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Traceless synthesis of 3*H*-quinazolin-4-ones via a combination of solid-phase and solution methodologies

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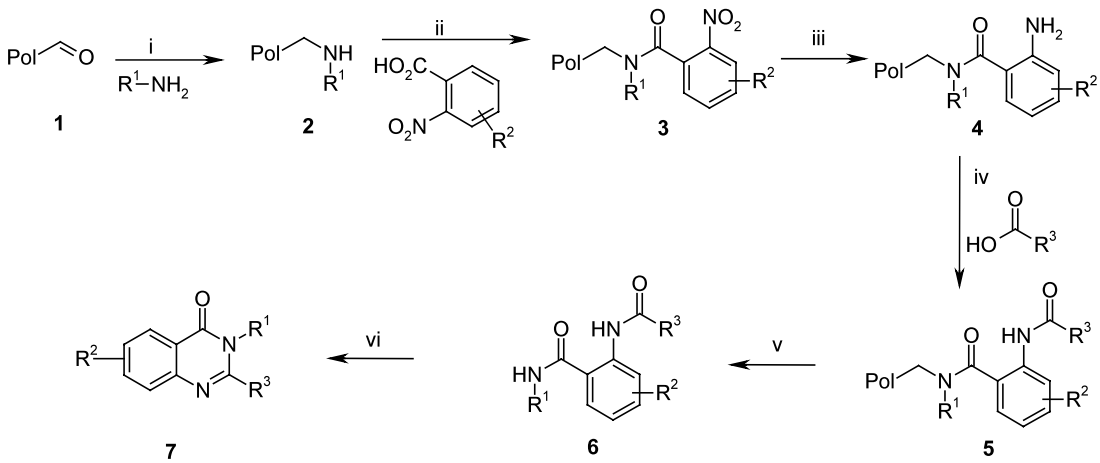
Abstract—A solid-phase traceless synthesis of quinazolin-4-ones is described. An aldehyde functionalized resin was reductively aminated with primary amines, and the resin-bound secondary amine acylated with *o*-nitro-benzoic acids. The nitro group was reduced with tin(II) chloride, and the aniline acylated with acid anhydrides. Acidolytic cleavage afforded a diamide, which was cyclized in solution phase to the 3*H*-quinazolin-4-one removing the trace of the linker.

We have recently described traceless syntheses of benzimidazoles,[1] quinoxalines[2] and tetrahydroquinoxalines.[3] These previous syntheses are based on the acid lability of electron-rich *N*-aryl-benzylamines. The synthesis of quinazolin-4-ones described below uses the more familiar strategy of acid cleavage of *N*-benzyl tertiary amides.

The route to 3*H*-quinazolin-4-ones is similar in philosophy to our previously described solid-phase synthesis of benzimidazoles and quinoxalinones—the initial product after cleavage from the resin is modified to remove the trace of the linker. For the case of 3*H*-quinazolin-4-ones, both traceable[4] and traceless syntheses[5] have been described, the latter of necessity leading to the 2-proto or 2-hetero derivatives. Shown in Scheme 1 is our route to the 2-carbo derivatives. In our case, the key step, cyclization of the diamide, occurs in solution. Although a number of procedures have been reported for conversion of diamides of type **6** to quinazolin-4-ones,[6] none fulfilled the requirements that we envisioned for synthesis of large libraries: reaction temperatures from ambient to 70°C, generality, tolerance of functional groups, and ready separation of by-products. Since the net



Scheme 1. Traceless synthesis of quinazolinones. *Reagents*: (i) $NaBH(OAc)_3$, DMF/AcOH; (ii) DIC, HOBt, DMF; (iii) $SnCl_2 \cdot 2H_2O$, DIEA, NMP; (iv) DIC, pyridine, dioxane; (v) gaseous HF; (vi) TMSCl, DMEA, MeCN.

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result of the cyclization is a dehydration, we reasoned that the use of a silicon electrophile would accomplish the necessary steps of activation of the anilide to nucleophilic attack, and sequestration of the formal water by-product.

The synthesis was developed on (4-(4-formyl-3-methoxyphenoxy)butyryl) aminomethyl resin (Novabiochem, Laufelfingen, Switzerland). The aldehyde resin **1** was reductively aminated with primary amines using the standard protocol developed by others[7] and us.[1] Analogous to our previous work,[1,2] the yield and purity of this initial step was evaluated after the secondary resin-bound amine **2** was reacted with fluorenylmethyl chloroformate (Fmoc-Cl). The resin-bound Fmoc protected amine was then cleaved by TFA and analyzed.

