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One-pot multicomponent synthesis of 1,2,3,4-tetrasubstituted pyrroles catalyzed by [NMPH]CH₃SO₃

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Introduction

Ionic liquid (IL) is a low melting point salt with weakly coordinated ions, being in liquid form at temperatures below 100 °C or even at room temperature, and can be used as solvents and catalysts in organic synthesis [1–3]. These salts offer many advantages, such as thermal stability, non-volatility, and it can be easily designed [4–7]. Protic ionic liquids (PILs) are a subset of ionic liquids and have another advantage: they can be easily prepared through proton transfer from a Brønsted acid to a base [8,9]. In this sense, *N*-methyl-2-pyrrolidonium methyl sulfonate, [NMPH]CH₃-SO₃, a Brønsted acidic ionic liquid, can be obtained by the stoichiometric neutralization reaction between methane sulfonic acid and *N*-methyl-2-pyrrolydone [10]. [NMPH]CH₃SO₃ has been used in several organic reactions, such as esterification processes [11], to convert fructose into 5-hydroxymethylfurfural [12], synthesis of imidazoles [13] and biodiesel [14,15].

Additionally, pyrroles and their derivatives are important compounds, being found in a wide variety of natural products [16]. Functionalized pyrroles are typically obtained by classical routes, such as the Knorr reaction (β -dicarbonyl with α -aminoketone), Paal-Knorr (amines with 1,4-diketone), Clauson-Kaas (2,5dimethoxytetrahydrofuran with primary amines), Hantzsch (β ketoester, α -haloketone and an amine), among others [17,18].

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ABSTRACT

A general method for the synthesis of 1,2,3,4-tetrasubstituted pyrroles by [NMPH]CH₃SO₃ is reported. A full factorial design was performed in order to obtain a more robust and statistically correct optimum condition. The products were obtained in moderate to excellent yields. The developed methodology is very simple, cost-effective, and applicable for tri- and tetra-component reactions.

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These strategies can be achieved with several catalysts, such as $CeCl_3 7H_2O$ [19], $NiCl_2 6H_2O$ [20], $FeCl_3$ [21], KI [22], $Yb(OTf)_3$ [23], ionic liquids [24,25], Cu/C [26], hypervalent iodine [27], I_2 [28,29], phosphazenes [30], Amberlyst-15 [31] or in a metal-free condition [32–36]. Pyrrole derivatives are of great interest in the field of chemical materials, with technological applications [37,38], well as in pharmaceutical applications, such as precursors of bioactive molecules [39,40]. Considering the sustainable chemistry, the study of new environmentally friendly synthetic routes is extremely interesting for modern chemistry. Moreover, the development of atom economy strategies and metal-free conditions are of great industrial and pharmacological interest [41–44].

Our group has been developing studies focused on clean and efficient strategies in organic synthesis for a long time [19,45–48]. Thus, we decided to investigate the synthesis of pyrrole derivatives via tri-component reaction (Scheme 1, path A) and tetra-component reaction (Scheme 1, path B) using [NMPH]CH₃SO₃ as a catalyst, in a metal-free condition.

Results and discussion

The limitations of the tri-component reaction were studied. It was observed that, without the use of the catalyst, using aniline (1.5 mmol), (*E*)-(2-nitrovinyl)benzene (1.0 mmol), pentane-2,4-dione (1.0 mmol), at 75 °C for 2 h, the desired product was not obtained. Thus, the proposition of the [NMPH]CH₃SO₃ catalyst for this reaction is justified. In order to obtain a more robust and

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Scheme 1. Synthesis of pyrroles catalyzed by [NMPH]CH₃SO₃.

statistically correct optimum condition, we decided to perform a full factorial design, whose variables and levels as well as the answers are shown in Table 1.

Further information about the design can be found in the supplementary materials. Fig. 1, named Pareto chart, indicates that all variables and their secondary interactions are significant, except for the ones between temperature and mass of aniline (1×3) , time and mass of aniline (3×4) and catalyst mass and reaction time (2×4) . Information on model validation and how the interpretation of effects should be conducted are contained in the supplementary material. In Fig. 1, it can also be observed that the curvature parameter was also significant. This means that one or more variables may not behave linearly between the chosen lower and upper levels.

