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Combinatorial Synthesis of Heterocycles: Solid Phase Synthesis of 2-Arylquinoline-4-carboxylic Acid Derivatives

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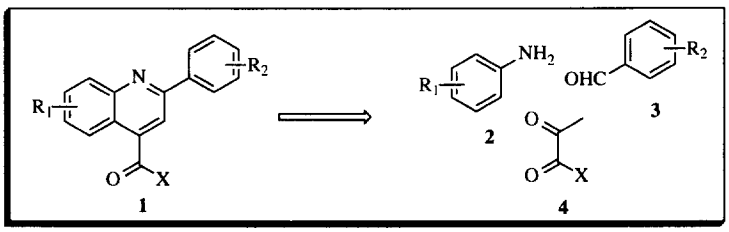
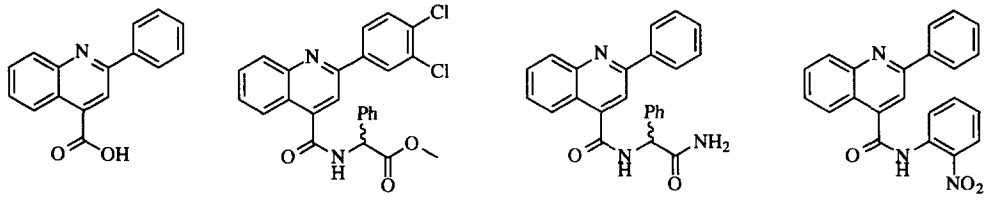
Abstract. The Doebner quinoline synthesis has been adopted to solid phase. Acylation of an amino acid coupled to the Rink polystyrene resin with pyruvyl chloride afforded the immobilized amide **11**. Further reaction of **11** with the preformed Schiff's base **12** or aldehyde **3** and aniline **2** gave, after trifluoroacetic acid cleavage, 2-arylquinoline-4-carboxylic acid amides **14** in good yields. © 1997, Elsevier Science Ltd. All rights reserved.

Combinatorial Chemistry[2], a new paradigm for drug discovery, has rekindled the interest in solid phase chemistry. While synthesis of peptide libraries[3] marked the emergence of this new field, the quest for non-peptidic small molecule drug candidates led to a surge of various synthetic methodologies[4] including the synthesis of different heterocycles[5] on solid support. Of the various methods developed for the synthesis of heterocycles, multi-component condensation[6] approach such as Ugi reaction stands out as a method of creating maximum diversity in single step operation. Application of such multi-component condensation approach based on Doebner reaction[7] for the synthesis of a clinically useful pharmacophore, 2-arylquinoline-4-carboxylic acid derivatives **1** is shown in **Scheme 1.**



Scheme 1

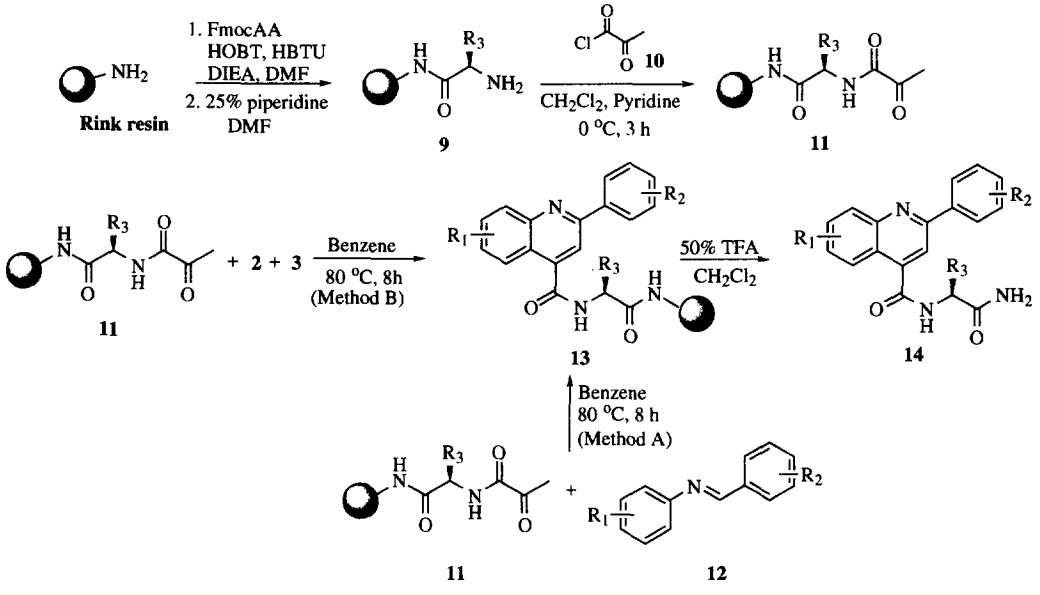
2-Phenylquinoline-4-carboxylic acid also known as Cinchophen acid **5** and its derivatives have shown a variety of biological effects[8] as anti-malarial, anti-microbial, anti-tumor, anti-oxidant and cardiovascular agents. In particular, 2-arylquinoline carboxamides **6** and **7** are potent tachykinin NK3 receptor antagonists[9], while compound **8** exhibited analgesic activity[10] (**Fig 1**).



