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Journal of Chemical and Pharmaceutical Research, 2013, 5(12):1062-1065

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of nitric oxide-releasing matrine derivatives as cardiovascular drugs

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ABSTRACT

This work describes the synthesis of two new benzoic nitrooxy derivatives of matrine (3-nitrooxymethylbenzoate and 4-nitrooxymethylbenzoate). Matrine was hydrolyzed under alkaline condition to give the ring-opening carboxylic acid derivative (matrine acid), and the coupling of nitrooxymethylbenzoyl group to the matrine acid was accomplished through amide linkage.

Keywords: Matrine, Nitric oxide, Nitrooxymethyl benzoate, Cardiovascular drug.

INTRODUCTION

Matrine (**2**, $C_{15}H_{24}N_2O$), a phytochemical in the *Sophora alopecuroides L*, is known to be a powerful antipyretic, anti-inflammatory, analgesic drug [1-4], and is clinically used for the treatment of lipopolysaccharide-induced liver injury [5]. Matrine could also regulate immunity, increase the number of white blood cells and relax cancer pain [6-9]. Recently, it was reported that matrine could increase the nitric oxide (NO) in blood, and could protect acute myocardial ischemic injury in rats [10]. Therefore, it is interesting to develop more matrine derivatives for cardiovascular drugs.

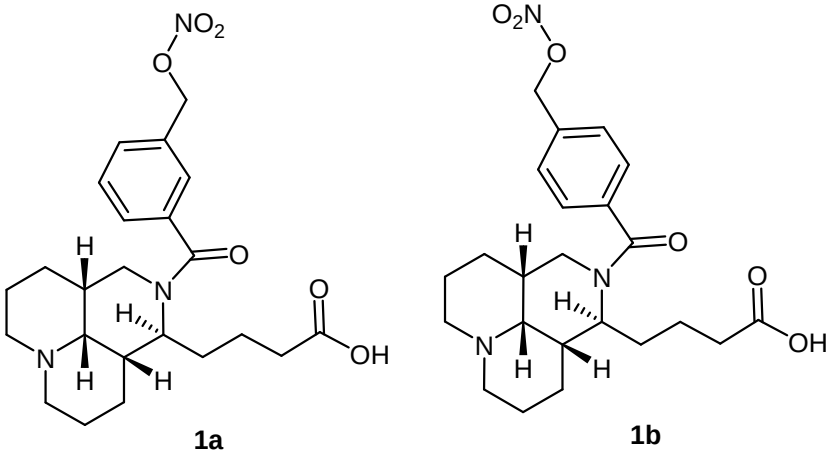


Fig. 1. The chemical structures of NO-releasing matrine derivatives

The so-called “nitric oxide-releasing drugs” have their pioneers in nitrates and nitrites used in the treatment of angina pectoris in view of their ability to release NO [11-13]. NO-releasing hybrid drugs, where a drug is integrated with an NO-donor group, confer an improved pharmacological profile or a reduction of adverse effects [14-17]. It is notable that NCX-4016, NO-releasing aspirin, significantly reduced infarct size in a rat model of myocardial infarction [18-21]. In recent years, NO-releasing ACE inhibitors, NO-releasing calcium antagonists, and

NO-releasing *β*-blocking agents have been reported to improve the antihypertensive effects of the "native" drugs [22-28].

Herein, the authors report the synthesis of NO-releasing matrine derivatives, two new benzoic nitrooxy derivatives of matrine (3-nitrooxymethylbenzoate **1a** and 4-nitrooxymethylbenzoate **1b**) as cardiovascular drugs (Fig. 1).

EXPERIMENTAL SECTION

Matrine (98% purity) was purchased from Zijinghua Pharmaceutical Ltd., 3-chloromethylbenzoic acid (97% purity) and 4-chloromethylbenzoic acid (98% purity) were purchased from Adamas Reagent Co. Ltd., and silver nitrate was purchased from Tianjin Damao Chemical Reagent Factory (99.8% purity). Dichloromethane (DCM) was dried by $CaCl_2$ for 12 h and distilled prior to use. All other chemical materials and reagents were of commercial grade, and used without further purification. The progresses of the reactions were monitored by TLC on 0.25-mm thick layers of silica gel GF_{254} developed with solvent system (AcOEt). The ESI-MS experiments were performed using a ThermoQuest Finnigan LCQ^{DECA} system equipped with an ESI source (ThermoQuest LC/MS Division, San Jose, CA, USA). NMR spectra were recorded on Bruker 400 spectrometer in D_2O and $CDCl_3$ solutions with TMS (tetramethylsilane) as standard.

