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

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GRAPHICAL ABSTRACT

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 the presence of catalytic amounts of iodobenzene and Oxone as oxidant. The protocol has been used to afford wide range of pyrroles in moderate to good yields.

Keywords Iodobenzene; Oxone; pyrrole; three-component

INTRODUCTION

The 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 the pyrrole ring system exhibited significant biological activities such as antitumor, anti-inflammatory, antibiotic, and hypolipidemic activities.[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 approaches. New methodologies for pyrrole synthesis include intramolecular cyclization,[5–7] transition-metal catalysis,[8–11] and multicomponent reactions.[12–15]

All these methods suffer from drawbacks of tedious workups, use of toxic or expensive transition metals, and unavailability of the starting materials. Therefore,
a 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 laboratory 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 amounts of iodobenzene and Oxone (2KHSO₅·KHSO₄·K₂SO₄) 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 substrates for optimization of reaction conditions and heated in acetonitrile in the presence of 1 equivalent iodobenzene and 1.5 equivalents Oxone. The desired product 1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone was obtained with moderate yield at reflux conditions (Scheme 1). No product was observed when the reaction was carried out at room temperature.

To study the solvent effect, this reaction was carried out in various solvents such as acetonitrile/water (1:1, v/v), tetrahydrofuran (THF), methanol, dimethylformamide (DMF), and ethanol instead of acetonitrile (Table 1). It was found that ethanol is the best suitable solvent for this reaction and it gives greater yield as compared to other solvents. Addition of 4-Å molecular sieves in small amounts improved the yield of the product. From a number of experiments we obtained comparative yield with 0.2 equivalent iodobenzene and 1 equivalent Oxone in the 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 greater yields (Table 2, entries 1–9). Under these 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 good yields. Strong electron-withdrawing groups 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**

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 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. The resultant reaction mixture was stirred at reflux temperature. After the completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and crude residue was purified by column chromatography to obtain the pure product.
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$_6$H$_4$ | CH$_3$ | 74           |
| 3     | Ph    | Ph    | OEt   | 83           |
| 4     | Ph    | $p$-MeC$_6$H$_4$ | OEt   | 78           |
| 5     | PhCH$_3$ | Ph    | CH$_3$ | 86           |
| 6     | PhCH$_2$ | $p$-FC$_6$H$_4$ | CH$_3$ | 80           |
| 7     | PhCH$_2$ | Ph    | OEt   | 82           |
| 8     | PhCH$_2$CH$_3$ | Ph    | CH$_3$ | 89           |
| 9     | PhCH$_2$CH$_3$ | Ph    | OEt   | 85           |
| 10    | $p$-OMeC$_6$H$_4$ | Ph    | CH$_3$ | 80           |
| 11    | $p$-BrC$_6$H$_4$ | $p$-OMeC$_6$H$_4$ | CH$_3$ | 79           |
| 12    | $p$-BrC$_6$H$_4$ | $p$-OMeC$_6$H$_4$ | OEt   | 75           |
| 13    | $p$-ClC$_6$H$_4$ | $p$-ClC$_6$H$_4$ | CH$_3$ | 82           |
| 14    | $p$-ClC$_6$H$_4$ | Ph    | OEt   | 80           |
| 15    | Cyclohexyl | $p$-ClC$_6$H$_4$ | CH$_3$ | 82           |
| 16    | $p$-NO$_2$C$_6$H$_4$ | 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.

White solid; mp 104–106 °C (lit.$^{[14]}$ 105–107 °C); IR (neat): 3059, 3029, 1651, 1503, 1402, 1223 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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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**SUPPLEMENTAL MATERIAL**

Experimental method and $^1$H NMR, $^{13}$C NMR, IR, and mp/bp data for this article can be accessed on the publisher’s website.
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