Synthesis of Substituted-Benzils from Diarylalkynes Oxidation

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Abstract In this review, oxidation of diarylalkynes leading to functionalized benzils (di(het)aryl-1,2-diketones) is summarized. Some synthetic “one pot” transformations of internal arylalkynes leading to the construction of heterocycles are presented.

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Key words: alkynes, catalysis, heterocycles, ketones, oxidation, palladium.

1 Introduction

Benzil derivatives, commonly known as diaryl-1,2-diketones are structural motifs found in natural products.¹ Benzil substrates have also been widely reported for their important properties in a variety of fields as for examples, antitumor agents,² photosensitive agents in photocurable coatings,³ photoinitiators in radical polymerization and polymer grafting⁴ and corrosion

inhibitors in mild steel.⁵ Moreover, benzil derivatives are useful key intermediates in a wide range of organic syntheses, especially for the construction of various heterocyclic compounds.⁶ Due to the growing interest in this type of chemical structures, the synthesis of benzil derivatives has been extensively studied these last decades by the scientific community. Benzils are classically obtained by oxidation of benzoin⁷ or hydrobenzoin.⁸ However, due to the easy access to diarylalkynes by Sonogashira-Linstrumelle couplings, the oxidation of tolanes (diarylalkynes) has become a method of choice for a rapid access to benzil derivatives and has been deeply reported. The oxidation of diphenylacetylene providing benzil has been investigated for a long time by many researchers.⁹ However, the oxidizing reagents used for this transformation have several drawbacks in term of harsh reactions conditions, long reaction time, low yields and appears to be effective only with diphenylacetylene. The greatest difficulty with these previous protocols is their total incompatibility with benzil derivatives having functional groups on aromatics and are not transposable for the synthesis of heteroaryl derivatives. In this review, we highlighted oxidation reactions only on functionalized di(hetero)arylalkynes directed towards the synthesis of various benzils. We will focus our attention on clean and safe methodologies which are compatible with a wide range of functional groups on aromatics useful for possible future chemical transformations.

In section 2, the oxidation of diarylalkynes using inorganic reagents will be presented and discussed. Next, we will report, in section 3 the metal-catalyzed oxidation of diarylalkynes leading to substituted benzil derivatives establishing a classification by transition-metal. In section 4, a single example dealing with the oxidation of diarylalkynes in the presence of a Lewis-acid is reported and to finish this review, in section 5, some “one-pot” applications for the construction of heterocycles, starting from substituted diarylalkynes, are presented.

2. Oxidation with inorganic reagents

 2.1 I₂, I⁺ and NIS

 Table 1. Oxidation of substituted tolanses using I₂

Entry	Ref.	Benzils	x	Solvents	Yield (%)
				(T °C)	
1	10		0.5	DMSO	93
				(155)	
2	10		0.5	DMSO	90
				(155)	
3	11		0.5	DMSO	84
				(155)	
4	10		2	DMSO	90
				(155)	
5	10		0.02	DMSO	45
				(155)	
6	12		1	DMSO	82
				(145)	
7	12		1	DMSO	82
				(145)	
8	13		2.1	H ₂ O/MeCN	92
				(rt)	
9	13		2.1	H ₂ O/MeCN	78
				(rt)	
10	13		2.1	H ₂ O/MeCN	63
				(rt)	
11	14		2.1	H ₂ O/MeCN	85
				(rt)	
12	14		2.1	H ₂ O/MeCN	70
				(rt)	
13	14		2.1	H ₂ O/MeCN	80
				(rt)	
14	14		2.1	H ₂ O/MeCN	70
				(rt)	

From all the approaches developed for the oxidation of tolanses into benzil derivatives, the use of molecular iodine is probably one of the methods of choice for this transformation and has been well studied by different groups. In Table 1 are reported some selected examples of the utilization of I₂ to successfully transform variously substituted diarylalkynes into benzils with good to excellent yields in the presence of DMSO or water. Preliminary results using I₂ as a general reagent for the oxidation of diarylalkynes in DMSO, were reported by Filimonov on very few examples in 1991.¹⁰ The authors demonstrated that, beside the oxidation of diphenylacetylene (entry 1), diarylalkynes bearing

electron-donating groups (EDG) as well as electron-withdrawing groups (EWG) are well tolerated to furnish the desired benzils in good yields without any by-products (entries 2-3). One note that, using 0.5 equiv of this oxidizing couple (I₂/DMSO) at 155 °C, a stilbene double bond was not affected by this process (entry 3).¹¹ Moreover, by increasing the quantities of I₂, the two triple bonds of 1,4-bis(phenylethynyl)benzene were readily oxidized in DMSO to give the corresponding 2,2'-(1,4-phenylene)bis(1-phenylethane-1,2-dione) with an excellent yield of 90% (entry 4). Later, this methodology was successfully used at 145 °C to transform electron-rich alkynes, which are more readily oxidizable, into their corresponding benzils (entries 6-7). In this work, Williams has compared the efficiency of this methodology with the use of a more expensive system (PdCl₂/DMSO) and concluded that results were equivalent in term of yields. If the mechanism of the oxidation of diarylalkynes by I₂/DMSO has not been reported by these authors, it is reasonable to think that, firstly, I₂ activated the triple bond of tolanses (diarylalkynes) to give an intermediate of type **I**. An addition of DMSO on **I** furnished the vinyl iodide species **II** (Scheme 1). Intermediate **II** was then trapped by a second molecule of DMSO to give Me₂S and species **III** which evolved into the expected benzil together with a second equiv of dimethylsulfide (SMe₂, DMS).

 Scheme 1. Plausible mechanism for the oxidation of tolanses by I₂/DMSO

Recently, the use of I₂ in alcohols/MeCN or water/MeCN has been investigated by Srinivasan and Sakthivel.^{13,14} They firstly studied the oxidation of tolanses bearing on the *ortho*-position of the aromatic ring an aldehyde function.¹³ By using 2.1 equiv of I₂ in H₂O/MeCN at rt, the oxidizing process occurred well with electron-rich or electron-poor tolanses to furnish the desired benzils (entries 8-9). A plausible mechanism was proposed in which the *ortho*-aldehyde group acted as a neighboring assistant during the oxidizing process (Scheme 2). I₂ activated the triple bond of such tolanses which were then attacked by the formyl group in the presence of H₂O to give a 4-iodoisochromen-1-ol intermediate **I**. This later reacted with a second equiv of I₂ to give a diiodoketo-aldehyde of type **II** which underwent a displacement of iodine atoms with H₂O.

It is also possible to use these experimental conditions with diarylalkynes having on the *ortho*-position a keto group (entries 11-14).

 Scheme 2. Oxidation of *ortho*-tolanecarbaldehydes with I₂ in H₂O/MeCN

Arylketones (entries 11, 12 and 14), heteroaromatic ketones as thiophenyl compound in entry 13 and alkylketones are well tolerated on the *ortho*-position of the aromatic ring to give the expected benzil derivatives with excellent yields. In entry 14, it should be noted that the *ortho*-ketogroup was important in this oxidative process since only the triple bond close to this group was oxidized. We can notice that, when replacing the *ortho*-formyl or *ortho*-keto-function by an ester group, a 4-iodo-isocoumarin was formed as the sole product with no trace of any benzil derivatives.¹⁴ In 2011, a comparative study between the use of I₂ or PhSe-SePh in the presence of [bis(trifluoroacetoxy)iodo] benzene (PIFA) for the conversion of tolanes into benzils showed that I₂ seems to be less effective than PhSe-SePh as co-oxidizing species.¹⁵ Some selected examples are reported in Table 2).

