ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 11, pp. 2084–2087. © Pleiades Publishing, Ltd., 2014.
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Oxidative Coupling of *N*-Hydroxyphthalimide with Toluene

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Received September 22, 2014

Abstract—Oxidative C–O-coupling of *N*-hydroxyphthalimide (NHPI) with toluene was studied. The reaction occurred in different organic solvents with a wide range of oxidants, such as $(NH_4)_2Ce(NO_3)_6$, $PhI(OAc)_2$, $KMnO_4$, $Mn(OAc)_3 \cdot 2H_2O$, $Pb(OAc)_4$, and $Co(OAc)_2/O_2$, to afford *N*-benzyloxyphthalimide in yield of 11–75%. Phthalimide-*N*-oxyl radicals, generated under the reaction conditions, could eliminate the hydrogen atom from the benzyl fragment of alkylarene at room temperature. Probably, formation of the product of the oxidative coupling occurred via recombination of benzyl and phthalimide-*N*-oxyl radicals.

Keywords: *N*-hydroxyphthalimide, free radicals, phthalimide-*N*-oxyl radical, oxidative coupling

DOI: 10.1134/S1070363214110061

Chemistry of *N*-hydroxyphthalimide and related *N*-hydroxyimide compounds has attracted emerging interest due to their ability to catalyze free-radical oxidation processes [1–4]. Phthalimide-*N*-oxyl radical, generated from *N*-hydroxyphthalimide under the action of oxidizing agents, is capable of eliminating hydrogen from alkylarenes [5–9], alkenes [7, 8, 10], alkynes [11], ethers [12, 13], alcohols [14], amides [15], amines [16], and alkanes [5–9, 17–19] to give the corresponding *C*-radicals. The latter is further converted into the final products to form new bonds: C–O [8–11, 14–16], C–N [5, 6], C–C [12, 13, 17], C–Hlg [7, 9, 19], or C–S [18].

Reactivity of phthalimide-*N*-oxyl radical is fundamentally different from that of other nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), due to the presence of two electron withdrawing carbonyl groups in the near the nitrogen atom in phthalimide-*N*-oxyl radical.

Among other *N*-hydroxyimides, *N*-hydroxyphthalimide is of special interest due to the combination of its availability, low cost, ease of generation of phthalimide-*N*-oxyl radical, and its high reactivity. *N*-Hydroxyphthalimide is regarded as a promising mediator of large-scale radical processes, for example, preparation of hydroperoxides, alcohols, ketones, aldehydes, carboxylic acids, hydrocarbons, and nitro derivatives starting from hydrocarbons and alkyl-substituted compounds, as well as for ethers oxidation and other oxidation processes comprising C–C-coupling step. *N*-Hydroxyphthalimide is used for "green chemistry" oxidation of 3-picoline, *p*-xylene, and cyclohexane into nicotinic acid, adipic acid, and terephthalic acid, respectively.

On top of wide application of *N*-hydroxyphthalimide as an initiator of free-radical oxidation processes, it is also a key reagent to produce *O*-substituted hydroxylamines [3], valuable intermediates in preparation of biologically active compounds exhibiting specific antagonist, inhibiting, fungicidal, and antiprotozoal activity. *O*-Substituted hydroxylamines can be prepared in two steps: introduction of phthalimide-*N*-oxyl fragment into the molecule of organic substrate by reacting with *N*-hydroxyphthalimide and removal of the phthalic acid moiety. *O*-Substituted *N*-hydroxyphthalimide can be obtained via nucleophilic substitution reaction between the *N*-hydroxyphthalimide anion and halide or via the Mitsunobu reaction between *N*-hydroxyphthalimide and alcohol. Synthesis of *O*-substituted *N*-hydroxyphthalimides via oxidative coupling of *N*-hydroxyphthalimide with CH-reagents [20–23] involves the more accessible substrates as compared with halides and alcohols, for which an additional step, halogenation or oxidation, is required. In addition, nucleophilic substitution of the halogen atom is accompanied by side processes.