The second combinatorial step involved acylation of the resin bound secondary amine with a variety of *o*-nitro benzoic acids. When R^1 is an alkyl or benzylic amine, this could be accomplished with a mixture of the acid, *N*,*N*′-diisopropylcarbodiimide (DIC), and 1-hydroxy-benzotriazole (HOBt) in DMF. Colorization of the resin with bromophenol blue allowed the reaction to be monitored in situ.[8]

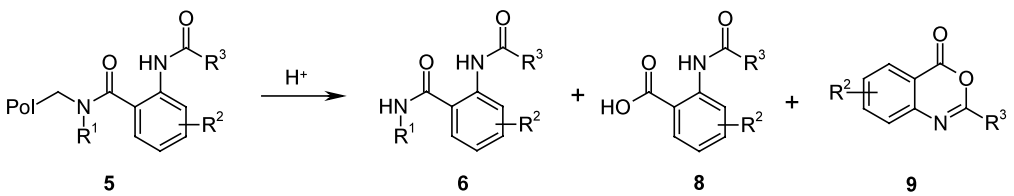
Reduction of the nitro group with 2 M tin(II) chloride in degassed *N*-methyl-pyrrolidone (NMP)[9] gave the aniline, ready for acylation with the third building block. Initial conditions (acid chloride, *N*,*N*-diisopropylethylamine (DIEA), DCM) lead to competing bis-acylation to give imides, especially when the R^2 nitro benzoic acid contained electron-withdrawing groups. Conditions optimized to avoid this side reaction involved the use of the acid, DIC and pyridine in dioxane as solvent. Generally less than 5% of starting aniline remained after 2 couplings.

Cleavage of the resin **5** (HF, HCl, or TFA) gave the desired diamide **6** along with varying portions of the acid **8** or benzoxazinone **9** by-products. The amount of byproducts **8** and **9** depended on the identity of the 3 building blocks and the cleavage acid (Scheme 2). The benzoxazine **9** ring-opens to the acid **8** during work-up, and could be selectively removed from the cyclized quinazolinone **7** (vide infra).

The final synthetic step involved cyclization of diamide **6** to the quinazolinone **7**. Given the sequence of diamide assembly, cyclization to the quinazolone could not be accomplished while still on the resin. Thus we sought a solution-phase cyclization method that would generate only volatile and/or water-soluble byproducts. In the event, chlorotrimethylsilane (TMSCl) in the presence of a tertiary amine base, *N*,*N*-dimethylethylamine (DMEA) performed this task admirably. The reaction is relatively insensitive to hindrance at the 2-position across the newly formed N–C bond, especially given the mildness of the conditions employed. Importantly, this method allows incorporation of OH and NH derivatives on the sidechains of the quinazolone core, which are protected in situ during cyclization, and then unmasked on work-up. Following cyclization, the reactant solution was evaporated, and the quinazolinone freed from the byproduct tertiary amine salt via a standard aqueous work-up.[10] Selective removal of the hydrophobic acid by-product **8** from product quinazolinone **7** was accomplished with a variety of basic scavenger resins (Dowex® 550A, polystyrene trisamine, CombiZorb trisamine). Yields and purities of selected quinazolinones are shown in Table 1.[11] LC/MS analysis of the samples showed a molecular ion corresponding to the expected quinazolinone.

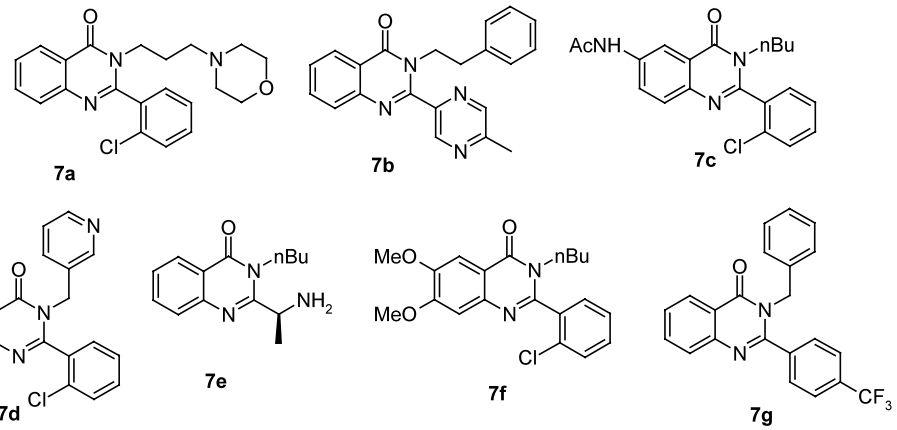
The synthetic scheme in Table 1 is also applicable to the synthesis of quinazolinones on a grafted surface with minor modifications. In light of our interest in encoding libraries using a 'string synthesis'[12] method, we attempted the synthesis of a small library on Mimotopes SynPhase™ Lanterns. Given the slower rates of reaction for this type of polymer matrix, we found that acylation of the secondary amine did not proceed to completion under our previously successful conditions. Instead, performing the reaction as described above, but with added *N*,*N*-4-dimethylamino-pyridine (DMAP) (1 equiv. relative to acid) gave efficient coupling. Reduction of the nitro group, and acylation with the R^3 acid as before afforded the desired diamides bound to the lanterns. Following cleavage with gaseous HF, the synthesis was completed in identical fashion.

