



An expeditious total synthesis of (±)-jamtine using condensation between imine and acid anhydride

Joelle Pérard-Viret, Florence Souquet, Marie-Line Manisse, Jacques Royer *

Synthèse et Structure de Molécules d'Intérêt Pharmacologique, UMR 8638 CNRS-Université Paris Descartes, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France

ARTICLE INFO

Article history:

Received 2 October 2009

Revised 15 October 2009

Accepted 19 October 2009

Available online 23 October 2009

Keywords:

Natural product synthesis

Microwave-assisted synthesis

Pyrroloisoquinoline

Isoquinoline alkaloid

Jamtine

Imine condensation

Acid anhydride condensation

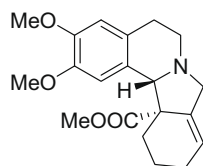
ABSTRACT

A totally convergent and very short (three steps) synthesis of (±)-jamtine was described. The key step of this sequence was the condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline and tetrahydrophthalic anhydride under microwave activation which occurred in good yield and high diastereomeric selectivity.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Our general interest in the synthesis of diversely substituted pyrrolidine derivatives¹ led us to launch a study on the total synthesis of jamtine (**1**). This compound is one of the medicinal alkaloids isolated from the climbing shrub *Cocculus hirsutus* which originates from Pakistan and India.² This plant is renowned for its therapeutic properties and is used in folk medicine. Jamtine together with other extracted substances was found to have significant antihyperglycemic activity.³



jamtine **1**

Up to now, only two total syntheses have been reported: the first one was based on a thionium/*N*-acyliminium ion cascade by Padwa and Danca⁴ and the second was an asymmetric synthesis using a chiral base desymmetrisation by Simpkins and Gill.⁵

We want to report herein our own efforts towards the synthesis of jamtine which allowed us to achieve an expeditious synthesis of this alkaloid.⁶ During the redaction of this Letter we were aware from a recent paper of Shaw⁷ which described the condensation reaction we used as a key step, with the same substrates and experimental conditions along a methodological study.

2. Results and discussion

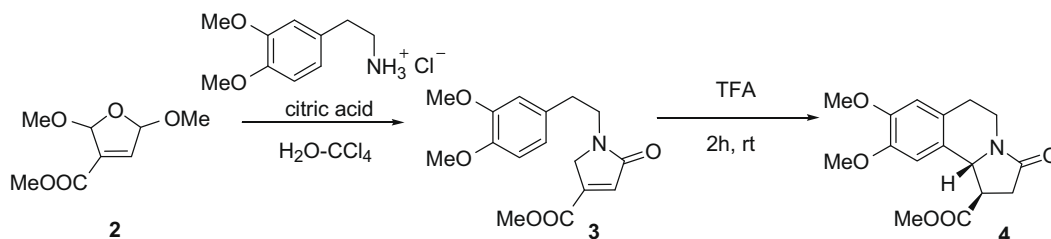
2.1. First synthetic plan: dimethoxydihydrofuran condensation

We already reported on the condensation of a primary amine with dimethoxydihydrofuran to prepare pyrrolidones.¹ The reaction was applied to the preparation of several pyrrolidine derivatives but also to polycyclic compounds including pyrroloisoquinolines.^{1b} We thought that this condensation could be extended to adequately substituted dimethoxydihydrofuran to prepare pyrroloisoquinoline ester **4** as a precursor of jamtine (**1**) (Scheme 1). We thus prepared dimethoxydihydrofuran methyl ester **2** according to the literature⁸ and engaged this compound in the condensation with 2-(3,4-dimethoxyphenyl)ethylamine.⁹ The reaction provided pyrrolidone **3** (50% yield) which was treated with TFA at rt for 2 h to give the pyrroloisoquinoline **4**⁹ in 76% yield as a single diastereomer.

Though this condensation gave a rapid access to the tricyclic intermediate **4**, the rest of the synthesis to jamtine (**1**) would consist in the introduction of the cyclohexene D-ring which would probably hamper the overall sequence by the further use of some

* Corresponding author.

E-mail address: jacques.royer@parisdescartes.fr (J. Royer).



Scheme 1. Substituted dimethoxydihydrofuran condensation.

