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A practical 'one-pot' synthesis of ethyl isoquinoline-3-carboxylate by domino reactions: a potential entry to constrained nonproteogenic amino acid derivatives

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Abstract—Two simple and efficient 'one-pot' preparations of isoquinoline-3-carboxylates by domino reactions using phthalaldehydes and imidate (route A) or diethyl aminomalonate (route B) are described. The third route involves the use of ethyl glycinate, aminoacetonitrile and phthalaldehyde which yields the respective ethyl isoquinoline-3-carboxylate and isoquinoline-3-carbonitrile.

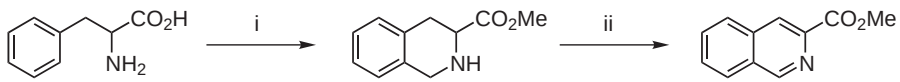
Isoquinoline-3-carboxylate and 1,2-dihydroisoquinoline-3-carboxylate (Dic) have led to considerable interest in the synthesis of conformationally constrained peptide moieties for alanine and tyrosine.[1] These peptidomimetics often provide enhanced biological activities.[2] Common methods for the preparation of Dic can be classified in two approaches: (a) reduction of isoquinolines or isoquinolinium salts[3] or (b) Wittig reaction of *N*-alkoxycarbonyl carbamates with ω-halogenated phosphorus ylides.[4]

Among the various methods available for the preparation of isoquinolines including the well-known Bischler–Napieralsky ring cyclization[5] and the Pictet–Spengler ring closure[6] (according to the method of Julian and Meyer et al.,[7] phenylalanine gives isoquinoline-3-carboxylate[8] in two steps (Scheme 1)), only the Pommeranz–Fritsch cyclization[9] provides a general and direct method for the construction of a fully unsaturated isoquinoline. A noticeable approach devised by Laude et al.[10] involves the dehydrogenation of 1,2-dihydro isoquinoline-3-carboxylate with a catalytic amount of sodium ethoxide.

Recently, we reported a 1,2-dihydro isoquinoline-3,3-dicarboxylate synthesis[11] based on the smooth thermolysis of 5-(2-formylphenyl)-2-methyl-4,5-dihydrooxazole-4,4-dicarboxylate and the starting 4,5-dihydrooxazolyl moiety was obtained by 1,3-dipolar cycloaddition from phthalaldehyde and imidate derived from dimethyl aminomalonate.[12]

Our current interest in the preparation of isoquinoline has led us to devise and develop a practical one-step preparation of isoquinoline-3-carboxylate **7**. The sequence is outlined in Scheme 2.

Ethyl 6,7-dimethoxy isoquinoline-3-carboxylate **7a** was obtained from an equimolar mixture of 3,4-dimethoxy phthalaldehyde[13a] **1a** and imidate **2** in refluxing dry ethanol during 3 days. This reaction was monitored by TLC. Analysis of the crude reaction mixture by ^{1}H



Scheme 1. *Reagents and conditions*: (i) (a) HCHO 37%, HCl. (b) MeOH, HCl. (ii) 10% Pd/C, xylene, Δ, 8 h.

