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Solid-phase synthesis of 3,4-dihydroquinazoline derivatives†

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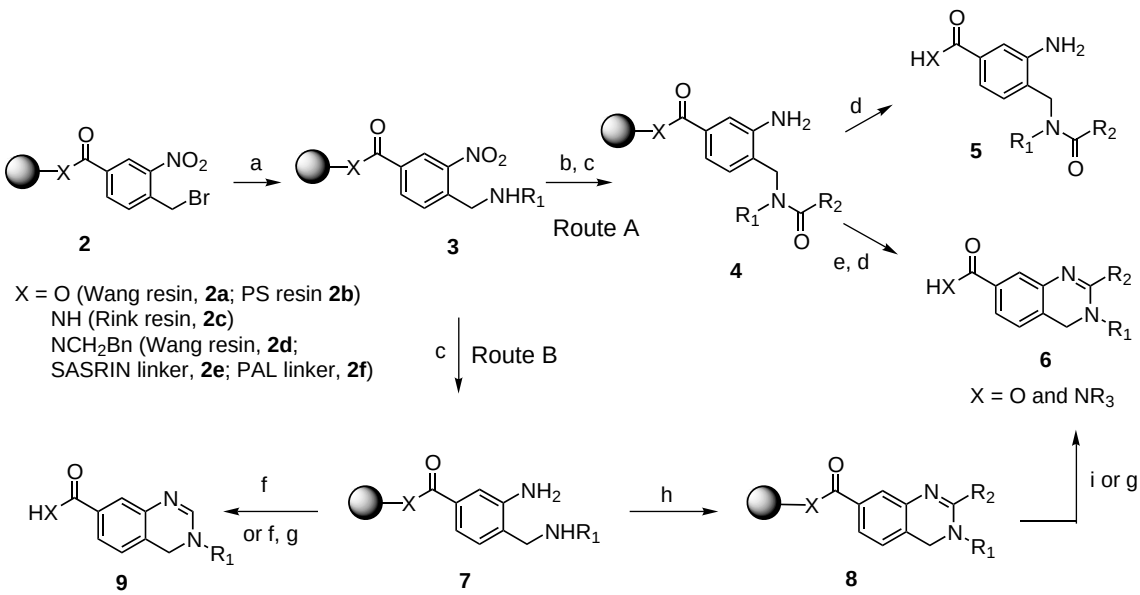
Abstract—A novel method for solid-phase synthesis of dihydroquinazoline derivatives is presented. Polymer-bound 4-bromomethyl-3-nitrobenzoate and the corresponding amide are utilized as versatile precursors that undergo nucleophilic displacement with amines followed by reduction and cyclocondensation reactions to afford structurally diverse dihydroquinazolines with excellent yield and purity.

Quinazoline and its related skeletons are presented as an important class of heterocycle scaffolds occurring in a large number of bioactive molecules for a variety of biological targets.[2] While a number of methods dealing with solid-phase synthesis of quinazolinone and quinazolinedione have been reported,[3] efforts directed toward the construction of the quinazoline scaffold and its 3,4-dihydro-form on the solid support are still limited.[4] We now report a straightforward, easily automated method for the solid-phase synthesis of 3,4-dihydroquinazoline derivatives via polymer-bound 4-bromomethyl-3-nitrobenzoate and the corresponding amides.



Scheme 1. *Reagents and conditions*: (a) 1 M R_1NH_2 in NMP, 45 min; (b) R_2CO_2H, DIC, DMF, overnight; (c) 2 M $SnCl_2$ in NMP, rt, overnight; (d) 20% TFA in DCM, rt, 30 min; (e) *o*-xylene, 100°C, 24 h; (f) TMOF/TFA/DCM (1:1:2), rt, 30 min; (g) polystyrene (Merrifield) resin: 48% $MeNH_2$ (aq.)/THF (1:1), rt, 16 h; (h) R_2CHO (6 equiv.), DDQ (3 equiv.), DMF, rt, 5 h; (i) Wang resin: 20% TFA in DCM, rt, 30 min; Rink resin: 10% TFA in DCM, rt, 30 min; SASRIN and PAL resins: 20% TFA in DCM, rt, 45–60 min.

