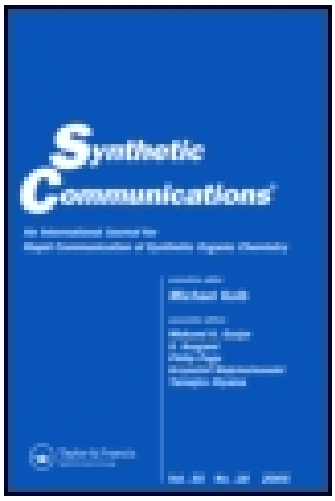

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An Efficient, Three-Component Synthesis of Pyrrole Derivatives Catalyzed by Iodobenzene and Oxone

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AN EFFICIENT, THREE-COMPONENT SYNTHESIS OF PYRROLE DERIVATIVES CATALYZED BY IODOBENZENE AND OXONE

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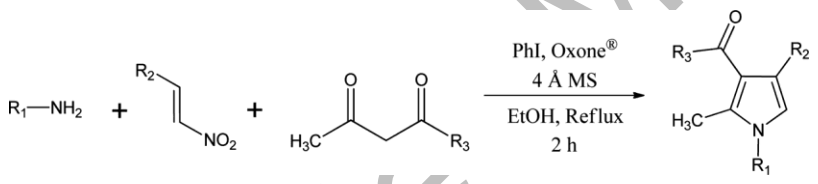
Abstract

A simple and highly efficient three-component method using easily available amines, nitrostyrene and diketones in one pot has been developed for synthesis of pyrroles in presence of catalytic amount of iodobenzene and Oxone® as oxidant. The protocol has been used to afford wide range of pyrroles in moderate to good yields.



KEYWORDS: Three-component; Pyrrole; Iodobenzene; Oxone®

INTRODUCTION

Pyrrole ring is an important structure, as it is found in pharmaceuticals, natural products, polymer sciences, and metal coordinating ligands. In pharmaceutical chemistry, compounds with pyrrole ring system exhibited significant biological activities like antitumor, anti-inflammatory, antibiotic, and hypolipidemic.[1-4] Thus, synthesis of pyrroles is of great importance in organic synthesis. Classical methods available for

pyrrole synthesis are Knorr, Pall-Knorr and Hantzsch approach. New methodologies for pyrrole synthesis include intramolecular cyclization,[5-7] transition-metal catalyzation,[8-11] and multi-component reactions.[12-15]

All these methods are suffering from drawbacks of tedious workups, use of toxic or expensive transition metals, and unavailability of the starting materials. Therefore, simple method to synthesize pyrrole derivatives under mild reaction conditions is still desirable. Previously, we reported three-component synthesis of pyrroles using (diacetoxyiodo)benzene.[16] Our lab is working on development of novel methodologies using iodine reagents. In recent years, many methodologies have been developed to avoid the use of iodoarene in an equimolar amount, by use of terminal oxidants such as *m*-chloroperoxybenzoic acid or Oxone®.[17-20]

Herein, we report three-component synthesis of pyrrole derivatives by using catalytic amount of iodobenzene and Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) as an environmentally safe and cheap terminal oxidant. It has been reported in the literature that when iodobenzene and Oxone® reacted an active iodine species called hydroxy(phenyl)iodonium ion is generated in situ.[21]

RESULTS AND DISCUSSION

Aniline, acetylacetone and nitrostyrene were chosen as the model substrate for optimization of reaction conditions and heated in acetonitrile in presence of 1 equivalent iodobenzene and 1.5 equivalents Oxone®. The desired product 1-(2-methyl-1,4-diphenyl-

1*H*-pyrrol-3-yl)ethanone was obtained with moderate yield at refluxed condition (scheme 1). No product was observed when reaction was carried out at room temperature.

To study the solvent effect, the above reaction was carried out in various solvents such as acetonitrile/water (1:1, v/v), THF, methanol, DMF and ethanol instead of acetonitrile (Table 1). It was found that ethanol is the best suitable solvent for this reaction and gives higher yield as compared to other solvents. Addition of 4 Å molecular sieves in small amount improved yield of a product. From number of experiments we obtained comparative yield with 0.2 equivalent iodobenzene and 1 equivalent Oxone® in presence of 4 Å molecular sieves. With these optimized reaction conditions, different amines, nitrostyrenes and 1,3-dicarbonyl compounds were used to evaluate the scope of the reaction and results are presented in Table 2.

The protocol was applicable to various ranges of amines and it was noteworthy that benzylamines and phenylethylamines reacted more smoothly than anilines to form product in higher yields (Table 2, entries 1-9). Under this reaction conditions methoxy groups are stable (Table 2, entries 10-12). Substitutions on phenyl ring of nitrostyrenes had no effect on reactivity and both electron-donating and electron-withdrawing groups afforded the good yields. Strong electron-withdrawing group like nitro substitution on aniline showed no reaction (Table 2, entry 16).

In summary, we have developed an efficient, catalytic, three-component method for synthesis of pyrrole from easily available chemical moieties like amines, nitrostyrenes

and 1,3-dicarbonyl compounds using iodobenzene and Oxone®. The protocol is versatile and moderate to good yields were obtained from a broad range of amines, nitrostyrenes, and 1,3-dicarbonyl compounds.

