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Microwave-Assisted One-Pot Preparation of Tetrahydro-β-carboline Hydrochlorides under Solvent-Free Conditions

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Abstract: An efficient and environmentally friendly synthesis of tetrahydro-β-carboline hydrochlorides via Pictet–Spengler reaction was described. Tryptamine hydrochlorides were used as the reactant and no additional acid catalyst was needed. This reaction was completed within 2.5–9 min in good yield.

Keywords: green chemistry, microwave reaction, Pictet–Spengler reaction, tetrahydro-β-carboline hydrochlorides

The tetrahydro-β-carbolines constitute an important part of indole alkaloids. Their broad spectrum of biological and pharmacological activity leads to considerable interest in the synthesis of tetrahydro-β-carboline analogs. One of the most powerful methods to synthesize the tetrahydro-β-carboline ring system is the Pictet–Spengler cyclization,[1,2] which involves two processes (Scheme 1): a condensation reaction between tryptamine and aldehydes to generate the corresponding imines and an intramocular cyclization catalyzed by Brønsted acids or Lewis acids.[3–5] It has also been reported that this reaction could be carried out in one step in aprotic solvent and in protic solvent with the aid of zeolite catalysts.[6,7]

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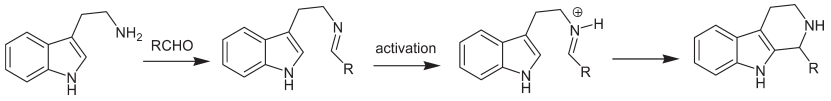
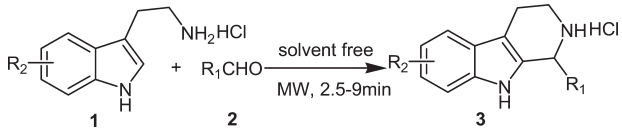


Scheme 1.

In recent years, microwave irradiation has been widely used in organic synthesis because of its reduction in reaction time and its good yields.[8] Several researchers have reported the application of microwave irradiation in the Pictet–Spengler cyclization for the preparation of tetrahydro-β-carbolines.[9–12] However, in most of these studies, this reaction was carried out in protic solvent with catalysis of acids (acetic acid or trifluoroacetic acid usually). One important symbol of green chemistry is the reduction of the use of organic solvents and catalysts because of the economical and environmental concerns associated with them. Therefore, the development of solvent-free or catalyst-free synthetic methods is of fundamental importance. Recently, in the study of Bikash et al., the Pictet–Spengler reaction was performed on silica gel in the domestic microwave oven under solvent-free conditions.[11] In that case, a large amount of glacial acetic acid was needed, and the yield was not good. In this article, we describe a more environmentally friendly and facile method for the synthesis of tetrahydro-β-carboline hydrochlorides under solvent-free conditions by the direct reaction of tryptamine hydrochlorides and aldehydes with the aid of microwave irradiation.

In our research, we used commercially available tryptamine hydrochlorides as the original reactant (Scheme 2). 4-Nitrobenzalaldhyde was selected as a representative aldehyde to optimize the reaction condition. First, we compared the reaction result between conventional heating and microwave. As shown in Table 1, there was a dramatic reduction in the reaction time under microwave irradiation. Second, in the reactions employing microwave, the reaction time had an important effect on the yield. After the tryptamine hydrochloride and 4-nitrobenzalaldehyde had been heated under microwave irradiation at 100 W for 2 min, a visible fall of the reactant's temperature occurred from 90 to 75°C; this phenomenon lasted for 0.5 min. Then the reaction was stopped. This change of temperature was due to the difference of microwave irradiation's absorbability between reactants and products. Any more reaction time would lead to a lower yield and bring by-products as well. The residue was recrystallized from ethanol (95%) to afford pure tetrahydro-β-carboline hydrochloride **3c** in good yield.



Scheme 2.

Table 1. Reaction time optimization in the synthesis under microwave irradiation and conventional conditions

Conditions	Reaction time (min)	Yield (%)[a]	Solvent	Temperature (°C)
Conventional heating	90	80	CH_3COOH	100
Conventional heating	90	72	—	100
Microwave	2	60	—	<100
Microwave	2.5	95	—	<100
Microwave	3	86	—	<100

[a]Isolated yields.

This methodology was also applicable for the reactions between tryptamine hydrochlorides and other aromatic aldehydes or aliphatic aldehydes in good yields within 2.5–9 min (Table 2). When this methodology was applied to 2-furancabox-aldehyde and tryptamine hydrochlorides, most of

Table 2. Synthesis of tetrahydro-β-carboline hydrochlorides under catalyst-free and additional solvent-free conditions with the aid of microwave

Entry	R_1	R_2	Products	Reaction time (min)	Yield (%)[a]
1	2-Cl-C_6H_4	H	**3a**	3	92
2	3-Cl-C_6H_4	H	**3b**	3	92
3	4-NO_2-C_6H_4	H	**3c**	2.5	95
4	3-CH_3-C_6H_4	H	**3d**	3	94
5	2-CH_3O-C_6H_4	H	**3e**	3.5	91
6	4-CH_3O-C_6H_4	H	**3f**	3.5	92
7	C_6H_5	H	**3g**	3	94
8	4-F-C_6H_4	H	**3h**	2.5	91
9	C_6H_5	5-Cl	**3i**	3	94
10	C_6H_5	5-CH_3	**3j**	3	92
11	C_6H_5	5-CH_3O	**3k**	3	87
12	2-Cl-C_6H_4	5-Cl	**3l**	2.5	91
13	3-CH_3-C_6H_4	5-CH_3	**3m**	3	90
14	C_6H_5-CH_2	H	**3n**	9	85
15	C_6H_5-CH_2	5-Cl	**3o**	9	82
16	2-Thienyl	H	**3p**	5	81
17	2-Thienyl	5-Cl	**3q**	6	76
18	CH_3CH_2	H	**3r**	6	79

[a]Isolated yields.

