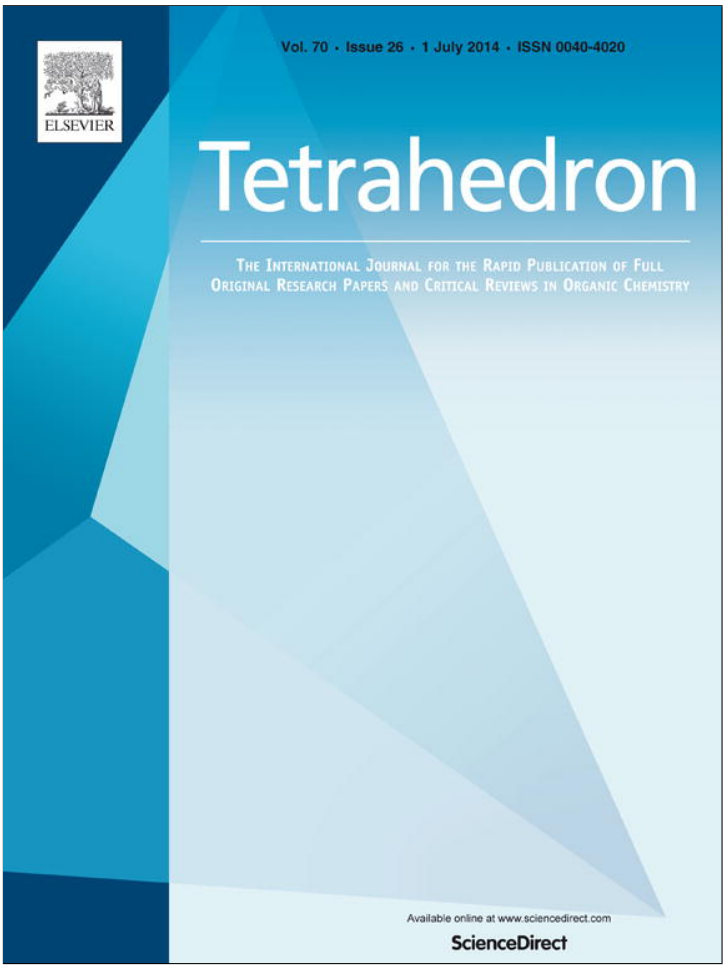


Tetrahedron 70 (2014) 3988–3993

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Transition metal-free oxidation of ynamides for synthesis of α-keto-imides

Takuya Chikugo, Yuta Yauchi, Masataka Ide, Tetsuo Iwasawa *

Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan

ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 25 April 2014
Accepted 26 April 2014
Available online 2 May 2014

Keywords:
Oxidation
α-Keto-imide
1,2-Diketone
Ynamide
Transition metal-free reaction

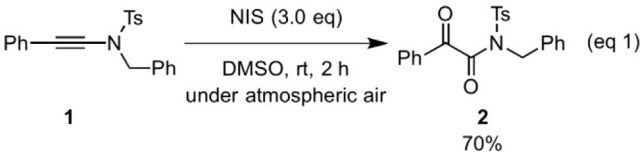
ABSTRACT

Transition metal-free double oxidation of triple bonds in ynamides for synthesis of α-keto-imides is described. The successful key was combination of NIS and DMSO under atmospheric air in CPME solvent, and the reaction quickly proceeds at 0 °C within 1 h. Although the yields and substrate generality are moderate, yet the prototype protocol avoids the use of expensive, moisture-sensitive, toxic, and explosive additives, which make it potentially and significantly greener than current alternatives.

1. Introduction

One significant goal in modern synthetic organic chemistry is the development of efficient and sustainable processes capable or replacing hazardous classical reactions.[1–3] The oxidation of organic molecules is a traditional and fundamental reaction that depends on harmful metals and dangerous oxidants.[4] Although transition metal-protocols and exquisitely elaborated oxidants are successful for oxidation reaction,[5] they usually have inherent limitations, such as moisture sensitivity, environmentally toxicity, costly materials, and potentially explosive.[6] Moreover, separation of metals from polar products, which is of particular importance for the synthesis of pharmaceutical fine chemicals because of their residual toxicity in the target drugs, is a critical issue to consider.[7] Hence, it is purposeful to exploit transition metal-free approach and handling-easy oxidant invention.

Recently we have developed the regio- and stereoselective iodobromination and hydrohalogenation of ynamides to synthesize varied haloenamides on diverse scaffolds.[8] In the course of our study, we encountered the unforeseen oxidation reaction (Eq. 1): ynamide **1** was transformed into α-keto-imides **2** in 70% yield under just NIS (*N*-iodosuccinimide)/DMSO (dimethyl sulfoxide) condition. So far only Hsung and co-workers elegantly achieved the direct oxidation of ynamides to α-keto-imides, and they employed both RuO_2–$NaIO_4$ and DMDO (dimethyldioxirane) oxidations, that is, the each procedure also consists of the transition metal approach and the labile oxidant system.[9] As a consequence, we immediately began exploring the scope and limitation of this transformation.



1 **2** 70%

Although the α-keto-imide is underrepresented so far owing to the limited protocol, its significance lies in the close analogy to α-keto-amide and α-keto-ester. The α-keto-imide has at least one electron-withdrawing group (EWG) on the nitrogen atom, which makes it more thermodynamically stable than the corresponding α-keto-amide: still, the α-keto-imide is well reactive. Actually, some successful transformations have been achieved on hetero-Diels–Alder reactions,[10a] and diastereoselective allylation,[10b] and Grignard-addition reaction.[10c] As the α-keto-amide and ester are capable of participating a wide range of complexity-generating transformations (e.g., stereochemical-controlled addition of nucleophiles,[10d] and pinacol-type couplings,[10e] and photo-cyclization to β-lactams[10f]), the α-keto-imide also would potentially work as a diverse synton. In addition, from the biological point of view, the α-keto-amide is responsible for several enzymatic reactions[11] and pharmaceutical function as an enzymatic

* Corresponding author. Tel.: +81 77 543 7461; fax: +81 77 543 7483; e-mail address: iwasawa@rins.ryukoku.ac.jp (T. Iwasawa).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.04.080