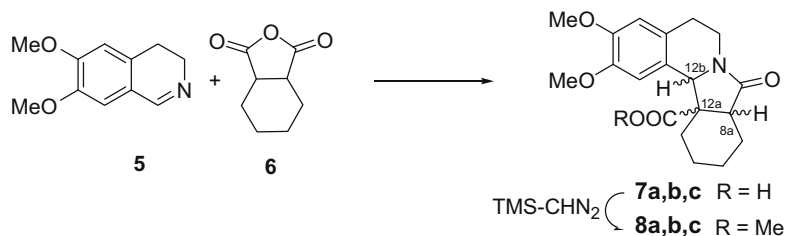
Scheme 2. Castagnoli condensation with 1,2-cyclohexanedicarboxylic anhydride (**6**).

Table 1
Condensation of imine **5** with anhydride **6**

Entry	Solvent	Experimental conditions	7 yield (%)	Diastereomeric ratio ^a a/b/c (%)
1	Toluene	Reflux, three days	29	68/5/27
2	Toluene	μ W ^b , 45 min, 150 °C	70	53/30/17
3	ClCH ₂ CH ₂ Cl	μ W, 45 min, 150 °C	20	61/36/3
4	DMF	μ W, 45 min, 150 °C	33	50/50/—
5	CH ₃ CN	μ W, 45 min, 150 °C	75	60/32/8

^a Estimated by NMR on the crude reaction mixture.

^b Microwaves reactor.

tedious steps. We then looked for a more convergent approach and turned our attention to the Castagnoli¹⁰ reaction which should offer a better solution to our synthetic task.

2.2. Second synthetic plan: Castagnoli condensation

Forty years ago, Castagnoli described a reaction between imines and cyclic anhydrides to form lactams. This process could be used to achieve convergent syntheses of natural or biologically active products.¹¹ We thought that this cycloaddition could be the exact answer to the synthesis of jamine (**1**) allowing the installation of the four rings of the natural product in a single step as well as the carboxylic acid function.

The reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**5**)¹² with 1,2-cyclohexanedicarboxylic anhydride (**6**) was first investigated in refluxing toluene (Scheme 2, Table 1, entry 1). After three

days, 29% of diastereomeric mixture of the expected carboxylic acid **7** was isolated.

It was rapidly found that the condensation could be dramatically improved by the use of microwave activation¹³ since 70% yield was obtained after a 45-min irradiation at 150 °C in toluene (Table 1, entry 2).¹⁴

Nevertheless, this better yield was accompanied by a lower diastereoselectivity. Then the effect of the solvent on the reaction was briefly examined. Toluene or acetonitrile was found to give the best yields while with similar and poor diastereoselectivity (Table 1, entries 2 and 5). In any cases, three isomers were detected among the four theoretically possible. The major isomer **8a**¹⁵ could be easily isolated after esterification (TMSCHN₂,¹⁶ 88–100% yield). This compound was not identical with that described by Simpkins (epimeric at C_{8a}), but it possessed the required *syn* (C_{12a}–C_{12b}) configuration¹⁷ and thus could be transformed to jamine through the already-described synthesis.⁵ Ester **8b** exhibited a reverse *anti* (C_{12a}–C_{12b}) configuration.¹⁸

Despite this success, we anticipated that the use of unsaturated anhydride **9** instead of **6** should provide a more convergent approach giving an intermediate possessing the required double bond. Indeed, under similar experimental conditions (CH₃CN, μ W reactor, and 150 °C for 45 min) it was our delight to find that isoindoloisoquinoline acid **10**¹⁴ was formed in a nice 78% yield and a 1:1 mixture of two diastereomers (Scheme 3, Table 2, entry 1).

By analogy with the previous study, we reasoned that the diastereomeric ratio might be modified by varying the experimental conditions (Table 2). We then investigated the reaction of **9** in different solvents (Table 2, entries 1–4). Using the same irradiation

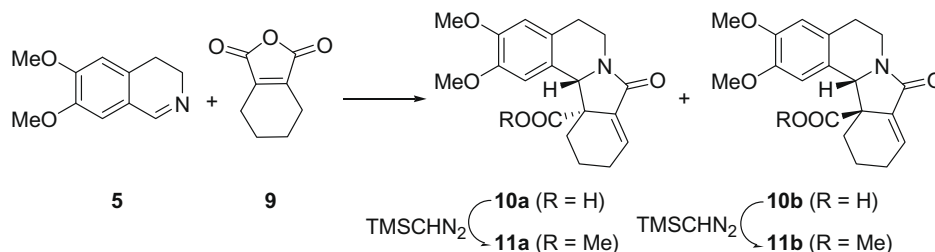
Scheme 3. Castagnoli condensation with tetrahydropthalic anhydride (**9**).

