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Iodine/Water-Mediated Oxidation of *o*-Alkynylaroyl Compounds and Application of the Products of Oxidation in the Synthesis of Nitrogen Heterocycles

Karuppusamy Sakthivel[a] and Kannupal Srinivasan*[a]

Keywords: Synthetic methods / Oxidation / Nitrogen heterocycles / Alkynes / Neighboring-group effects

A facile iodine/water-mediated oxidation of the triple bond of *o*-alkynylaroyl compounds to furnish tricarbonyl compounds is reported. The reaction proceeds through the formation of isochromenol intermediates by the assistance of the neighbouring aroyl group. The product tricarbonyl compounds are versatile synthetic precursors that, upon treatment with mono- and diamines, hydrazines and amino alcohols, afford various heterocyclic scaffolds such as isoindolinones, phthalazines, benzimidazoisoquinolinones, quinoxalines and benzimidazole-quinoxaline hybrid compounds. Mechanistic aspects of the formation of the above heterocycles are discussed. Finally, a short synthetic route to the isoindolinone natural product, aristolactam BII is reported.

Introduction

o-Alkynylarenecarbaldehydes are useful building blocks in organic synthesis. They undergo cycloisomerisation in the presence of transition-metal compounds or other electrophiles to form isochromenylium intermediates.[1–10] The addition of oxygen,[1a,1b,2b,10] nitrogen[8] or carbon nucleophiles[1c,3a,3b,4b,9a] to the intermediates gives various isochromenes. Cycloaddition reactions of these intermediates with suitable partners furnish naphthalenes,[2a,4a,5b,9b,9c,11] dihydronaphthalenes[12] or polycyclic structures.[6,7,13] The intermediates also lead to interesting carbazoles,[14] dihydroisoquinolines[15] and isoquinolines.[16] Furthermore, they have been applied in the total synthesis of azaphilones,[4c,17] fascaplysin,[18] heliophenanthrone,[5a] and (+)-ochromycinone.[19]

Numerous reagents have been used for the oxidation of the C–C triple bond of internal alkynes to the corresponding α-diketo derivatives.[20] We have recently reported an environmentally benign, metal-free procedure for the oxidation of the triple bond of *o*-alkynyl arenecarbaldehydes using an iodine/water system[21] and, more generally, molecular iodine has been recognised as a valuable reagent in organic synthesis.[22] Scheme 1 exemplifies our work. The *o*-alkynylbenzaldehyde **1**, upon exposure to iodine, undergoes triple bond activation to give isochromenylium intermediate **A**, which undergoes nucleophilic addition by water to form isochromenol **B**. Subsequent displacement of iodine by water in **C** eventually leads to the oxidised product **2**. Thus, the neighbouring formyl group in **1** assists the oxidation of the alkyne unit so that the reaction takes place in a facile manner under mild conditions. By adapting this procedure, a series of tricarbonyl analogues of **2** were prepared from various *o*-alkynlarenecarbaldehydes in yields ranging from 63 to 93%.[21]

It was clear that the above oxidation methodology should be applicable to other *o*-alkynylaroyl compounds such as ketones, acids, esters and amides. The development of these possibilities would generate a multitude of compounds with a range of carbonyl groups. These compounds could be potential precursors of a diverse array of carbo- and heterocycles including natural products, and are thus welcome in diversity-oriented synthesis (DOS), which concerns with transformation of a set of given precursors into a library of diverse compounds.[23]

In this article, we report the scope of our oxidation methodology with respect to various *o*-alkynylaroyl compounds and application of the resulting products for the synthesis of several hetereocycles such as isoindolinones, phthalazines, benzimidazoisoquinolinones, quinoxalines and benzimidazole-quinoxaline hybrids, and a natural product, aristolactam BII.

Results and Discussion

Oxidation of *o*-Alkynylarene Ketones

We began the study by applying our standard oxidation procedure[21] to *o*-alkynylarene ketone **3a** (Table 1, entry 1). When **3a** was stirred with iodine (2 equiv.) in water/aceto-

[a] School of Chemistry, Bharathidasan University, Tiruchirappalli 620024, Tamil Nadu, India
Fax: +91-431-2407043
E-mail: srinivasank@bdu.ac.in
Homepage: www.bdu.ac.in/schools/chemistry/chemistry/dr_k_srinivasan.php

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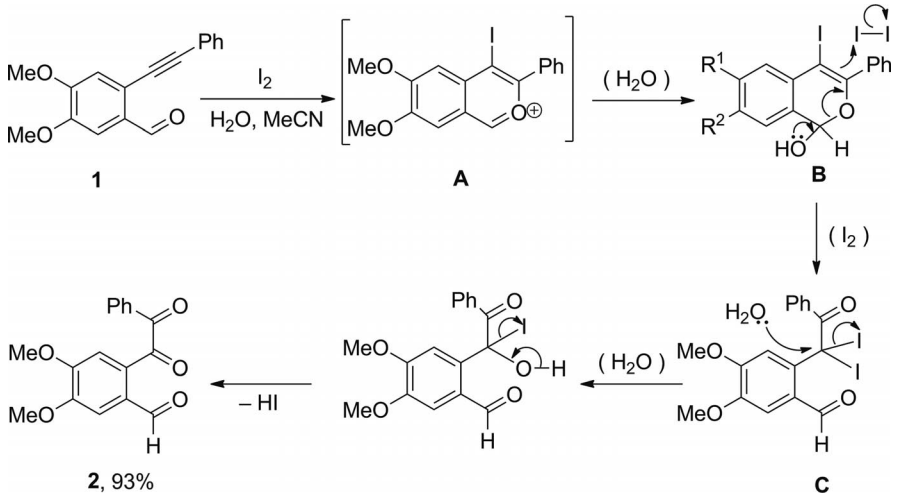
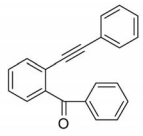
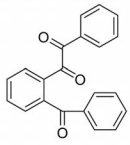
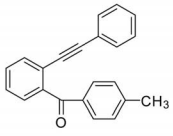
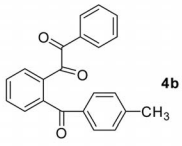
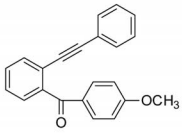
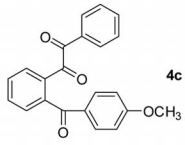
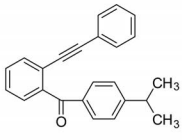
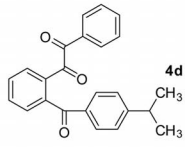
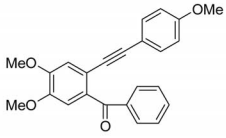
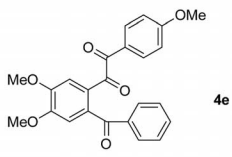
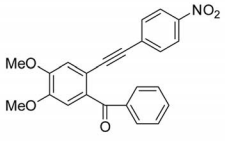
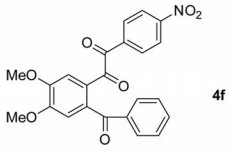
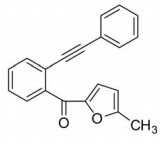
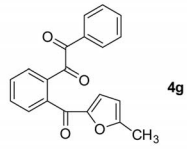
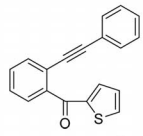
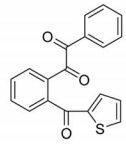
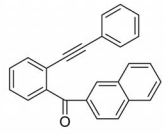
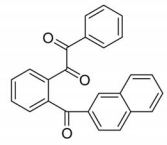
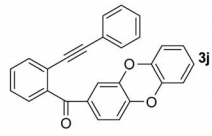
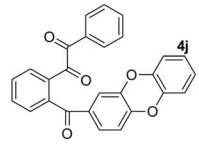
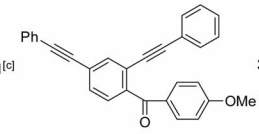
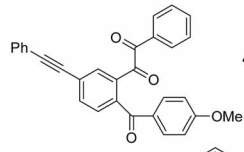
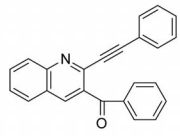
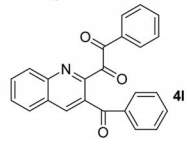
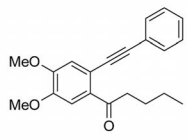
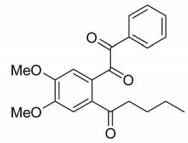


Scheme 1. Oxidation of *o*-alkynylbenzaldehyde **1** into tricarbonyl compound **2**.

