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A convenient protocol for C–H oxidation mediated by an azido radical culminating in Ritter-type amidation

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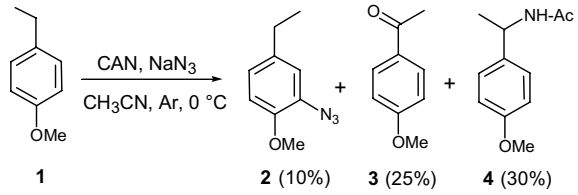
Abstract—Cerium(IV) ammonium nitrate in combination with sodium azide reacts with unactivated hydrocarbons in acetonitrile to furnish acetamides in one pot. The strategy can be used to introduce nitrogen functionality into a variety of compounds; a carboxylic ester directly afforded the corresponding α-amino acid.

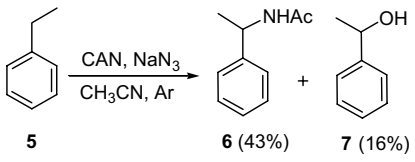
In recent years there has been considerable interest in C–H functionalisation by oxidative processes.[1,2] In this letter we report a convenient protocol that was uncovered in this area. During the course of our work on cerium(IV) ammonium nitrate (CAN) mediated carbon–carbon and carbon–hetero atom bond forming reactions[3,4] we came across some remarkable transformations, most notably the conversion of styrene to aminotetralin derivatives, in a one-pot operation.[5] In this context, we began exploring the possibility of CAN mediated addition of azide to electron rich aromatic systems. In the event, when 4-ethylanisole was exposed to a solution of CAN in acetonitrile, the expected azidation product **2** was obtained, albeit only in 10% yield. Interestingly two products, both resulting from side chain oxidation were obtained in larger amounts (Scheme 1).



Scheme 1.

Formation of the products **2**–**4** could be rationalised by the initial oxidation of **1** by CAN to a cation radical followed by further transformations of the latter. A reaction sequence triggered by abstraction of the benzylic C–H by an azido radical followed by subsequent reactions of the resulting benzylic radical can also account for the formation of **3** and **4**. In view of this possibility, and the prospect it offered for a simple procedure for the useful functionalisation of benzylic positions, we examined the reaction with ethyl benzene. Gratifyingly, the reaction led to the formation of two products **6** and **7** (Scheme 2).

A mechanistic rationalisation portraying the probable sequence of events is given in Scheme 3. Arguably the initial event could be the oxidation of the azide ion to the azido radical, which can abstract a benzylic hydrogen to generate the radical **8**.[6] Oxidation of the latter to the cation and its Ritter trapping by acetonitrile followed by aqueous work up would deliver the amide **6**. Formation of the nitrate **10** from **8** via ligand transfer from CAN, followed by solvolysis can account for the formation of **7**. Such transformations are precedented,[7] but the factors governing the single electron transfer (SET) versus ligand transfer pathway, from the intermediate **8**, are not clear at the present time.



Scheme 2.

Keywords: Cerium ammonium nitrate; CH activation; Ritter reaction; Azides; Radicals.
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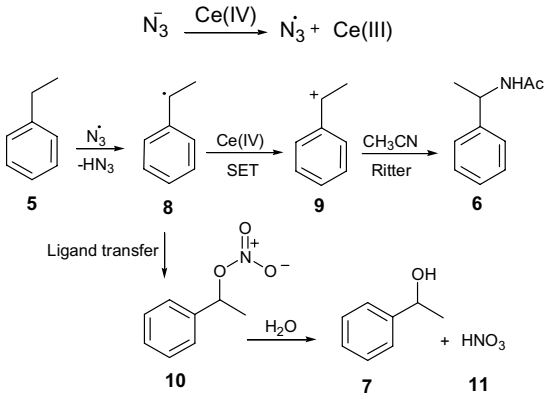


Scheme 3.

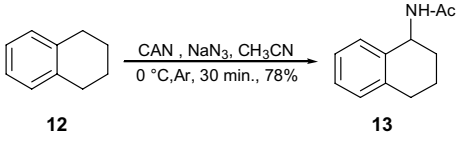
The possibility that the products **6** and **7** are formed by the direct oxidation of ethyl benzene by CAN to the benzylic radical and/or cation followed by further transformations of the latter can be discounted by the inertness of ethyl benzene towards CAN in a blank experiment.

Although the yield of the Ritter product was not high, in view of its potential application in the synthesis of benzylic and other amines, the facility and simplicity of the reaction, and its mechanistic implications, it was obligatory to examine the scope of the reaction. Since the aminotetralin framework is present in many therapeutic agents like the top-selling anti-depressant Sertraline[8] we used tetralin as a substrate in the reaction; an exceedingly facile reaction occurred and 1-acetamidotetralin **13** was obtained in high yield (Scheme 4).[9,10]

Subsequently we found that the reaction is applicable to the C–H oxidation of a variety of substrates and our results are presented in Table 1.

