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COMMUNICATION

Racemic and diastereoselective construction of indole alkaloids under solvent- and catalyst-free microwave-assisted Pictet–Spengler condensation†

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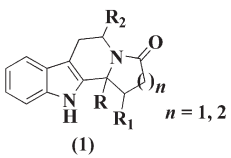
An environment-friendly high-yielding method for the racemic and asymmetric diastereoselective preparation of indole alkaloids *via* Pictet–Spengler reaction is reported. The reaction proceeds with short reaction times under solvent-free and microwave-irradiation conditions.

The synthesis of indole alkaloid (**1**) moieties has received particular attention in the field of medicinal chemistry due to their interesting biological activity.[1] This family of compounds is used as intermediates toward the preparation of diuretic compounds, and are also known to exhibit analgesic and anti-inflammatory activities[2] (Fig. 1).

Several methods have been developed for the synthesis of these indole alkaloids in which the Pictet–Spengler condensation represents a key step.[3] Furthermore, several strategies have been applied to the synthesis of indole alkaloids in enantiomerically pure form. One approach is to start with an enantiomerically pure, chiral tryptamine, such as a tryptophanol derivative.[3b,c] More recently, several groups reported the asymmetric synthesis of these indole alkaloids using a chiral ligand.[4] Though broadly useful, the reactions are usually carried out in the presence of solvent and an excess of a Brønsted acid[5] or catalytic amounts of Lewis acids.[6] In addition, these can be lengthy reactions, requiring days under reflux conditions, and result in low yields and moderate diastereoselectivity, except for a few examples.[7]

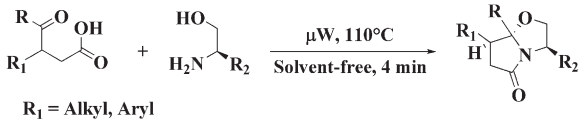
In recent years, several groups have shown the efficiency of the microwave-assisted Pictet–Spengler condensation for the preparation of heterocyclic compounds, requiring shorter reaction times and affording good product yields.[8] However, in most cases, the reactions were carried out in the presence of solvent and an excess of acids. Circumventing the use of organic solvents and catalysts represents an important factor of green chemistry because of the associated economical and environmental concerns. Therefore, the development of solvent- and catalyst-free conditions is of fundamental importance. Recently, Liu and You have reported the microwave-assisted one-pot preparation of tetrahydro-β-carboline hydrochlorides under solvent- and catalyst-free conditions in short times and good yields.[9] In our laboratory, we have studied microwave-assisted organic reactions and we are particularly interested in developing reactions under solvent- and catalyst-free conditions.[10] Towards this end, we have reported a solvent-free microwave-assisted Meyers' lactamization (that required short reaction times and afforded the products in good yields) by using enantiopure amino-alcohols and γ-ketocarboxylic acids[10a] (Scheme 1).



(1)

Fig. 1 Structure of indole alkaloids.

In the pursuit of this work, we herein describe the first solvent- and catalyst-free racemic and asymmetric diastereoselective preparation of indole alkaloids (**1**). The Pictet–Spengler reaction was carried out under microwave irradiation conditions by the reaction of tryptamine or tryptophanol derivatives with ketocarboxylic acids. In our earlier investigation of this reaction, we used a conventional Pictet–Spengler synthetic protocol by conventional heating of tryptamine (**3**) and the 2-oxocyclopentaneacetic acid (**4**) under Dean–Stark conditions in toluene for 48 hours. We found that only the amide product was obtained quantitatively. However, under microwave conditions (110 °C, 100 W), 5% of (**5**) was detected by LC/MS after 2 minutes. Without solvent under the same conditions (110 °C, 100 W), 16% of (**5**) was detected after 2 minutes. We thus turned our attention to explore the irradiation parameters to optimize the conversion reaction. The results are summarized in Fig. 2. At 110 °C for 100 W power, the conversion increases slowly during 2–8 minutes. A marked increase in the rate of conversion was



R_1 = Alkyl, Aryl
R_2 = H, Alkyl
R =Alkyl, Aryl

85-96% yield

Scheme 1

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†Electronic supplementary information (ESI) available. CCDC 856036 and 749287. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2gc16596a

