Asian Journal of Chemistry; Vol. 28, No. 7 (2016), 1519-1522

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19743

An Efficient Two-Step Synthesis of 2,5-Disubstituted Oxazole Derivatives Involving Cu-Promoted Carbon-Carbon Single Bond Formation

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Received: 24 November 2015; *Accepted*: 16 February 2016; *Published online*: 31 March 2016; AJC-17841

Environment sensitive fluorescence probe to detect various organelles is emerging as an excellent tool to attract the attention of a large number of researchers around the globe. The recent developments have shown that oxazole dyes are very competent and can exhibit a useful fluorescence property in this direction. An efficient synthetic procedure towards 2,5-diaryl substituted oxazole derivatives have been reported. It is a two-step technique involving classical van Leusen protocol followed by copper-mediated coupling with aryl halides to introduce the required carbon-carbon single bond. The aryl groups are chosen in such a way so that the aryl functionalities at 2- and 5-positions of oxazole can act as acceptor and donor moiety respectively. Thus, in turn, the extended conjugation from donor moiety to acceptor moiety *via* the oxazole ring is set up therein. The oxazole derivatives were characterized by various spectroscopic measurements like NMR, IR and MS.

Keywords: Oxazole, Dye, C-C coupling, Fluorescence, Arylation.

INTRODUCTION

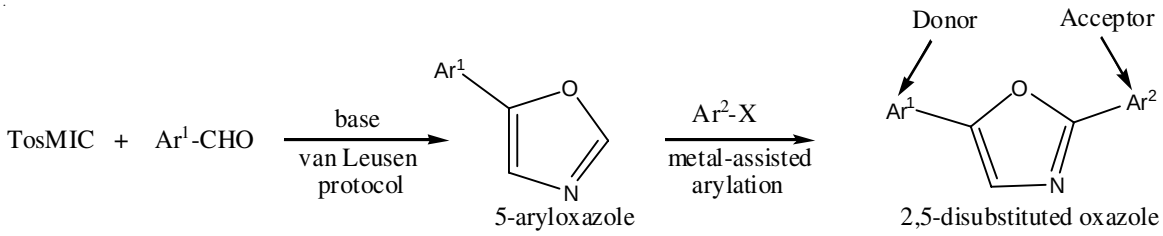
Oxazoles, the five membered heterocyclic ring systems, are known for well over a century. Although, they have been of considerable interests ever since late 1980s, when a large number of oxazole containing cyclic and acyclic bio-active natural products [1,2] have been isolated. These have attracted both the synthetic chemists and biochemists over the world owing to their fascinating structural architecture and immense biological activities ranging from cytotoxicity, antineoplastic activity to antibiotic properties [3,4].

Moreover, since the fluorescence property have demonstrated [5,6] advantages towards the detection of various bio-analytes, oxazole containing dyes [7] have been emerging as promising environment-sensitive fluorescent compounds. This unique property of oxazole based dyes have been utilized for specific detection of different organelles [8]. We also engaged our efforts towards this and recently published a paper on the photophysical study of such a 2,5-disubstituted oxazole dye, namely sodium salt of 5-(4"-dimethylaminophenyl)-2-(4'-sulfophenyl)oxazole (DMO) in micelles [9].

In this paper we wish to report the synthesis of some 2,5-disubstituted oxazoles, which are expected to show promising environment-sensitive or solvent polarity sensitive fluorescence. Mostly, different research groups around the globe have synthesized these 2,5-disubstituted oxazole motifs involving few steps to afford acylamino ketone at first followed by another step of cyclodehydration using relatively harsh reagent [10] sulphuric acid to milder reagents [11]. However, we took a two-step synthetic process [12] involving classical van Leusen protocol at first to get 5-substituted oxazole followed by metal-assisted arylation at C-2 to afford our targeted 2,5-disubstituted oxazole (**Scheme-I**). Strategically, we chose our substrates in such a way that the substituents at C-5 and C-2 of the oxazole motifs can act as donor and acceptor, respectively. Moreover, our literature survey has revealed that synthetically, carboxyl group containing aryl functionality at C-2 position of 2,5-disubstituted oxazole motif is still to be explored. This, in turn, led to our targeted 2,5-disubstituted oxazole having 'Donor-Oxazole-Acceptor' combination, which was expected to show considerable environment-sensitive fluorescent property.

