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Lewis Acid-Induced Reaction of Homophthalic Anhydride with Imines : a Convenient Synthesis of *trans*-Isoquinolonic Acids

Niefang Yu[a], Line Bourel[a], Benoit Deprez[b] and Jean-Claude Gesquiere[a] *

[a] Faculté de Pharmacie, 3 rue Laguesse, 59000 Lille, France and Institut Pasteur and CNRS, 1 rue Calmette, 59000 Lille, France.

[b] CEREP, 1 rue Calmette, 59000 Lille, France.

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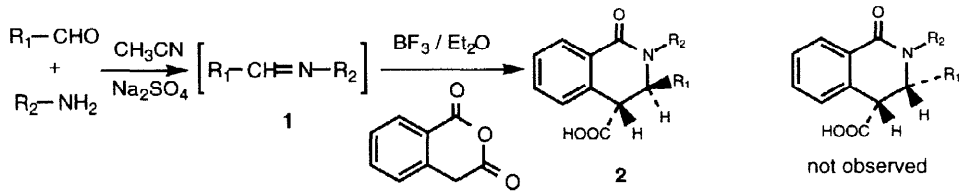
Abstract: Cycloaddition of imines with homophthalic anhydride in the presence of BF_3 leads to the *trans* isomers of isoquinolonic acids with a high stereoselectivity and avoids the formation of homophtalic amides. This catalyst extends the scope of the reaction to imines which did not react under previously described conditions.

The cycloaddition of homophthalic anhydride with imines to give 2,3-disubstituted-3,4-dihydroisoquinolone-4-carboxylic acids is an important tool in the synthesis of heterocyclic compounds presenting various biological activities[1]. The reaction products resulting from these condensations possess two asymmetric centres and are therefore capable of existing as *cis*- and *trans*-diastereoisomers. An empirical relationship between solvents polarities and the ratios of diastereoisomers formed has been recognised in the condensation of Schiff bases and homophthalic anhydride[2]. Although a study of the mechanism was described[3], the factors that determine the stereochemical outcomes of the reactions remained to be confirmed. When reactions are performed under classical conditions[4] using no catalyst or basic catalysts, mixtures of isomers are generally obtained with *cis*-compounds being the main products. To our knowledge, no control of the stereochemical outcomes was previously described. Usually, the thermodynamically more stable *trans*-products were prepared by treating the mixture of isomers in refluxing acetic acid[5].

We report here a fast and efficient procedure, using the boron trifluoride diethyl ether complex (BF_3-Et_2O) as a Lewis acid catalyst (**Scheme 1**), allowing the direct formation of *trans*-isoquinolonic acid derivatives.



Scheme 1

Imines **1** were prepared according to the literature[6] with minor modifications. Acetonitrile or dichloroethane were used as solvents and Na_2SO_4 was added to trap the water generated during the reactions. Na_2SO_4 was then filtered off, and the imines were used for the following condensation without further purification. In the presence of BF_3-Et_2O, the cycloaddtion proceeded very quickly in good to excellent yields. This new procedure allows the cyclisation of various imines **1** directly to the corresponding *trans*-isoquinolonic acid derivatives. Interestingly, there is no evidence for the formation of any *cis*-diastereoisomers. **Table 1** summarises the yields obtained from a representative set of 9 imino compounds.

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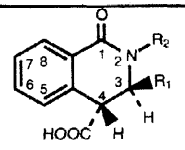
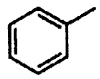
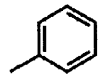
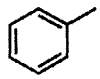
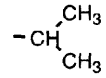
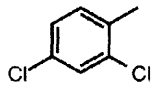
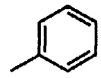
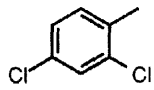
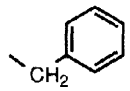
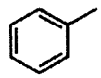
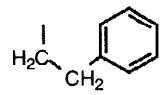
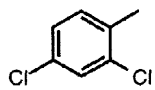
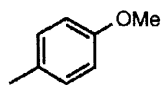
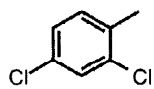
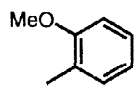
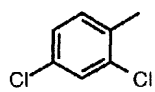
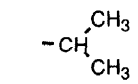
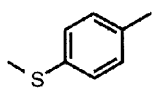
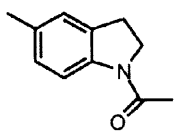
Table 1 : Cycloaddition of imines and homophtalic anhydride



