

# First Ritter-type reaction of alkylbenzenes using *N*-hydroxyphthalimide as a key catalyst

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The first Ritter-type reaction of alkylbenzenes with nitriles has been successfully achieved by the use of *N*-hydroxyphthalimide (NHPI) as a key catalyst. Thus, treatment of ethylbenzene with ammonium hexanitratocerate(IV) (CAN) in the presence of a catalytic amount of NHPI in EtCN under argon produced the corresponding amide in good selectivity.

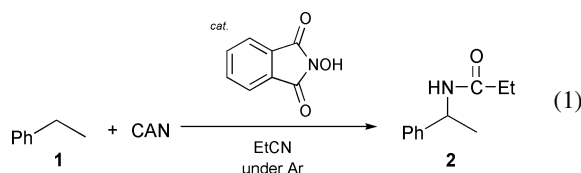
Functionalization of saturated hydrocarbons *via* C–H activation is of considerable interest and remains a challenge to chemists.<sup>1</sup> Ritter-type reaction of alkanes such as adamantane is known as a synthetic tool for the preparation of amide derivatives and accomplished by the use of Br<sub>2</sub>–H<sub>2</sub>SO<sub>4</sub>,<sup>2</sup> NO<sub>2</sub>BF<sub>4</sub>,<sup>3</sup> AlCl<sub>3</sub>–CH<sub>2</sub>Cl<sub>2</sub>,<sup>4</sup> electrolysis,<sup>5</sup> Pb(OAc)<sub>4</sub>,<sup>6</sup> and HNO<sub>3</sub>–CCl<sub>4</sub>.<sup>7</sup> However, these methods are limited to the reaction of adamantane or its derivatives. Recently, Hill *et al.* demonstrated that lower alkanes such as isobutane react with acetonitrile in the presence of a polyoxometalate under photo-assistance to form the corresponding acetamide in high selectivity.<sup>8</sup> The reaction is postulated to proceed through the formation of an alkyl radical followed by one-electron oxidation by a W ion to a carbocation.

In our previous papers, we showed that *N*-hydroxyphthalimide (NHPI) acts as an efficient catalyst for the generation of alkyl radicals from alkanes under O<sub>2</sub><sup>9</sup> and NO<sub>2</sub><sup>10</sup> to form oxygenated products, such as alcohols and carboxylic acids, and nitroalkanes, respectively. To extend the synthetic application using NHPI as a key catalyst, our effort has been directed toward the generation of carbocations through the formation of alkyl radicals assisted by NHPI.<sup>11</sup> Our strategy is as follows: (i) abstraction of a hydrogen atom from alkane by phthalimide *N*-oxyl (PINO) generated from NHPI and an appropriate oxidant leading to an alkyl radical, (ii) one-electron oxidation of the resulting alkyl radical by the oxidant to a carbocation, (iii) trapping of the carbocation by a nucleophile like alkyl nitrile.

Now, we have found that NHPI combined with ammonium hexanitratocerate(IV) (CAN) serves as an efficient system for the generation of both PINO from NHPI and carbocations from alkyl radicals. Thus, benzylic compounds first undergo amidation with an alkyl nitrile under mild conditions to form amides in good yields.

Ethylbenzene (**1**) was chosen as a model substrate and allowed to react with CAN in the presence of a catalytic amount of NHPI in EtCN.† Table 1 summarizes the representative results for the Ritter-type reaction of **1** under selected reaction conditions.

The reaction of **1** in the presence of CAN and NHPI in EtCN under argon at 80 °C for 6 h produced *N*-(1-phenylethyl)propionamide (**2**)‡ in 84% selectivity at 61% conversion (eqn. (1), Table 1, run 1).



To the best of our knowledge, no reports have appeared on the Ritter-type reaction of alkylbenzenes. Needless to say, no reaction took place in the absence of either NHPI or CAN (runs 2 and 3). When the reaction was carried out under O<sub>2</sub> atmosphere, the yield of **2** decreased (19%) and large amounts of oxygenated products such as acetophenone (35%) and benzaldehyde (17%) were formed at 87% conversion (run 4). This is believed to be due to the fact that the benzyl radical, generated by the hydrogen abstraction from **1** by the PINO, would be rapidly trapped by O<sub>2</sub>. The optimum reaction temperature was found to be 80 °C (runs 5 and 6).