Table 1. Oxidation of *o*-alkynylarene ketones.

Entry	*o*-Alkynylarene ketones		Product		Yield [%][a]
1		**3a**		**4a**	77
2		**3b**		**4b**	83
3		**3c**		**4c**	83
4		**3d**		**4d**	81
5		**3e**		**4e**	85
6		**3f**		**4f**	—[b]
7		**3g**		**4g**	81
8		**3h**		**4h**	80
9		**3i**		**4i**	76
10		**3j**		**4j**	74
11[c]		**3k**		**4k**	70
12[c]		**3l**		**4l**	70
13		**3m**		**4m**[d]	83

[a] Isolated yield. [b] Compound **4f** could not be isolated in pure form. [c] The reaction time was 20 min. [d] The isolated compound decomposed readily.

nitrile (1:9) at room temperature for 10 min, it smoothly underwent oxidation to give triketone **4a** in 77% yield after purification.

The reaction was found to be quite general, and ketones **3b**–**e**, bearing a range of substituents, were also oxidised to the corresponding triketones **4b**–**e** in good yields under the developed conditions (Table 1, entries 2–5; the structure of **4b** was confirmed by X-ray crystallographic analysis[24]). However, although ketone **3f**, having a nitro group on the aryl ring attached to the yne unit, afforded triketone **4f**, the product could not be isolated in pure form (entry 6). The presence of heteroaryl groups was tolerated and ketones **3g** and **3h** afforded high yields of triketones **4g** and **4h**, respectively, without giving rise to any side reactions such as cycloaddition[25a] or electrophilic cyclisation[25b] (entries 7 and 8). Ketones **3i** and **3j**, bearing naphthyl and dibenzodioxinyl groups, respectively, also furnished the desired triketones **4i** and **4j** in good yields (entries 9 and 10). The oxidation of diynyl ketone **3k** to triketone **4k** is especially interesting to note (entry 11); in this case, the alkyne group *ortho* to the carbonyl was oxidised, whereas the second alkyne group *para* to the carbonyl moiety remained unchanged (even when five equivalents of iodine were employed). This clearly reveals that the reaction proceeds through formation of an isochromenol intermediate, as proposed in the mechanism of oxidation of *o*-alkynylarenecarbaldehydes (Scheme 1). The oxidation was also successful with quinoline-based *o*-alkynylarene ketone **3l**, which afforded triketone **4l** in 70% yield (entry 12). Finally, the procedure was also applied to aryl alkyl ketone **3m**; in this case, the corresponding triketone **4m** was isolated in 83% yield (entry 13), however, this product was found to be unstable.

Oxidation of Other *o*-Alkynylbenzoyl Compounds

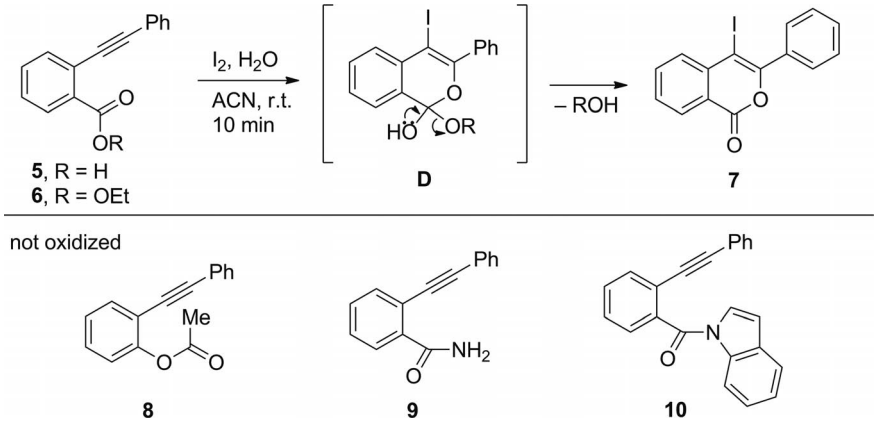
We extended the oxidation methodology to other *o*-alkynylaroyl compounds such as acids, esters and amides (Scheme 2). When acid **5** and ester **6**[21] were subjected to oxidation under the usual conditions, instead of the expected oxidation products, these substrates afforded iodoisochromenone **7**, presumably via intermediate **D** (iodocyclisation). Ester **8**, for which the formation of isochromenylium intermediate is not possible, remained inert under the reaction conditions. Amides **9** and **10** were also inert, probably due to the lower reactivity of the amide carbonyl group under the reaction conditions.

Reactions of Tricarbonyl Compounds Derived from *o*-Alkynylarene Aldehydes and Ketones with Amines

The 1,2,5-tricarbonyl compounds arising from oxidation of *o*-alkynylarene aldehydes/ketones were previously unknown and, hence, their reactivity patterns were not described. In addition to showing unique reactivity as 1,2,5-tricarbonyl compounds, they were also expected to display reactivities of 1,2-, 1,4- or 1,5-dicarbonyl compounds. A systematic investigation of their reactivity patterns was therefore expected to lead to the discovery of new reactions and materials. Thus, the tricarbonyl compounds could serve as resourceful precursors in diversity-oriented organic synthesis, in analogy with polyketides in natural product synthesis.[26] With this idea in mind, we treated some of the tricarbonyl compounds with a range of amines and found that they are indeed versatile precursors for nitrogen heterocycles.

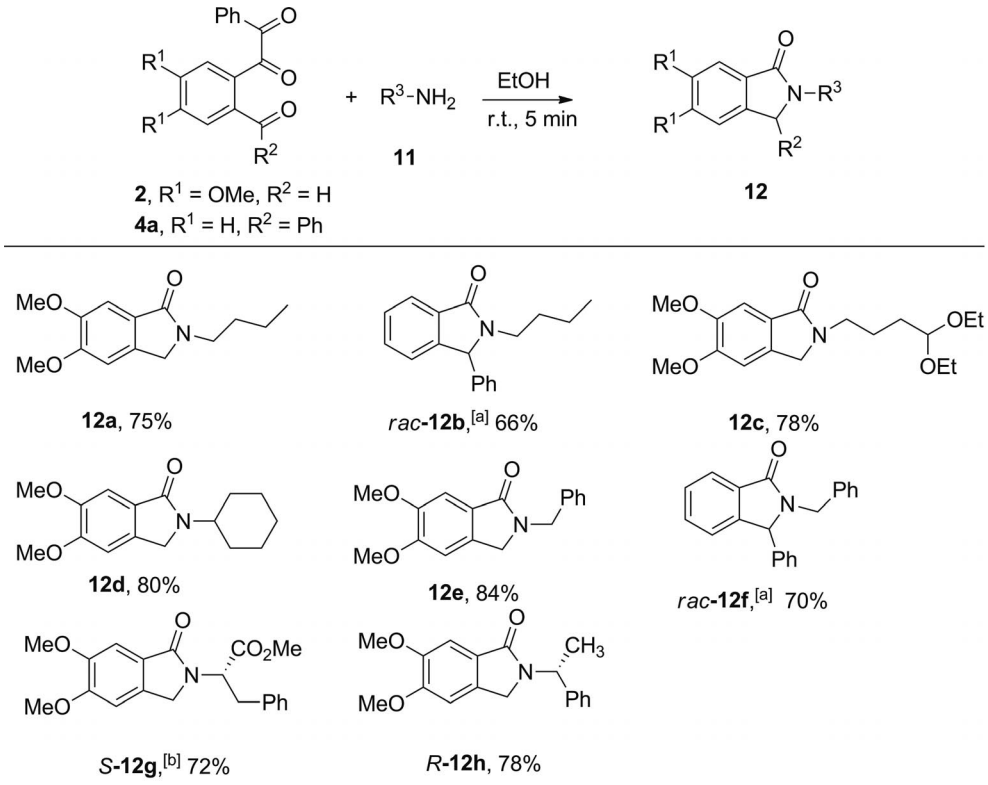
Reactions with Monoamines

Tricarbonyl compounds **2** and **4a** were reacted with various monoamines in ethanol at room temperature (Table 1). Primary aliphatic and aryl alkylamines (*n*-butylamine, 4,4-diethoxybutylamine, cyclohexylamine, benzylamine, (*S*)-methyl-2-amino-3-phenylpropionate and (*R*)-1-phenylethylamine) were employed in the reactions. In all cases, **2** and **4a** behaved as though they were 1,4-dicarbonyl (*o*-phthaloyl) compounds and formed isoindolinones with the loss of a benzoyl group. The product isoindolinones **12a**–**h** were obtained in 66–84% yields after purification (Table 2). The scope of the reaction was also investigated with aromatic primary amines such as aniline, *p*-toluidine and *p*-anisidine. These reactions, however, failed to give the expected isoindolinones.