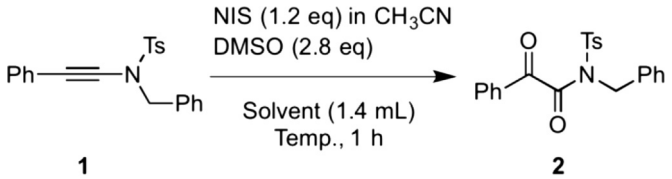
inhibitor.[12] Thus, the similarity strongly implies how valuable role a facile route to α-keto-imide performs. On the other hand, unlike α-keto-imide, the importance of diarylalkynes (benzils) is well known to underlie the many research fields of science. For example, such benzils are employed as the critical synthetic intermediates in material science[13] and medicinal chemistry;[14] however, synthetic availability of unsymmetrical benzils remains a challenge. The structural resemblance between α-keto-imide and benzil, which is composed of α-diketone moiety, anticipates the expansion of the possibilities and importance of unexplored α-keto-imide.

Herein we report a transition metal-free synthesis of α-keto-imides from ynamides. The combination of NIS, and DMSO, and atmospheric air was useful for one-step construction of α-keto-imides skeleton from ynamide substrates. The reaction proceeds within 1 h at 0 °C, giving moderate yields. The method was also applicable to the double oxidation of diarylalkynes. Our synthetic protocol does not require pesky metals and scary oxidants, which is advantageous as compared to the conventional heavy metal and sensitive-, and expensive-oxidant approaches. Thus, the protocol provides contribution to an alternative oxidation method and greener reaction process.

2. Results and discussion

First, we evaluated the outcome of the NIS/DMSO-controlled oxidation of the ynamide **1** by varying two elements, solvent and temperature (Table 1). The larger amount of DMSO as a solvent than as a stoichiometric reagent is prone to be not generally accepted, particularly by process chemists, because DMSO and its resultant dimethyl sulfide have malodorous nature.[15] This oxidation was observed as an exothermic reaction,[16] and so the reaction temperature was initially conducted at 0 °C. Treatment of **1** with 1.2 equiv of NIS and 2.8 equiv of DMSO for 1 h in cyclopentyl methyl ether (CPME) provided the desired **2** in 83% yield, consuming all of the starting material **1** (entry 1). Although various solvents, such as THF[17] (entry 2), DMSO (entry 3), DMF (entry 4), acetone (entry 5), 2-propanol (entry 6), and toluene (entry 7) were applicable for the present transformation, the most effective solvent in terms of the yield was found to be CPME at entry 1. Presumably the tolerance to acidity inherent in CPME is effective in yielding **2** under the current NIS/DMSO system. When the reactions under CPME solvent were performed at room temperature (entry 8) and −20 °C (entry 9), the yields decreased in 61% and <33%, respectively. Through all entries, generation of succinimides was confirmed in the crude products.

Table 1
Screening of conditions[a]

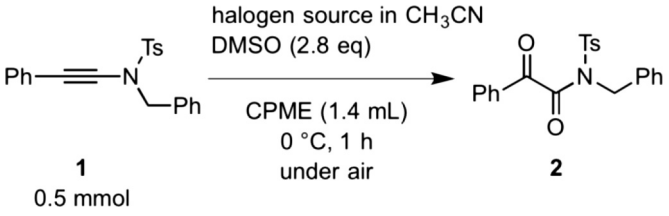


Entry	Solvent	Temp/°C	Yield%
1	CPME[b]	0	83
2	THF	0	51
3	DMSO	0	74
4	DMF	0	63
5	Acetone	0	68
6	2-Propanol	0	39
7	Toluene	0	58
8	CPME[b]	rt	61
9[c]	CPME[b]	−20	<33

[a] Reactions were performed under atmospheric air.
[b] Cyclopentyl methyl ether.
[c] CPME (10 mL) was needed for dissolving **1**.

Next we examined the effect of iodine sources and other halogens on the oxidation as shown in Table 2. When the employment of NIS decreased to 0.6 equiv, the yield reduced to 63% (entry 2); the oxidation required stoichiometric amount of NIS (entry 1). For entries 3–5, actions of I_2 were attempted[18] and nearly complete consumption of the starting ynamide **1** was observed; however, the high yielding transformations were not achieved. For entries 6 and 7, the additives of KI and NH_4I did not work at all. For entries 8 and 9, NBS afforded in only 20%, and NCS resulted in no reaction. Thus, NIS and I_2 would work as I^+ sources,[19,20] and the I^+ performs electrophilic attack to a triple bond of ynamide. Although the NIS might generate a molecular I_2 in situ, there would be difference between I_2 and NIS in the efficacy of each I^+, that is, NIS is a better source of I^+ than neat and bulk I_2. Actually, the experiments at entries 3–5 gave dark brown solution and multi spots on TLC monitoring, which imply that the I_2 induce many unknown side-products.

Table 2
Halogen sources for the formation of α-keto-imides



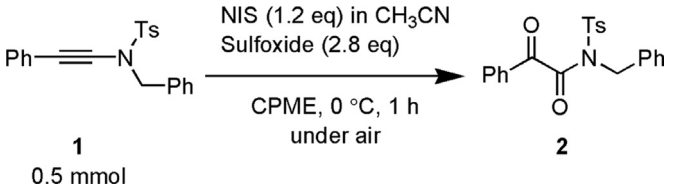
Entry	Iodine sources	Yield%	Recovered **1**, %
1	NIS (1.2 equiv)	83	0
2	NIS (0.6 equiv)	63	14
3	I_2 (1.2 equiv)	49	5
4	I_2 (1.0 equiv)[a]	31	0
5	NIS (1.2 equiv), I_2 (1.2 equiv)	72	0
6	NIS (1.2 equiv), KI (1.2 equiv)	25	0
7[b]	NIS (1.2 equiv), NH_4I (1.2 equiv)	<22	0
8	NBS (1.2 equiv)	20	5
9	NCS (1.2 equiv)	Trace	~100

[a] The reaction was performed under DMSO solvent at 150 °C for 1 h.
[b] Many unknown byproducts were observed on TLC and NMR analyses.

