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Solid Phase Synthesis of Substituted Quinolin-2(*1H*)-one-3-Carboxylic Acids via an Intramolecular Knoevenagel Condensation

Brett T. Watson* and Gerda E. Christiansen

Novo Nordisk A/S, Medicinal Chemistry Research
Novo Nordisk Park, DK-2760 Måløv, Denmark

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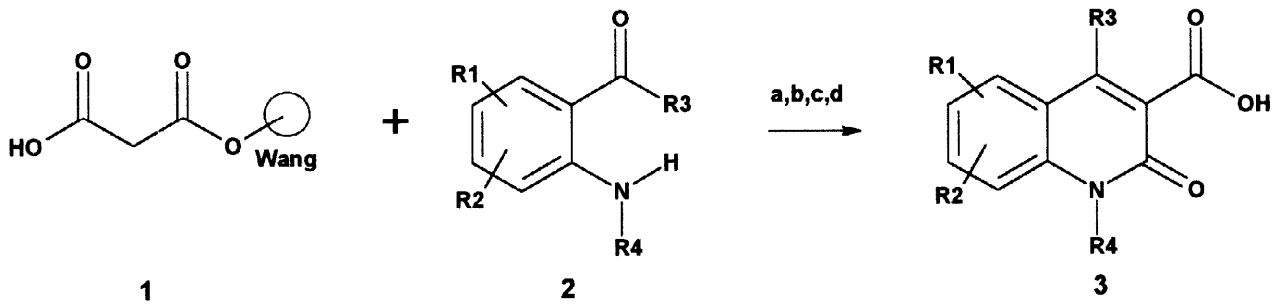
Abstract: A solid phase synthesis of substituted quinolin-2(*1H*)-one-3-carboxylic acids is described. The products are formed in a two-step synthesis in which *ortho*-aminophenones are first coupled to malonic acid bound to the Wang Resin followed by ring closure via an intramolecular Knoevenagel condensation.

Keywords: combinatorial chemistry; Knoevenagel condensation; quinolinones; solid-phase synthesis

As heterocyclic compounds are an important resource for the pharmaceutical and agrochemical industries, there exists a need for clean and efficient solid phase syntheses of these substances. Recently we reported on the solid phase synthesis of coumarin-3-carboxylic acids by an intermolecular Knoevenagel condensation.[1] Isoquinolinones,[2] quinolin-4(*1H*)-ones,[3] quinoline-N-oxides,[4] have been the focus of solid phase syntheses; a solution phase synthesis of quinolin-2(*1H*)-ones was reported in which an ion-exchange resin was used as a noncovalent solid support to temporarily bind the final product.[5] Herein, we describe the use of an intramolecular Knoevenagel condensation reaction on solid support to prepare substituted quinolin-2(*1H*)-ones in a mild and facile manner with high purity and in very good yields (Scheme I).

Scheme I



1 2 3

a) EDAC, HOBT, DMF, RT, 16 h; b) Wash Resin; c) Repeat Steps a, b; d) piperidine, pyridine, RT, 16 h; e) TFA/CH_2Cl_2

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The reaction sequence is as illustrated above in which malonic acid attached to the Wang resin[6] (**1**) was treated with an *ortho*-aminophenone (**2**), EDAC and HOBT to form the corresponding amide. This was followed by a thorough washing of the resin and, in order to insure that all of the resin-bound malonic acid was utilized, these steps were repeated. An intramolecular Knoevenagel reaction between the methylene group of the malonate and the carbonyl moiety was then effected by suspending the resin in pyridine, adding a catalytic amount of piperidine and shaking at room temperature overnight. The final quinolin-2(*1H*)-one-3-carboxylic acids (**3**) were cleaved from the resin with TFA/CH_2Cl_2, isolated in quantities of 31-61 mg which translate into yields of 65-99%.[7] The purity of each compound was measured by HPLC at both 214 and 254 nm as shown in the table below. No extra purification steps were performed and all of the compounds were characterized by ^1H NMR, ^{13}C NMR and LC-MS. The reaction tolerates aldehyde, alkyl- and benzophenone starting materials equally well (R3). N-alkylated starting materials (R4) also work as shown by **3f**.

	2				**3**	HPLC Purity (%)	
Entry	R1	R2	R3	R4	Yield (%)	214 nm	254 nm
a	H	H	H	H	81	81	74
b	H	H	Me	H	94	>98	>98
c	4-MeO	5-MeO	Me	H	65	72	84
d	H	H	Ph	H	88	96	>98
e	5-Cl	H	Ph	H	99	96	98
f	5-Cl	H	Ph	Me	58	93	>98
g	5-Cl	H	2-ClPh	H	60	95	>98

In summary, we have developed a facile and selective two step synthesis of substituted quinolin-2(*1H*)-one-3-carboxylic acids by addition of an *ortho*-aminophenone to resin-bound malonic acid followed by an intramolecular Knoevenagel condensation. The ease of this synthesis makes it very suitable for automation and the high yields and purities of the isolated products should allow it to be considered for use in a multi-step solid phase synthesis.

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References and Notes

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7. Preparation of **1** was carried out according to reference 6 using Wang Resin (0.92 mmol/g) purchased from Bachem. Preparation of **3a-g**: **1** (1 eq) was suspended in DMF, treated with **2** (10 eq) followed by HOBT (1-hydroxybenzotriazole) (10 eq), EDAC (N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride), (10 eq). The reaction was allowed to shake for 16 h, the resin was filtered, washed with H_2O (5x), DMF/H_2O (9/1) (5x), DMF (5x), CH_2Cl_2 (5x), CH_3CN (2x), CH_2Cl_2 (4x), suspended in DMF, retreated with the reagents and washed as described. The resin was then suspended in pyridine; piperidine (40 µL) was added and the reaction was allowed to shake for 16 h. The resin was washed as described above, suspended in TFA/CH_2Cl_2 (1/1), allowed to shake for 1h. The reaction was filtered, the resin washed with CH_2Cl_2 (2x) and the filtrate was evaporated to give the product.