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Synthesis of tetrahydro-β-carbolinediketopiperazines in [bdmim][PF_6] ionic liquid accelerated by controlled microwave heating

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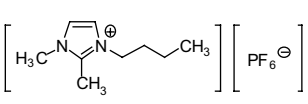
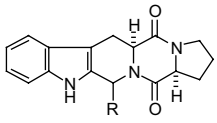
Abstract—Because of their negligible vapor pressures and large dipoles, ionic liquids are excellent media for microwave-accelerated organic reactions. Using low-power microwave irradiation in the new [bdmim][PF_6] ionic liquid with temperature controlled at 60 °C, a three-step synthesis (Pictet–Spengler, Schotten–Baumann, and intramolecular ester amidation) of tetrahydro-β-carboline-diketopiperazines starting from tryptophan methyl ester was achieved with good isolated yields (49–69%) in only 5 min.

We recently reported that the base-mediated Baylis–Hillman reaction proceeds smoothly and effectively in a new [bdmim][PF_6] ionic liquid.[1] The room-temperature ionic liquids are a new class of organic solvents that are entirely constituted of ions.[2] Typically, ionic liquids are miscible with polar organic solvents but immiscible with water and less-polar organic solvents such as aliphatic or aromatic hydrocarbons, and diethylether. Because of this unique solubility property, we rationalize that ionic liquids for use in organic synthesis should offer great potential of the ease of product separation during workup. In addition, since highly polar ionic liquids can interact efficiently with microwaves, rate enhancement in reactions upon microwave irradiation is expected. In literature, microwaves have been known to expedite a large array of synthetic organic reactions in conventional solvents.[3] In our laboratory, we have studied microwave-assisted organic synthesis[4] and are particularly interested in employing microwaves for organic reactions performed in ionic liquids ('microwaves in ionic liquid'),[5] simply for reasons that ionic liquids couple well with microwaves and are rapidly heated without any significant vapor pressure increase in closed or open reaction vessels. This should lead to, at least in principle, safer experimental operations. In this report, we focus our attention on extending the usefulness of 'microwaves in ionic liquid' for a multistep synthesis of differently substituted tetrahydro-β-carbolinediketopiperazines.[6]



[bdmim][PF_6]



Tetrahydro-β-carbolinediketopiperazines

Tetrahydro-β-carbolinediketopiperazines are a part of indole alkaloids.[6,7] This family of natural products has been demonstrated as a new group of the G_2/M-phase inhibitors for the mammalian cell cycle.[7] Among them, demethoxyfumitremorgin C blocks G_2 cell cycle progression with a spectacular MIC value of 0.45 μM.[7] Though total syntheses of several tetrahydro-β-carboline-diketopiperazines of natural forms have been achieved and reported,[6] both the unique structural feature and their important biological activities prompted us to develop *rapid* synthesis of tetrahydro-β-carbolinediketopiperazines using the methodology of 'microwave in ionic liquid', with a long term goal that less toxic and more selective compounds may ultimately be found as potential therapeutic agents for cancer treatment.

Up to now, ionic liquids have not been routinely employed as reaction media for multistep organic synthesis or microwave-accelerated multistep synthesis.[8–10] Only

