

Oxygenation of alkynes to α,β -acetylenic ketones with dioxygen catalyzed by *N*-hydroxyphthalimide combined with a transition metal

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Alkynes were successfully converted into α,β -acetylenic carbonyl compounds through radical-catalyzed aerobic oxidation using *N*-hydroxyphthalimide (NHPI) combined with a transition metal under mild conditions.

α,β -Acetylenic carbonyl compounds, ynones, are highly valuable precursors in the preparation of a variety of heterocyclic compounds,¹ α,β -unsaturated ketones,² cyclopentenones,³ C-nucleosides⁴ and chiral pheromones.⁵ The conjugated ynones are usually prepared by a coupling reaction of acetylenides with activated acylating reagents such as acid chloride^{6b} or anhydrides.^{6c,d} Although the oxygenation of prop-2-ynyl C–H bonds is straightforward in the preparation of ynones, only a limited number of methods are available for this purpose. For instance, some chromium complexes are reported to oxidize internal alkynes to conjugated ynones in moderate yields,⁷ while the oxidation of alkynes by $\text{Th}(\text{NO}_3)_2$,^{8a} OsO_4 ,^{8b} permanganates^{8c} or RuO_4 ^{8d} results in ketones and/or cleaved products such as carboxylic acids as major products. Using electrophilic oxidants such as dimethyldioxirane^{9a,b} or H_2O_2 ,^{9c} alkynes are converted into conjugated enones or diketones rather than ynones.

For the synthesis of ynones, one candidate methodology is thought to be the direct introduction of oxygen into a prop-2-ynyl C–H bond via a free-radical process, since the abstraction of the hydrogen atom from alkynes by a radical would occur at the energetically favorable prop-2-ynyl position. Recently, we have developed a mild generation method of an active radical species, phthalimide *N*-oxyl radical (PINO), which can readily abstract a benzylic hydrogen atom from toluene, from *N*-hydroxyphthalimide (NHPI) under the influence of dioxygen. Thus, toluene and ethylbenzene could be oxidized to benzoic acid and acetophenone, respectively, under a dioxygen atmosphere (1 atm) at room temperature.¹⁰ Since the bond dissociation energy of the prop-2-ynyl C–H bonds of alkynes ($87.3 \pm 2 \text{ kcal mol}^{-1}$ for pent-2-yne) is approximately equal to that of the benzylic C–H bond of alkylbenzenes ($88.0 \pm 1 \text{ kcal mol}^{-1}$ for toluene),¹¹ our interest was directed toward the NHPI-catalyzed oxidation of alkynes.

Here we report the first successful catalytic aerobic oxidation of alkynes to conjugated ynones under mild conditions.

Oct-4-yne **1a** was chosen as a model substrate and allowed to react with dioxygen in the presence of a catalytic amount of NHPI and a transition metal [eqn. (1), Table 1]. Surprisingly, the oxidation of **1a** with molecular oxygen (1 atm) under the influence of NHPI (10 mol%) at room temperature produced oct-4-yn-3-one **3a** (69%) along with oct-4-yn-3-ol **2a** (23%) at 34% conversion (run 1). In analogy with the aerobic oxidation

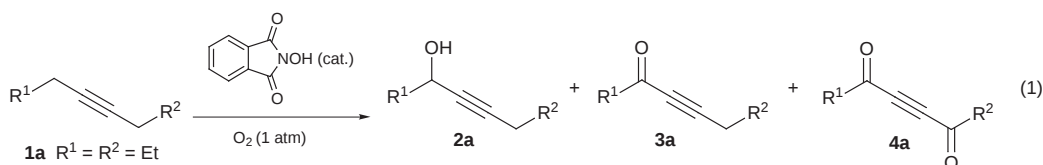
of alkylbenzenes by NHPI,^{10b} the oxidation of **1a** was found to be significantly accelerated by adding a transition metal such as $\text{Co}(\text{acac})_2$. Thus, the oxidation of **1a** catalyzed by NHPI (10 mol%) in the presence of $\text{Co}(\text{acac})_2$ (0.5 mol%) gave **3a** (75%) and **2a** (20%) with 70% conversion (run 2).‡ The same oxidation using $\text{Cu}(\text{acac})_2$ (0.5 mol%) in place of $\text{Co}(\text{acac})_2$ (0.5 mol%) afforded **3a** with 77% selectivity together with **2a** (22%) at 69% conversion (run 3). However, no reaction took place when $\text{Mn}(\text{acac})_2$ was employed in place of $\text{Co}(\text{acac})_2$ under these conditions. When the reaction of **1a** with $\text{NHPI}/\text{Co}(\text{acac})_2$ was carried out at elevated temperature (50 °C), the oxidation was almost complete after 6 h to give **3a** with 72% selectivity along with a small amount of a cleaved product, butanoic acid **5a** (run 6). Similar results were also obtained in the oxidation with $\text{NHPI}/\text{Cu}(\text{acac})_2$. In the oxidation of **1a** using the $\text{NHPI}/\text{Mn}(\text{acac})_2$ system at 50 °C, **3a** was formed with 62% selectivity at 63% conversion.