EXPERIMENTAL

General Procedure For Synthesis Of 1-(2-Methyl-1,4-Diphenyl-1*H*-Pyrrol-3-Yl)Ethanone (Table 2, Entry 1)

To a previously stirred mixture of iodobenzene (0.041 g, 0.2 mmol) and Oxone® (0.307 g, 1.0 mmol) in ethanol (10 mL) for 15 min at room temperature, aniline (0.093 g, 1 mmol), nitrostyrene (0.164 g, 1.1 mmol), acetylacetone (0.100 g, 1 mmol) and 4 Å molecular sieves (0.100 g) were added. The resultant reaction mixture was stirred at reflux temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated and crude residue was purified by column chromatography to obtain the pure product.

White solid; Mp 104-106 ^{o}C (Lit.[14] 105-107 ^{o}C); IR (neat): 3059, 3029, 1651, 1503, 1402, 1223 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.42 (s, 3H), 6.67 (s, 1H), 7.31-7.43 (m, 7H), 7.45-7.50 (m, 3H).

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SUPPORTING INFORMATION

Experimental method, ^{1}H NMR, ^{13}C NMR, IR and MP/BP for this article can be accessed on the publisher's website.

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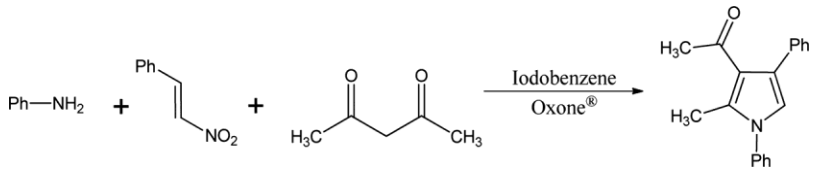
Table 1. Optimization of reaction conditions[a]

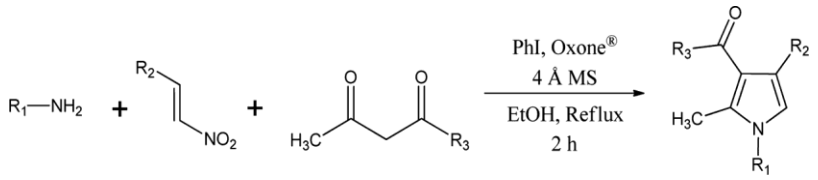


Entry	Iodobenezene (equiv.)	Oxone® (equiv.)	Solvent	Temp/Time (ºC/h)	% Yield[b]
1	1	1.5	Acetonitrile	RT/8	No reaction
2	1	1.5	Acetonitrile	Reflux/5	45
3	1	1.5	acetonitrile/water (1:1, v/v)	Reflux/5	36
4	1	1.5	THF	Reflux/5	43
5	1	1.5	Methanol	Reflux/5	50
6	1	1.5	DMF	100/5	38
7	1	1.5	Ethanol	Reflux/5	70
8	1	1.5	Ethanol	Reflux/2	71
9[c]	1	1.5	Ethanol	Reflux/2	78
10[c]	1	1	Ethanol	Reflux/2	77
11[c]	0.8	1	Ethanol	Reflux/2	78
12[c]	0.6	1	Ethanol	Reflux/2	77
13[c]	0.4	1	Ethanol	Reflux/2	78
14[c]	0.2	1	Ethanol	Reflux/2	78
15[c]	0.1	1	Ethanol	Reflux/5	55

[a]Reaction conditions: aniline (1 mmol), nitrostyrene (1.1 mmol) and acetylacetone (1 mmol).

[b]Isolated yields. [c] 4 Å molecular sieves (0.100 g) added

Table 2. Synthesis of pyrroles using Oxone® and Iodobenzene [a,b]



Entry	R_1	R_2	R_3	% Yield[c]
1	Ph	Ph	CH_3	78
2	Ph	*p*-ClC_6H_4	CH_3	74
3	Ph	Ph	OEt	83
4	Ph	*p*-MeC_6H_4	OEt	78
5	$PhCH_2$	Ph	CH_3	86
6	$PhCH_2$	*p*-FC_6H_4	CH_3	80
7	$PhCH_2$	Ph	OEt	82
8	$PhCH_2CH_2$	Ph	CH_3	89
9	$PhCH_2CH_2$	Ph	OEt	85
10	*p*-$OMeC_6H_4$	Ph	CH_3	80
11	*p*-BrC_6H_4	*p*-$OMeC_6H_4$	CH_3	79
12	*p*-BrC_6H_4	*p*-$OMeC_6H_4$	OEt	75
13	*p*-ClC_6H_4	*p*-ClC_6H_4	CH_3	82
14	*p*-ClC_6H_4	Ph	OEt	80
15	Cyclohexyl	*p*-ClC_6H_4	CH_3	82
16	*p*-$NO_2C_6H_4$	Ph	CH_3	NR

[a]Reaction conditions: amines (1 mmol), nitrostyrenes (1.1 mmol) and 1,3-dicarbonyl compounds (1 mmol) using iodobenzene (0.2 mmol), Oxone® (1 mmol) and 4 Å molecular sieves at reflux temperature in ethanol. [b]All previously reported products were identified by comparison of their NMR spectra and melting points with literature data.

[c]Isolated yields of analytically pure products. NR: No reaction

Scheme 1: Synthesis of pyrrole using iodobenzene and Oxone®