



DDQ-mediated oxidative cross-coupling between propargylic sp^3 and indoles sp^2 carbons

G. L. V. Damu^b, J. Jon Paul Selvam^a, C. Venkata Rao^{b,*}, Y. Venkateswarlu^{a,*}

^a Natural Products Laboratory, Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

^b Department of Chemistry, Sri Venkateswara University, Tirupathi 517 507, India

ARTICLE INFO

Article history:

Received 20 July 2009

Revised 19 August 2009

Accepted 22 August 2009

Available online 26 August 2009

Keywords:

Indoles

Propargyl indole

1,3-Diarylpropyne

DDQ

Nitromethane

ABSTRACT

DDQ-catalyzed oxidative cross-coupling reaction between indoles and propargyl compounds is reported for the first time. The reaction involves direct carbon–carbon bond formation between sp^2 carbons of indoles and sp^3 carbons of propargylates to yield the corresponding propargyl indoles in good yields with high selectivity.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Allylation¹ and propargylation² of indoles have attracted much attention in the synthesis of substituted indole alkaloids since facile transformations of the double and triple bonds in the products to the other functional groups, which can provide pharmaceutical intermediates and various important heterocycles. Indole moiety is a most common structural motif found in plenty of natural products and other biologically active compounds with numerous biological activities.³ Consequently, the synthesis and reactions on indole and its derivatives have received great attention in organic synthesis.^{4–6} There are numerous examples cited in the literature for the synthesis of propargylic indoles derived from propargylic alcohols using various Lewis acid and Brønsted acid catalysts.⁷

Recently, Weiliang Bao and co-workers reported a novel oxidative cross-coupling propargylation of 1,3-dicarbonyl compounds using DDQ as the oxidant in nitromethane.⁸ In continuation of our interest for developing various useful synthetic methods for drug-like molecules and pharmaceutical intermediates⁹ we studied the synthesis of propargyl indoles from indoles and 1,3-diarylpropynes in the presence of DDQ.

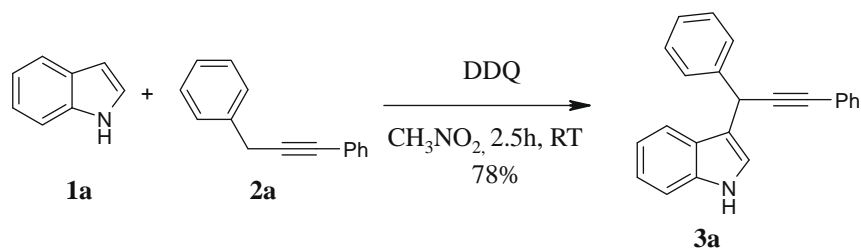
The reaction involves oxidative cross-coupling between indoles and 1,3-diarylpropynes in the presence of DDQ as an oxidant in nitromethane solvent (Scheme 1). To the best of our knowledge,

no report has been cited in the literature on the oxidative cross-coupling of indoles and 1,3-diarylpropynes. To verify the reaction, we initiated our studies with simple indole **1a** and 1,3-diarylpropyne **2a** using DDQ as the oxidant in nitromethane as a solvent medium. The reaction was completed in 2.5 h at room temperature and afforded **3a** in 78% yield with good regioselectivity at position 3 on indole (Scheme 1) and without any side products leaving starting materials. Furthermore, in order to optimize the conditions, the reaction was carried out with various oxidants namely, $Cu(OTf)_2$ and $FeCl_3 \cdot 6H_2O$ as well as in different solvent systems which includes nitromethane, toluene, dichloromethane, dimethylsulfoxide, tetrahydrofuran and *N,N*-dimethylformamide. After several trials, nitromethane has been found to be the most effective solvent for the reaction, in terms of reaction time and yield (Table 1). It has been noticed that DDQ is essential for the reaction to take place. Lewis acids like metal triflates and other inorganic salts are found to be not useful for the reaction.

