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CARBON DIOXIDE-MEDIATED SYNTHESIS OF PYRROLES IN WATER

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Abstract

A novel carbon dioxide-mediated synthesis of diverse pyrroles using 2,5-dimethoxytetrahydrofuran and primary amines has been achieved in excellent yield. Despite the importance of pyrroles, no study has been performed using carbon dioxide as a reagent to accomplish Paal-Knorr reaction.

Key words

Carbon dioxide, Pyrrole, Dimethoxytetrahydrofuran, Paal-Knorr reaction

Introduction

Many pyrroles and their derivatives are essential components of natural and non-natural molecules. These types of molecules have diverse medicinal activities. Paal Knorr reaction is the most versatile method for the synthesis of pyrroles. This reaction requires primary amine, dicarbonyl compound and an acidic catalyst or reagent [1]. Pyrroles are also prepared by other methods [2]. Our research has identified a novel carbon dioxide-mediated reaction of primary amines and 2,5-dimethoxytetrahydrofuran. This method produces pyrroles. The value of this method deserves special and significant attention since carbon dioxide-mediated synthesis of pyrroles has not been reported [3].

Results and Discussions

2,5-Dimethoxytetrahydrofuran is an acid-sensitive labile molecule and it liberates 1,4-butanedialdehyde. Therefore, the idea behind our approach was to generate the necessary reactant 1,4-butanedialdehyde in the reaction media which would react with primary amines following Paal-Knorr protocol. Considering the mild acidity of carbon dioxide, we envision that it may serve as an effective promoter for the Paal Knorr reaction. Consequently, carbon dioxide gas was generated by the reaction of sodium bicarbonate and acetic acid and it was then bubbled through a solution of amine and 2,5-dimethoxytetrahydrofuran in water and THF (9:1) at 0 to 5°C for 2h. This reaction gave N-substituted pyrrole as the only product in excellent yield (**Table 1**). Diverse pyrroles were prepared following this method. However, electron withdrawing group at the amine component did not yield pyrrole in good yield.

Table 1: Carbon Dioxide-Mediated Preparation of N-Substituted Pyrroles

Entry	Starting Compounds	Products	Yield(%)
1	2,5-Dimethoxytetrahydrofuran and aniline	N-Phenylpyrrole	90
2	2,5-Dimethoxytetrahydrofuran and 4-methoxyaniline	N-4-Methoxyphenylpyrrole	90
3	2,5-Dimethoxytetrahydrofuran and 4-methylaniline	N-4-Methylphenylpyrrole	85
4	2,5-Dimethoxytetrahydrofuran and allylamine	N-Allylpyrrole	88
5	2,5-Dimethoxytetrahydrofuran and benzylamine	N-Benzylpyrrole	92
6	2,5-Dimethoxytetrahydrofuran and 4-methoxybenzylamine	N-4-Methoxybenzylpyrrole	90
7	2,5-Dimethoxytetrahydrofuran and 4-Nitroaniline	N-4-Nitrophenylpyrrole	50

Carbon dioxide is soluble in water and this generates weak carbonic acid in the media. Although carbonic acid is weak in nature, it has sufficient acidity to generate reactive dialdehyde in the media of this reaction. Once formed, the dialdehyde reacts with primary amines through nucleophilic pathways. The whole process finally produces N-substituted pyrroles [1]. Interestingly, the use of organic solvent (methanol, ethanol, THF and dichloromethane) alone was not satisfactory for the preparation of pyrroles following this method. The reaction proceeded well in the presence of water indicating the affinity of carbon dioxide to water. The dissolved carbonic acid is good enough to catalyze the entire process.

Experimental

Carbon dioxide was generated by reacting sodium bicarbonate and acetic acid and bubbled through a reaction mixture containing primary amine (1 mmol), dimethoxytetrahydrofuran (1.1 mmol) in water-THF (2 ml, 9:1) at ice-cold condition. The process of passing the gas was continued for 2h at ice-cold condition. The reaction mixture was then extracted with dichloromethane (2X5 mL), the organic layer was dried over sodium sulfate (2 gm), evaporated and purified through a short column of silica gel. The known products were isolated in good yields. The NMR and IR spectral data of the pyrroles obtained from this study was compared with the known molecules reported earlier [1].

Conclusion

Synthesis of N-substituted pyrrole derivatives were performed through carbon dioxide-mediated novel and new reaction. This method is simple and produces pyrroles under very mild conditions. Being a sensitive molecules, pyrroles should be prepared under very mild condition. This method described herein is one of the mildest, if not the mildest for the preparation of diverse pyrroles. The success of carbon dioxide-mediated reaction will open up the possibility of performing many other reactions in which mild acidic conditions are necessary.

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