Table 3 illustrates different sulfoxide patterns tested. While the comparable yields between DMSO (entries 1 and 2), diphenyl sulfoxide (entry 3), and methyl phenyl sulfoxide (entry 4) were observed, longer alkyl-chained dibutyl sulfoxide (entry 5) and didodecyl sulfoxide (entry 6) lowered yields, and dimethyl sulfite (entry 7) gave the miserable yields. For entry 8, no use of sulfoxide afforded any target **2**. For entry 9, addition of diphenyl sulfide[21] instead of sulfoxide didn't work at all. Noteworthy is that all through entries 1–7 the starting **1** disappeared in appreciably shorter time: the reactions would end up in only 5 min on TLC monitoring. In addition, the NMR spectra in the crude states showed unknown byproduct peaks even in entries 1–4, and the terrible messy peaks appeared in the entries 5–7, that is, the NIS/sulfoxide system proves to be rather reactive toward ynamide substrates, and among them DMSO happens to be a most opportune reagent for the substrate.

As shown in Scheme 1, the oxidation of **1** (0.5 mmol) employing diphenyl sulfoxide (1.4 mmol) gave 0.64 mmol of diphenylsulfane. If the sulfoxide would work as an oxygen source, the resultant amount of diphenylsulfane should be 0.76 mmol, that is, twice of the keto-imide **2** (0.38 mmol): however, the observed amount was 0.64 mmol, that is, 84% of stoichiometric 0.76 mmol. Is the oxygen atom in atmospheric air involved in this reaction system? Then, the effect of atmosphere on the oxidation was examined, and the results were summarized in Table 4. For entry 1, to our surprise, an argon atmosphere didn't enable to control the reaction at all, and the crude

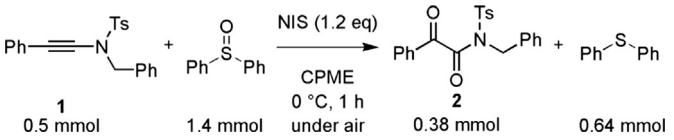
Table 3
Sulfoxide-mediated formation of α-keto-imides



Entry	Sulfoxides	Yield%
1	DMSO	83
2	DMSO[a]	67
3	Diphenyl sulfoxide	75
4	Methyl phenyl sulfoxide	77
5	Dibutyl sulfoxide	62
6	Didodecyl sulfoxide	<44[b]
7	Dimethyl sulfite	Trace[c]
8	—[d]	0
9	—[e]	0

[a] DMSO (1.4 equiv) was used, and 7% of **1** remained.
[b] Messy spectrum in the crude state.
[c] The starting **1** was disappeared on TLC.
[d] Without any sulfoxide.
[e] Diphenyl sulfide was added instead of the sulfoxide.

was terribly complicated with unidentified byproducts. For entries 2 and 3, an oxygen atmosphere did not improve the yield that an atmospheric air furnished. These revealed that the reaction system needs a certain quantity of gaseous oxygen, and impelled us to add an antioxidant on this oxidation reaction (Scheme 2). In the presence of 2,6-di-*tert*-butyl-4-methyl phenol, the oxidation under atmospheric air was found to occur in 80% yield, which was nearly comparable yield to entry 2 in Table 4. Considering the antioxidant effect of 2,6-di-*tert*-butyl-4-methyl phenol, the mechanism of our oxidation system would be similar in radical processes of Matsumoto's report.[19] Actually, as shown in Scheme 3, an attempt to oxidize ynamide **1** under Matsumoto's condition provided α-keto-imide **2** in acceptable 32% yield. Furthermore, indeed, the reaction conditions employing I_2 at entries 3 and 4 in Table 2, which yielded 49% and 31%, are close to Matsumoto's radical protocol. Thus, the necessary O_2 in atmospheric air might be somewhat involved and take a critical part of the present oxidation system.

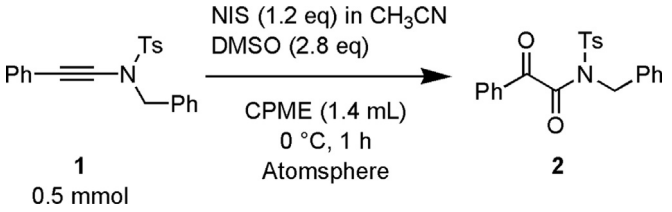


Scheme 1. A byproduct of diphenylsulfane.

The carbon–carbon triple bonds of various ynamides were converted to the corresponding diketones **3**–**9** (Table 5), giving moderate and acceptable yields.[22,23] The starting ynamides were totally and quickly consumed through entries; however, several spots on TLC monitoring and unidentified peaks on ^{1}H NMR were observed, and so the loss of the yields necessarily accompanied the oxidations. For Evans auxiliary **4**, the reaction at gram-scale successfully proceeded to afford 1.23 g in 70% yields. The methyl carbamate **3**, and *N*-methyl tosylamide **5** were isolated in moderate 54% and 65% yields, respectively. The nitrile **6**, methoxy **7**, and cyclohexyl **8** required laborious purification with column chromatography, yet each was given in 65%, 48%, and 41% yield. The 2-substituted indole **9** was barely isolable[24] although the 3-substituted indoles with acetyl and methyl ester didn't undergo the oxidation cleanly.

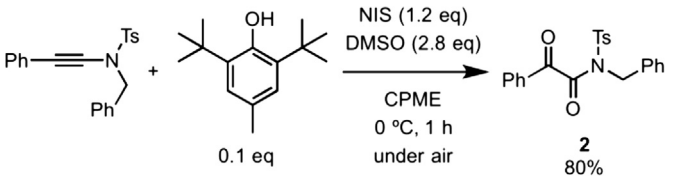
The reaction system also proved to be applicable to symmetrical and unsymmetrical diarylalkynes[14] (Table 6), where the

Table 4
Effect of atmosphere on the oxidation

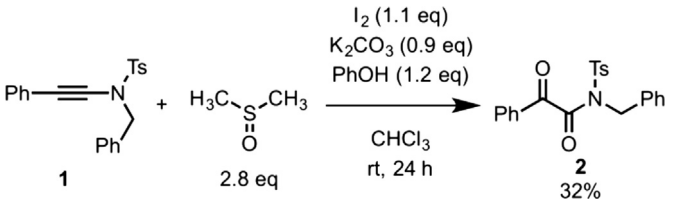


Entry	Atmosphere	Yield%
1	Ar[a]	0[b,c]
2	Atmospheric air	83
3	O_2	85

[a] Balloon was used.
[b] Multi spots on TLC and terribly messy spectrum were observed in the crude state.
[c] The reproducibility was confirmed.



