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DMSO–PdI_2 as a powerful oxidizing couple of alkynes into benzils: one-pot synthesis of nitrogen-containing five- or six-membered heterocycles

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Abstract

PdI_2 in DMSO promoted the oxidation of functionalized diarylalkynes into benzil derivatives in excellent yields. This new oxidation reaction was achieved with short reaction times and low loading of palladium catalyst. This efficient catalytic process has been applied successfully to the one-pot construction of a series of nitrogen-containing heterocycles of biological interest according to a tandem oxidation–nitrogen nucleophiles condensation–cyclization.

Keywords: Benzils; Palladium; DMSO; Alkynes; Oxidation; Tandem reactions; Heterocyclic compounds

1. Introduction

In the manufacture of pharmaceutical targets, increasing attention is now being paid to simplification and improvement of the existing methods. The oxidation of substituted diarylalkynes, readily accessible via Sonogashira–Linstrumelle (S–L) coupling,[1] constitutes one of the most versatile processes in organic chemistry for the synthesis of benzils.[2] The latter have received a great deal of attention because of their properties and as useful synthetic intermediates in the preparation of various heterocyclic compounds of biological interest[3] including, imidazoles or quinoxalines. The oxidation reaction has been widely explored using various oxidant systems such as $KMnO_4$,[4] SO_3/dioxane,[5] H_5IO_6,[6] $Co(OAc)_2/Mn(OAc)_2$/NaBr,[7] or $H_2O_2/Fe(PA)_2$[8] (bis-(picolinato)iron(II)). Though all these transformations are suitable methods with a range of simple diarylalkynes, many of them display low chemoselectivity and provide low yields with substrates having sensitive functionalities. During the last decade, DMSO has been successfully used as an oxidant either in the presence of $CH_3SO_3H/HCO_2H/HBr$[9] mixture or $PdCl_2$.[10] Typically in the latter case, the reaction is reported to require high loading of catalyst (10 mol %) and long reaction times, sometimes extending into days that can seriously affect the yield and the outcome of the oxidation reaction, particularly with substrates having strong electron-withdrawing groups[5,11] (e.g., CN, NO_2) or an *ortho* substituent.[12] Additionally, the oxidation reaction of the triple bond is far from trivial with substrates containing a heteroaryl nucleus including for instance a pyridine or a pyrazole.[10,13] Therefore, alternative routes and more reliable procedures for the synthesis of benzils are welcome. The remaining challenge is to obtain highly substituted benzils from functionalized diarylalkynes without compromising reagent safety, simplicity, and practicality.

Recently, we reported the DMSO-oxidation of functionalized diarylalkynes in the presence of various transition metal

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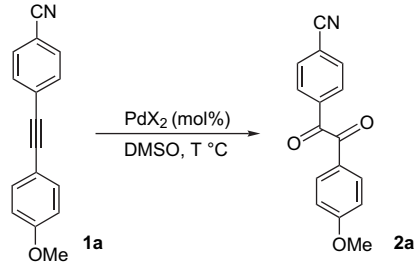
salts.[14] We have found that the better results were obtained using a catalytic amount (10 mol %) of environmentally friendly $FeBr_3$ or $FeBr_3$/TfOH combination that act as Lewis acids to activate the triple bond, and further allowing successive additions of DMSO. However, during this study we noticed that substrates having a free phenolic function or a cyano group, for instance, were resistant to the oxidation reaction, and gave in best cases the corresponding benzils with moderate to low yields.

In an ongoing medicinal chemistry program toward the synthesis of substituted heterocyclic compounds,[15] we required a more reliable and chemoselective procedure for the synthesis of several benzils that could be used in situ as intermediates for the elaboration of the desired target molecules. The procedure should be environmentally benign and not involve the use of highly toxic and hazardous reagents. To this end, we explored the use of PdI_2 as a catalyst for the oxidation of diarylalkynes with DMSO with the hope that its best Lewis acid character in comparison with $PdCl_2$, would confer to the Pd(II) catalyst a better catalytic activity, thus reducing the reaction times and the quantity of catalyst. Herein, we report the results of this study and disclose that catalytic PdI_2 in DMSO can be conveniently combined with the condensation reaction of various nitrogen nucleophiles with benzil intermediates to prepare efficiently in a one-pot procedure nitrogen-containing heterocycles.

2. Results and discussion

At first, the oxidation reaction in DMSO was studied with the model substrate **1a** bearing a *p*-CN group, which is usually resistant to oxidation.[14] The results summarized in Table 1 describe the effects of various palladium salts catalysts, additives, and temperature on the outcome of this reaction.