Scheme 2. Oxidation of various *o*-alkynylaroyl compounds.

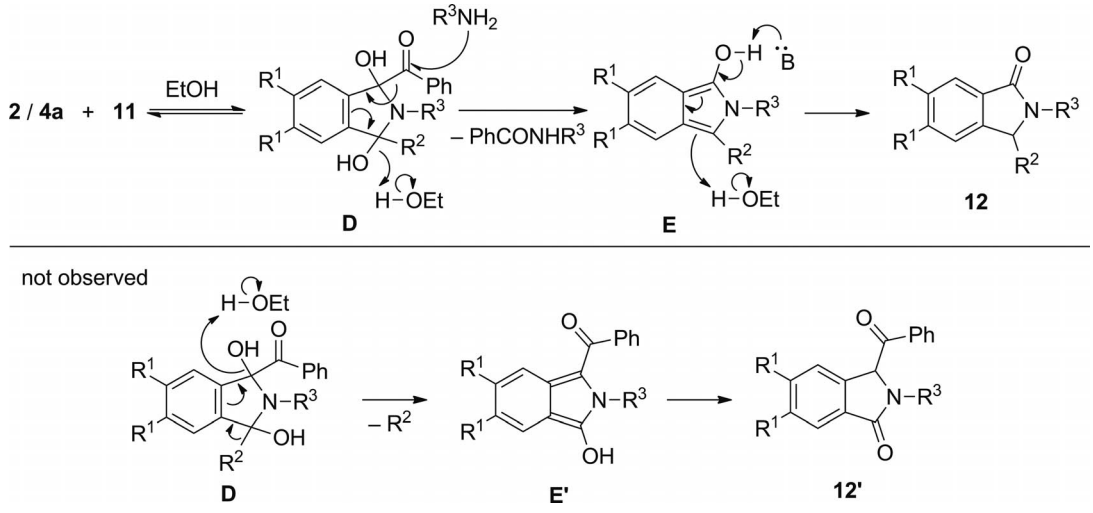
Table 2. Formation of isoindolinones.



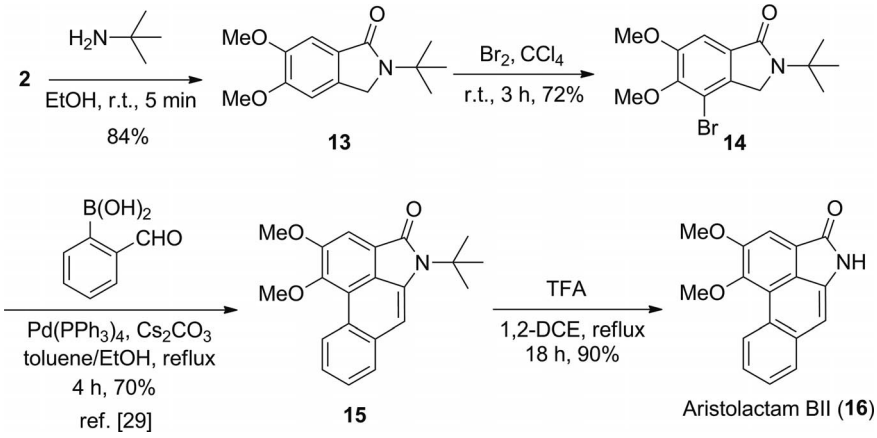
[a] The reaction time was 20 min. [b] The reaction time was 2 h.

There have been many reports in which *o*-phthaloyl compounds react in a similar manner with amines and amides to give isoindolinones.[27] Taking inspiration from these reports, we propose the mechanism depicted in Scheme 3 for the formation of isoindolinones with concomitant loss of a benzoyl group in the above reactions. Thus, the reaction of **2** or **4a** with **11** generates hemiaminal **D**; this compound loses a benzoyl group to form hydroxy isoindole **E**, which, upon tautomerisation, affords isoindolinone **12**. We never observed the other possible isoindolinone **12′** in any of the above reactions. Clearly, the proton or phenyl group was not eliminated from **D** to give **E′**, presumably owing to the difficulty of forming an sp^2 carbon adjacent to the carbonyl group in **E′**.

To demonstrate the versatility of the above methodology, we devised a short synthetic route to the naturally occurring isoindolinone alkaloid (Scheme 4), aristolactam BII (**16**), which is known to display appreciable antitumor activity.[28]



Scheme 3. Mechanism for the formation of isoindolinones **12**.



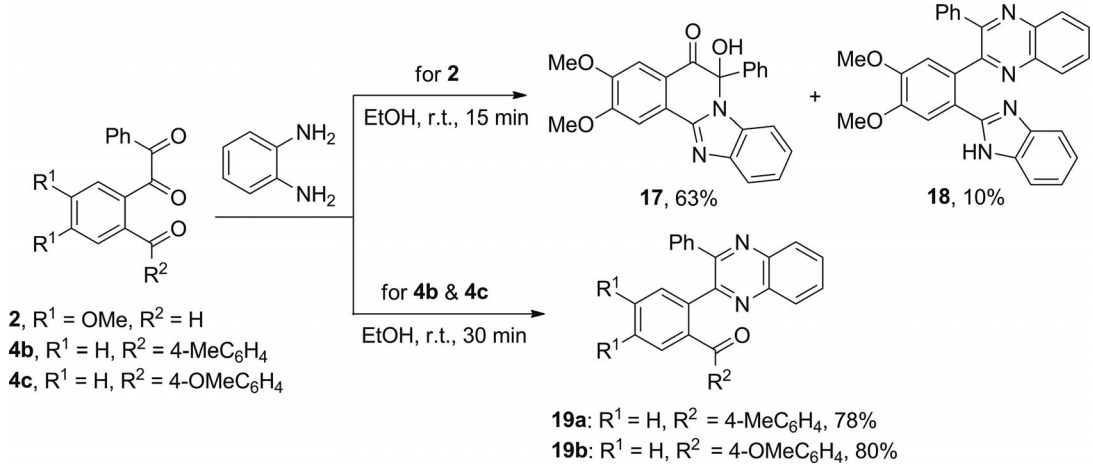
Scheme 4. Total synthesis of aristolactam BII.

Accordingly, tricarbonyl compound **2** was converted into isoindolinone **13** by treatment with *tert*-butylamine in 84% yield under standard conditions. Bromination of **13** in CCl_4 gave bromoisoindolinone **14** in 72% yield. Adapting a thermal version of the procedure developed by Heo et al.,[29] **14** was subjected to tandem Suzuki–Miyura coupling/aldol condensation with (2-formylphenyl)boronic acid to give *N*-protected lactam **15** in 70% yield. Removal of the protecting group from **15** by treatment with trifluoroacetic acid (TFA) furnished the target compound **16** in 90% yield (the overall yield over four steps was 38%).