2	R_1	R_2	method*	React. time (hours)	Yield**, %
a			A	8	47
b			B	14	56
c			B	14	56
d			B	14	56
e			A	12	49
f			A	14	57
g			B	14	96
h			B	14	41
i* **			C	14	64

* In method A, the condensation was performed with isolated imino-compounds while in method B they were not isolated

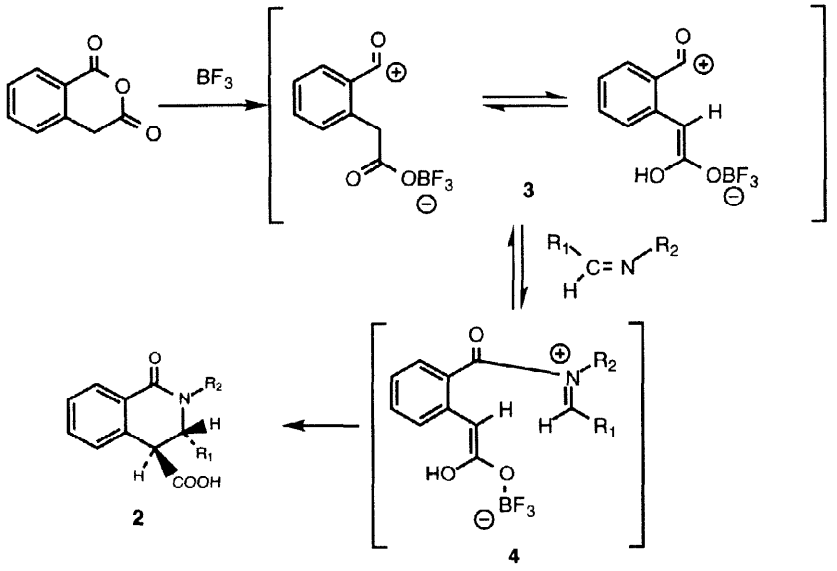
** isolated yield, without optimisation of the conditions.

*** method B was applied, but the reaction needed two equivalents of R_2-NH_2 and the final product was isolated as the carboxylic salt of the starting amine.

The usefulness of BF_3-Et_2O as a catalyst is exemplified by compounds **2d** to **2i** which were obtained as the *trans*-isomers with satisfactory yields, while no cycloaddition products were isolated under previously described conditions. Various catalysts including Lewis acids ($FeCl_3$, $AlCl_3$, $ZnCl_2$), protic acids (CH_3COOH, HCl), or bases (TEA, DIEA) etc., were tested: in most cases the reactions gave mixtures of *cis*- and *trans*-products or very complicated mixtures.

The reason for this high stereoselectivity is not yet clear but isomerisation of the isoquinolonic acids is not the key step. Under the conditions allowing the condensation, in the presence of BF_3-Et_2O, some *cis*-

products (R_1= R_2=C_6H_5) can not be isomerised to their *trans*-isomers. The pure cis-isomer of **2a** was stirred with BF_3-Et_2O, in acetonitrile, similarly to condensation conditions during 2 days, and we did not detect any *trans*-product. Therefore, among the previous proposals of Cushman, for reactions performed in other media, the cycloaddition under the presence of BF_3-Et_2O is probably involved in the pathway given in **Scheme 2**. According to this proposal, reaction of homophthalic anhydride with BF_3 leads to highly reactive intermediates **3**. These intermediates, in which steric factors are increased by BF_3, react with imines, which are classically obtained in the reaction medium as Z isomers, to give the less sterically hindered intermediates **4** and finally compound **2** as the *trans*--isomers.



Scheme 2

In conclusion, this method uses boron trifluoride etherate which has the advantage of being readily available, inexpensive, stable and easy to handle. The present procedure using a Lewis acid as a catalyst leads to *trans*-isoquinolonic acid derivatives in moderate to excellent yields, avoiding the formation of homophthalic amides and other side reactions. Moreover optically pure derivatives **2** have considerable potential in drug synthesis, as evidenced by a recent report[7]. It should also be pointed out that this method, due yo its mildness and simplicity, can be used to prepare a wide variety of isoquinolonic acids, even some which can not be obtained otherwise. Further results on the mechanism and

General procedure :