Table 1
Oxidation of diarylalkyne **1a** to benzil **2a**



Entry	Catalyst (mol %)		*T* (°C)	Time (h)	Yield[a] (%)
1	$PdBr_2$	10	140	2.5	95
2	$PdBr_2$/TfOH	10:20	140	0.25	92
3	PdI_2	10	140	0.15	93
4	PdI_2/TfOH	10:20	140	0.20	91
5	PdI_2	10	100	2	93
6	PdI_2	5	140	1	93
7	**PdI_2**	**2**	**140**	**1**	**91**
8	PdI_2	1	140	5	97
9	$PdCl_2$	2	140	1	38
10	$PdCl_2$	2	140	8	59

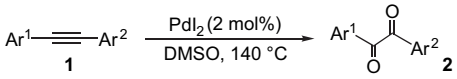
[a] Isolated yield.

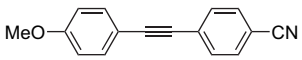
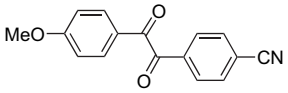
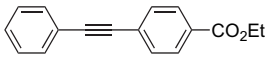
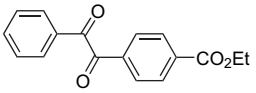
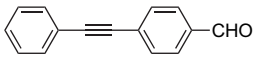
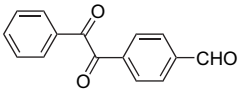
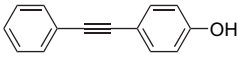
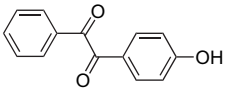
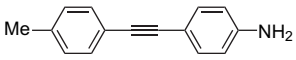
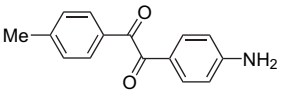
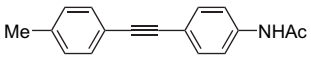
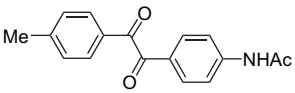
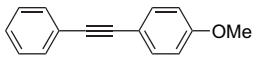
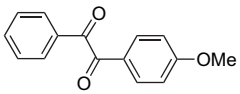
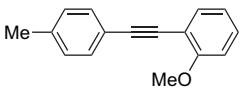
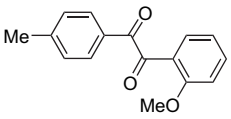
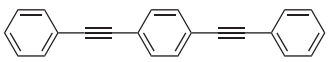
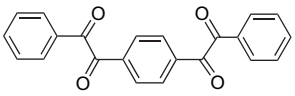
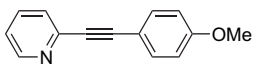
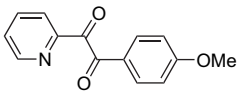
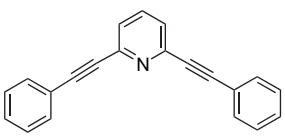
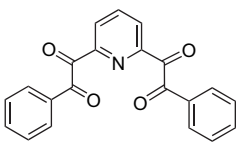
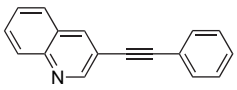
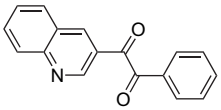
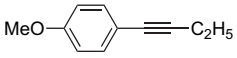
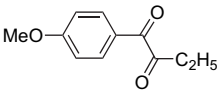
To evaluate the efficiency of Pd(II) salts catalysts, first attempts were carried out by using the same reaction parameters (140 °C, catalyst: 10 mol %) as we previously described in the alkyne activation by iron bromide.[14] We were pleased to observe that $PdBr_2$ (10 mol %) efficiently catalyzed the oxidation of **1a** within 2.5 h in an excellent isolated yield and no hydrolyzed by-products could be detected (entry 1). In order to increase the Lewis acidity of the Pd(II) catalyst, the next experiment was achieved by adding TfOH (20 mol %) to $PdBr_2$. Accordingly, the oxidation occurred within only 25 min and **2a** was formed in 92% yield (entry 2). Similar experiments were achieved by changing $PdBr_2$ to PdI_2. We found that PdI_2 proves to be a more efficient catalyst to oxidize **1a** even without the additional help of TfOH (entries 3 and 4). Next, the effect of the temperature was investigated. At a lower temperature (100 °C; entry 5), total disappearance of the starting alkyne **1a** was observed but after a prolonged reaction time (entry 5, 2 h). We then decided to determine at 140 °C the useful amount of PdI_2 to properly carry out this oxidation in a reasonable time. Results described in entries 6–8 clearly showed that the quantity of catalyst could be decreased to 2 mol % without loss of efficiency, whereas a longer reaction time was required when using only 1 mol % of PdI_2. The supremacy of PdI_2 toward $PdCl_2$ was clearly demonstrated in term of shortened reaction time and efficiency by the next attempts. Thus, replacing PdI_2 by $PdCl_2$ (2 mol %, 1 h, 140 °C) induced a lowering of the conversion rate and gave **2a** in only 38% yield (entry 9). In this case, as shown in entry 10, 8 h were required to observe total conversion of **1a**, and **2a** was isolated in only 59% yield.

