

Ceric Ammonium Nitrate (CAN) Mediated Novel Dimerizations of 4-Hydroxyquinolin-2(1*H*)-ones: the First Example of Reactions of Oxygen-centered Radicals from 1,3-Dicarbonyl Compounds

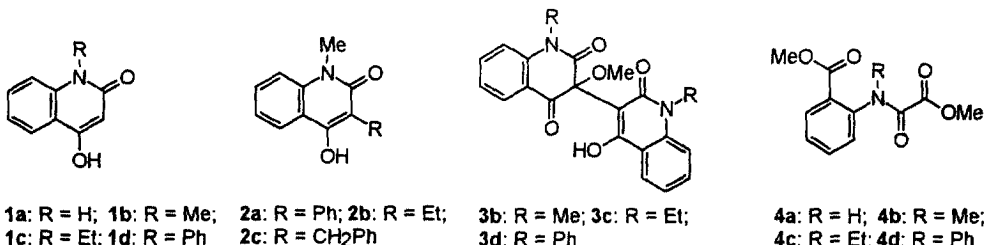
Jia-Hai Ye, Jie Xue, Ke-Qing Ling, Jian-Hua Xu*

Department of Chemistry, Nanjing University, Nanjing 210093, P. R. China

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Abstracts Reactions of 4-hydroxyquinolin-2(1*H*)-ones (**1**) and 3-alkylated 4-hydroxyquinolin-2(1*H*)-ones (**2**) with CAN in methanol gave quinolin-2(1*H*)-one dimers **3**, **10** and **11** with C-C and C-O linkages between the two nitrogen containing six-member rings, respectively, showing the ambident reactivities of α, α' -dicarbonylalkyl radicals as carbon- and oxygen-centered radicals.
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As an integrated part of the rapidly growing area of radical methodology in organic syntheses,¹ the application of carbon centered free radicals derived from high valent metal salt mediated redox processes has emerged as a powerful tool for C-C bond formation in recent years.² One of the most frequently used reagents for the oxidative generation of carbon centered radicals is the strong one electron oxidant ceric ammonium nitrate (CAN),^{2a,b} which has proved especially efficient in generating α -carbonylalkyl radicals from enolizable ketones³ and α, α' -dicarbonylalkyl radicals from β -dicarbonyl compounds.⁴ Research work in this field has mainly been focused on electrophilic addition reactions of the carbon radicals generated from simple acyclic and alicyclic ketones and β -dicarbonyl compounds to unsaturated substrates such as alkenes, and this synthetic methodology has been successfully used in a variety of C-C bond formation reactions for the construction of different carbocyclic^{4,5} and heterocyclic^{4,6} frameworks and for the derivatization of β -dicarbonyl compounds at the 2-position.^{4,7} However, although it is natural to anticipate that structural changes around the 1,3-dicarbonyl moiety should result in a wide range of different reactivities of the cation radicals and radicals derived from them, there has, so far, been very few reports on CAN mediated reactions of 1,3-dicarbonyl compounds with complicated structural features such as 2-substitution or dicarbonyls based on an amide.⁸



4-Hydroxyquinolin-2(1*H*)-ones **1** and the 3-alkylated derivatives **2** are enolizable heterocyclic β -dicarbonyl compounds which include an amide. These compounds have a wide range of biological activities⁹ and are biogenetic or synthetic precursors for many naturally occurring quinoline^{10a} and dimeric quinoline alkaloids.^{10b,c} Many research efforts have therefore been drawn to this class of compounds to elaborate the structure with the aim of preparing new derivatives with potential medical applications.^{9,10} We report here the CAN mediated dimerization reactions of **1** and **2** giving dimeric quinoline derivatives with C-C and C-O linkage

between the two nitrogen containing six-member rings. These dimerization reactions are a new reaction mode¹¹ for CAN induced transformations of organic compounds and display the special reactivity of the radicals oxidatively generated from 1,3-dicarbonyl compounds as both carbon- and oxygen-centered radicals.

