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A FACILE SYNTHESIS OF 1-ARYL PYRROLES BY CLAUSON-KAAS REACTION USING OXONE AS A CATALYST UNDER MICROWAVE IRRADIATION

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ABSTRACT. A new and efficient methodology to synthesize N-substituted pyrrole derivatives by Clauson Kaas reaction employing Oxone as catalyst was developed. The transformation was performed in acetonitrile under microwave irradiation. This procedure has several advantages such as high yield, clean product formation, and short reaction time.

KEY WORDS: Synthesis, Pyrrole, Oxone, Microwave irradiation

INTRODUCTION

The study of heterocyclic compounds is an evergreen field in organic chemistry. It always attracts the attention of scientists working not only in the area of natural compounds but also in synthetic organic chemistry, specifically with Nitrogen containing heterocyclic structural unit exhibits a wide range of biological activities through effective binding to enzyme receptor site.

As per the present research reports, thousands of new heterocyclic compounds either isolated from natural sources or synthesized in the laboratories are added to the literature every year. Many of these compounds have drawn the attention in various fields like natural product synthesis, functional materials, ligands, biological and pharmacological activities [1-6]. Among nitrogen containing five-member heterocycles, pyrrole is one of the modest class of heterocyclic compounds possessing wide range of biological activities, such as antimicrobial [7-8], antiviral [9], antitumor [10], anti-inflammatory [11] and antioxidant [12]. In addition, there is a growing interest in the synthesis of substituted pyrroles in the area of materials chemistry [13-14].

The Clauson-Kaas reaction between primary amines and 2,5-dimethoxytetrahydrofuran remains as an attractive possibility [15-18], which has received great attention because it allows the synthesis of pyrroles without substituents on the carbon atoms of the heterocycle. Different catalysts and reaction conditions for this reaction have been published during the last decade [19-24].

EXPERIMENTAL

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected. Reaction progress was observed by TLC plates, Bruker 400 MHz instrument was used to record ^{1}H NMR and 100 MHz for ^{13}C NMR spectra in DMSO using TMS as internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra were measured on a GC/MS-QP1000EX (EI, 70 eV) mass spectrometer. Elemental analyses were performed on a PerkinElmer 240 CHN analyser.

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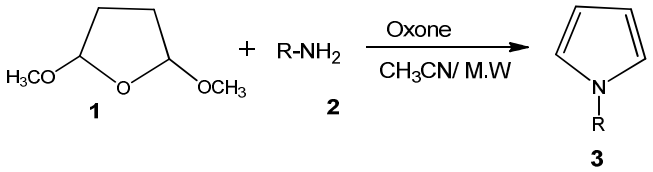
*General procedure for the synthesis of 1-substituted aryl-pyrroles (**3a-h**)*

Oxone (0.09 g, 0.30 mmol) was added to a solution of the aromatic primary amines (2.5 mmol) and 2,5-dimethoxytetrahydrofuron (3.0 mmol) in a solvent (5 mL) was further added (Scheme 1). The reaction mixture was heated under microwave irradiation for 10 min at 110 ± 10 °C. The reaction mixture was irradiated until total consumption of the amine was verified by TLC. Water was added and the products were extracted with EtOAc (3x20 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified on a silica gel column chromatography eluted with mixture of ethyl acetate/hexane (1:4) to afford the product.



Scheme 1

Characteristic data of synthesised compounds

*1-Phenyl-1H-pyrrole (**3a**)*. M.P. 58-60 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 7.38–7.35 (m, 4H), 7.24–7.17 (m, 1H), 7.08 (m, 2H), 6.35–6.33 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 140.7, 129.5, 125.5, 120.4, 119.2, 110.3. MS, *m/z* (%), 143 (M^+). Anal. calcd. for $C_{10}H_9N$; C, 83.88; H, 6.34; N, 9.78. Found: C, 82.50; H, 6.30; N, 9.52.