Table 2 Oxidation of substituted tolanes with PIFA with I₂ (method A) or PhSe-SePh (method B)

It is noteworthy that, in the absence of I₂ or (PhSe)₂, the oxidation-reaction occurred slowly with PIFA (5% yield after 24 h of reaction). By adding I₂ in the media, the reaction accelerated but was not complete, on the contrary of (PhSe)₂ for which the starting materials were totally consumed. Whatever the nature of the substituents on the aromatic rings, PhSe-SePh was found to be superior to I₂ as activating species because, when I₂ was treated with PIFA, a series of polyatomic iodine-containing cations, which were stable but ineffective for this reaction can be produced beside I⁺ species. Another example concerning the use of hypervalent iodine (PhI(Ac)₂) as a catalyst for the oxidation of tolanes was developed by the group of Wang and Chung in a work dedicated to the “one-pot” synthesis of quinoxalines from tolanes.¹⁶ The reaction was carried out in hot DMSO in the presence of diamines, 10% of PhI(Ac)₂ and O₂ to give the desired heterocycles with good to excellent yields. In this work, about 25 examples were described with excellent yields ranging from 72% to 91% (for the two oxidation steps followed by condensation) but only one example starting with an electron-rich tolane was showed. NIS in water as a convenient reagent to prepare benzils from diarylalkynes has been studied by Fu¹⁷ and Iwasawa (Table 3).¹⁸ The reaction worked well with electron-rich or electron-deficient tolanes as indicated in Table 3. The reported methods (A): NIS 2 equiv in MeCN at 70 °C and (B) NIS (1.2 equiv), DMSO (2.8 equiv), and air in cyclopentyl methyl ether (CPME) as solvent were equivalent in term of yields when compared with same substrates.

NIS was evoked as the source of I⁺ in an ionic mechanism¹⁷ which activated the triple bond of tolanes as with I₂ (Scheme 3). The activated tolanes were subjected to an addition of water (A) or DMSO (B) to give I. Intermediate I added then H⁺ (A) or DMSO (B) to give α -iodoketones which evolved into the desired benzil derivatives in the presence of NIS. Note that the experimental protocol (B) used for the preparation of benzils was also

successfully applied for the synthesis of a variety of α -ketoimides from the oxidation of ynamides.

Table 3 Oxidation of substituted tolanes with NIS using (A)¹⁷ or (B)¹⁸

Scheme 3. Oxidation of tolanes mediated by NIS

As it has been seen with I₂, NIS or hypervalent iodine species, these inexpensive reagents are efficient to oxidize substituted-tolanen into benzils in DMSO or water, even if high reactional temperatures are often required to achieve these synthetic transformations.

2.2 Potassium permanganate (KMnO₄)

The use of KMnO₄ as a powerful agent to oxidize alkynes into the corresponding 1,2-diketones has been firstly studied by Lee and Srinivasan¹⁹ in 1979 (Table 4). The authors demonstrated that dialkylalkynes as well as diphenylacetylene were successfully treated with KMnO₄ in neutral conditions and good yields to 1,2-diketones (88% for diphenylacetylene) were obtained. This experimental protocol was next used by different teams^{20–22} to oxidize various internal alkynes, including heteroarylalkynes. In a project devoted to the synthesis of phenanthrenes quinones,²⁰ Waldvogel applied this method to a variety of electron-rich aryl-alkynes bearing -OMe and -Me substituents on the aromatic rings. A few years earlier, in a project dedicated to the synthesis of cyclopentadienones,²¹ Walsh and Mandal also showed that this protocol was efficient with heteroaromatic-arylalkynes. Thiophene and pyridine rings were well tolerated and furnished the expected 1,2-diketones with good yields (ranging from 55 to 98%) whatever the position of the heteroatom in rings. The use of KMnO₄ under the above conditions was compared to other methodologies for the oxidation of pyrimidylarylalkynes (see Table 3, last example) by Mani and Deng.²²

Table 4 Oxidation of diaryl- and heteroarylalkynes with KMnO₄ under neutral conditions

Oxidation procedures using KMnO₄ in various solvents, I₂/DMSO (over-oxidation), NBS/DMSO (bromination), PdCl₂/DMSO (53%) and others were examined. After screening numerous conditions, the protocol previously reported by Srinivasan¹⁹ was the more suitable in terms of yields, easy purifications and large-scale preparations (5 g).

It appears that, using a very finely powdered form of KMnO₄ in neutral conditions and with a good control of the reaction time (to avoid over-oxidation) is an efficient method to oxidize numerous diarylalkynes and heteroarylalkynes into diketones. However, one can regret that very few oxidation examples of electron-poor diarylalkynes were described using this process which was only described with poorly-functionalized molecules.

2.3 Sulfur trioxide (SO₃)

Table 5 Oxidation of substituted tolanes with SO₃ in dioxane

During their research on mild conditions to prepare sultone rings from alkynes, Filimonov *et al* had serendipitous discover that SO₃ in 1,4-dioxane was an efficient oxidizing system of the diarylalkynes triple bond.²³ The scope of this reaction, using a safe and convenient oxidizing agent, was investigated with a series of acetylenic substrates. 1,4-dioxane was found to be the more efficient solvent when compared with CHCl₃ or acetic anhydride and the optimal temperature was 60 °C (Table 5). SO₃ in this reaction was reduced to SO₂ and the reaction was found to be equally effective in the presence and in the absence of air. Good yields were obtained but only with electron-rich tolanes as

4-methyltolane (92%) or with phenylacetylene (57%). The yield of the oxidation decreased considerably with electron-poor tolanes as 4-nitrotolane (19%) thereby limiting this process. As an illustration (Table 5), when 1,4-bis(phenylethynyl)benzene was mixed with SO₃, only one of the two triple bonds was oxidized to provide the resulting diketone (70%). Due to the strong electron withdrawing -COCOPh group in this 1,2-diketone, as it was observed with 4-nitrotolane, the SO₃-oxidizing process failed and no tetraketone was obtained, even by increasing the quantities of SO₃. To corroborate these observations, with substrates having two separated triple bonds, tetraketones were obtained in excellent yields (95 to 98%).

2.4 Potassium peroxymonosulfate (Oxone)

A fast, convenient, inexpensive and non-toxic protocol using Oxone has been described by Chen and Wu²⁴ and is complementary to the SO₃-procedure as it was showed to be more efficient with electron-deficient diarylalkynes than with electron-rich tolanes (Table 6).