In summary, we have described a traceless solid-phase synthesis of 2-carbo-3*H*-quinazolin-4-ones with 3 points of diversity. The reaction conditions are amenable to the synthesis of large combinatorial libraries, and the purities of final products are excellent. Additionally, our strategy of using a silicon halide is a novel method for dehydrative cyclization, which has not, to the best of our knowledge, been described elsewhere for condensation of diamide derivatives.



Scheme 2. Acidic cleavage of diamide.

Table 1. Purity and yield of quinazolinones



Compound	t_R (min)	Purity (%)[a]	Yield (%)[b]	MW	$[M+H]^+$
7a	4.0	100	15	400	401.2
7b	6.6	87	11	342	343.4
7c	6.1	95	20	369	370.2
7d	4.1	97	15	364	365.1
7e	3.7	100	19	245	246.2
7f	6.8	94	20	372	373.1
7g	7.8	100	15	326	327.3

[a] Determined at 280 nm.
[b] Average plate yield.

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10. A representative procedure follows: The aldehyde resin (0.3 mmol) in a 10 mL fritted syringe, reductively aminated with R^1 primary amine as previously described,[1,7] was acylated with the R^2 *o*-nitro-benzoic acid (3 equiv.), HOBt (3 equiv.) and DIC (3 equiv.) in DMF (0.9 mL/syringe). After 16 h, the resin was washed with DMF, methanol and DCM. The nitro group was reduced to the aniline with a solution of $SnCl_2 \cdot 2H_2O$ (2 M) and DIEA (1 M) in degassed NMP (4 mL/syringe) for 24 h, then washed with NMP, NMP/water (2/1), methanol, DMF and DCM. The resins were transferred to a 96 well plate (ca. 60 mg/well), and treated with a solution of the acid (7 equiv.), DIC (3.5 equiv.) and pyridine (7 equiv.) in dioxane (0.3 mL) for 24 h. After a second coupling, the

resins were washed with dioxane, DMF, methanol, and ether/DCM (3/1). The resins were then cleaved with gaseous HF for 2 h, and the diamide extracted from the resin with methanol/acetonitrile/water (10/10/1, 0.8 mL/well) overnight. The filtered solutions were evaporated to dryness, and the residue taken up in a solution of DMEA (1.25 M) and TMSCl (1 M) in acetonitrile (1 mL/well). The sealed plate was agitated for 1 h, and then aged at 30°C for 70 h. Residual TMSCl was quenched with water (0.1 mL/well), and the residue evaporated to dryness. The residue was partitioned between 2 M NaOH solution (0.6 mL/well) and ethyl acetate (0.6 mL/well). Freezing of the plate in a dry ice/isopropanol bath accomplished the desired physical separation of the phases in 96 well format.[13] The organic layer was evaporated to dryness, and the residue dissolved in acetonitrile (0.6 mL/well) and shaken with polystyrene trisamine (110 mg/well) overnight. The crude product was obtained by filtration and analyzed directly by LC/MS. Yields were averaged over a plate, and calculated based on the loading of the starting aldehyde resin (0.88 mmol/g).

11. Analytical gradient HPLC profile was run on a Phenomenex Aqua C18 4.6×30 mm analytical column, gradient 0–100% of acetonitrile in 8 min at 1.2 mL/min. The purity was estimated based on analytical traces at $\lambda = 280$ nm. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **7g** δ: 8.40 (dd, $J = 1.5$, 7.8 Hz, 1), 7.82 (app dt, $J = 1.5$, 7.3 Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 2H), 7.58 (dt, $J = 1.0$, 7.3 Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 2H), 7.25–7.21 (m, 3H), 6.93–6.88 (m, 2H), 5.25 (s, 2H).
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13. See also the 'lollipop phase separator' at www.radleys.co.uk.