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New efficient organocatalytic oxidation of benzylic compounds by molecular oxygen under mild conditions

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Abstract—Efficient aerobic oxidation of benzylic compounds has been achieved under no irradiation using a new organocatalytic system in the presence of acridine yellow and *N*-hydroxyphthalimide with assistance of a catalytic amount of molecular bromine. Various substrates, especially alkylaromatics, were effectively oxygenated to the corresponding carbonyl compounds with molecular oxygen as oxidant under mild conditions. For instance, indan was oxidized with 92% conversion and 79% selectivity for 1-indanone under 0.3 MPa of O_2 at 75 °C.

Oxidation is one of the most fundamental transformations in organic chemistry. Direct benzylic oxidation is the foundation of many current important industrial and fine-chemical processes,[1] which is utilized in a diverse field from natural product chemistry to 'bucky-bowl' synthesis.[2] Traditionally, a stoichiometric amount of oxidant such as manganese dioxide, chromic acid, potassium dichromate, or selenium dioxide was employed for these transformations.[3] In recent years, the use of molecular oxygen as terminal oxidant has received great attention for both economical and environmental benefits. Simultaneously, many highly efficient systems have been developed for catalytic aerobic benzylic oxidation. For example, metallic catalyst systems containing cobalt, ruthenium, copper, or iron element have been reported.[4–7] Typically, the extensive research of using metalloporphyrins as catalysts in the oxidation process has been carried through by several groups.[8] Furthermore, the attractive work by Ishii and Einhorn showed that the benzylic oxidation process could be fulfilled with the combination of *N*-hydroxyphthalimide (NHPI) and metal compound (or aldehydes).[9] However, due to metallic toxicity and the high expense, researches have been concentrated on developing nonmetallic organocatalytic system.[10] Recently, our group reported a biomimetic aerobic oxidation system, in which some hydrocarbons were successfully oxidized with a nonmetallic combination of anthraquinones, NHPI, and HY zeolite.[11] On the other hand, in photocatalytic oxidation, acridines analogues (e.g., 9-mesityl-10-methylacridinium ion), which have been used as efficient organocatalysts for highly selective oxidation of hydrocarbons under light irradiation,[12] can act as active radical cations via photoinduced electron transfer and sequentially activate oxygen and substrates to achieve oxidation process. But these types of acridines compounds have never been described for hydrocarbons oxidation without irradiation. In this letter, by utilizing the electron-transferring character of acridine yellow, we emphasize a new organocatalytic system of acridine yellow and NHPI with the assistance of molecular bromine (Br_2) for a highly efficient aerobic benzylic oxidation under mild and no radiant conditions. Thereinto, choosing molecular bromine as a co-catalyst is based on the fact that it can simply oxidize nitrogen atom to radical cation through one electron oxidation;[13] Moreover, molecular bromine has exhibited outstanding promotion action in some oxidation processes.[14]

In a first series of experiments, we have investigated the aerobic oxidation of indan (**1**) as a model substrate (Scheme 1) under various experimental conditions (Table 1). The experiments were performed in a sealed Teflon-lined stainless steel autoclave equipped with magnetic stirring and automatic temperature control. It was observed that only 3% of indan was oxidized

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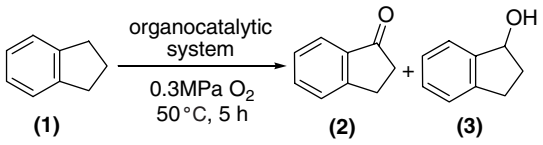


Scheme 1. Oxidation of indan with molecular oxygen.

under 0.3 MPa of O_2 at 50 °C for 5 h when 7.5 mol % NHPI was used separately (entry 1), and nearly no reaction occurred when only 2.5 mol % acridine yellow was used (entry 2). When acridine yellow and NHPI were coupled as a catalytic system, the conversion was improved to 29% under the same reaction condition (entry 3). To our surprise, further research investigation showed that an 87% conversion and 54% selectivity for 1-indanone (**2**) were obtained when 2.5 mol % Br_2 was added as a co-catalyst (entry 4). In succession, we investigated the oxidation of indan with only 'NHPI–Br_2' or 'acridine yellow–Br_2' under the same conditions. Nevertheless, just 4% or 3% of indan was, respectively, oxidized (entries 5 and 6). These data clearly showed that the combination of 'NHPI–acridine yellow–Br_2' system could effectively promote oxidation of **1**. As a result, we found when the content of NHPI–acridine yellow–Br_2 was 7.5–2.5–2.5 mol %, the selective catalytic oxidation efficiently proceeded and the result was satisfying. It is worth noting that when other acridines compounds were tested instead of acridine yellow, no high effectiveness was observed in the oxidation and it could be ascribed to the matching effect of electron transferring (entries 7–9).