EXPERIMENTAL

Chemicals were mainly purchased from Aldrich Chemical Companies, Spectrochem and Merck. Column chromatography was performed using 60-120 mesh silica gel purchased from spectrochem. Melting point was determined in capillary and uncorrected. NMR data were obtained using Buker DRX-300 spectrometer with TMS as internal standard. IR data were obtained using Perkin-Elmer Spectrum Two spectrometer.



Scheme-I

Synthesis of 5-aryloxazole (2a, 2b): Potassium carbonate (K_2CO_3) (0.28 g, 2 mmol) was added into the solution of TosMIC (0.23g, 1.2 mmol) in dry methanol (10 mL). Aromatic aldehyde (**1**) (1 mmol) was then added and the whole mixture was refluxed for 4 h under inert atmosphere (N_2). The mixture was allowed to come to room temperature and was concentrated *in vacuo* under reduced pressure to make it free from methanol. It was then diluted with dichloromethane (50 mL). The organic mixture was washed with 3 % HCl (20 mL), water (20 mL) and brine (25 mL). Organic layer was dried using anhydrous sodium sulphate and then concentrated *in vacuo* under reduced pressure. This was then purified by column chromatography using petroleum ether-ethyl acetate (4:1) as eluent to get the product as almost colourless solid (**2a**, **2b**). The compound was further confirmed by the spectroscopic data.

Procedure of Cu-promoted direct arylation of 5-aryloxazole to prepare 2,5-diaryl oxazoles (3a, 3b, 3c, 3d): 5-Aryl oxazole **2** (0.69 mmol) and 4-iodobenzene/4-iodobenzoic acid (0.83 mmol) were taken in dry DMF (10 mL). Copper iodide (0.69 mmol) and triphenyl phosphine (0.2 mmol) were then added sequentially. To this mixture sodium carbonate (1.39 mmol) in little excess was added at one portion and the resulting mixture was stirred at 120 °C for 16 h under inert atmosphere (N_2). The whole mixture was concentrated by removing excess DMF using vacuum pump and then it was diluted with dichloromethane (30 mL). The entire organic solution was sequentially washed with water (15 mL × 3), 3 % HCl (15 mL) and half saturated brine solution (20 mL). Finally the organic layer was dried over anhydrous sodium sulphate. It was then concentrated *in vacuo* and was purified by column chromatography using petroleum ether-ethyl acetate (3:1) as eluent to get the product as colourless solid. The formation of the product was further confirmed by spectroscopic data.

5-Phenyl oxazole (2a): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (1H, s), 7.27-7.30 (1H, t), 7.36-7.39 (2H, *J* = 6.4 Hz), 7.60-7.62 (2H, d, *J* = 6. Hz), 7.87 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.4, 127.6, 128.4, 128.7, 128.9, 130.1, 133.5. MS (ESI): *m/z* 146.0832 $(M+H)^+$, 147.1776 (M+2).

5-(4-Methoxy phenyl)oxazole (2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s), 6.95 (2H, d, *J* = 8.8 Hz), 7.22 (1H, s), 7.58 (2H, d, *J* = 8.4 Hz), 7.87 (1H, s). MS (ESI): *m/z* 176.1015 $(M+H)^+$. IR (KBr, ν_{max}, cm^{-1}): 3100, 2967, 2838, 1619, 1490, 1253.

2,5-Diphenyl oxazole (3a): m.p.: 75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (1H, s), 7.34-7.45 (6H, m), 7.63-7.65 (2H, m), 8.02-8.04 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.4, 124.2, 126.3, 127.4, 128, 128.5, 128.8, 128.9, 130.4, 151.2, 161.2. MS (ESI): *m/z* 222.0914 $(M+H)^+$. IR (KBr, ν_{max}, cm^{-1}): 3118, 2923, 1608, 1587, 1481, 1245, 1132.