*Synthesis of matrine acid (**3**)*

To a solution of matrine **2** (21.02 g; 84.76 mmol) in 50% aqueous ethanol (400 cm^3), NaOH (16.14 g; 403.50 mmol) was added at room temperature. Then the mixture was refluxed at 85 °C for 8 h, and concentrated to dry in vacuo. The residue was dissolved in H_2O (180 cm^3), and subsequently extracted with $CHCl_3$ (3×40 cm^3). The aqueous layer was separated, adjusted to pH 2.0 by the addition of 1.0 M HCl, and concentrated in vacuo. Then the residue was triturated with anhydrous ethanol (2×100 cm^3), and filtered off. The filtrate was evaporated to give **3** as white solids. Yield: 76.6%. ESI-MS: *m/z* 267 ($[M+H]^+$). ^{13}C NMR (D_2O): *δ* 175.7; 61.2; 55.5; 55.4; 52.2; 42.3; 35.8; 33.1; 31.1; 28.8; 23.8; 22.8; 18.2; 18.0; 13.3.

*Synthesis of 3-chloromethylbenzoate of matrine acid (**4a**)*

To a solution of 3-chloromethylbenzoic acid (1.02 g, 6.00 mmol) in 30 cm^3 DCM, oxalyl chloride (1.3 cm^3) was added at room temperature. After the addition of three drops of dry DMF, evolution of gas occurred. The mixture was stirred overnight. After completion of the reaction, the excess oxalyl chloride was removed in vacuo. Thus, the crude 3-chloromethylbenzoyl chloride was obtained and dissolved in DCM (10.0 cm^3), which was used in the next step.

To a solution of **3** (1.77 g, 5.22 mmol) in 40 cm^3 DCM, Et_3N (3.8 cm^3) was added dropwise. The above crude 3-chloromethylbenzoyl chloride in DCM was added, and the mixture was stirred at 0 °C for 4 h while allowing it to stand at room temperature for 20 h. It was evaporated, and the crude product was purified by column chromatography eluting with ethyl acetate to give **4a** as brown oil. Yield: 58.1 %. ESI-MS: *m/z* 457 ($[M+K]^+$). ^{13}C NMR ($CDCl_3$): *δ* 173.6; 171.4; 138.6; 137.6; 129.3; 128.8; 127.2; 126.9; 62.8; 60.3; 56.8; 56.6; 46.0; 45.8; 39.8; 34.2; 28.7; 22.1; 21.4; 21.1; 18.5; 18.3; 14.4.

Synthesis of 4-chloromethylbenzoate of matrine acid *(**4b**)*

Compound **4b** was synthesized from **3** (1.80 g; 5.31 mmol) and 4-chloromethylbenzoic acid (1.00 g; 5.88 mmol) following the same procedure described above for the preparation of **4a**. This compound was purified by column chromatography eluting with ethyl acetate to give **4b** as brown oil. Yield: 42.2 %. ESI-MS: *m/z* 457 ($[M+K]^+$). ^{13}C NMR ($CDCl_3$): *δ* 173.7; 171.5; 138.1; 130.3; 128.6; 127.5; 62.9; 60.3; 56.8; 56.6; 45.9; 45.4; 39.9; 34.2; 28.5; 22.1; 21.3; 21.1; 18.5; 18.2; 14.4.