Table 6 Oxidation of diarylalkynes with Oxone in TFA

The triple bond oxidation of diphenylacetylene was successfully oxidized by Oxone at 0 °C to give benzil with a good yield of 80%. On the contrary, when the phenyl ring contained electron-rich substituents as Me, OMe or OH, yields of desired benzils dropped considerably (15-45%) with 2 equiv of Oxone and large amounts of starting materials were also recovered in the crude mixture. As it was showed in Table 5, electron-poor phenyl ring having CN, NO₂, halogens, CF₃ substituents on *para*- and *meta*-positions were more suitable for this oxidation reaction with yields ranging from 70 to 90%. Push-pull tolanes were also well tolerated and were converted into the corresponding benzil derivatives with satisfactory yields. One note that *ortho*-substituents on the phenyl ring led to lower yields in benzils (40 to 60%) and *ortho*-nitro substituents disturbed the oxidation process. The oxidation of 1-nitro-2-(phenylethynyl)benzene led to only 20% of the diketone and the major product (40%) resulted from the cyclization of the *ortho*-NO₂-substituent on the alkyne triple bond in the presence of Oxone to give a benzo[c]isoxazol-3-one as side-product. A plausible mechanism for the formation of benzils from tolanes was proposed by Wu and Chen and is outlined in Scheme 4.

Scheme 4. Oxidation of tolanes with Oxone in TFA

According to a “double oxidation mechanism”²⁵ and by analogy to the epoxidation of olefins with peracids, it might be expected that an oxirene of type **I** would be the first product of the oxidation of the tolane substrate. A further oxidation step of **I** would give intermediate bisoxirane of type **II** which further underwent rearrangement into the desired benzil.

2.5 O₂, hv, MgBr₂.Et₂O

In the course of photo-oxidation studies, Itoh found that substituted diarylalkynes were oxidized to their corresponding benzils using O₂, hv in the presence of MgBr₂.Et₂O.²⁶ This method which used molecular oxygen as oxidant and an easy handle bromine source as MgBr₂.Et₂O (1 eq) was of interest in a viewpoint of green chemistry. Moreover, the oxidation-reactions were achieved at rt and tolerated a variety of substituents (EDG and EWG) and heterocycles on the alkyne triple bond as for example a pyridine ring. Some selected examples are reported in Table 7.

Table 7 Photo-oxidation of substituted diarylalkynes with O₂, hv, MgBr₂.Et₂O

Solvents (acetone, CH₂Cl₂, THF, hexane, EtOAc, MeCN) and the sources of bromine (MgBr₂.Et₂O, Br₂, LiBr, NiBr₂, SmBr₂, YbBr₃,...) were evaluated and best results were obtained when using MgBr₂.Et₂O (1 equiv) in MeCN. Additionally, irradiation which was crucial for oxidation was optimal for oxidation using a 300 Watts Xe lamp.

The results depicted in table 7 showed that this protocol was efficient for electron-poor arylalkynes and was limited to electron-rich alkyne substrates and to *ortho*-substituted arylalkynes. Moreover, if the presence of a pyridine-ring was tolerated, the yield of the resulting α -diketone remained weak (32 to 33%), whatever the position of the nitrogen atom in the ring. Itoh suggested for this photo-oxidation reaction the following mechanism²⁶ depicted in scheme 5. In the presence of O₂ under irradiation, a bromide ion was converted into a bromide radical which added to diarylalkyne to generate a vinylradical of type **I**. Radical **I** trapped O₂ to give hydroperoxides radical **II**. Radical of type **II** was then protonated into **III** and then reduced into enol **IV** by the reducing agent HBr generated *in situ*. This later added an equiv of Br₂ to give the α - α -dibromoketone **V** (detected by NMR). After hydrolysis **V** the expected 1,2-diketone was obtained together with HBr. At the end of this process, a yellow coloring of the reaction medium was observed that

suggested the formation of Br₂ by an addition of two bromine radicals.

Scheme 5. Proposed mechanism for the photo-oxidation reaction of diarylalkynes

2.6 Cerium ammonium nitrate (CAN)

The oxidation of diarylalkynes having an *ortho*-amide function on one of the phenyl ring has been developed by Wang in 2012.²⁷ In this study, the influence of various oxidative reagents was screened. By using ZrCl₄, InCl₃, NiCl₂, PCC, AgNO₃, Mn(OAc)₃, ZnCl₂, PdCl₂, K₃Fe(CN)₆, at different temperatures in various solvents, no trace of the corresponding α -diketones was observed. With CeF₄ as the oxidant, the yield in 1,2-diketones was around 30% and increased significantly with KMnO₄ (51%) and with CAN (62%).

Table 8 CAN and O₂ promoted the oxidation of diarylalkynes having an *ortho*-amide function

After a careful examination of the reaction conditions on a model substrate, the authors found that the optimized conditions were obtained when the reaction was conducted with CAN (1.5 equiv) in (MeCN/CH₂Cl₂ : 3/1) in the presence of O₂ (1.0133 bar) at rt. A variety of diarylalkynes bearing different substituents on the aromatic rings were evaluated as well as the nature of the aromatic ring linked to the amide function (Table 8). The presence of EDG and EWG on the phenyl ring linked to the amide function was well tolerated giving 1,2-diketones with high to excellent yields. On the phenyl ring linked to the alkyne triple bond, it was also showed that a variety of substituents were also well tolerated (CF₃, F, and Et). However, it is regrettable that functional groups such as esters, nitriles, phenols and others have not been tested in this study. The presence of the *ortho*-amide substituent is crucial for the CAN-oxidation as it was demonstrated with unreactive non-substituted substrates. Moreover, in the absence of O₂, the yield in α -diketones decreased significantly (20% vs 92% with O₂).

Scheme 6. CAN-promoted the oxidation of *ortho*-amide tolanes

The proposed mechanism (Scheme 6) suggested a first coordination of CAN with the amide substituent to direct the addition of two nitrate anions on the alkyne triple bond. The diaryl-1,2-diyl-dinitrate species **I** was then oxidized and evolved into a radical of type **II** or its mesomeric form **III** and after the loss of a second nitrogen dioxide radical ($\text{NO}_2^\bullet$), **III** was transformed into the desired *ortho*-amide benzil derivatives.

To conclude this section, we have reported in Scheme 7 the most effective protocols using inorganic reagents which are useful for the transformation of functionalized-tolanes into their counterpart's 1,2-diketones.

Scheme 7. Methods and inorganic reagent systems for the oxidation of diaryl- and heteroaryl-alkynes into benzil derivatives

It seems that I_2 and iodine derivatives as PIFA or NIS are useful reagents for the oxidation of the alkyne triple bond whatever the position and the nature of the substituent on the aromatic rings. For the oxidation of electron-poor alkynes, possibly sensitive, the use of Oxone in TFA can be applied with success at 0 °C. On the contrary, the use of KMnO_4 or SO_3 in solvents is rather recommended for electron-rich arylalkynes which were transformed at low temperatures into α -diketones. Moreover, the use of KMnO_4 under neutral conditions is also a method of choice for the transformation of a variety of heteroarylalkynes into 1,2-diketone substrates.