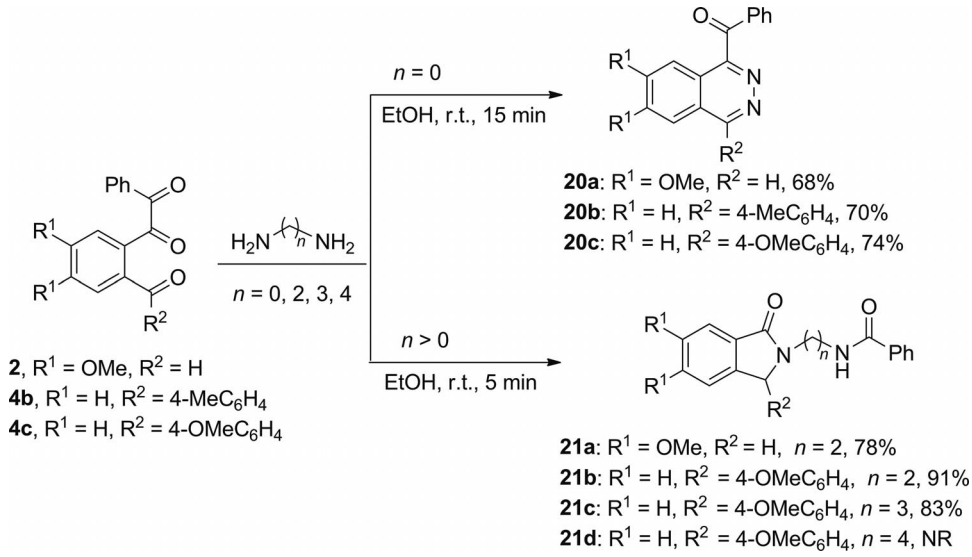
Reactions with Diamines

The tricarbonyl compounds underwent assorted transformations when treated with aliphatic and aromatic diamines. Thus, tricarbonyl compound **2**, when reacted with *o*-phenylenediamine (*o*-PDA), gave benzimidazo-isoquinolinone **17** in 63% yield along with the quinoxaline-benzimidazole hybrid compound **18** in 10% yield (Scheme 5; the structure of **18** was confirmed by X-ray crystallographic analysis[30]). Clearly, *o*-PDA undergoes initial cyclocondensation (and self-oxidation) with the formyl group of **2** to form a benzimidazole derivative, which either undergoes cyclisation to give **17** or further cyclocondensation with another molecule of *o*-PDA to give **18**. In contrast, tricarbonyl compounds **4b** and **4c** behaved like 1,2-diketones and gave quinoxalines **19a** and **19b** in 78 and 80% yields, respectively, under the same conditions.

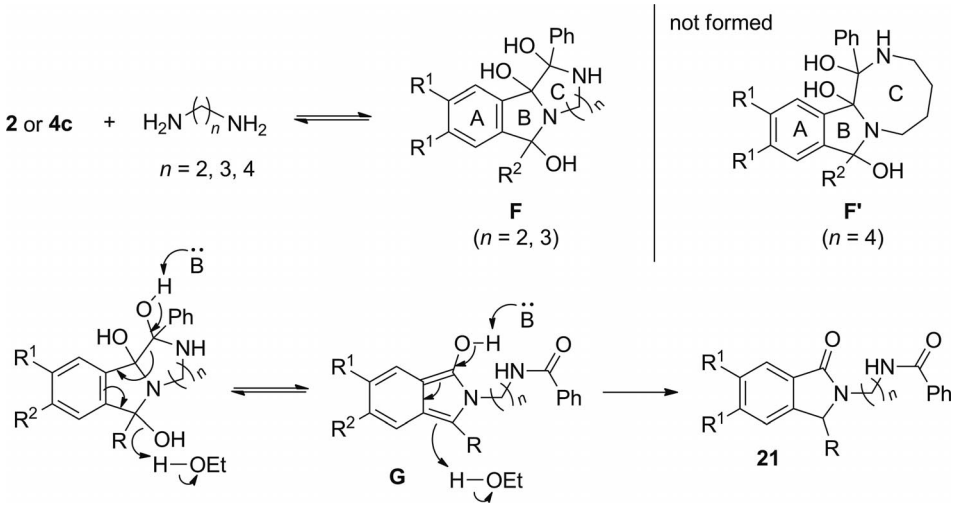
With hydrazine, tricarbonyl compounds **2**, **4b** and **4c** acted as 1,4-diketones and underwent cyclocondensation to form the phthalazine ketones **20a**–**c** in 68–74% yields (Scheme 6; the structure of **20b** was confirmed by X-ray crystallographic analysis[31]). Interestingly, when **2** was treated with ethylene diamine, isoindolinone **21a** was produced in 78% yield, with migration of the benzoyl group to the terminal nitrogen. Similarly, isoindolinones **21b** and **21c** were obtained in very good yields when **4c** was treated with ethylene diamine and 1,3-diaminopropane, respectively. The reaction, however, failed to form isoindolinone **21d** when **4c** was treated with 1,4-diaminobutane. This suggested to us the mechanism shown in Scheme 7. Accordingly, the reaction might proceed via tricyclic hemiaminal **F**. In case of 1,4-diaminobutane, the formation of the corresponding hemiaminal **F′** did not occur because it would require the formation of an energetically unfavourable eight-membered



Scheme 5. Formation of benzimidazoisoquinolinones, quinoxaline-benzimidazole hybrid and quinoxalines.



Scheme 6. Formation of phthalazines and isoindolinones.

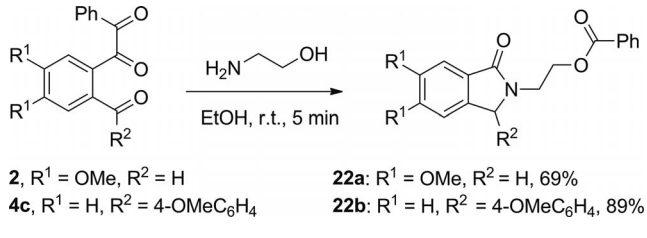


Scheme 7. Mechanism for the formation of isoindolinones **21**.

C ring. Hemiaminal **F** then underwent opening of the C ring to form hydroxyisoindole **H**, which, upon tautomerisation, gave isoindolinones **21**.

Reactions with Amino Alcohols

Finally, tricarbonyl compounds **2** and **4c** were reacted with aminoethanol (Scheme 8). As with aliphatic diamines, these reactions also generated isoindolinones **22a** and **22b** in 69 and 89% yields, respectively, with migration of the benzoyl group, possibly through a similar mechanistic pathway to that outlined in Scheme 7.



Scheme 8. Formation of isoindolinones **22**.

Conclusions

We have developed a simple, environmentally benign procedure for the oxidation of a variety of *o*-alkynylarene aldehydes and ketones into the corresponding tricarbonyl compounds using an iodine/water system. The facile nature of the reaction is attributed to the involvement of isochromenol intermediates formed through intramolecular nucleophilic attack of the neighbouring carbonyl oxygen on the triple bond. The tricarbonyl compounds resulting from the present oxidation methodology are potential precursors of various nitrogen heterocycles, including isoindolinones and a natural product, aristolactam BII. We are exploring further synthetic potential of the tricarbonyl compounds.

Experimental Section

General Remarks: Melting points were determined with the open capillary tube method and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz NMR spectrometer. HRMS (ESI) were recorded with a Q-Tof mass spectrometer. Low-resolution mass spectra (ESI) were recorded with an LC-MS spectrometer. Elemental analyses were performed with a CHN analyzer. X-ray crystallographic data were collected with a CCD diffractometer using graphite-monochromated Mo-K_α radiation. Thin-layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

General Procedure for the Oxidation of *o*-Alkynylarene Ketones: To a solution of *o*-alkynylarene ketone (0.250 mmol) in acetonitrile (9.0 mL) were added iodine (0.525 mmol) and water (1 mL) and the mixture was stirred at room temperature for 10 min (20 min for **3k** and **3l**). The reaction mixture was then 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 tricarbonyl compound.