Table 2 summarizes the Ritter-type reaction of various alkylbenzenes and adamantanes using the NHPI–CAN system. In a similar manner to **1**, the reaction of 1-phenyl-2-methylpropane (**5**) in EtCN using the NHPI–CAN system afforded the corresponding amide **6** (93%), in which the amide group was introduced at the benzylic position in preference to the methine one, at 63% conversion (run 2). The amidation of *p*-ethyltoluene (**7**) with EtCN took place selectively at the ethyl moiety to afford *N*-(1-*p*-tolylethyl)propionamide (**8**) (run 3). Indane (**9**) was also amidated with EtCN even at rt to give **10** in high conversion (93%) and selectivity (74%) (run 4). Notably, the NHPI–CAN system was also efficient for the Ritter-type reaction of adamantanes. The reaction of 1,3-dimethyladamantane (**13**) in EtCN, <sup>n</sup>PrCN, or PhCN afforded the corresponding amides **14a**, **14b** or **14c** in fair to good yields, respectively (run 6). A lower alkane such as isobutane (**15**) was also amidated to give *N*-*tert*-butylpropionamide (**16**), although the yield of the product was relatively low (run 7).§

It is reasonable to assume that the present reaction is initiated by the reaction of NHPI with CAN to form PINO, which is thought to be a key species for the generation of alkyl radicals (Scheme 1).<sup>9–11</sup> In fact, PINO was generated upon treatment of NHPI with CAN in MeCN at 70 °C.¶ The resulting PINO abstracts a hydrogen atom from these hydrocarbons to generate the corresponding alkyl radicals (**A**), which undergoes the one-electron oxidation by Ce(IV) to form carbocations (**B**). The carbocations **B** thus generated are trapped by nitriles, followed by H<sub>2</sub>O, which would be contained in the solvent, to afford amide derivatives. When the reaction was carried out under dioxygen, the alkyl radicals **A** formed react with O<sub>2</sub> in

Table 1 Ritter-type reaction of **1** by the NHPI–CAN system<sup>a</sup>





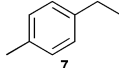
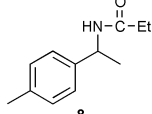

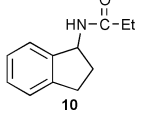

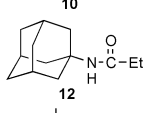
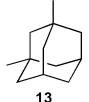
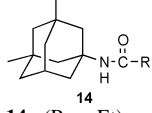

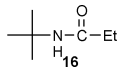
Run	Conv. (%)	Selectivity of <b>2</b> (%)
1	61	84
2 <sup>b</sup>	No reaction	
3 <sup>c</sup>	No reaction	
4 <sup>d</sup>	87	19 <sup>e</sup>
5 <sup>f</sup>	58	47
6 <sup>g</sup>	74	53

<sup>a</sup> **1** (1 mmol) was allowed to react with CAN (1.5 mmol) in the presence of NHPI (0.1 mmol) in EtCN (5 mL) at 80 °C for 6 h under Ar. <sup>b</sup> In the absence of NHPI. <sup>c</sup> In the absence of CAN. <sup>d</sup> Under O<sub>2</sub>. <sup>e</sup> See text. <sup>f</sup> At 60 °C. <sup>g</sup> At 100 °C

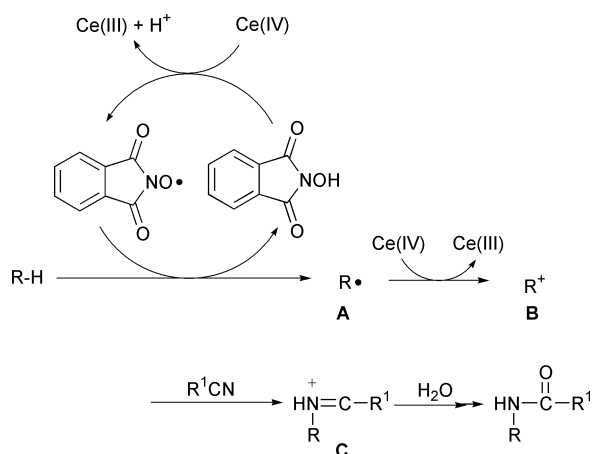
preference to Ce(IV) to give the oxygenated products as shown in Table 1, run 4.