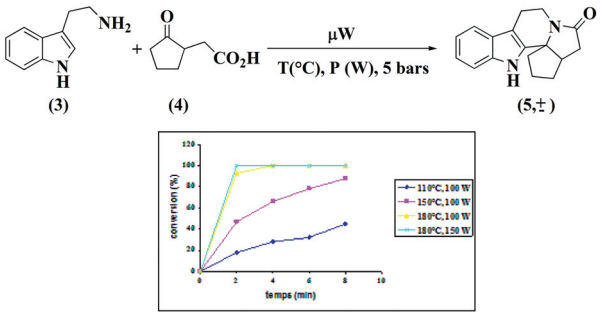
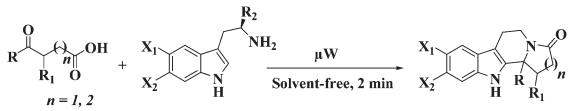
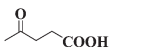
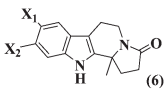
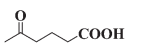
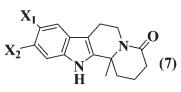
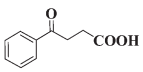
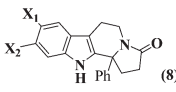
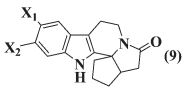
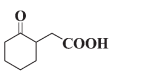
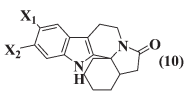
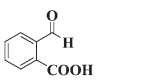
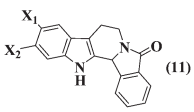
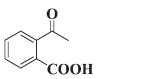
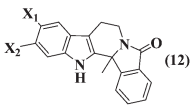


Fig. 2 Exploration of the irradiation parameters to optimize the conversion reaction.

Table 1 Indolizinoindole product results from tryptamine (R_2 = H)



Entry	Oxo carboxylic acid	Indole alkaloids	Yield (%)[a,b]
1		 (6)	X_1, X_2 = H (91) (**6a**) X_1 = Cl, X_2 = H (95) (**6b**) X_1 = H, X_2 = Cl (93) (**6c**) X_1 = Me, X_2 = H (93) (**6d**) X_1 = OMe, X_2 = H (94) (**6e**) X_1 = H, X_2 = F (93) (**6f**)
2		 (7)	X_1 = X_2 = H (92)
3		 (8)	X_1 = X_2 = H (90)
4		 (9)	X_1 = X_2 = H (98)
5		 (10)	X_1 = X_2 = H (95)
6[c]		 (11)	X_1 = X_2 = H (95)
7[c]		 (12)	X_1 = X_2 = H (97)

[a] Isolated yields. Purity was determined by LC/MS analysis. [b] Purification by simple extraction. [c] Purification by simple precipitation in MeOH.

observed at 150 °C under same power and reaction times. An excellent conversion was obtained at 180 °C for 2 minutes, and after only 4 minutes the reaction was complete, affording a 90% isolated yield of (**5**). Raising the power from 100 to 150 W at the same temperature afforded total conversion just after 2 minutes, with a 98% isolated yield of (**5**). It should be noted that only one diastereoisomer was observed by ^{1}H NMR.

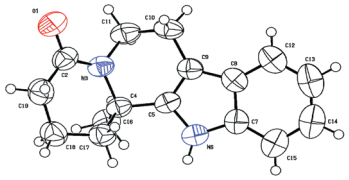
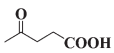
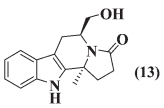
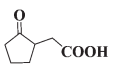
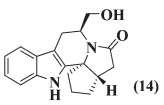
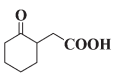
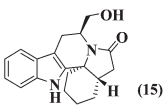
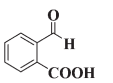
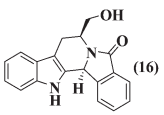
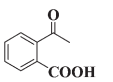
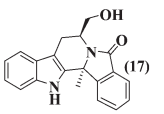


Fig. 3 ORTEP plot of X-ray crystal structure of (**7**).

