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Traceless solid-phase synthesis of 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinoline-2-ones

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Abstract—A traceless solid-phase route to 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones is described. *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid was tethered to Rink resin via its carboxylic group. The protected amine was coupled with an organic acid after Alloc-deprotection and the arylfluorine was displaced with a primary amine to generate a resin-bound aniline with two diversity points. The aniline was released via cleavage to produce the desired products in high yield and purity.

Quinolinones represent an important class of heterocyclic compounds with interesting biological properties that include antitumor[1] and anti-malarial activity[2] as well as farnesyl transferase inhibition.[3] As a member of the quinolinone family, substituted 3,4-dihydroquinoline-2-ones have attracted considerable interest in medicinal chemistry because they can be used as intermediates for drug synthesis as well as drug candidates for biological screening. Although synthetic approaches have been reported for such compounds,[4] most of these methods are tedious, require harsh reaction conditions, and generated limited molecular diversity. We believe there is a need for the development of a more convenient and efficient approach for the synthesis of 3,4-dihydroquinoline-2-ones on solid support using a scaffold strategy so that large libraries of these heterocyclic compounds can be prepared with high yield and purity. We herein report an efficient approach to 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones using traceless solid-phase synthesis.

We have recently used the tetrafunctional scaffold, 3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid to prepare 1,2-disubstituted-6-nitro-1,4-dihydro-quinazolines.[5] Since the arylfluorine of the scaffold can be efficiently displaced with a primary amine to generate an aniline, we reasoned that the resulting aniline could be easily reacted with its own carboxylic group to generate the 3,4-dihydro-1*H*-quinazolin-2-one skeleton while the original amino group of the scaffold is used as a handle to tether the scaffold to a cleavable resin. To explore the feasibility of this hypothesis, the carboxylic group of the scaffold was allyl protected according to the literature procedures.[6] The scaffold was then anchored to the pre-modified Rink resin with succinic anhydride (Scheme 1). The arylfluoride was displaced with benzylamine by overnight treatment in the presence of DIEA (*N*,*N*′-diisopropylethylamine)/DMAP (*N*,*N*′-dimethylaminopyridine).[7] A chloranil test indicated the generation of the secondary aniline. After the carboxylic group of the scaffold was liberated with $Pd(PPh_3)_4$/$PhSiH_3$ in CH_2Cl_2 for 1 h,[8] a strong coupling reagent, PyBrop (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate)/DMAP, was employed for coupling via heterocyclization. However, upon cleavage with 95% TFA (trifluoroacetic acid), we failed to achieve the expected cyclic product and only obtained the uncyclized precursor.

Recently, Kundu et al. reported the solid-phase synthesis of quinazolinones.[9] To explore the applicability of their cleavage strategy for the synthesis of 3,4-dihydro-1*H*-quinazolin-2-one scaffold, we developed the synthetic

Keywords: Solid-phase synthesis; Traceless cleavage; 3,4-Dihydro-1*H*-quinoline-2-one.
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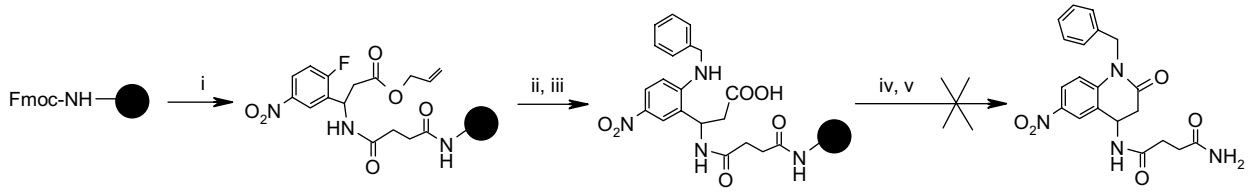
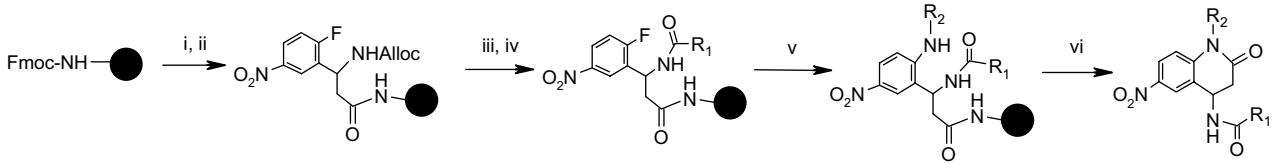


Scheme 1. A solid-phase synthesis approach to 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones. Reagents and conditions: (i) 25% piperidine, 15 min; succinic anhydride, DIEA, 12 h; then allyl 3-amino-3-(2-fluoro-5-nitrophenyl)propionate (5 equiv), DIC (5 equiv), DIEA, 12 h; (ii) benzylamine (5 equiv), DIEA/DMAP, 12 h; (iii) $Pd(PPh_3)_4$ (0.24 equiv), $PhSiH_3$ (20 equiv), CH_2Cl_2, 1 h; (iv) PyBrop (5 equiv), DMAP (5 equiv), 12 h; (v) 95% TFA/H_2O, 2 h.