These effects are best visualized by the estimates of response surfaces generated by the data (Fig. 2). An optimum temperature range between 75 and 90 °C and a catalyst mass between 30 and 150 mg (Fig 2A) is observed, with a slight tendency towards 30 mg. There is weak evidence of interaction between the mass of catalyst and temperature of reaction in this range. A significant interaction can be attributed when the optimum of a variable is a function of the value of another variable. For instance, at a temperature of 75 °C, the optimum mass of catalyst is 30 mg. Contrarily, at a temperature of 125 °C, the optimum mass of catalyst is 150 mg.



Fig. 1. Pareto chart of standardized effects generated by the data obtained in the full factorial design. Effects surpassing the vertical dashed line are considered statistically larger compared to experimental error at 95% confidence level.

This analysis corroborates the significant 1×2 interaction shown in the Pareto chart. In the interaction between the temperature of reaction and the amount of aniline, an optimum response can be observed when aniline is in the highest evaluated amount, and temperature in the range of 75–90 °C. The reaction behavior with respect to excess aniline was already expected, as reported by Maiti *et al.* [21] There is no evidence of interaction between the variables, confirming the result of the non-significant 1×3 interaction in the Pareto chart. The time of reaction was not significant in the range of 30–90 min at 75–90 °C (Fig 2B).

On the other hand, at higher temperatures, for example 125 °C, even with 90 min, the reaction is not finished. The formation of some intermediate may be disadvantageous at elevated temperatures, or the deprotonation of the catalyst (consequently the

Table 1

Combination of the four relevant factors, their levels and the response obtained for each experiment in the full factorial design carried out in this study.^a

Ph	+	Me Me	+	NH ₂ Ph	[NMPH]CH ₃ SO ₃	Ph Me
1002						Ρh

Entry	Temperature (°C)	Catalyst (mg)	Aniline (mmol)	Time (min)	Yield (%) ^b
1	75	30	1.00	30	86
2	75	150	1.50	30	90
3	75	150	1.50	90	87
4	75	150	1.00	30	24
5	75	30	1.00	90	93
6	75	30	1.50	30	100
7	75	150	1.00	90	31
8	75	30	1.50	90	100
9	100	90	1.25	60	83
10	100	90	1.25	60	85
11	125	30	1.50	30	64
12	125	30	1.50	90	100
13	125	30	1.00	30	52
14	125	30	1.00	90	83
15	125	150	1.00	30	16
16	125	150	1.00	90	55
17	100	90	1.25	60	85
18	125	150	1.50	30	81
19	125	150	1.50	90	100

^a The reactions were performed using aniline (4thcolumn), β-nitrostyrene (1.0 mmol), 1,3-dicarbonyl compounds (1.0 mmol), [NMPH]CH₃SO₃ (3rd column), at temperature (2nd column) and stirred for time (5th column).

^b Conversion by ¹H NMR.

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Fig. 2. Response surfaces generated by the full-factorial experimental design applied in this study to evaluate four variables. Each response surface was plotted with the other two variables in their optimal value: catalyst mass at 30 mg, time of reaction at 30 min, temperature of reaction at 75 °C and 1.5 mmol of aniline. Response surface for aniline versus temperature can be found in supplementary material.

protonation of the aniline) can be favored at high temperatures, which is suggested to be the cause of delay in the reaction progress. Again, it is verified that the optimal value of a variable is a function of the value of another variable, which justifies the significant interaction between temperature and time of reaction (1×4) , as shown in the Pareto chart. In Fig. 2C, it can be verified that the catalyst range of 30-150 mg can be used only when aniline is at its maximum level of 1.5 mmol. When aniline is at its minimum level, a smaller amount of catalyst should be used, but even in that condition the yield is not maximized. This strong interaction is due to the acidic character of the catalyst, which may protonate the aniline and slows the reaction progress. This is the strongest interaction observed in this study (2×3 , see Fig. 1), with an effect that could only be assessed through multivariate design, in which combinations between variables are evaluated simultaneously.