In order to further understand the reaction characters, *N*-bromosuccinimide (NBS) or sodium bromide (NaBr) was employed instead of molecular bromine as a co-catalyst. The conversion was reduced to 61% or 57% under similar conditions (entries 10 and 11 in Table 1). On the other hand, the effect of temperature on the oxidation of **1** was investigated and is outlined in Figure 1. It shows that the selectivity for **2** was increased and the selectivity for peroxide was reduced gradually along with the increase of temperature from 35 to 75 °C. At 75 °C, 92% conversion with 79% selectivity for **2**, 18% selectivity for **3** was observed (entry 12).

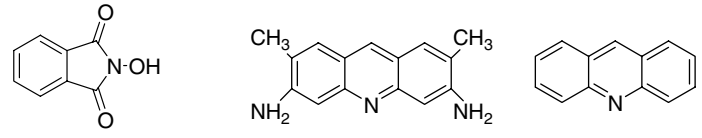
A variety of benzylic compounds were next effectively oxidized by dioxygen using our organocatalytic system (Table 2). Tetralin was similarly oxidized with 93% conversion and 95% selectivity for 1-tetralone (entry 1). When ethylbenzene was oxidized, 67% conversion and 94% selectivity for acetophenone were obtained after 5 h (entry 2). Moreover, 4-ethylbenzonitrile was oxidized with 51% conversion and 99% selectivity for 4-acetylbenzonitrile under same conditions (entry 3). When diphenylmethane was oxidized, 65% conversion

Table 1. Oxidation of indan in different catalyst combinations[a]

Entry	Catalyst[b]	Conversion[c]	Product selectivity		
			Indanol	Indanone	Peroxide
1	NHPI	3	12	21	67
2	Acridine yellow	0	—	—	—
3	Acridine yellow+NHPI	29	23	33	44
4	Acridine yellow+NHPI+Br_2	87	14	54	32
5	NHPI+Br_2	4	35	34	31
6	Acridine yellow+Br_2	3	21	72	7
7	Acridine+NHPI+Br_2	19	22	13	65
8	Acridine orange+NHPI+Br_2	12	19	61	20
9	Acridine red+NHPI+Br_2	39	18	52	30
10	Acridine yellow+NHPI+NBS	61	23	32	45
11	Acridine yellow+NHPI+NaBr	57	23	65	12
12[d]	Acridine yellow+NHPI+Br_2	92	18	79	3

[a] Reaction conditions: Indan was performed on a 1 mL scale, in the presence of NHPI (7.5 mol %), acridine yellow or analogues (2.5 mol %), Br_2 (2.5 mol %), in 10 mL CH_3CN, pressure = 0.3 MPa, time = 5 h, temperature = 50 °C.

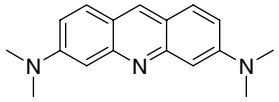
[b] The corresponding chemical structures of some compounds:



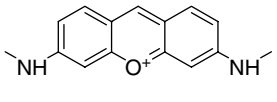
N-hydroxyphthalimide

Acridine yellow

Acridine



Acridine orange



Acridine red

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[c] The data were obtained by GC and GC–MS analysis using 1,3-dichlorobenzene as an internal standard.

[d] Temperature was increased to 75 °C.

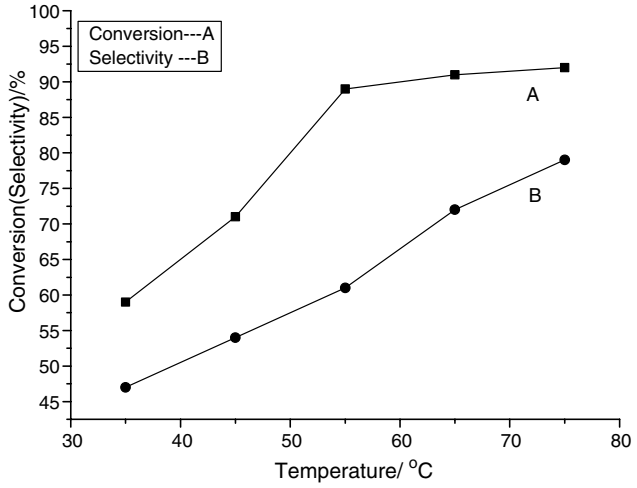


Figure 1. The temperature effect on the oxidation of indan.