In a typical procedure, 2,4-dichlorobenzaldehyde (3.5 g, 20 mmoles), orthomethoxyaniline (3.6 ml, 20 mmoles) and sodium sulphate (10 g) were added in THF (50 mL) and the reaction was stirred at room temperature for 14 hours. The sodium sulphate was filtered off and the filtrate was added to a solution of homophthalic anhydride (3.2 g, 20 mmole) in acetonitrile (50 mL) and boron trifluoride etherate (14 mL) at room temperature. The progress of the reaction was monitored by HPLC, following the consumption of homophthalic anhydride. Usually most of the reactants disappeared in the first few minutes. After 3 hours, the solvent was evaporated at reduced pressure (~20 mm Hg). Water (50 mL) and ether (50 mL) were added, with vigorous stirring for 5 minutes, and then the mixture was allowed to stand at 0-5 °C without stirring for 1 hour. The product was obtained in 96% yield, as a white, crystalline solid by filtration, washed three times with ether (90 mL) and dried under vacuum.

The other reactions gave very similar yields, using isolated imines or working on crude compound. The all-*trans* stereochemistry of cycloadducts **2** was attributed from the two doublets (J = 0-2 Hz) observed close to 4 ppm and 5.5 ppm, respectively for the *H*-3 and *H*-4 hydrogens.

Acknowledgements

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References and Notes

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8. Spectra data of products **2.** (^1H-NMR : 300 MHz, DMSO-d6, δ)

   Product 2a : H-NMR : 4.26 (1H, d, *H*-3, J=1.5Hz), 5.75 (1H, d, *H*-4, J=1.5Hz), 7.16-7.53 (14H, m), 8.03 (1H, m), 13.21 (1H, s, COO*H*). IR (cm^{-1}) : 3120, 1735 (COOH).
   Product 2b : H-NMR: 0.84 and 1.18 (2 x 3H, 2 x d, J=6.9Hz), 4.05 (1H, d, *H*-3, J=1.1Hz), 4.84 (1H, septet, J=6.8 Hz), 5.38 (1H, d, *H*-4, J=1.1Hz), 7.08-7.96 (9H, m), 13.08 (1H, s, COO*H*). IR (cm^{-1}) : 3050, 1720 (COOH).
   Product 2c : H-NMR: 4.25 (1H, s, *H*-3), 5.99 (1H, s, *H*-4), 7.14-8.05 (12H, m), 13.48 (1H, s).
   IR (cm^{-1}) : 3050, 1720 (COOH).
   Product 2d : H-NMR: 4.03 et 5.11 (2 x 1H, 2 x d, CH_2, J=14.6Hz), 4.05 (1H, d, *H*-3, J=1.7Hz), 5.56 (1H, d, *H*-4, J=1.7Hz), 6.64-8.06 (12H, m), 13.3 (1H, broad s, COO*H*). IR (cm^{-1}) : 3200, 1730 (COOH).
   Product 2e : H-NMR : 4.16 (1H, d, *H*-3, J=1.2Hz), 5.74 (1H, d, *H*-4, J=1.2Hz), 6.69-7.99 (12H, m). IR (cm^{-1}) : 3050, 1720 (COOH).
   Product 2f : H-NMR : 3.72 (3H, s), 4.21 (1H, s, *H*-3), 5.91 (1H, s, *H*-4), 6.91-8.15 (11H, m), 13.45 (1H, s, COO*H*). IR (cm^{-1}) : 3220, 1735 (COOH).
   Product 2g : H-NMR: 3.78 (3H, s, OCH_3), 4.13 (1H, d, *H*-3, J=1.6Hz), 5.86 (1H, d, *H*-4, J=1.6Hz), 6.88-8.04 (11H, m). IR (cm^{-1}) : 3125, 1725 (COOH).
   Product 2h : H-NMR: 0.86 and 1.20 (2 x 3H, 2 x d, J=6.8 Hz), 4.04 (1H, d, *H*-3, J=1.1Hz), 4.86 (1H, septet, J=6.8Hz), 5.64 (1H, d, *H*-4, J=1.1 Hz), 6.73-7.98 (7H, m), 13.25(1H, s). IR (cm^{-1}) : 3150, 1735 (COOH).
   Product 2i : H-NMR: 2.13 (3H, s), 2.19 (3H, s), 2.38 (3H, s), 3.06-3.20 (4H, m), 4.04-4.15 (5H, m), 5.57 (1H, s, *H*-4), 6.88-8.08 (14H, m), 9.95 (3H, broad s, NH_3^+). IR (cm^{-1}) : 3050, 1720 (COOH).