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Iron/acetic acid-mediated carbon degradation: a facile route for the synthesis of quinoline derivatives

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ABSTRACT

A new carbon degradation protocol which results in the formation of quinoline derivatives is described. The reactions involved the use of mild reaction conditions and an inexpensive reducing reagent (Fe/AcOH).

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1. Introduction

Degradation of carbon, a common phenomenon of the nature, is also an efficient process for the synthesis of a large variety of organic molecules.[1] Hoffman degradation, Curtius degradation, Ruff degradation, and Kolbe electrolysis for the synthesis of hydrocarbons are well-known degradation reactions, where loss of carbon atom(s) occurs during the product formation.[2] Some of the reported examples of carbon degradation during the formation of synthetic and biomedically important products are depicted in Scheme 1.[3]

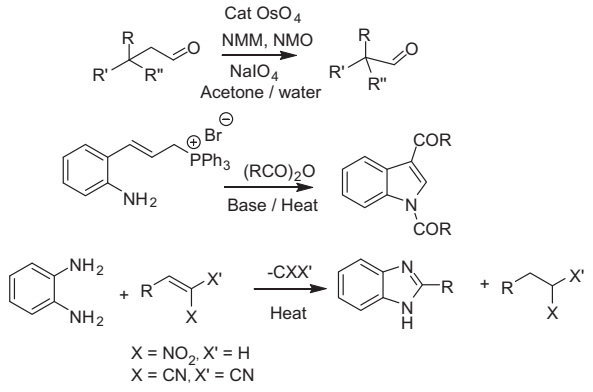
Fe/AcOH is an attractive reagent for the reduction of nitro group due to its easy availability, environmental safety, and low cost. It has been used as a reagent in reductive cyclization reactions in the synthesis of aziridines, thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one, 3,6-dimethyl-9*H*-4,5,9-triazaphenanthren-10-one, and pyrrolo-[3,2-*b*] indole.[4] Moreover, it is also being used in the preparation of the chiral 3-substituted benzodiazepinone and pyrrolo[2,1-*c*][l,4]benzodiazepines derivatives.[5] α-Methylene-γ-butyrolactams are very important pharmacological active compounds which can also be synthesized by Fe/AcOH.[6] In addition to these, the reagent system was successfully applied to the synthesis of indole derivatives.[7] Furthermore, it is also being used in the synthesis of various quinoline derivatives from Baylis–Hillman adducts.[8]

On the other hand, quinoline derivatives are well-known structural scaffolds in medicinal chemistry. These derivatives have been found to possess useful pharmacological and biological activities including antimalarial, antiasthmatic, antihypertensive, antibacterial, and tyrosine kinase-inhibiting agents.[9] In addition to these, quinolines have been used for the preparation of nano- and meso-structures with enhanced electronic and photonic properties.[10] Moreover, quinoline-based polymers find applications in the fields of electronics, optoelectronics, and nonlinear optics.[11] All the above-described facts indicate that the synthesis of quinolines is an important and useful task in organic chemistry and hence a number of synthetic strategies including Skraup, Doebner–von Miller, Friedlander, Camps Combes, Conrad–Limpach–Knorr Gould–Jacobs reaction, and Meth–Cohn have been developed for the construction of these 'privileged' structural motifs.[12] Most of the known procedures are associated with several short comings with respect to the formation of side product(s) and the use of toxic solvents and expensive catalysts. Hence the development of a more convenient method for the synthesis of quinoline derivatives is still a welcoming topic in organic synthesis.

In continuation to our work on Fe/AcOH-mediated reductive cyclization of nitro derivatives,[13] herein we report the synthesis of quinolines through reductive degradation of Michael adducts obtained from 1-nitro-2-(2-nitrovinyl)benzenes and ketones.

2. Results and discussions

Recently, we reported the reaction of Michael adduct derived from indole and 1-nitro-2-(2-nitrovinyl)benzene in the presence



Scheme 1. Examples of carbon degradation during the product formation.