Scheme 2. The oxidation in the presence of 2,6-di-*tert*-butyl-4-methyl phenol.

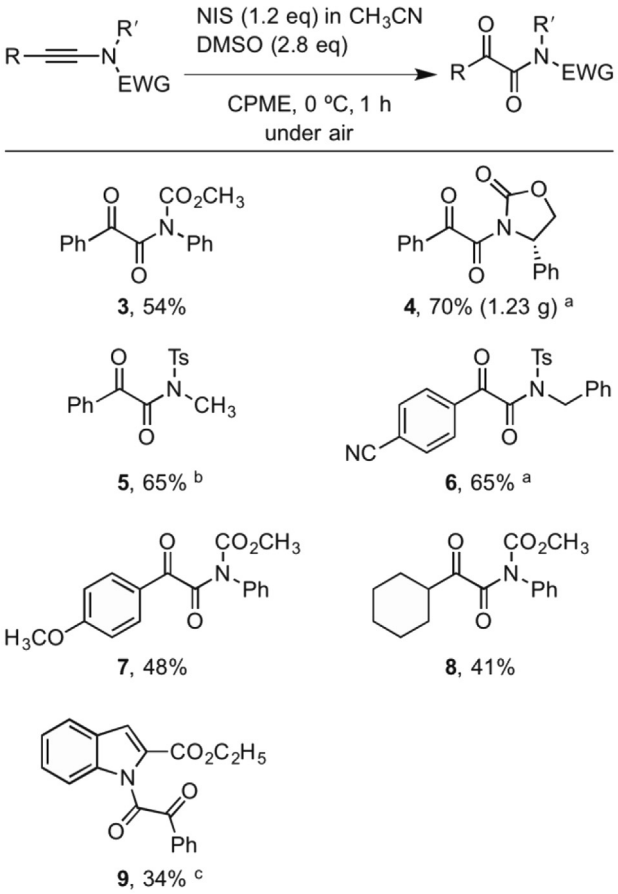


Scheme 3. Oxidation of **1** under Matsumoto's condition.

corresponding 1,2-diketones are created.[25–28] Compared to ynamide in Table 5, the oxidation required higher reaction temperature (100 °C) and prolonged reaction time (overnight stirring). For entries 1–3, diphenyl acetylene was oxidized to give **10** in 70%, and no reaction was ensured in the absence of NIS or DMSO. For entries 4 and 5, the 3-methoxy **11** was obtained in 73% yield, although the sterically hindered 2-methoxy **12** around the triple bond resulted in only 10% yield. For entries 6–8, the phenol **13**, and naphtyl **14**, and 3-chlorophenyl **15** were provided in acceptable yield with complete consumption of the starting alkynes. For entry 9,4-(phenylethynyl)benzonitrile had the reaction time lengthened to 30 h, and barely reached to 56% yield of **16** along with 22% of unreacted starting alkyne.[29]

The mechanism in this oxidation is not yet fully known; however, some points of reaction process would be estimated as a working hypothesis, which was depicted in Fig. 1 on the basis of the reaction in Scheme 1. Initially, NIS works as an I^+ source to activate ynamide **1**, providing oxysulfonium **17**. The intermediate **17**[26] could then undergo an addition of molecular oxygen, O_2, to form peroxide **18** and thiyl radical cation. The radical cation could receive one electron from succinimide anion to bring the diphenyl sulfide. Finally, the intermediate **18** is engaged by the resultant succinimide radical to create **19**, which can access to the desired **2**. Every step in the route includes quite labile species, and this explains the oxidation was observed as a fast but an unregulated reaction. Presumably, argon atmosphere did not enable to advance from **17** to **18**, and the labile **17** totally decomposed to give complicated crude products (Table 4, entry 1).

Table 5
Substrate scope

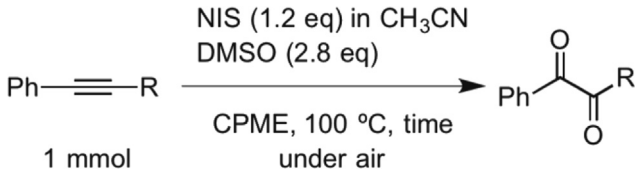


[a]CH_3CN was used as a solvent instead of CPME for dissolving the starting ynamide.

[b]1.5 equiv of NIS was used.

[c]CH_2Cl_2 was used as a solvent instead of CPME for dissolving the starting ynamide.

Table 6
Oxidation of diarylalkynes for preparation of 1,2-diketones



Entry	R	Products	Time/h	Yield %	Recovered alkyne/%
1	Phenyl	**10**	26	70	0
2[a]	Phenyl	**10**	12	0	>99
3[b]	Phenyl	**10**	12	0	>99
4	3-MeOPh	**11**	21	73	7
5	2-MeOPh	**12**	21	10	16
6	4-OHPh	**13**	15	46	0
7	1-Naphtyl	**14**	11	81	0
8	3-ClPh	**15**	11	68	0
9	4-CNPh	**16**	30	56	22

[a] Without NIS.
[b] Without DMSO.

