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Solid-Phase Synthesis of Substituted Quinoline and Isoquinoline Derivatives Using Heterocyclic *N*-oxide Chemistry

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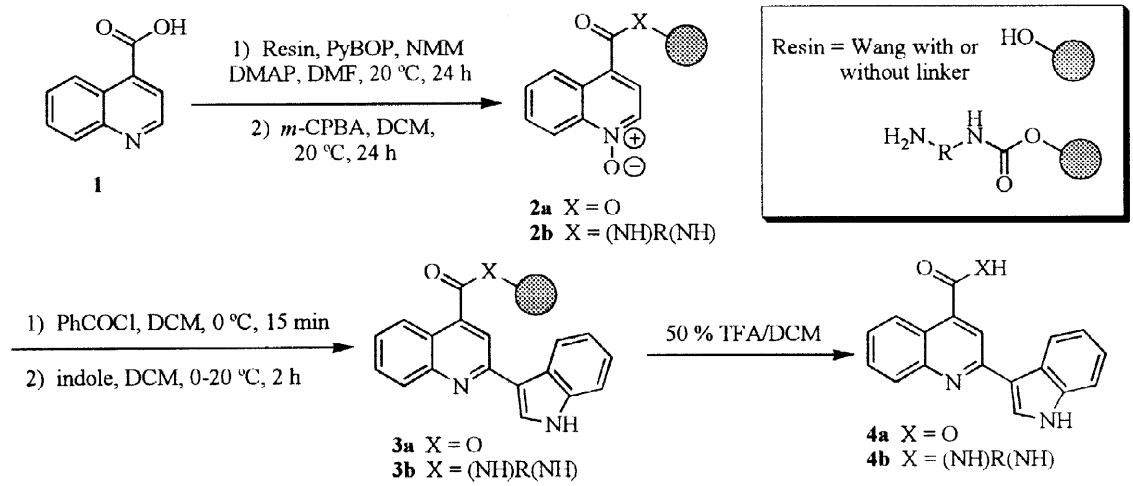
Abstract: Using heterocyclic-*N*-oxide chemistry, various substituted quinoline and isoquinoline compounds were synthesized on the solid support in excellent purity and good to excellent yield.

The regioselective and stereoselective solid-phase synthesis of small organic molecules and its application to the generation of drug-like molecules has attracted widespread attention.[2] For example, various metal-catalyzed carbon-carbon bond forming reactions have been adapted to solid-phase synthesis as a means of constructing a wide range of structures.[3] Alternatively, more traditional synthetic approaches to drug-like molecules also have been adapted for use on a solid phase,[4] specifically, a solid-phase synthesis of 2-arylquinoline-4-carboxylic acid derivatives utilizing the Doebner reaction, a condensation of pyruvic acid, an aniline and an aryl aldehyde, was recently published.[5] This report prompts us to disclose our related studies of the non-metal catalyzed carbon-carbon bond forming reactions using heterocyclic-*N*-oxide chemistry on solid support.



Scheme 1

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Heteroaromatic-*N*-oxides in the presence of an acylating agent react with various nucleophiles to produce 2-substituted nitrogen heterocycles.[6] For example, Hamana and Kumadaki[7] reported that when quinoline *N*-oxide was allowed to react with indoles in the presence of an acylating agent, such as benzoyl chloride, under refluxing conditions, 2-(3-indolyl)quinolines were produced. Substituted quinoline and isoquinoline compounds have shown various biological activities. For example, 2-heteroaryl substituted 4-quinolinecarboxylic acids are useful as immunosuppressants for the prevention of organ transplant rejection and for treating chronic inflammatory diseases.[8] In addition, 2-heterocinchoninic acid derivatives are useful as antibacterial agents.[9]

Based on these observations, our initial studies were designed to evaluate heterocyclic-*N*-oxide chemistry on a solid support. Attachment of quinoline-4-carboxylic acid (**1**) to Wang resin, with or without a diamine linker, was accomplished using standard PyBOP coupling conditions (**Scheme 1**). The resin bound quinoline was then exposed to an excess of *m*-CPBA in dichloromethane at room temperature producing resin **2a**. The resulting quinoline-*N*-oxide resin **2a** was then sequentially treated with benzoyl chloride at 0 °C for 15 min followed by indole in dichloromethane at 20 °C for 2 h to afford the resin-bound coupled product **3a**. The final product **4a** was obtained, in an overall 80% yield, by cleavage from the resin with a 50% mixture of trifluoroacetic acid and dichloromethane. HPLC analysis of the crude reaction mixture indicated a purity of 94% and the structural assignment was confirmed by NMR and mass spectral analysis.

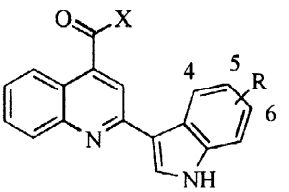
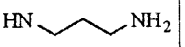


Table 1. Solid-phase synthesis of 2-indolylquinoline-4-carboxylic acid derivatives

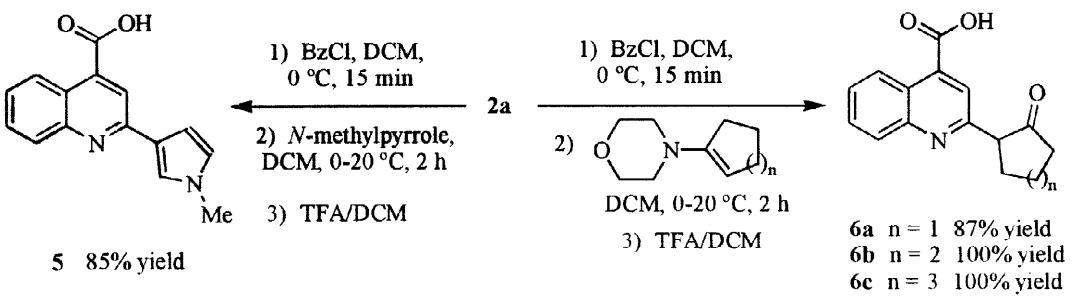
Entry	X	R	% Yield	% Purity[a]
1	OH	H	83	94
2	OH	4-F	75	78
3	OH	5-F	100	93
4	OH	6-F	76	86
5	OH	5-Cl	86	91
6	OH	5-Br	66	97
7	OH	5-NO_2	38	100
8		H	84	100
9		H	100	100

[a]purity was determined by integration of the HPLC traces.