and 99% selectivity for benzophenone were obtained at 100 °C for 20 h (entry 4). Acenaphthene was oxidized with 70% conversion and 88% selectivity for acenaphthylenone after 24 h (entry 5). From these results, we can see that the ketones were obtained with higher efficiency and selectivity under milder reaction conditions over conventional benzylic oxidation systems when alkylaromatics were oxidized by our organocatalytic system.[3–8] Meanwhile, when the oxidation of 1-phenylethanol was performed with this catalytic system, the reaction was very slow and the conversion was less than 10% under the same conditions. Therefore, a direct pathway leading from alkylaromatics to the corresponding ketones seemed likely.[15]

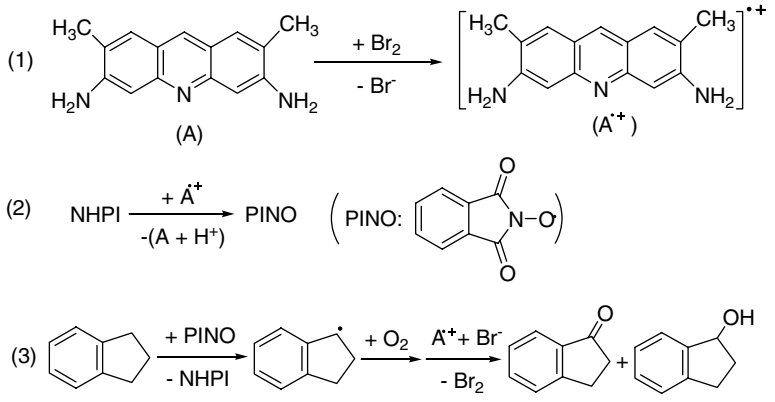
Here, a hypothetical reaction mechanism is proposed for indan oxidation (Scheme 2). Firstly, acridine yellow is converted to cation radical through a single-electron oxidation of nitrogen atom by molecular bromine (step 1), and then the cation radical impels generation of phthalimide *N*-oxyl radical (PINO) via electron and proton transfer between cation radical and NHPI (step 2). The final step involves the hydrogen atom abstraction from indan by PINO, and the resulting indan radical being trapped by dioxygen provides peroxy radical, which is eventually converted into products through hydroperoxide (step 3). Further investigations on the direct information of acridine yellow cation radical and selective transformation process in the reaction are underway.

In summary we have developed a new catalytic system for aerobic oxidation using NHPI and acridine yellow with assistance of a catalytic amount of molecular bromine. This system allows efficient oxidation of benzylic compounds under mild conditions without any metal component. The extension of this approach is underway.

Table 2. Oxidation of various substrates by 'NHPI–acridine yellow–Br_2' system[a]

Entry	Substrate	Conversion[b]	Product selectivity[c]			
1	Tetralin	93	1-Tetralone	95	1-Tetralol	4
2	Ethylbenzene	67	Acetophenone	94	1-Phenylethanol	5
3	4-Ethylbenzonitrile	51	4-Acetylbenzonitrile	99	4-(1-Hydroxyethyl)benzonitrile	1
4[d]	Diphenylmethane	65	Benzophenone	99	Diphenylmethanol	1
5[e]	Acenaphthene	70	Acenaphthylenone	88	Dihydroacenaphthylenol	12

[a] Reaction conditions: Indan was performed on a 1 mL scale, in the presence of NHPI (7.5 mol %), acridine yellow or analogues (2.5 mol %), Br_2 (2.5 mol %), in 10 mL CH_3CN, pressure = 0.3 MPa, time = 5 h, temperature = 75 °C.
[b] The data were obtained by GC and GC–MS analysis using 1,3-dichlorobenzene as an internal standard.
[c] Selectivity for peroxide was left out owing to less than 1%.
[d] Oxidation of diphenylmethane was employed at 100 °C under 0.3 MPa of O_2 for 20 h.
[e] Acenaphthene was performed on a 0.77 g scale for oxidation at 100 °C under 0.3 MPa of O_2 for 24 h.



Scheme 2. Proposed mechanisms for indan oxidation.

Acknowledgments

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Supplementary data

General procedure for the oxidation and products analysis, detailed GC measurement conditions and GC–MS diagrams for all the products are contained in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.028.

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