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

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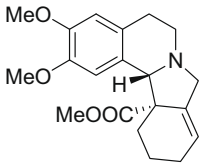
ABSTRACT

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.

1. Introduction

Our general interest in the synthesis of diversely substituted pyrrolidine derivatives[1] 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 Danca[4] 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 Shaw[7] 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 literature[8] 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

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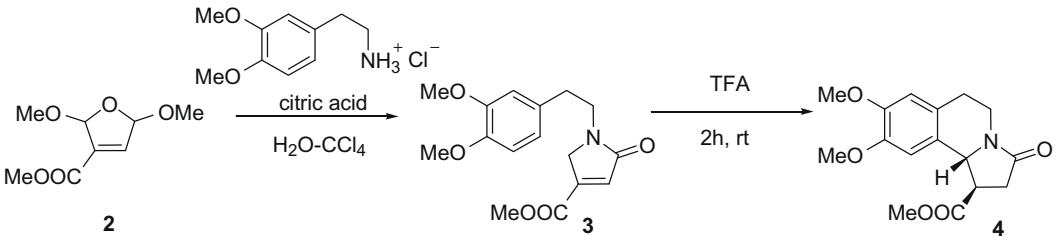
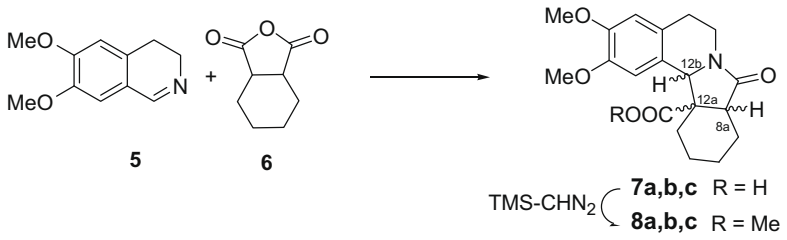


Scheme 1. Substituted dimethoxydihydrofuran condensation.



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	μW[b], 45 min, 150 °C	70	53/30/17
3	$ClCH_2CH_2Cl$	μW, 45 min, 150 °C	20	61/36/3
4	DMF	μW, 45 min, 150 °C	33	50/50/—
5	CH_3CN	μW, 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 Castagnoli[10] 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 jamtine (**1**) allowing the installation of the four rings of the natural product in a single step as well as the carboxylic acid function.

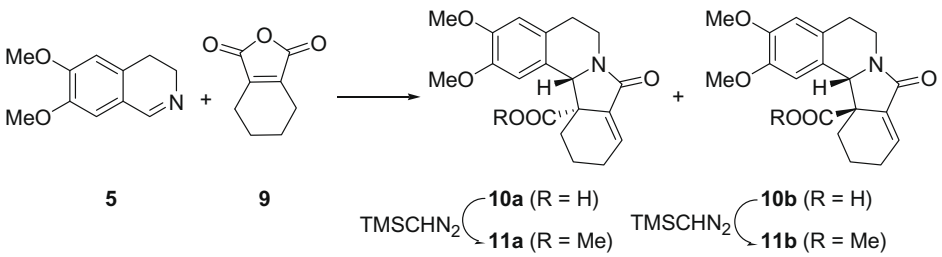
The reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline (**5**)[12] with 1,2-cyclohexanedicarboxylic anhydride (**6**) was first investigated in refluxing toluene (Scheme 2, Table 1, entry 1). After three days, 29% of diastereomeric mixture of the expected carboxylic acid **7** was isolated.

It was rapidly found that the condensation could be dramatically improved by the use of microwave activation[13] 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 ($TMSCHN_2$,[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}) configuration[17] and thus could be transformed to jamtine 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 (CH_3CN, μW 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 tetrahydrophthalic 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_3CN	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_3CN	90 min, 150 °C	84	62/38
6	CH_3CN	90 min, 160 °C	76	83/17
7	CH_3CN	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 (μW 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 Et_3N, Et_3N–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 method[5] (Et_3OBF_4 then $NaBH_4$, 64%) gave jamtine (**1**).

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

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9. To 2-(3,4-dimethoxyphenyl)ethylamine–HCl (2.17 g, 10 mmol) and citric acid (3.84 g, 20 mmol) in H_2O (80 mL) was added **2** (2.0 g, 10 mmol) in CCl_4 (35 mL). The solution was vigorously stirred under reflux for 8 h. The organic layer was washed with satd $NaHCO_3$ soln, dried with $MgSO_4$, concentrated in vacuo and the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/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 CH_2Cl_2 and washed with satd $NaHCO_3$ soln. After solvent evaporation, the residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/AcOEt 70:30) to lead to **4** (770 mg, 76%). Mp 125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 2.35–2.62 (4H, m); 2.68–2.86 (2H, m); 3.53 (3H, s, OCH_3); 3.55 (3H, s, OCH_3); 3.59 (3H, s, OCH_3); 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}); ^{13}C NMR (75 MHz, $CDCl_3$) (ppm) :27.7 (CH_2); 35.1 (CH_2); 36.9 (CH_2); 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).
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14. *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 CH_2Cl_2. The aqueous layer was acidified by concentrated HCl and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried with anhydrous $MgSO_4$ and concentrated in vacuo.
15. *Analytical data for* **8a**: ^{1}H NMR ($CDCl_3$, 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, OCH_3); 3.84 (3H, s, OCH_3); 4.33 (1H, m); 4.62 (1H, s, CHN); 6.53 (1H, s, H_{ar}); 6.59 (1H, s, H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$) (ppm): 21.9 (CH_2); 23.0 (CH_2); 25.1 (CH_2); 28.1 (CH_2); 32.4 (CH_2); 36.5 (CH_2); 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).
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17. The *syn* isomer is characterized by a strong upfield shift of the methyl group of the ester; see Ref. 2a.
18. 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**.
19. The analytical data of our synthetic material were identical with those described by Padwa[4] and Simpkins[5] who mentioned some doubt on the structure of the natural product.