Extending our studies of oxidative coupling reactions, herein we report a possibility of the reaction of *N*-hydroxyphthalimide with toluene [22], with dif-

Oxidative coupling of toluene with *N*-hydroxyphthalimide under catalysis with various oxidizing agents

Exp. no.	Oxidant (molar ratio of the oxidant : *N*-hydroxyphthalimide)	Solvent	*T*, °C	Yield, %
1	$(NH_4)_2Ce(NO_3)_6$ (2 : 1)	AcOH (5 mL) (H_2O, 3 mL)	20–25	75
2	$(NH_4)_2Ce(NO_3)_6$ (2 : 1)	AcOH	60	40
3	$PhI(OAc)_2$ (1 : 1)	MeCN	20–25	45
4	$PhI(OAc)_2$ (1 : 1)	AcOH	60	62
5	$Pb(OAc)_4$ (1 : 1)	AcOH	20–25	36
6	$Pb(OAc)_4$ (1 : 1)	$CHCl_3$	20–25	40
7	$Pb(OAc)_4$ (1 : 1)	$CHCl_3$	60	39
8	$Pb(OAc)_4$ (1 : 1)	$CHCl_3$ (2×5 mL)	20–25	37
9	$Pb(OAc)_4$ (1 : 1)	EtOAc (10 mL) ($CHCl_3$, 5 mL)	20–25	29
10	$Mn(OAc)_3 \cdot 2H_2O$ (2 : 1)	AcOH	60	45
11	$KMnO_4$ (0.4 : 1)	AcOH	60	54
12	$Fe(ClO_4)_3 \cdot nH_2O$ (2 : 1)	MeCN	20–25	7
13	$Fe(ClO_4)_3 \cdot nH_2O$ (2 : 1)	MeCN	60	14
14	$Fe(ClO_4)_3 \cdot nH_2O$ (2 : 1)	MeCN (2×3 mL)	60	19
15	$Cu(ClO_4)_2 \cdot 6H_2O$ (2 : 1)	MeCN	60	<5
16	$(NH_4)_2Ce(NO_3)_6$–$(NH_4)_2S_2O_8$ (0.1 : 1 : 1)	$C_2H_4Cl_2$ (5 mL) (H_2O, 5 mL)	80	<5
17	$Co(OAc)_2 \cdot 4H_2O$–34% H_2O_2 aqueous solution (0.05 : 1 : 1)	AcOH	60	<5
18	$Co(OAc)_2 \cdot 4H_2O$–70% *t*-BuOOH aqueous solution (0.05 : 1 : 1)	AcOH	60	<5
19	$Co(acac)_2$–70% *t*-BuOOH aqueous solution (0.05 : 1 : 1)	MeCN	60	<5
20[a]	$Co(OAc)_2 \cdot 4H_2O$–O_2 (0.05 : 1)	AcOH	60	11

[a] Oxygen was bubbled through the reaction mixture (0.3 mL/s).

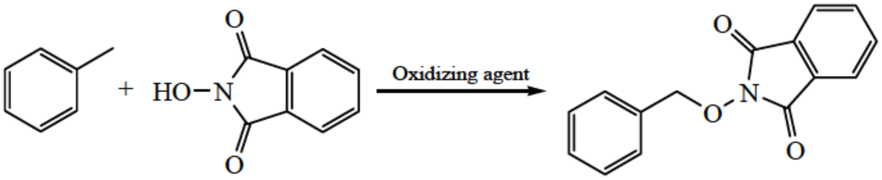
ferent oxidizing agents and under different reaction conditions.

Only two examples of oxidative C–O-coupling of *N*-hydroxyphthalimide with alkylarene in the presence of CuCl–$PhI(OAc)_2$ [20, 21] or $(NH_4)_2Ce(NO_3)_6$ (CAN) [21, 22] have been reported so far. In this work we investigated the reaction of *N*-hydroxyphthalimide with alkylarene under action of a number of oxidants involving transition metal salts (Scheme 1).

Oxidative coupling of *N*-hydroxyphthalimide with toluene was carried out at 20–80°C using acetic acid, acetonitrile, chloroform, dichloroethane, or ethyl acetate as solvent (see table).

