This article was downloaded by: [University of Otago] On: 21 July 2015, At: 20:16 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: 5 Howick Place, London, SW1P 1WG



# Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

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

Prashant B. Jagadhane<sup>a</sup>, Nikhil C. Jadhav<sup>a</sup>, Omkar P. Herlekar<sup>a</sup> & Vikas N. Telvekar<sup>a</sup> <sup>a</sup> Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai, India Accepted author version posted online: 15 Jul 2015.



To cite this article: Prashant B. Jagadhane, Nikhil C. Jadhav, Omkar P. Herlekar & Vikas N. Telvekar (2015): An Efficient, Three-Component Synthesis of Pyrrole Derivatives Catalyzed by Iodobenzene and Oxone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: <u>10.1080/00397911.2015.1066392</u>

To link to this article: <u>http://dx.doi.org/10.1080/00397911.2015.1066392</u>

Disclaimer: This is a version of an unedited manuscript that has been accepted for publication. As a service to authors and researchers we are providing this version of the accepted manuscript (AM). Copyediting, typesetting, and review of the resulting proof will be undertaken on this manuscript before final publication of the Version of Record (VoR). During production and pre-press, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal relate to this version also.

# PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any

form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <a href="http://www.tandfonline.com/page/terms-and-conditions">http://www.tandfonline.com/page/terms-and-conditions</a>

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

Prashant B. Jagadhane<sup>1</sup>, Nikhil C. Jadhav<sup>1</sup>, Omkar P. Herlekar<sup>1</sup>, Vikas N. Telvekar<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai, India

Address correspondence to Vikas N. Telvekar, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai, India. E-mail: vikastelvekar@rediffmail.com

#### 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<sup>®</sup> as oxidant. The protocol has been used to afford wide range of pyrroles in moderate to good yields.

$$R_{1}-NH_{2} + NO_{2} + H_{3}C - R_{3} + R_{$$

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.<sup>[1-4]</sup> 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,<sup>[5-7]</sup> transition-metal catalyzation,<sup>[8-11]</sup> and multi-component reactions.<sup>[12-15]</sup>

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.<sup>[16]</sup> 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<sup>®</sup>.<sup>[17-20]</sup>

Herein, we report three-component synthesis of pyrrole derivatives by using catalytic amount of iodobenzene and Oxone<sup>®</sup> (2KHSO<sub>5</sub>.KHSO<sub>4</sub>.K<sub>2</sub>SO<sub>4</sub>) as an environmentally safe and cheap terminal oxidant. It has been reported in the literature that when iodobenzene and Oxone<sup>®</sup> reacted an active iodine species called hydroxy(phenyl)iodonium ion is generated in situ.<sup>[21]</sup>

#### **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<sup>®</sup>. The desired product 1-(2-methyl-1,4-diphenyl-

1*H*-pyrrol-3-yl)ethanone was obtained with moderate yield at refluxed condition (scheme1). 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<sup>®</sup> 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<sup>®</sup>. 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-1H-Pyrrol-3-

## Yl)Ethanone (Table 2, Entry 1)

To a previously stirred mixture of iodobenzene (0.041 g, 0.2 mmol) and Oxone<sup>®</sup> (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 °C (Lit.<sup>[14]</sup> 105-107 °C); IR (neat): 3059, 3029, 1651, 1503, 1402, 1223 cm-1; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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).

### FUNDING

PBJ thanks Rajiv Gandhi National Fellowship (RGNF) and VNT thanks the Science and Engineering Research Board (SERB), New Delhi, India, for providing financial support

#### SUPPORTING INFORMATION

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

### REFERENCES

- 1. Bandyopadhyay, D.; Mukherjee, S.; Granados, J. C.; Short, J. D.; Banik, B. K.
- Eur. J. Med. Chem. 2012, 50, 209-215.
- Harrak, Y.; Rosell, G.; Daidone, G.; Plescia, S.; Schillaci, D.; Pujol, M. D.
  *Bioorg. Med. Chem.* 2007, *15*, 4876-4890.
- 3. Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. Org.
- Lett. 2008, 10, 629-631.
- 4. Procopiou, P. A.; Draper, C. D.; Hutson, J. L.; Inglis, G. G.; Ross, B. C.; Watson,
- N. S. J. Med. Chem. 1993, 36, 3658-3662.
- 5. Xin, X.; Wang, D.; Li, X.; Wan, B. Angew. Chem., Int. Ed. 2012, 51, 1693-1697.
- 6. Jiang, Y.; Chan, W. C.; Park. C. J. Am. Chem. Soc. 2012, 134, 4104-1407.
- 7. Egi, M.; Azechi, K.; Akai, S. Org. Lett. 2009, 11, 5002-5005.
- 8. Chiba, S.; Wang, Y.; Lapointe, G.; Narasaka, K. Org. Lett. 2008, 10, 313-316.
- Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. Adv. Synth. Catal. 2009, 351, 129-134.
- 10. Galliford, C. V.; Scheidt, K. A. J. Org. Chem. 2007, 72, 1811-1813.