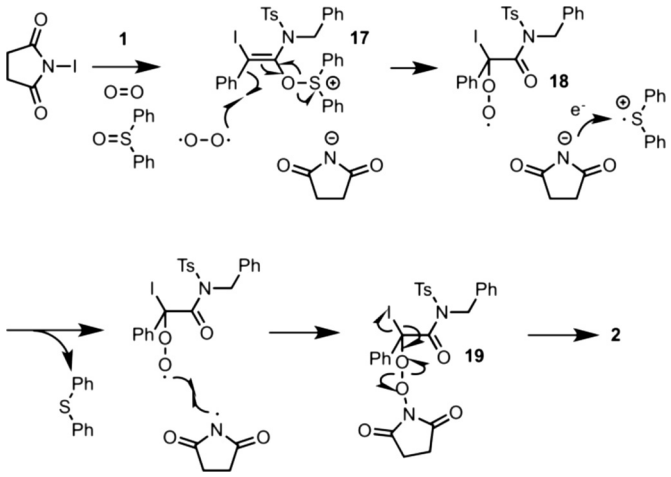


Fig. 1. Plausible reaction path to **2** via **17**, **18**, and **19**.

3. Conclusion

In conclusion, we have developed a transition metal-free approach for double oxidation of ynamide triple bonds as a synthetic method to prepare α-keto-imide. The reaction employs the quite conventional reagents of NIS and DMSO as oxidants, and quickly proceeds under atmospheric air within 1 h at 0 °C. The molecular oxygen is indispensable, and would play crucial role as a radical source. The radical based oxidation would get ahead by way of oxysulfonium intermediate and peroxide species, resulting in installation of two oxygen units. The method also proved to be applicable to diarylalkynes for preparation of 1,2-diketones. The process is still prototype protocol, yet this avoids the use of expensive, moisture-sensitive, and explosive additives, which make it potentially greener than current alternatives. Application and mechanistic elucidation are ongoing for further development of the related reactions and will be reported in due course.

4. Experimental section

4.1. General

All reactions sensitive to air or moisture were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Dry solvents were purchased and used without further purification and dehydration. All reagents were purchased and used without further purification. Column chromatography was carried out with silica gel. HRMS were reported on the basis of TOF (time of flight)-MS, and EB (double-focusing)-MS. Mass spectra were reported on the basis of FAB-MS. ^1H and ^{13}C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in d (parts per million) with reference to residual solvent signals [^1H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.2. General procedure for the oxidation

For preparation of *N*-benzyl-2-oxo-2-phenyl-*N*-tosylacetamide **2** (Table 1, entry 1): to a solution of **1** (181 mg, 0.5 mmol) in CPME (1.4 mL) and DMSO (0.1 mL, 1.4 mmol) at 0 °C was added NIS (135 mg, 0.6 mmol) in 1 mL of acetonitrile drop-wise over 5 min. After stirring for 1 h at 0 °C, the reaction was quenched with 8 mL of saturated aqueous $Na_2S_2O_3$, and the mixture was transferred into a separatory funnel. The aqueous phase was extracted with ethyl acetate (10 mL×3), and the combined organic phases were washed

with brine (10 mL), and dried over Na_2SO_4, and concentrated in vacuo to give a crude product of 241 mg as brown viscous materials. Purification by column chromatography (eluent; hexane/dichloromethane=1/1) afforded 164 mg of **2** in 83% yield as yellow viscous materials. Analytical data are identical to the previously reported.[9a] ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (d, J=7.4 Hz, 2H), 7.75 (d, J=8.4 Hz, 2H), 7.65–7.61 (m, 1H), 7.50 (dd, J=7.4, 7.4 Hz, 2H), 7.27–7.22 (m, 7H), 4.99 (s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 185.0, 167.8, 145.9, 134.9, 134.72, 134.70, 133.1, 130.1, 129,9, 129.1, 128.75, 128.73, 128.3, 128.1, 48.5, 21.9 ppm.

*4.2.1. Methyl (2-oxo-2-phenylacetyl)(phenyl)carbamate (**3**).* Yield 54%, colorless viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.98 (d, J=7.3 Hz, 2H), 7.66 (t, J=7.3 Hz, 1H), 7.57–7.46 (m, 5H), 7.34–7.31 (m, 2H), 3.71 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 187.7, 169.7, 154.5, 135.2, 134.5, 133.0, 129.8, 129.5 (two peaks are overlapped), 129.2, 128.5, 54.8 ppm; FAB-MS m/z: 283 (M^+); IR (neat): 3064, 2958, 1739, 1681, 1439, 1281, 1243, 1094 cm^{-1}; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.85; H, 4.63; N, 4.80.

*4.2.2. (S)-1-(2-Oxo-4-phenyloxazolidin-3-yl)-2-phenylethane-1,2-dione (**4**).* Yield 70%, pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (d, J=7.2 Hz, 2H), 7.63 (t, J=7.4 Hz, 1H), 7.50–7.41 (m, 7H), 5.54 (dd, J=8.7, 4.0 Hz, 1H), 4.89 (dd, J=8.7, 8.7 Hz, 1H), 4.45 (dd, J=8.7, 4.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 187.9, 166.3, 153.7, 137.8, 135.1, 132.7, 129.8, 129.6, 129.5, 129.3, 126.4, 72.3, 57.0 ppm; FAB-MS m/z: 296 ($[MH]^+$); IR (neat): 1795, 1705, 1596, 1389, 1336, 1224 cm^{-1}; Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.41; H, 4.59; N, 4.74.

*4.2.3. N-Methyl-2-oxo-2-phenyl-N-tosylacetamide (**5**).* Yield 65%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.95 (d, J=7.4 Hz, 2H), 7.89 (t, J=8.4 Hz, 2H), 7.65 (t, J=7.4 Hz, 1H), 7.54 (dd, J=7.4, 7.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 3.25 (s, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 188.3, 167.6, 146.2, 134.8, 133.7, 133.1, 130.4, 130.0, 129.2, 128.7, 31.0, 22.0 ppm; MS (EI) m/z: 317 (M^+); IR (neat): 1672, 1597, 1450, 1368, 1162, 948 cm^{-1}; Anal. Calcd for $C_{17}H_{13}NO_4$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.56; H, 4.80; N, 4.29.

