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Ruthenium-catalyzed oxidation of alkynes to 1,2-diketones under room temperature and one-pot synthesis of quinoxalines

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ABSTRACT

A ruthenium-catalyzed alkyne oxidation to 1,2-diketones using Oxone under room temperature is reported. Both substrate scope and mechanism were discussed. Notably, combination of the alkyne oxidation and condensation cyclization in one pot offers a very efficient and convenient entry into quinoxaline derivatives.

Introduction

1,2-Diketones appear frequently as structural sub-units in molecules of biological and medicinal interest[1] and are versatile building blocks capable of undergoing a variety of chemical transformations, especially for the synthesis of heterocyclic compounds.[2] The direct oxidation of properly substituted alkynes, which are prepared via Sonogashira coupling, might be the most straightforward method to synthesize the 1,2-diketone derivatives. The stoichiometric oxidation of alkynes has been widely studied, which suffers from generation of large amounts of wastes. Recently, the development of catalytic methods for the oxidation of alkynes to 1,2-diketones has been an attractive research area in organic chemistry.[3] In addition, C–C bond cleavage of 1,3-diketones represents another promising method for producing 1,2-diketones.[4] Despite these great achievements, from the standpoint of environmental benignity and overall cost, pursuing more efficient and practical catalytic systems with improved turnover is paramount. As part of our ongoing project to investigate new oxidation methods for 1,2-diketone,[3j,l,n] we attempted to develop a mild process catalyzed by ruthenium with low catalyst loadings.

Results and discussions

Recently, Yang et al. reported a Ru-catalyzed oxidative cleavage of alkynes to carboxylic acids using Oxone.[5a] Inspired by this work, we investigated the Ru-catalyzed oxidation of 1,2-diphenylethyne **1a** for benzil **2a** using Oxone as the oxidant under room temperature. Sodium bicarbonate was used as the buffer to maintain the neutral conditions.[5] To our delight, a small amount of benzil **2a** was formed in the catalytic system (Table 1, entry 11). Interestingly, the use of TEMPO as a cocatalyst enhanced the conversion in a remarkable manner, resulting in the product **2a** in excellent yield. The catalyst is capable of up to 4600 turnovers with the substrate **1a** (Table 1, entry 1). In sharp contrast with Yang's work, no carboxylic acid was detected in this transformation. Negligible product **2a** was generated in the absence of Ru catalyst (Table 1, entry 10). When other Ru catalysts were used, product **2a** was achieved in moderate yield (Table 1, entries 13 and 14). In addition to Oxone, various oxidants were also employed in this study. The results are shown in Table 1, which indicated that Oxone is the best oxidant for the transformation (Table 1, entries 15–18). The effect of the solvent was also dramatic. Among the various solvents examined, $MeNO_2/H_2O$ was the most suitable for the transformation under the catalytic system. Replacement of $MeNO_2/H_2O$ with other solvents leads to a drop in yield (Table 1, entries 2–9). Finally, when the transformation was scaled up to 10 mmol, product **2a** was still achieved in excellent yield (Table 1, entry 19).

With the optimized oxidation conditions available, we embarked on the investigation of the alkynes' scope. A series of alkynes with different substituents on the aromatic ring were examined (Table 2). To our delight, aromatic alkynes bearing both electron-rich and electron-poor functional groups were oxidized to the corresponding 1,2-diketones in moderate to excellent yields.

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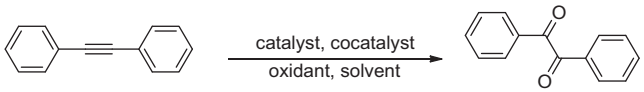
Table 1
Optimization of reaction conditions[a]