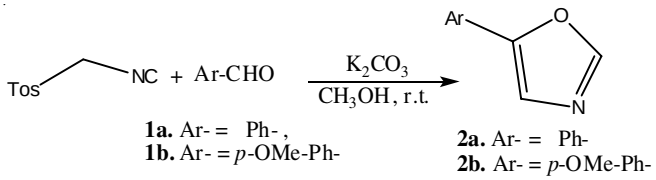
4-(5-Phenyl oxazole-2-yl)benzoic acid (3b): m.p.: 248 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.28 (2H, t), 7.36-7.4 (2H, t), 7.45 (2H, d, *J* = 8 Hz), 7.64 (2H, d, *J* = 8 Hz), 7.69 (1H, d), 7.71 (1H, s0, 12.9 (1H, bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 101.6, 129, 129.7, 130.7, 131.2, 131.5, 133.3, 138, 167.4, 167.8.MS (ESI): *m/z* 266.0811 $(M+H)^+$. IR (KBr, ν_{max}, cm^{-1}): 3085, 2924, 2852, 1679, 1586, 1294.

5-(4-Methoxy phenyl)-2-phenyl oxazole (3c): m.p.: 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (3H, s), 6.88-6.9 (2H, dd, *J* = 1.6, 8.8 Hz), 7.2 (1H, s), 7.36-7.41 (3H, m), 7.56-7.58 (2H, dd, *J* = 2, 8.8 Hz), 8-8.02 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 114.4, 120.8, 121.9, 125.8, 126.1, 127.6, 128.8, 130.1, 151.3, 159.8.MS (ESI): *m/z* 252.1016 $(M+H)^+$, 153.1015 (M+2). IR (KBr, ν_{max}, cm^{-1}): 3054, 2924, 2830, 1613, 1560, 1484, 1298, 1180.

4-(5-(4-Methoxy phenyl)oxazole-2-yl)benzoic acid (3d): m.p.: 264 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (3H, s), 6.93-6.97 (4H, m), 7.57-7.6 (2H, dd, *J* = 1.6, 8.8 Hz), 7.89 (1H, s), 8.04-8.06 (2H, dd, *J* = 1.6, 8.8 Hz), 12.8 (1H, bs). MS (ESI): *m/z* 296.0917 $(M+H)^+$, 297.1013 (M+2). IR (KBr, ν_{max}, cm^{-1}): 2925, 2852, 1931, 1681, 1425, 1272, 1119.

RESULTS AND DISCUSSION

As the first part of our work, we put our efforts to synthesize 5-aryl oxazole. Based on van Leusen protocol [12], the reaction (**Scheme-II**) of commercially available *p*-toluene sulfonylmethyl isocyanide (TosMIC) and suitable aromatic aldehydes (**1**) in presence of potassium carbonate as base led to corresponding 5-phenyloxazole (**2a**) and 5-(4-methoxy phenyl)-oxazole (**2b**).



Scheme-II

Then, we engaged our efforts towards C-2 arylation of formed 5-aryloxazole motifs. Recent advancements in metal-assisted C-H arylation to heteroarenes, using aryl halides, have shown that this can be carried out with palladium catalyzed coupling in presence of copper, silver as promoters [13] or even with copper alone which can selectively arylate oxazole at less electron rich C-2 position [14]. It has been found that an excess amount of aryl halide is required for copper-based coupling which further involves a strong base like *t*-BuOLi or *t*-BuOK too. We rather decided to take less expensive combi-

nation together with milder base like potassium carbonate or sodium carbonate.

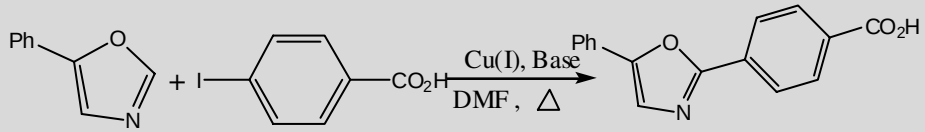
Although, direct arylations of heteroaromatics including arylation at C-2 of 5-substituted oxazole motif are known [15], the optimized reaction condition towards the similar arylation technique with carboxyl group containing aryl halide is still to be explored. Thus, initially, an experimentation was carried out to establish the optimized condition of reaction by treating 5-phenyloxazole (**2.1**) with 4-iodobenzoic acid in dimethyl formamide at elevated temperature under inert (N_2) atmosphere (Table-1).

Thus, the reaction of 5-aryl oxazoles with suitably substituted carboxyl group containing aryl halides in presence of Cu(I)/PPh_3 and sodium carbonate afforded corresponding 2,5-disubstituted oxazoles (Table-2).

