Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

DDQ-mediated oxidative cross-coupling between propargylic sp³ and indoles sp² carbons

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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 sp² carbons of indoles and sp³ carbons of propargylates to yield the corresponding propargyl indoles in good yields with high selectivity.

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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 crosscoupling 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 FeCl₃·6H₂O 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 crosscoupling 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,





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Scheme 1. Reaction of indole and 1,3-diarylpropyne.

Table 1Optimization 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



Table 2 (continued)







^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.

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- 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.

0.78 minlol in 78% yield. *Compound* **3***j*: 3-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)-1*H*-indole: Yellow liquid; IR (KBr): v 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, 166.8, 80.0, 55.9, 23.4 mpm Mc (FL 70.04), m/c 238. IMULT 86.8, 80.9, 55.8, 32.4 ppm. MS (EI, 70 eV): m/z 338 [M+H⁺].

^{8.}