

Addition of *sec*-Alcohols to Alkynes through a Radical Process Using NHPI/Co^{II}/O₂ System

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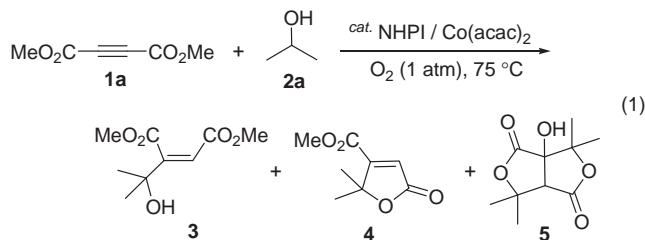
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α -Hydroxy carbon radicals generated from alcohols by the action of NHPI smoothly added to electron-deficient alkynes like acetylenedicarboxylates. For instance, the reaction of 2-propanol with dimethyl acetylenedicarboxylate afforded maleate derivative **3**, 3-methoxycarbonyl-4,4-dimethyl-2-buten-4-olide (**4**), and a fused bis- γ -butyrolactone **5** formed by further addition of 2-hydroxy-2-propyl radical to **4**.

Although many methodologies have been developed for the generation of carbon radicals from various substrates,¹ a limited number of methods have appeared for the generation of hydroxy carbon radicals from alcohols, e.g., peroxide-^{2a} and photo-initiated techniques^{2b} and the method using metal ions.^{2c} Ketones are transformed into α -hydroxy carbon radical equivalents via hydrazones.³ However, α -hydroxy carbon radicals are still difficult to generate efficiently from alcohols. Recently, we have reported that a novel catalytic method for the generation of α -hydroxy carbon radicals from alcohols using *N*-hydroxyphthalimide (NHPI) as a key catalyst.⁴ Thus, 2-propanol under the influence of NHPI and molecular oxygen generates 2-hydroxy-2-propyl radical which readily added to electron-deficient alkenes like acrylates to give α -hydroxy- γ -butyrolactones in good yields. The generation of α -hydroxy carbon radicals from alcohols provides a very convenient synthetic tool for the concomitant introduction of both alkyl and oxygen moieties to alkenes. This method was extended to the addition to electron-deficient alkynes.

In this paper, we wish to report the addition of secondary alcohols to dimethyl acetylenedicarboxylate or methyl propiolate under the influence of NHPI combined with Co(acac)₂ and molecular oxygen (eq 1).



The addition of 2-propanol (**2a**) to dimethyl acetylenedicarboxylate (**1a**) was chosen as a model reaction and carried out under various conditions to confirm an optimum reaction condition (Table 1).

The reaction of **2a** (5 mmol) with **1a** (1 mmol) by NHPI (0.1 mmol, 10 mol %) in the presence or absence of a transition metal (50 μ mol, 0.5 mol %) under O₂ (1 atm) without solvent at 75 °C for 1 h afforded 2-(1-hydroxy-1-methylethyl)-2-butenedioic acid dimethyl ester (**3**) (31%) and 3-methoxycarbonyl-4,4-

Table 1. Addition of 2-propanol (**2a**) to dimethyl acetylenedicarboxylate (**1a**) catalyzed by NHPI under various conditions^a

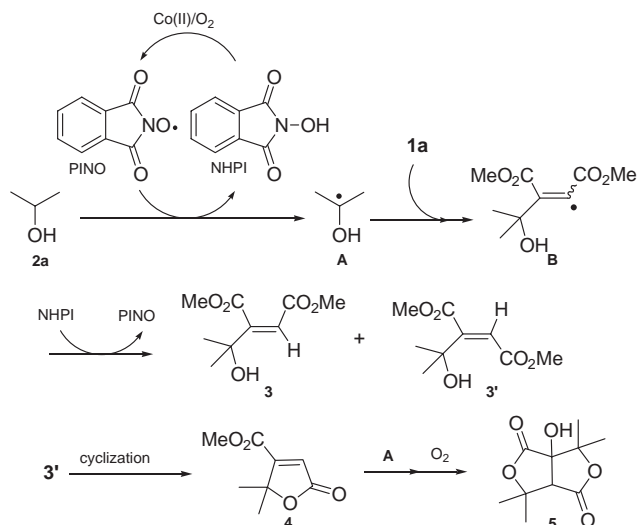
Entry	Additive	Time /h	Conv. /% ^b	Products/% ^b		
				3	4	5
1	—	1	70	31	28	<1
2	—	6	>99	37	41	12
3	—	15	>99	36	0	19
4 ^c	—	6	98	9	<1	5
5	Co(acac) ₂	15	>99	43	0	40
6	Cu(acac) ₂	15	67	6	7	<1
7	Mn(acac) ₂	15	48	5	6	1
8	Fe(acac) ₂	15	99	2	1	0
9 ^d	Co(acac) ₂ ZnCl ₂	15	>99	44	0	45

^a**1a** (1 mmol) reacted with **2a** (5 mmol) in the presence of NHPI (0.1 mmol) and additive (50 μ mol) under O₂ (1 atm) at 75 °C without solvent. ^bBased on **1a** used. ^cAt 60 °C. ^dCo(acac)₂ (50 μ mol) and ZnCl₂ (50 μ mol) were used.

dimethyl-2-buten-4-olide (**4**) (28%) as major products (entry 1). When the reaction was prolonged to 6 h and 15 h, a fused hydroxy bis-lactone **5** was formed in 12 and 19% yields, respectively (entries 2 and 3). The compound **5** was found to be formed by the further addition of **2a** to the resulting **4**. The same reaction at 60 °C resulted in the decrease of these adducts and polymeric complex mixtures were considerably formed (entry 4).

