesis of benzimidazoles.[11] Fortunately, such a side reaction was not observed in our experiment. Compound **4** did not convert to lactam **7** during the reduction unless the obtained resin-supported intermediate **5** was treated with trifluoroacetic acid (TFA). Treatment of **5** with TFA resulted in lactam **7** as the major product.

Initial attempts to cyclize the 1,3-diamine **5** using DDQ (2,3-dichloro-5,6-dicyanoquinone)-assisted oxidative cyclocondensation with aldehydes failed to give clean reaction for **8**.[7] The complex mixture obtained after TFA cleavage was not elucidated. In contrast, carbodiimide-mediated cyclization of **5** with aryl isothiocyanates afforded 3-alkyl-2-arylamino-3,4-dihydroquinazolines **6** in high purity.[12,13] A variety of aryl isothiocyanates representing a wide range of steric and electronic characteristics were examined for their effects on cyclization. We have found that the substituents on the aryl group did not have any significant effect on cyclization. Cyclization was neither hindered by the alkyl groups on the scaffold (R and R′), nor by the substituent on 2-position of the aryl isothiocyanate, unless both 2- and 6-positions were occupied. Unlike aryl isothiocyanates, alkyl isothiocyanates did not successfully undergo the carbodiimide-mediated cyclization. This is consistent with the assumption that carbodiimide-mediated cyclization proceeds via a carbodiimide intermediate generated in situ from the desulfurization of the thiourea intermediate,[12,14] because the desulfurization efficiency of alkyl thioureas is low.[12,15]

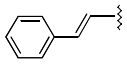
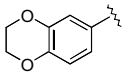
Using the synthetic method outlined above,[16] a library containing 19 3-alkyl-2-arylamino-3,4-dihydroquinazolines (**6a**–**s**) was prepared. The final products were released from the resin via TFA cleavage, analyzed and purified by HPLC, and characterized by ^1H NMR, ^{13}C NMR, and ESI-MS.[17] All of the 19 compounds were obtained in high purity with moderate to good isolated yield (Table 1).

In summary, we have developed a solid-phase method for the parallel synthesis of 3-alkyl-2-arylamino-3,4-dihydroquinazolines using a β-amino-2-nitrobenzenepropanoic acid scaffold. The final products were obtained in high purity with moderate to good yield

Table 1. Synthesis of compounds **6a–s** produced via Scheme 1



6a-s

Entry	R	R′	Ar	Yield[a] (%)	Purity[b] (%)	ESI-MS (MH^+)
6a	C_6H_5	H	C_6H_5	79	89	371.2
6b		H	C_6H_5	67	85	397.2
6c	C_2H_5	H	4-FC_6H_4	78	86	341.2
6d	$C_6H_5(CH_2)_2$	H	4-ClC_6H_4	71	72	419.1
6e	$(CH_3)_2CH$	H	4-BrC_6H_4	64	84	415.1
6f	*c*-C_6H_{11}	H	4-IC_6H_4	59	82	503.1
6g	$(CH_3)_3$ C	H	3-FC_6H_4	83	94	369.2
6h	CH_3	CH_3	3-ClC_6H_4	82	87	357.2
6i	$(CH_2)_5$		3-BrC_6H_4	78	92	441.1
6j	2-$CH_3C_6H_4$	H	4-$CH_3OC_6H_4$	67	73	415.2
6k	2,6-$Cl_2C_6H_3$	H	3,4-$Cl_2C_6H_3$	72	91	507.1
6l	3-$CF_3C_6H_4$	H	2-$C_2H_5OOCC_6H_4$	66	71	511.2
6m	1-$C_{10}H_7$	H	3-$CH_3OC_6H_4$	64	78	451.2
6n		H	1-$C_{10}H_7$	82	88	479.2
6o		H	2-FC_6H_4	83	90	390.2
6p		H	3-$O_2NC_6H_4$	83	88	417.2
6q		H	2-ClC_6H_4	46	90	408.2
6r		H	2,4-$Cl_2C_6H_3$	69	91	445.1
6s		H	3,5-$Cl_2C_6H_3$	64	92	445.1

[a] Yields were based on the purified products.
[b] Purity was determined by HPLC analysis (UV detection at 220 nm) of crude products.

after six reaction steps. The compounds prepared using this method have two points of diversity. To obtain an additional diversity point, we have successfully coupled an amino acid prior to the scaffold attachment. This synthetic methodology is ideally suited for automated application, because all the reactions were carried out under ambient conditions.