*4.2.4. N-Benzyl-2-(4-cyanophenyl)-2-oxo-N-tosylacetamide (**6**).* Yield 65%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97 (d, J=8.1 Hz, 2H), 7.80 (d, J=8.1 Hz, 2H), 7.72 (d, J=8.4 Hz, 2H), 7.28–7.21 (m, 7H), 4.80 (s, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 186.4, 167.0, 146.3, 136.3, 134.5, 134.3, 132.9, 130.2, 130.1, 128.9, 128.7, 128.3, 123.2, 118.0, 117.7, 48.6, 22.0 ppm; FAB-MS m/z: 419 ($[MH]^+$); IR (neat): 2233, 1697, 1661, 1363, 1202, 1160 cm^{-1}; Anal. Calcd for $C_{23}H_{18}NO_4S$: C, 66.01; H, 4.34; N, 6.69. Found: C, 65.70; H, 4.49; N, 6.57.

*4.2.5. Methyl (2-(4-methoxyphenyl)-2-oxoacetyl)(phenyl)carbamate (**7**).* Yield 48%, whitish green solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, J=9.0 Hz, 2H), 7.54–7.44 (m, 3H), 7.32–7.30 (m, 2H), 7.02 (d, J=9.0 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 186.7, 169.9, 164.8, 154.5, 135.5, 132.0, 129.8, 129.5, 128.6, 126.0, 114.7, 56.0, 54.8 ppm; FAB-MS m/z: 313 ($[MH]^+$); IR (neat): 2958, 2844, 1740, 1670, 1596, 1285, 1245, 1162, 1092 cm^{-1}; Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.44; H, 4.90; N, 4.40.

*4.2.6. Methyl (2-cyclohexyl-2-oxoacetyl)(phenyl)carbamate (**8**).* Yield 41%, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 7.49–7.41 (m, 3H), 7.20 (dd, J=8.1, 1.7 Hz, 2H), 3.77 (s, 3H), 2.80–2.73 (m, 1H), 2.15–2.11 (m, 2H), 1.87–1.84 (m, 2H), 1.73–1.70 (m, 1H), 1.57–1.48 (m, 2H), 1.38–1.23 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 200.6, 170.3, 154.8, 135.2, 129.7, 129.4, 128.5, 54.8, 47.5, 28.1, 26.1, 25.9 ppm; FAB-MS m/z: 290 ($[MH]^+$); IR (neat): 1740, 1692, 1492, 1440, 1283, 1057 cm^{-1}; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.13; H, 6.57; N, 4.84.

*4.2.7. Ethyl 1-(2-oxo-2-phenylacetyl)-1H-indole-2-carboxylate (**9**).* Yield 34%, pale green viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (d, J=8.4 Hz, 1H), 8.16 (d, J=8.4 Hz, 2H), 7.70–7.66 (m, 2H), 7.58–7.51 (m, 3H), 7.44 (s, 1H), 7.38 (t, J=8.4 Hz, 2H), 4.14 (q, J=7.16 Hz, 2H), 1.23 (t, J=7.16 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 185.5, 165.6, 161.9, 139.0, 134.5, 133.6, 130.9, 129.9, 128.9, 128.9, 128.3, 125.2, 123.0, 118.7, 116.3, 62.1, 14.4 ppm; MS (EI) m/z: 321 (M^+); IR (neat): 3058, 2979, 1680, 1445, 1336, 1203, 1173 cm^{-1}; HRMS (DI) calcd for $C_{19}H_{15}NO_4$: 321.1001, found 321.1016.

*4.2.8. 1-Methoxy-3-(phenylethynyl)benzene (**10**).*[10] Yield 70%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.98 (d, J=8.4 Hz, 4H), 7.67 (t, J=5.7 Hz, 2H), 7.52 (dd, J=8.4, 5.7 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 194.9, 135.2, 133.3, 130.2, 129.3 ppm.

*4.2.9. 1-(3-Methoxyphenyl)-2-phenylethane-1,2-dione (**11**).*[10] Yield 73%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.98 (d, J=7.1 Hz, 2H), 7.68–7.64 (m, 1H), 7.55–7.47 (m, 1H), 7.40 (t, J=7.8 Hz, 2H), 7.22–7.19 (m, 2H), 3.87 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 194.80, 194.78, 160.4, 135.2, 134.5, 133.3, 130.4, 130.2, 129.3, 123.5, 122.2, 113.2, 55.8 ppm.

*4.2.10. 1-(2-Methoxyphenyl)-2-phenylethane-1,2-dione (**12**).*[10] Yield 10%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 8.03 (dd, J=7.8, 1.8 Hz, 1H), 7.94 (d, J=7.8 Hz, 2H), 7.64–7.58 (m, 2H), 7.50 (dd, J=8.0, 7.8 Hz, 2H), 7.14 (t, J=8.0 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 3.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 195.0, 193.8, 160.8, 136.8, 134.1, 133.3, 130.9, 129.7, 129.0, 124.2, 121.9, 112.7, 56.0 ppm.

*4.2.11. 1-(4-Hydroxyphenyl)-2-phenylethane-1,2-dione (**13**).*[10] Yield 46%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, J=8.4 Hz, 2H), 7.85 (d, J=8.8 Hz, 2H), 7.65 (t, J=7.5 Hz, 1H), 7.50 (dd, J=8.4, 7.5 Hz, 2H), 7.06 (br s, 1H), 6.89 (d, J=8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 195.8, 194.1, 162.7, 135.5, 133.24, 133.18, 130.3, 129.4, 126.0, 116.5 ppm.

*4.2.12. 1-(Naphthalen-1-yl)-2-phenylethane-1,2-dione (**14**).*[12] Yield 81%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 9.33 (d, J=8.2 Hz, 1H), 8.11 (d, J=8.2 Hz, 1H), 8.04 (d, J=7.2 Hz, 2H), 7.93 (dd, J=8.4, 7.2 Hz, 2H), 7.75 (t, J=8.4 Hz, 1H), 7.67–7.61 (m, 2H), 7.53–7.45 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 197.5, 194.9, 136.3, 135.4, 135.0, 134.4, 133.6, 131.2, 130.3, 129.7, 129.3, 129.1, 128.9, 127.4, 126.2, 124.7 ppm.