3. Metal-catalyzed oxidation of diarylalkynes

3.1 Palladium catalysts

In this section is presented all methodologies developed these last decades using metal salts as activators of the alkyne triple bond. The paragraphs constituting this section are classified by metal and when possible, comparisons between species of the same metal is established. Undoubtedly, among the various metal

salts used as catalysts for the oxidation of diarylalkynes into diketones, palladium salts have been, from far, the most studied. In 2011, J. Muzard published an excellent review concerning the Pd-catalyzed oxidation of alkynes including acetylene, diaryl- and dialkyl alkynes, enynes and diynes into 1,2-diketones.²⁸ The effects of substituents on the reactivity were discussed and plausible reactional mechanisms were proposed in which the Pd^{II} -catalysts activated the triple bond and therefore facilitated the nucleophilic addition of the oxygen sources (DMSO, water in solvent or pyridine N-Oxide). In the case of DMSO-oxidation, a loss of dimethylsulfide (DMS) followed by a second addition of DMSO accompanied by the leaving of a second equivalent of DMS provided the α -diketone and regenerated the catalyst.^{28, 29, 31}

In Table 9 are summarized a selection of examples anterior and posterior to the review of J. Muzard²⁸ concerning the oxidation of diarylalkynes having electron-donating and electron-withdrawing groups into diaryl-1,2-diketones. It appears that Pd^{II} species were found to be very efficient catalysts to activate diarylalkynes which were furthermore oxidized in the presence of oxidant species and additives. All of these catalytic systems were efficient with electron-rich (entries 1a-2d) or electron-poor arylalkynes (entries 3a-6), as well as with push-pull and pull-pull diarylalkynes (entries 7-11).

All of these methods which tolerated a large variety of functional groups were generally comparable in term of yields. From a practical point of view, the use of $\text{Pd-Fe}_3\text{O}_4$ nano-catalyst (entries 1f and 4c) is particularly interesting because, owing to its magnetic properties, this catalyst was removed easily using an external magnet to be recycled and re-used five times without any loss of efficiency. From all the Pd-catalyzed process reported in Table 9, none of them could be successfully applied to the oxidation aniline derivatives (entry 12) This type of oxidation reactions requiring Pd^{II} catalyst to form a $\text{Pd}^{\text{II}}-\pi$ -complex remained complicated probably because these catalysts are Lewis acids can also complexed to the nitrogen atom of anilines. To overcome this difficulty, the oxidation of a less coordinating acetamide derivative was achieved successfully using PdI_2 in hot DMSO (entry 13), the cleavage of the amide function can be easily carried out later. For probably similar complexation reasons, the Pd^{II} -catalyzed oxidation of heteroarylalkynes is poorly documented. The pioneer works with nitrogen containing heterocycles were published in 2002 by the Russian team of Yubusov. In the presence of 10 mol% of PdCl_2 in hot DMSO (120–125 °C), Yusubov and co-workers³⁶ successfully oxidized a variety of alkynylpyrazoles bearing a variety of functional groups (Table 10). The reaction rate was influenced by the position and the nature of the substituents on the pyrazole and aromatic rings. Under these conditions, Yusubov reported that if the $\text{PdCl}_2/\text{DMSO}$ combination was efficient with some pyrazoles substrates, this methodology was totally ineffective to oxidize a variety of pyridine containing alkynes and complex mixtures of reaction products were obtained³⁶.

Table 9 Pd-catalyzed oxidation of diarylalkynes into benzils

Entry	Ref	R	R ¹	[Pd]	Additive	Solvent	T °C	Time (h)	Yield (%)
1a	29	<i>p</i> -OMe	H	10% Pd/C (0.1)	O ₂	DMSO	120	24	85
1b	30	<i>p</i> -OMe	H	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	85
1c	31	<i>p</i> -OMe	H	Pd(OAc) ₂ (0.1)	air, CuBr ₂ (0.1)	DMSO	120	20	70
1d	32	<i>p</i> -OMe	H	PdBr ₂ (0.05)	O ₂ , CuBr ₂ (0.1)	dioxane/H ₂ O	60	24	90
1e	6a	<i>p</i> -OMe	H	PdI ₂ (0.02)	-	DMSO	140	2	98
1f	33	<i>p</i> -OMe	H	Pd-Fe ₃ O ₄ (0.01)	CuBr ₂ (0.05), O ₂	dioxane/H ₂ O	95	28	90
2a	29	<i>p</i> -Me	H	10% Pd/C (0.1)	O ₂	DMSO	120	24	74
2b	30	<i>p</i> -Me	H	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	93
2c	31	<i>p</i> -Me	H	Pd(OAc) ₂ (0.1)	air, CuBr ₂ (0.1)	DMSO	120	20	83
2d	34	<i>p</i> -Me	H	PdCl ₂ (0.05),	CuCl ₂ (0.05)	PEG/H ₂ O	rt	14	78
3a	29	<i>p</i> -NO ₂	H	10% Pd/C (0.1)	O ₂	DMSO	120	24	41
3b	30	<i>p</i> -NO ₂	H	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	2
3c	31	<i>p</i> -NO ₂	H	Pd(OAc) ₂ (0.1)	air, CuBr ₂ (0.1)	DMSO	120	20	75
3d	35	<i>p</i> -NO ₂	H	PdCl ₂ (0.1)	-	DMSO	145	4	60
3e	34	<i>p</i> -NO ₂	H	PdCl ₂ (0.05),	CuCl ₂ (0.05)	PEG/H ₂ O	rt	10	87
4a	29	<i>p</i> -Cl	H	10% Pd/C (0.1)	O ₂	DMSO	120	24	84
4b	35	<i>p</i> -Cl	H	PdCl ₂ (0.1)	-	DMSO	140	6	86
4c	33	<i>p</i> -Cl	H	Pd-Fe ₃ O ₄ (0.01)	CuBr ₂ (0.05), O ₂	dioxane/H ₂ O	95	28	85
5	30	<i>p</i> -CN	H	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	82
6	30	<i>p</i> -CHO	H	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	78
7	30	<i>p</i> -OMe	<i>p</i> -Ac	10% Pd/C (0.1)	O ₂ , pyridine <i>N</i> -oxide (5)	-	120	24	76
8	29	<i>p</i> -OMe	<i>p</i> -NO ₂	10% Pd/C (0.1)	O ₂	DMSO	120	24	62
9	31	<i>p</i> - <i>t</i> Bu	<i>p</i> -CN	Pd(OAc) ₂ (0.1)	air, CuBr ₂ (0.1)	DMSO	120	20	75
10	6a	<i>p</i> -NHAc	<i>p</i> -Me	PdI ₂ (0.02)	-	DMSO	140	3	93
11	6a	<i>p</i> -OMe	<i>o</i> -OMe	PdI ₂ (0.02)	-	DMSO	140	8	96
12	6a	<i>p</i> -Me	<i>p</i> -NH ₂	PdI ₂ (0.02)	-	DMSO	140	3	0
13	6a	<i>p</i> -Me	<i>p</i> -NHAc	PdI ₂ (0.02)	-	DMSO	140	3	93

Table 10 PdCl₂ / DMSO promoted the oxidation of alkynyl pyrazoles

In 2008, we reported that catalytic amounts of PdI₂ in hot DMSO (140 °C) allowed the oxidation of pyridine or quinoline substrates.^{6a} We showed that the catalytic use of PdI₂ proved to be superior to that of PdCl₂ with these heterocyclic substrates

(Table 11). One note that a single pyrimidine substrate was successfully oxidized by Mani and Deng using PdCl₂ in DMSO with a modest yield of 53% which was increased (65-70%) using KMnO₄.²²

Table 11 Pd-catalysts promoted the oxidation of pyridine, quinolone, pyrimidine and thiophene substrates

Reagents and conditions: (i) PdI₂ (2 mol%), DMSO 140 °C. (ii) PdCl₂ (10 mol%), DMSO 140 °C. (iii) PdCl₂ (10 mol%), DMSO 130 °C. (iv) 10% of Pd/C (10 mol%), air, pyridine *N*-oxide (5 equiv), 120 °C.