1-(2-Benzoylphenyl)-2-phenylethane-1,2-dione (4a): Yield 61 mg (77%); brown solid; m.p. 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 2 H), 7.84–7.81 (m, 1 H), 7.71–7.68 (m, 2 H), 7.60–7.46 (m, 5 H), 7.40–7.33 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 193.2, 191.2, 140.4, 136.8, 135.9, 134.4, 133.2, 133.1, 132.4, 131.4, 130.5, 129.91, 129.89, 128.6, 128.5 ppm. HRMS: *m*/*z* calcd. for $C_{21}H_{14}O_3$ [M + Na]$^+$ 337.0835; found 337.0841.

1-[2-(4-Methylbenzoyl)phenyl]-2-phenylethane-1,2-dione (4b): Yield 68 mg (83%); yellow solid; m.p. 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.91 (dd, *J* = 8.2, 1.0 Hz, 2 H), 7.82–7.80 (m, 1 H), 7.60–7.46 (m, 6 H), 7.38–7.34 (m, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 193.3, 191.2, 144.3, 140.7, 135.8, 134.4, 134.3, 133.1, 132.4, 131.33, 131.30, 130.5, 130.2, 129.8, 129.3, 128.6, 21.7 ppm. MS (ESI): *m*/*z* = 329 [M + H]$^+$. $C_{22}H_{16}O_3$: calcd. C 80.47, H 4.91; found C 80.60, H 4.85. Single crystals suitable for X-ray studies were grown from a solution of **4b** in chloroform.

1-[2-(4-Methoxybenzoyl)phenyl]-2-phenylethane-1,2-dione (4c): Yield 71 mg (83%); brownish-yellow solid; m.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 8.2, 1.0 Hz, 2 H), 7.92–7.89 (m, 1 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 7.65–7.61 (m, 2 H), 7.59–7.55 (m, 2 H), 7.48–7.44 (m, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 193.2, 191.3, 163.8, 141.0, 135.5, 134.3, 133.1, 132.5, 132.4, 131.4, 131.0, 130.4, 129.7, 129.5, 128.6, 113.8, 55.5 ppm. HRMS: *m*/*z* calcd. for $C_{22}H_{16}O_4$ [M + H]$^+$ 345.1121; found 345.1127.

1-[2-(4-Isopropylbenzoyl)phenyl]-2-phenylethane-1,2-dione (4d): Yield 72 mg (81%); yellow solid; m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 2 H), 7.93–7.91 (m, 1 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.68–7.59 (m, 4 H), 7.49–7.46 (m, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 2.96 (sept., *J* = 6.8 Hz, 1 H), 1.27 (d, *J* = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 193.3, 191.2, 154.9, 140.6, 135.9, 134.6, 134.3, 133.2, 132.3, 131.3, 130.5, 130.3, 129.9, 128.6, 126.7, 34.3, 23.7 ppm. HRMS: *m*/*z* calcd. for $C_{24}H_{20}O_3$ [M + H]$^+$ 357.1485; found 357.1509.

1-[(2-Benzoyl-4,5-dimethoxyphenyl)]-2-(4-methoxyphenyl)ethane-1,2-dione (4e): Yield 86 mg (85%); yellow solid; m.p. 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.8 Hz, 2 H), 7.78–7.76 (m, 2 H), 7.54–7.52 (m, 1 H), 7.44–7.40 (m, 3 H), 7.01 (s, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 192.5, 190.1, 164.5, 151.9, 150.7, 137.2, 134.9, 133.1, 132.9, 129.8, 128.9, 128.5, 126.3, 113.9, 113.5, 112.3, 56.4, 56.3, 55.5 ppm. HRMS: *m*/*z* calcd. for $C_{24}H_{20}O_6$ [M + H]$^+$ 405.1333; found 405.1336.

1-{[2-(2-Methylfuran-5-carbonyl)phenyl]}-2-phenylethane-1,2-dione (4g): Yield 64 mg (81%); brown solid; m.p. 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.90–7.83 (m, 2 H), 7.67–7.60 (m, 3 H), 7.51–7.47 (m, 2 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 6.19 (d, *J* = 3.6 Hz, 1 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 188.9, 180.2, 158.0, 149.0, 137.4, 134.6, 132.4, 131.4, 130.5, 129.9, 129.4, 128.8, 127.6, 126.8, 122.1, 107.9, 12.4 ppm. HRMS: *m*/*z* calcd. for $C_{20}H_{14}O_4$ [M + H]$^+$ 319.0965; found 319.0970.

1-Phenyl-2-[2-(thiophene-2-carbonyl)phenyl]ethane-1,2-dione (4h): Yield 64 mg (80%); brown solid; m.p. 74–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2 H), 7.86–7.84 (m, 1 H), 7.69–7.67 (m, 1 H), 7.64–7.50 (m, 5 H), 7.43–7.39 (m, 2 H), 7.07–7.04 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 190.0, 187.3, 142.2, 139.0, 134.4, 134.3, 133.3, 132.0, 131.5, 130.4, 129.3, 128.1, 127.5, 127.3 ppm. HRMS: *m*/*z* calcd. for $C_{19}H_{12}O_3S$ [M + H]$^+$ 321.0580; found 321.0585.

1-{[2-(2-Naphthoyl)phenyl]}-2-phenylethane-1,2-dione (4i): Yield 69 mg (76%); brown solid; m.p. 73–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.92–7.89 (m, 3 H), 7.86–7.81 (m, 4 H), 7.65–7.45 (m, 6 H), 7.36–7.32 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 193.2, 191.3, 140.7, 135.8, 135.7, 134.4, 134.3, 133.1, 132.6, 132.3, 132.2, 131.5, 131.4, 130.5, 130.0, 129.6, 128.8, 128.6, 128.4, 127.9, 126.9, 125.2 ppm. HRMS: *m*/*z* calcd. for $C_{25}H_{16}O_3$ [M + H]$^+$ 365.1172; found 365.1177.

1-[2-(Dibenzo[1,4]dioxine-2-carbonyl)phenyl]-2-phenylethane-1,2-dione (4j): Yield 78 mg (74%); yellow solid; m.p. 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2 H), 7.94–7.91 (m, 1 H), 7.70–7.57 (m, 4 H), 7.50–7.46 (m, 2 H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.31 (d, *J* = 2.0 Hz, 1 H), 6.94–6.81 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 193.0, 191.3, 146.6, 142.1, 141.6, 141.3, 140.4, 135.3, 134.4, 132.8, 132.6, 131.5, 131.2, 130.4, 129.4, 128.6, 126.8, 124.6, 124.2, 118.0, 116.5, 116.3 ppm. MS (ESI): *m*/*z* = 421 [M + H]$^+$. $C_{27}H_{16}O_5$: calcd. C 77.14, H 3.84; found C 77.36, H 3.76.

1-[2-(4-Methoxybenzoyl)-5-(2-phenylethynyl)phenyl]-2-phenylethane-1,2-dione (4k): Yield 78 mg (70%); brown solid; m.p. 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.2, 1.0 Hz, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.82–7.75 (m, 3 H), 7.68 (d, *J* = 1.6 Hz, 1 H), 7.64–7.60 (m, 1 H), 7.55–7.53 (m, 2 H), 7.50–7.46 (m, 2 H), 7.38–7.36 (m, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 192.4, 191.2, 164.0, 141.4, 134.4, 134.3, 133.5, 133.0, 132.5, 132.1, 131.9, 131.5, 130.5, 129.5, 129.2, 128.6, 128.5, 128.0, 122.2, 114.0, 93.9, 87.9, 55.6 ppm. HRMS: *m*/*z* calcd. for $C_{30}H_{20}O_4$ [M + H]$^+$ 445.1434; found 445.1441.

1-(3-Benzoylquinolin-2-yl)-2-phenylethane-1,2-dione (4l): Yield 64 mg (70%); pale-yellow solid; m.p. 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 8.17 (d, *J* = 8.6 Hz, 1 H), 8.03–8.01 (m, 2 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.89–7.86 (m, 2 H), 7.85–7.82 (m, 1 H), 7.76–7.72 (m, 1 H), 7.65–7.59 (m, 2 H), 7.52–7.48 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 193.4, 192.6, 151.5, 147.4, 137.8, 136.7, 134.5, 133.6, 133.2, 132.6, 131.8, 130.7, 130.1, 130.0, 129.6, 128.8, 128.7, 128.3, 127.9 ppm. HRMS: *m*/*z* calcd. for $C_{24}H_{15}NO_3$ [M + H]$^+$ 366.1125; found 366.1130.

