

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 reagents² that can be readily removed by filtration. Recent examples include immobilized Sc^{III},³ hydroxybenzotriazole,⁴ carbodiimides⁵ 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 reagent⁸ as well as a purification aid,⁹ and we have recently reported¹⁰ 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.

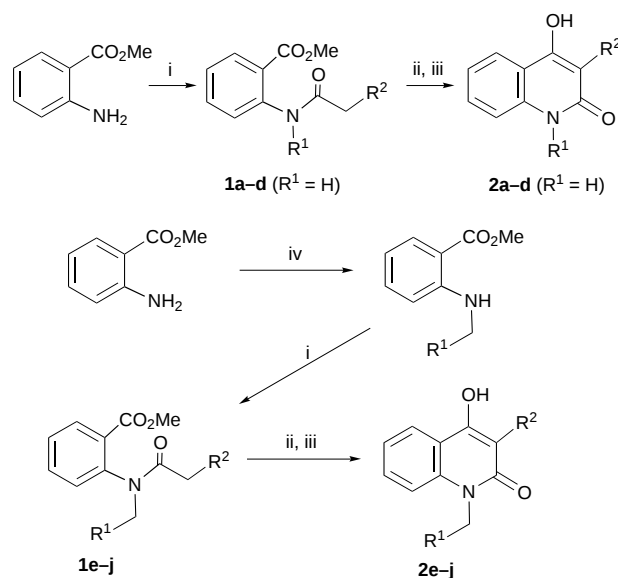
4-Hydroxyquinolin-2(1*H*)-ones have attracted considerable attention for various therapeutic areas including antimicrobial and antitumour activity,¹¹ local anaesthetics¹² and anti-inflammatory agents,¹³ as well as being antagonists of thyroid hormone,¹⁴ *N*-methyl-*D*-aspartate¹⁵ and serotonin.¹⁶ A common route to these compounds is the intramolecular Claisen-type condensation of *N*-acylated anthranilate esters. Various bases were used¹⁷ 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 alkylated¹⁸ 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 R² = 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, R²CH₂COCl, 10% aq. Na₂CO₃–CH₂Cl₂, room temp., 30 min; ii, Amberlyst A-26 (OH[−] form), MeOH, room temp., 16 h; iii, TFA, MeOH, room temp., 30 min; iv, R¹CHO, NaBH(OAc)₃, CH₂Cl₂, 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 ₆ H ₄	SPh	2e	94	94
1f	4-MeOC ₆ H ₄	2-NO ₂ C ₆ H ₄	2f	96	95
1g	4-MeOC ₆ H ₄	CO ₂ Me	2g	89	95
1h	CH ₂ CHMe ₂	2-NO ₂ C ₆ H ₄	2h	96	94
1i	4-MeOC ₆ H 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(1H)-ones prepared