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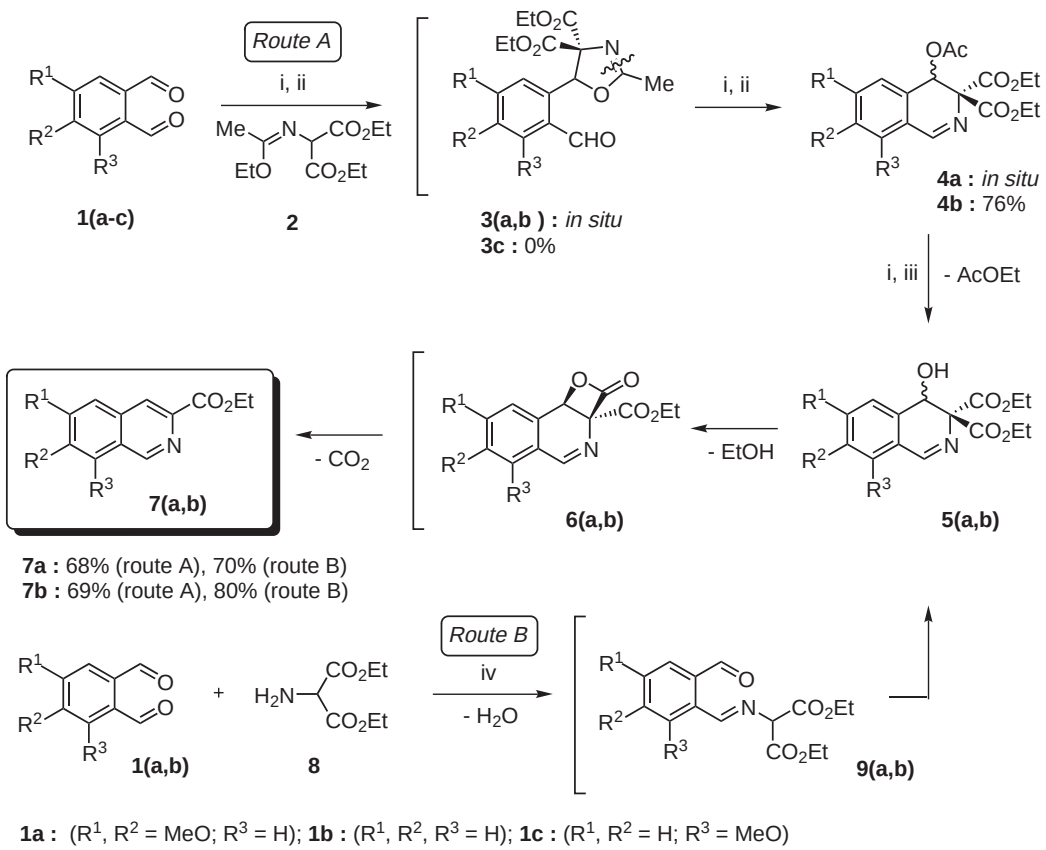
NMR spectroscopy indicated the formation of the expected compound **7a**, and purification by recrystallization in AcOEt gave **7a** in 68% yield.

The mechanism for the domino synthesis of **7a** (route A) involves successively: (a) a regioselective [3+2] cycloaddition to give **3a**; (b) cleavage of the oxazolinyl moiety of **3a** to provide **4a**; (c) transesterification of **4a** with ethanol to produce **5a**, which undergoes (d) lactonization to give **6a**, followed by (e) the decarboxylation of **6a**. From phthalaldehyde **1b** and imidate **2** using solvent-free conditions, it was possible to isolate **4b** in 76% yield (reaction time: 7 days) by flash chromatography on silica gel 60F 254 (Merck) with AcOEt/petroleum ether (1:1) as eluant (**4b**: $R_f = 0.67$). Then **4b** was converted to **7b** in refluxing dry ethanol under nitrogen with 1.1 equivalent of EtONa. Compound **7b** was separated from the crude reaction mixture by fractional crystallization in AcOEt in 69% yield. Attempts to produce ethyl isoquinoline-3-carboxylate **7c** by domino reaction from 3-methoxy phthalaldehyde **1c**[13b] were unsuccessful.

