Three-Component Fischer Indole Synthesis

Laurent El Kaïm,* Laurence Grimaud,* Caroline Ronsseray

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France Fax +33(1)45528322; E-mail: laurent.elkaim@ensta.fr; E-mail: laurence.grimaud@ensta.fr *Received 24 June 2010*

Abstract: Three-component coupling between acyl chlorides, diazonium salts, and alcohols or amines allows the formation of α hydrazono carboxylic acid derivatives which may be directly converted into indoles by a Fischer-type cylization.

Key words: indoles, Fischer, Japp–Klingeman, diazonium, hydrazone, acid chloride, multicomponent reaction

Indoles certainly represent one of the most important heterocyclic families.¹ The search for new approaches to this bicyclic core has constantly been triggered by the impressive diversity of its biological activities.² Among the numerous methods available, the early Fischer indole synthesis has always been the most relevant.³ More recent trends in indole synthesis have focused on the use of organometallic processes⁴ as well as the disclosure of new multicomponent synthetic pathways for high-throughput screenings.⁵

A few years ago, we reported a convenient access to α -hydrazono carboxylic acid derivatives by addition of diazonium salts to acyl chlorides (Scheme 1).⁶ The reaction may be related to a Japp–Klingeman coupling⁷ as the diazonium salt is trapped by the carbanion derived from the deprotonation of the acylpyridinium. The resulting azaketene intermediate rearranges, and finally a nucleophile is added to trap the acyl moiety. The whole process might be considered as a three-component coupling even if most examples reported involved ethanol as the final nucleophile. Therefore, we decided to benefit from this former work to develop a new multicomponent access to indole derivatives. Indeed, under acidic conditions, the resulting

hydrazones could be directly transformed into indoles through a Fischer-type cyclization. Herein, we wish to present our results on this study.

Before working on the Fischer cyclization, sets of alcohols and amines were evaluated as nucleophiles in the three-component hydrazone formation. After addition of an excess of pyridine to the acyl chloride in dichloromethane, the diazonium salt was added at 0 °C and the mixture stirred at room temperature for 2 hours. Then, the resulting acyl pyridinium salt was transformed into an ester or an amide by the addition of 1-1.2 equivalents of an alcohol or an amine. Under these optimized conditions, various hydrazones can be synthesized in moderate yields (Scheme 1).

Before trying to perform the direct conversion of these hydrazones into indoles from the crude mixture, the conditions for the Fischer reaction had to be optimized working with the pure hydrazones. Different sets of acidic conditions were tested for this purpose: the addition of AlCl₃, $BF_3 \cdot OEt_2$ was attempted in refluxing dichloromethane but failed to give any product. However, on heating the hydrazones in acetic acid as solvent, the expected indoles were obtained quite efficiently. Optimum conditions involved heating the hydrazones over 100 °C for several hours (Scheme 2). It is worth noting that the reaction can be carried out under microwave irradiation (100 W, 120 °C) within 10 minutes for ester derivatives, but complex mixtures are obtained with amides under such conditions.

Next, we decided to evaluate the three-component formation of indoles through sequential diazonium coupling and Fischer cyclization wherein, after completion of the first





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Synthesis of Various Functionalized Indoles (continued)

Table 1



Scheme 2 Fischer synthesis

step, the dichloromethane was evaporated, acetic acid was added, and the mixture refluxed overnight. Following this one-pot, two-step procedure, various functionalized indoles could be synthesized, starting from an aromatic or an aliphatic acyl chloride and using either an alcohol or an amine as the trapping agent. This method affords a straightforward access to polysubstituted indoles in moderate to good yields as outlined in Table 1.

Table 1 Synthesis of Various Functionalized Indoles





The simplicity of the procedure compensates for the relatively moderate overall yields of the isolated compounds, which represent such important scaffolds. If proper difunctional acyl chlorides and amines (or alcohols) are chosen in the initial three-component coupling, further cyclizations involving the initial Fischer adducts may lead to highly complex indole derivatives. Our research group is currently working on such possibilities as well as oxidative cyclizations onto indoles.

To a CH_2Cl_2 solution of acid chloride (0.25 M) was added pyridine (3 equiv). After 10 min, the mixture was cooled at 0 °C and the diazonium salt (1.1 equiv) added. The solution was stirred for 10 min at 0 °C and then 2 h at r.t. The nucleophile was added (1.2 equiv),

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and the mixture was stirred at r.t. for a further 2 h. The CH_2Cl_2 was evaporated in vacuo, the residue dissolved in AcOH (0.25 M) and the solution heated at reflux temperature overnight. The solvent was removed by evaporation, and the crude product purified by silica gel flash column chromatography eluting with a mixture of PE–Et₂O (for amides) or CH_2Cl_2 (for esters)–Et₃N (1%).

Representative Analytical Data

Methyl 5-Fluoro-3-phenyl-1H-indole-2-carboxylate

¹H NMR (400 MHz, CDCl₃): δ = 9.05 (s, 1 H), 7.55 (d, *J* = 7.8 Hz, 2 H), 7.49 (dd, *J* = 7.8, 7.3 Hz, 2 H), 7.44–7.41 (m, 1 H), 7.40 (dd, *J* = 9.0 Hz, *J*_{H-F} = 4.8 Hz, 1 H), 7.30 (dd, *J*_{H-F} = 8.8 Hz, *J* = 2.5 Hz, 1 H), 7.15 (ddd, *J* = 9.0 Hz, *J*_{H-F} = 8.8 Hz, *J* = 2.8 Hz, 1 H), 3.85 (s, 3 H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 162.5, 158.9 (d, *J*_{C-F} = 234.9 Hz), 133.4, 132.7, 130.7, 128.6 (d, *J*_{C-F} = 10.2 Hz), 128.4, 127.9, 124.6 (d, *J*_{C-F} = 5.1 Hz), 124.3, 115.5 (d, *J*_{C-F} = 27.1 Hz), 113.1 (d, *J*_{C-F} = 10.3 Hz), 106.5 (d, *J*_{C-F} = 24.2 Hz), 52.3. IR (thin film): 1685, 1537, 1497, 1458, 1344 cm⁻¹. HRMS: *m*/z calcd: 269.0852; found: 269.0855.

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