Table 2
Condensation of imine **5** with anhydride **9**

Entry	Solvent	Experimental ^a conditions	10 yield (%)	Diastereomeric ratio ^b a (syn)/b (anti) (%)
1	CH ₃ CN	45 min, 150 °C	78	43/57
2	Toluene	45 min, 150 °C	62	25/75
3	THF	45 min, 150 °C	84	20/80
4	CHCl ₃	45 min, 150 °C	62	36/64
5	CH ₃ CN	90 min, 150 °C	84	62/38
6	CH ₃ CN	90 min, 160 °C	76	83/17
7	CH ₃ CN	45 min, 180 °C	48	95/5

^a All the reactions were performed under microwave activation.

^b Estimated by NMR.

time and temperature, it appeared that when acetonitrile or tetrahydrofuran was employed, highest yields were observed, but varying diastereomeric ratios were found. With THF (Table 2, entry 3), a clean and high yielding reaction was observed but unfortunately the *anti* diastereoisomer **10b** was the major isomer.

In order to reverse the diastereomeric ratio, we focussed on the reaction in acetonitrile and changed the irradiation time and the temperature (Table 2, entries 1, 5–7)). It was then found that a longer reaction time led predominantly to **10a**. In the same way, a slight increase in the temperature (Table 2, entry 6) led to a 76% yield and a good 83:17 ratio in favour of the *syn* diastereomer. Eventually higher temperature (Table 2, entry 7) gave a 95:5 ratio albeit in lower yield (some degradation occurred).

The supposed thermodynamic control of the reaction was checked. On heating (μ W reactor, 150 °C, 90 min), the 20:80 mixture of *syn/anti* diastereomers **10** (arising from THF experiment) was converted into a 50:50 mixture in 80% yield. The reaction was thus reversible and an acyliminium intermediate could be invoked. This clearly suggested that the *syn* isomer should be the thermodynamic product of this condensation as proposed by Shaw,⁷ on the basis of theoretical calculations. Nevertheless, this author did not experimentally verify his proposal and suggested an inverse diastereomeric ratio according to the presence, or not, of Et₃N, Et₃N–HCl.

The *syn* methyl ester **11a** was obtained in 56% from **5** after treatment of the crude mixture (83:17) of acids **10** with trimethylsilyl diazomethane and separation on silica gel column chromatography. The reduction of the amide function following the published method⁵ (Et₃OBF₄ then NaBH₄, 64%) gave jamtine (**1**).

In summary, we described an efficient and highly convergent synthesis of ($\pm$)-jamtine (**1**)¹⁹ in three steps and 36% overall yield.

References and notes

- (a) Baussanne, I.; Dudot, B.; Pérard-Viret, J.; Planas, L.; Royer, J. *Arkivoc* **2006**, 7, 57–66. and references cited herein; (b) Fontaine, H.; Baussanne, I.; Royer, J.

