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$NH_4I/EtOCS_2K$ promoted synthesis of substituted benzils from diphenylacetylene derivatives

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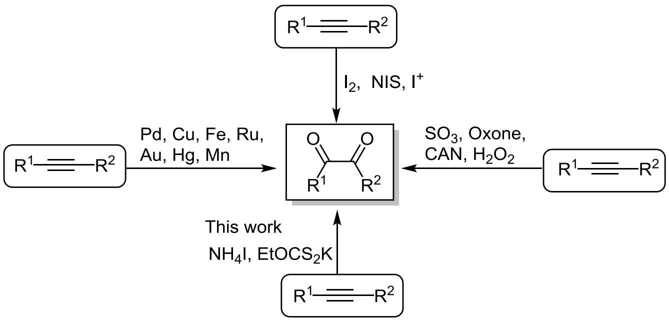
ABSTRACT

A facile protocol is described for the synthesis of benzil derivatives from readily accessible diarylacetylene derivatives using the $NH_4I/EtOCS_2K$ system. This novel protocol results in excellent chemoselectivity and provided good to excellent yields. A control experiment indicated that the reaction proceeds *via* NH_4I promoted $EtOCS_2K$ dimerization to give the corresponding dixanthogen and subsequent dixanthogen assisted oxidation.

Introduction

The development of practical alkyne oxidation strategies has received considerable attention because as one of the most useful transformations in organic synthesis, the process offers low-cost and straightforward access to highly synthetically valued building blocks from commercially available starting materials.[1] Among the various methods for the stoichiometric oxidation of C(sp)-C(sp) triple bonds, the use of $KMnO_4$,[2] $TlNO_3$,[3] OsO_4,[4] H_3PO_5,[4] dioxiranes,[6] organic peracids[7] and transition-metal-catalyzed conditions[8] has been widely developed. Despite remarkable progress in this area, examples of environmentally friendly methods are still under underexplored; these established methods require the use of expensive transition-metal catalysts, high temperatures, or toxic reaction conditions.

Recently, catalytic systems for the oxidation of 1,2-diarylalkynes to benzils have been widely developed. Among them, the transition-metal complexes containing Pd,[9] Cu,[10] Fe,[11] Ru,[12] Au,[13] Hg,[14] and Mn[15] have proven to be useful for this transformation. However, these transition-metal reagents still have drawbacks, such as high price, generation of toxic waste, and the need for air sensitive or expensive ligands. From an economical and environmentally friendly viewpoint, it would be advantageous to develop transition-metal-free systems for the synthesis of benzils from 1,2-diarylalkynes. The use of a stoichiometric amount of inorganic oxidants, such as sulfur trioxide (SO_3),[16] Oxone,[17] CH_3SO_3H[18] and CAN,[19] as well as photo-oxidation,[20] is essential for such reactions. Among the various transition-metal-free syntheses of 1,2-diarylalkynes from benzils, I_2/DMSO[21] and its variants are the most popular choices. At high temperatures, carbon-carbon double bonds are not affected. As shown in Scheme 1, NIS[22] and hypervalent iodine species,[23] were used as inexpensive and efficient oxidants. Although the mechanism for the oxidation of diarylalkynes by I_2, NIS and hypervalent iodine species has not been fully determined, it is reasonable to propose an iodonium ion is generated as the key intermediate. There have been no literature reports that the oxidation reaction can be initiated by an iodide anion or iodine radical initiation. Herein, we report that the $NH_4I/EtOCS_2K$ system can efficiently oxidize diarylacetylene to benzil compounds as well as mechanistic studies that indicate that the reaction is likely triggered by radical initiated iodooxidation.

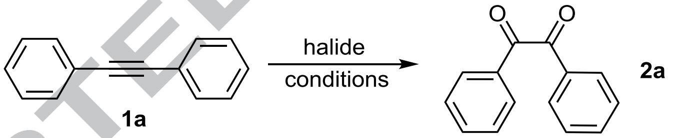


Scheme 1. Synthesis of benzils from diarylalkyne oxidation.

Results and Discussion

Initially, 1,2-diphenylethyne, NH_4I and DMSO were selected as model substrates for optimization of the reaction conditions. Initial attempts in the presence of NH_4I (2.0 equiv.) at 130 °C using DMSO/H_2O (3.0 mL) as the solvent only gave benzil **2a** in trace amounts (Table 1, entry 1). The reaction efficiency did not change in the presence of $EtOCS_2K$ (1.2 equiv.) at 130 °C (Table 1, entry 2). When using NH_4I (1.0 equiv.) and $EtOCS_2K$ (0.5 equiv.), benzil **2a** was not obtained and only trace 1,2-diphenylethene was detected by GC-MS. Conversely, moderate yields of benzil **2a** were obtained using NH_4I (1.0 equiv.) and $EtOCS_2K$ (1.2 equiv.) (Table 1, entries 3-5). It was found that the reaction of NH_4I (2.0 equiv.) and $EtOCS_2K$ (1.2 equiv.) at 130 °C for 12 h gave benzil **2a** in 91% yield (Table 1, entries 6-7). In is noteworthy that ammonium iodide plays an important role in the reaction. No reaction was observed when similar ammonium salts such as Et_4NI, NH_4Br and ICl were used (Table 1, entries 9-11). In addition, screening other solvents such as DMF, NMP, DMAc, and 1,4-dioxane did not provide better results (Table 1, entries 12-14). It was found that lower reaction temperatures (120 °C) led to only a 37% yield, and prolonged reaction times did not improve the reaction (Table 1, entry 15). Finally, no product **2a** was detected when the chemistry was performed in the presence of the radical scavenger butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (Table 1, entries 16 and 17). These results suggested that the iodooxidation reaction presumably proceeded through a radical pathway. Under a nitrogen atmosphere, the yield did not improve significantly (Table 1, entry 18).