*1-p-Tolyl-1H-pyrrole (**3b**)*. M.P. 80-82 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 7.27 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.06–7.04 (m, 2H), 6.34–6.32 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 138.4, 135.2, 130.0, 120.4, 119.2, 110.0, 20.8. MS, *m/z* (%), 158 (M^+). Anal. calcd. for $C_{11}H_{11}N$, C, 84.04; H, 7.05; N, 8.91. Found: C, 83.50; H, 6.85; N, 8.25.

*1-(4-Methoxy phenyl)-1H-pyrrole (**3c**)*. M.P. 108–110 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 7.30 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.10–6.99 (m, 2H), 6.33–6.31 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 157.5, 134.4, 122.1, 119.6, 114.6, 109.8, 55.4. MS, *m/z* (%), 173 (M^+). Anal. calcd. for $C_{11}H_{11}NO$, C, 76.28; H, 6.40; N, 8.08. Found: C, 75.85; H, 6.05; N, 7.95.

*(4-Nitrophenyl)-1H-pyrrole (**3d**)*. M.P. 182–183 °C; ^{1}H NMR (DMSO- d_6, 400 MHz, δ in ppm): 8.31 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.18–7.17 (m, 2H), 6.43–6.42 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 144.5, 143.8, 125.4, 119.3, 118.8, 112.2. MS, *m/z* (%), 188 (M^+). Anal. calcd. for $C_{10}H_8N_2O_2$, C, 63.82; H, 4.28; N, 14.89. Found: C, 63.25; H, 4.20; N, 14.35.

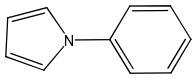
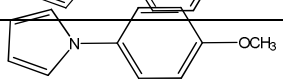
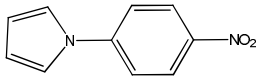
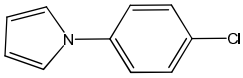
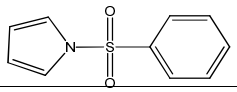
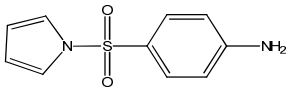
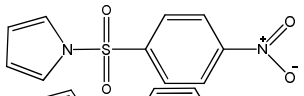
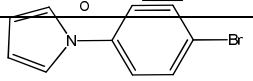
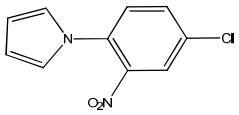
*(4-Chlorophenyl)-1H-pyrrole (**3e**)*. M.P. 86–88 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 7.39 (d, *J* = 9.2 Hz, 2H), 7.31 (d, *J* = 9.2 Hz 2H), 7.04 (m, 2H), 6.35 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 139.2, 130.9, 129.5, 121.5, 119.2, 110.8. MS, *m/z* (%), 179 (M^+). Anal. calcd. for $C_{10}H_8N_2O_2$, C, 67.62; H, 4.54; N, 7.89; Found: C, 61.25; H, 4.30; N, 7.49.

*4-((1H-pyrrol-1-yl) sulfonyl) aniline (**3g**)*. M.P. 247-250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 7.98 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.39 (2H), 6.61 (s, 2H), 6.35 (t, *J* =

2.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 143.9, 141.6, 128.8, 120.2, 119.9, 112.3. MS, *m/z* (%), 222 (M^+). Anal. calcd. for $C_{10}H_{10}N_2O_2S$; C, 54.04; H, 4.54; N, 12.60; Found: C, 53.95; H, 4.30; N, 12.19.

*1-(4-Nitrophenyl sulfonyl)-1H-pyrrole (**3h**)*. M.P. 137-139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ in ppm): 8.34 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.16 (t, *J* = 2.3 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ in ppm): 150.6, 144.4, 128.1, 124.6, 121.0, 114.8. MS *m/z* (%), 252 (M^+). Anal. calcd. for $C_{10}H_8N_2O_4S$; C, 47.61; H, 3.20; N, 11.11; Found: C, 47.05; H, 3.02; N, 10.89.

Table 1. Compounds and yields.