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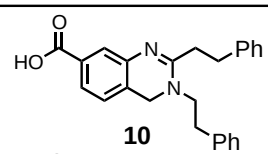
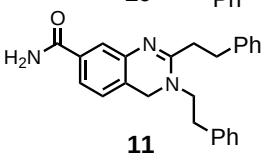
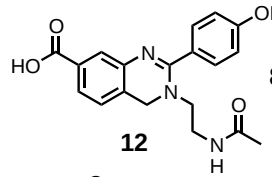
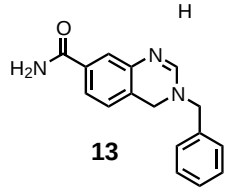
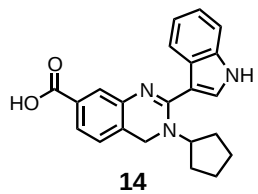
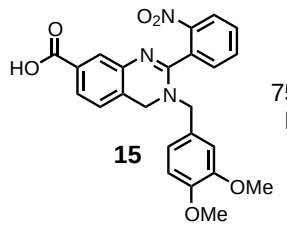
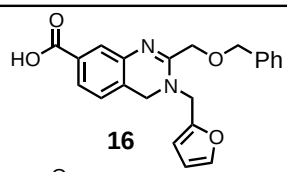
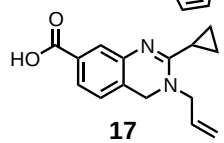
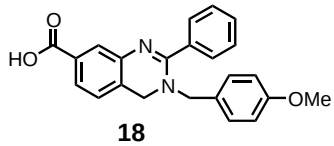
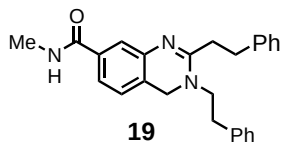
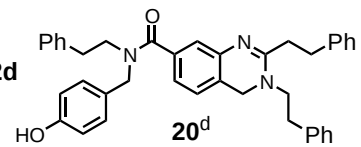
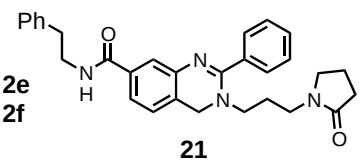
4-Bromomethyl-3-nitrobenzoic acid **1** has been widely used as a photolabile linker in solid-phase synthesis of peptides and small organic compounds.[5] However, utilizing it as a precursor for the construction of biologically interesting heterocyclic scaffolds on solid support was introduced only recently.[1,6] In order to exploit a wide range of applications of this precursor in solid-phase syntheses and to maximize the chemical diversity of combinatorial libraries generated therefrom, we prepared a series of polymer-bound 4-bromomethyl-3-nitrobenzoic acids **2a**–**f** under the standard conditions (DIC/DMF or THF). In all the cases, the reactions succeeded in 90% to nearly quantitative yields. The obtained polymer-bound precursors can be stored in dark at 0°C for three months without any detectable decomposition.

Scheme 1 outlines our strategies (Routes A and B) for the construction of the dihydroquinazoline scaffold. Displacement of the bromide on resin **2** was readily achieved by treatment of amines in NMP for 45 min. Route A began with coupling of carboxylic acids and resin **3** (DIC/DMF) followed by reduction of nitro groups in the presence of $SnCl_2$ to afford aniline–amide intermediates, resin **4**. Conversion of **4** into the desired dihydroquinazoline scaffold was then attempted under various conditions. Exposure of **4** to TFA/DCM in different ratios gave the open form **5** predominantly.

Table 1.

Entry	Resins	Products	Purity[a] (yield[b])
1	2a	 **10**	90% (78% [c]) Route A
2	2c	 **11**	90% (80% [c]) Route A
3	2a	 **12**	85% (90%) Route A
4	2c	 **13**	90% (95%) Route B
5	2a	 **14**	85% (90%) Route B
6	2a	 **15**	75% (80%) Route B
7	2a	 **16**	90% (95%) Route B
8	2a	 **17**	80% (90%) Route B
9	2a	 **18**	95% (84% [c]) Route B
10	2b	 **19**	90% (95%) Route B
11	2d	 **20**[d]	90% (70%) Route B
12 13	2e 2f	 **21**	90% (69%) 90% (75%) Route B

[a] determined by LC-MS using both UV and ELSD detectors; further confirmed by ^{1}H NMR analysis;

[b] determined by weight of the crude products based on the loading of the resins. [c] isolated yield.

[d] The Wang linker was cleaved to give the corresponding 4-hydroxybenzyl amide.

Pre-treatment of the resins with 10% HOAc in DCM for 12 h did not improve the cyclization process. Use of other dehydrating agents, such as DIC[7] and EDC,[8] resulted in complex mixtures. Finally, a complete and clean cyclodehydration was achieved by heating resin **4** in *o*-xylene at 100°C for over 24 h. In the process of developing the synthetic protocol, after each step the intermediates were cleaved from the resins and analyzed by LC–MS or ^{1}H NMR to determine the reaction process.