Table 1. Optimization of the reaction conditions.[a]



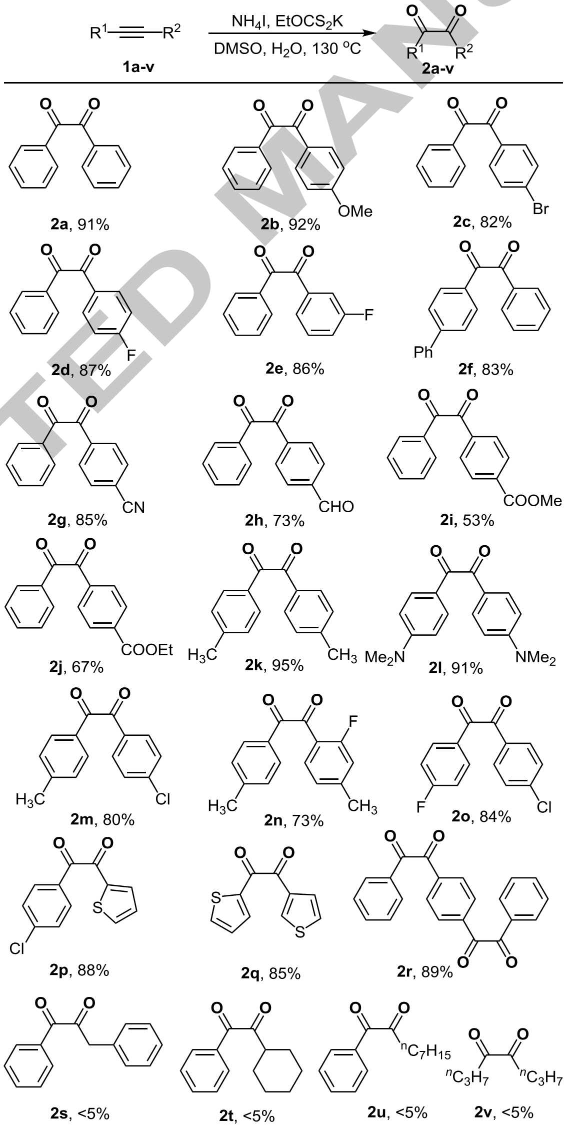
Entry	Halide (mmol)	$EtOCS_2K$ (mmol)	Solvent	Yield **2a** (%)[b]
1	NH_4I (2)	-	DMSO/H_2O (2:1)	-
2	-	1.2	DMSO/H_2O (2:1)	-
3	NH_4I (1)	0.5	DMSO/H_2O (2:1)	<5
4	NH_4I (1)	1.2	DMSO/H_2O (2:1)	45
5	NH_4I (2)	0.5	DMSO/H_2O (2:1)	35
6	NH_4I (2)	1.2	DMSO/H_2O (2:1)	93 (91)
7	NH_4I (2)	2	DMSO/H_2O (2:1)	87
8	NH_4I (2)	2	DMSO/H_2O (3:0)	68
9	Et_4NI (2)	1.2	DMSO/H_2O (2:1)	-
10	NH_4Br (2)	1.2	DMSO/H_2O (2:1)	-
11	ICl (2)	1.2	DMSO/H_2O (2:1)	<5
12	NH_4I (2)	1.2	NMP/H_2O (2:1)	<5
13	NH_4I (2)	1.2	DMAc/H_2O (2:1)	<5
14	NH_4I (2)	1.2	DMF/H_2O (2:1)	<5
15[c]	NH_4I (2)	1.2	DMSO/H_2O (2:1)	37

16[d]	NH_4I (2)	1.2	DMSO/H_2O (2:1)	<5
17[e]	NH_4I (2)	1.2	DMSO/H_2O (2:1)	<5
18[f]	NH_4I (2)	1.2	DMSO/H_2O (2:1)	86

[a] Reagents and conditions: diphenylacetylene **1a** (1.0 mmol), halide, $EtOCS_2K$, solvent (v/v) (3.0 mL), 130 °C, 12 h; [b] Yield determined by GC-MS analysis; [c] Reaction was carried out at 120 °C for 18 h; [d] TEMPO (1.0 mmol); [e] BHT (1.0 mmol); [f] Under a N_2 atmosphere.