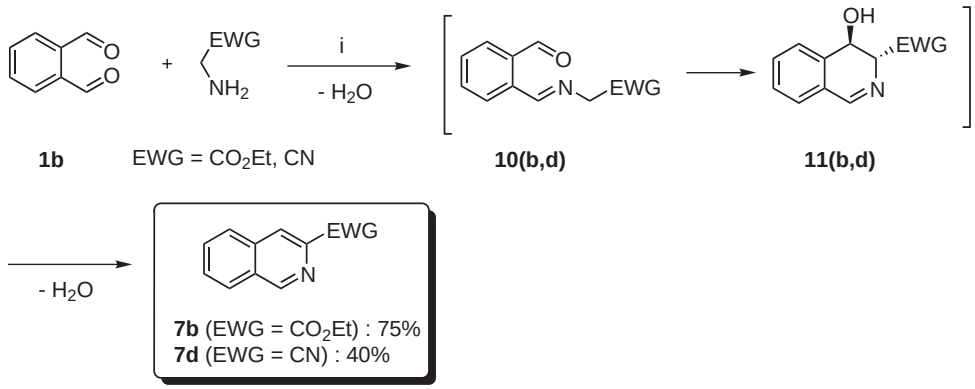
Next, we directed our efforts toward a simple and direct route to isoquinoline-3-carboxylate **7** by reaction of an equimolar amount of diethyl aminomalonate[14] **8** and 1,2-dialdehydes **1**(**a**,**b**) (route B). It was found that the reaction was best carried out in the presence of EtONa (1.1 equiv.) and solid $MgSO_4$. After 4 h, the preparation was essentially complete and consistent isolated yields of 70–80% were obtained for **7**(**a**,**b**) after treatment of the crude reaction mixture with AcOEt. The mechanism of this 'one-pot' reaction proceed via the intermediates **9**(**a**,**b**) which were not isolated.

In a similar way, we have tested the reaction conditions of the procedure for route B with ethyl glycinate, aminoacetonitrile and phthalaldehyde **1b** (Scheme 3). Ethyl isoquinoline-3-carboxylate **7b** was produced in good isolated yield (75%) and isoquinoline-3-carbonitrile **7d** in moderate yield (40%). The intermediates **10**(**b**,**d**), **11**(**b**,**d**) were not isolated.

In summary, the major significance of these results is the development of a straightforward route to isoquinoline-3-carboxylates by 'domino' reactions. Isoquinoline-3-carboxylates[15] **7** can be synthesized in good yields by one of the three complementary approaches using a 'one-pot' procedure from phthalaldehydes and commercial aminoesters. To our knowledge, these 'domino' reactions have never been reported and the three approaches may complement those existing in the literature[16] for the synthesis of isoquinoline by the usual two-step Pommeranz–Fritsch cyclization. Work is now in progress to study the potentialities of these 'domino' reactions.



Scheme 2. *Reagents and conditions*: (i) Dry EtOH, Δ, ~72 h. (ii) 70°C, N_2, ~7 days. (iii) EtONa 1.1 equiv., dry EtOH, Δ, N_2, ~15 days. (iv) EtONa 1.2 equiv., dry EtOH, Δ, $MgSO_4$, 4 h.



Scheme 3. *Reagents and conditions*: (i) EtONa 2 equiv., dry EtOH, Δ, N_2, $MgSO_4$, 4 h.

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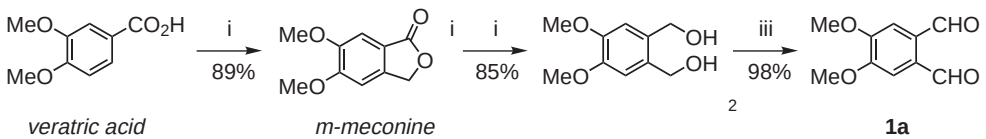
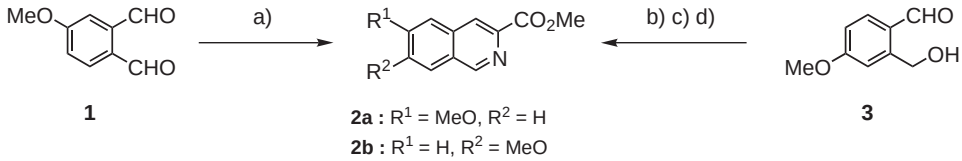
13. (a) 4,5-Dimethoxy phthalaldehyde **1a** is readily available from veratric acid in a three-step sequence involving the intermediate lactone *m*-meconine. (b) 3-Methoxy phthalaldehyde **1c** is prepared with the same sequence from *m*-anisic acid.