In order to improve the selectivity of the reaction, the effect of additives, transition metal salts, on the NHPI catalyst was examined. As expected, the addition of a small amount of Co(acac)₂ resulted in a considerable improvement of the yields of **3** (43%) and **5** (40%) (entry 5).⁵ In contrast, the addition of Cu(acac)₂, Mn(acac)₂, and Fe(acac)₂ led to the decrease of the selectivity (entries 6–8). In a previous paper, we showed that Co^{II} ion reacts with molecular oxygen to give Co^{III}-oxygen complex which can accelerate the generation of phthalimide *N*-oxyl (PINO) radical from NHPI, and the PINO abstracts the hydrogen atom from 2-propanol to form 2-hydroxy-2-propyl radical as discussed later. Shono et al. reported that the reaction of **1** with isopropyl iodide (2.5 equiv.) in the presence of Zn powder (4.6 equiv.) afforded **3** in 35% yield.⁶ On the other hand, it is reported that the compound **3** was converted into **4** by allowing it to react with (PhS)₂ under irradiation.⁷ Yield of bis-lactone **5** was slightly improved by the addition of ZnCl₂ which seems to accelerate the lactonization (entry 9). It is interesting to note that bis-lactone **5** was first synthesized through a catalytic process from **1a** and **2a**, since **5** was difficult to synthesize by other methods.

The formation of adducts, **3**, **4**, and **5** from **1a** and **2a** catalyzed by NHPI combined with Co^{II} could be rationally explained



Scheme 1.

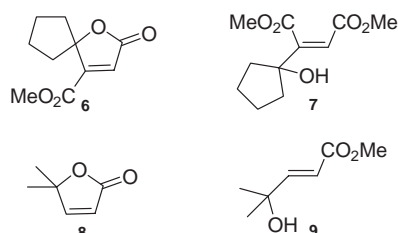


Chart 1.

by the following reactions (Scheme 1).

2-Hydroxy-2-propyl radical (**A**) generated from **2a** under the influence of NHPI adds to **1a** to give about 1:1 mixture of E- and Z-adduct radicals (**B**). The adduct radical **B** abstracts hydrogen atom from NHPI to produce maleate-type adduct **3** and fumarate-type adduct **3'**, which readily undergoes the cyclization to give **4**. Under the present reaction conditions in which molecular oxygen lies in the reaction system, **4** reacts with **A** and O_2 to form an alcohol followed by intramolecular cyclization to give bis-lactone **5**.

On the other hand, the reaction of **1a** (1 mmol) with cyclopentanol (**2b**) (5 mmol) at 80 °C for 3 h afforded spiro lactone (**6**) (27%) and maleate derivative (**7**) (33%). Compound **6** is prepared by the reaction of **7**, obtained by the base-mediated reaction of dialkyl maleate esters and cyclopentanone, in the presence of $(PhS)_2$ under irradiation.^{7,8} The reaction of methyl propiolate (**1b**) and **2a** under the same conditions as entry 4 in Table 1 afforded 4,4-dimethyl-2-buten-4-olide (**8**) (32%) and methyl *trans*-4-hydroxy-4-methyl-2-pentenoate (**9**) (23%). Chart 1 shows the structure of the resulting adducts from these alkynes and alcohols.

In conclusion, α -hydroxy carbon radicals generated from alcohols added to alkynes bearing electron-deficient substituent to give the corresponding E- and Z-adducts in good total yields.

Adduct **4** underwent the further addition of α -hydroxy carbon radical (**A**) followed by intramolecular cyclization to give bis- γ -butyrolactone **5** which is difficult to synthesize by conventional methods.

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- A typical experimental procedure is as follows; to a mixture of NHPI (0.1 mmol) and $Co(acac)_2$ (50 μ mol) were added **1a** (5 mmol) and **2a** (1 mmol). The reaction mixture was stirred at 75 °C for 15 h under dioxygen. The product was isolated by column chromatography (230–400 mesh silica gel, *n*-hexane:ethyl acetate = 5–20:1). The yields of products were estimated from the peak areas based on the internal standard technique using GC. The products **3** and **4** were reported previously.^{6,7} Data for **5**: IR (KBr, cm^{-1}): 3589, 2994, 1792, 1393, 1252, 1142, 1075, 971. 1H NMR (270 MHz, CD_3OD): δ 2.80 (s, 1H), 0.94 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (68 MHz, CD_3OD): δ 172.7, 170.4, 85.9, 83.0, 82.1, 56.5, 30.1, 24.6, 24.6, 23.6. Anal. Calcd for $C_{10}H_{14}O_4$: C, 56.07; H, 6.59%. Found: C, 55.91; H, 6.42%.
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