It is reported that dodec-5-yne, upon treatment with Bu^tOOH in the presence of SeO_2 catalyst, leads to the acetylenic alcohol dodec-5-yn-4-ol rather than the ynone dodec-5-yn-4-one.¹² However, the present aerobic oxidation of **1a** by the NHPI catalyst formed ynone **3a** in preference to ynol **2a**. In a previous paper, we showed that the NHPI-catalyzed oxidation of alcohols affords ketones in good yields.^{10d} In fact, treatment of oct-1-yn-3-ol under dioxygen in the presence of NHPI and $\text{Cu}(\text{acac})_2$ gave oct-1-yn-3-one, with 95% selectivity at 57%

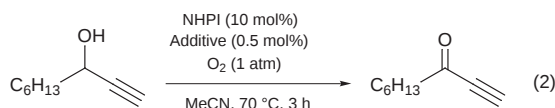
Table 1 Aerobic oxidation of **1a** catalyzed by NHPI under selected conditions^a

Run	Metal	Conversion (%)	Selectivity (%) ^b			
			2a	3a	4a	5a
1	–	34	23	69	<1	<1
2	$\text{Co}(\text{acac})_2$	70	20	75	<1	<1
3	$\text{Cu}(\text{acac})_2$	69	22	77	<1	<1
4	$\text{Mn}(\text{acac})_2$	no reaction				
5 ^c	–	48	18	63	<1	<1
6 ^c	$\text{Co}(\text{acac})_2$	85	2	72	2	2
7 ^c	$\text{Cu}(\text{acac})_2$	83	5	70	2	3
8 ^c	$\text{Mn}(\text{acac})_2$	63	4	62	3	5

^a Compound **1a** (2 mmol) was allowed to react under O_2 atmosphere (1 atm) in the presence of NHPI (10 mol%) and a metal species (0.5 mol%) in MeCN (5 cm³) at room temperature (25 °C) for 30 h. ^b Selectivity of the products was determined by GC analysis using an internal standard. ^c The reaction was carried out at 50 °C for 6 h.



conversion, but in the absence of $\text{Cu}(\text{acac})_2$ oct-1-yn-2-ol was converted into the ynol in low yield [eqn. (2)]. This shows that



$\text{Cu}(\text{acac})_2$ plays an important role in the conversion of ynol into ynolone.

Conventionally, oxidation of alkynes with molecular oxygen is carried out at higher temperatures, i.e. 110–150 °C. Under such conditions the reaction results in undesired over-oxidation products such as oxidatively cleaved carboxylic acids.¹³ For instance, the oxidation of dodec-6-yne under 70 atm of air at 110 °C is reported to lead to cleaved products such as hexanoic acid and pentanoic acid as principal products.

It is noteworthy that the NHPI-catalyzed oxidation of alkynes with molecular oxygen could be achieved at room temperature, since undesired side reactions arising from high reaction temperatures could be suppressed.

The present successful conversion of alkynes into ynones is believed to result from the fact that the phthalimide *N*-oxyl radical (PINO) can be generated from NHPI under the influence of dioxygen and **1a** at room temperature. Thus, EPR analysis of PINO formed from NHPI under atmospheric dioxygen in the presence or absence of alkyne **1a** at room temperature was performed. As expected, the EPR signal attributed to PINO was observed in the presence of **1a** after 14 h, but in the absence of **1a** no EPR signal was observed. At this stage, we cannot make an accurate assessment of the interaction between NHPI and the alkyne **1a**. The generation of PINO from NHPI in the presence of alkyne **1a** may be facilitated by the weak coordination of NHPI, which is a weak acid having $\text{p}K_a = 7.0$,¹⁴ to the acetylenic π -bond of the alkyne.