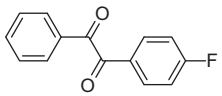


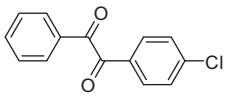
1a **2a**

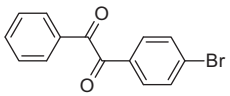
Entry	Catalyst	Cocatalyst	Oxidant	Solvent	Yield[b]
1	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$MeNO_2/H_2O$	92%
2	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	DMF/H_2O	<5%
3	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	DME/H_2O	<5%
4	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	EA/H_2O	<5%
5	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$^tBuOH/H_2O$	35%
6	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$MeCN/H_2O$	<5%
7	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$Dioxane/H_2O$	<5%
8	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$Toluene/H_2O$	<5%
9	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	DCE/H_2O	<5%
10	—	TEMPO	Oxone	$MeNO_2/H_2O$	<5%
11	$[Ru(cymene)Cl_2]_2$	—	Oxone	$MeNO_2/H_2O$	26%
12	—	—	Oxone	$MeNO_2/H_2O$	N.O.[c]
13	$RuCl_2(PPh_3)_3$	TEMPO	Oxone	$MeNO_2/H_2O$	41%
14	$RuCl_3$	TEMPO	Oxone	$MeNO_2/H_2O$	67%
15	$[Ru(cymene)Cl_2]_2$	TEMPO	O_2	$MeNO_2/H_2O$	N.O.
16	$[Ru(cymene)Cl_2]_2$	TEMPO	Benzoquinone	$MeNO_2/H_2O$	N.O.
17	$[Ru(cymene)Cl_2]_2$	TEMPO	$PhI(OAc)_2$	$MeNO_2/H_2O$	40%
18	$[Ru(cymene)Cl_2]_2$	TEMPO	H_2O_2	$MeNO_2/H_2O$	N.O.
19	$[Ru(cymene)Cl_2]_2$	TEMPO	Oxone	$MeNO_2/H_2O$	94%[d]

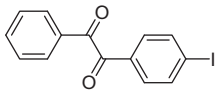
[a] All reactions were carried out in the scale of 0.2 mmol in 4.0 mL of nitromethane and 0.5 mL of water in the presence of 0.5 mmol $NaHCO_3$, 10 mol % TEMPO, and 0.02 mol % Ru catalyst using Oxone (330 mg, 5% active oxygen) under room temperature for 12 h unless noted otherwise.
[b] Isolated yield.
[c] Not observed.
[d] 10 mmol substrate was used.

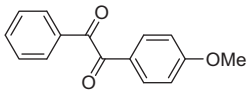
Table 2
Ru-catalyzed alkyne oxidation for 1,2-diketones[a]

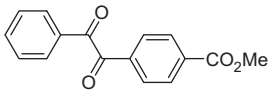

2b, 94%

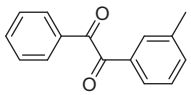

2c, 80%

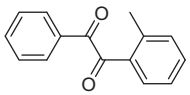

2d, 88%

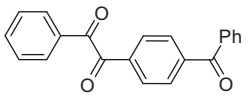

2e, 93%

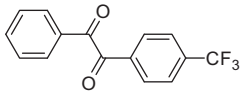

2f, 92%

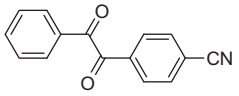

2g, 85%

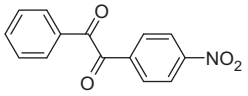

2h, 80%

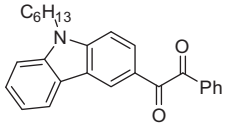

2i, 75%

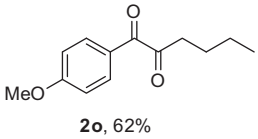

2j, 76%

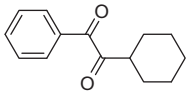

2k, 93%

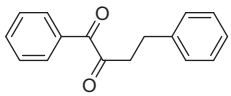

2l, 81%[b]

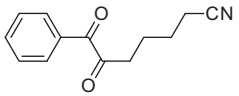

2m, 91%[b]

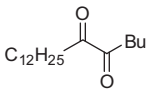

2n, 62%[b]


2o, 62%


2p, 51%

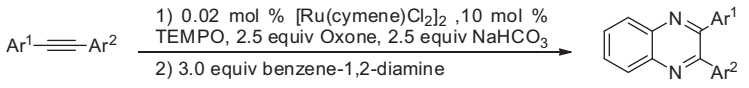

2q, 56%

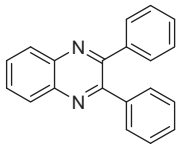

2r, 71%

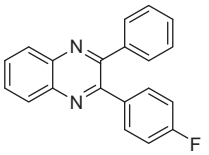

2s, 52%

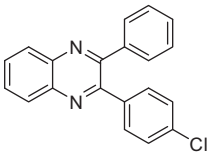
[b] 50 °C.
[a] All reactions were carried out in the scale of 0.2 mmol in 4.0 mL of nitromethane and 0.5 mL of water in the presence of 0.5 mmol $NaHCO_3$, 10 mol % TEMPO, and 0.02 mol % $[Ru(cymene)Cl_2]_2$ using Oxone (330 mg, 5% active oxygen) under room temperature for 12 h unless noted otherwise.