Having established the reaction conditions, we further explored the generality and efficiency of the DDQ-mediated oxidative cross-coupling reaction between various heterocycles representing the substituted indoles (Table 2), pyrrole (Table 2, entry g), furan (Table 2, entry h), etc., and with various 1,3-diarylpropyne compounds. In general the reaction proceeded smoothly on simple indoles (Table 2, entries a, f, j, and l) and the presence of electron-donating groups on indoles such as Me and Br (Table 2, entries b, d, and m) also afforded the corresponding propargyl indoles with good yields and selectivity in short times. In cases of indoles having electron-withdrawing groups such as COOMe,

* Corresponding authors. Tel.: +91 40 27193167; fax: +91 40 27160512.

E-mail addresses: luchem@iict.res.in, luchem@yahoo.com, padalu@gmail.com (Y. Venkateswarlu).

**Scheme 1.** Reaction of indole and 1,3-diarylpropyne.**Table 1**
Optimization of reaction conditions

Entry	Solvent	Oxidant	Time (h)	Yield (%)
1	Toluene	DDQ	12	10
2	THF	DDQ	12	10
3	DMSO	DDQ	12	17
4	DCM	DDQ	12	35
5	CH ₃ NO ₂	DDQ	2–12	78
6	DMF	DDQ	12	21
7	CH ₃ NO ₂	Cu(OTf) ₂	24	Trace
8	CH ₃ NO ₂	FeCl ₃ ·6H ₂ O	24	No reaction

NO₂ and CN (Table 2: entries c, e, n, o and p), the coupling reaction time has increased and the yield has reduced considerably. The propargylation reaction on carbazole and *N*-methyl indole (Table 2, entries f and q) has proceeded well with good yields. Furthermore, it has been noticed that an electron-withdrawing group in arylpropyne made the coupling reaction sluggish; for example, the reaction of 1-fluoro-4-(3-phenyl-prop-2-ynyl)-benzene with indole was found to be sluggish with low yield (Table 2, entry k). On the other hand an electron-donating group (OMe) in arylpropyne made the coupling reaction very efficient (Table 2, entries j and l). Also, no coupling product is noticed between indoles and

Table 2
Oxidative cross-coupling reaction of propargylic sp³ CH and indole sp² CH bonds

Entry	Substrate 1	Substrate 2	Product ^a 3	Time (h)	Yield ^b (%)
a				2.5	78 ^{7d}
b				4	67 ^{7e}
c				12	34 ^{7e}
d				2	77 ^{7d}
e				12	29 ^{7e}

(continued on next page)

Table 2 (continued)

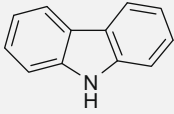
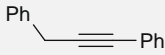
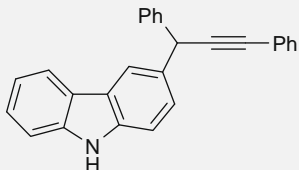

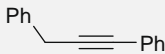
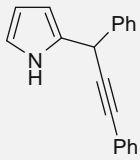