2-furancabox-aldehyde was decomposed, and a only little product was obtained after 2 min of irradiation with microwaves. The ends of these reactions were also determined by the changes in temperature respectively.

In summary, an efficient microwave-assisted Pictet–Spengler cyclization of tryptamine hydrochlorides with aldehydes under additional catalyst-free and solvent-free conditions was developed with high yields for the first time. And there are several advantages to this methodology: environmentally friendliness, high yields, and short reaction times.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AV 500 spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). The EI-MS were obtained on Shimadzu GCMS-QP2010. Elemental analyses were performed on a Carlo Erba 1106 instrument. Melting points (uncorrected) were obtained on a Thomas Hoover apparatus.

General Procedure of the Pictet–Spengler Reaction between Tryptamine Hydrochloride and Aldehydes

All of the experiments were carried out in the Discover microwave synthesizer from CEM Corp. The maximum temperature was set to 100°C. To control the temperature, the melting point of all of the aldehydes should be less than 100°C. A mixture of 1 mmol of tryptamine hydrochloride and 1.2 mmol of aldehyde was heated in the microwave synthesizer at 100 W for 2–9 min. The residue was recrystallized from ethanol (95%) to yield pure products.

The structures of products **3a–r** were confirmed from the spectroscopic data and elemental analysis. The spectroscopic data were all consistent with the data that reported in the literature.[13]

Analytical and Spectroscopic Data for Some Representative Compounds and New Compounds

Compound **3a**: White solid, mp 267–268°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.03 (m, 1H), δ 3.17 (m, 1H), δ 3.36 (m, 2H), δ 6.18 (s, 1H), δ 7.05 (t, 1H), δ 7.15 (m, 2H), δ 7.29 (d, 1H), δ 7.38 (m, 1H), δ 7.53 (m, 2H), δ 7.68 (m, 1H), δ 9.8 (s, 2H), δ 10.94 (s, 1H). Anal. calcd. for $C_{17}H_{16}Cl_2N_2$: C, 63.96; H, 5.05; N, 8.78. Found: C, 63.78; H, 5.02; N, 8.60.

Compound **3c**: Light yellow solid, mp 236–238°C. ^{1}H NMR (500 MHz, DMSO-d_6): 3.07 (m, 1H), δ 3.3.15 (m, 1H), δ 3.47 (m, 2H), δ 6.18 (s, 1H),

δ 7.08 (m, 2H), δ 7.30 (d, 1H), δ 7.56 (d, 1H), δ 7.82 (m, 2H), δ 8.35 (d, 2H), δ 10.0 (s, 2H), δ 10.92 (s, 1H). Anal. calcd. for $C_{17}H_{16}ClN_3O_2$: C, 61.92; H, 4.89; N, 12.74. Found: C, 61.57; H, 5.10; N, 12.45.

Compound **3e**: White solid, mp 263–264°C. ^{1}H NMR (500 MHz, DMSO-d_6): 3.06 (m, 2H), δ 3.23 (m, 1H), δ 3.44 (m, 1H), δ 3.93 (s, 3H), δ 6.04 (s, 1H), δ 6.87 (m, 1H), δ 6.96 (m, 1H), δ 7.05 (m, 1H), δ 7.12 (m, 1H), δ 7.21 (d, 1H), δ 7.30 (d, 1H), δ 7.47 (m, 1H), δ 7.53 (d, 1H), δ 9.50 (s, 2H), δ 10.91 (s, 1H). Anal. calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.68; H, 6.19; N, 8.55.

Compound **3j**: White solid, mp 242–246°C. ^{1}H NMR (500 MHz, DMSO-d_6): 2.35 (s, 3H), 3.16 (m, 2H), δ 3.58 (m, 2H), δ 6.14 (s, 1H), δ 6.87 (m, 1H), δ 6.98 (m, 1H), δ 7.10 (m, 2H), δ 7.18 (m, 1H), δ 7.35 (m, 2H), δ 7.40 (m, 1H), δ 9.30 (s, 2H), δ 10.10 (s, 1H). Anal. calcd. for $C_{18}H_{19}ClN_2$: C, 72.35; H, 6.41; N, 9.37. Found: C, 72.24; H, 6.28; N, 9.50.

Compound **3m**: White solid, mp 238–240°C. ^{1}H NMR (500 MHz, DMSO-d_6): 2.36 (m, 6H), 3.16 (m, 2H), δ 3.55 (m, 2H), δ 6.14 (s, 1H), δ 6.85 (m, 2H), δ 6.97 (m, 1H), δ 7.03 (m, 2H), δ 7.09 (m, 1H), δ 7.23 (m, 1H), δ 9.15 (s, 2H), δ 10.21 (s, 1H). Anal. calcd. for $C_{19}H_{21}ClN_2$: C, 72.95; H, 6.77; N, 8.95. Found: C, 72.83; H, 6.69; N, 9.02.

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