According to this reaction pathway (Scheme 1), 2 equiv. of CAN with regard to the substrate is required to complete the reaction. In the reactions using 1.5 equiv. of CAN, the conversion would be less than 75%. However, the conversions of substrates, **7**, **9** and **13**, in the present reactions were much higher than 75% (Table 2, runs 3, 4, and 6). This is believed to be due to the generation of PINO from NHPI by the action of

**Table 2** Ritter-type reaction of various alkanes by the NHPI–CAN system<sup>a</sup>

Run	Substrate	Conv. (%)	Product	Selectivity (%)
1		69		69
2 <sup>b</sup>		63		93
3 <sup>b</sup>		93		74
4 <sup>c</sup>		93		74
5		51		80
6 <sup>d</sup>		57 82 <sup>e</sup> 72 <sup>f</sup>	 <b>14a</b> (R = Et) 93 <b>14b</b> (R = <sup>n</sup> Pr) 91 <b>14c</b> (R = Ph) 83	93 91 83
7		—		28 <sup>g</sup>

<sup>a</sup> Substrate (1 mmol) was allowed to react with CAN (1.5 mmol) in the presence of NHPI (0.1 mmol) in EtCN (5 mL) at 100 °C for 6 h under Ar. <sup>b</sup> At 80 °C. <sup>c</sup> At 25 °C. <sup>d</sup> At 50 °C. <sup>e</sup> <sup>n</sup>PrCN was used as a solvent. <sup>f</sup> PhCN was used as a solvent. <sup>g</sup> The yield was based on CAN (See footnote§).



**Scheme 1** A possible reaction path.

nitrogen oxides like NO<sub>2</sub> from CAN during the reaction. In fact, for **13**, a small amount (1%) of nitrated product, 1-nitro-3,5-dimethyladamantane, was obtained.

In addition, the NHPI–CAN system was found to promote the acetoxylation of **5** in AcOH in the presence of Na<sub>2</sub>CO<sub>3</sub>. Treatment of **5** with 1.5 equiv. of CAN under the influence of NHPI catalyst (10 mol %) and 1.2 equiv. of Na<sub>2</sub>CO<sub>3</sub> in AcOH under Ar atmosphere afforded the corresponding acetylated compound, 1-acetoxy-1-phenyl-2-methylpropane (**17**) (88%), at 66% conversion. The reaction with AcONa in place of Na<sub>2</sub>CO<sub>3</sub> resulted in 67% selectivity of **17** (84% conversion).

In conclusion, the Ritter-type reaction of alkylbenzenes was first achieved by the use of NHPI combined with CAN. Thus, various benzylic compounds as well as adamantanes were successfully converted into the corresponding amides.

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## Notes and references

† A typical procedure for the Ritter-type reaction of **1**: to a solution of **1** (1 mmol) and CAN (1.5 mmol) in EtCN (5 mL) in a three-necked flask was added NHPI (0.1 mmol). The flask was cooled to –78 °C to freeze the solvent, and degassed *in vacuo* and filled with Ar gas. Then the frozen solvent was melted at rt, and refrozen to reiterate the evacuation–Ar purge procedure. The series of operations was repeated three times. The reaction mixture was allowed to react under an atmospheric pressure of Ar at 80 °C for 6 h. Selectivity (%) of the product was based on the substrate reacted. All starting materials were commercially available and used without any purification.

‡ Spectral data for **2**: <sup>1</sup>H NMR δ 7.36–7.21 (m, 5H), 5.81 (s, 1H), 5.18–5.08 (m, 1H), 2.20 (q, *J* = 7.3 Hz 2H), 1.48 (d, *J* = 7.3 Hz, 3H), 1.14 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR δ 172.6, 143.2, 128.5, 127.2, 126.0, 48.6, 29.8, 21.8, 9.89; IR (neat) 3289, 2977, 1644, 699 cm<sup>–1</sup>; MS (70 eV) *m/e* = *M*<sup>+</sup> 177, 120, 106, 77.

§ A procedure for the Ritter-type reaction of **15**: the reaction was carried out in a 50 mL glass autoclave. **15** was treated as a liquid at –15 °C. To a solution of CAN (1 mmol) and NHPI (0.1 mmol) in EtCN (5 mL) was added **15** (2 mL, *ca.* 20 mmol). After the atmosphere in the autoclave was replaced with Ar, the reaction mixture was allowed to react at 100 °C for 15 h.

¶ Electron spin resonance (ESR) measurements were carried out under selected conditions. To an ESR tube was added NHPI (0.025 mmol) and CAN (0.025 mmol) in PhCN (0.05 mL), and the mixture was reacted under argon at 25 °C for 5 min. The ESR spectrum attributed to PINO was clearly observed as a triplet signal based on hyperfine splitting (hfs) by the nitrogen atom (*g* = 2.0074, *a<sub>N</sub>* = 0.46 mT). The *g*-value and hfs constant observed for PINO were consistent with those reported by Mackor *et al.*<sup>12</sup>

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