In 2011, Sajiki reported that diarylalkynes possessing 2-pyridinyl or a 2-thienyl ring within the molecule tolerated the oxidation conditions (Pd/C, air, pyridine *N*-oxide, 120 °C)(Table 11).³⁰ Using these conditions, yields in the desired 1,2-diketones were excellent and the catalytic activity of the Pd species was maintained over 5 runs by simple acid wash (HCl followed by MeOH) after filtration on paper.

To conclude this section dedicated to Pd species as efficient catalysts for the oxidation of alkynes into benzils in the presence of various oxidizing species, all methodologies reported in Table 9 are useful methods whatever the nature of substituents on the aromatic rings leading to α -diketones with comparable yields. However, few cases concerning the oxidation of heterocyclic systems have been reported with Pd-catalysts, probably for complexing reasons. This research domain is really challenging and remains to be developed.

3.2 Copper catalysts

Copper catalysts in combination with additive agents have been studied by several groups to oxidize diarylalkynes into benzil derivatives. In this section dedicated to copper catalysts we will present the methodologies by a classification of copper catalysts starting from Cu⁰ to Cu^{II} species.

The use of Cu⁰ which was transformed into Cu^{II}BF₄ using Selectfluor was reported by the group of Y. Liu in China in 2013.³⁷ This 1,2-dicarbonylation of alkynes process using a Cu⁰/Selectfluor combination was found to be very effective and occurred at room temperature with O₂ and H₂O as oxidizing species (Table 12).

Table 12 Cu and Selectfluor catalyzed the oxidation of alkynes into benzils in CH₃CN/H₂O at rt.

The selected examples described in Table 12 show that this process was very effective with diarylalkynes bearing various electron-donating and/or electron-withdrawing group on *ortho*, *meta* and *para* positions. This methodology tolerated a variety of functional groups (halogens, ethers, esters, alkyls and aldehyde). In the last example depicted in table 12, a α -diketone bearing a 2-formylphenyl ring was obtained with a modest yield of 30%, probably because the aldehyde function may be over-oxidized by Selectfluor.³⁸

Concerning the use of Cu^I as a catalyst for these transformations, Guo and Wu, reported that diarylalkynes were successfully transformed into 1,2-diketones in DMSO and air at 140 °C in the

presence of CuI and Na₂S₂O₈. Some representative examples are selected in Table 13³⁹.

Table 13 CuI and Na₂S₂O₈ promoted the 1,2-dicarbonylation of diarylalkynes

A screening of copper catalysts (Cu(OAc)₂, CuO, CuCl₂, CuCl, CuI), oxidant species (K₂S₂O₈, TBHP, benzoquinone, PhI(OAc)₂, K₂S₂O₈) and solvents revealed that best results were obtained with experimental conditions described in table 13. Electron-rich and electron-poor arylalkynes were then obtained with acceptable yields together with a pyridine containing-diketone (1-phenyl-2-(pyridin-2-yl)ethane-1,2-dione, 60%). Firstly, Na₂S₂O₈ oxidized CuI into a Cu^{III} species³⁹ useful to activate the triple bond of alkyne derivatives. Then, as it was observed with Pd-catalysts, a nucleophilic addition of two molecules of DMSO and subsequent loss of DMS afforded the desired diketones and regenerated the Cu^{III} catalyst.

The combination of CuI and Cu(OTf)₂ has also proven to be very effective to prepare 1,2-diketones from several aryl iodides and phenylpropionic acid.⁴⁰ The formation of benzil derivatives was initiated via the tandem CuI/Cu(OTf)₂ which catalyzed a decarboxylative coupling reaction of aryl propionic acid and aryl iodides. The previous copper catalysts combination then allowed the activation of the resulted phenylaryalkynes which were finally oxidized by DMSO at 140 °C (Table 14). It appeared that CuI associated with Cu(OTf)₂ was superior to other single copper catalysts as CuCl, Cu(OAc)₂, CuI or Cu(OTf)₂ in this process. After the decarboxylative coupling step, it was suggested that HI was necessary to quench the alkaline property of Cs₂CO₃ which inhibited the second diaryl oxidation-step.

Table 14 CuI/Cu(OTf)₂ catalyzed the synthesis of benzils from aryl iodides and phenylpropionic acid.

This sequential reaction which required an inexpensive “green” catalytic association promoted a rapid and efficient access to a large variety of 1,2-diketones bearing various functional groups useful for further possible transformations.

The use of a Cu^{II} species as a catalyst for the oxidation of diarylalkynes into diketones has been recently reported by Xia and co-workers.⁴¹ In the presence of PhI(OAc)₂, Cu(OTf)₂ was oxidized into Cu^{III}(OAc)₂(OTf) which coordinated to the alkyne triple bond. The proposed mechanism of this diarylalkyne oxidation suggested then the transfer of an acetate group from the Cu^{III} catalyst to the alkyne triple bond followed by a cyclization and oxidation process.⁴¹ Thereby, some diarylalkynes were converted into the corresponding 1,2-diketones bearing on the aromatic rings electron-donating and electron-withdrawing groups but with moderate to low yields (Table 15).

Table 15 Cu(OTf)₂ and PhI(OAc)₂ catalyzed the synthesis of benzil derivatives from diarylalkynes in AcOH and HFIP.

With Cu⁰, Cu^I (with or without Cu(OTf)₂) or with Cu(OTf)₂ as catalysts, benzil derivatives were obtained from diarylalkynes, generally with acceptable to excellent yields. These copper catalysts were oxidized by additives (Selectfluor, PhI(OAc)₂, Na₂S₂O₈) to further activate the alkyne triple bond which was next subjected to a nucleophilic attack by O₂, H₂O or DMSO. As it was observed with Pd-catalysts, it is unfortunate that these Cu-catalytic systems did not give very significant results in heterocyclic series.

3.3 Iron catalysts

There are only two papers that reported the 1,2-dicarbonylation of diarylalkynes using iron catalysts. The first study, in 2006, reported the comparison of some transition metal-catalysts (CuCl, CuBr, InCl₃, NiCl₂, MnCl₂, Fe(acac)₃, FeCl₃ and FeBr₃) in the oxidation of diarylalkynes in hot DMSO.⁴² On the exception of MnCl₂ which did not catalyzed the oxidation reaction, all of these catalysts were efficient and FeBr₃ appeared to be the best of them. After optimizing the experimental reaction conditions, the scope and limitation of this reaction were studied with a variety of diarylalkynes which were subjected to oxidation by the DMSO-FeBr₃ couple under microwaves irradiation (Table 16).

Table 16 Oxidation of diarylalkynes into benzil derivatives under microwaves irradiation using FeBr₃ in DMSO at 200 °C

This non-toxic procedure has been successfully applied to a variety of alkynes leading rapidly (from 8 to 30 min) to a variety of functionalized benzils. However, the reaction failed with phenol derivatives and arylalkynes substituted with a cyano group were converted into the desired benzil derivatives in moderate yields (*para*-CN; 46%, *ortho*-CN 43%). One note that this protocol could be conducted without the need of microwaves but required a longer reaction time (e.g. for *p*-MeO derivative: MWI, 75%, 20 min, 200 °C vs normal heating, 80%, 10 h, 140 °C).