The interaction between the time of reaction and the aniline amount can be observed in Fig. 2D, in which it is verified that the optimum condition occurs in any time interval of 30-90 min, but only when aniline is in its level at 1.5 mmol. When aniline is at the 1 mmol-level, at least 90 min of reaction time is required. It is suggested, therefore, that the aniline should be involved in the slow reaction step, since its quantity influences the time required for the reaction to be completed. Finally, the optimal condition attributed to the reaction is: aniline (1.5 mmol), (*E*)-(2-nitrovinyl)benzene (1.0 mmol), pentane-2,4-dione (1.0 mmol), 30 mg of [NMPH]CH₃SO₃, at 75 °C, under magnetic stirring for 30 min.

Thus, in order to explore the scope and the limitations of this synthetic method, the protocol was extended to other examples (Scheme 2). The corresponding pyrroles were obtained from different β -nitrostyrenes, noting that this protocol tolerates a variety of aromatic nitrostyrenes containing electron-donating and electronwithdrawing substituents. Methyl and chloride groups as substituents provided the corresponding products with good to excellent yields (4b, 4c respectively). However, a lower yield (4d, 44%) was observed in the case of the aliphatic β -nitrostyrene. The use of a β-ketoester as the 1,3-dicarbonyl component further extended the scope of this methodology, and the corresponding product was obtained in good yield (4e, 81%). Different amines were employed as well, and the products were obtained in good yields (4f-k), with exception of 4i from o-Methylaniline, and 4j and 4k from benzylic and aliphatic amine, respectively. Unfortunately, the catalyst cannot be recovered at the end of reactions due to the small amount employed.

Subsequently, we directed our attention to the tetra-component reactions, from aldehydes (Scheme 3). At first, the reaction conditions employed were the same as those of the reactions from β -nitrostyrenes. Then, we performed the tetra-component reaction with benzaldehyde (1.0 mmol), nitromethane (1.0 mL), aniline (1.5 mmol) and acetylacetone (1.0 mmol). After 30 min under stirring at 75 °C the product **4a** was obtained in 87% yield. Encouraged by this result, we decided to use these reaction conditions also for tetra-component reactions. The scope of the tetra-component reaction was expanded using other aldehydes and amines (Scheme 3).

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Scheme 2. Synthesis of 1,2,3,4-tetrasubstituted pyrroles catalyzed by [NMPH]CH₃-SO₃. Conditions: ^a The reactions were performed using aniline (1.5 mmol), β -nitrostyrene (1.0 mmol), 1,3-dicarbonyl compounds (1.0 mmol), 30 mg of [NMPH] CH₃SO₃, at 75 °C and stirred for 30 min. ^b Reaction time: 2 h.

Good to excellent yields were obtained for the products from tetra-component reaction. However, it was observed that the NO₂-deactivated aniline provided lower reaction yield (**4h**, 71%) compared to aniline (**4a**, 87%). However, when the reaction was performed with butylamine, **4k** was obtained in 69%, a better yield compared to the three-component reaction.

Mechanism studies in analogous transformations for the synthesis of pyrrole derivatives have already been widely discussed [21,49]. Under the conditions studied here, the need for a promoter was observed. [NMPH]CH₃SO₃ acts as a facilitator, being able to activate the 1,3-dicarbonyl substrate functionalities, providing imine and β -aminocarbonyl intermediates. The promoter facilitates the Michael addition to nitrostyrene, with subsequent intramolecular cyclization and aromatization (by elimination reaction) leading to the pyrrole.

Conclusion

In conclusion, *N*-methyl-2-pyrrolidonium methyl sulfonate, [NMPH]CH₃SO₃, proved to be an effective catalyst for synthesis of 1,2,3,4-tetrasubstituted pyrroles. Tri and tetra-component reactions provided products in moderate to excellent yields with high atomic economy. The significant advantages offered by this method are simple operation, good cost effectiveness, and applicable for tri and tetra-component reactions.



Scheme 3. Synthesis of 1,2,3,4-tetrasubstituted pyrroles from tetra component reaction. Conditions: ^a The reactions were performed using aldehyde(1.0 mmol), nitromethane (1.0 mL), acetylacetone(1.0 mmol), amine (1.5 mmol), and [NMPH] CH₃SO₃ (30 mg), at 75 °C for 30 min. ^b The reaction was performed using aldehyde (1.3 mmol), nitromethane (1.0 mL), acetylacetone (1.0 mmol), butylamine (1.0 mmol), and [NMPH]CH₃SO₃ (30 mg), at 75 °C for 30 min.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151043.

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