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A comparative study using conventional methods, ionic liquids, microwave irradiation and combinations thereof for the synthesis of 5-trifluoroacetyl-1,2,3,4-tetrahydropyridines

Valquiria P. Andrade, Mateus Mittersteiner, Márcio M. Lobo, Clarissa P. Frizzo, Hélio G. Bonacorso, Marcos A.P. Martins, Nilo Zanatta *

Núcleo de Química de Heterociclos (NUQUIMHE), Universidade Federal de Santa Maria, Santa Maria, RS 97105-900, Brazil

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ABSTRACT

This study reports a comparison between conventional methods, ionic liquids, microwave (MW) irradiation, and combinations thereof for the synthesis of a series of fourteen 1-aryl-2-arylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines. In all of the reactions tested, the products were obtained at very good yields (87–97%), but the reaction times were very different, depending on the method used. Comparing to other methods, the time decreased to 1 min when [BMIM]BF_4 under MW irradiation was used, thus evidencing a synergic effect.

Introduction

Functionalized piperidines or tetrahydropyridines are crucial building blocks for the synthesis of numerous natural products and other classes of nitrogen heterocyclic compounds.[1] The synthetic procedures reported for the preparation of this class of compounds involve difficult reaction work-up or purification, the usage of toxic organic solvents under high temperatures, long reaction periods, and multi-step reactions.[2–7] Tetrahydropyridines can be prepared from a large range of known reactions, but due to extensive synthetic routes, they usually furnish the products at low yields.[8] On the other hand, 6-ethoxy-3-trifluoroacetyl-4,5-dihydro-6*H*-pyran (**1**), although, little explored for organic synthesis, was demonstrated to be a suitable building block for the construction of libraries of 6-alkoxy-1-alkyl(aryl)-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines and 1-alkyl(aryl)-6-amino-3-trifluoroacetyl-1,4,5,6-tetrahydropyridines,[9,10] and oxa- and aza-condensed tetrahydropyridines.[11] In its turn, tetrahydropyrimidines with structure similar to the target compounds of this study were rarely reported.[12,13]

The biological activity of these six-membered nitrogen heterocycles has been widely reported; for example, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine is a neurotoxin that induces Parkinson's disease.[14–16] Recently, three tetrahydropyridines—NUNL02, NUNL09, and NUNL10 (Fig. 1)—were able to inhibit ethidium bromide efflux in the *Escherichia coli* strains AG100 and $AG100_{TET}$.[17]

In the past few years, ionic liquids (ILs) have become compounds of great interest in the replacement of organic solvents, mainly because of their unique properties—non-flammability, non-volatility, possibility of reuse, high thermal stability, chemical factors such as stabilization of charges formed during the course of the reaction and the promotion of catalysis are some of the advantages that have been widely reported.[18–20] Their use as reaction media has been reported to be an efficient and practical alternative to the use of volatile and toxic organic solvents, and they lead to a reduction in reaction time and higher yields.[21] The combination of ILs with microwave (MW) irradiation is a technique that has been widely explored.[22,23] This combined system is very efficient in the synthesis of different heterocycles—given that ILs are polar and ionic, they promote a more effective interaction with the MW than regular solvents. In our previous studies,[9] we reported the synthesis of a series of 1-aryl-2-arylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines by conventional method, which resulted in long reaction times and difficulties in obtaining products with certain substituents (Scheme 1). In this study we focused on the reactions with arylamines because with other primary amines such as alkyl, benzyl, and phenethyl, for example, reactions are much faster.[10] Additionally, the reaction of enone **1** with some

* Corresponding author.
E-mail address: nilo.zanatta@ufsm.br (N. Zanatta).

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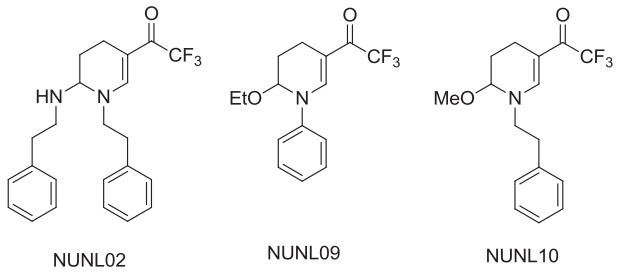
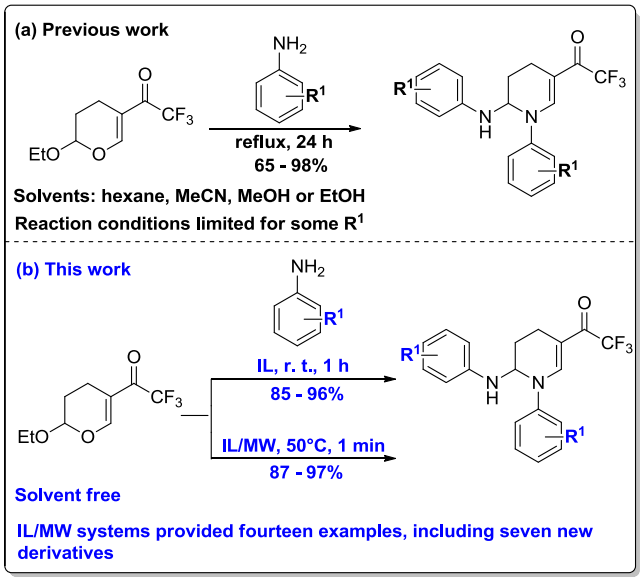


Fig. 1. Tetrahydropyridines which exhibited drug efflux inhibition.