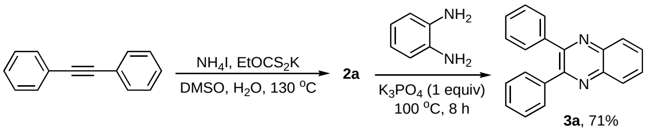
With the optimized reaction conditions in hand, we next examined the substrate scope for the synthesis of substituted benzil derivatives (Scheme 2). By varying the R^1 and R^2 substituents of alkynes **3**, it was shown that both electron-donating as well as electron-withdrawing substituents on the aromatic rings could be introduced and gave the benzil products in moderate to good yields. The reaction tolerated a range of substituents including: -OMe, -CN, -CHO, -COOEt, -F, -Cl, -Br, -Me, -NMe_2 and thiophenyl groups. The use of diphenylethyne derivatives with electron-donating substituents afforded the corresponding products in higher yields (Scheme 2, **2b, 2k** and **2l**). The steric hindrance associated with the diphenylethyne derivatives also affected the reaction, as the introduction of a 2-F group onto the aromatic ring lowered the yield of the corresponding benzils (Scheme 2, **2n**). It was noteworthy that the reaction of sulphur-containing heterocycles such as 2-(2-phenylethynyl)thiophene and 2-(2-(thiophen-3-yl)ethynyl)thiophene proceeded well and afforded benzils **2p**-**q** in good yields. Finally, the reaction of 1,4-bis(2-phenylethynyl)benzene gave 1,4-bisbenzil **2r** in 89% yield. Unfortunately, the reactions with 1-aryl-2-alkyl-acetylenes (prop-1-yne-1,3-diyldibenzene, cyclohexylethynyl)benzene, non-1-yn-1-ylbenzene), 1,2-dialkyl-acetylenes (4-octyne) and phenylacetylene, were unsuccessful under the current reaction conditions.

Scheme 2. Synthesis of benzils from alkynes.[a,b]



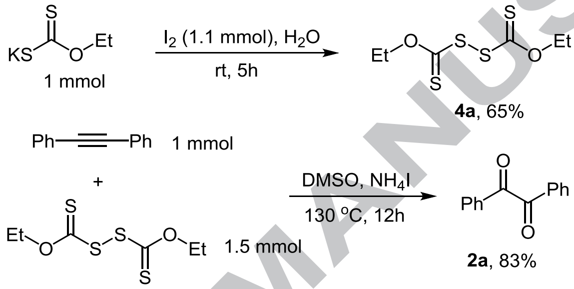
[a] Reagents and conditions: alkyne **1** (1.0 mmol), NH_4I (2.0 mmol), $EtOCS_2K$ (1.3 mmol), DMSO/H_2O (2/1) (3.0 mL), 130 °C, 12 h; [b] Isolated yield.

This synthetic method can also be used for the direct synthesis of heterocyclic compounds *via* cyclization. During the course of these studies, we discovered that the one-pot synthesis of 2,3-diphenylquinoxaline proceeded in 71% yield, which is potentially useful for the pharmaceutical industry.[23, 24]



Scheme 3. One-pot synthesis of quinoxaline **3a** from 1,2-diphenylethyne.

Although the mechanism of this reaction is not clear, we were able to gain insight from control experiments. We used I_2-catalyzed potassium xanthate to synthesise dixanthogen,[25] then diphenylacetylene and dixanthogen in the absence of $EtOCS_2K$ give the benzil product in 83% yield. Wang and co-workers reported a similar thiyl radical catalyzed oxidation of diarylalkynes to α-diketones using 4,4'-dinitrodiphenyldisulfide as the radical source.[26]



Scheme 4. Synthesis of benzil **2a** from dixanthogen **4a**.

Conclusion

In conclusion, we have developed a transition-metal-free $NH_4I/EtOCS_2K$ ($EtOCS_2K$, 25g/$10) system for the reaction of 1,2-diarylalkynes to give the corresponding benzil products in moderate to good yields. This novel protocol proceeds with excellent chemoselectivity and high functional group tolerance. A control experiment indicated that the reaction proceeds *via* NH_4I promoted $EtOCS_2K$ dimerization to give the corresponding dixanthogen and subsequent dixanthogen assisted oxidation. The further applications of this general methodology to other reactions is the subject of ongoing investigations.

Acknowledgements

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Supplementary Material

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Synthesis benzils from easily accessible diarylacetylene derivatives

Mild conditions, good functional groups tolerance and good yield was obtained

Proceeded smoothly through a dixanthogen assisted thiyl radical catalyzed oxidation

Transformation of diarylalkynes leading to the quinoxalines *via* cyclization

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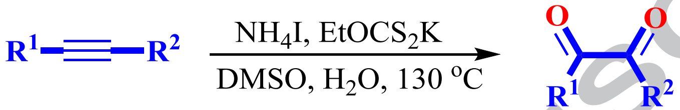

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