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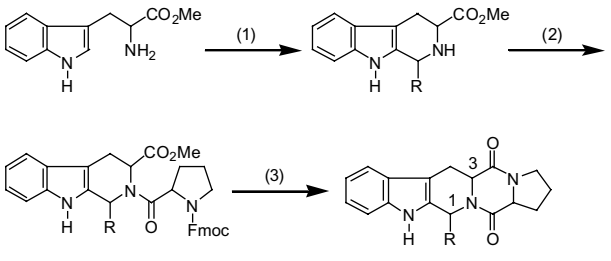
recently, Taddei and co-workers employed conventional heating to facilitate the preparation of a small library of isoxazolines via a three-step synthesis starting from acryloyl chloride in [bmim][BF_4] ionic liquid.[8] Under heated conditions in two steps, their three-step synthesis proceeded, however, with slow reaction rates (30 h in total) and moderate isolated yields (38–50%). Also, Bazureau and co-workers have developed the methodology of ionic liquid-phase organic synthesis and applied the tethered ionic liquids for multistep preparations of both 2-thioxo tetrahydropyrimidin-4-(1*H*)-ones and 4-thiazolidinones by incorporating microwave heating at the final, ring cylization step.[9,10] Scheme 1 outlines our microwave-accelerated total synthesis of tetrahydro-β-carbolinediketopiperazines in [bdmim][PF_6], an ionic liquid that is chemically more stable than the popular [bmim][PF_6].[1] Three reactions are incorporated in the synthetic scheme: the Pictet–Spengler condensation used in step 1,[11] the Schotten–Baumann acylation as the second step, and an intramolecular ester amidation for the last step. In this three-step synthesis, the Schotten–Baumann acylation itself is a fast reaction and, therefore, microwaves were only employed in the first and last steps to establish rapid synthesis of tetrahydro-β-carbolinediketopiperazines (Scheme 1).

As the first step of the synthesis, the Pictet–Spengler reaction of tryptophan methyl ester with aldehydes was utilized to yield the desired tetrahydro-β-carboline adducts.[11] In this reaction, TFA was employed to facilitate the formation of the adducts.[11,12] We[4] and others[13] have previously demonstrated that the Pictet–Spengler reaction carried out in conventional solvents could be accelerated by microwaves. To establish the 'microwaves in ionic liquids' at this step, we investigated the reaction under a number of experimental conditions. We were pleased to find that the Pictet–Spengler reaction worked effectively in the mixed solvent of [bdmim][PF_6] and THF (1:1, v/v) using low-power microwaves (60 W) with the temperature controlled at 60 °C. Simple aliphatic and aromatic aldehydes performed well. Under our optimized microwave condition, it typically required a short reaction time of 25 s to complete the reaction (Table 1). As shown in Table 1, all aldehydes studied give slower reaction rates at ambient temperature and normally complete the Pictet–Spengler reaction in 2–3 h. We noted that, if the same Pictet–Spengler reaction



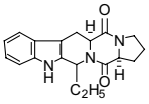
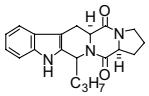
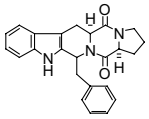
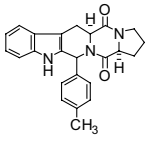
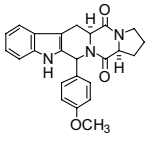
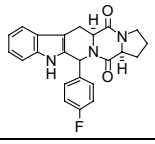
Scheme 1. Synthesis of tetrahydro-β-carbolinediketopiperazines. Reagents and conditions: (1) RCHO (12 equiv), 10% TFA, [bdmim][PF_6]/THF (1:1), microwaves (60 W), 60 °C, 25 s; (2) Cbz-Pro-Cl (5 equiv), DIEA (5 equiv), [bdmim][PF_6]/THF (1:1), rt, 3 min; (3) 20% piperidine, [bdmim][PF_6]/THF (1:1), microwaves (60 W), 60 ° C, 60 s.

was carried out only in conventional solvents such as dichloromethane, it required 7–8 h to complete the reaction at ambient temperature. In addition, reaction times of 8–12 min were needed if the same reactions were microwaved in THF alone. All these results clearly demonstrated that, in the presence of microwaves, ionic liquids as reaction media readily accelerate the Pictet–Spengler reaction. Since we desired access to both *cis*- and *trans*-isomers for further chemical transformations, the Pictet–Spengler reaction used in the first step of the synthesis was carried out under nonspecific conditions and the products were isolated as mixtures of diastereoisomers. The assignment for *cis*/*trans*-tetrahydro-carbolines could be readily made following the ^{13}C NMR method previously established by Cox and Cook;[11] that is to say, the signals for C-1 and C-3 in the *trans*-isomer appeared at higher field in the carbon spectrum than the analogous carbons of the corresponding *cis*-isomer, due to the 1,3-interactions present in the *trans*-isomer. Also, because the Pictet–Spengler reaction is known to proceed efficiently,[11] no attempts were made for products separation and both diastereomers were used directly for the subsequent acylation step.