In most cases, the products were characterised by comparison of spectroscopic data with those reported in the literature.

Reflecting on the mechanism of the reaction, it was of interest to employ other anionic species like bromide and iodide to generate radicals that can potentially abstract a benzylic hydrogen. However, such experi-



Scheme 4.

Table 1. CAN/NaN_3 mediated functionalisation of hydrocarbons

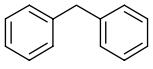
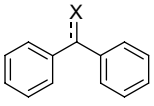
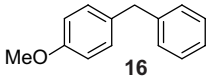
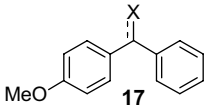
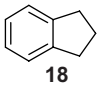
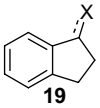
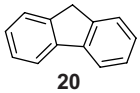
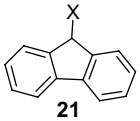
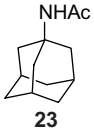
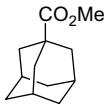
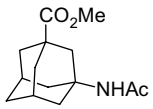
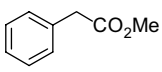
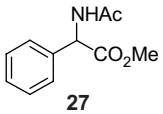
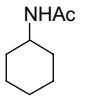
Entry	Substrate	Products	Temp (°C)	Yields (%)[a]
1	 **14**	 **15** **15a,** X = NHAc **15b,** X = O	70	**15a** = 58 **15b** = 20
2	 **16**	 **17** **17a,** X = NHAc **17b,** X = O	70	**17a** = 35 **17b** = 40
3	 **18**	 **19** **19a,** X = NHAc **19b,** X = O	0	**19a** = 39 **19b** = 25
4	 **20**	 **21** **21a,** X = NHAc **21b,** X = O	70	**21a** = 36 **21b** = 40
5	 **22**	 **23**	30	**23** = 85

Table 1 (*continued*)

Entry	Substrate	Products	Temp (°C)	Yields (%)[a]
6	 **24**	 **25**	30	**25** = 40(51)[b]
7	 **26**	 **27**	70	**27** = 30(56)[b]
8	 **28**	 **29**	70	**29** = 16

[a] Isolated yeild.
[b] (Yield) based on recovered starting material.

ments afforded poor yields of products, presumably due to the easy recombination of the halogen radicals compared to azido radicals. Precedent for the special propensity of the azido radical for hydrogen atom abstraction is available in the literature.[6]

Very pertinent to the present work is the Ritter type reaction of alkyl benzenes using *N*-hydroxyphthalimide and CAN reported recently by Ishii and co-workers.[11] It is noteworthy that the present method is applicable to functionalised substrates (Table 1; entries 6 and 7) and uses reaction conditions that are much milder and simpler than those reported by Ishii.

In conclusion, we have uncovered an experimentally simple and mechanistically interesting reaction for C–H oxidation culminating in Ritter amidation. It appears that the method will be applicable to the synthesis of α-amino acids and the functionalisation of a variety of hydrocarbons. Further work is in progress.

Acknowledgements

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9. Typical procedure (Scheme 4): A deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (15 mL) was added dropwise to a solution of tetralin (0.132 g, 1 mmol) and sodium azide (0.098 g,1.5 mmol) in acetonitrile (10 mL) stirred at 0 °C. Argon, thoroughly deoxygenated by passing through Fieser's solution, was continuously bubbled through the reaction mixture. It was stirred until the complete consumption of the starting material was confirmed by TLC. The solvent was removed and the residue diluted with water (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extract was washed with water, brine and dried over anhydrous sodium sulfate. After removal of the solvent the residue was subjected to column chromatography on silica gel. Elution with 70% ethyl acetate–hexane furnished a white solid **13** (0.147 g, 78%). Mp 148–149 °C (lit. 145–146 °C). IR (KBr): 3234, 3058, 2913, 1637, 1532, 1439, 1362, 1087, 741 cm^{-1}. ^1H NMR: δ 7.24–7.06 (m, 4H), 5.77 (br s, 1H), 5.19–5.13 (m, 1H), 2.79–2.75 (m, 2H), 2.01 (br s, 4H), 1.86–1.82 (m, 3H). ^{13}C NMR: δ 168.9, 137.4, 136.7, 129.1, 128.7, 127.2, 126.2, 47.4, 30.1, 29.2, 23.4 and 19.9. Elemental analysis calculated for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.34; H, 8.22; N, 7.52.
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