In experiments nos. 1–11, the reaction proceeded with moderate to good yields (29–75%) in the presence of various oxidants: $(NH_4)_2Ce(NO_3)_6$ (CAN), $Pb(OAc)_4$, $PhI(OAc)_2$, $Mn(OAc)_3$, and $KMnO_4$. The best results were obtained when using CAN, $PhI(OAc)_2$, $Mn(OAc)_3 \cdot 2H_2O$, and $KMnO_4$ in acetic acid. Lead tetraacetate was a less efficient oxidant: the product yield did not exceed 40%. Copper and iron perchlorates as well as oxidizing systems based on CAN or cobalt salts in

Scheme 1.



combination with peroxides or oxygen were proved inefficient: yield of *N*-benzyloxyphthalimide did not exceed 19% (experiments nos. 12–20).

To conclude, we have shown that oxidizing agents of different classes can be used for C–O coupling of *N*-hydroxyphthalimide with toluene. In future, the results of the research can be applied to other reactions of CH-active compounds with *N*-hydroxyimide.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of the solutions in $CDCl_3$ were recorded with a Bruker AM300 instrument. Reagents and solvents were purchased from Acros Organics.

Oxidative coupling of *N*-hydroxyphthalimide with toluene. *a. Experiments nos. 2–7, 10–13, and 15.* An oxidizing agent (77.5–1344 mg, 0.49–2.45 mmol) was added to a stirred mixture of *N*-hydroxyphthalimide (200 mg, 1.23 mmol), toluene (565 mg, 6.13 mmol), and solvent (5 mL) within 5–10 s at certain temperature (see table). Then the mixture was stirred at the same temperature during 20 min. Then, 15 mL of chloroform and 20 mL of water were added to the mixture. If the precipitate was formed, it was filtered off. The organic layer was separated off, and the aqueous layer was extracted with chloroform (2 × 10 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ solution (15 mL) and water (20 mL), and dried over $MgSO_4$. After the solvent removal, *N*-benzyloxyphthalimide was isolated by column chromatography on silica gel, eluting with a EtOAc–CH_2Cl_2 mixture. White crystals, mp 144–146°C (mp 143–146°C [20]). ^{1}H NMR spectrum (300.13 MHz), δ, ppm: 5.22 s (2H, CH_2), 7.33–7.44 m (3H, ArH), 7.49–7.59 m (2H, ArH), 7.68–7.85 m (4H, ArH). ^{13}C NMR spectrum (75.47 MHz), δ_C, ppm: 79.9 (CH_2); 123.5, 128.6, 129.0, 129.4, 129.9, 133.8, 134.5 (Ar); 163.5 (C=O).

b. Experiments nos. 1, 8, 9, and 14. A solution of oxidizing agent (experiment no. 1, in AcOH, 5 mL; no. 8, in $CHCl_3$, 5 mL, no. 9, in EtOAc, 10 mL; no. 14, in MeCN, 3 mL) was added dropwise to a mixture of *N*-hydroxyphthalimide and toluene in a suitable solvent (experiment no. 1, H_2O, 3 mL; no. 8, $CHCl_3$, 5 mL; no. 9, $CHCl_3$, 5 mL; no. 14, MeCN, 3 mL) within 10 min at certain temperature (see table). Then the mixture was stirred at the same temperature for 10 min. When using a single solvent, the oxidizing agent was added in a solution in the same solvent. Isolation and purification of *N*-benzyloxyphthalimide were performed similarly to the above-described *a*.

c. Experiments nos. 16–20. $(NH_4)_2Ce(NO_3)_6$ (67.2 mg, 123 μmol), $Co(OAc)_2{\cdot}4H_2O$ (15.3 mg, 61.3 μmol), or $Co(acac)_2$ (15.8 mg, 61.3 μmol) was added to a mixture of *N*-hydroxyphthalimide (200 mg, 1.23 mmol), toluene (565 mg, 6.13 mmol), and a solvent (5 mL, except experiment no. 16, when 5 mL of $C_2H_4Cl_2$ and 5 mL of H_2O were used) with stirring at a given temperature. After 1 min, a peroxide oxidant (123–280 mg, 1.23 mmol) was added to the mixture within 5–10 sec. Then the mixture was stirred at the same temperature for 20 min. In experiment no. 20, the reaction mixture was bubbled with oxygen (0.3 mL/s) for 20 min at 60°C instead of adding a peroxide reagent. Isolation and purification of *N*-benzyloxyphthalimide were performed similarly to the above-described *a*.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Science Foundation (grant no. 14-23-00150).

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