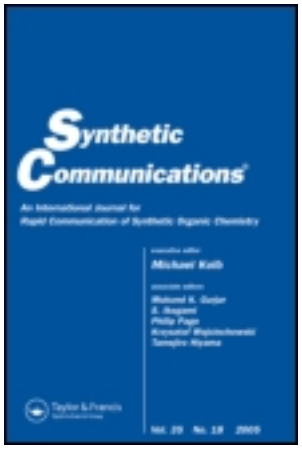

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NOVEL APPROACH FOR THE SYNTHESIS OF *N*-SUBSTITUTED PYRROLES STARTING DIRECTLY FROM NITRO COMPOUNDS IN WATER

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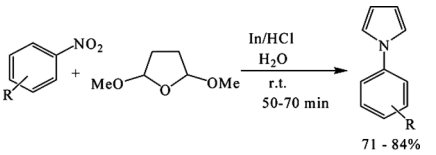
GRAPHICAL ABSTRACT



Abstract *A novel approach for a facile high-yielding synthesis of* N-*substituted pyrroles has been discovered by the treatment of nitroarenes with 2,5-dimethoxytetrahydrofuran using indium in dilute aqueous HCl at room temperature.*

Keywords Aqueous HCl; indium; nitro compound; *N*-substituted pyrroles; Paal–Knorr reaction

INTRODUCTION

Pyrroles represent an important class of heterocycles whose structural motifs are present in various bioactive natural molecules such as chlorophyll and hemoglobin.[1] They are useful precursors in the synthesis of these natural products and related compounds. Bioactive indolizidine alkaloids and different lactam derivatives are also prepared using pyrroles as the intermediates.[2] Pyrrole derivatives exhibit various pharmacological activities including antitumoral, antiviral, and antibacterial properties.[3] Several valuable drugs such as Cloripac (anti-inflammatory agent) and Lipitor (cholesterol-lowering agent) contain pyrrole units.[4] Pyrroles are also applied in materials science.[5] Thus, the synthesis of pyrrole derivatives is an important task in organic chemistry. A most attractive method for the synthesis of these compounds in the Paal–Knorr reaction in which amines are converted into pyrroles.[6] Herein we report a distinct approach for the preparation of *N*-substituted pyrroles starting from nitro compounds.

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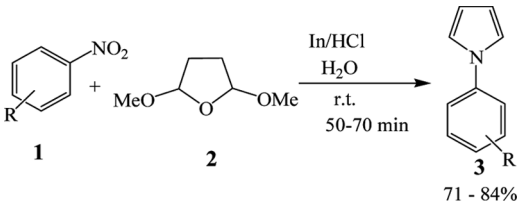


Scheme 1. Synthesis of *N*-substituted pyrroles from nitroarenes.

RESULTS AND DISCUSSION

In continuation of our work[7] on the development of useful synthetic methodologies in aqueous medium, we have discovered that *N*-substituted pyrroles can be synthesized efficiently by the reaction of nitro compounds with 2,5-dimethoxytetrahydrofuran using indium in dilute aqueous HCl at room temperature (Scheme 1).

Initially, the reaction of nitrobenzene and 2,5-dimethoxytetrahydrofuran was carried out using various metals such as Fe, Zn, In, and Sn in aqueous HCl at room temperature (Table 1). Considering the reaction time and yield, In was found to be most effective. Subsequently, an In / aqueous HCl system was used to prepare a series of *N*-substituted pyrroles from different nitro arenes (Table 2). The products were formed within 50–70 min in good yields (71–84%). The nitrobenzenes containing electron-donating as well as electron-withdrawing groups underwent the conversion smoothly. Different functionalities including hydroxyl, ether, and halogen remained unchanged. Even nitrile and acyl groups were not reduced under the present reaction conditions (Table 2, entries j and k). The reaction with a dinitrobenzene afforded only an *N*-substituted pyrrole containing an intact nitro group (Table 2, entries h and n). A sterically hindered nitrocompound such as 1-nitronaphthalene furnished the desired pyrrole in good yield (Table 2, entry r). However, with a nitroalkane, a mixture of products was obtained. The structures of the pyrroles were settled from their spectral [infrared (IR), ^{1}H NMR, ^{13}C NMR and, mass (MS)] and analytical data.

