DOI: 10.1002/ejoc.201001746

Neighbouring Formyl Group Assisted Oxidation of *o*-Alkynylarenecarbaldehydes by an Iodine/Water System

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Keywords: Alkynes / Oxidation / Iodine / Neighboring-group effects

The oxidation of *o*-alkynylarenecarbaldehydes into tricarbonyl compounds by an iodine/water system is described. The reaction takes place via isochromenol intermediates formed by intramolecular assistance of the formyl group. The procedure was applied to various *o*-alkynylarenecarbaldehydes to afford the corresponding products in good to excellent yields.

Introduction

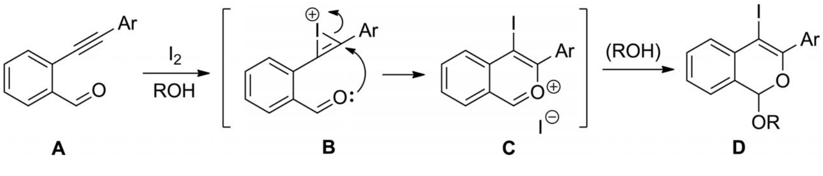
The neighbouring group participation (NGP) – in which an intramolecular nucleophile assists in the departure of a leaving group thereby forming a cyclic intermediate – is a well-established concept in aliphatic nucleophilic substitution and rearrangements. This kind of assistance is also possible in other types of organic reactions, and a few reports are available on the NGP in oxidation reactions.[1a–1g] To complement these reports, we herein report neighbouring group assistance by a formyl group in the oxidation of *o*-alkynylarenecarbaldehydes. These aldehydes are versatile precursors for the synthesis of various carbocycles and heterocycles, and the basis for all these syntheses is the activation of their carbon–carbon triple bond by metal catalysts or other electrophiles to give isochromenylium intermediates.[2a–2i]

The oxidation of internal alkynes to 1,2-diketones is an important synthetic transformation, because the resulting diketones are readily converted into various biologically active compounds.[3a–3c] This oxidation could be effected with a range of reagents such as $KMnO_4$,[4] I_2/DMSO,[5] SO_3/1,4-dioxane,[6] $FeBr_3$/DMSO,[7] PdI_2/DMSO,[8] $PdBr_2$,$CuBr_2$/DMSO,[9] $PdCl_2$/$CuCl_2$/PEG,[10] Pd/C/O_2,[11] [Ru(cymene)Cl_2]$_2$/I_2/H_2O_2,[12] etc. In a similar way, the oxidation of *o*-alkynylarenecarbaldehydes would provide *ortho*-(1,2-dioxoethyl)arenecarbaldehydes, which have previously not been reported, and these tricarbonyl compounds could be potential precursors for the synthesis of a wide range of bridged carbocycles and heterocycles.

Results and Discussion

Recently, Larock and co-workers reported an iodine-mediated cyclization of *o*-alkynylbenzaldehydes **A** in the presence of alcohols (ROH) to form isochromenes **D** (Scheme 1).[13a,13b] The reaction was taking place through the isochromenium intermediate **C** formed by a 6-*endo*-dig cyclization.

We serendipitously found that when water is employed in the place of alcohol in the above reaction, the aldehyde **A** is oxidized to the tricarbonyl compound **F**, instead of the expected isochromenol **D′** (Scheme 2). We envisage that the reaction may occur through I_2-triggered ring opening of the initially formed isochromenol intermediate **D′** as indicated in Scheme 2. This may give diiodide **E**, which undergoes nucleophilic displacement with water to form the tricarbonyl compound **F**. In other words, the formyl group in the *ortho* position of **A** acts as neighbouring group during the overall oxidation process. Due to this kind of intramolecular assistance of the formyl group, the oxidation is expected to proceed in a facile manner. It was found to be true and



Scheme 1. Conversion of *o*-alkynylarenecarbaldehydes into isochromenes.