With optimized conditions in hand, we subsequently explored the scope of this reaction with a series of substrates, well-known to be resistant to the oxidation reaction. As summarized in Table 2, various diarylalkynes undergo efficiently the oxidation reaction with the catalytic system PdI_2/DMSO. The representative examples in Table 2, illustrate the generality of this reaction. Diarylalkynes **1b** and **1c**, containing electron-withdrawing groups, were oxidized, respectively, in 3 and 5 h to the corresponding benzil derivatives in excellent isolated yields (entries 2 and 3). When substrate **1d** containing a free phenolic group was treated under these conditions, we were pleased to observe that the expected *p*-OH substituted benzil **2d** was obtained in a good yield and in a reasonable reaction time (entry 4). However, with alkyne **1e** having a free amino function, the reaction turned out to be less effective even if other palladium salt sources were used (entry 5) and gave a complex mixture of non-identified by-products. Fortunately, this limitation could be circumvented by decreasing the nucleophilicity of the nitrogen atom as we observed with an acetamide function (entry 6, 93%). Results depicted in entries 7 and 8 clearly showed that switching the substituent's position on the aromatic from *para* to *ortho* did not affect the yield of the reaction but a prolonged reaction time was required for the oxidation of the more hindered aromatic ring.

The efficiency of the PdI_2/DMSO system was also demonstrated with alkyne **1i** having two carbon–carbon triple bond as it proved to be a suitable substrate for this oxidation

Table 2
PdI_2 mediated oxidation of alkynes **1** into benzil derivatives **2** in DMSO



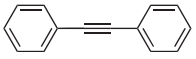
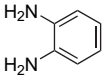
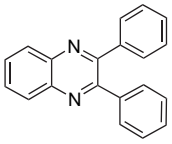
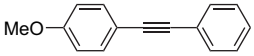
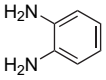
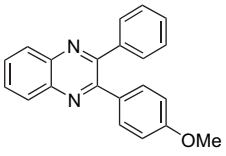
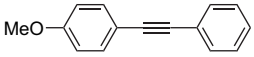
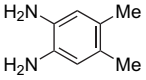
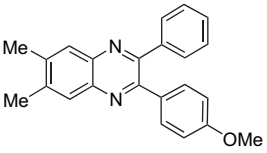
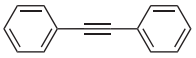
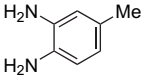
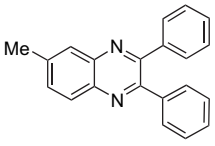
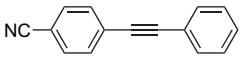
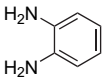
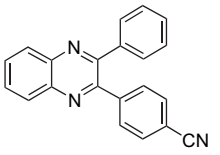
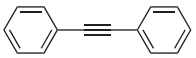
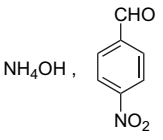
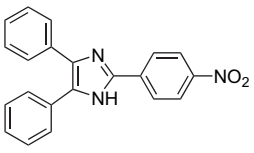
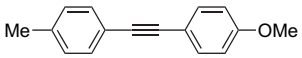
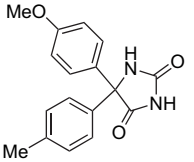
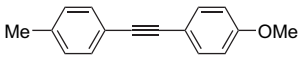
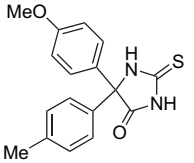
Entry	Akynes **1**		Benzils **2**		Time (h)	Yield[a] (%)
1		**1a**		**2a**	1	91
2		**1b**		**2b**	3	96[b]
3		**1c**		**2c**	5	93[c]
4		**1d**		**2d**	4	84
5		**1e**		**2e**	—	0
6		**1f**		**2f**	3	93
7		**1g**		**2g**	2	98[d]
8		**1h**		**2h**	8	96
9		**1i**		**2i**	6	90
10		**1j**		**2j**	9	62[e]
11		**1k**		**2k**	9	57
12		**1l**		**2l**	2	90[f]
13		**1m**		**2m**	1.5	58

[a] Isolated yield. All new compounds exhibited satisfactory spectral properties and microanalyses.
[b] Using $PdCl_2$ (10 mol %) instead of PdI_2 (2 mol %), **2b** was obtained within 12 h in only 60% yield.
[c] Using $PdCl_2$ (10 mol %) instead of PdI_2 (2 mol %), **2c** was obtained in only 68% yield; see Ref. 12b.
[d] No oxidation occurred when using $PdCl_2$ (10 mol %) instead of PdI_2 (2 mol %); see Ref. 12b.
[e] A 26% yield of **2j** was obtained in the presence of $PdCl_2$ (10 mol %).
[f] A 45% yield of **2l** was obtained in the presence of $PdCl_2$ (10 mol %).

