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New synthesis of isoquinoline-3-carboxylates

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Abstract

A new and general synthesis of methyl isoquinoline-3-carboxylates is described starting from aromatic 1,2-dialdehydes by reaction with protected phosphonoglycine derivatives. Methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylates are obtained from 2-formylbenzoate derivatives. This new method allows the preparation of isoquinolines having electron-withdrawing groups on the benzene ring. © 1999 Elsevier Science Ltd. All rights reserved.

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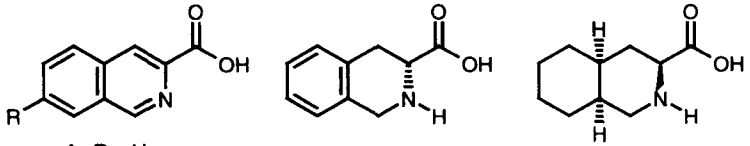
Isoquinoline derivatives **1–3** (Scheme 1) are used by medicinal chemists as important conformationally constrained peptide motifs for phenylalanine and tyrosine in peptides.[1,2] The replacement of D-phenylalanine in somatostatin derived μ-opioid antagonists by 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **2** resulted in one of the most potent and selective μ-opioid receptor antagonists.[3] In addition, decahydroisoquinoline-3-carboxylic acid **3** is a constituent of saquinavir, the first HIV protease inhibitor to reach the market, for use in combination with nucleoside analogues for the treatment of advanced HIV infection.[4,5]



1a R = H
1b R = OH

2

3

Scheme 1.

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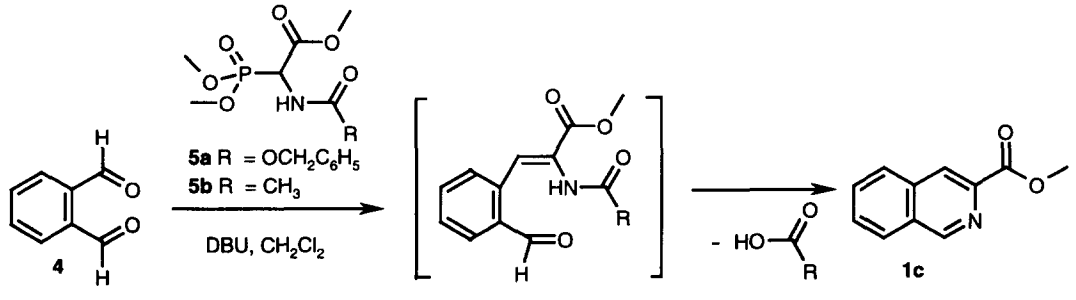
The standard method for the synthesis of isoquinoline-3-carboxylates makes use of the Pictet–Spengler reaction.[6] This reaction involves an electrophilic attack on a benzene ring and is facilitated by electron donating substituents. Electron withdrawing groups inhibit the reaction. The relatively harsh acidic or dehydrating conditions necessary to form the isoquinoline ring system are an additional drawback.

To overcome the limitations of the Pictet–Spengler reaction, ring closure methods, which do not involve electrophilic attack on an aromatic ring system, have been developed. One such method reported in the literature is the ozonolysis of indene derivatives yielding homophthalaldehyde derivatives, which on treatment with aqueous ammonia gave the desired isoquinolines.[7,8] Although this elegant approach can be used to prepare isoquinolines containing electron withdrawing substituents, its generality is somewhat limited by the availability of the required indene starting materials. Another method[9–11] is based on an intramolecular aza-Wittig reaction. While useful, this reaction is limited by the need for multistep preparations of azidocinnamates from 1,2-dicarboxaldehydes and the difficulties handling the azido compound on a large scale. Therefore, the development of alternative synthetic strategies for one of our research programs was necessary. Our retrosynthetic analysis revealed that isoquinoline-3-carboxylic acid derivatives should be available from aromatic 1,2-dialdehydes by reaction with an appropriate protected glycine derivative.

Unfortunately, the reaction of *ortho*-phthalaldehyde **4** with Cbz-phosphonoglycine methyl ester **5a**[12] (see Scheme 2) gave only traces of methyl isoquinoline-3-carboxylate **1c** (identified by ^{1}H NMR as singlets at 9.31 and 8.57 ppm) in the crude material.[13] When 1 equivalent of the corresponding acetyl protected glycine derivative **5b**[12] was used instead of **5a**, the desired isoquinoline derivative **1c** was isolated after crystallization in 78% yield. Even in the presence of 2 equivalents of **5b**, isoquinoline **1c** was the main product and no bis-enamide (formed by double Wittig–Horner reaction) could be detected.[13]