- Synth. Commun.* **1997**, 27, 2817–2824; (c) Halie, D.; Pérard-Viret, J.; Dufour, S.; Royer, J. *Tetrahedron* **2009**, 65, 1402–1414.
- (a) Ahmad, V. U.; Rahman, A.; Rasheed, T.; Rehman, H. *Heterocycles* **1987**, 26, 1251–1255; (b) Rasheed, T.; Khan, M. N. I.; Zhadi, S. S. A.; Durrani, S. J. *J. Nat. Prod.* **1991**, 54, 582–584.
- Badole, S.; Patel, N.; Bodhankar, S.; Jain, B.; Bhardwaj, S. *Indian J. Pharmacol.* **2006**, 38, 49–53.
- (a) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, 4, 715–717; (b) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, 68, 929–941.
- (a) Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, 5, 535–537; (b) Gill, C. D.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron* **2003**, 59, 9213–9230.
- Preliminary Communication at the XIIth ICSN Symposium: 'From Organic Chemistry to Chemical Biology', July 11–12th, 2009. Gif-sur-Yvette, France.
- Tang, Y.; Fettingner, J. C.; Shaw, J. T. *Org. Lett.* **2009**, 11, 3802–3805.
- Stibor, I.; Srogl, J.; Janda, M.; Piricova, N.; Vlazny, K. *Collect. Czech. Chem. Commun.* **1982**, 47, 3261–3267.
- To 2-(3,4-dimethoxyphenyl)ethylamine–HCl (2.17 g, 10 mmol) and citric acid (3.84 g, 20 mmol) in H₂O (80 mL) was added **2** (2.0 g, 10 mmol) in CCl₄ (35 mL). The solution was vigorously stirred under reflux for 8 h. The organic layer was washed with satd NaHCO₃ soln, dried with MgSO₄, concentrated in vacuo and the residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/AcOEt 80:20), to give **3** (1.59 g, 50%). A solution of **3** (1 g, 3.3 mmol) in TFA (4 mL) was stirred at rt for 2 h. After concentration, the residue was extracted with CH₂Cl₂ and washed with satd NaHCO₃ soln. After solvent evaporation, the residue was purified by flash column chromatography (SiO₂, CH₂Cl₂/AcOEt 70:30) to lead to **4** (770 mg, 76%). Mp 125 °C; ¹H NMR (CDCl₃, 300 MHz): δ (ppm): 2.35–2.62 (4H, m); 2.68–2.86 (2H, m); 3.53 (3H, s, OCH₃); 3.55 (3H, s, OCH₃); 3.59 (3H, s, OCH₃); 3.89 (1H, m); 4.68 (1H, d, J = 7.5 Hz, CHN); 6.34 (1H, s, H_{ar}); 6.49 (1H, s, H_{ar}); ¹³C NMR (75 MHz, CDCl₃) (ppm): 27.7 (CH₂); 35.1 (CH₂); 36.9 (CH₂); 45.4 (CH); 52.3 (COOMe); 55.4 (OMe); 55.5 (OMe); 58.4 (CH); 107.6 (CH_{ar}); 111.5 (CH_{ar}); 125.6 (C_{ar}); 127.7 (C_{ar}); (147.8 (C_{ar}); 147.9 (C_{ar}); 169.7 (CO); 173.4 (CO).
- Castagnoli, N. J. *Org. Chem.* **1969**, 34, 3187–3189.
- (a) Cushman, M.; Castagnoli, N. J. *Org. Chem.* **1971**, 36, 3404–3406; (b) Cushman, M.; Gentry, J.; Dekow, F. W. J. *Org. Chem.* **1977**, 42, 1111–1116; (c) Gonzalez-Lopez, M.; Shaw, J. T. *Chem. Rev.* **2009**, 109, 164–189.
- Warrener, R. N.; Liu, L.; Russel, R. A. *Tetrahedron* **1998**, 54, 7485–7496.
- Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, 30, 741–744.
- General procedure*: Imine **5** (96 mg; 0.5 mmol) and anhydride **6** or **9** (0.5 mmol) in 2 mL of solvent were heated in a microwave reactor under stirring. The solution was concentrated in vacuo, extracted with NaOH 1 M and washed twice with CH₂Cl₂. The aqueous layer was acidified by concentrated HCl and extracted with CH₂Cl₂ (3 $\times$ 15 mL). The organic layers were dried with anhydrous MgSO₄ and concentrated in vacuo.
- Analytical data for 8a*: ¹H NMR (CDCl₃, 300 MHz): δ (ppm): 1.15–1.35 (3H, m); 1.60–1.85 (3H, m); 2.06 (1H, m); 2.35 (1H, m); 2.47 (1H, m); 2.65–2.76 (3H, m); 3.16 (3H, s, COOMe); 3.80 (3H, s, OCH₃); 3.84 (3H, s, OCH₃); 4.33 (1H, m); 4.62 (1H, s, CHN); 6.53 (1H, s, H_{ar}); 6.59 (1H, s, H_{ar}); ¹³C NMR (75 MHz, CDCl₃) (ppm): 21.9 (CH₂); 23.0 (CH₂); 25.1 (CH₂); 28.1 (CH₂); 32.4 (CH₂); 36.5 (CH₂); 51.1 (CH); 51.2 (COOMe); 55.8 (OMe); 56.0 (OMe); 58.8 (C_q); 64.4 (CHN); 111.4 (CH_{ar}); 109.5 (CH_{ar}); 123.5 (C_{ar}); 127.2 (C_{ar}); (147.6 (C_{ar}); 148.1 (C_{ar}); 171.3 (CO); 173.4 (CO).
- Presser, A.; Hüfner, A. *Monatsh. Chem.* **2004**, 135, 1015–1022.
- The *syn* isomer is characterized by a strong upfield shift of the methyl group of the ester; see Ref. **2a**.
- Compound **8c** has not been obtained in pure form, its configuration was tentatively assigned as *anti* (C_{12a}–C_{12b}) after examination of the NMR spectra of the mixture **8a–c**.
- The analytical data of our synthetic material were identical with those described by Padwa⁴ and Simpkins⁵ who mentioned some doubt on the structure of the natural product.