In 2011, Enthaler has re-investigated the use of iron catalysts in the diarylalkyne oxidation in the presence of ligands (10 mol%) and by replacing DMSO with a mixture H₂O₂/CH₃CN at rt.⁴³ After screening iron catalysts (FeCl₂, FeCl₃, FeBr₃, Fe(ClO₄), FePO₄,...), solvents (MeOH, CH₃CN, toluene, *n*-hexane, CH₂Cl₂) and nitrogen-donor ligands (NEt₃, Pyridine, TMEDA,...), the best conditions found for this oxidative protocol required: FeCl₃ (5 mol%), pyridine (10 mol%), in H₂O₂/CH₃CN at rt for 4 h (Table 17).

Table 17 FeCl₃ and pyridine catalyzed the oxidation of diarylalkynes in H₂O₂ and CH₃CN at rt.

Except in the case of nitro-substitution, it was observed that the iron-catalyzed oxidation of diarylalkynes with H₂O₂, as an eco-friendly oxidant, was efficient with a range of alkynes substrates providing the expected benzils in high yields. For this oxidation process, Enthaler proposed a reasonable mechanism in which the alkyne triple bond was firstly oxidized by the combination iron/H₂O₂ to give an oxirene intermediate **I**. Then a further oxidation of **I** occurred to provide a 2,4-dioxo-bicyclo[1,1,0]butane intermediate **II** which rearranged into the desired benzil derivative (Scheme 8).

Scheme 8. Plausible mechanism for the FeCl₃/H₂O₂-oxidation of benzils

3.4 Ruthenium catalysts

The use of ruthenium catalysts in the dicarbonylation of diarylalkynes was firstly studied by X. Wan in 2010.⁴⁴ From the Ru-catalysts tested to oxidize alkynes into 1,2-diketones, [Ru(cymene)Cl₂]₂ and RuCl₃ gave best results when used with I₂ as additive and *tert*-butyl hydroperoxide (TBHP) as oxidant in dioxane at 80 °C (Table 18). The major advantage of this process is the low loading of catalyst (0.001 mol%) and the good yields obtained with a variety of alkynes substrates including diarylalkynes, dialkylalkynes and arylalkylalkynes. Three years after, Wan proposed a complementary protocol^{6b} which used the same Ru-catalyst for this transformation achieved at rt in the presence of TEMPO (10 mol%), Oxone (5 mol%) and NaHCO₃ in

nitromethane/H₂O as the solvent combination. The results of these two studies with some selected examples are reported in Table 18.

Table 18 [Ru(cymene)Cl₂]₂ catalyzed the oxidation of alkynes to 1,2-dicarbonyl compounds.

Method (a): [Ru(cymene)Cl₂]₂ (0.001 mol%), I₂ (10 mol%), TBHP (1.8 equiv) in dioxane at 80 °C. Method (b) [Ru(cymene)Cl₂]₂ (0.02 mol%), TEMPO (10 mol%), Oxone (2.5 equiv), NaHCO₃ (0.5 mol%), nitromethane/H₂O 8:1, rt.

The results depicted in Table 18 revealed that [Ru(cymene)Cl₂]₂ is very efficient for these transformations with the need of a very low charge of catalyst (from 0.001% to 0.02%). These oxidative systems showed a good functional group tolerance with both electron-donating and electron-withdrawing groups on the aromatic rings. When using 0.001 mol% of Ru-catalyst, no residual impurity was detected by ICP (Inductively coupled plasma) mass analysis in the benzils after recrystallization or column chromatographic purification. The method (b) using 0.02 mol% of Ru-catalyst, TEMPO and Oxone was also effective and was interesting for the preparation of fragile benzil derivatives at rt, when reaction (a) using 0.001 mol% Ru-catalyst, I₂ and TBHP required to heat the mixture at 80 °C.

In 2007, Roengsumran studied the oxidation of some diarylalkynes using RuCl₃ in combination with NaIO₄ in a mixture H₂O/CH₃CN/CCl₄ buffered with NaHCO₃ and MgSO₄ (Table 19, method a).⁴⁵ More recently, Fischmeister and co-workers used a combination of RuCl₃ (10 mol%) in the presence of NaOCl (3 equiv) as an oxidant and diethylcarbonate as a base to oxidize diarylalkynes in hexadecane at rt⁴⁶ (method b). As showed in Table 19, a variety of diarylalkyne substrates were successfully oxidized whatever the nature and the position of the functional groups on aromatic rings. In general, yields were satisfactory but one note that there is a notable difference between the conversion yields which were excellent and isolated yields for the method (b).⁴⁶

Fischmeister proposed a plausible mechanism for method (b) in which the RuCl₃ catalyst is first oxidized by NaOCl to RuO₄ species. Then, a cycloaddition between RuO₄ and the alkyne triple bond occurred to provide a Ru-metallacycle **I**. A fragmentation of **I** provided rapidly the desired 1,2-diketone and RuO₂ which was then oxidized by NaOCl into RuO₄ which can then add another molecule of the diarylalkyne species to continue the Ru-catalytic cycle (Scheme 9).

Table 19 RuCl₃ and NaOCl promoted the oxidation of various diarylalkynes.

Method (a): RuCl₃ (1 mol%), NaIO₄ (3 equiv), NaHCO₃ (8 mol%), MgSO₄ (25 mol%) in CH₃CN/H₂O (3:4) at rt. Method (b) RuCl₃ (0.5 mol%), NaOCl (3 equiv), Et₂CO₃ (excess), hexadecane, rt.

Scheme 9. Plausible mechanism for the RuCl₃/NaOCl-oxidation of benzil derivatives

3.5 Gold catalysts

Gold catalysts were recently evaluated by Li in 2011 in the oxidation of diarylalkynes.⁴⁷ Among the Au-catalysts studied, AuCl in combination with AgSbF₆ (4 mol%) appeared to be the most effective association for this transformation when mixed with diarylalkynes and diphenylsulfoxide as the oxidant (3 equiv). Some examples are presented in Table 20.

Table 20 AuCl/AgSbF₆ in association with Ph₂SO catalyzed the oxidation of diarylalkynes into benzil derivatives.

It has been showed on a model substrate, that the combination AuCl/AgSbF₆ was superior to the independent use of AuCl or AgSbF₆. Moreover, among the sulfoxides tested, Ph₂SO was the best one when compared to MePhSO, Bn₂SO, Me₂SO and others. Concerning the mechanism, it was proposed that AuCl activated the triple bond which was then attacked by the sulfoxide as it was described with palladium salts. The diketonization of alkynes by Au^I catalyst was re-investigated by Liu with diarylalkynes having an ethylester on the *ortho*-position.⁴⁸ With these substrates, Liu found best conditions for the transformation of *ortho*-substituted diarylalkynes into benzil derivatives using Ph₃PAuNTf₂ (2.5 mol%), Selectfluor (2 equiv) in CH₃CN/H₂O (100:1) at 80 °C and yields were satisfactory.

3.6 Mercury-catalyst

If the mercury-hydration of alkynes is known since the pioneer works of Kucherov in 1881,⁴⁹ there is only one paper that reports the synthesis of 1,2-dicarbonyl compounds from the oxidation of diarylalkynes using mercury salts.⁵⁰ It was found that, if two equiv of mercury sulfate, chloride, acetate and trifluoroacetate did not provide the oxidation of diarylalkynes into benzils, on the contrary, their nitrate and triflate homologs were very efficient mercury salts for this transformation. The scope of this reaction that required large quantities of Hg-salts was well studied and showed that a large range of substituted tolanses was successfully transformed in DMF at rt (Table 21).