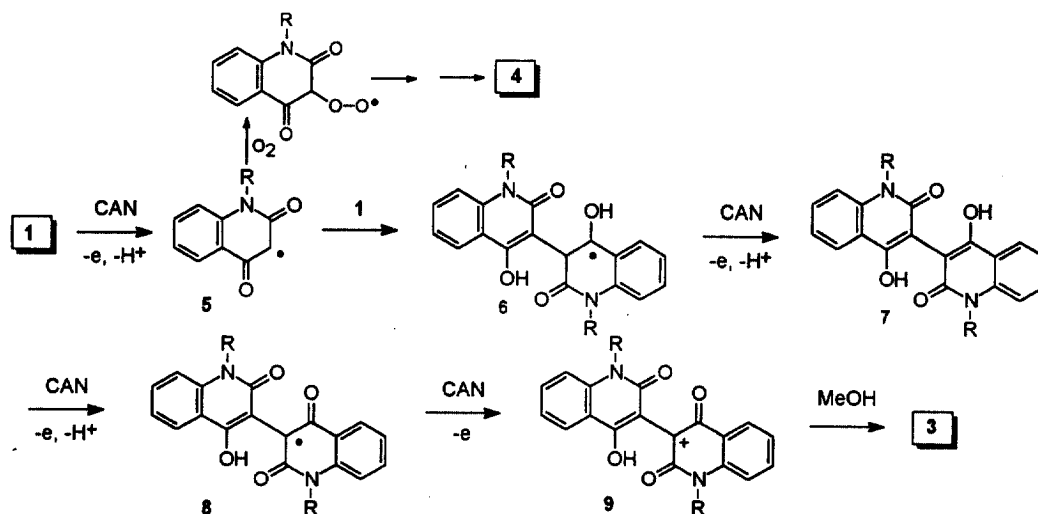
Table 1 Reactions of 1 and 2 with CAN in Methanol

Entry	Compound	E_p^{ox} (SCE, CH ₃ CN) (v) ^a	Reaction Time (h)	Products and Yields(%) ^b
1	1a		1	4a (94)
2	1b	1.53	0.5	3b (69), 4b (28)
3	1c	1.55	0.5	3c (60), 4c (31)
4 ^c	1c	1.55	1	3c (83), 4c (9)
5	1d	1.59	0.5	3d (57), 4d (24)
6	2a	1.58	1	10a (46), 11a (42)
7	2b	1.53	1	10b (25), 11b (55)
8	2c	1.56	1	10c (21), 11c (75)

^a Peak potentials measured by cyclic voltammetry in CH₃CN with Bu₄NClO₄ (0.1 mol dm⁻³) as supporting electrolyte vs SCE. ^b Yield of pure product based on consumed 1 or 2. ^c Reaction carried out under deaerated condition by purging with dry argon for half an hour prior to and throughout the reaction.

Reaction of 1b (0.03 mol dm⁻³) with 2 equiv. of CAN in methanol at room temperature afforded the methoxylated dimer 3b¹² in 69% yield together with the methyl ester of *N*-(2-methoxycarbonylphenyl)oxalamic acid 4b in 28% yield. As the reaction proceeded, product 3b precipitated from solution. Reactions of 1c and 1d with CAN under the same conditions gave results similar to 1b, with the corresponding dimers 3c and 3d as major products, respectively (Table 1). On the other hand, similar treatment of 1a with CAN (2 equiv.) in methanol gave the methyl *N*-(2-methoxycarbonylphenyl)oxalamate 4a as the sole product in 94% yield.

Scheme 1



According to the stoichiometry of the reactions and the structure of the products, 3 and 4 are proposed to be formed *via* mechanisms shown in Scheme 1. In accord with a fully enolized structure in solution, compounds 1b-1d have relatively low oxidation potentials (See Table 1). Single electron transfer (SET) from 1 to CAN generates the cation radical of 1, which are strongly acidic¹³ and undergo rapid proton loss to give the α, α' -dicarbonyl radical 5. Product 4 is derived from trapping of 5 by dissolved oxygen in solution. Similar oxygen trapping of the α, α' -dicarbonyl radicals derived from simple acyclic β -dicarbonyl compounds has been observed.¹⁴ Therefore, the yield of the dimeric products 3 could be significantly raised at the expense of 4 when

the reactions were carried out under deaerated conditions (entry 4, Table 1). The radical intermediate **5** could otherwise attack a neutral molecule of **1** to give the radical **6**. From **6**, two successive SET-deprotonation sequences lead to **9**,¹⁵ which on trapping by methanol gave **3**.