*4.2.13. 1-(Naphthalen-1-yl)-2-phenylethane-1,2-dione (**15**).*[10] Yield 68%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.98–7.96 (m, 3H), 7.84 (d, J=7.8 Hz, 1H), 7.70–7.62 (m, 2H), 7.55–7.44 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 193.9, 193.3, 135.7, 135.5, 135.1, 134.8, 133.0, 130.7, 130.3, 129.9, 129.4, 128.4 ppm.

*4.2.14. 4-(2-Oxo-2-phenylacetyl)benzonitrile (**16**).*[10] Yield 56%; yellow solid materials; ^{1}H NMR (400 MHz, $CDCl_3$) 8.10 (d, J=8.7 Hz, 2H), 7.98 (d, J=8.4 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H), 7.71 (t, J=7.4 Hz, 1H), 7.75 (dd, J=8.4, 7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 193.3, 192.7, 136.1, 135.7, 133.0, 132.7, 130.5, 130.3, 129.5, 118.1, 117.8 ppm.

Acknowledgements

We are pleased to thank Dr. Toshiyuki Iwai at OMTRI for assistance with HRMS. We are very grateful to Professor Michael P. Schramm at CSULB for helpful discussion.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.080.

References and notes

1. (a) Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*; Oxford University: Oxford, UK, 1998; (b) Anastas, P. T.; Williamson, T. C. *Green Chemistry, Frontiers in Benign Chemical Syntheses and Processes*; Oxford University: Oxford, UK, 1998; (c) *Handbook of Green Chemistry & Technology*; Clark, J., Macquarrie, D., Eds.; Blackwell: MA, 2002.
2. *Chemical Reaction Hazards*, 2nd ed.; Barton, J. A., Rogers, R. L., Eds.; Institution of Chemical Engineers: Rugby, UK, 1997.
3. (a) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943–2989; (b) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253–258; (c) Etchells, J. C. *Org. Process Res. Dev.* **1997**, *1*, 355–358.
4. (a) Cainelli, G. *Chromium Oxidations in Organic Chemistry*; Springer: New York, NY, 1984; (b) Buchner, W.; Schliebs, R.; Winter, G.; Buchel, K. H. *Industrielle Anorganische Chemie*, 2nd ed.; VCH: Weinheim: Germany, 1986; (c) Haines, A. H. *Methods for Oxidation of Organic Compounds*; Academic: London, UK, 1988; (d) Hudlicky, M. *Oxidations in Organic Chemistry*; Am. Chem. Soc. Monograph 186: Washington, DC, 1990; (e) Luzzio, F. A. *Org. React.* **1998**, *53*, 1–122; (f) Donohoe, T. J. *Oxidation and Reduction in Organic Synthesis*; Oxford University: Oxford, UK, 2000.
5. *Modern Oxidation Methods*; Backvall, J.-E., Ed.; Wiley-VCH: Weinheim, Germany, 2004.
6. (a) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977–1986; (b) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386–12387; (c) Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646–1647; (d) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469–2476.
7. (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900; (b) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198–205; (c) Qiu, F.; Norwood, D. L. *J. Liq. Chromatogr. Relat. Technol.* **2007**, *30*, 877–935.
8. (a) Sato, A. H.; Mihara, S.; Iwasawa, T. *Tetrahedron Lett.* **2012**, *53*, 3585–3589; (b) Sato, A. H.; Ohashi, K.; Iwasawa, T. *Tetrahedron Lett.* **2013**, *54*, 1309–1311; (c) Sato, A. H.; Ohashi, K.; Ito, K.; Iwasawa, T. *Tetrahedron Lett.* **2013**, *54*, 2878–2881; (d) Ohashi, K.; Mihara, S.; Sato, A. H.; Ide, M.; Iwasawa, T. *Tetrahedron Lett.* **2014**, *55*, 632–635; (e) Ide, M.; Ohashi, K.; Mihara, S.; Iwasawa, T. *Tetrahedron Lett.* **2014**, *55*, 2130–2133; (f) Ide, M.; Yauchi, Y.; Iwasawa, T. *Eur. J. Org. Chem.* **2014**, http://dx.doi.org/10.1002/ejoc.201402057
9. (a) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780–8784; (b) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661–663.
10. (a) Kosior, M.; Asztemborska, M.; Jurczak, J. *Synthesis* **2004**, *1*, 87–91; (b) Chen, J.-H.; Venkatesham, U.; Lee, L.-C.; Chen, K. *Tetrahedron* **2006**, *62*, 887–893; (c) Raszplewicz, K.; Sikorska, L.; Kiegiel, K.; Jurczak, J. *Pol. J. Chem.* **2002**, *76*, 1600; (d) Young, S. W.; Kim, Y. H.; Hwang, J.-W.; Do, Y. *Chem. Commun.* **2001**, 996–997; (e) Kim, S. M.; Byun, I. S.; Kim, Y. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 728–731; (f) Hashizume, D.; Kogo, H.; Sekine, A.; Ohashi, Y.; Miyamoto, H.; Toda, F. *J. Chem. Soc., Perkin Trans. 2* **1995**, 61–65.
11. For the biological activity of α-keto-amide and α-keto-ester, e.g.: (a) Wada, C. K.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Garland, R. B.; Holms, J. H.; Li, J.; Pease, L. J.; Guo, J.; Glaser, K. B.; Marcotte, P. A.; Richardson, P. L.; Murphy, S. S.; Bouska, J. J.; Tapang, P.; Magoc, T. J.; Albert, D. H.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3331–3335; (b) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11–13.
12. Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451–456.
13. (a) Francke, R.; Little, R. D. *J. Am. Chem. Soc.* **2014**, *136*, 427–435; (b) Zhang, N.; Zeng, C.; Lam, C. M.; Gbur, R. K.; Little, R. D. *J. Org. Chem.* **2013**, *78*, 2104–2110.