reaction affording **2i** in an excellent yield (95% per triple bond, entry 9). In the following examples, it is interesting to note that the reaction conditions were successfully applied to a series of alkynes having a heteroaromatic nucleus without any difficulty. Thus, replacing a phenyl ring by a 2-pyridyl substituent, the procedure was still efficient and furnished the corresponding benzil **2j** in a satisfactory isolated yield and a reasonable reaction time (entry 10). The catalytic activity of PdI_2 proved to be superior to $PdCl_2$, as the use of $PdCl_2$ induced a lowering of the conversion rate and gave **2j** in only 26% yield. When carrying out the reaction with 2,6-disubstituted pyridine **1k**, we were pleased to observe that the oxidation process occurred leading to benzil **2k** in a good yield (57% for the two triple bonds, entry 11). As expected, the presence of a quinoline moiety on the triple bond did not impact the outcome of the oxidation reaction and gave benzil **2l** in 90% yield (entry 12), while a much lower yield was obtained when using $PdCl_2$ instead of PdI_2 (45% not shown in table). Finally, aliphatic arylalkyne **1m** was also effective for the reaction and its oxidation provided the enolizable adduct 1,2-diketone **2m** in a 58% non-optimized isolated yield (entry 13).

Being given the high efficiency of this oxidation reaction, we expected that the newly developed procedure would serve

Table 3
Tandem oxidation–nitrogen nucleophiles condensation–cyclization: one-pot synthesis of heterocycles **3**

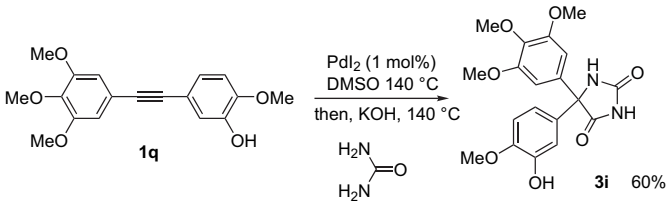
Entry	Akynes **1**		Nitrogen-nucleophile	Heterocycles **3**		Time (h) **1**→[**2**]→**3**	Yield[a] (%)
1		**1n**			**3a**	2+3	82
2		**1g**			**3b**	2+6	80
3		**1g**			**3c**	2+8	77
4		**1n**			**3d**	2+3	88
5		**1o**			**3e**	2+2	97
6		**1n**			**3f**	2+10	96
7		**1p**			**3g**	2+2	90
8		**1p**			**3h**	2+1	88

[a] Isolated yield. All compounds exhibited satisfactory spectral properties and analyses.

as an extremely useful and quick synthetic route to obtain nitrogen-containing heterocyclic including quinoxaline and imidazole derivatives. These classes of substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as biologically active compounds. In this context, we were interested to investigate the construction of these heterocyclic skeletons in a one-pot procedure as it would be economically and environmentally advantageous over multi-step syntheses.

Initially, the reagents and catalyst are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. Typically, the reaction was carried out by heating at 140 °C diphenylalkyne **1n** with PdI_2 (2 mol %) in DMSO in the presence of 1,2-phenylenediamine (2 equiv). Unfortunately, under these conditions, no significant formation of the desired quinoxaline **3a** was observed, even after prolonged stirring, owing to probable nitrogen-oxidation side reactions. We then decided to achieve this transformation in a sequential way by heating DMSO in a first step, **1n** with PdI_2 (2 mol %) then, by introducing 1,2-phenylenediamine (2 equiv) in a second step. Thus under the protocol described above, we were pleased to observe that the tandem sequence worked very well and provided the desired quinoxaline **3a** in 82% yield. The results summarized in Table 3 show that this tandem oxidation–nitrogen nucleophiles condensation–cyclization was highly effective with a variety of diarylalkynes and nitrogen nucleophile reagents including anilines, NH_4OH, urea… Thus, quinoxalines **3b–e** variously substituted (Me, OMe, CN) were synthesized according to the procedure described above in good yields ranging from 77% (entry 3) to 97% (entry 5). Moreover, this protocol is also convenient as it opens up an easy access to substituted imidazoles. As expected (entry 6), imidazole **3f** was obtained in an excellent 96% yield from alkyne **1n** (1 equiv), 4-nitrobenzaldehyde (1 equiv), and NH_4OH (10 equiv). Interestingly, when alkyne **1p** was heated in DMSO in the presence of PdI_2, the corresponding 1,2-diketone, which upon refluxing with urea or thiourea cyclized to form in good yields the imidazolidin-2,4-dione **3g** and thioxoimidazolidin-2,4-dione **3h**, respectively (entries 7 and 8). Altogether, these results demonstrated the efficiency of this tandem oxidation–nitrogen nucleophiles condensation–cyclization to provide in a one-pot way a broad variety of nitrogen-containing heterocycles of biological interest.