In the present conversion, initially nitro compounds on treatment with In/aqueous HCl reduced to amines,[8] which then react with 2,5-dimethoxytetrahydrofuran to form the corresponding *N*-substituted pyrroles (Scheme 2).[9]

In recent years, organic reactions in water have attracted much attention because of economic and environmental benefits. The present synthesis of pyrroles is an important addition to these reactions.

Table 1. Synthesis of an *N*-phenyl pyrrole using different metals[a]

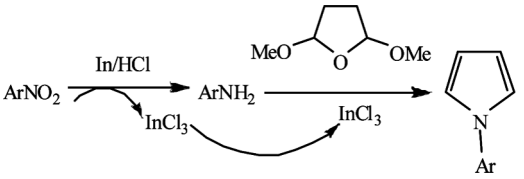
Entry	Metal	Time	Yield (%)[b]
1	Sn	8 h	45
2	Zn	5 h	55
3	In	55 min	79
4	Fe	12 h	20

[a]Reaction conditions: Nitrobenzene (1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol), metal (2.0 mmol), and 1*N* HCl (1 mL) at room temperature.
[b]Isolated yields of pure compound after column chromatography.

Table 2. Synthesis of *N*-substituted pyrroles[a,b]

Entry	Ar	Product	Time (min)	Yield[c] (%)	Ref.
a	C_6H_5	**3a**	55	79	[10a,c]
b	4-MeC_6H_4	**3b**	50	82	[10a]
c	4-$MeOC_6H_4$	**3c**	50	81	[10a,c]
d	4-ClC_6H_4	**3d**	50	80	[10a,c]
e	4-BrC_6H_4	**3e**	65	76	[10a]
f	4-FC_6H_4	**3f**	55	84	[10e]
g	4-HOC_6H_4	**3g**	65	79	[10f]
h	4-$NO_2C_6H_4$	**3h**	65	75	[10a,c]
i	4-$CF_3C_6H_4$	**3i**	60	79	[10c]
j	4-CNC_6H_4	**3j**	65	80	[10f]
k	4-$MeCOC_6H_4$	**3k**	70	73	[10d]
l	3-MeC_6H_4	**3l**	60	78	[10a,d]
m	3-$MeOC_6H_4$	**3m**	65	71	[10a,d]
n	3-$NO_2C_6H_4$	**3n**	65	74	[10a,d]
o	3-ClC_6H_4	**3o**	60	75	[10a,d]
p	2-ClC_6H_4	**3p**	70	78	[10d]
q	2,3-$Cl_2C_6H_3$	**3q**	70	72	
r	$C_{10}H_7$	**3r**	70	77	[10b,c]

[a]Reaction conditions: Nitroarene (1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol), indium metal (2.0 mmol), and 1*N* HCl (1 mL) at room temperature.
[b]All products were fully characterized by the usual spectroscopic techniques.
[c]Yields of pure isolated products after column chromatography.



Scheme 2. Mechanism of the synthesis of *N*-substituted pyrroles.

CONCLUSION

In conclusion, we have developed a novel, efficient method for the synthesis of *N*-substituted pyrroles by the treatment of nitro compounds with 2,5-dimethoxytetrahydrofuran using indium in dilute aqueous HCl at room temperature. The direct application of nitro compounds, conversion in water, mild reaction conditions, and good yields are the notable advantages of the present method.