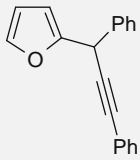
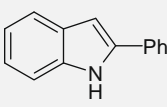
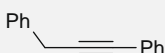
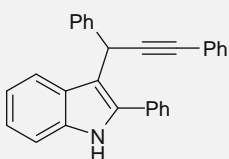
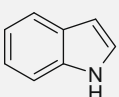
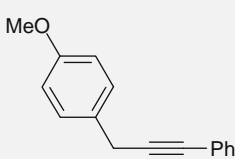
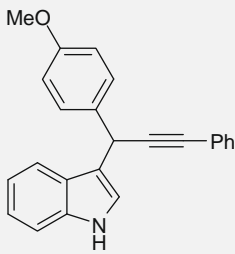
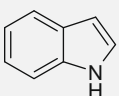
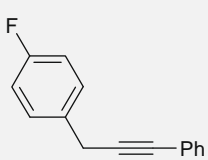
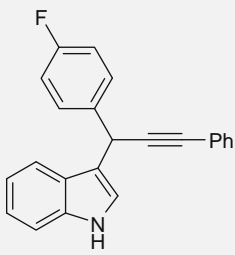
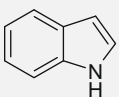
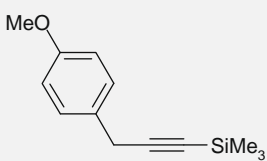
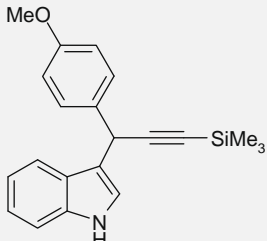
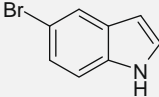
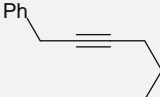
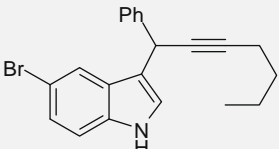
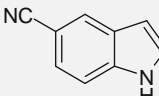
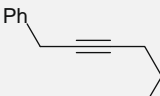
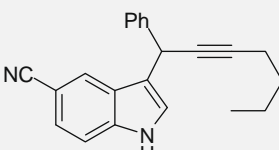
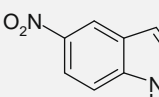
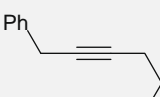
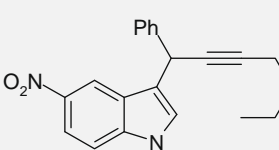
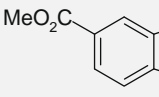
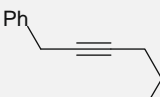
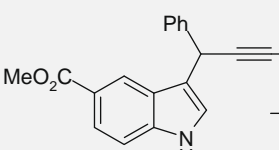
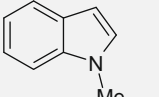
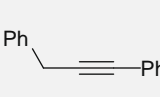
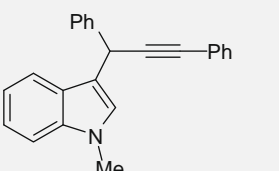
Entry	Substrate 1	Substrate 2	Product ^a 3	Time (h)	Yield ^b (%)
f				3.5	80 ^{7e}
g				2.5	78 ^{7e}
h				3	76 ^{7e,7g}
i				3.5	68 ^{7e}
j				2	84
k				6	33 ^{7c}
l				4	79 ^{7c}

Table 2 (continued)

Entry	Substrate 1	Substrate 2	Product ^a 3	Time (h)	Yield ^b (%)
m				4	72 ^{7g}
n				12	45 ^{7e}
o				12	31 ^{7g}
p				12	35 ^{7e}
q				4	81 ^{7d}

^a Products characterized by ¹H NMR, ¹³C NMR, IR, MASS spectrometry.

^b Isolated yield after silica gel column chromatography.

aliphatic propargylic compounds. All the compounds are characterized by their IR, ¹H NMR and mass spectral data.¹⁰

2. Conclusion

In conclusion, the present method has potential use for direct carbon–carbon bond formation between arylpropargylic compounds and with a variety of heterocycles such as indole, furan, pyrrole and carbazoles with regioselectivity, good yields and in short reaction times. Due to its efficiency, simplicity and mild reaction conditions, this will add as an attractive procedure to the existing armory for the preparation of propargyl indoles.

Acknowledgements

The authors (G.L.V.D. and J.J.P.S.) are thankful to CSIR, New Delhi, India, for award of fellowships and to the Director IICT for his encouragement.