In the second step, our initial attempts to carry out the amide formation reaction, including the coupling of the tetrahydro-β-carbolines with Fmoc-proline using the standard peptide coupling reagent recipe (HOBT/HBTU), were unsuccessful. This problem of unusual low reactivity of the free secondary amine of tetrahydro-β-carbolines in solution as well as on solid support has been previously encountered by others.[6e,14] Later, we turned our approach to the Schotten–Baumann acylation that used Fmoc-proline acid chloride prepared using Fmoc-proline and thionyl chloride. We were pleased to find that, in the presence of DIEA base, the Pictet–Spengler adducts readily react with Fmoc-Pro-Cl in [bdmim][PF_6]/THF mixed solvent. Since this acylation reaction proceeded smoothly and could be efficiently completed in 3 min at ambient temperature, no attempt was made to further accelerate the reaction by microwaves.

We performed the last, cyclization-upon-deprotection reaction (step 3 in Scheme 1) without the aid of additional bases. Our results indicated that, under the standard Fmoc-deprotection condition (20% piperidine), the desired tetrahydro-β-carbolinediketopiperazines were readily formed as sole products. Again, we were pleased to find that the use of low-power microwaves (60 W) with temperature controlled at 60 °C in [bdmim][PF_6]/THF (1:1) mixed solvent greatly facilitated the formation of diketopiperazine ring and conveniently furnished the total synthesis of tetrahydro-β-carbolinediketopiperazines.[15] Under our optimized experimental condition, this microwaved reaction was complete in 60 s while the same reaction carried out at ambient temperature required 2 h for completion. Our results shown in Table 1 clearly indicate that, regardless of the nature of aldehydes studied, the three-step syntheses of tetrahydro-β-carbolinediketopiperazines were all with higher total isolated yields under microwaves (49–69%) than at ambient temperature (20–41%) in the [bdmim][PF_6]/

Table 1. Synthesis of tetrahydro-β-carbolinediketopiperazines in [bdmim][PF_6] ionic liquid[a]

Entry	Products	Room temperature					Microwaves				
		Reaction time			Yield[b] (%)	Diastereomeric *cis*/*trans* ratio[c]	Reaction time			Yield[b] (%)	Diastereomeric *cis*/*trans* ratio[c]
		Step 1 (h)	Step 2 (min)	Step 3 (h)			Step 1 (s)	Step 2 (min)	Step 3 (s)		
1		2	3	2	41	27:73	25	3	60	69	41:59
2		2.5	3	2	30	68:32	25	3	60	56	66:34
3		2.5	3	2	20	9:91	25	3	60	62	10:90
4		2	3	2	35	67:33	25	3	60	55	38:62
5		3	3	2	30	15:85	25	3	60	49	42:58
6		2	3	2	25	59:41	25	3	60	49	65:35

[a] The reaction conditions: (step 1) L-tryptophan methyl ester (40 mg, 0.16 mmol), [bdmim][PF_6]/THF (1:1, 1 mL), rt or microwaves (60 W) at 60 °C; (step 2) Fmoc-L-Pro-Cl (5 equiv), DIEA (5 equiv), [bdmim][PF_6]/THF (1:1, 1 mL), rt, 3 min; (step 3) 20% piperidine, [bdmim][PF_6]/THF (1:1, 1 mL), rt or microwaves (60 W) at 60 °C.

[b] Overall isolated yield.

[c] The stereochemistry of the diastereomers was determined by C-13 NMR and its diastereomeric ratio was measured by C18-HPLC. In a pair of diastereomers, the second number represents the *trans*-isomer in this table.