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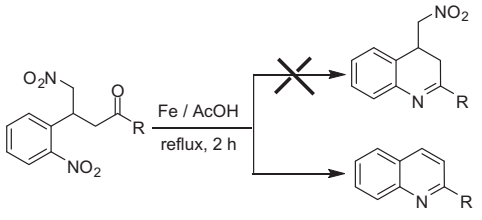
of Fe/AcOH to obtain the 3,3′-bis-indoles in high yields.[13b] This result prompted us to study the reaction further by replacing indoles with other C-nucleophiles such as ketones. We anticipated the formation of 2-methyl-4-(nitromethyl)-3,4-dihydroquinoline derivatives from the reductive cyclization of a Michael adduct derived from 1-nitro-2-(2-nitrovinyl)benzene and acetone. Surprisingly no trace of 2-methyl-4-(nitromethyl)-3,4-dihydroquinoline was observed, rather the 2-methyl quinoline observed as the sole product (Scheme 2). Being buoyant by this result we focused our attention to study this reaction with various 1-nitro-2-(2-nitrovinyl) benzenes and a variety of ketones containing α-hydrogen.

In preliminary experiments, 4-nitro-3-(2-nitrophenyl)butan-2-one was treated with Fe/AcOH at reflux for 2 h to obtain 2-methylquinoline in excellent yield. To extend the scope of the reaction further, we investigated the reaction of various Michael adducts obtained from the reaction of 1-nitro-2-(2-nitrovinyl)benzene with a variety of ketones. Under the present reaction conditions, the Michael adducts of a 1-nitro-2-(2-nitrovinyl)benzene and acyclic ketones reacted to produce 2-alkyl quinoline derivatives in good yields (Table 1).

Regardless of the nature of the functional group present on the phenyl moiety of the Michael adducts, we got a comparable yield in all cases. On the other hand, an inseparable mixture of the Michael adducts was obtained from 1-nitro-2-(2-nitrovinyl)benzene and heptan-2-one. This crude mixture was further treated with Fe/AcOH at reflux for 2 h affording the corresponding two quinoline derivatives, which were easily separated by column chromatography. Unfortunately, we did not obtain the expected 4-(nitromethyl)-3,4-dihydroquinoline derivatives in any of these reactions. However, we obtained equally interesting and biological important molecules such as 2-methyl quinoline derivatives.

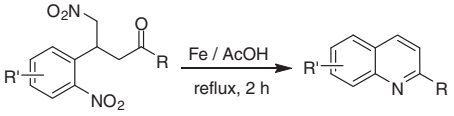
Encouraged by the results obtained with Michael adducts of acyclic ketones, we further investigated the reactions with the Michael adducts derived from the cyclic ketones with different 1-nitro-2-(2-nitrovinyl) benzene derivatives. Analogous to the previous case, the substitution on the aromatic ring had no influence on the outcome of the reaction, as systems substituted with neutral (Table 2, entries 1, 4, 6, 7, and 9), electron-withdrawing (entries 3 and 8), or electron-releasing groups (entries 2 and 5) provided similar results. It is interesting to note that the reaction of the five-membered and six-membered cyclic ketones similarly provides the corresponding tricyclic compounds in good yields (entries 1–6). The substrates containing oxygen and sulfur ring remained intact under the present reaction condition. It is note worthy that acid-sensitive group such as methoxy (entries 2 and 5) survived under these conditions.

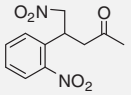
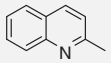
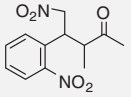
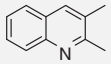
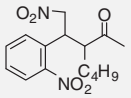
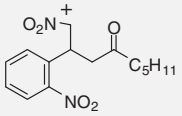
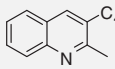
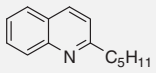
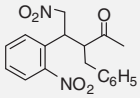
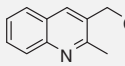
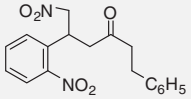
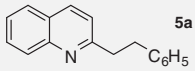
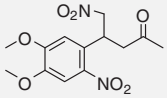
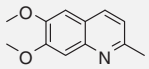
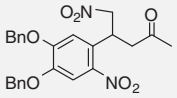
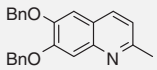
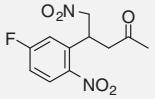
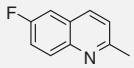
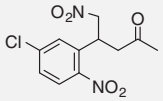
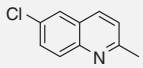
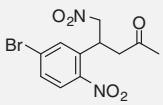
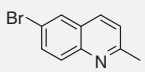
The mechanism for the formation of quinoline derivatives may be through the reductive cyclization of 2-(2-nitro-1-(2-nitrophenyl)ethyl) cyclohexanone (**1**), and followed by loss of a nitro methane or methylamine. The driving force here is aromatization to form larger conjugated system. We envisioned two pathways to form quinoline derivatives from **1** (Scheme 3). Among them the first one involves the reduction of an aromatic nitro group to amine in the presence of iron/acetic acid which further undergoes



Scheme 2. Reaction of 4-nitro-3-(2-nitrophenyl)butan-2-one with Fe/AcOH.