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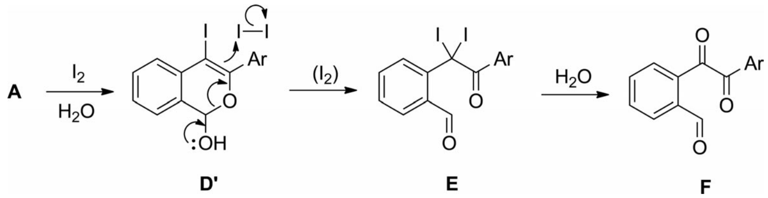
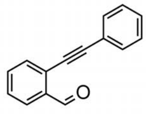
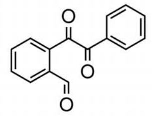
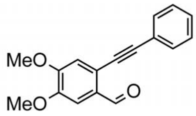
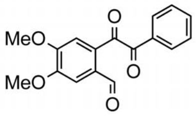
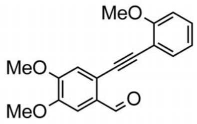
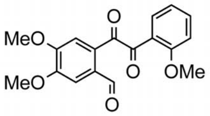
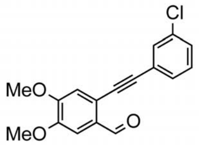
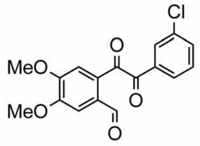
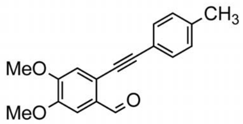
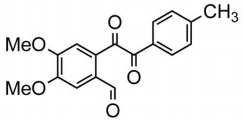
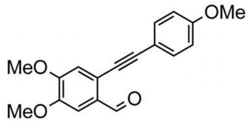
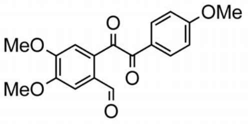
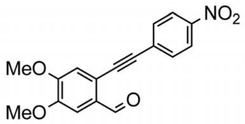
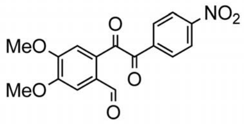
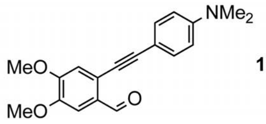
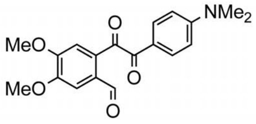
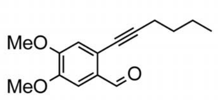
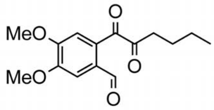
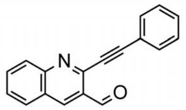
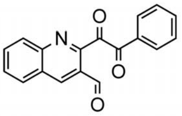
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001746.



Scheme 2. Oxidation of *o*-alkynylarenecarbaldehydes to tricarbonyl compounds.

Table 1. Oxidation of *o*-alkynylcarbaldehydes to tricarbonyl compounds.[a]

Entry	*o*-Alkynyl carbaldehyde		Product		*t* [min]	Yield[b] [%]
1		**1a**		**2a**	30	80
2		**1b**		**2b**	18	93
3		**1c**		**2c**	25	90
4		**1d**		**2d**	35	85
5		**1e**		**2e**	30	80
6		**1f**		**2f**	20	92
7		**1g**		**2g**	40	78
8		**1h**		**2h**	30	68
9		**1i**		**2i**	50	75
10		**1j**		**2j**	45	63

[a] Reaction conditions: *o*-alkynlbenzaldehyde (1.0 mmol), I_2 (2.1 mmol), H_2O (10 mmol), MeCN (10 mL), room temp. [b] Isolated yield.

several *o*-alkynylarenecarbaldehydes underwent smooth oxidation with iodine and water in acetonitrile at room temperature in a short reaction time. It may be noted that there is only one example in the literature for the oxidation of an internal alkyne (diphenylacetylene) to an 1,2-diketone (benzil) by using an iodine/water system (the reaction was carried out at 70 °C for 10 h to give the product in 19% yield).[14]