Entry	Compound	Time (min)	Yield (%)
3a		10	80
3b		16	78
3c		18	76
3d		15	75
3e		16	72
3f		19	70
3g		22	68
3h		20	65
3i		18	70
3j		14	65

RESULTS AND DISCUSSION

In the present work, a new methodology for the synthesis of 1-aryl pyrroles **3** has been described by a Clauson-Kaas reaction employing three-component synthesis of pyrrole derivatives by using catalytic amount of Oxone. The catalyst Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is a transition-metal-free, mild and easy to handle, not toxic, cheap and stable commercial product and used various organic transformations [25-28]. In the present study, the catalyst Oxone involving in the efficient synthesis of aryl pyrroles is shown by mechanism in Figure 1. The reaction was performed in acetonitrile at 110 ^oC under microwave irradiation.

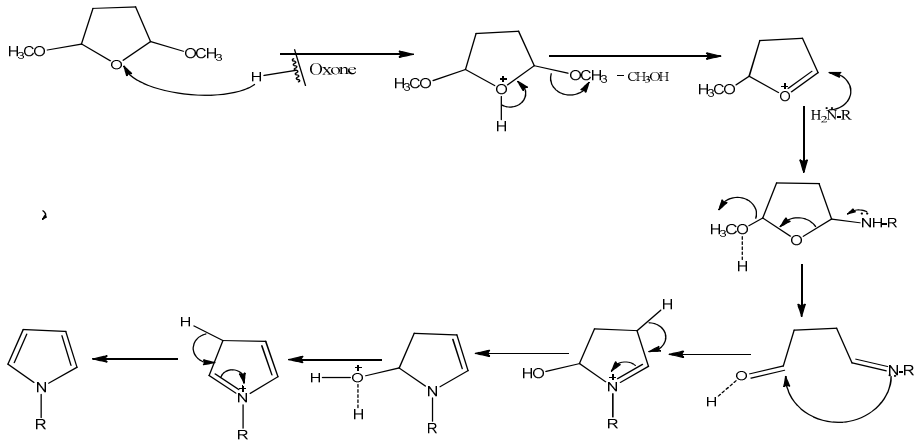


Figure 1. Possible mechanism for Oxone supported synthesis of 1-substituted aryl-pyrroles.

In order to establish the best conditions, the investigation started with the reaction of primary amines (2.5 mmol) and 2,5-dimethoxytetrahydrofuran (3.0 mmol). The influence of various solvents and amount of catalyst were verified. Running the reaction with 0.30 mmol of Oxone in the solvent free conditions gave 60% yield of **3a** after 20 min (Table 1, entry 5). Use of ethanol as solvent improved the yields to 75% (Table 2, entry 1), employing water afforded 55% of **3a** (Table 2, entry 6). Better yields were observed in acetonitrile (80%) which also shortened the reaction time to 10 min (Table 2, entry 2). Therefore, the latter was selected as the solvent of choice. Next, effect of the nature and quantity of catalyst added on the reaction performance were evaluated. The reaction was performed under microwave irradiation, which furnished comparable yields in shorter times (Table 1, entries **3a-j**). These results suggested that the best condition required is use of 0.30 mmol of Oxone in refluxing acetonitrile. In order to find out the scope and limitations of the method, the reaction was extended to other amines employing the optimized conditions (Table 2). The aromatic amines furnished the products in good to excellent yields after 10-22 min of reaction under microwave irradiation.

Table 2. Optimization of reaction conditions.

Entry	Solvent	Oxone®	Time (min)	Yield (%)
1	Ethanol	0.09 g	12	75
2	Acetonitrile	0.09 g	10	80
3	DMF	0.09 g	13	70
4	THF	0.09 g	16	72
5	Solvent free	0.09 g	20	60
6	H_2O	0.09 g	22	55

CONCLUSION

It has been shown that Oxone is a highly convenient catalyst for the Clauson-Kaas reaction of 2,5-dimethoxytetrahydrofuran with aryl amines, cleanly furnishing excellent yields of *N*-aryl pyrroles, under microwave irradiation in short reaction times. In conclusion, a new protocol has been developed for the synthesis of pyrroles using microwave irradiation and Oxone as catalyst. The products were obtained in high yields and with shorter reaction times.

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