EXPERIMENTAL

General Procedure for the Synthesis *N*-Substituted Pyrrole

To a mixture of nitro compound (1.0 mmol) and indium (325 mesh, 2.0 mmol), 1*N* aqueous HCl (1 mL) and water (2 mL) were added. The mixture was stirred at room temperature for 10 min, followed by addition of 2,5-dimethoxytetrahydrofuran

(1.2 mmol), and the stirring was continued. The reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was washed with saturated $NaHCO_3$ solution (3×5 mL) and water (3×5 mL) and subsequently extracted with EtOAc (3×5 mL). The extract was concentrated, and the residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure *N*-substituted pyrrole.

The spectral (IR, ^1H and ^{13}C NMR and MS) data of the known compounds (references in Table 2) agreed well with those reported earlier. However, for the compounds whose spectral data are incomplete as well as for the unknown compound (**3q**), the relevant spectral and analytical data are given here.

Selected Data

Compound 3f: 1-(4-Fluorophenyl)-1*H*-pyrrole. IR υ_{max} (KBr): 1617, 1525, 1345, 1254 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.29–7.03 (4H, m), 6.91 (2H, brs), 6.28 (2H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 158.7, 136.1, 122.2, 120.2, 116.4, 110.2; ESIMS m/z 162 $[M+H]^+$. Anal. calcd. for $C_{10}H_8FN$: C, 74.53; H, 4.94; N, 8.70%. Found: C, 74.62; H, 4.88; N, 8.76%.

Compound 3g: 1-(4-Hydroxyphenyl)-1*H*-pyrrole. IR υ_{max} (KBr): 3385, 1638, 1524, 1384, 1254 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.24 (2H, d, $J = 8.0$ Hz), 6.91 (2H, brs), 6.82 (2H, d, $J = 8.0$ Hz), 6.24 (2H, brs), 4.81 (1H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 153.9, 133.0, 122.3, 120.2, 116.4, 110.1; ESIMS m/z 160 $[M+H]^+$. Anal. calcd. for $C_{10}H_8NO$: C, 74.47; H, 5.66; N, 8.81%. Found: C, 75.38; H, 5.62; N, 8.86%.

Compound 3j: 4-(1*H*-Pyrrol-1-yl) benzonitrile. IR υ_{max} (KBr) 2223, 1603, 1515, 1455, 1332 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.70 (2H, d, $J = 8.0$ Hz), 7.46 (2H, d, $J = 8.0$ Hz), 7.09 (2H, brs), 6.36 (2H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 143.8, 133.9, 120.1, 118.9, 118.1, 112.5, 109.0; ESIMS m/z 169 $[M+H]^+$. Anal. calcd. for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67%. Found: C, 78.63; H, 4.82; N, 16.73%.

Compound 3p: 1-(2-Chlorophenyl)-1*H*-pyrrole. IR υ_{max} (KBr) 1608, 1532, 1465, 1343, 1267 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.52-7.19 (4H, m), 6.84 (2H, brs), 6.28 (2H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 136.6, 131.3, 131.0, 128.1, 127.8, 12.0, 109.8; ESIMS m/z 178, 180 $[M+H]^+$. Anal. calcd. for $C_{10}H_8ClN$: C, 67.61; H, 4.51; N, 7.89%. Found: C, 67.69; H, 4.56; N, 7.81%.

Compound 3q: 1-(2,3-Dichlorophenyl)-1*H*-pyrrole. IR υ_{max} (KBr) 1579, 1490, 1425, 1334 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ ppm 7.41 (1H, t, $J = 8.0$ Hz), 7.24–7.11 (2H, m), 6.90 (2H, brs), 6.62 (2H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 140.8, 134.7, 129.2, 127.4, 126.2, 122.1, 110.0, 96.2; ESIMS m/z 212, 214, 216 $[M+H]^+$. Anal. calcd. for $C_{10}H_7Cl_2N$: C, 55.60; H, 3.30; N, 6.60%. Found: C, 56.68; H, 3.25; N, 6.54%.

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