1-(4,5-Dimethoxy-2-pentanoylphenyl)-2-phenylethane-1,2-dione (4m): Yield 78 mg (83%); pale-orange solid; m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.20 (m, 2 H),7.65–7.61 (m, 1 H), 7.55–51 (m, 2 H), 7.28 (s, 1 H), 7.20 (s, 1 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 2.81 (t, J = 7.4 Hz, 2 H), 1.58–1.54 (m, 2 H), 1.33–1.25 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 193.5, 189.7, 152.5, 150.9, 133.7, 133.6, 131.9, 131.7, 130.7,128.4, 112.9, 110.9, 56.4, 38.7, 26.4, 22.3, 13.8 ppm. No satisfactory mass/elemental analysis data could be obtained due to the instability of the compound.

General Procedure for the Synthesis of Isoindolinones 12a–h and 13: To a solution of tricarbonyl compounds **2** or **4a** (0.20 mmol) in ethanol (5 mL) was added amine **11** (0.4 mmol; for **12g**, 0.40 mmol of NaOAc was also included) and the mixture was stirred at room temperature for 5 min (20 min for **12b** and **12f**, and 2 h for **12g**). The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried with $NaSO_4$, filtered and the solvents evaporated. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:1 v/v).

2-Butyl-5,6-dimethoxyisoindolin-1-one (12a): Yield 64 mg (75%); white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 1 H), 6.92 (s, 1 H), 4.29 (s, 2 H), 3.94 (s, 3 H), 3.935 (s, 3 H), 3.59 (t, J = 7.2 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.43–1.35 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 152.3, 149.6, 134.6, 125.4, 105.4, 105.0, 56.2, 49.6, 42.2, 30.6, 20.1, 13.8 ppm. MS (ESI): m/z = 250 $[M + H]^+$. $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45, H 7.68, N 5.62; found C 67.66, H 7.76, N 5.77.

2-Butyl-3-phenylisoindolin-1-one (12b): Yield 35 mg (66%); white solid; m.p. 87–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.88 (m, 1 H), 7.47–7.44 (m, 2 H), 7.37–7.33 (m, 3 H), 7.17–7.12 (m, 3 H), 5.45 (s, 1 H), 3.95–3.93 (m, 1 H), 2.88–2.84 (m, 1 H), 1.54–1.50 (m, 2 H), 1.34–1.26 (m, 2 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 146.3, 137.2, 131.8, 131.6, 129.1, 128.6, 128.3, 127.6, 123.5, 123.0, 64.4, 39.9, 30.4, 20.1, 13.7 ppm. HRMS: m/z calcd. for $C_{18}H_{19}NO$ $[M + H]^+$ 266.1539; found 266.1545.

2-(4,4-Diethoxybutyl)-5,6-dimethoxyisoindolin-1-one (12c): Yield 52 mg (78%); yellow solid; m.p. 64–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 1 H), 6.92 (s, 1 H), 4.52 (t, J = 5.6 Hz, 1 H), 4.30 (s, 2 H), 3.94 (s, 3 H), 3.937 (s, 3 H), 3.67–3.60 (m, 4 H), 3.51–3.45 (m, 2 H), 1.77–1.68 (m, 4 H), 1.17 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 152.5, 149.7, 134.7, 125.3, 105.4, 105.1, 102.6, 61.5, 56.24, 56.21, 49.6, 42.2, 31.0, 23.7, 15.3 ppm. HRMS: m/z calcd. for $C_{18}H_{27}NO_5$ $[M + Na]^+$ 360.1781; found 360.1787.

2-Cyclohexyl-5,6-dimethoxyisoindolin-1-one (12d): Yield 44 mg (80%); white solid; m.p. 135–136 °C (ref.[27e] 136–138 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 6.93 (s, 1 H), 4.26 (s, 2 H), 4.23–4.17 (m, 1 H), 3.94 (s, 6 H), 1.87–1.84 (m, 4 H), 1.74–1.71 (m, 1 H), 1.51–1.40 (m, 4 H), 1.21–1.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 152.2, 149.6, 134.8, 125.7, 105.3, 105.0, 56.2, 50.6, 45.7, 31.5, 25.6, 25.5 ppm.

2-Benzyl-5,6-dimethoxyisoindolin-1-one (12e): Yield 47 mg (84%); yellow solid; m.p. 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (s, 1 H), 7.34–7.24 (m, 5 H), 6.85 (s, 1 H), 4.77 (s, 2 H), 4.17 (s, 2 H), 3.94 (s, 3 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 152.6, 149.7, 137.3, 134.8, 128.8, 128.0, 127.6, 124.8, 105.5, 105.1, 56.2, 49.1, 46.4 ppm. HRMS: m/z calcd. for $C_{17}H_{17}NO_3$ $[M + H]^+$ 284.1281; found 284.1286.

2-Benzyl-3-phenylisoindolin-1-one (12f): Yield 42 mg (70%); white solid; m.p. 135–136 °C (ref.[27f] 136 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 1 H), 7.46–7.43 (m, 2 H), 7.37–7.34 (m, 3 H), 7.29–7.25 (m, 3 H), 7.19–7.17 (m, 2 H), 7.17–7.06 (m, 3 H), 5.40 (d, J = 14.8 Hz, 1 H), 5.24 (s, 1 H), 3.73 (d, J = 14.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 146.4, 137.1, 136.8, 131.8, 131.4, 129.1, 128.7, 128.5, 128.3, 127.8, 127.6, 123.8, 123.2, 63.6, 43.8 ppm.

(*S*)-Methyl 2-(5,6-Dimethoxy-1-oxoisoindolin-2-yl)-3-phenylpropanoate (12g): Yield 51 mg (72%); pale-yellow solid; m.p. 76–77 °C (ref.[27e] 138–139 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 7.26–7.15 (m, 5 H), 6.86 (s, 1 H), 5.37 (dd, J = 10.4, 6.0 Hz, 1 H), 4.43 (d, J = 16.4 Hz, 1 H), 4.24 (d, J = 16.4 Hz, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.72 (s, 3 H), 3.48 (dd, J = 14.8, 5.8 Hz, 1 H), 3.18 (dd, J = 14.8, 10.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 169.2, 152.8, 149.7, 136.5, 135.3, 128.7, 128.5, 126.9, 124.1, 105.5, 105.0, 56.21, 56.19, 54.7, 52.4, 47.2, 35.9 ppm. HRMS: m/z calcd. for $C_{20}H_{21}NO_5$ $[M + Na]^+$ 378.1312; found 378.1283.

(*R*)-5,6-Dimethoxy-2-(1-phenylethyl)isoindolin-1-one (12h): Yield 46 mg (78%); pale-orange solid; m.p. 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 5 H), 7.28–7.24 (m, 1 H), 6.84 (s, 1 H), 5.76 (q, J = 7.0 Hz, 1 H), 4.24 (d, J = 16.8 Hz, 1 H), 3.93 (s, 4 H), 3.89 (s, 3 H), 1.67 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 152.5, 149.7, 140.9, 134.9, 128.6, 127.5, 127.1, 125.1, 105.5, 105.1, 56.23, 56.20, 49.2, 45.3, 17.4 ppm. HRMS: m/z calcd. for $C_{18}H_{19}NO_3$ $[M + Na]^+$ 320.1257; found 320.1231.

2-*tert*-Butyl-5,6-dimethoxyisoindolin-1-one (13): Yield 42 mg (84%); pale-yellow solid; m.p. 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 1 H), 6.88 (s, 1 H), 4.37 (s, 2 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 1.56 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 152.3, 149.6, 134.1, 126.8, 104.9, 104.7, 56.21, 56.15, 54.3, 48.1, 28.1 ppm. HRMS: m/z calcd. for $C_{14}H_{19}NO_3$ $[M + Na]^+$ 272.1257; found 272.1236.