Conclusion

A two-step process towards 2,5-disubstituted oxazole motifs involving the classical van Leusen methodology together with a modern and less expensive, easily affordable Cu(I)-mediated arylation route was carried out. Moderate to good yields of the desired products and endurance of

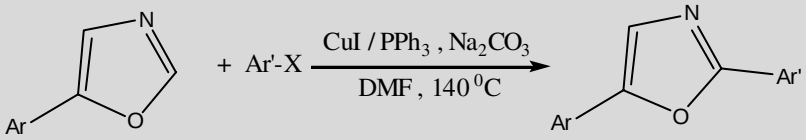
TABLE-1
OPTIMIZATION OF THE REACTION CONDITION FOR THE SECOND STEP

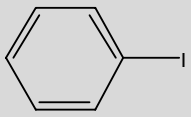
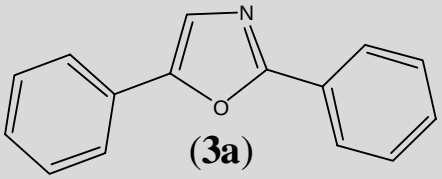
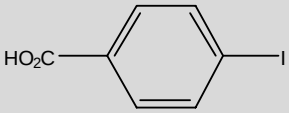
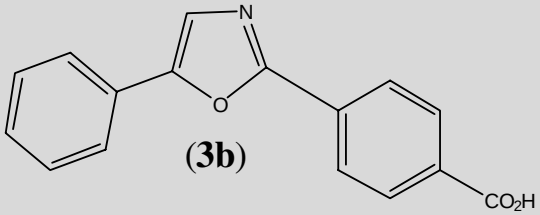
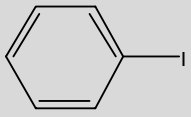
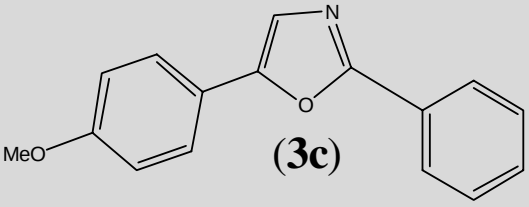
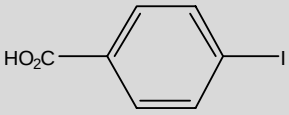
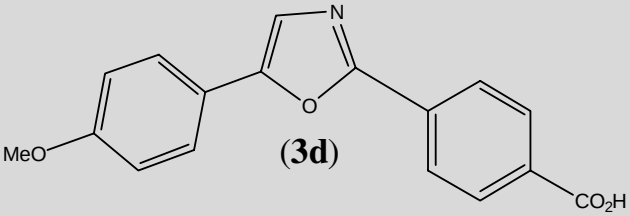


Entry	Cu(I) and PPh_3	Amount	Base	Temperature (°C)	Time (h)	Yield (%)
1	CuI	1.0 equiv	Na_2CO_3	140	16	< 30
2	CuI/PPh_3	1.0 equiv/0.1 mmol	K_2CO_3	140	16	39
3	CuI/PPh_3	1.0 equiv/0.1 mmol	Na_2CO_3	140	16	48
4	CuI/PPh_3	1.0 equiv/0.1 mmol	Na_2CO_3	120	16	48

Optimized combination: 5-Phenyl oxazole:Ph-I:CuI:PPh_3:Na_2CO_3 = 0.69:0.83:0.69:0.2:1.39

TABLE-2
Cu-MEDIATED DIRECT 'ARYLATION' TOWARDS 2,5-DIARYLOXAZOLES



Entry	Ar	Ar'-X	Product	Yield (%)
1	C_6H_5-		 **(3a)**	69
2	C_6H_5-		 **(3b)**	48
3	*p*-OMe-C_6H_4-		 **(3c)**	62
4	*p*-OMe-C_6H_4-		 **(3d)**	46

carboxylic group have rendered it highly applicable. Further studies on photophysical properties of these compounds are in progress in our laboratory.

ACKNOWLEDGEMENTS

The authors are thankful to CSIR (Project No. 01(2445)/10/EMR-II) for their financial support. We are also thankful to University of Kalyani, IIT, Kharagpur, India; IACS, Kolkata, India for providing the spectral data including NMR data and Mass.

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