5 6 7 8

Fig 1

Initial studies on the solid phase protocol were carried out using acid labile Rink polystyrene resin[11] as the polymer support. Fmoc-Rink resin was deprotected, acylated with the required N-Fmoc-amino acid and deprotected again to give the support bound free amine **9** in 90% yield. The resin bound amine **9** was acylated with pyruvyl chloride[12] **10** in CH_2Cl_2 using pyridine as the base at 0 °C. The immobilized pyruvic amide **11** was refluxed with excess of preformed benzylidine aniline **12** in benzene for 8 h (Method A[13]). The resin bound cyclized product **13** was cleaved using TFA to give 2-arylquinoline-4-carboxamide **14** (**Scheme 2**). The variation in the substitutents and the corresponding yield obtained for **14** are illustrated in **Table 1**.



Scheme 2

Condensation of the pyruvic amide **11** carried out using an excess of equimolar mixture of aldehyde **3** and aniline **2** also afforded the cyclized product **13** in comparable yield and purity (method B[14]). While benzene was the solvent of choice for better swelling of the resin, ethanol was found to be equally efficient in the formation of **14a**. Regioselective cyclization was noticed in the meta substituted aniline as observed in solution (eg. entry **14a**). Although electron withdrawing groups in the aldehyde **3** improved the overall yield,

the reaction was smooth in the case of benzaldehyde as well (entry **14d**). There was no significant effect on the cyclization by varying the amino acid employed. This solid phase protocol offers a convenient alternative to solution phase synthesis of 2-arylquinoline-4-carboxylic acid derivatives since the immobilization of the pyruvic acid on the solid phase avoids its polymerization at higher temperature[8a].

Table 1. Solid phase synthesis of 2-Arylquinoline-4-carboxamides **14**

Entry	R_3	R_1	R_2	Method	Yield(%)[a,b]
a	H	3-OCH_3	4-NO_2	A or B	92 (88)
b	H	3-OCH_3	4-CN	A or B	88 (80)
c	H	H	4-NO_2	A	62
d	H	3-OCH_3	H	B	60
e	H	3-OCH_3	4-Cl	B	85
f	H	H	4-Cl	B	66
g	CH_2Ph	3-OCH_3	4-NO_2	A	75
h	CH_3	3-OCH_3	4-NO_2	A	72

(a) Overall yields were determined from the mass balance of the material obtained by passing through a small pad of neutral alumina, based on the initial substitution level of the Rink resin. (b) Purity >90% from HPLC[15] analysis.

In conclusion, the above method provides an efficient solid phase synthesis of 2-arylquinoline-4-carboxylic acid derivatives in good yields. This versatile method can be readily adopted for combinatorial synthesis by 'mix and split' method[16] or parallel synthesis. The high purity of the crude isolated material provides the possibility of directly using them in various biological assays.

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13. Method A: A suspension of 100 mg (0.045 mmol) of resin **11** and an appropriate preformed benzylidine aniline **12** (0.45 mmol) was refluxed in 4 mL of benzene in a sealed vial for 8 h. The resin was filtered, washed subsequently with MeOH (4 x 8 mL), DMF (2 x 8 mL) and CH_2Cl_2 (4 x 8 mL), and dried. The resin was treated with TFA:H_2O: CH_2Cl_2 (45:5:50) mixture (2 mL) for 30 min and filtered. The filtrate was concentrated *in vacuo* and analyzed by HPLC, ^{1}H NMR, MS (FAB) and HRMS in some cases.

14. Method B: Method B was carried out analogously to method A, but using appropriate aldehyde **3** (0.45 mmol) and aniline **2** (0.45 mmol) instead of the benzylidine aniline **12**.

15. The HPLC analysis was carried out using 5 μm 3.9 x 150 mm reverse phase column using gradient 100% H_2O and 0.1% TFA (eluent A) to 60% of aqueous MeCN and 0.1% TFA (eluent B) over 35 min with a flow rate of 1 mL/min.

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