Finally, starting from the alkyne **1q** the newly developed one-pot procedure have been successfully used for the synthesis of the thioxoimidazolidin-2,4-dione **3i** having both a 3,4,5-trimethoxyphenyl and a 3-hydroxy-4-methoxyphenyl rings (Scheme 1). The latter may be regarded as an analogue of the natural combretastatin A-4 (CA-4),[16] well-known to act as both antimitotic and as a selective inhibitor of tumor vasculature growth. Compound **3i** was evaluated for cytoxicity in human colon cancer HCT116 cells and was compared in contemporaneous experiment to the CA-4. Unfortunately, the newly synthesized compound was significantly less potent (IC_{50}=100 μM) in the growth inhibition assay in HCT116 cells than CA-4 (IC_{50}=2 nM) and was no further studied.



Scheme 1. One-pot synthesis of thioxoimidazolidin-2,4-dione **3i** related to combretastatin A-4 (CA-4).

3. Conclusion

In summary, we successfully described a simple, rapid, and high yielding synthesis of functionalized benzils from diarylalkynes using the couple PdI_2/DMSO. The chemoselectivity of this procedure, which requires low loading of catalyst, must be underlined as different substituents on the aromatic rings were tolerated as well as nitrogen-containing heterocycles' nucleus. More interestingly, the procedure can be extended to the one-pot preparation of various heterocyclic compounds (quinoxalines, imidazoles, imidazolidine-2,4-diones…) based on a tandem oxidation–nitrogen nucleophiles condensation–cyclization. Variation is allowed in each of the partners, thus making a wide range of accessible heterocycles. This process is not only of interest for combinatorial synthesis of heterocycles, but in many cases, also offers considerable synthetic advantages in term of yield, selectivity, and simplicity of the reaction procedure.

4. Experimental

4.1. Instrumentation

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker Avance 300 (300 MHz). ^{1}H chemical shifts are reported in parts per million from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet). ^{13}C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Mass spectra were obtained with a Esquire LC Bruker spectrometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

4.2. General procedure for the preparation of benzils *2a–p* from alkynes

A mixture of alkyne **1** (1 mmol) and PdI_2 (7.2 mg; 0.02 mmol) in 7 mL of DMSO was stirred at 140 °C for an appropriate time (see Table 2). After cooling to room temperature, H_2O (15 mL) was added and the mixture was extracted

with EtOAc (3×15 mL). Organic layers were then washed with an aqueous saturated NH_4Cl solution, dried, and concentrated. The crude mixture was then purified by column chromatography on silica gel to give benzil compounds **2**.

4.2.1. 1-(4-Methoxyphenyl)-2-(4-cyanophenyl)ethane-1,2-dione **2a**

Yield: 91%. Yellow solid, mp: 164–166 °C. TLC: R_f 0.81 (CH_2Cl_2, SiO_2). IR (neat) ν_{max}/cm^{-1}: 2940, 2229, 1674, 1650, 1597, 1570, 1510, 1427, 1408, 1312, 1267, 1213, 1166, 1048, 1028, 884, 841, 781, 745. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.09 (d, 2H, J=8.7 Hz), 7.95 (d, 2H, J=9.0 Hz), 7.80 (d, 2H, J=8.7 Hz), 7.00 (d, 2H, J=9.0 Hz), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 192.6 (C), 191.4 (C=O), 165.4 (C=O), 136.1 (C), 132.6 (2CH), 132.5 (2CH), 130.2 (2C), 125.5 (C), 117.6 (2C), 114.5 (2CH), 55.7 (OCH_3). MS (APCI): m/z 266 $(M+H)^+$.

4.2.2. Ethyl 4-(2-oxo-2-phenylacetyl)benzoate **2b**

Yield: 96%. Yellow solid, mp: 75–77 °C. TLC: R_f 0.48 (cyclohexane/EtOAc, 60:40, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1719, 1670, 1596, 1580, 1503, 1450, 1408, 1368, 1273, 1206, 1177, 1105, 1018, 887, 847, 782, 734, 711. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.15 (d, 1H, J=8.4 Hz), 8.02 (d, 2H, J=8.4 Hz), 7.96 (d, 2H, J=7.5 Hz), 7.66 (t, 1H, J=7.5 Hz), 7.51 (t, 2H, J=7.5 Hz), 4.40 (q, 2H, J=7.2 Hz), 1.39 (t, 3H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 193.8 (CO), 193.7 (CO), 165.3 (C), 136.0 (C), 135.7 (CH), 135.1 (CH), 132.7 (C), 130.0 (2CH), 129.9 (2CH), 129.7 (2CH), 129.1 (2CH), 61.6 (CH_2), 14.2 (CH_3). MS (APCI): m/z 283 $(M+H)^+$.

4.2.3. Ethyl 4-(2-oxo-2-phenylacetyl)benzaldehyde **2c**

Yield: 93%. Yellow solid, mp: 73–75 °C. TLC: R_f 0.35 (cyclohexane/EtOAc, 80:20, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1704, 1669, 1595, 1576, 1501, 1450, 1418, 1385, 1304, 1202, 1180, 1014, 881, 822, 791, 752, 719. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 10.11 (s, 1H), 8.12 (d, 2H, J=8.4 Hz), 7.95–8.02 (m, 4H), 7.67 (tt, 1H, J=7.2, 1.2 Hz), 7.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 193.5 (CO), 193.4 (CO), 191.2 (CHO), 139.9 (C), 136.9 (C), 135.2 (CH), 132.5 (C), 130.3 (2CH), 130.0 (2CH), 129.9 (4CH), 129.1 (2CH). MS (APCI): m/z 283 $(M-H)^-$.