Table 2 summarizes the results for the NHPI-catalyzed oxidation of a variety of alkynes in the presence of $\text{Co}(\text{acac})_2$ or $\text{Cu}(\text{acac})_2$ under oxygen atmosphere. The conversions of substrates were generally high except for terminal alkynes, and the corresponding α,β -acetylenic carbonyl compounds were obtained in moderate to good yields. Symmetric alkynes such as hex-3-yne **1b** and dodec-6-yne **1c** were oxidized into conjugated ynones hex-3-yn-2-one **3b** and dodec-6-yn-5-one **3c**, respectively, in good yields, (runs 1–3). Unsymmetrical alkyne, oct-3-yne **1d** gave a 1:1 mixture of the corresponding conjugated ynones, **3d** and **3d'** (run 4), although the oxidation of

dec-3-yne with Bu^tOOH catalyzed by CrO_3 produced only dec-3-yn-2-one.^{7c} Under the same conditions, oct-2-yne **1e** afforded oct-2-yn-4-one **3e** with high regioselectivity (run 5). The terminal alkyne oct-1-yne **1f** was oxidized to oct-1-yn-3-one **3f** with high selectivity, although the conversion was moderate (50%) (run 6). On the other hand, for oct-2-yn-1-al **1g**, the aldehyde moiety was selectively oxidized rather than the prop-2-ynyl C–H bond, giving oct-2-ynoic acid **6g** (run 7).

In conclusion, various alkynes were converted into α,β -acetylenic carbonyl compounds by aerobic oxidation using NHPI combined with Co^{II} or Cu^{II} complexes. The present method provides a facile method for preparing conjugated ynones from alkynes.

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Notes and References

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‡ Typical procedure for the aerobic oxidation of alkyne: To a solution of NHPI (0.2 mmol, 10 mol%) and a transition metal complex (0.01 mmol, 0.5 mol%) in MeCN (5 cm^3) was added alkyne (2 mmol), then the flask was flushed with oxygen and equipped with a balloon filled with O_2 . The reaction mixture was stirred at 25 °C for 30 h. The solvent was evaporated under reduced pressure. The products were purified by column chromatography on silica gel [hexane–EtOAc (10:1 to 3:1)], and characterised by ^1H and ^{13}C NMR, GC–MS and IR spectroscopy.

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Table 2 Aerobic oxidation of several alkynes catalyzed by NHPI combined with $\text{Co}(\text{acac})_2$ or $\text{Cu}(\text{acac})_2$ ^a

Run	Substrate	Product	Conversion (%)	Selectivity (%) ^b
1 ^c	$\text{EtC}\equiv\text{CEt}$ 1b	$\text{AcC}\equiv\text{CEt}$ 3b	93	81
2 ^{d,e}	$\text{EtC}\equiv\text{CEt}$ 1b	$\text{AcC}\equiv\text{CEt}$ 3b	96	75
3 ^e	$\text{C}_5\text{H}_{11}\text{C}\equiv\text{CC}_5\text{H}_{11}$ 1c	$\text{BuC}(\text{O})\text{C}\equiv\text{CC}_5\text{H}_{11}$ 3c	89	75
4 ^c	$\text{BuC}\equiv\text{CEt}$ 1d	$\text{PrC}(\text{O})\text{C}\equiv\text{CEt}$ 3d $\text{BuC}\equiv\text{CAc}$ 3d'	92	70 ^f
5 ^e	$\text{C}_5\text{H}_{11}\text{C}\equiv\text{CMe}$ 1e	$\text{BuC}(\text{O})\text{C}\equiv\text{CMe}$ 3e	94	70
6 ^{c,e}	$\text{C}_6\text{H}_{13}\text{C}\equiv\text{CH}$ 1f	$\text{C}_5\text{H}_{11}\text{C}(\text{O})\text{C}\equiv\text{CH}$ 3f	50	80
7 ^{c,e}	$\text{C}_5\text{H}_{11}\text{C}\equiv\text{CCHO}$ 1g	$\text{C}_5\text{H}_{11}\text{C}\equiv\text{CCO}_2\text{H}$ 6g	43	74 ^g

^a Substrate (2 mmol) was allowed to react under O_2 atmosphere (1 atm) in the presence of NHPI (10 mol%) and $\text{Cu}(\text{acac})_2$ (0.5 mol%) in MeCN (5 cm^3) at 50 °C for 6 h. ^b Yields of the products were determined by GC analysis using an internal standard. Other products were α -alkynyl alcohols (~5%) and cleaved products such as carboxylic acids (~3%) except for run 7. ^c 20 h. ^d $\text{Co}(\text{acac})_2$ was used instead of $\text{Cu}(\text{acac})_2$. ^e 70 °C. ^f A 1:1 regioisomeric mixture was obtained. ^g Isolated yield.