Table 1
The reaction of various Michael adducts with Fe/AcOH to form quinoline derivatives[15,16]



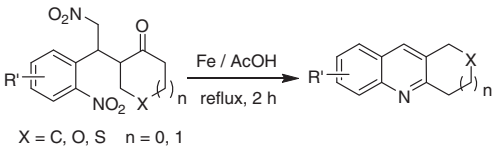
Entry	Substrate[a]	Product	Yield%[b]
1		 **1a**	79
2		 **2a**	81
3	 + 	 **3a**  **3b**	43 41
4		 **4a**	85
5		 **5a**	82
6		 **6a**	83
7		 **7a**	83
8		 **8a**	80
9		 **9a**	80
10		 **10a**	81

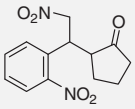
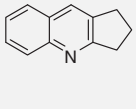
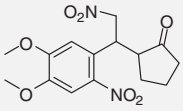
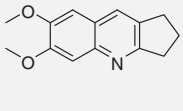
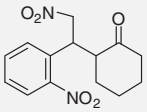
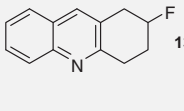
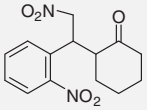
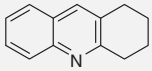
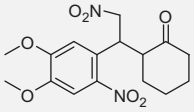
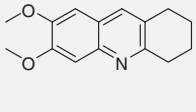
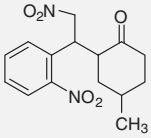
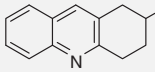
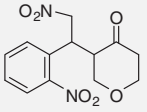
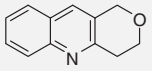
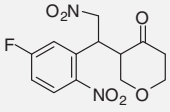
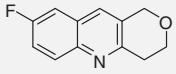
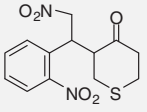
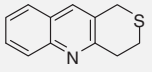
[a] Starting materials were prepared by the known procedure.[14]
[b] Isolated yields.

cyclization to form intermediate **A**. The intermediate upon losing nitro methane forms the quinoline moiety. Another alternative approach may be in the presence of iron/acetic acid in which both the nitro groups present in compound **1** reduce to its corresponding amines followed by the cyclization to form intermediate **B**. The intermediate B gets protonated and lose as the stable methyl ammonium acetate to form quinoline derivatives. The details of the mechanism are shown in Scheme 3.

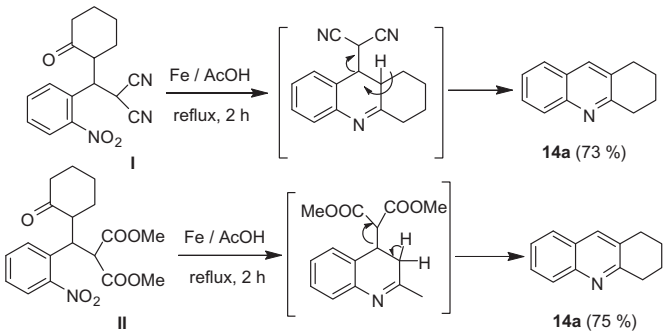
Employing similar reaction conditions (Fe/AcOH) with 2-((2-nitrophenyl) (2-oxocyclohexyl)methyl) malononitrile and dimethyl 2-((2-nitrophenyl) (2-oxocyclohexyl)methyl) malonate also afforded similar quinoline derivatives by the loss of a malon-

Table 2
The reaction of various Michael adducts with Fe/AcOH to form tricyclic quinoline derivatives[15,16]



Entry	Substrate[a]	Product	Yield %[b]
1		 **11a**	83
2		 **12a**	82
3		 **13a**	81
4		 **14a**	81
5		 **15a**	83
6		 **16a**	83
7		 **17a**	81
8		 **18a**	83
9		 **19a**	84

[a] Starting materials were prepared by the known procedure.[14].
[b] Isolated yields.