The formation of the oxalamates **4** are of synthetic value,¹⁶ and it was found that further reaction of **3**, dissolved in chloroform, with CAN gave **4** in 69% yield.

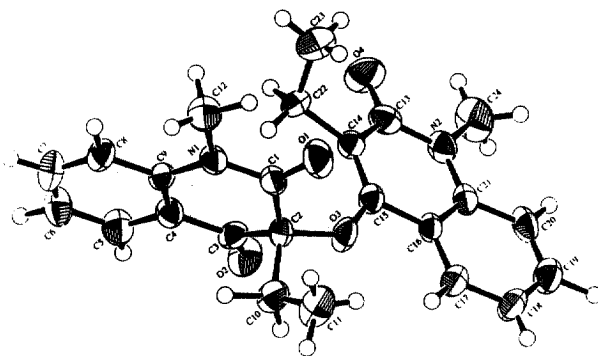
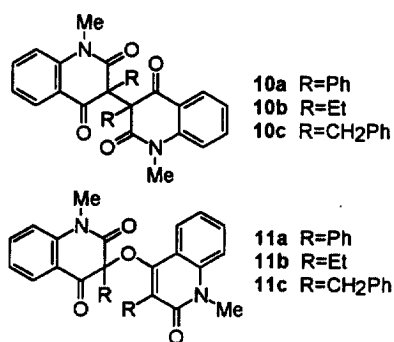
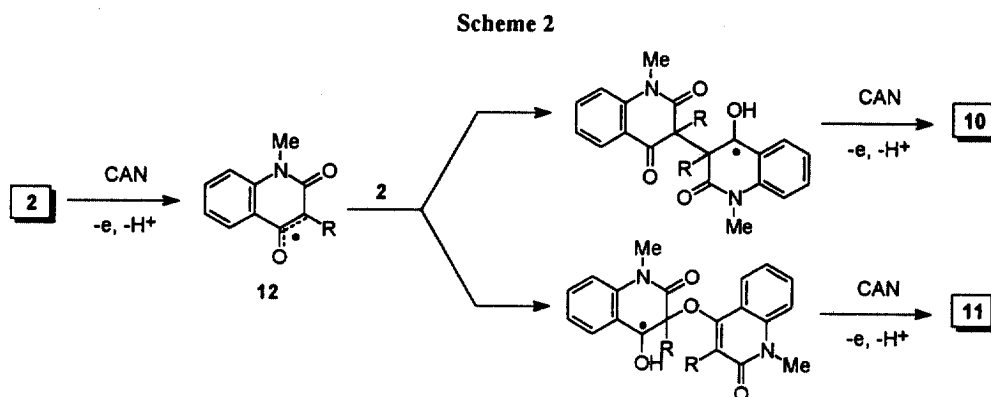


Fig. 1 ORTEP Drawing of **11b**

We have further investigated the reactions of 3-alkylated 4-hydroxyquinolin-2(1*H*)-ones **2** with CAN and found that, reaction of **2a** with CAN in methanol at room temperature gave two dimeric products **10a** and **11a**¹⁷ (Table 1). Since the assignment of the structure of **11** from spectral data (IR, ¹HNMR and MS) is not straightforward, an X-ray crystallographic analysis of **11b** (*vide infra*) has been undertaken and definitely established the structure as shown in Fig.1. Reactions of **2b** and **2c** with CAN under the same conditions similarly gave the corresponding dimers **10b**, **11b**, **10c** and **11c** respectively (Table 1).