14. (a) Turiso, F. G. L.; Sun, D.; Rew, Y.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chow, D.; Correll, T. L.; Huang, X.; Julian, L. D.; Kayser, F.; Lo, M.-C.; Long, A. M.; McMinn, D.; Oliner, J. D.; Osgood, T.; Powers, J. P.; Saiki, A. Y.; Schneider, W.; Shaffer, P.; Xiao, S.-H.; Yekowec, P.; Yan, X.; Ye, Q.; Yu, D.; Zhao, X.; Zhou, J.; Medina, J. C.; Olson, S. H. *J. Med. Chem.* **2013**, *56*, 4053–4070; (b) Tron, G. C.; Pagliai, F.; Grosso, E. D.; Genazzani, A. A.; Sorba, G. *J. Med. Chem.* **2005**, *48*, 3260–3268; (c) Zheng, C.; Zhang, N.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314–1317; (d) Hu, P.; Wang, Q.; Yan, Y.; Zhang, S.; Zhang, B.; Wang, Z. *Org. Biomol. Chem.* **2013**, *11*, 4304–4307; (e) Malamas, M. S.; Erdei, J.; Gunawan, I.; Turner, J.; Hu, Y.; Wagner, E.; Fan, K.; Chopra, R.; Olland, A.; Bard, J.; Jacobsen, S.; Magolda, R. L.; Pangalos, M.; Robichaud, A. J. *J. Med. Chem.* **2010**, *53*, 1146–1158; (f) Cumming, J. N.; Smith, E. M.; Wang, L.; Misiaszek, J.; Durkin, J.; Pan, J.; Iserloh, U.; Wu, Y.; Zhu, A.; Strickland, C.; Voigt, J.; Chen, X.; Kennedy, M. E.; Kuvelkar, R.; Hyde, L. A.; Cox, K.; Favreau, L.; Czarniecki, M. F.; Greenlee, W. J.; McKittrick, B. A.; Parker, E. M.; Stamford, A. W. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2444–2449; (g) Singh, D. P.; Kumar, R.; Singh, J. *Eur. J. Med. Chem.* **2009**, *44*, 1731–1736; (h) Muccioli, G. G.; Martin, D.; Scriba, G. K. E.; Poppitz, W.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2005**, *48*, 2509–2517; (i) Campillo, N.; García, C.; Goya, P.; Páez, J. A.; Carrasco, E.; Grau, M. *J. Med. Chem.* **1999**, *42*, 1698–1704; (j) Harada, T.; Nakagawa, Y.; Wadkins, R. M.; Potter, P. M.; Wheelock, C. E. *Bioorg. Med. Chem.* **2009**, *17*, 149–164.
15. For accounts of DMSO/O_2 mediated alkyne double oxidation, see: (a) Sawama, Y.; Takubo, M.; Mori, S.; Monguchi, Y.; Sajiki, H. *Eur. J. Org. Chem.* **2011**, 3361–3367; (b) Mori, S.; Takubo, M.; Yanase, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2010**, *352*, 1630–1634; (c) Gao, A.; Yang, F.; Li, J.; Wu, Y. *Tetrahedron* **2012**, *68*, 4950–4954; (d) Kobayashi, S.; Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J. D. *Tetrahedron* **2006**, *62*, 7667–7673.
16. NIS was employed as an acetonitrile stock-solution, because the high yielding oxidation needed to suppress the extra-exothermic property and to keep the reaction homogeneous.
17. The employment of THF is disagreeable to oxidation reaction owing to the risk of peroxide products. In contrast, CPME has a preferable characteristic of fairly low formation of peroxide, see: Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, *11*, 251–258.
18. Yusybov, M. S.-O.; Filimonov, V. D. *Synthesis* **1991**, 131–132.
19. For an account on oxidation of *o*-alkynylarenesulfoxide, this is engaged by molecular oxygen as a radical source even in the presence of antioxidant phenol, see: Matsumoto, S.; Shibata, H.; Akazome, M. *J. Org. Chem.* **2013**, *78*, 1650–1654.
20. (a) Sakthivel, K.; Srinivasan, K. *Eur. J. Org. Chem.* **2011**, 2781–2784; (b) Chen, D.; Song, G.; Jia, A.; Li, X. *J. Org. Chem.* **2011**, *76*, 8488–8494.
21. Diphenyl sulfide in CPME at 0 °C was mixed up with NIS under air, and we checked whether the diphenyl sulfoxide was formed or not. However, none of the sulfoxide was observed, and the sulfide remained at all.
22. A substrate of *N*-ethynyl-4-methyl-*N*-phenylbenzenesulfonamide, that is, an ynamide bearing terminal alkyne, was attempted on this oxidation, and the starting ynamide was totally consumed; however, the crude was formed from complicated mixture, and the desired dicarbonyl of 2-oxo-*N*-phenyl-*N*-tosylacetamide was not observed.
23. α-Keto-amide preparation from oxidation of ynamines, see: (a) Muller, P.; Godoy, J. *Tetrahedron Lett.* **1982**, *23*, 3661–3664; (b) Schank, K.; Beck, H.; Werner, F. *Helv. Chim. Acta* **2000**, *83*, 1624; (c) Schank, K.; Beck, H.; Himbert, G. *Synthesis* **1998**, 1718–1719; (d) Foote, C. S.; Lin, J. W.-P. *Tetrahedron Lett.* **1968**, *29*, 3267–3270.
24. 1,3-Diiodo-dimethylhydantoin was used instead of NIS on the synthesis of **9**, and the comparable yield was just observed.
25. Mono- or dialkylalkynes were not applicable to the present oxidation.
26. NBS-induced dimethyl sulfoxide oxidation of diphenylacetylene was reported, see: Wolfe, S.; Pilgrim, W. R.; Garrard, T. F.; Chamberlain, P. *Can. J. Chem.* **1971**, *49*, 1099–1105.
27. (a) Ruan, L.; Shi, M.; Li, N.; Ding, X.; Yang, F.; Tang, J. *Org. Lett.* **2014**, *16*, 733–735; (b) Tan, K. J.; Wille, U. *Chem. Commun.* **2008**, 6239–6241.
28. Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y. *Synthesis* **2008**, 2879–2882 This paper reports a convenient and environmentally benign method for the oxidation of internal aryl alkynes, because it employs water as an oxidant: the protocol uses NIS in a solvent of acetonitrile/water, and the reaction proceeded at 70 °C under air to give eleven entries in 29–66% yields.
29. (*E*)-Stilbene was attempted on the present oxidation; all starting olefin totally remained, and no reaction was observed.