Scheme 4. Plausible mechanistic route for the formation of quinoline derivative.

onitrile, dimethyl malonate, respectively, which is presented in Scheme 4.

Itoh et al. reported that the reaction of benzylidene malononitriles and β-nitrostyrenes with *o*-phenylene diamines in boiling ethanol produced the 2-phenylbenzimidazolines.[3c] In this reaction, they found the elimination of nitromethane or malononitrile during the product formation. Based on our experimental results and the literature reports, we expect that both the pathways are possible for the formation of quinolines.

In conclusion, we have described a new degradation protocol which results in the formation of quinoline derivatives. The overall reactions involved the use of mild reaction conditions and an inexpensive reducing reagent (Fe/AcOH). The fact that the reactions were clean and devoid of side reaction products constitutes additional attractive feature of this method. In summary, this method finds an alternative procedure for the synthesis of quinoline derivatives to the reported protocols.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.063.

References and notes

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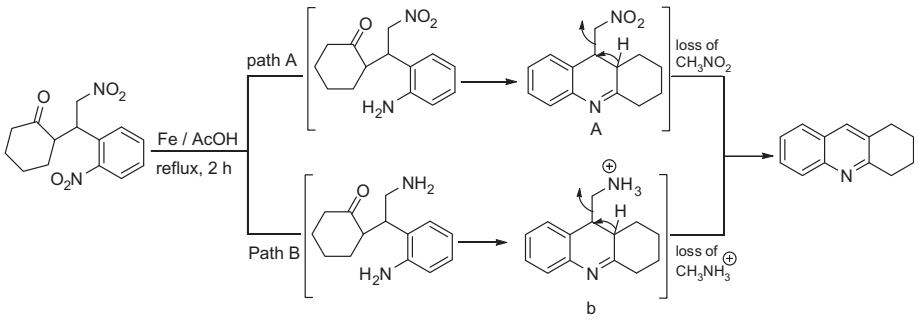

Scheme 3. Plausible mechanistic route for the formation of quinoline derivative.

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15. To a stirred solution of 4-nitro-3-(2-nitrophenyl)butan-2-one **1** (1 mmol) in acetic acid (5 mL), powdered Fe (6 mmol) was added and the reaction mixture was refluxed for 2 h. The mixture was cooled to room temperature and the acetic acid was removed under reduced pressure, EtOAc (10 mL) was added, then the mixture was stirred for 2 min and then filtered to remove any iron impurities. The insoluble iron residue was washed with EtOAc (10 mL). The filtrate and washings were combined and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate) to yield the expected product.
16. *Spectral data: 1,2,3,4-tetrahydroacridine* (**11a**): White solid; mp: 46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.61–7.57 (m, 1H), 7.44–7.40 (m, 1H), 3.12 (t, J = 6.5 Hz, 2 H), 2.97 (t, J = 6.1 Hz, 2H), 2.02–1.96 (m, 2H), 1.92–1.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 146.4, 134.8, 130.7, 128.3, 128.1, 127.0, 126.7, 125.3, 33.4, 29.0, 23.0, 22.7. MS (EI) (*m/z*) (relative intensity) 183(M^+, 100), 182(40). HRMS calcd for $C_{13}H_{13}N$ (M^+) 183.1043 found 183.1037. *8-Fluoro-3,4-dihydro-1H-pyrano[4,3-b]quinoline* (**15a**): White solid; mp: 107–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.2, 5.3 Hz, 1H), 7.70 (s, 1H), 7.45–7.40 (m, 1H), 7.34 (dd, J = 8.8, 2.6 Hz, 1H), 4.95 (s, 2H), 4.17 (t, J = 5.9 Hz, 2H), 3.21 (t, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, J = 246.0 Hz), 154.4, 144.1, 130.9 (d, J = 10.0 Hz), 130.3 (d, J = 5.0 Hz), 129.5, 127.3 (d, J = 10.0 Hz), 119.4 (d, J = 26.0 Hz), 110.1 (d, J = 21.0 Hz), 67.7, 65.9, 32.6. MS (EI) (*m/z*) (relative intensity) 203 (M^+, 100), 173(27). HRMS calcd for $C_{12}H_{10}FNO$ (M^+) 203.0741 found 203.0735.