*Synthesis of 3-nitrooxymethylbenzoate of matrine acid (**1a**)*

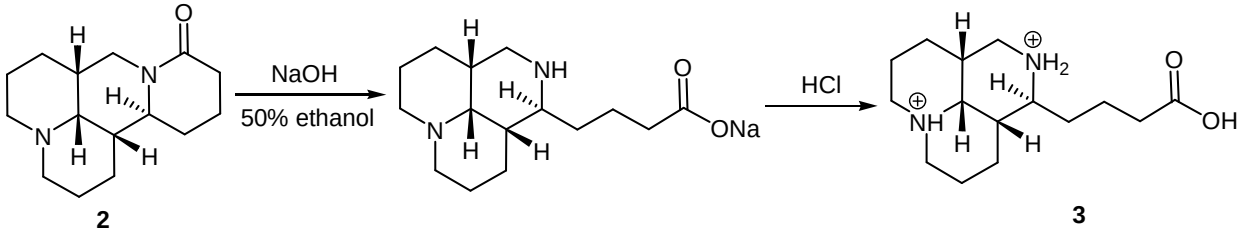
To a solution of **4a** (1.45 g, 3.47 mmol) in 5 cm^3 CH_3CN, $AgNO_3$ (2.49 g, 14.65 mmol) in CH_3CN (14 cm^3) was added. The suspension was stirred for 4 h at room temperature in the dark. It was filtered off, and evaporated. The crude product was purified by column chromatography eluting with ethyl acetate to give **1a** as brown oil. Yield: 40.1%. ESI-MS: *m/z* 427 ($[M-H_2O]^+$). ^{13}C NMR ($CDCl_3$): *δ* 173.5; 167.8; 134.6; 130.1; 129.4; 129.1; 128.1; 127.8; 74.2; 65.8; 60.4; 58.5; 56.7; 55.9; 37.1; 34.1; 28.5; 25.7; 21.8; 19.3; 18.7; 18.5; 14.3.

*Synthesis of 4-nitrooxymethylbenzoate of matrine acid (**1b**)*

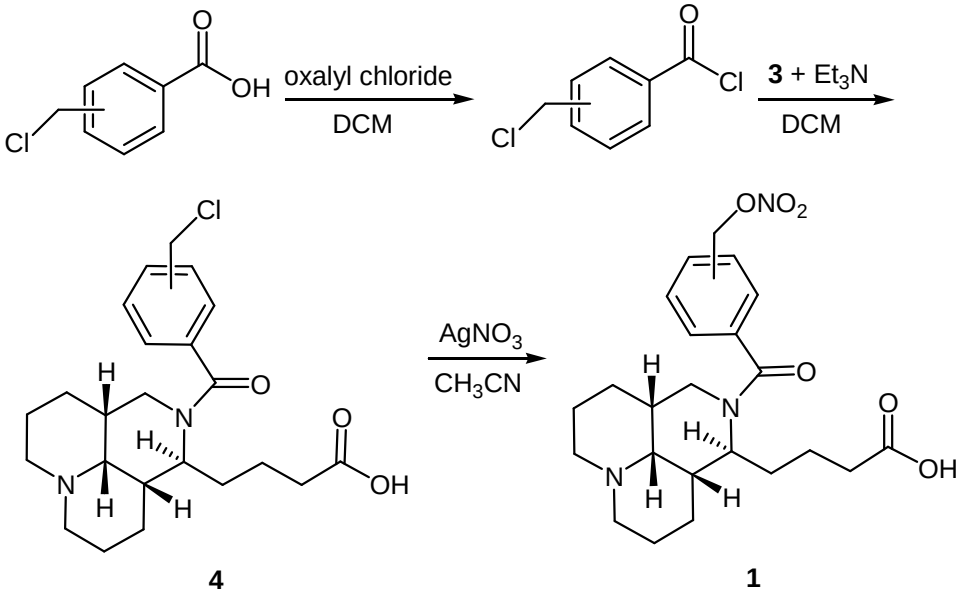
Compound **1b** was synthesized from **4b** (1.06 g; 2.53 mmol) and $AgNO_3$ (1.92 g; 11.29 mmol) following the same procedure described above for the preparation of **1a**. This compound was brown oil. Yield: 33.2%. ESI-MS: *m/z* 427 ($[M-H_2O]^+$). ^{13}C NMR ($CDCl_3$): *δ* 171.3; 166.1; 137.2; 130.4; 129.3; 128.6; 74.2; 73.9; 61.4; 60.5; 54.8; 54.4; 34.6; 31.2; 29.8; 22.5; 22.2; 21.2; 19.2; 18.8; 14.3.