4.2.4. N-(4-(2-Oxo-2-p-tolylacetyl)phenyl)acetamide **2f**

Yield: 93%. Yellow solid, mp: 123–125 °C. TLC: R_f 0.38 (cyclohexane/EtOAc, 60:40, SiO_2). IR (neat) ν_{max}/cm^{-1}: 3323, 1671, 1589, 1526, 1410, 1371, 1318, 1265, 1220, 1169, 1121, 1017, 887, 851, 766, 745. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.22 (s, 1H), 7.80–7.74 (m, 4H), 7.57 (d, 2H, J=7.5 Hz), 7.21 (d, 2H, J=7.8 Hz), 2.34 (s, 3H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 194.7 (CO), 193.7 (CO), 169.1 (NHCO), 146.4 (C), 144.1 (C), 131.3 (2CH), 130.4 (C), 130.0 (2CH), 129.7 (2CH), 129.3 (C), 119.2 (2CH), 24.7 (CH_3), 21.9 (CH_3). MS (APCI): m/z 282 $(M+H)^+$.

4.2.5. 1-(2-Methoxyphenyl)-2-p-tolylethane-1,2-dione **2h**

Yield: 98%. Yellow solid, mp: 98–101 °C. TLC: R_f 0.38 (cyclohexane/EtOAc, 80:20, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1660, 1599, 1485, 1466, 1438, 1266, 1203, 1178, 1161, 1114, 1018, 883, 831, 732, 703. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 7.93 (dd, 1H, J=7.8, 1.8 Hz), 7.73 (d, 2H, J=8.4 Hz), 7.52–7.47 (m, 1H), 7.20 (d, 2H, J=8.4 Hz), 7.05–7.00 (m, 1H), 6.84 (d, 1H, J=8.4 Hz), 3.48 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 194.7 (CO), 193.3 (CO), 160.4 (C), 144.7 (C), 136.3 (CH), 130.5 (CH), 130.4 (C), 129.4 (4CH), 123.9 (C), 121.4 (CH), 112.3 (CH), 55.6 (CH_3), 21.8 (CH_3). MS (ESI): m/z 277 $(M+Na)^+$.

4.2.6. 1,4-Bis(phenylglyoxalyl)benzene **2i**

Yield: 90%. Yellow solid, mp: 124–125 °C. TLC: R_f 0.19 (cyclohexane/CH_2Cl_2, 80:20, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1665, 1596, 1582, 1502, 1449, 1406, 1307, 1203, 1181, 1000, 936, 880, 831, 790, 725, 710. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.10 (s, 4H), 7.96 (d, 4H, J=7.5 Hz), 7.68 (t, 2H, J=7.5 Hz), 7.52 (t, 4H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 193.3 (2CO), 193.2 (2CO), 137.0 (2C), 135.2 (2C), 132.4 (2CH), 130.2 (4CH), 130.9 (4CH), 129.1 (4CH). MS (ESI): m/z 343 $(M+H)^+$.

4.2.7. 1-(4-Methoxyphenyl)-2-(pyridine-2-yl)ethane-1,2-dione **2j**

Yield: 62%. Brown solid, mp: 97–98 °C. TLC: R_f 0.22 (cyclohexane/EtOAc, 70:30, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1696, 1666, 1597, 1575, 1511, 1464, 1440, 1424, 1312, 1258, 1225, 1169, 1113, 1060, 1022, 995, 890, 843, 812, 795, 746. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.63 (d, 1H, J=4.5 Hz), 8.15 (d, 1H, J=7.8 Hz), 7.92–7.88 (m, 3H), 7.50–7.46 (m, 1H), 6.87 (d, 2H, J=9 Hz), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 195.4 (CO), 194.6 (CO), 164.5 (C), 151.9 (C), 149.9 (CH), 137.4 (CH), 132.1 (2CH), 128.1 (CH), 126.4 (C), 123.3 (CH), 114.4 (2CH), 55.7 (CH_3). MS (ESI): m/z 242 $(M+H)^+$.