Scheme 2. A solid-phase synthesis of 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones. Reagents and conditions: (i) 25% piperidine, 15 min; (ii) *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid (3 equiv), DIC (3 equiv), HOBt (3 equiv); (iii) $Pd(PPh_3)_4$ (0.24 equiv), $PhSiH_3$ (20 equiv), CH_2Cl_2, 1 h; (iv) R_1COOH (3 equiv), DIC (3 equiv), HOBt (3 equiv); (v) R_2NH_2 (5 equiv), DIEA/DMAP, 24 h; (vi) 50% HCOOH/CH_2Cl_2, 24 h.

scheme illustrated in Scheme 2. Initially, the *N*-Alloc-3-3-(2-fluoro-5-nitrophenyl)propionic acid scaffold was linked to Rink amide resin in the presence of DIC (1,3-diisopropylcarbodiimide) and HOBt (1-hydroxybenzotriazole). The protected amino group of the scaffold was liberated by palladium chemistry[8] followed by coupling with 2,5-dimethoxyphenylacetic acid (R_1COOH). At this stage, the arylfluorine was displaced with 3-ethoxypropylamine (R_2NH_2) to generate a secondary aniline. We anticipated that this resin-bound aniline could be released from the resin to form the 3,4-dihydro-1*H*-quinazolin-2-one skeleton via cleavage. The reported protocol of acetic acid in CH_2Cl_2 solution at different concentrations was tested as the cleavage reagent.[9] The cleavage solution was filtered and analyzed by ES-MS. Unfortunately, we were unable to isolate the desired product under any cleavage conditions, even after allowing the reaction to proceed for up to 48 h. In contrast, when 10% TFA/CH_2Cl_2 was used for cleavage, mass spectrometry analysis revealed the presence of the cyclic product. However, HPLC analysis showed that the ratio of cyclic product to uncyclized precursor was at ca. 20%:80%. We optimized the cleavage condition by using HCOOH/CH_2Cl_2 solution. Under 50% HCOOH/CH_2Cl_2 for 24 h cleavage, the cyclic product was obtained in acceptable purity (70%) although a small amount of the uncyclized aniline still remained in the reaction mixture. Fortunately, this uncyclized impurity can be easily extracted with aqueous hydrochloric acid.

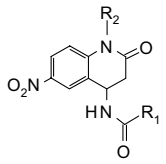
Once the cleavage condition was established, we performed parallel synthesis of 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones. A diverse set of organic acids and primary amines were used as building blocks for diversity points R_1 and R_2, respectively (Scheme 2). The synthetic results are shown in Table 1. In most cases (entries 1–5, 7, and 8), the cyclic products were obtained as expected in good yield and purity. In entry 6, no cyclic product was obtained due to the steric hindrance of the *N*-linked cyclohexyl. All cyclic products were confirmed by ES-MS as well as ^1H and ^{13}C NMR.

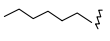
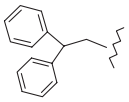
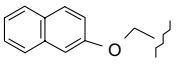
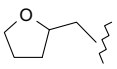
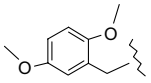
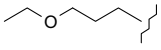
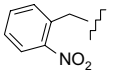
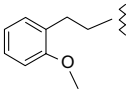
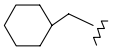
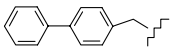
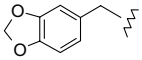
In conclusion, we have developed a traceless solid-phase approach for the convenient synthesis of 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones in high yield and satisfactory purity. Because the nitro group on the scaffold remains unmodified in this approach, it potentially could be reduced after cleavage as a third diversity point for the combinatorial synthesis of 1,4,6-trisubstituted-3,4-dihydro-1*H*-quinazolin-2-one derivatives.