Scheme 1. Synthetic route adopted for the synthesis of 1,2,3,4-tetrahydropyridines.

arylamines could not be obtained by conventional methods and the reason for this remains unclear.

Given the long reaction time and difficulties in obtaining the expected products with some arylamines, when conventional methods were used, we decided to use alternative methods. ILs, microwave irradiation, and combinations thereof were used in order to explore new and more efficient methodologies that would reduce the reaction time, extend the scope of the reaction, and further improve the reaction yields. The strategy was quite successful because it yielded a series of fourteen 1-aryl-2-arylamino-5-trifluoroacetyl-1,2,3,4-tetrahydropyridines: seven of these compounds had already been prepared by the conventional method,[9] and seven were newly synthesized products that could not be obtained by conventional methods.

Results and discussion

The synthetic route adopted for this work is outlined in Scheme 1, part b. The cyclic enone **1** was obtained in accordance with the previously described procedure.[9] The reaction between enone **1** and the different arylamines (**2a–n**) was carried out using a molar ratio of 1:2 (enone:arylamine) at different reaction times and in the presence of the following ILs: 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4), 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM]BF_4), 1-methyl-3-octylimidazolium tetrafluoroborate ([OMIM]BF_4), and 1*H*-3-methylimidazolium *p*-toluenesulfonate ([HMIM]OTs).

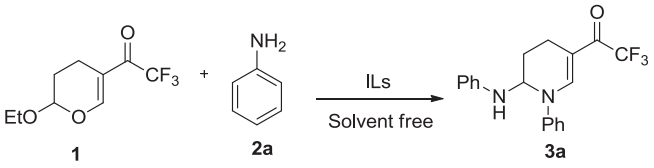
IL mediated synthesis

The optimization of the reaction conditions was carried out using aniline as the arylamine, since there were no influences from any substituent group. The results obtained for these tests are reported in Table 1. All the ILs furnished the product at very good yields and at different optimal times. It is important to highlight that [EMIM]BF_4 and [OMIM]BF_4 furnished more enone than the product in the thin layer chromatography analysis for reaction times less than 3 h. For the control reactions done in the absence of the IL, no formation of the product was detected. Once the best reaction time for each IL was established for the aniline, several arylamines were used for each IL. When the reaction was kept longer than the ideal time, a decrease of yield was observed probably due to decomposition of the product. Table 2 shows the yields for the products **3a–n** and a comparison with the previously reported data.

Table 2 shows the significant changes in the reaction time. Under the best conditions, the time was reduced from 24 h to 1 h when using [HMIM]OTs, and the product was obtained at the same reported yield (entry 7). The isolated yields of the known products suffered no significant changes, although it is important to highlight entries 8, 9, 11, 12, and 14, in which the products could not be obtained using the methodology proposed in Ref. 9. When comparing the ILs, the performance of [HMIM]OTs stands out due to the addition acidity—this IL can be considered to be a Bronsted acid, which increases the electrophilicity of the carbonyl group. This is due to the complexation of IL with the oxygen atom, which results in a more efficient attack of the nucleophile at the β-carbon and, therefore, a shorter reaction time compared to the other ILs.

To verify the efficiency of [HMIM]OTs, an attempt was made to prepare product **3a** using HCl (Bronsted acid) and boron trifluoride (Lewis acid). The reaction was carried out under the same experimental conditions, but the IL was replaced by the aforementioned

Table 1
Optimization of the reactions conditions, using ILs to obtain product **3a**.



Entry	IL[a]	Time (h)	Yield (%)[b]
1	[BMIM]BF_4	1	–
2	[BMIM]BF_4	3	[c]
3	[BMIM]BF_4	5	94
4	[BMIM]BF_4	6	88
5	[BMIM]BF_4	7	85
6	[EMIM]BF_4	3	90[d]
7	[EMIM][BF_4	4	87
8	[EMIM]BF_4	5	72
9	[OMIM]BF_4	3	96[d]
10	[OMIM]BF_4	4	90
11	[OMIM]BF_4	5	84
12	[HMIM]OTs	1	90[e]
13	[HMIM]OTs	2	75
14	[HMIM]OTs	3	50

[a] Reaction conditions: enone **1** (1.0 mmol), aniline (2.0 mmol), ILs (1.0 mmol), r. t.
[b] Isolated yield.
[c] Enone was not completely consumed.
[d] Enone was not completely consumed in 1 or 2 h.
[e] Enone was not completely consumed in 0.5 h.