Table 21 Oxidation of tolanses with mercuric nitrate hydrate.

In this work, it was demonstrated that the oxidation process occurred rapidly from 20 min (for arylalkylalkynes) to 1-2h (for diarylalkyne derivatives). It was also showed in the proposed mechanism, that the mercury counter ion (nitrate or triflate) played an important role, as a nucleophile, in this transformation.⁵⁰ Of course, the main problem with this process is the need of a large amounts of mercuric salts (2 equiv) that limited the use of this method for large-scale and industrial applications.

In this section dedicated to the use of metal-catalysts in the transformation of functionalized tolanses into 1,2-diketones, we showed that there is a panel of metal salts available to activate the alkyne triple bond. Among them, palladium and copper salts were the most used in combination with a variety of oxidizing systems. One note that henceforth, an effort was made with non-toxic metal-catalysts as for example iron salts (FeBr_3). From an industrial point of view and for environmental considerations, the methodology developed by Wan⁴⁴ which required a very low charge of catalyst (10 ppm of $[\text{Ru}(\text{cymene})\text{Cl}_2]_2$) together with I_2 and TBHP as oxidants is of particular interest.

4. Sequential-hydration-oxidation

A useful and practical method for transforming tolanses into benzils was proposed by Wan in 2006.⁵¹ In a “one-pot” process, diarylalkynes were firstly converted into a mixture of regioisomeric deoxybenzoins (ArCOCH_2Ar) after the hydration of the alkyne triple-bond by $\text{HCOOH}/\text{MeSO}_3\text{H}$ combination and the hydration products were then oxidized in the presence of HBr and DMSO to furnish the expected benzils. The scope of this reaction is reported in Table 22.

Electron-rich and electron-poor arylalkynes, naphthylarylalkynes, free NH_2 - and COOH derivatives, as well as heteroarylalkynes, underwent the required transformation with good to excellent yields thus making this method very general and particularly effective. Moreover, as observed the reaction seems to be efficient with *ortho*-, *meta*- and *para*-substituents on the phenyl rings. The

only drawback of this elegant method is the use of acidic conditions at 105 °C which may be not compatible with acid-sensitive substrates. The mechanism proposed by Wan was particularly well studied by detecting the off gas with headspace GC-MS and the reaction intermediates by LC-MS.

Table 22 $\text{HCOOH}/\text{MeSO}_3\text{H}$ and DMSO/HBr promoted the transformation of alkynes into α -diketones

Me_2S and CO were identified and monoketones A and A' (deoxybenzoins) and bromoketones B and B' were also detected. On the basis of these results, the authors proposed the following reactional mechanism (Scheme 10). Firstly, tolans

s added 2 equiv of formic acid to give a possible intermediate of type I which decomposed to provide monoketones A and A' and carbon monoxide. In the presence of DMSO and HBr , monoketones were brominated into B and B' (also identified by LC-MS).

Scheme 10. Proposed mechanism for the transformation of tolans into benzil derivatives

A further addition of DMSO on B furnished a sulfonium intermediate II which was oxidized into benzil derivatives jointly with the liberation of Me_2S and HBr . It is also possible that after the first addition of formic acid on tolanses, the resulting enol formate underwent bromination directly to give B and B'.

5. Applications to the synthesis of heterocycles

5.1 “One-pot” access to various heterocycles

Some oxidative methodologies presented above were found to be compatible with the “one-pot” synthesis of various heterocycles as quinoxalines, imidazoles, imidazolidin-2,4-diones and thioxo imidazolidin-2,4-diones. From these nitrogen-containing heterocycles, the synthesis of quinoxalines from the oxidation-condensation process starting from diarylalkynes was the most studied and some selected examples are depicted in Table 23.

Using PdI_2 (A)^{6a} or $\text{PhI}(\text{OAc})_2$ (B)¹⁶ in DMSO , $\text{PdCl}_2/\text{CuCl}_2$ in $\text{PEG}/\text{H}_2\text{O}$ (C)³⁴ or $[\text{Ru}(\text{cymene})\text{Cl}_2]_2$ -TEMPO-Oxone (D)^{6c} methodologies in the presence of an *ortho*-phenylene diamine furnished the expected quinoxalines in comparable yields. These

methods tolerate a variety of functional groups on each phenyl rings of the quinoxalines. Electron-donating groups such as Me, OMe, NH₂ and electron-poor substituents as CN, CO₂R, NO₂, halogens and others are welcome in these transformations. The method (E)⁴⁸ using Ph₃PAuNTf₂ and selectfluor with *ortho*-ester diarylalkynes (ethyl-2-(phenylethynyl)benzoates) is also particularly suitable for the synthesis of quinoxalines because the yields obtained for quinoxalines were similar to those obtained for 1,2-diketones showing that the presence of a diamine possibly substituted in the reactional media does not disturb the progress of this efficient process.

Table 23 One-pot access to quinoxalines from diarylalkynes

To show the versatility of the PdI₂/DMSO method in view of synthesizing nitrogen-containing heterocycles from alkynes, we reported the synthesis of three other heterocycles^{6a} starting from diarylalkynes variously substituted with different nucleophiles as NH₄OH in the presence of a benzaldehyde, urea, and thiourea (Table 24).

The PdI₂/DMSO procedure applied to diphenylacetylene followed by the addition of NH₄OH and 4-nitrobenzaldehyde in the same pot furnished in a nearly quantitative yield the expected imidazole (96%). Interestingly, when 1-methoxy-4-(*p*-tolylethynyl)benzene (or other arylalkynes) were heated in DMSO in the presence of 1% of PdI₂, the 1,2-diketone which upon refluxing urea or thiourea cyclized to form after migration of a phenyl ring, a imidazolidin-2,4-dione and a thioimidazolidin-2,4-dione with excellent yields of 90% and 88%, respectively.

Table 24 One-pot access to other nitrogen-containing heterocycles from diarylalkynes

All of these results demonstrated the efficiency of the tandem oxidation-nitrogen nucleophiles condensation-cyclization to provide rapidly in the same pot, a large variety of nitrogen containing heterocycles useful for further synthetic transformations of for biological studies.

5.2 Access to various heterocycles

Beside the synthesis of heterocycles from alkynes in a one-pot process which was poorly documented, a large number of studies reported the synthetic usefulness of 1,2-diketones and particularly tolane derivatives as precursors of various heterocycles. From all these studies, the synthesis of polysubstituted imidazoles and quinoxalines was the most studied and documented. In Scheme 11, a selection of cyclic and heterocyclic systems prepared from the condensation of nucleophiles on various benzils is depicted.

Scheme 11. Transformation of benzils to furnish various heterocycles

Functionalized quinoxalines which represent an important class of nitrogen-containing heterocycles having a broad spectrum of biological properties as for example antitumor activities⁵³ have been well studied and one of the most common strategies relied on the condensation of *ortho*-phenylenediamines with benzil derivatives. For example, Lindsley reported an efficient microwave-assisted protocol for the synthesis of various quinoxalines and heterocyclic pyrazines from α -diketones in EtOH.⁵⁴ After 5 min of stirring at 160 °C under MWI, the desired heterocycles were obtained with good to excellent yields without traces of polymers which were obtained as side-products and with variable amounts under a conventional heating.