THF solvent system. Finally, the 'microwaves in ionic liquid' synthesis of tetrahydro-β-carbolinediketopiperazines could be achieved within 5 min.[16]

In summary, we have demonstrated here that microwaves greatly accelerate the rates of reactions performed in ionic liquids. In the three-step synthesis of tetrahydro-β-carbolinediketopiperazines from tryptophan methyl ester, we found that the overall time of our synthesis was significantly reduced from previously reported long reaction times (hours to days)[6] or here 4–4.5 h at ambient temperature down to less than 5 min in a new [bdmim][PF_6] ionic liquid by low-power microwaves (60 W) with temperature controlled at 60 °C. We are exploiting the scope and potential of microwave-accelerated multistep organic synthesis of other heterocycles of biological significance in ionic liquids.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.056.

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15. General procedure for the microwave-accelerated synthesis of tetrahydro-β-carbolinediketopiperazines. In a typical reaction, (*S*)-tryptophan methyl ester (40 mg, 0.16 mmol) was dissolved in [bdmim][PF_6]/THF (1:1, v/v; 1 mL) containing trifluoroacetic acid (10%, v/v). The aldehyde (1.89 mmol) was added in one portion and allowed to react at 60 °C under microwave irradiation (60 W, Synthewave 402, Prolabo, France) condition in an open reaction vessel. The reaction was allowed to proceed until tryptophan methyl ester was completely consumed as monitored by TLC using the ninhydrin test (typically 25 s). Upon completion of the reaction, the reaction mixture was concentrated to dryness under reduced pressure to obtain the Pictet–Spengler adduct as a dissolved residue in ionic liquid. At the end of the first step, no attempts for product isolation and purification were made.
The Pictet–Spengler reaction product, tetrahydro-β-carboline methyl ester, was then mixed with DIEA (5 equiv) in [bdmim][PF_6]/THF (1:1, v/v; 1 mL). To the reaction solution, the Fmoc-protected (*S*)-proline acid chloride (5 equiv) prepared from Fmoc-proline and excess thionyl chloride in dichloromethane (1 mL) was added to proceed the acylation reaction for 3 min at ambient temperature. After the acylation reaction, the solution mixture was washed with 5% citric acid solution (3×) and dried over anhydrous Na_2SO_4. The resulting organic layer was evaporated in vacuo to yield a viscous oil.
The oil was dissolved in [bdmim][PF_6]/THF (1:1, v/v; 1 mL) containing 20% (v/v) piperidine to carry out the final cyclization-upon-deprotection reaction at 60 °C under microwave irradiation (60 W) condition, again, in an open reaction vessel. The reaction was allowed to proceed until the protected dipeptide ester was completely consumed and cyclized as monitored by TLC (typically 60 s). Upon completion of the total three-step synthesis, the solution mixture containing the desired tetrahydro-β-carboline-diketopiperazine was concentrated in vacuo and purified by silica gel flash column chromatography (ethyl acetate/hexane = 1:3). The products were afforded as off-white solid.
16. In this work, the desired products were isolated as a mixture of *cis*/*trans*-isomers of tetrahydro-β-carboline-diketopiperazines with various diastereomeric ratios. Because we would like to have the access to both isomers for further biological activity investigation, our synthesis of tetrahydro-β-carbolinediketopiperazines was carried out under nonstereoselective conditions and both diastereomers could be separated and purified chromatographically (ethyl acetate in hexane, from 40% to 60%). Although previous studies on the Pictet–Spengler reactions (the first step of this three-step synthesis) have documented that several factors including reaction temperature and the size of substituents at C-1 and N-2 of the tetrahydro-β-carboline can influence the outcome of diastereomeric ratios of the products[11] and, in addition, our preliminary result has showed that no reaction racemization was observed under rapid microwave-accelerated chemical synthesis of tetrahydro-β-carbolines,[4] it appeared that in this work our three-step synthesis of tetrahydro-β-carbolinediketopiperazines from tryptophan methyl ester carried out at ambient temperature and under low-power microwave irradiation gave no apparent similar preference for a particular product isomer.