Synthesis of allyl 3-amino-3-(2-fluoro-5-nitrophenyl)-propionate: A mixture of 3-amino-3-(2-fluoro-5-nitrophenyl) propionic acid (5.0 g, 22 mmol, prepared according to the reported procedure[5]), toluenesulfonic acid (3.8 g, 22 mmol) and allyl alcohol (10.0 mL, 147 mmol) in benzene (40 mL) was refluxed overnight using a Dean–Stark trap. Heating was stopped and the solvent was removed under reduced pressure. The residue was crystallized from ether to afford the product as a yellowish solid (5.7 g). Yield: 97%. Mp 108–110 °C. FT-IR (selected, cm^{-1}): 1732, 1533, 1350. ES-MS (M^+): 268.6. ^1H NMR (400 MHz, D_2O): δ 8.03 (d, 1H), 7.94 (m, 1H), 7.21 (d, 1H), 6.87 (d, 1H), 5.42 (m, 2H), 4.72 (m, 1H), 4.16 (d, 2H), 2.86 (m, 2H). ^{13}C NMR (400 MHz, D_2O): δ 172.0, 164.1 (d, $^1J_{CF}$ = 245 Hz), 143.9, 132.7, 129.3 (d, $^2J_{CF}$ = 24.0 Hz), 126.8 (d, $^3J_{CF}$ = 10.1 Hz), 126.6 (d, $^3J_{CF}$ = 10.6 Hz), 120.4, 119.1 (d, $^2J_{CF}$ = 24.3 Hz), 68.1, 46.9, 38.1.

Typical procedure: synthesis of 1-hexyl-4-cyclohexylcarbamyl-6-nitro-3,4-dihydro-1*H*-quinazolin-2-one. Swollen Rink resin (0.1 g, 0.54 mmol/g) was deprotected

Table 1. Synthesis of 1,4-disubstituted-6-nitro-3,4-dihydro-1*H*-quinazolin-2-ones via Scheme 2



Entry	R_1	R_2	Crude yield[a] (%)	Purity[b] (%)	ES-MS[c] (M^+) Found (calc.)
1			95	97	401.7 (401.2)
2			75	75	505.7 (505.2)
3			83	63	475.6 (475.2)
4			65	70	471.6 (471.2)
5			85	91	412.6 (412.1)
6			—	—	390.7 (373.2)[d]
7			72	62	465.7 (465.2)
8			90	95	535.7 (535.2)

[a] Yield of the crude product was based on Rink resin loading.
[b] Purity was obtained by measuring the crude samples prior to aqueous HCl washing using RP-HPLC at $\lambda = 254$ nm.
[c] Molecular weight was measured by ES-MS.
[d] No desired product was obtained.

with 25% piperidine for 15 min and coupled with *N*-Alloc-3-amino-3-(2-fluoro-5-nitrophenyl)propionic acid (3 equiv)/DIC (3 equiv)/HOBt (3 equiv). After washing with DMF and CH_2Cl_2 three times each, the beads were incubated with a mixture of $Pd(PPh_3)_4$ (0.24 equiv) and $PhSiH_3$ (20 equiv) in CH_2Cl_2 for 1 h, followed by coupling with cyclohexanecarboxylic acid (3 equiv) in the presence of DIC (3 equiv) and HOBt (3 equiv). The Kaiser test was used to establish coupling completion. The beads were then incubated with a mixture of hexylamine (5 equiv), DIEA (5 equiv), and DMAP (0.2 equiv) in DMF for 24 h. After thorough washing with DMF (3×10 mL), MeOH (3×10 mL), and CH_2Cl_2 (3×10 mL), the resulting beads were incubated with 50% $HCOOH/CH_2Cl_2$ for 24 h. The cleavage solution was obtained by filtration and then dried in vacuo. The residue was dissolved in ethyl acetate (15 mL) and washed with 2 M aqueous hydrochloride three times. The organic layer was concentrated to yield the yellowish product. Weight: 20.6 mg, yield: 95%, purity: >99%. ES-MS (M^+): 401.7. ^1H NMR (DMSO-d_6 400 MHz): δ 8.34 (d, 1H), 8.19 (q, 1H), 8.01 (m, 1H), 7.38 (d, 1H), 5.11 (q, 1H), 3.95 (m, 2H), 2.76 (d, 2H), 2.22–2.16 (m, 1H), 1.72 (br, 4H), 1.60–1.52 (m, 14H), 0.87 (t, 3H). ^{13}C NMR (DMSO-d_6): δ 177.6, 169.1, 145.2, 142.8, 128.4, 125.5, 122.6, 117.1, 44.8, 44.4, 42.6, 37.1, 31.6, 30.2, 29.8, 27.2, 26.5, 26.1, 25.9, 25.8, 22.8, 14.6.

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