Dedicated to the memory of Prof. Nuket Ocal who passed away so early

# Solvent Free Synthesis of N-Substituted Pyrrole Derivatives Catalyzed by Silica Sulfuric Acid<sup>1</sup>

## A. J. Khammas<sup>a</sup>, C. Yolacan<sup>a</sup>, and F. Aydogan<sup>a</sup>\*

<sup>a</sup> Department of Chemistry, Yildiz Technical University, Davutpasa Campus, Esenler, Istanbul, 34010 Turkey \*e-mail: feray aydogan@yahoo.com

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**Abstract**—Sulfuric acid immobilized on silica gel is used as an efficient catalyst in the synthesis of *N*-substituted pyrrole derivatives by the Clauson–Kaas pyrrole synthesis. The solvent free reaction mixture is stirred by grinding. Within very short reaction time the process leads to the corresponding products without any decomposition recorded.

Keywords: Clauson-Kaas reaction, grinding method, pyrrole, silica sulfuric acid, solid acid catalyst

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### **INTRODUCTION**

The compounds containing pyrrole ring systems demonstrate a wide range of biological activities including antimicrobial, antiviral, anticancer, antiinflamatory, antimalarial, and many more [1–6]. There are developed several efficient methods of synthesis of pyrrole derivatives including the Clauson–Kaas pyrrole synthesis which is based on 2,5-dimethoxy-tetrahydrofuran (DMTHF) as a four carbon atoms source for *N*-substituted pyrrole derivatives. The high temperature and acidic conditions needed in the process lead to decomposition of the products, leading to low yields and difficulty of products separation. These drawbacks of the classical Clauson–Kaas reaction were surmounted by development of the new synthetic methods [7–12].

The immobilized solid supported catalysts are characterized by distinctive advantages including mild reaction conditions, simple manipulations, improved yields, high purity of products, short reaction time, and recyclability of the catalysts [13–15].

In this study, sulfuric acid immobilized on silica gel was used as an efficient catalyst in the Clauson–Kaas synthesis of *N*-substituted pyrrole derivatives. Silica sulfuric acid (SSA) is an advantageous catalyst over sulfuric acid in many respects. It provides highly

<sup>1</sup> The text was submitted by the authors in English.

efficient and eco-friendly synthetic protocols with minimal environmental impact [16–18]. The presented herein method involved solvent-free simple grinding, gave high yields of products within short reaction time, and met the green chemistry requirements.

### **RESULTS AND DUSCUSSION**

Initially efficiency of SSA in the Clauson–Kaas reaction was studied in the model reaction of DMTHF with benzylamine. Synthesis of 1-benzyl-1*H*-pyrrole

 Table 1. Optimization of the synthesis conditions



| Amine, 2 mmol      | Amount of SSA, mg | Yield, % |
|--------------------|-------------------|----------|
| NH <sub>2</sub>    | 30                | 65       |
|                    | 60                | 66       |
| ~                  | 125               | 74       |
|                    | 250               | 78       |
| NH <sub>2</sub>    | 30                | 45       |
| $\wedge \sim \sim$ | 60                | 56       |
|                    | 125               | 72       |
|                    | 250               | 76       |

**Table 2.** Influence of the catalyst amount

Table 3. Optimization of the reaction with solid 3-aminopyridine

(1) was carried out upon stirring of the starting reagents and SSA (500 mg) at room temperature or under refluxing in ethanol, methanol or diethyl ether. At room temperature, a product formation did not take place within two days of stirring. Refluxing of the reaction mixture induced the product decomposition. Reaction carried out under the action of ultrasound (US) and microwave (MW) irradiation resulted in quick decomposition of the product. MW irradiation supported formation of a product with the yield 60% under solvent free conditions. Grinding the reaction mixture under solvent free conditions led to 80% yield of the product (Table 1). The process was facilitated by addition of silica gel to the reaction mixture. The reaction in the presence of silica gel without sulfuric acid did not proceed, which indicated that it could not take place with the acidic effect of silica gel only.

The most efficient amount of the catalyst was determined (Table 2) for the reaction of liquid amines, benzylamine and 2-aminoheptane.

The optimum conditions were also determined for the reaction of the solid primary amine, 3-aminopyridine (Table 3).

The above studies indicated that the optimum reaction conditions were grinding the reagents with 125 mg of SSA under solvent free conditions.