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16. An example procedure: synthesis of 2-(phenylamino)-3-benzyl-3,4-dihydroquinazoline-4-acetamide **6a**. Rink amide MBHA resin (100 mg, 0.045 mmol) was swollen in DMF overnight. The supernatant was removed, and a 20% piperidine solution in DMF (1 mL) was added to the resin. The mixture was shaken for 15 min, and the supernatant was removed. This process was repeated. The resin was washed with DMF, MeOH, and DMF. To the resin was added a solution of *N*-Fmoc-β-amino-2-nitrobenzenepropanoic acid (38.9 mg, 0.090 mmol), HOBt (12.2 mg, 0.090 mmol), and DIC (14.1 μL, 0.090 mmol) in DMF (1 mL). The resulting mixture was shaken overnight. Complete coupling was confirmed by a negative ninhydrin test. The supernatant was removed, and the resin was washed with DMF. The Fmoc protecting group was removed with 20% piperidine/DMF as mentioned above. The resin was washed with DMF, MeOH, DMF, and TMOF. To the resin was added a solution of benzaldehyde (45.7 μL, 0.45 mmol) in TMOF (1 mL). The mixture was shaken for 30 min, and a solution of $NaCNBH_3$ (28.3 mg, 0.45 mmol) in TMOF (1 mL) was added, followed by the addition of HOAc (20 μL). The resulting mixture was shaken for 30 min. The supernatant was removed, and the resin was washed with MeOH, water, DMF, dichloromethane (DCM), MeOH, and DMF. To the resin was added a 2 M $SnCl_2 \cdot H_2O$ solution in DMF (2 mL), and the resulting mixture was shaken for 16 h. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. To the resin was added a solution of 1 M phenyl isothiocyanate and 1 M DIC in DMF (2 mL). The resulting mixture was shaken overnight. The supernatant was removed. The resin was washed with DMF, DCM, MeOH, and DCM, and then dried in vacuo. To the dried resin was added 2 mL of 95% TFA solution in water at ice-bath temperature. The mixture was slowly warmed to room temperature and allowed to mix for 2 h. The supernatant was then collected and the resin was washed with neat TFA (3 × 1 mL). The combined supernatants were concentrated to dryness under a stream of nitrogen, and further dried in vacuo. The crude product was analyzed and purified by HPLC.
17. NMR data for selected compounds (compounds were characterized as TFA salts). Compound **6a**: ^{1}H NMR (DMSO-d_6) δ 11.44 (s, 1H), 10.46 (s, 1H), 7.55 (s, 1H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.36–7.26 (m, 5H), 7.24–7.12 (m, 8H), 5.22 (d, $J = 16.0$ Hz, 1H), 5.14 (t, $J = 7.0$ Hz, 1H), 4.68 (d, $J = 16.0$ Hz, 1H), 2.74 (dd, $J = 14.5$, 7.0 Hz, 1H), 2.49 (dd, $J = 14.5$, 7.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 171.1, 150.7, 137.0, 135.8, 132.9, 130.5, 129.7, 129.6, 128.9, 128.1, 126.8, 126.4, 126.3, 124.6, 123.8, 117.5, 57.3, 53.9, 41.1. Compound **6g**: ^{1}H NMR (DMSO-d_6) δ 11.61 (s, 1H), 10.44 (s, 1H), 7.57 (s, 1H), 7.52 (dd, $J = 14.8$, 8.1 Hz, 1H), 7.40 (m, 1H), 7.31 (d, $J = 6.5$ Hz, 1H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.16–7.06 (m, 4H), 5.05 (t, $J = 6.9$ Hz, 1H), 4.09 (d, $J = 15.2$ Hz, 1H), 3.34 (d, $J = 15.2$ Hz, 1H), 2.66 (dd, $J = 14.7$, 7.6 Hz, 1H), 2.38 (dd, $J = 14.5$, 6.4 Hz, 1H), 0.85 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 170.8, 163.3 (d, $^1J_{CF} = 243.0$ Hz), 150.6, 138.9 (d, $^3J_{CF} = 10.4$ Hz), 133.0, 132.3, 129.8, 126.6 (d, $^3J_{CF} = 16.3$ Hz), 125.1, 119.2, 117.9, 113.3 (d, $^2J_{CF} = 20.9$ Hz), 110.4 (d, $^2J_{CF} = 24.8$ Hz), 60.6, 59.6, 40.9, 34.1, 27.8. Compound **6i**: ^{1}H NMR (DMSO-d_6) δ 11.54 (s, 1H), 10.60 (s, 1H), 7.58 (t, $J = 1.8$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 7.44 (t, $J = 8.1$ Hz, 2H), 7.37 (m, 2H), 7.32–7.26 (m, 2H), 7.22 (t, $J = 7.4$ Hz, 1H), 7.14 (d, $J = 7.9$ Hz, 1H), 5.26 (m, 1H), 4.04 (m, 1H), 2.43 (m, 1H), 2.06 (d, $J = 12.4$ Hz, 1H), 1.82 (d, $J = 12.4$ Hz, 1H), 1.72–1.55 (m, 5H), 1.29–1.13 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 170.4, 150.9, 139.3, 133.1, 132.3, 129.6, 129.2, 126.5, 126.3, 126.2, 125.9, 122.9, 122.8, 117.3, 60.2, 51.3, 42.0, 31.6, 30.7, 25.8, 25.7, 25.0. Compound **6s**: ^{1}H NMR (DMSO-d_6) δ 11.51 (s, 1H), 10.66 (s, 1H), 7.54 (m, 3H), 7.48 (s, 1H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.32 (s, 2H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 8.3$ Hz, 2H), 7.08 (m, 2H), 5.13 (d, $J = 15.4$ Hz, 1H), 5.11 (t, $J = 6.6$ Hz, 1H), 4.73 (d, $J = 15.4$ Hz, 1H), 2.65 (dd, $J = 14.9$, 6.8 Hz, 1H), 2.46 (dd, $J = 14.9$, 6.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 171.0, 150.4, 139.9, 135.9, 135.5, 132.7, 129.7, 128.2, 128.1, 126.5, 126.4, 126.1, 125.7, 124.4, 122.6, 117.4, 56.3, 49.1, 40.9.