The scope of the oxidation was investigated for various *o*-alkynylarenecarbaldehydes, which were prepared by Sonogashira coupling of appropriate alkynes and haloarenes. When *o*-alkynylbenzaldehyde **1a** was treated with I_2 (2.1 equiv.) and water (10 equiv.) in CH_3CN at room temperature, the starting material was consumed within 30 min, and the workup and column purification afforded the tricarbonyl compound **2a** in 80% yield (Table 1, Entry 1). Change of the solvent or the amounts of reagents did not improve the yield. By using the same reaction conditions, the oxidations of *o*-alkynylarenecarbaldehydes **1b–j** were carried out to give the tricarbonyl compounds **2b–j** in good to excellent yields (Table 1, Entries 2–10).

In general, the aldehydes underwent facile oxidation to afford the tricarbonyl compounds in good to excellent yields. Among these aldehydes, **1c** is unique as it contains both formyl and methoxy groups in *ortho* position with respect to –C≡C– unit; however, the competitive benzofuran formation[15] did not take place. All the products were thoroughly characterized by spectroscopic techniques, and for the tricarbonyl compound **2b**, the structure was also confirmed by X-ray analysis (Figure 1).

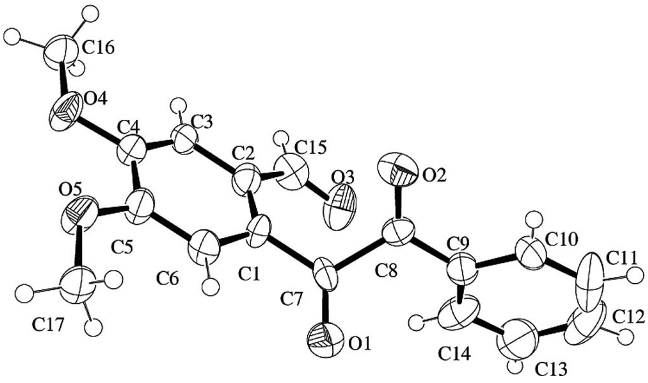
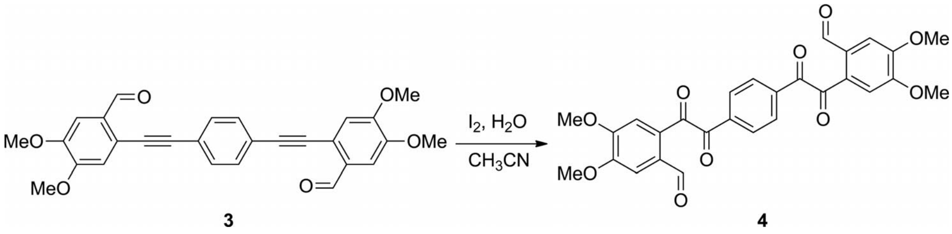


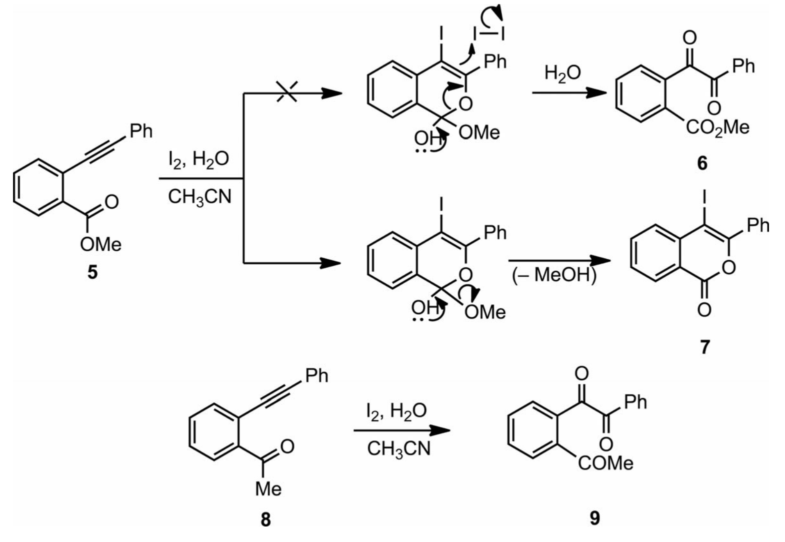
Figure 1. ORTEP plot of **2b** in the crystal (50% probability level).

