Solution-phase combinatorial synthesis of 4-hydroxyquinolin-2(1*H*)-ones

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Ion-exchange resins catalyse an intramolecular Claisen-type condensation leading to the title compounds, and also serve to purify the products.

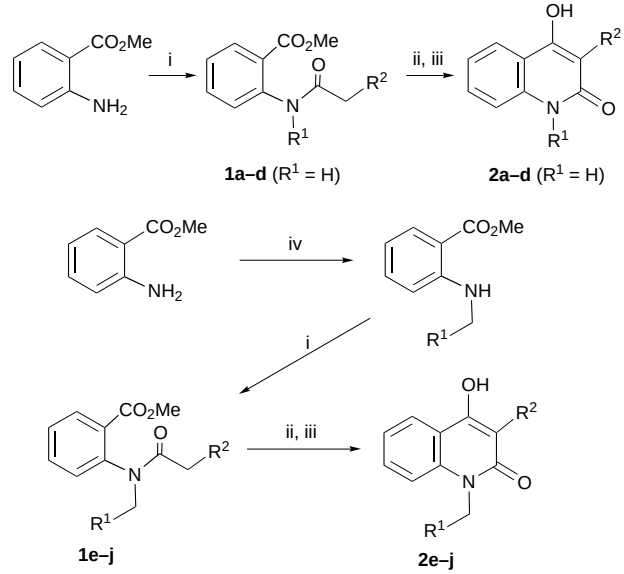
In recent years, much effort has been devoted to the synthesis of chemical libraries, particularly for the generation and optimisation of biologically active compounds.[1] High-throughput synthesis by traditional solution-phase chemistry (as opposed to solid-phase techniques) is gaining in popularity with the advent of efficient methods for compound purification. One approach employs polymer-supported reagents[2] that can be readily removed by filtration. Recent examples include immobilized Sc^{III},[3] hydroxybenzotriazole,[4] carbodiimides[5] and guanidines.[6] Another application[5,7] of polymer-supported functional groups is to scavenge unreacted or excess starting materials in solution. Conventional ion exchange resins have been used both as a reagent[8] as well as a purification aid,[9] and we have recently reported[10] a synthesis of tetramic acids in which the resin performs both functions. Here, we demonstrate the application of this technique to the preparation of a pharmacologically important heterocyclic ring system.

4-Hydroxyquinolin-2(1*H*)-ones have attracted considerable attention for various therapeutic areas including antimicrobial and antitumour activity,[11] local anaesthetics[12] and antiinflammatory agents,[13] as well as being antagonists of thyroid hormone,[14] *N*-methyl-D-aspartate[15] and serotonin.[16] A common route to these compounds is the intramolecular Claisen-type condensation of *N*-acylated anthranilate esters. Various bases were used[17] for the cyclization (*e.g.* NaOH, alkoxides, lithium amides, TBAF), but removing these and other impurities is relatively tedious in the context of parallel synthesis. We envisioned that an insoluble quaternary ammonium resin would be more suitable, as in our tetramic acid synthesis.

We prepared a set of Claisen-type condensation precursors from methyl anthranilate by Schotten–Baumann two-phase acylation to give primary amides **1a**–**d** (Scheme 1). For increased diversity, additional examples were first reductively alkylated[18] before acylation to afford secondary amides **1e**–**j**. Treatment of compounds **1** with Amberlyst A-26 resin (OH^- form) uniformly resulted in cyclization. As expected, the 4-hydroxyquinolin-2(1*H*)-ones **2** remain tightly bound to the quaternary ammonium resin, enabling impurities to be removed by simple filtration. Subsequent acidification then releases the product in high yield and purity (Table 1). These cyclizations proceed more readily than with the tetramic acids, as shown by the ability of R^2 = Ph and SPh to be sufficiently activating.

We have further extended this procedure to substituted anthranilic acids (for examples, see Table 2, entries **1k**–**p**). Finally, the selectivity of product sequestration by the resin after the Claisen-type condensation enables the use of crude precursors **1** (Table 2, entries **1q**–**t**). These were obtained without purification after the reductive alkylation or acylation steps, the workup consisting of only aqueous washing. The ability to carry forward intermediates without full purification facilitates the overall sequence for high-throughput synthesis.

In summary, this protocol is suitable for the preparation of diverse 4-hydroxyquinolin-2(1*H*)-ones from commercially available building blocks, while permitting wide variations in the substitution pattern.



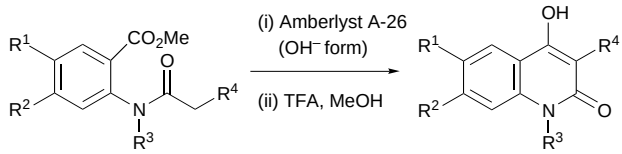
Scheme 1 *Reagents and conditions*: i, R^2CH_2COCl, 10% aq. Na_2CO_3–CH_2Cl_2, room temp., 30 min; ii, Amberlyst A-26 (OH^- form), MeOH, room temp., 16 h; iii, TFA, MeOH, room temp., 30 min; iv, R^1CHO, $NaBH(OAc)_3$, CH_2Cl_2, room temp., 18 h

Table 1 Yield and purity of 4-hydroxyquinolin-2(1*H*)-ones prepared by the intramolecular Claisen-type condensation

Precursor	R^1	R^2	Product	Yield (%)	Purity[a] (%)
1a	H	CN	**2a**	82	98
1b	H	3-pyridyl–S	**2b**	78	97
1c	H	SPh	**2c**	80	99
1d	H	Ph	**2d**	86	85
1e	4-$MeOC_6H_4$	SPh	**2e**	94	94
1f	4-$MeOC_6H_4$	2-$NO_2C_6H_4$	**2f**	96	95
1g	4-$MeOC_6H_4$	CO_2Me	**2g**	89	95
1h	CH_2CHMe_2	2-$NO_2C_6H_4$	**2h**	96	94
1i	4-$MeOC_6H_4$	Ph	**2i**	89	95
1j	Ph	SPh	**2l**	91	99

[a] Assessed by HPLC analysis with UV detection (254 nm). All compounds were characterised spectroscopically (NMR, MS).

Table 2 Yield and purity of additional 4-hydroxyquinolin-2(1*H*)-ones prepared



1k–t **2k–t**

Precursor	R^1	R^2	R^3	R^4	Product	Yield (%)	Purity[a] (%)
1k	H	H	Me	Ph	**2k**	86	98
1l	H	H	Ph	SPh	**2l**	91	97
1m	H	Cl	Bn	CO_2Me	**2m**	89	79
1n	F	F	Bn	CO_2Me	**2n**	90	95
1o	H	CO_2Me	Bn	Ph	**2o**	88[a]	97
1p	OMe	OMe	4-$MeOC_6H_4CH_2$	CO_2Me	**2p**	72	91
1q[b]	H	H	H	CO_2Me	**2q**	84	90
1r[b]	H	H	Me	CO_2Me	**2r**	97	97
1s[b]	H	H	4-$MeOC_6H_4CH_2$	SPh	**2s**	83	91
1t[b]	H	H	Bn	SPh	**2t**	92	95

[a] Two products were isolated (*ca.* 1 : 1 ratio), due to the partial hydrolysis of the ester (R^2 = CO_2Me to CO_2H). [b] Crude material used without chromatographic purification after either the reductive alkylation or acylation.

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Notes and References

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