



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

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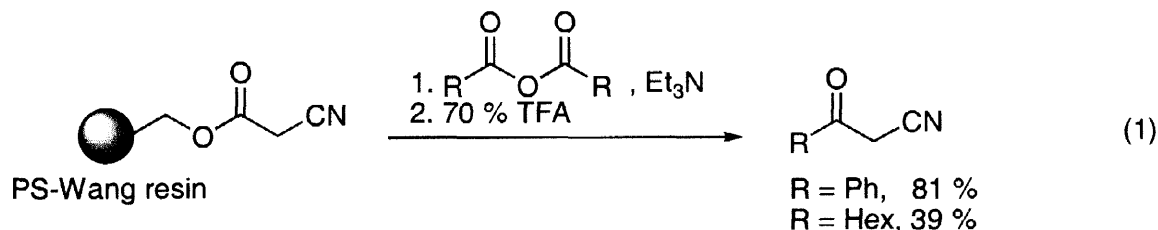
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Abstract: Cyanoacetic acid was loaded on Wang resin and C-acylated using acid anhydrides and triethylamine as base. Resin cleavage with concomitant decarboxylation produces β -keto nitriles. In the case of isatoic anhydrides, the resin-bound acylated intermediates undergo cyclative cleavage upon heating, leading to 4-hydroxyquinolin-2(1H)-ones. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: solid-phase synthesis, combinatorial chemistry, acylation, quinolinones

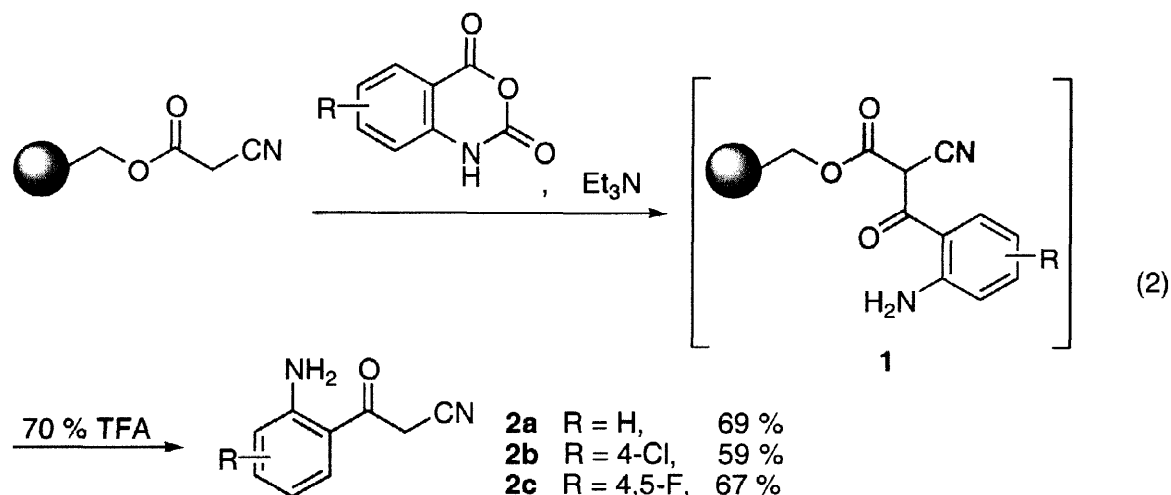
Combinatorial chemistry is of growing importance for pharmaceutical lead discovery and optimization.¹ Early libraries emphasized the use of large pools, which can result in problems during synthesis and screening as well as deconvolution of active samples. Consequently, parallel synthesis of discrete compounds is currently more popular, either by traditional solution-phase² chemistry or solid-phase³ techniques. The latter, originally developed for biopolymers, is perhaps easier to automate and a variety of synthesizers are commercially available. Nevertheless, many organic reactions and reaction sequences have yet to be adapted to solid-phase conditions.

Recently, we have been exploring the synthetic potential of resin-bound active methylene compounds. C-acylation was achieved⁴ using a mild base (triethylamine) and an acylating species formed by reacting carboxylic acids with diethyl phosphorocyanidate (DEPC).⁵ We have found that the acylation can also be accomplished with acid anhydrides (eq. 1). Aromatic substrates appear to work best, as seen in the relative yields with benzoic and hexanoic anhydrides. This trend was also observed in the DEPC acylations.