Reactivity of some other aromatic and aliphatic primary amines, an aminoalcohol and diamine were studied under the optimized conditions (Table 4). The pyrrole derivatives produced in the current study had been synthesized earlier by the different methods [10, 20–25]. The spectroscopic data accumulated for the compounds 1–10 correlated well with their structures and matched the literature data.

| Amine, 2 mmol   | Condition | Amount of<br>SSA, mg | Yield,<br>% | Time,<br>min |
|-----------------|-----------|----------------------|-------------|--------------|
| NH <sub>2</sub> | Grinding  | 30                   | 30          | 10–15        |
|                 | MW        | 30                   | 36          | 5            |
| N N             | Grinding  | 60                   | 65          | 10–15        |
|                 | MW        | 60                   | 60          | 5            |
|                 | Grinding  | 125                  | 87          | 10–15        |
|                 | MW        | 125                  | 80          | 5            |

Reusability of the catalyst was studied with the model reaction under optimized conditions. Upon completion of the process, the reaction mixture was treated with diethyl ether and filtrated. The solid SSA was washed with ethanol and dried at 120°C for 1 h. The recycled SSA was used in the next cycle (Table 5). Some decrease in its activity was determined.

So, silica sulfuric acid has been used as an efficient catalyst in the Clauson–Kaas synthesis of *N*-substituted pyrrole derivatives. The optimized high yield reaction conditions were determined to be simple grinding of the mixture, solvent free and short reaction time. These also meet the most of requirements of green chemistry.

### EXPERIMENTAL

All reagents were of reagent quality, solvents were used without further purification. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer. NMR spectra were measured on a Bruker Avance III 500 MHz NMR spectrometer in CDCl<sub>3</sub> using TMS as an internal standard. Column chromatography was conducted on silica gel 60 (40-63 µM). TLC was carried out on aluminum sheets precoated with silica gel  $60F_{254}$  (Merck). Reactions under MW irradiation were carried out in a household oven, Arçelik-MD 554. Ultrasound assisted reactions were carried out in an ultrasound cleaner BANDELIN SONOREX with frequency of 35 KHz and output power of 350 W. Melting points were recorded on a GALLENKAMP instrument equipped by a digital thermometer in open capillary tubes.

Preparation of the catalyst  $H_2SO_4$ ·SiO<sub>2</sub>. To a slurry of silica gel (10 g) in dry diethyl ether (50 mL),

| $O \rightarrow O + RNH_2 \xrightarrow{SSA (125 mg)}_{Grinding}$<br>Solvent free R |              |                             |           |          |                  |
|---|--------------|-----------------------------|-----------|----------|------------------|
| Amine   | Comp.<br>no. | Compound                    | Time, min | Yield, % | References       |
| NH <sub>2</sub>   | 1            |                             | 5         | 80       | [20]             |
| NH <sub>2</sub>   | 2            |                             | 5         | 64       | [10]             |
| NH <sub>2</sub>   | 3            |                             | 5         | 81       | [21]             |
| NH <sub>2</sub>   | 4            |                             | 5         | 72       | [21]             |
| NH <sub>2</sub>   | 5            |                             | 10–15     | 60       | [19, 22]         |
| NH <sub>2</sub><br>OH   | 6            | <sup>N</sup><br>∧ N<br>∧ OH | 5         | 88       | [10]             |
| NH <sub>2</sub>   | 7            |                             | 5         | 84       | [19, 22]         |
| H <sub>2</sub> N NH <sub>2</sub>  | 8            |                             | 10–15     | 88       | [23]             |
| N NH2   | 9            |                             | 10–15     | 87       | [24]             |
| NH <sub>2</sub>   | 10           |                             | 10–15     | 74       | [19, 20, 22, 25] |

Table 4. Data for the optimized reaction of aromatic and aliphatic primary amines

concentrated  $H_2SO_4$  (3 mL) was added upon shaking for 5 min. The solvent was evaporated under reduced pressure, and the catalyst was dried at 120°C for 3 h [26].

General procedure for SSA catalyzed Clauson-Kaas reaction. To the mixture of SSA catalyst (125 mg) with silica gel (875 mg), 2,5-dimethoxytetrahydrofuran (DMTHF) (2 mmol) and a primary amine (2 mmol) (for compound 10, 5 : 1 mmol) were added. The mixture was grinded in a glass mortar with a pestle for 5-15 min. Progress of the reaction was monitored by TLC. After completion of the reaction,

| Cycle | Yield, % | Time, min |
|-------|----------|-----------|
| 1     | 74       | 5         |
| 2     | 60       | 5         |
| 3     | 52       | 5         |
| 4     | 46       | 5         |

**Table 5.** Recyclability of the catalyst

the mixture was dissolved in diethyl ether, then filtrated. The filtrate solvent was evaporated under vacuum. Thus obtained the corresponding crude product was purified by column chromatography on silica gel with n-hexane and ethyl acetate as eluents.

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### CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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