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 ₂ Me	2m	89	79
1n	F	F	Bn	CO ₂ Me	2n	90	95
1o	H	CO ₂ Me	Bn	Ph	2o	88 ^a	97
1p	OMe	OMe	4-MeOC ₆ H ₄ CH ₂	CO ₂ Me	2p	72	91
1q^b	H	H	H	CO ₂ Me	2q	84	90
1r^b	H	H	Me	CO ₂ Me	2r	97	97
1s^b	H	H	4-MeOC ₆ H ₄ CH 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 (R² = CO₂Me to CO₂H). ^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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- For recent journal issues devoted to combinatorial chemistry, see: *Chem. Rev.*, 1997, **97**, Issue 2; *Curr. Opin. Chem. Biol.*, 1997, **1**, Issue 1.
- For a review on functionalised polymers including combinatorial chemistry applications, see S. J. Shuttleworth, S. M. Allin and P. K. Sharma, *Synthesis*, 1997, 1217.
- S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, 1996, **118**, 8977; S. Kobayashi, S. Nagayama and T. Busujima, *Tetrahedron Lett.*, 1996, **37**, 9221.
- I. E. Pop, B. P. Déprez and A. L. Tartar, *J. Org. Chem.*, 1997, **62**, 2594.
- D. L. Flynn, J. Z. Crich, R. V. Devraj, S. L. Hockerman, J. J. Parlow, M. S. South and S. Woodard, *J. Am. Chem. Soc.*, 1997, **119**, 4874; J. J. Parlow, D. A. Mischke and S. S. Woodard, *J. Org. Chem.*, 1997, **62**, 5908.
- W. Xu, R. Mohan and M. M. Morrissey, *Tetrahedron Lett.*, 1997, **38**, 7337.
- S. W. Kaldor, M. G. Siegel, J. E. Fritz, B. A. Dressman and P. J. Hahn, *Tetrahedron Lett.*, 1996, **37**, 7193; S. W. Kaldor, J. E. Fritz, J. Tang and E. R. McKinney, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 3041; R. J. Booth and J. C. Hodges, *J. Am. Chem. Soc.*, 1997, **119**, 4882; J. J. Parlow, W. Naing, M. S. South and D. L. Flynn, *Tetrahedron Lett.*, 1997, **38**, 7959; M. M. Sim, C. L. Lee and A. Ganesan, *J. Org. Chem.*, 1997, **62**, 9358.
- J. J. Parlow, *Tetrahedron Lett.*, 1996, **37**, 5257.
- L. M. Gayo and M. J. Suto, *Tetrahedron Lett.*, 1997, **38**, 513; R. M. Lawrence, S. A. Biller, O. M. Fryszman and M. A. Poss, *Synthesis*, 1997, 553; M. G. Siegel, P. J. Hahn, B. A. Dressman, J. E. Fritz, J. R. Grunwell and S. W. Kaldor, *Tetrahedron Lett.*, 1997, **38**, 3357; A. J. Shuker, M. G. Siegel, D. P. Matthews and L. O. Weigel, *Tetrahedron Lett.*, 1997, **38**, 6149.
- B. A. Kulkarni and A. Ganesan, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2454.
- M. Rideau, C. Verchere, P. Hibon, J.-C. Cheniéux, P. Maupas and C. Veil, *Phytochemistry*, 1979, **18**, 155.
- I. V. Ukrainets, S. V. Slobodzyan, V. I. Krivobok, P. A. Bezuglyi, V. I. Treskach, A. V. Turov, S. V. Gladchenko and G. V. Obolentseva, *Farm. Zh. (Kiev)*, 1991, **2**, 78.
- I. V. Ukrainets, O. V. Gorokhova, S. G. Taran and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 1994, 1397.
- I. V. Ukrainets, P. A. Bezugly, O. V. Borokhova, V. I. Treskach and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 1993, 105.
- P. D. Leeson, R. Baker, R. W. Carling, J. J. Kulagowski, I. M. Mawer, M. P. Ridgill, M. Rowley, J. D. Smith, I. Stansfield, G. I. Stevenson, A. C. Foster and J. A. Kemp, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 299; M. Rowley, P. D. Leeson, G. I. Stevenson, A. M. Moseley, I. Stansfield, I. Sanderson, L. Robinson, R. Baker, J. A. Kemp, G. R. Marshall, A. C. Foster, S. Grimwood, M. D. Tricklebank and K. L. Saywell, *J. Med. Chem.*, 1993, **36**, 3386; J. J. Kulagowski, R. Baker, N. R. Curtis, P. D. Leeson, I. M. Mawer, A. M. Moseley, M. P. Ridgill, M. Rowley, I. Stansfield, A. C. Foster, S. Grimwood, R. G. Hill, J. A. Kemp, G. R. Marshall, K. L. Saywell and M. D. Tricklebank, *J. Med. Chem.*, 1994, **37**, 1402.
- H. Hayashi, Y. Miwa, S. Ichikawa, N. Yoda, I. Miki, A. Ishii, M. Kono, T. Yasuzawa and F. Suzuki, *J. Med. Chem.*, 1993, **36**, 617.
- A. Detsi, V. Bardakos, J. Markopoulos and O. Igglessi-Markapoulou, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2909 and references cited therein.
- A. K. Szardenings, T. S. Burkoth, G. C. Look and D. A. Campbell, *J. Org. Chem.*, 1996, **61**, 6720.

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