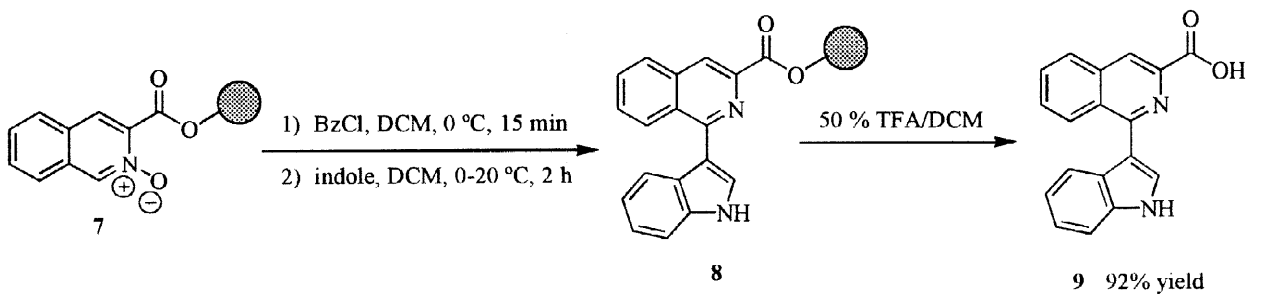
In order to increase the diversity of the compounds prepared, as well as to assess the tolerance of additional functionality in the substrates, the chemistry was repeated with two diamine linkers bound to the solid support (**Scheme 1**). The diamine linkers were attached to the Wang resin using a standard protocol[10] and the chemistry was repeated under identical conditions to give 2-indolyl-4-quinolinecarboxamides **4b**.[11] No significant reduction of yield or purity was observed for these products (**Table 1**).

In general, the reaction tolerated an array of substituted indoles, however, indoles containing strong electron-withdrawing groups (Table 1, entry 7) were much less reactive with the *N*-oxide **2a** under the conditions described. Presumably, this lack of reactivity reflects the reduced nucleophilicity of the indole. In addition to indoles, we have succesfully used pyrroles and enamines as nucleophiles in this reaction sequence (**Scheme 2**).[12]

Finally, other resin bound heterocyclic-*N*-oxides were employed utilizing the reaction conditions described herein. Isoquinoline-*N*-oxide 7 was allowed to react with indole followed by cleavage with TFA producing 1-(3-indoyl)isoquinoline-4-carboxylic acid (**9**) as a single regioisomer (**Scheme 3**), again in excellent yield and purity. Meanwhile, pyridine-*N*-oxides lead to complex mixtures of products.



Scheme 2



Scheme 3

In conclusion, we have illustrated a simple method for carbon-carbon bond formation on a solid support utilizing heterocyclic-*N*-oxide chemistry. This method provides access to substituted quinoline- and isoquinoline-carboxylic acid derivatives in excellent yield and purity.

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11. General Procedure: *Preparation of the diamine linker*: Wang resin was treated with a 0.4 M solution of 1,1'-carbonyldiimidazole (CDI) in THF for 12 h at 20 °C and then filtered and washed with THF. The resin was then treated with a 0.4 M solution of a diamine linker in THF for 4 h at 20 °C. The resin was filtered and washed with THF, MeOH and DCM, then dried. *Coupling of 4-quinolinecarboxylic acid with the diamine linker*: 4-Quinolinecarboxylic acid (3.75 mmol) and PyBOP (4.5 mmol) were dissolved in DMF (3 mL) followed by the addition of 4-methylmorpholine (NMM) (7.5 mmol). The mixture was stirred for 15 min and then added to the diamine resin (1 g; 0.75 mmol) along with DMAP (0.4 mmol). The mixture was agitated overnight at 20 °C, filtered and washed with DMF, MeOH, and DCM, then dried. *Oxidation*: The resin (0.75 mmol) was treated with a solution of *m*-CPBA (3.75 mmol) in DCM (10 mL) for 48 h at 20 °C. The resin was filtered and washed with DCM, MeOH, and DCM, then dried. *Coupling of indole with quinoline-N-oxide*: The resin (50 mg, 0.035 mmol) was added to 1 mL of DCM and cooled to 0 °C. To the suspension was added benzoyl chloride (0.11 mmol) and the mixture was agitated for 10 min. Indole was added to the suspension and agitation was continued for an additional 2 h at 20 °C. The resin was filtered, washed with DCM, MeOH, and DCM, then dried. *Cleavage*: The resin was added to a 1:1 mixture of TFA/DCM (1 mL) and agitated for 1 h. The liquid was filtered and concentrated *in vacuo* and then lyophilized in a 1:1 mixture of CH_3CN/H_2O to give a crude product 38-100% overall yield. Compounds were analyzed by HPLC (78-100% purity), mass spectrometry and NMR.
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