The formation of product **11** is especially noteworthy since the attack of α -carbonylalkyl or α, α' -dicarbonylalkyl radicals to alkenes as an oxygen-centered radical is unprecedented in CAN mediated oxidative additions of enolizable ketones and β -dicarbonyl compounds with alkenes. This ambident reactivity of the α, α' -dicarbonylalkyl radicals as carbon- and oxygen-centered radicals is derived from the fact that spin density is delocalized between C₃ and the oxygen atom in the α, α' -dicarbonyl radical intermediate **12** (Scheme 2). Therefore, both sites could act as radical centers to add to a molecule of **2** to lead to the formation of **10** and **11** simultaneously. It is further noted that the product ratio **10/11** is sensitive to the steric effect of the substituent at C₃ and changes from 1.10 for **2a** to 0.28 for **2c**. This showed that in these radical addition reactions, the C₃-centered radical in **12** is more sterically demanding than the oxygen-centered radical, therefore, in the case of **2b** and **2c**, steric hindrance around C₃ by the bulky substituent caused the radical addition to **2** to take place from

the oxygen atom of **12** preferentially and gave **11** as the main product.

In summary, reactions of 4-hydroxyquinolin-2(1*H*)-ones **1b-1d** and 3-alkylated 4-hydroxyquinolin-2(1*H*)-ones **2a-2c** with CAN in methanol led to the efficient dimerization of the substrates. These reactions showed that, 2-substituted 1,3-dicarbonylalkyl radicals have twofold reactivities to act as carbon- and oxygen-centered radicals simultaneously, and revealed the subtle effect of steric factors on the partitioning between the two reaction pathways of these delocalized radicals. In addition, these reactions provide straightforward and efficient access to dimeric quinolinone derivatives with C-C and C-O linkages between the two nitrogen containing six-member rings.

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References and Notes

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- Typical procedures for the reaction of **1** and **2** with CAN: A solution of **1** (or **2**) (0.03 mol dm⁻³) and 2 equiv. (or 1 equiv. for **2**) of CAN in methanol was magnetically stirred for the time indicated in the table at room temperature. The solvent was removed *in vacuo*, the residue subjected to silica gel column chromatographic separation with petroleum ether (b.p. 60-90 °C)-ethyl acetate as eluents. Compound **3b**: Colourless prisms (from CH₃CO₂Et), m.p. 220-222 °C. IR (KBr) 3280, 1695, 1666, 1642, 1600, 1580, 1468, 1352, 1300, 1068, 762 cm⁻¹. ¹HNMR (CDCl₃, 500MHz, TMS) δ 3.45 (s, 3H, CH₃), 3.49 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 7.2-8.2 (m, 8H, ArH), 10.17 (s, 1H, OH). m/z (EI) (relative intensity) 378 (M⁺, 5.75), 363 (38.18), 331 (61.39), 290 (7.67), 202 (34.07), 134 (base). (Anal. Calcd. for C₂₁H₁₈N₂O₅: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.58; H, 4.83; N, 7.27).
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- Compound **11b**: Yellow prisms (from CH₃CO₂Et). m.p. 188-190 °C. IR (KBr) 3040, 3000, 2980, 2950, 1720, 1674, 1622, 1596, 1500, 1490, 1464, 1354, 1260, 1186, 1162, 1098, 768, 758 cm⁻¹. ¹HNMR (CDCl₃, 60MHz, TMS) δ 0.80 (t, 3H, CH₃, J = 7 Hz), 0.90 (t, 3H, CH₃, J = 7 Hz), 1.8-2.5 (m, 4H, 2×CH₂, J = 7 Hz), 3.33 (s, 3H, CH₃), 3.53 (s, 3H, CH₃), 6.8-8.1 (m, 8H, ArH). m/z (EI) (relative intensity) 404 (M⁺, 0.62), 214 (1.8), 203 (base), 188 (50), 134 (15). (Anal. Calcd. for C₂₄H₂₄N₂O₄: C, 71.29; H, 5.94; N, 6.93. Found: C, 71.49; H, 5.80; N, 6.88).