Table 2 Asymmetric indole alkaloids product results from (L)-tryptophanol (R_2 = –CH_2–OH)

Entry	Oxocarboxylic acids	Indole alkaloids	Yield (%)[a]	d.e. (%)[b]
1		 (13)	92	>99
2		 (14)	95	>99
3[c]		 (15)	95	>99
4		 (16)	96	>99
5		 (17)	94	>99

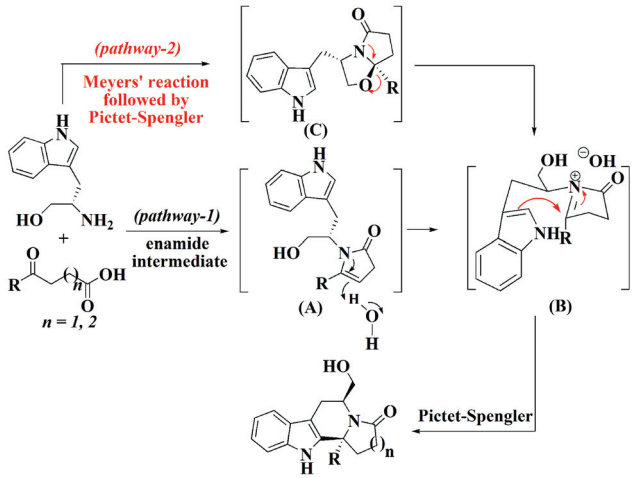
[a] Isolated yields. Purity was determined by LC/MS analysis. [b] Diastereoisomeric excess determined by ^{1}H NMR. [c] (**18**, 93%) was isolated from D-tryptophanol.

After establishing the optimal conditions with 2-oxocyclopentaneacetic acid (**5**), the substrate scope was examined. Results are summarized in Table 1. Excellent yields were achieved for alkyl and aryl ketone substrates (entries 1–3). In the case of cyclic ketones, the desired products were obtained with excellent yields (entries 4–5) and only one diastereoisomer was observed in racemic form. Similar results were observed with 2-formyl or 2-acetyl benzoic acid (entries 6–7). The general structures of indole alkaloid products were proved by X-ray crystallographic analysis of (**7**) (Fig. 3).

We next turned our attention to achieve the asymmetric synthesis of the indole alkaloids (**1**). Thus, we started the reaction with enantiopure (L)-tryptophanol under the same conditions optimized above. Results are summarized in Table 2.

The desired products (**13–17**) were obtained with excellent yields (entries 1–5) and the *trans*-diastereoisomer of indole alkaloids products (relative configuration) were confirmed by X-ray crystallographic analysis of (**14**).[10a]

Two pathways could be considered to explain the formation of indole alkaloids (**13–17**): **1**. At 180 °C for 2 minutes, the condensation of (L)-tryptophanol and ketocarboxylic acid generates the enamide intermediate (**A**). This latter react rapidly with H_2O



Scheme 2

generated *in situ* to afford the *N*-acyliminium ion intermediate (**B**) which then affords the final products *via* a stereoselective Pictet–Spengler reaction by attack of the aromatic ring onto the *Re* face of the *N*-acyliminium ion (pathway 1).[3d,4b] **2**. At 180 °C for 2 minutes, the condensation of L-tryptophanol and ketocarboxylic acid generates the bicyclic lactam intermediate (**C**) *via* a stereoselective Meyers' reaction. This bicyclic lactam could be converted, under microwave conditions, into intermediate (**B**), which then affords the final products *via* a stereoselective Pictet–Spengler reaction (pathway 2)[3b,11] (Scheme 2). It should be noted that, to date, the intermediates (**A**) and (**B**) have not been observed by us. However, under microwave conditions we were able to isolate the intermediate (**C**) in some cases by performing the reaction at 110 °C for 10 minutes. This result may support the second hypothesis.

In summary, we have described an environment-friendly efficient method for the racemic and asymmetric diastereoselective preparation of indole alkaloids using a microwave-assisted Pictet–Spengler reaction of tryptamine or tryptophanol derivatives with ketocarboxylic acids under solvent- and catalyst-free conditions. Desired products were obtained in short reaction times and were isolated with high yields after simple extraction or by precipitation in methanol.

Acknowledgements

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Notes and references

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