Reagents and conditions: (i) HCHO 37%, dry HCl, 15°C, 8 h then 30°C, 12 h, NH_4OH. (ii) $LiAlH_4$, dry THF, Δ, 4 h. (iii) MnO_2, CH_2Cl_2, 25°C, 24 h.

14. Compound **8** was obtained by treatment of commercial diethyl aminomalonate hydrochloride (30 g, 0.14 mol) with saturated sodium hydrogenocarbonate (225 ml) in methylene chloride (300 ml) during 20 min. After drying the organic layer over $MgSO_4$ and elimination of solvent, **8** (22.6 g, 91%) was stored under an inert atmosphere at 4°C. ^1H NMR ($CDCl_3$, 200 MHz, TMS) δ 1.30 (t, 3H, $J=7$ Hz); 2.08 (br. s, 2H, NH); 4.25 (q, 2H, $J=7$ Hz); 4.18 (s, 1H).

15. Typical procedures for the preparation of *ethyl 6,7-dimethoxy isoquinoline-3-carboxylate (**7a**):* (Route A) A mixture of 4,5-dimethoxy phthalaldehyde[13] **1a** (2.84 g, 18 mmol) and imidate[12a] **2** (3.5 g, 18 mmol) in dry ethanol (20 ml) was refluxed with vigorous stirring during 3 days (monitored by TLC). Removal of solvent in vacuo gave an oil which crystallized on standing. Recrystallization in AcOEt gave **7a** in 68% yield as yellow needles (mp = 174–176°C, lit.[10] = 181°C). (Route B) **7a** was prepared from a mixture of **1a** (1 g, 5.15 mmol) and freshly prepared diethyl aminomalonate[14] (0.9 g, 5.15 mmol) in dry refluxing ethanol under nitrogen with stirring during 4 hours. After elimination of solvent in a rotary evaporator and repeated washings of the crude residue with AcOEt, **7a** was recrystallized (yield: 70%). ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.48 (t, 3H, J = 7 Hz); 4.04 (s, 3H); 4.05 (s, 3H); 4.52 (q, 2H, J = 7 Hz); 7.26 (s, 1H, H-8); 8.43 (s, 1H, H-4); 9.12 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 14.56 (qt, J = 127, 2.5 Hz); 56.56 (q, J = 145 Hz); 56.59 (q, J = 145 Hz); 62.02 (tq, J = J = 147, 4.5 Hz); 106.03 (dd, J = 160, 5.1 Hz, C-8); 106.42 (dd, J = 165, 4.8 Hz, C-5); 123.34 (dd, J = 165, 4.8 Hz, C-4); 127.12 (m, C-8a); 132.10 (m, C-4a); 140.68 (d, J = 12 Hz, C-3); 149.90 (dd, J = 180, 4.8 Hz, C-1); 152.00 (m, C-6, C-7); 154.30 (m, C-6, C-7); 166.00 (m, CO). HRMS, m/z = 261.1001 found (calculated for $C_{14}H_{15}NO_4$ requires 261.0998).
16. The results of a regio-controlled synthesis of isoquinoline-3-carboxylates was presented recently at the 220th ACS National Meeting, Washington, DC, August 20–24, 2000, Abstr. 422 by Steven B. Shetzline (SmithKline Beecham Pharmaceuticals, King of Prussia, USA). The isoquinoline-3-carboxylates can be prepared selectively using a new stepwise approach (Horner–Emmons reaction, benzylic oxidation and base treatment) in good overall yields.



1 **2a :** R^1 = MeO, R^2 = H **3**
2b : R^1 = H, R^2 = MeO

Reagents and conditions: (a) $(MeO)_2POCH(NHAc)CO_2Me$, CH_2Cl_2, –30°C → rt, 81% for **2a**. (b) $(MeO)_2POCH(NHAc)CO_2Me$, DBU, CH_2Cl_2, rt, 71%. (c) MnO_2, CH_2Cl_2, 78%. (d) DBU, CH_2Cl_2, 93% for **2b**.