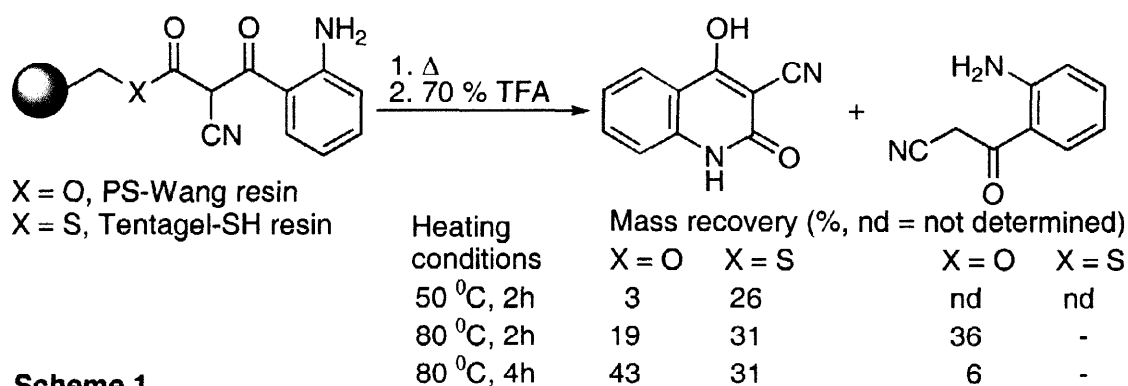
We were unable to obtain acylation products with *N*-carboxyanhydrides (Leuchs anhydrides), probably due to the highly reactive nature of these compounds and their ease of polymerization. Isatoic anhydrides, containing a less nucleophilic aniline, were however suitable substrates (eq. 2)⁶ and yields were superior to our solid-phase DEPC acylation with anthranilic acids. We are unaware of precedents for C-acylation with isatoic

anhydrides under such mild conditions, as solution-phase examples with active methylene compounds used strong bases (sodium hydride, lithium diisopropylamide).^{7,8}



With isatoic anhydrides, there was the additional possibility of acylated intermediate **1** undergoing lactamization. In solution, this was reported⁷ to occur spontaneously at room temperature over varying lengths of time. In our solid-phase context, this would amount to a cyclative release of product. The resulting 4-hydroxyquinolin-2(*1H*)ones have previously displayed biological activity across a wide range of therapeutic targets.⁹ We have recently developed¹⁰ a solution-phase combinatorial approach to this scaffold, which features a quite different disconnection involving an intramolecular Claisen-type condensation.

Upon heating, the hydroxyquinolinone was indeed released from both Wang and Tentagel-SH resins, although the ¹H NMR spectrum indicated an approximately equimolar amount of triethylamine. Presumably, the highly acidic nature of **1** leads to formation of a stable triethylamine salt which survives resin washing. The cyclization with Tentagel-SH was faster than with Wang resin, consistent with the better leaving group ability of thiolate versus alkoxide. However, acylation yields were better with Wang resin, as shown by residual uncyclized material, which gave **2a** on TFA cleavage (Scheme 1). Increasing the reaction time and temperature improved the extent of cyclization.



Having established suitable conditions for cyclative cleavage, we turned to the parallel synthesis of hydroxyquinolinones. A series of isatoic anhydrides was prepared from the corresponding commercially available anthranilic acids following literature procedures.¹¹ For additional diversity, the isatoic anhydrides were also *N*-alkylated.¹² Examples of hydroxyquinolinones synthesized by this solid-phase procedure are given in Figure 1.