4-Bromo-2-*tert*-butyl-5,6-dimethoxyisoindolin-1-one (14): To a stirred solution of **13** (125 mg, 0.5 mmol) in CCl_4 (15 mL) was added bromine (321 mg, 2.0 mmol) in CCl_4 (5 mL) over 5 min. The reaction mixture was stirred at room temperature for 3 h, then quenched with a 10% aq. $Na_2S_2O_5$ solution to remove excess bromine. The organic layer was separated, washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to give a pale-brown solid. The crude product was purified by column chromatography (EtOAc/hexane). Yield 118 mg (72%); m.p.100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 4.29 (s, 2 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 1.57 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 154.2, 149.2, 134.1, 130.9, 112.3, 105.5, 60.9, 56.4, 54.7, 48.8, 28.0 ppm. HRMS: m/z calcd. for $C_{14}H_{18}BrNO_3$ $[M + H]^+$ 328.0543; found 328.0548.

5-*tert*-Butyl-1,2-dimethoxy-5*H*-dibenzo[*cd*,*f*]indol-4-one (15): To a stirred solution of **14** (99 mg, 0.30 mmol) in toluene/EtOH (10 mL/5 mL), were added 2-formylboronic acid (54 mg, 0.36 mmol), $[Pd(PPh_3)_4]$ (14 mg, 4 mol-%), and Cs_2CO_3 (88 mg, 0.9 mmol). The reaction mixture was heated at reflux for 4 h, then cooled to room temperature and filtered through a Celite pad. The solution was diluted with EtOAc and the mixture was concentrated under reduced pressure and purified by column chromatography (EtOAc/hexane) to give **15**. Yield 70 mg (70%); yellow solid; m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22–9.18 (m, 1 H), 7.80–7.76 (m, 1 H), 7.72 (s, 1 H), 7.57–7.51 (m, 2 H), 7.41 (s, 1 H), 4.09 (s, 3 H), 4.05 (s, 3 H), 1.88 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 154.2, 151.0, 137.2, 134.9, 129.4, 127.4, 127.2, 126.4, 126.0, 123.3, 122.1, 120.9, 109.2, 108.6, 60.3, 58.4, 56.9,

29.8 ppm. HRMS: *m*/*z* calcd. for $C_{21}H_{21}NO_3$ [M + Na]$^+$ 358.1414; found 358.1419.

Aristolacatam BII (16): To solution of **15** (67 mg, 0.2 mmol) in 1,2-dichloroethane (5 mL) was added TFA (1.6 mL, 2.0 mmol). The reaction mixture was heated to reflux for 18 h, then the solvent was removed under vacuum. The residue was diluted with dichloromethane (10 mL), and triethylamine (1 mL) and water (2 mL) were added with stirring. The organic layer was separated, washed with brine, dried with Na_2SO_4 and concentrated to give a residue that was purified by column chromatography (EtOAc/hexane) to give **16**. Yield 50 mg (90%); pale-yellow solid; m.p. 253–254 °C (ref.[29] 254 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.85 (s, 1 H), 9.09 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 9.2 Hz, 1 H), 7.82 (s, 1 H), 7.58–7.54 (m, 2 H), 7.15 (s, 1 H), 4.012 (s, 3 H), 4.005 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 154.2, 150.5, 134.9, 134.7, 129.1, 127.6, 126.8, 125.9, 125.7, 123.2, 121.3, 119.9, 109.8, 105.0, 60.0, 56.9 ppm.

General Procedure for the Condensation of Tricarbonyl Compounds with Diamines/Aminoethanol: To a solution of **2**, **4b** or **4c** (0.2 mmol) in EtOH (5 mL), diamine (0.22 mmol; for **21a**–**c**, 0.42 mmol was used) or amino ethanol (0.42 mmol) was added. The reaction mixture was stirred at room temperature for 5–30 min, then diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried with Na_2SO_4, filtered and the solvents evaporated. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:1 v/v).

6-Hydroxy-2,3-dimethoxy-6-phenylbenzo[4,5]imidazo[2,1-*a*]isoquinolin-5-one (17) and 2-[2-(1*H*-Benzo[*d*]imidazol-2-yl)-4,5-dimethoxyphenyl]-3-phenylquinoxaline (18): From **2** (53.2 mg) and *o*-phenylenediamine (24 mg), the products **17** and **18** were obtained as yellow solids.

Compound 17: Yield 48 mg (63%); m.p. 215–216 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.32 (s, 1 H), 7.98 (s, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.37–7.22 (m, 7 H), 7.18–7.16 (m, 1 H), 4.14 (s, 3 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 191.0, 155.2, 151.2, 145.5, 143.7, 138.7, 134.4, 128.8, 128.7, 125.4, 124.5, 123.1, 122.8, 120.4, 119.5, 113.4, 108.7, 106.6, 87.9, 56.3, 55.8 ppm. MS (ESI): *m*/*z* = 387 [M + H]$^+$. $C_{23}H_{18}N_2O_4$: C 71.49, H 4.70, N 7.25; found C 71.68, H 4.60, N 7.39.

Compound 18: Yield 9 mg (10%); m.p. 242–243 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 1 H), 7.66–7.62 (m, 1 H), 7.52 (br. s, 1 H), 7.38–7.19 (m, 7 H), 7.02–6.98 (m, 3 H), 6.73 (d, *J* = 7.6 Hz, 2 H), 6.57 (s, 1 H), 3.92 (s, 3 H), 2.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 153.2, 151.2, 149.7, 149.5, 141.5, 139.8, 137.2, 130.5, 130.2, 129.7, 129.0, 128.4, 128.1, 128.0, 125.9, 124.3, 122.5, 113.8, 112.7, 56.0, 55.2 ppm. MS (ESI): *m*/*z* = 481 [M + Na]$^+$. $C_{29}H_{22}N_4O_2$: C 75.97, H 4.84, N 12.22; found C 76.18, H 4.92, N 12.35. Single crystals suitable for X-ray studies were grown from a solution of **18** in ethanol/ethyl acetate (1:1).

[2-(3-Phenylquinoxalin-2-yl)phenyl](*p*-tolyl)methanone (19a): Obtained from **4b** (66 mg) and *o*-phenylenediamine (24 mg). Yield 63 mg (78%); white solid; m.p. 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 1 H), 8.01–7.98 (m, 1 H), 7.71–7.67 (m, 2 H), 7.60–7.54 (m, 2 H), 7.46–7.34 (m, 6 H), 7.25–7.22 (m, 1 H), 7.18–7.14 (m, 2 H), 7.09–7.07 (m, 2 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 153.8, 153.4, 143.3, 141.3, 141.0, 140.8, 139.1, 138.5, 134.5, 131.4, 130.9, 130.19, 130.15, 130.05, 129.8, 129.6, 129.2, 129.1, 128.7, 128.6, 128.1, 127.8, 21.6 ppm. MS (ESI): *m*/*z* = 402 [M + 2 H]$^{2+}$. $C_{28}H_{20}N_2O$: C 83.98, H 5.03, N 7.00; found C 84.27, H 5.18, N 7.21.

(4-Methoxyphenyl)[2-(3-phenylquinoxalin-2-yl)phenyl]methanone (19b): Obtained from **4c** (69 mg) and *o*-phenylenediamine (24 mg). Yield 66 mg (80%); brown semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 1 H), 7.99–7.97 (m, 1 H), 7.74–7.52 (m, 4 H), 7.47–7.42 (m, 6 H), 7.26–7.21 (m, 1 H), 7.18–7.14 (m, 2 H), 6.79–6.76 (m, 2 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1, 163.2, 153.8, 153.4, 141.3, 141.0, 140.7, 139.3, 138.5, 132.4, 131.4, 130.8, 130.2, 130.0, 129.8, 129.6, 129.3, 129.1, 128.7, 128.1, 127.8, 113.2, 55.4 ppm. HRMS: *m*/*z* calcd. for $C_{28}H_{20}N_2O_2$ [M + H]$^+$ 417.1598; found 417.1625.