Imidazole nucleus, which displayed an important role in biological active drugs was easily obtained from the condensation of benzils with aldehydes in the presence of NH_4OAc . Very recently, a series of polysubstituted imidazoles catalyzed by ZrO_2 -supported- β -cyclodextrins have been synthesized by this way under solvent-free conditions at 100 °C with yields ranging from 80 to 98%.⁵⁵

Sulfur containing heterocycles, as 3,4-diarylthiophenes having a COOH function on C-2 and C-5 were prepared from benzils. Traversone and Brill reported the synthesis of such polysubstituted thiophenes according to the Hinsberg thiophene synthesis⁵⁶ by the condensation of supported thioglycolic carbanions.⁵⁷ Benzils having EDG- and EWG substituents were well tolerated in this process to give the desired thiophenes with satisfactory yields.

Concerning the synthesis of highly functionalized pyrroles (Scheme 11) from benzils, a domino approach to these compounds was proposed in 2012 by Maiti.⁵⁸ Under $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ catalysis, various enaminoesters reacted with benzils and ketones in the presence of KI to give after a cascade cyclization highly functionalized pyrroles. This domino process appears to be selective, substrate specific and high yielding.

Pyridazines⁵⁹ and 1,2,4-triazines⁶⁰ were also obtained rapidly from benzil substrates in the presence of nucleophiles as hydrazine or acylhydrazides. In a "one-pot" synthesis and according to an aldolization reaction, substituted benzils reacted with acetophenones in the presence of *t*-BuONa to give 1,4-diketones which underwent cyclization in the presence of hydrazine to give 2,4,5-trisubstituted pyridazines.⁵⁹ Zhao and Lindsley used a similar protocol developed for the synthesis of quinoxalines⁵⁴ under MWI, to the synthesis of 1,2,4-triazines which were obtained from the condensation of acylhydrazines and benzils in the presence of NH_4OAc .

Disubstituted indoles in C-2 and C-3 positions, which are important units in biological products⁶¹ have been successfully prepared by Cabrera⁶² and co-workers. $[(S)\text{-BINAP}]\text{PdBr}_2$ catalyzed the condensation of anilines with benzil substrates under reductive (H_2) conditions. Anilines reacted with benzils (or dialkyl- α -ketones) to give enamines which were reduced by H_2 and the resulting aminoketones underwent cyclization with the help of Pd to give the desired 2,3-disubstituted indoles with good yields.

Finally, beside the syntheses of organic heterocycles starting from benzil substrates, Moineau-Chane Ching also demonstrated that heteroleptic nickel complexes having optical properties could be prepared rapidly with diaryl- α -diketones.⁶³ Functionalized benzils were reacted with P_4S_{10} to give their dithione sulfur analogs which were transformed in homoleptic Ni-complexes in the presence of NiCl_2 . Further ligand-exchange reactions between two different homolytic complexes furnished the desired heteroleptic-Ni complexes having a possible potential as conjugated materials for organic field-effect transistors and organic solar cells.

In this section, we abstracted and showed that many methodologies used for the oxidation of substituted diarylalkynes, including heteroarylalkynes are fully compatible with the condensation of nucleophiles leading to different heterocycles in a one-pot manner. Very often, yields are excellent since the second condensation reaction is nearly quantitative. So it is now possible, starting from functionalized diarylalkynes to have many quick

pathways to a range of diverse heterocyclic having interesting and varied properties.

6. Conclusion

Due to their intrinsic properties or their role as pivotal molecules in the construction of heterocycles, benzil derivatives have been well studied these last three decades. Under the leadership of the Russian chemistry, first syntheses of benzils were achieved using I_2 or I^+ sources as activating agents of the alkyne triple bond. This latter was then subjected to the attack of various oxidants in which H_2O and DMSO predominated. These efficient protocols required, however, high reactional temperatures and liberated DMS in the case of DMSO-oxidation as main drawbacks. Using KMnO_4 as oxidizing species allowed this transformation at rt but henceforth, for environmental considerations, these protocols cannot be applied on a large scale. More recently, more convenient procedures were proposed with metallic salts (Pd, Cu, Ru, Fe, Au, Hg) in which Pd^{II} salts predominated (PdI_2 , PdCl_2 , and PdBr_2). A large variety of oxidizing agents were associated with all of these metallic salts to afforded a wide range of functionalized benzils and, to our opinion, it is really difficult to define a predominant protocol while yields are comparable and most of these methodologies tolerated electron-rich and electron-poor tolanes. One note that some experimental oxidizing conditions, using metallic salts, were showed to be compatible with the one-pot synthesis of various heterocycles in the presence of nucleophiles making these protocols extremely attractive. Henceforth, the main challenge in this area will be to find mild experimental conditions to oxidize a variety of heteroarylalkynes using low loading of catalysts. The oxidation of nitrogen-containing heterocycles, which can easily complexed to metallic salts, represents a real challenge in this area in extension.

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<p>Ling-Zhi YUAN was born in 1987 in Huang-shi (Hubei Province, China) and granted with National Scholarship (2007-2008) during undergraduate period. After he received his master degree in 2013 with Prof. Jing-Yuan XU at Tianjin Medical University, he began his PhD on selective metal-free deoxygenation of unsymmetrical 1,2-dicarbonyl compounds under the supervision of Dr. Olivier Provot in the Faculty of Pharmacy, University Paris-Sud 11.</p>
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<p>Mouad Alami biography, PhD, 56 years is a Research Director at the CNRS (Faculty of Pharmacy, BioCIS, France). He did his PhD at the University Pierre and Marie Curie (1987). After a two years (1987-89) post-doctoral position in collaboration with the Elf- Atochem company, he joined on 1989 the CNRS at the ENS-Paris (Dr. G. Linstrumelle). In 1993, he spent one year at the University of Santa-Barbara (Pr. B. H. Lipshutz) and in 1997, he moved as an independent researcher at the CNRS to Cergy-Pontoise University. In 1999, he accepted a position at the, Faculty of Pharmacy (University Paris-Sud) where he became CNRS Research Director. Dr Alami's field of specialization includes: (i) the development of novel selective synthetic methodologies involving organometallic chemistry and (ii) the synthesis of structurally challenging and biologically relevant products with antitumoral activity, particularly on small molecules, vascular disrupting agents (VDAs), and their application in the context of antibody-drug conjugates (ADC).</p>
<p>Olivier Provot was born in 1963 in the beautiful city of Caen (Normandy, France) and received his basic chemical education at the University Paris 6. After finishing his PhD in total synthesis of ant venom alkaloids in the Lab of Prof. G. Lhomme in 1991, he pursued his interest in chemistry in Industry for two years, and after in the Lab of Medicinal Chemistry of Prof. R. Milcent (University Paris 7). He then moved in the Lab of Prof. H. Moskowitz as assistant Professor in 1993 (University of Paris 11) and worked on the synthesis of peroxides having antimalarial activities (Artemisinin's analogs). In 2003, he joined the group of Prof. J.-D. Brion and Dr. M. Alami (University Paris-Sud 11) to develop novel organometallic methodologies in view of a rapid access to novel anti-cancer drugs related to Combretastatin A-4.</p>

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