4.2.8. 1-Phenyl-2-(quinolin-3-yl)ethane-1,2-dione **2l**

Yield: 90%. Yellow solid, mp: 127–129 °C. TLC: R_f 0.33 (cyclohexane/EtOAc, 80:20, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1665, 1616, 1594, 1570, 1495, 1450, 1420, 1374, 1319, 1298, 1259, 1209, 1172, 1127, 1000, 974, 926, 894, 840, 787, 760, 744, 716. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 9.47 (s, 1H), 8.71 (d, 1H, J=2.1 Hz), 8.16 (d, 1H, J=8.4 Hz), 8.04–8.01 (m, 2H), 7.90–7.82 (m, 2H), 7.70–7.59 (m, 2H), 7.55–7.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 193.0 (CO), 192.7 (CO), 150.3 (C), 149.1 (C), 140.1 (CH), 135.2 (CH), 133.0 (CH), 132.5 (C), 130.1 (2CH), 129.6 (2CH), 129.5 (2CH), 127.9 (CH), 126.4 (C), 125.3 (C). MS (ESI): m/z 262 $(M+H)^+$.

4.3. General procedure for the preparation of quinoxalines **3a–e** from alkynes **1**

Following the procedure described for benzils **2**, and after cooling, a DMSO solution of the arylenediamine (2 mmol,

2 equiv) was added to the mixture and heated at 140 °C for the appropriate reaction time (see Table 3). After cooling to room temperature, H_2O (15 mL) was added, and the mixture was extracted with EtOAc (3×15 mL). Organic layers were then washed with an aqueous saturated NH_4Cl solution, dried, and concentrated. The crude mixture was then purified by column chromatography on silica gel to give quinoxalines **3a–e**.

2,3-Diphenylquinoxaline **3a**[17] (yield: 82%) and 6-methyl-2,3-diphenylquinoxaline **3d**[18] (yield: 88%), which are known compounds gave satisfactory data.

4.3.1. 2-(4-Methoxyphenyl)-3-phenylquinoxaline *3b*

Yield: 80%. Orange oil. TLC: R_f 0.57 (CH_2Cl_2, 70:30, SiO_2). IR (neat) ν_{max}/cm^{-1}: 3062, 2934, 2837, 2226, 1606, 1578, 1558, 1537, 1513, 1477, 1463, 1444, 1418, 1394, 1344, 1293, 1222, 1175, 1142, 1128, 1112, 1077, 1058, 1025, 978, 907, 837, 808, 785, 761, 727. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.30–8.17 (m, 2H), 7.76–7.70 (m, 2H), 7.57–7.54 (m, 2H), 7.49 (d, 2H, J=8.8 Hz), 7.37–7.35 (m, 2H), 6.83 (d, 2H, J=8.8 Hz), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 160.1 (C), 153.3 (C), 152.9 (C), 141.2 (C), 140.9 (C), 139.3 (2C), 131.3 (2CH), 129.7 (CH), 129.6 (2CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.2 (2CH), 113.6 (2CH), 55.2 (CH_3). MS (APCI): *m/z* 313 $(M+H)^+$.

4.3.2. 2-(4-Methoxyphenyl)-6,7-dimethyl-3-phenylquinoxaline *3c*

Yield: 80%. Brown oil. TLC: R_f 0.21 (cyclohexane/EtOAc, 90:10, SiO_2). IR (neat) ν_{max}/cm^{-1}: 1606, 1578, 1514, 1481, 1461, 1416, 1398, 1344, 1296, 1249, 1208, 1174, 1110, 1061, 1026, 972, 909, 870, 837, 810, 776, 758. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 7.85 (s, 2H), 7.53–7.46 (m, 2H), 7.45 (d, 2H, J=8.8 Hz), 7.36–7.33 (m, 3H), 6.81 (d, 2H, J=8.8 Hz), 3.81 (s, 3H), 2.50 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 159.9 (C), 152.4 (C), 152.0 (C), 140.3 (C), 140.2 (C), 140.1 (C), 139.9 (C), 139.6 (C), 131.7 (C), 131.2 (2CH), 129.7 (2CH), 128.4 (CH), 128.2 (2CH), 128.1 (CH), 128.0 (CH), 113.6 (2CH), 55.2 (CH_3), 20.4 ($2CH_3$). MS (APCI): *m/z* 341 $(M+H)^+$.

4.3.3. 4-(3-Phenyl-quinoxalin-2-yl)benzonitrile *3e*

Yield: 97%. Yellow solid, mp: 168–170 °C. TLC: R_f 0.49 (cyclohexane/EtOAc, 70:30, SiO_2). IR (neat) ν_{max}/cm^{-1}: 2225, 1477, 1342, 1057, 1022, 976, 844, 813, 775, 723. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.12 (m, 2H), 7.75 (m, 2H), 7.65–7.50 (m, 4H), 7.50–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ 153.1(C), 151.3 (C), 143.6 (C), 141.5 (C), 141.1 (C), 138.3 (C), 132.1 (2CH), 130.8 (CH), 130.6 (2CH), 130.5 (CH), 129.8 (2CH), 129.3 (3CH), 128.6 (2CH), 118.6 (C), 112.5 (CN). MS (APCI): *m/z* 308 $(M+H)^+$.