Abdukader, A.; Xue, Q.; Lin, A.; Zhang, A.; Cheng, Y.; Zhu, C. *Tetrahedron Lett*.
 2013, *54*, 5898-5900.

12. Lin, X.; Mao, Z.; Dai, X.; Lu, P.; Wang, Y. Chem. Commun. 2011, 47, 6620-6622.

13. Goyal, S.; Patel, J. K.; Gangar, M.; Kumar, K.; Nair, V. A. *RSC Adv.* **2015**, *5*,

3187-3195.

14. Maiti, S.; Biswas, S.; Jana, U. J. Org. Chem. 2010, 75, 1674-683.

15. Silveira, C. C.; Mendes, S. R.; Martins, G. M.; Schlösser, S. C.; Kaufman, T. S. *Tetrahedron*, **2013**, *69*, 9076-9085.

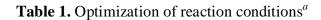
16. Jadhav, N. C.; Jagadhane, P. B.; Patile, H. V.; Telvekar, V. N. *Tetrahedron Lett.*2013, *54*, 3019-3021.

- Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T. Org. Lett. 2013, 15, 1334-1337.
- 18. Kashiwa, M.; Sonoda, M.; Tanimori, S. Eur. J. Org. Chem. 2014, 4720-4723.
- 19. Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.;

Maskaev, A. V.; Zhdankin, V. V. Org. Lett. 2013, 15, 4010-4013.

20. Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. Org. Lett. 2005, 7, 2933-2936.

 Zagulyaeva, A. A.; Banek, C. T.; Yusubov, M. S.; Zhdankin, V. V. Org. Lett. 2010, 12, 4644-4677.



$Ph-NH_2 + H_3C + H_3C$								
Entry	Iodobenezene	Oxone®	Solvent	Temp/Time	% Yield <sup>b</sup>			
	(equiv.)	(equiv.)		(°C/h)				
1	1	1.5	Acetonitrile	RT/8	No			
					reaction			
2	1	1.5	Acetonitrile	Reflux/5	45			
3	1	1.5	acetonitrile/water	Reflux/5	36			
			(1:1, v/v)					
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 <sup><i>c</i></sup>	1	1.5	Ethanol	Reflux/2	78			
10 <sup>c</sup>	1	1	Ethanol	Reflux/2	77			
11 <sup>c</sup>	0.8	1	Ethanol	Reflux/2	78			
12 <sup>c</sup>	0.6	1	Ethanol	Reflux/2	77			
13 <sup>c</sup>	0.4	1	Ethanol	Reflux/2	78			
14 <sup>c</sup>	0.2	1	Ethanol	Reflux/2	78			
15 <sup>c</sup>	0.1	1	Ethanol	Reflux/5	55			

<sup>a</sup>Reaction conditions: aniline (1 mmol), nitrostyrene (1.1 mmol) and acetylacetone (1

mmol).

<sup>b</sup>Isolated yields. <sup>c</sup> 4 Å molecular sieves (0.100 g) added

**Table 2.** Synthesis of pyrroles using  $Oxone^{\mathbb{R}}$  and Iodobenzene a, b

R <sub>1</sub> —NH <sub>2</sub> +	+ 0 0 H <sub>3</sub> C R <sub>3</sub>	PhI, Oxone <sup>®</sup> $R_3$ 4 Å MS EtOH, Reflux $H_3$ C <sup>-</sup> 2 h		
Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	% Yield <sup>c</sup>
1	Ph	Ph	CH <sub>3</sub>	78
2	Ph	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	74
3	Ph	Ph	OEt	83
4	Ph	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	OEt	78
5	PhCH <sub>2</sub>	Ph	CH <sub>3</sub>	86
6	PhCH <sub>2</sub>	p-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	80
7	PhCH <sub>2</sub>	Ph	OEt	82
8	PhCH <sub>2</sub> CH <sub>2</sub>	Ph	CH <sub>3</sub>	89
9	PhCH <sub>2</sub> CH <sub>2</sub>	Ph	OEt	85
10	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	Ph	CH <sub>3</sub>	80
11	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	79
12	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	OEt	75
13	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	82
14	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ph	OEt	80
15	Cyclohexyl	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	82
16	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	CH <sub>3</sub>	NR

<sup>*a*</sup>Reaction conditions: amines (1 mmol), nitrostyrenes (1.1 mmol) and 1,3-dicarbonyl compounds (1 mmol) using iodobenzene (0.2 mmol), Oxone<sup>®</sup> (1 mmol) and 4 Å molecular sieves at reflux temperature in ethanol. <sup>*b*</sup>All previously reported products were identified by comparison of their NMR spectra and melting points with literature data. <sup>*c*</sup>Isolated yields of analytically pure products. NR: No reaction