(6,7-Dimethoxyphthalazin-1-yl)(phenyl)methanone (20a): Obtained from **2** (53 mg) and hydrazine hydrate (11 mg). Yield 40 mg (68%); white solid; m.p.142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 8.07–8.04 (m, 2 H), 7.66–7.62 (m, 1 H), 7.59 (s, 1 H), 7.52–7.48 (m, 2 H), 7.27 (s, 1 H), 4.10 (s, 3 H), 4.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 155.0, 154.5, 150.2, 136.5, 134.0, 131.2, 128.5, 121.9, 104.7, 103.4, 56.52, 56.49 ppm. HRMS: *m*/*z* calcd. for $C_{17}H_{14}N_2O_3$ [M + H]$^+$ 295.1077; found 295.1082.

Phenyl(4-*p*-tolylphthalazin-1-yl)methanone (20b): Obtained from **4b** (66 mg) and hydrazine hydrate (11 mg). Yield 46 mg (70%); pale-yellow solid; m.p. 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.20 (m, 2 H), 8.12 (d, *J* = 7.2 Hz, 2 H), 7.92–7.87 (m, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.41 (d, *J* = 7.6 Hz, 2 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 160.9, 155.0, 140.0, 136.3, 134.1, 133.0, 132.8, 132.7, 131.1, 130.3, 129.4, 128.6, 126.9, 126.0, 125.5, 125.4, 21.5 ppm. HRMS: *m*/*z* calcd. for $C_{22}H_{16}N_2O$ [M + H]$^+$ 325.1341; found 325.1371. Single crystals suitable for X-ray studies were grown from a solution of **20b** in dichloromethane.

[4-(4-Methoxyphenyl)phthalazin-1-yl](phenyl)methanone (20c): Obtained from **4c** (69 mg) and hydrazine hydrate (11 mg). Yield 50 mg (74%); pale-yellow solid; m.p. 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31–8.24 (m, 2 H), 8.14–8.12 (m, 2 H), 7.93–7.91 (m, 2 H), 7.83–7.80 (m, 2 H), 7.67–7.64 (m, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 161.0, 160.4, 154.8, 136.3, 134.1, 132.8, 132.7, 131.8, 131.1, 128.6, 128.2, 126.9, 125.9, 125.6, 125.4, 114.2, 55.5 ppm. MS (ESI): *m*/*z* = 341 [M + H]$^+$. $C_{22}H_{16}N_2O_2$: C 77.63, H 4.74, N 8.23; found C 77.84, H 4.89, N 8.38.

5,6-Dimethoxy-2-(*N*-benzoylaminoethyl)-2,3-dihydroisoindol-1-one (21a): Obtained from **2** (53 mg) and 1,2-diaminoethane (25 mg). Yield 53 mg (78%); yellow solid; m.p. 204–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.82 (m, 2 H), 7.61 (br. s, 1 H), 7.47–7.39 (m, 3 H), 7.24 (s, 1 H), 6.90 (s, 1 H), 4.41 (s, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.89–3.87 (m, 2 H), 3.77–3.74 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 167.7, 152.8, 149.8, 135.1, 134.0, 131.4, 128.5, 127.1, 124.4, 105.2, 105.0, 56.24, 56.21, 50.7, 42.4, 40.4 ppm. HRMS: *m*/*z* calcd. for $C_{19}H_{20}N_2O_4$ [M + H]$^+$ 341.1496; found 341.1501.

3-(4-Methoxyphenyl)-2-(*N*-benzoylaminoethyl)-2,3-dihydroisoindol-1-one (21b): Obtained from **4c** (69 mg) and 1,2-diaminoethane (25 mg). Yield 70 mg (91%); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 3 H), 7.70 (br. s, 1 H), 7.49–7.37 (m, 5 H), 7.16 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.55 (s, 1 H), 4.02–3.97 (m, 1 H), 3.81 (s, 3 H), 3.79–3.74 (m, 1 H), 3.42–3.32 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 167.7, 160.1, 146.8, 134.0, 132.2, 131.4, 131.0, 129.1, 128.5, 128.4, 128.1, 127.1, 123.4, 123.3, 114.7, 65.0, 55.3, 40.24, 40.18 ppm. HRMS: *m*/*z* calcd. for $C_{24}H_{22}N_2O_3$ [M + Na]$^+$ 409.1523; found 409.1516.

3-(4-Methoxyphenyl)-2-(*N*-benzoylaminopropyl)-2,3-dihydroisoindol-1-one (21c): Obtained from **4c** (69 mg) and 1,2-diaminopro-

pane (31 mg). Yield 66 mg (83%); orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.89 (m, 4 H), 7.51–7.42 (m, 5 H), 7.20–7.18 (m, 1 H), 7.04 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.43 (s, 1 H), 3.88–3.86 (m, 1 H), 3.79 (s, 3 H), 3.70–3.65 (m, 1 H), 3.21–3.10 (m, 2 H), 1.73–1.61 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 167.2, 160.1, 146.6, 134.4, 132.1, 131.3, 131.1, 129.0, 128.5, 128.2, 127.1, 123.5, 123.3, 114.6, 64.5, 55.3, 37.2, 35.8, 27.5 ppm. HRMS: m/z calcd. for $C_{25}H_{24}N_2O_3$ $[M + H]^+$ 401.1860; found 401.1872.

5,6-Dimethoxy-2-(benzoyloxyethyl)-2,3-dihydroisoindol-1-one (22a): Obtained from **2** (53 mg) and 2-aminoethanol (26 mg). Yield 47 mg (69%); pale-yellow solid; m.p. 106–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.59–7.55 (m, 1 H), 7.47–7.43 (m, 2 H), 7.32 (s, 1 H), 6.91 (s, 1 H), 4.57 (t, J = 5.4 Hz, 2 H), 4.44 (s, 2 H), 4.01 (t, J = 5.4 Hz, 2 H), 3.93 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 166.4, 152.6, 149.7, 134.9, 133.2, 129.8, 129.6, 128.5, 124.6, 105.4, 105.0, 63.5, 56.2, 50.7, 41.7 ppm. HRMS: m/z calcd. for $C_{19}H_{19}NO_5$ $[M + Na]^+$ 364.1155; found 364.1161.

3-(4-Methoxyphenyl)-2-(benzoyloxyethyl)-2,3-dihydroisoindol-1-one (22b): Obtained from **4c** (69 mg) and 2-aminoethanol (26 mg). Yield 69 mg (89%); pale-brown solid; m.p. 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.98 (m, 2 H), 7.91–7.89 (m, 1 H), 7.58–7.54 (m, 1 H), 7.48–7.41 (m, 4 H), 7.16–7.14 (m, 1 H), 7.01 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 5.56 (s, 1 H), 4.58–4.52 (m, 1 H), 4.42–4.36 (m, 1 H), 4.33–4.27 (m, 1 H), 3.77 (s, 3 H), 3.33–3.28 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 166.3, 160.0, 146.7, 133.1, 131.9, 131.2, 129.9, 129.7, 128.9, 128.5, 128.4, 128.3, 123.6, 123.2, 114.6, 64.7, 62.9, 55.3, 39.2 ppm. HRMS: m/z calcd. for $C_{24}H_{21}NO_4$ $[M + H]^+$ 388.1543; found 388.1549.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all compounds and ORTEP plots of **4b**, **18** and **20b**.

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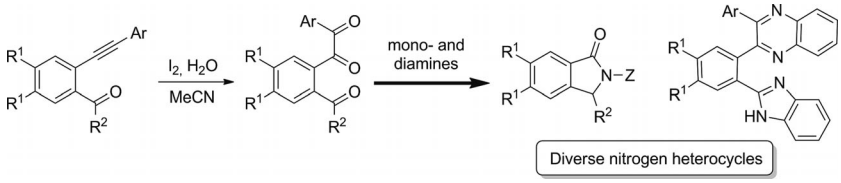

Tricarbonyl compounds obtained from the oxidation of *o*-alkynylaroyl compounds using an iodine/water system act as useful precursors for the synthesis of a diverse range of heterocycles, including a natural product.

Keywords: Synthetic methods / Oxidation / Nitrogen heterocycles / Alkynes / Neighboring-group effects