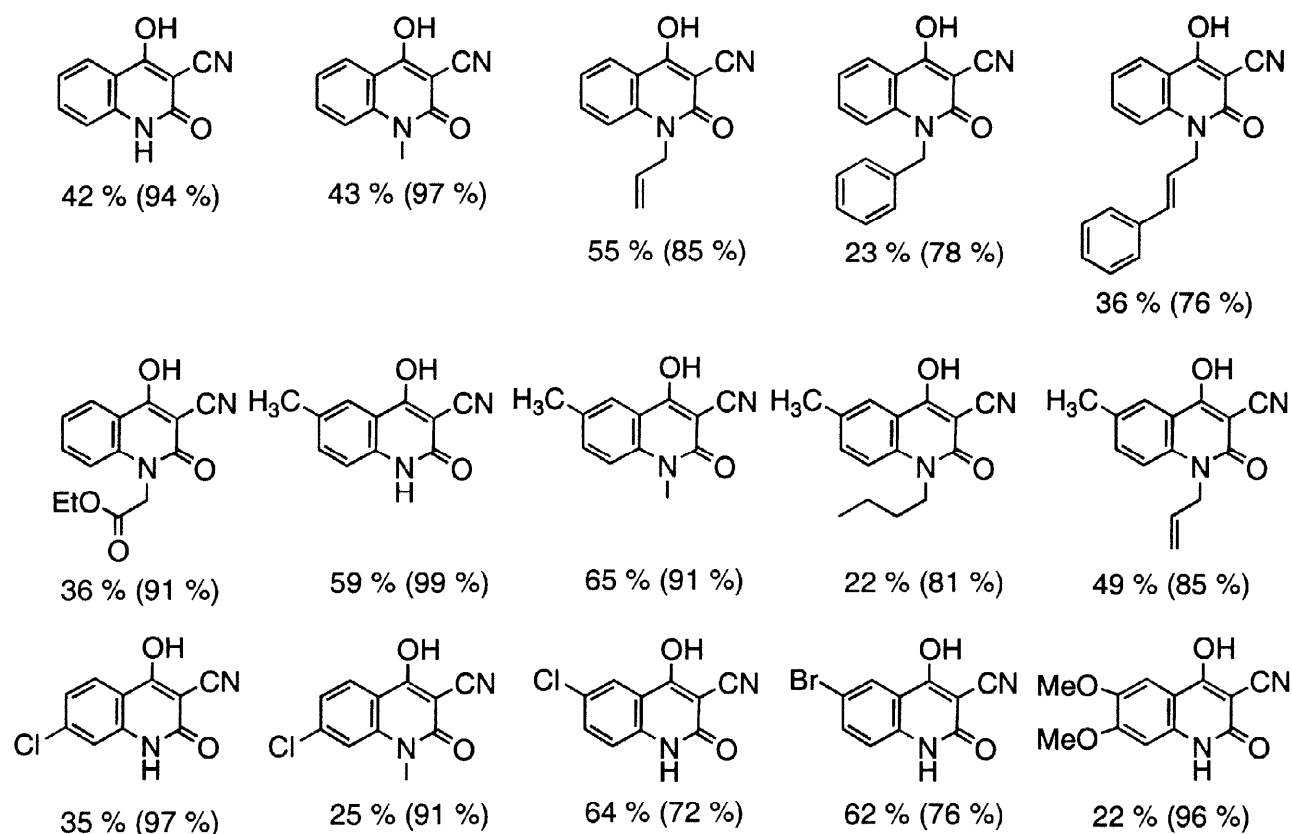


Figure 1^a

^a All compounds were characterized spectroscopically (NMR, MS). The mass recovery of crude hydroxyquinolinones as their triethylamine salts is given, based on the original resin capacity. Bracketed numbers indicate purity assessed by HPLC (UV detection).

Typical procedure: A pre-dried mixture of Wang resin-cyanoacetate (0.1 mmol; Wang resin from Novabiochem, with a loading capacity of 0.58 mmol/g) and *N*-methylisatoic anhydride (177 mg, 10 equiv) was suspended in anhydrous DMF (2.5 mL) and triethylamine (0.14 mL, 10 equiv, freshly distilled). After overnight shaking at room temperature, the resin was washed (DMF, MeOH, CH₂Cl₂, MeOH). For hydroxyquinolinone cyclative cleavage, the resin was suspended in toluene and heated at 80 °C for 24 h. Alternatively, acid cleavage (70 % TFA, 1 h) yielded the β-keto nitrile.

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References and Notes

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² For example, see Tetrahedron Symposia-in-Print #70, *Tetrahedron* **1998**, *54*, issue 16.

³ For recent reviews, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527-4554. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643-5678.

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⁵ These conditions were first employed by Shiori for solution-phase C-acylation: Shiori, T.; Hamada, Y. *J. Org. Chem.* **1978**, *43*, 3631-3632.

⁶ Yields in eq. 1 and 2 are for chromatographically purified material, based on the initial loading capacity of the resin.

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⁹ For examples, see: (a) Ukrainets, I. V.; Slobodzyan, S. V.; Krivobok, V. I.; Bezuglyi, P. A.; Treskach, V. I.; Turov, A. V.; Gladchenko, S. V.; Obolenteseva, G. V.; *Farm. Zh. (Kiev)* **1991**, *2*, 78-80. (b) Hayashi, H.; Miwa, Y.; Ichikawa, S.; Yoda, N.; Miki, I.; Ishii, A.; Kono, M.; Yasuzawa, T.; Suzuki, F. *J. Med. Chem.* **1993**, *36*, 617-626. (c) Ukrainets, I. V.; Gorokhova, O. V.; Taran, S. G.; Turov, A. V. *Khim. Geterotsykl. Soedin.* **1994**, 1397-1399. (d) Ukrainets, I. V.; Taran, S. G.; Kodolova, O. L.; Gorokhova O. V.; Kravchenko V. N. *Khim. Geterotsykl. Soedin.* **1997**, 1100-1104. (e) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Moyes, C. R.; Duncton, M.; Hudson, M. L.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1997**, *40*, 754-765.

¹⁰ Kulkarni, B. A.; Ganesan, A. *Chem. Commun.* **1998**, 785-786.

¹¹ Hardtmann, G. E.; Koletar, G.; Pfister, O. R. *J. Heterocycl. Chem.* **1975**, *12*, 565-572. We modified the procedure slightly by using triphosgene instead of phosgene. The precipitated crude isatoic anhydrides were washed (H₂O, ether), dried and used without further purification.

¹² N-alkylisatoic anhydrides were recrystallized (CH₂Cl₂, hexanes) prior to use.