RESULTS AND DISCUSSION

In order to increase the solubility of matrine, 50% aqueous ethanol solution was used as the reaction solvent. Thus, matrine was hydrolyzed with sodium hydroxide to give the ring-opening carboxylic acid derivatives (Scheme 1). The unreacted matrine could easily been extracted with chloroform.



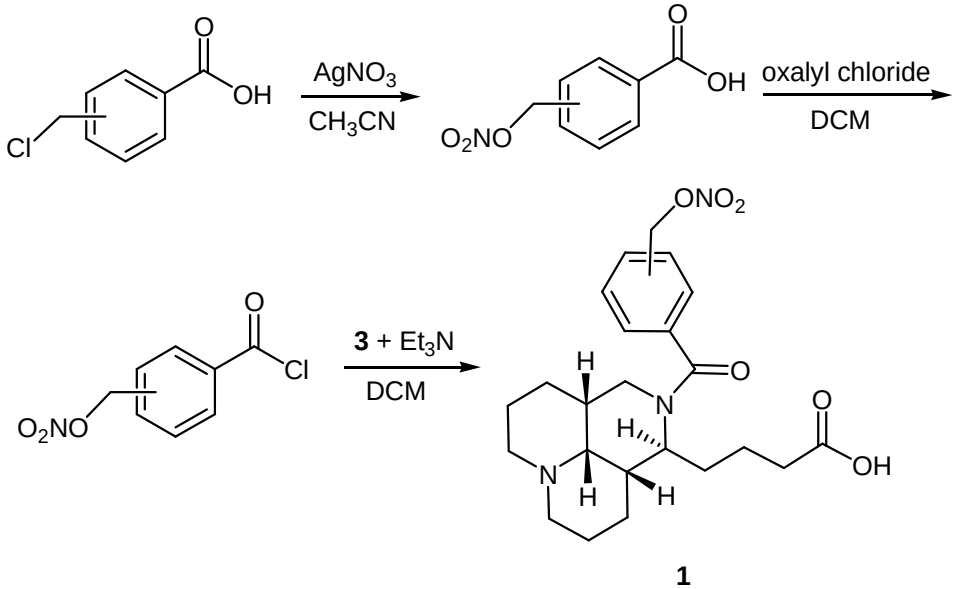
Scheme 1. The synthesis routes of matrine acid



4a = 3-chloromethylbenzoate;
4b = 4-chloromethylbenzoate.

1a = 3-nitrooxymethylbenzoate;
1b = 4-nitrooxymethylbenzoate.

Scheme 2. One routes of NO-releasing matrine derivatives



1a = 3-nitrooxymethylbenzoate;
1b = 4-nitrooxymethylbenzoate.

Scheme 3. The other routes of NO-releasing matrine derivatives

There are two methods for the synthesis of NO-releasing matrine derivatives starting from **3**. One was coupling of **3** and 3-chloromethylbenzoic acid, and then be nitrated by silver nitrates in an acetonitrile solution (Scheme 2). The other way was based on the nitration of 3-chloromethylbenzoic acid, and subsequently condensated with **3** to give the corresponding NO-releasing matrine derivatives (Scheme 3). Evaluated and compared the two methods, we found that the yields of the former method (23.2%) were higher than that of the latter one (13.0%).

The optimized conditions for the synthesis of nitrooxymethylbenzoate are matrine acid/oxalyl chloride/chloromethylbenzoic acid = 1.1/3/1 (mol/mol). The structures were confirmed by ESI-MS and NMR.

CONCLUSION

NO-releasing hybrid drugs confer an improved pharmacological profile or a reduction of adverse effects. Matrine could protect acute myocardial ischemic injury. In order to strengthen the anti-myocardial ischemia activity of matrine, two new benzoic nitrooxy derivatives of matrine (3-nitrooxymethylbenzoate and 4-nitrooxymethylbenzoate) were synthesized. First, matrine was hydrolyzed under alkaline condition to give the ring-opening carboxylic acid derivative (matrine acid). Secondly, the coupling of nitrooxymethylbenzoyl group to the matrine acid was accomplished through amide linkage. The activities of NO-releasing matrine derivatives are in progress.

Acknowledgements
B. P. Li and P. P. Ma contributed equally to this work, and are joint first authors. Financial support from the Natural Science Foundation of Ningxia (No. NZ11110) is gratefully acknowledged.

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