Inspired by a successful synthesis of benzimidazole derivatives based on the DDQ-assisted oxidative condensation of aldehydes and polymer-bound phenylenediamines reported by Mayer and co-workers,[9] we further investigated an alternative approach to the dihydroquinazolines (Route B). After reduction of resin **3**, as we expected, cyclocondensation was successfully achieved by employing this aldehyde/DDQ combination recipe. The dihydroquinazoline derivatives **6** were obtained with excellent purity and high yields. Interestingly, we found that mixing resin **7** with TFA/TMOF/DCM (rt, 30 min), previously used in the formation of benzimidazoles,[10] resulted in 2-unsubstituted dihydroquinazolines. If acid-labile resins were employed, the cyclized products **9** were directly liberated under this condition.

The combination of Routes A and B offers rapid access to the dihydroquinazoline derivatives with a high level of diversity by using numerous readily available amines, acids and aldehydes. R_3 substitutes, such as the phenethyl group in resins **2e** and **2f**, can be easily introduced by reductive amination of the corresponding commercially available aldehyde resins[11] [R_3NH_2/$NaBH(OAc)_3$/HOAc/DMF]. A protocol suitable for high throughput automated synthesis was validated, by which a dihydroquinazoline library was then synthesized in high yield with excellent purity.[12] Some examples selected from the validation library are shown in Table 1.

In conclusion, an efficient high-yielding solid-phase synthesis of 3,4-dihydroquinazoline derivatives has been developed. This novel method is amenable to combinatorial synthesis and offers a broad scope for structural and chemical diversity. Further applications to the construction of other important heterocyclic scaffolds based on the polymer-bound 4-bromomethyl-3-nitrobenzoic acid will be reported in due course.

Acknowledgements

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10. Huang, W.; Scarborough, R. M. *Tetrahedron Lett.* **1999**, *40*, 2665–2668.
11. Advanced ChemTech, Louisville, KY, (800) 456–1403.
12. **Typical procedures**:
Route A: 4-(Bromomethyl)-3-nitrobenzoic acid Wang resin (1 g, ~0.6 mmol) was mixed with a solution of 1 M phenethylamine in NMP (10 mL). The slurry was shaken at rt for 45 min. The resin was filtered and washed with DMF (3×), MeOH (3×), DCM (3×) and MeOH (3×). To the dry resin (200 mg, 0.12 mmol) were added a solution of 1 M dihydrocinnamic acid in DMF (1.2 mL) and a solution of 1 M DIC in DCM (1.2 mL). The resulting suspension was shaken at rt for 6 h. Filtration followed by washing (DMF/MeOH/DCM) gave the resin which was then treated with 2 M $SnCl_2 \cdot 2H_2O$ in NMP (2 mL) overnight. The resin was filtered and washed thoroughly

as above. A mixture of the obtained resin (100 mg, 0.5 mmol/g) and *o*-xylene (2 mL) was heated at 100°C for 24 h. The resin was filtered and washed with MeOH and DCM. After treating with 20% TFA in DCM for 30 min, the resin was filtered and rinsed with DCM (10 mL). The combined filtrates were concentrated to give a residue which was re-dissolved in acetonitrile (10 mL). The solvent was then removed on a rotavapor to give the crude product **10** (20.8 mg, >90% purity).

Route B: 4-(*p*-Methoxybenzylaminomethyl)-3-nitrobenzoic acid Wang resin (100 mg, ~0.5 mmol/g) was treated with 2 M $SnCl_2 \cdot 2H_2O$ in NMP (3 mL) overnight. The slurry was filtered and washed with DMF (3×), MeOH (3×), DCM (3×) and MeOH (3×). To the resin were added DMF (400 μL), 1 M benzaldehyde in DMF (400 μL) and 0.5 M DDQ in DMF (400 μL). The resulting suspension was shaken at rt for 6 h. The resin was filtered and washed with DMF (3×), 0.5 M DIEA in DMF (2×), MeOH (6×), DCM (6×) and MeOH (3×). After treating with 20% TFA in DCM for 30 min, the resin was filtered and rinsed with DCM (10 mL). The combined filtrates were concentrated to give a residue which was re-dissolved in acetonitrile (10 mL). The solvent was then removed on a rotavapor to give the crude product **18** (20.1 mg, 95% purity).