References and notes

- (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315; (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425; (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, *46*, 639–641; (d) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865–9868; (e) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273–6283; (f) Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435–3438; (g) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593.
- (a) Smith, J. J. K.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325–1327; (b) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, *2006*, 881–890.
- (a) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (c) Ninomiya, I. *J. Nat. Prod.* **1992**, *55*, 541–564; (d) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
- (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556; (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173; (c) Jensen, K. B.; Thorhauge, J.; Hazel, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160–163.
- (a) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114; (b) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594–4597.
- (a) Yoshiaki, N.; Masato, Y.; Youichi, I.; Masnobu, H.; Sakae, U. *J. Am. Chem. Soc.* **2002**, *124*, 11846–11847; (b) Wenkert, E.; Angell, E. C.; Ferreira, V. F.; Michelotti, E. L.; Piettre, S. R.; Sheu, J. H.; Sindell, C. S. *J. Org. Chem.* **1986**, *51*, 2343–2351; (c) Prajapati, D.; Gohain, M.; Gogoi, B. *J. Tetrahedron Lett.* **2006**, *47*, 3535–3539.
- (a) Yadav, J. S.; Subba Reddy, B. V.; Pandurangam, T.; Raghavendra Rao, K. V.; Praneeth, K.; Narayana Kumar, G. G. K. S.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2008**, *49*, 4296–4301; (b) Feng, X.; Tan, Z.; Chen, D.; Shen, Y.; Guo, C.-C.; Xiang, J.; Zhu, C. *Tetrahedron Lett.* **2008**, *49*, 4110–4112; (c) Srihari, P.; Dinesh, B. C.; Seedhar, P.; Mandal, S. S.; Shyam Sunder Reddy, J.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8120–8124; (d) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963–3967; (e) Yadav, J. S.; Subba Reddy, B. V.; Raghavendra Rao, K. V.; Narayana Kumar, G. G. K. S. *Synthesis* **2007**, 3205–3210; (f) Zhan, Z.-P.; Cui, Y.-Y.; Liu, H.-J. *Tetrahedron Lett.* **2006**, *47*, 9143–9146.

- (g) Zhan, Z.-P.; Yu, J.-L.; Liu, H.-J.; Cui, Y.-Y.; Yang, R.-F.; Yang, W.-Z.; Li, J.-P. *J. Org. Chem.* **2006**, *71*, 8298–8301; (h) Yadav, J. S.; Subba Reddy, B. V.; Raghavenrda Rao, K. V.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 5573–5576; (i) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160–7163.
8. Cheng, D.; Bao, W. *J. Org. Chem.* **2008**, *73*, 6881–6883.
9. (a) Jon Paul Selvam, J.; Suresh, V.; Rajesh, K.; Chanti Babu, D.; Suryakiran, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2008**, *49*, 3463–3465; (b) Suryakiran, N.; Rajesh, K.; Prabhakar, P.; Jon Paul Selvam, J.; Venkateswarlu, Y. *Catal. Commun.* **2007**, *8*, 1635–1640; (c) Suryakiran, N.; Prabhakar, P.; Srikanth Reddy, T.; Chinni Mahesh, K.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 877–881; (d) Chinni Mahesh, K.; Narasimhulu, M.; Srikanth Reddy, T.; Suryakiran, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 55–59.
10. *General experimental procedure:* To a stirred solution of indole **1a** (0.117 g, 1 mmol) and 1,3-diaryl propyne **2a** (0.211 g, 1.1 mmol) in MeNO₂ (5 mL) was added DDQ (0.248 g, 1.1 mmol). The resulting mixture was stirred at room temperature for 2.5 h. After completion of the reaction as noticed by TLC, water was added and extracted into ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get crude product, which was purified on silica gel column chromatography using hexane and ethyl acetate (8:2) as eluent to give product **3a** (0.239 g, 0.78 mmol) in 78% yield.
- Compound 3j:* 3-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)-1H-indole: Yellow liquid; IR (KBr): ν 3416, 3056, 2923, 2853, 1601, 1503, 1453, 1222, 1156, 1093, 846, 746, 692 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.72 (s, 3H), 5.08 (s, 1H), 6.65–6.79 (m, 4H), 6.89–6.93 (m, 3H), 7.03–7.30 (m, 6H), 7.37 (d, J = 7.5 Hz, 1H), 7.77 (br s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 158.2, 136.4, 133.1, 132.3, 130.0, 128.5, 128.4, 127.4, 122.9, 122.7, 120.2, 118.9, 114.2, 112.1, 111.1, 86.8, 80.9, 55.8, 32.4 ppm. MS (EI, 70 eV): m/z 338 [M+H⁺].