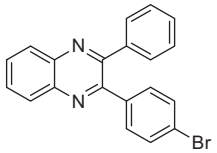
Table 3
Synthesis of quinoxaline derivatives via a one-pot procedure[a]

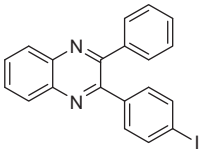


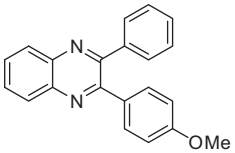

3a, 95%

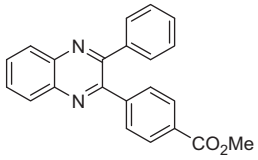

3b, 96%

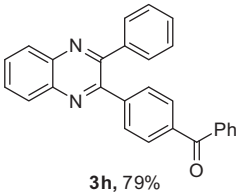

3c, 59%

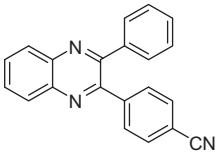

3d, 82%


3e, 95%


3f, 78%


3g, 88%


3h, 79%


3i, 72%

[a] Step 1: 0.2 mmol alkynes in 5.0 mL of nitromethane and 0.8 mL of water in the presence of 0.5 mmol $NaHCO_3$, 10 mol % TEMPO, and 0.02 mol % Ru catalyst using Oxone (330 mg, 5% active oxygen) under room temperature for 12 h. Step 2: 3.0 equiv of benzene-1,2-diamine, room temperature for 24 h.

Notably, the presence of halogen substituents on the aromatic rings did not interfere with the triple bond oxidation process, affording products that could be further functionalized by transition-metal-catalyzed cross-coupling reactions (products **2b**–**2e**). Heteroarenes such as carbazole also underwent clean oxidation to give the corresponding 1,2-diketone **2n** in satisfactory yield. Usually, alkyl-substituted alkynes were not suitable partners for 1,2-diketone synthesis.[3] In sharp contrast, when alkyl-substituted alkynes were employed under the optimized conditions, products **2o**–**2s** were achieved in moderate to good yields.

Quinoxalines occur widely in biologically active compounds, functional material, and therapeutic drug molecules.[6] With high efficiency and mild conditions of the oxidation reaction in our hand, we next explored the possibility of the construction of quinoxalines directly from alkynes and 1,2-diamine via a one-pot two-step procedure. The alkyne oxidation was carried out under the optimized conditions, followed by condensation cyclization with benzene-1,2-diamine, affording the corresponding quinoxalines in moderate to excellent yields. As shown in Table 3, several functional groups, such as methoxy, halide, ester, CN, and benzoyl, on the aromatic moiety were well-tolerated.

Conclusion

In summary, we have developed a new protocol for the 1,2-diketone synthesis through alkyne oxidation catalyzed by ruthenium under room temperature. The mild and neutral conditions, wide substrate scope, and relatively safe oxidant, as well as its application in one-pot synthesis of quinoxalines, render this method a powerful alternative to previous approaches. Further investigations of detailed mechanism and related processes are ongoing in our laboratories.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.142.

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1. For example, see: (a) Wadkins, R. M.; Hyatt, J. L.; Wei, X.; Yoon, K. J. P.; Wierdl, M.; Edwards, C. C.; Morton, C. L.; Obenauer, J. C.; Damodaran, K.; Beroza, P.; Danks, M. K.; Potter, P. M. *J. Med. Chem.* **2005**, *48*, 2906–2915; (b) Ngadjui, B. T.; Kouam, S. F.; Dongo, E.; Kapche, G. W. F.; Abegaz, B. M. *Phytochemistry* **2000**, *55*, 915–919.
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