



## AMMONIUM CHLORIDE-INDUCED SYNTHESIS OF PYRROLES VIA PAAL-KNORR REACTION

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### Abstract

Reaction of commercially available 2,5-hexanedione and primary amino compounds in the presence of ammonium chloride produced N-substituted pyrroles in excellent yield. In contrast to other available methods, this current procedure for the preparation of pyrroles is exceedingly simple, efficient, and eco-friendly and therefore, may find numerous applications in this field.

**Key words** Ammonium chloride, Pyrrole, Paal-Knorr reaction, Green chemistry

### Introduction

Pyrrole skeletons are present in the structure of porphyrins of heme, the chlorins, vitamin B12, bilirubin, biliverdin, chlorophyll, bacteriochlorins, and porphyrinogens [1]. These are distributed in numerous natural products. Some pyrrole-containing metabolites include pyrroloquinoline (PQQ), makaluvamine M, ryanodine, rhazinilam, lamellarin, prodigiosin, myrmicarin, and sceptrin. Medicines, for example, atorvastatin, ketorolac, and sunitinib have pyrrole systems in their structures. As a result of various uses and important components of biologically active molecules, many scientists prepared pyrroles independently. These methods include: Hantzsch pyrrole synthesis; Knorr pyrrole synthesis; Paal-Knorr pyrrole synthesis; Van Leusen reaction; Barton-Zard synthesis; Piloty-Robinson pyrrole synthesis; Cycloaddition-based routes. These methods are described in several text books. Many other methods for the synthesis of pyrroles are also reported [2].

Reaction of primary amines with dicarbonyl compound for the preparation of pyrroles is known as Paal-Knorr reaction [3]. This reaction is one of the best known procedures for the preparation of pyrroles. However, excess amount of strong acids were used in this method. Because of the high acidity of the reaction media and basicity and sensitivity of pyrroles under acid media, expert scientists can only perform this reaction effectively. To simplify the existing methods, our laboratory developed a few catalytic methods for the synthesis of pyrroles via iodine, bismuth nitrate, polystyrene sulfonate and NBS-catalyzed reactions in very mild acid media [4].

Our continued efforts in this area have identified a highly feasible, economical and eco-friendly ammonium chloride-catalyzed procedure for the preparation of N-1,C-2,C-5-substituted pyrroles starting from aromatic amines and 2,5-hexanedione. This is first report of ammonium chloride-catalyzed organic reactions toward the preparation of pyrroles.

### Results and Discussions

The use of ammonium chloride as an expectorant in cough medicine, in treatment of severe metabolic alkalosis, to diagnose distal renal tubular acidosis, in the treatment of urinary-tract disorders is known. It is also used as food additive in bread industry as a yeast nutrient and improving crispness of snacks and cookies. A dilute aqueous solution of ammonium chloride is slightly acidic in nature. Despite its practical application of ammonium chloride in our daily life, we do not find examples in which this inexpensive edible inorganic solid was utilized as a catalyst for organic reactions.

Paal-Knoor reaction requires acidic catalysts or reagents. In the old days, strong acids were used for the preparation of pyrroles following Paal-Knoor method. During the course of investigation of heterocyclic compounds (pyrroles, indoles, beta lactams, quinazolines, imidazoles, dihydropyrimidines and pyridines), we identified ammonium chloride as a catalyst for the preparation of pyrroles (**Table 1**). Ammonium chloride is a salt of a strong acid and weak base. Therefore, it liberates hydrochloric acid in the reaction media. The mechanism of the reaction is considered an acid-catalyzed nucleophilic addition and subsequent dehydration process.

Table 1: Ammonium chloride-catalyzed synthesis of N-substituted pyrroles

Entry	Starting Compounds	Products	Yield (%)
1	2,5-Hexanedione and aniline	N-Phenyl 2,5-dimethylpyrrole	90
2	2,5-Hexanedione and 4-methoxyaniline	N-4-Methoxyphenyl 2,5-dimethylpyrrole	92
3	2,5-Hexanedione and 4-methylaniline	N-4-Methylphenyl 2,5-dimethylpyrrole	90
4	2,5-Hexanedione and allylamine	N-Allyl 2,5-dimethylpyrrole	88
5	2,5-Hexanedione and benzylamine	N-Benzyl 2,5-dimethylpyrrole	92

### Experimental

The reaction was conducted using diketone (1.1 mmol), amine (1 mmol) and ammonium chloride (200 mg) overnight at room temperature with THF (1 mL) as the solvent. Various amines (aromatic, allylic and benzyl) produced products in extremely high yield. After the reaction was over, the product was isolated through filtration and crystallization (diethyl ether). No chromatographic separation was required. This is the first example in which ammonium chloride was used for the preparation of pyrroles. The compounds described in this paper are compared with our previous compounds prepared using a different method. All physical and spectroscopy data of the compounds prepared by ammonium chloride-catalyzed method were identical with the reported data from our laboratory [4].

### Conclusion

Synthesis of pyrrole derivatives through non-toxic ammonium chloride-catalyzed reaction is new and environmentally benign. The method is very simple, but has significant potential to create pyrroles with complex structures.

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