We extended this procedure to the bis(aldehyde) **3**, which also produced the corresponding hexacarbonyl compound **4** in 90% yield (Scheme 3).

As outlined in Scheme 2, the oxidation proceeds by initial formation of an isochromenol intermediate, which further reacts with I_2 and water to give the product. An evidence for this mechanism comes from ^{1}H NMR spectra. The oxidation reaction of **2b** was carried out in an NMR tube with I_2 and D_2O in CD_3CN, and the ^{1}H NMR spectrum of the reaction mixture was recorded at different time intervals. The spectra clearly revealed that isochromenol (1-



Scheme 3. Oxidation of a bis(aldehyde) to the corresponding hexacarbonyl compound.



Scheme 4. Reactions of *o*-alkynyl ester or ketone with the I_2/H_2O system.

H resonance at δ = 6.29 ppm) is indeed the intermediate in the reaction (see Supporting Information).

Another indirect evidence for the mechanism comes from the reactions of the *o*-alkynyl ester **5** and the *o*-alkynyl ketone **8** with the I_2/water system (Scheme 4). Like the –CHO group, the –CO_2R group could also act as neighbouring group, and this has been well proven in the case of the Au^{3+}-catalyzed regioselective hydration of 3-alkynoates.[16a,16b] The isochromenol formed in the case of **5** may undergo either ring cleavage to give the dioxo ester **6** or elimination of the methoxy group to give isochromenone **7**. The latter seems to be facile, and the isochromenone **7** was produced in 95% yield with no sign of formation of **6**. On the other hand, the *o*-alkynyl ketone **18** (in which the oxo group could also act as neighbouring group, but the methyl group is not a leaving group) formed the triketone **9** in 95% yield.

Conclusions

A simple, environmentally benign, metal-free procedure for the oxidation of *o*-alkynylarenecarbaldehydes to the corresponding tricarbonyl compounds has been developed. The reaction proceeds via isochromenol intermediates formed by neighbouring group participation of the formyl group. The utility of the product tricarbonyl compounds in the synthesis of various carbocycles and heterocycles is currently being investigated and will be reported in due course.

Experimental Section

General Procedure for the Oxidation of *o*-Alkynylarenecarbaldehydes: To a solution of an *o*-alkynylarenecarbaldehyde (1.0 mmol) in acetonitrile (10 mL) were added iodine (2.1 mmol) and water (10 mmol). The reaction mixture was stirred at room temperature for the appropriate time, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with satd. $Na_2S_2O_3$ solution, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2; EtOAc/hexane, 1:9, v/v) to afford the corresponding tricarbonyl compound.

2-(2-Oxo-2-phenylacetyl)benzaldehyde (2a): Light brown semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H, CHO), 8.12–8.10 (m, 2 H, Ar-H), 7.85–7.83 (m, 1 H, Ar-H), 7.70–7.64 (m, 3 H, Ar-H), 7.61–7.57 (m, 1 H, Ar-H), 7.49–7.45 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 191.4, 188.5, 136.1, 134.9, 133.3, 133.2, 132.0, 131.4, 131.3, 129.8, 129.6, 127.6 ppm. HRMS: calcd. for $[C_{15}H_{10}O_3 + H]^+$ 239.0708; found 239.0698.

CCDC-819787 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental details; spectroscopic characterization data and copies of ^{1}H and ^{13}C NMR spectra of **2a**–**d** and **2f**.

Acknowledgments

The authors thank the Department of Science and Technology (DST) and Council of Scientific and Industrial Research (CSIR), India for financial support and Prof. P. Thomas Muthiah, Bharathidasan University and Dr. K. Saminathan, Anna University of Technology Tirunelveli for X-ray structural determination.

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Received: December 31, 2010