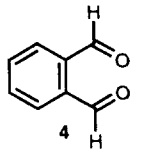
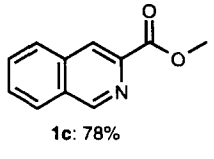
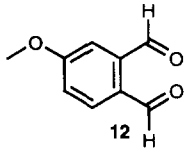
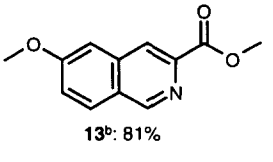
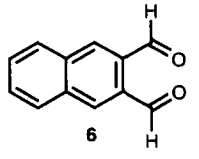
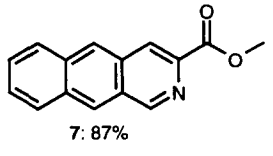
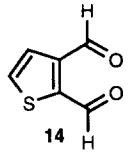
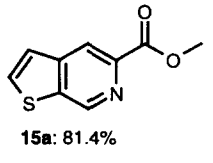
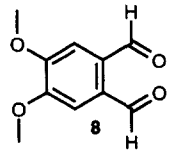
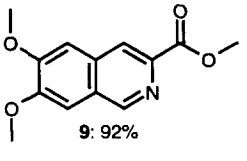
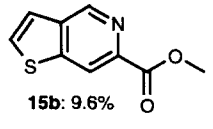
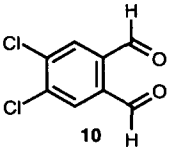
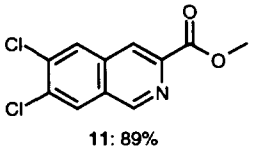
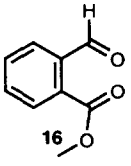
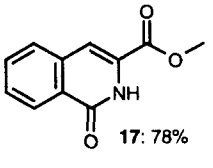


Scheme 2. Reaction mechanism.

It was hypothesized that the Wittig–Horner reaction took place at only one aldehyde group because of steric hindrance. The *Z*-enamide formed (see Scheme 2) is ideally suited for the heterocyclization reaction with the remaining aldehyde group to form the isoquinoline ring system. The nature of the protecting group (acetyl versus Cbz group) at the nitrogen explains the difference in the yield of this heterocyclization reaction. Based on this result **5b** was used for all other experiments. The successful preparation of **1c** motivated us to investigate other dialdehydes for this reaction. These results are summarized in Table 1. Dialdehydes **4**, **6**, and **14** were purchased from Aldrich. In all examples we observed a very fast conversion of the dialdehydes into the title compounds at 0°C. The corresponding methyl isoquinoline-3-carboxylates could be detected by TLC immediately after the addition of the anion was finished. This indicates that both the Wittig–Horner reaction and the heterocyclization step are very fast. In general, high yields were obtained in all investigated cases.

2,3-Naphthalenedicarboxaldehyde **6** and 4,5-dimethoxyphthalaldehyde **8**[14] yielded the novel isoquino-

Table 1
Synthesized isoquinoline derivatives[a]

Dialdehyde	Product	Dialdehyde	Product
 4	 1c: 78%	 12	 13[b]: 81%
 6	 7: 87%	 14	 15a: 81.4%
 8	 9: 92%		 15b: 9.6%
 10	 11: 89%	 16	 17: 78%

[a] Typical experimental procedure: The dialdehyde (10mmol) was dissolved in dichloromethane (100mL) and cooled to 0°C (ice bath). N-Acetyl-phosphonoglycine **6** (11mmol, 2.62g) was dissolved in dichloromethane (50mL) and DBU (11mmol, 1.65mL) was added at ambient temperature under stirring. This solution was added dropwise to the cold solution of the dialdehyde under stirring. The color of the solution changed to yellow during the addition of anion. The solution was stirred at for 1h at 0°C and overnight at ambient temperature. The reaction mixture was concentrated and the desired product was isolated by chromatography. Typical yields: 78-92%.

[b] This compound has been synthesized recently starting from 3-methoxyphenylalanine in only 9.6% yield. See Ref. 17.

line derivative **7** (87%, mp 196–198°C) and compound **9** (92%, mp 215–217°C, lit.[15] mp 211–211.5°C), respectively. The availability of unknown 5,6-dichloroisoquinoline derivative **11** (89%, mp 214.5–216°C) from dialdehyde **10**[16] with two electron-withdrawing groups on the benzene ring demonstrates the usefulness of this new method.

Unsymmetrically substituted dialdehydes **12**[16] and **14**[9] were selected to investigate the regioselectivity of the new isoquinoline synthesis. When **12** was reacted with **5b** compound **13**[17] (81%, mp 147–148°C) was the only regioisomer formed indicating that the Wittig–Horner reaction took place at the more electrophilic carbonyl group. An 8.5:1 mixture of the regioisomeric compounds **15a** (81.4%, mp 107–108°C) and **15b** (9.6%, glass) was obtained from thiophene 2,3-dicarboxyaldehyde **14**. Both compounds were separable by chromatography in a combined yield of 91%. The structure of compounds **13**, **15a**, and **15b** was elucidated by ^{1}H NMR and ^{13}C NMR spectroscopy. On the other hand, reaction of methyl 2-formylbenzoate **16**[18] with **5b** gave methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate **17** (76%; mp

162–163°C, lit.[10] mp 162–163°C). In this case the reaction is regioselective because the anion of the phosphonoglycine was reacting first with the aldehyde group followed by the heterocyclization reaction.

In summary, we have developed a new isoquinoline synthesis. The advantage of this general method is the availability of isoquinolines with electron withdrawing groups in the benzene ring. The scope and the limitations of this new reaction are currently under investigation and the results of this study will be reported in due course.

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