4.4. Synthesis of 2-(4-nitrophenyl)diphenylimidazole *3f*

Following the procedure described for benzils **2**, and after cooling, an AcOH (25 mL) solution of NH_4OAc (10 mmol, 10 equiv, 0.77 g) and 4-nitrobenzaldehyde (1.2 mmol, 0.18 g) were added to the mixture and heated at 140 °C for 12 h. After cooling, the crude was concentrated and extracted with CH_2Cl_2 (3×15 mL). Organic layers were then washed with an aqueous saturated NH_4Cl solution, dried, and concentrated. The crude mixture was then purified by column chromatography on silica gel to give **3f** (Yield: 96%). Spectral data of **3f** were identical to those previously reported.[19]

4.5. Synthesis of compounds *3g–i*

Following the procedure described for benzils **2**, and after cooling, a solution of urea or thiourea (2 mmol, 2 equiv) and KOH (3 mL, 1.2 M) were added to the mixture and heated at 140 °C for the appropriate reaction time (see Table 3). After cooling, H_2O (15 mL) was added, and the mixture was extracted with EtOAc (3×15 mL). Organic layers were then washed with an aqueous saturated NH_4Cl solution, dried, and concentrated. The crude mixture was then purified by column chromatography on silica gel to give **3g–i**.

4.5.1. 5-(4-Methoxyphenyl)-5-p-tolylimidazolidine-2,4-dione *3g*

Yield: 90%. Yellow solid, mp: 214–218 °C. TLC: R_f 0.35 (cyclohexane/EtOAc, 60:40, SiO_2). IR (neat) ν_{max}/cm^{-1}: 3193, 2359, 1776, 1698, 1608, 1508, 1420, 1299, 1251, 1175, 1119, 1035, 973, 926, 757, 718. ^1H NMR (CD_3COCD_3, 300 MHz, 298 K): δ 9.96 (s, 1H), 8.22 (s, 1H), 7.39 (d, 2H, J=9.0 Hz), 7.36 (d, 2H, J=9.0 Hz), 7.22 (d, 2H, J=9.0 Hz), 6.96 (d, 2H, J=9.0 Hz), 3.81 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz, 298 K): δ 175.6 (CO), 160.4 (C), 156.6 (CO), 138.6 (C), 138.4 (C), 133.1 (C), 129.9 (2CH), 129.0 (2CH), 127.7 (2CH), 114.6 (2CH), 71.4 (C), 55.6 (OCH_3), 21.0 (CH_3). MS (ESI): *m/z* 319 $(M+Na)^+$.

4.5.2. 5-(4-Methoxyphenyl)-2-thioxo-5-p-tolylimidazolidin-4-one *3h*

Yield: 88%. Orange oil. TLC: R_f 0.28 (cyclohexane/EtOAc, 60:40, SiO_2). IR (neat) ν_{max}/cm^{-1}: 3196, 1721, 1692, 1608, 1508, 1389, 1301, 1248, 1163, 1121, 1028, 928, 816, 735. ^1H NMR (CD_3COCD_3, 300 MHz, 298 K): δ 10.59 (s, 1H), 9.75 (s, 1H), 7.09 (d, 2H, J=8.9 Hz), 7.06 (d, 2H, J=8.4 Hz), 6.98 (d, 2H, J=8.4 Hz), 6.72 (d, 2H, J=8.9 Hz), 3.55 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz, 298 K): δ 182.2 (CS), 175.9 (CO), 160.6 (C), 139.1 (C), 136.8 (C), 131.5 (C), 130.0 (2CH), 129.0 (2CH), 127.6 (2CH), 114.8 (2CH), 74.1 (C), 55.6 (OCH_3), 21.0 (CH_3). MS (ESI): *m/z* 312.8 $(M+H)^+$.

4.5.3. 5-(3-Hydroxy-4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)imidazolidine-2,4-dione *3i*

Yield: 60%. White solid, mp: 240 °C. TLC: R_f 0.35 (cyclohexane/EtOAc, 60:40, SiO_2). IR (neat) ν_{max}/cm^{-1}: 3377, 3224, 2937, 1769, 1716, 1591, 1509, 1462, 1414, 1399, 1333, 1272, 1227, 1129, 1104, 1016, 1003, 859, 823, 810, 754, 735, 686. ^1H NMR (CD_3COCD_3, 300 MHz, 298 K): δ 9.70 (s, 1H), 8.05 (s, 1H), 7.55 (s, 1H), 6.80–6.68 (m, 5H), 3.70 (s, 3H), 3.64 (s, 6H), 3.60 (s, 3H). ^{13}C NMR (CD_3COCD_3, 75 MHz,

298 K): δ 175.2 (CO), 156.2 (CO), 154.2 (2C), 148.3 (C), 147.3 (C), 136.3 (2C), 134.2 (C), 118.7 (CH), 114.9 (CH), 112.1 (CH), 105.6 (2CH), 71.3 (C), 60.5 (OCH_3), 56.5 (2 OCH_3), 56.2 (OCH_3). MS (ESI): *m/z* 319 $(M+Na)^+$.

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References and notes

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