A Facile CAN-Mediated Transformation of Acetoacetamides to Oxamates†

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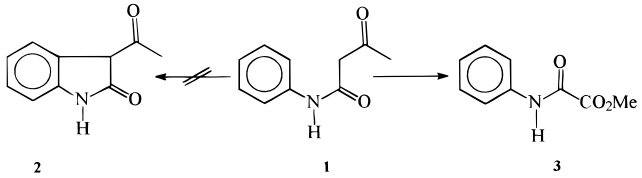
Introduction

Carbon−carbon bond-forming reactions mediated by one-electron oxidants have been of considerable topical interest.[1−4] Early investigations by Heiba and Dessau,[5] Baciocchi,[6,7] and the more recent studies in our laboratory[8−12] and elsewhere[13] have convincingly demonstrated that cerium(IV) ammonium nitrate (CAN) is an exceptionally useful reagent for accomplishing intermolecular C−C bond formation. In this context, it was of interest to probe the usefulness of CAN in intramolecular reactions. With this objective and with the expectation that an oxindole derivative **2** would result from acetoacetanilide **1**, the latter was treated with CAN in methanol. Surprisingly, no cyclization occurred, and instead the corresponding oxamate **3** was obtained as the only isolable product in 51% yield.

Scheme 1

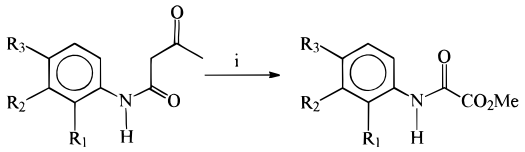


Although the expected reaction did not occur, the facility of formation of the oxamate **3** prompted us to examine the generality of the reaction from the vantage point of using it as a synthetic method for oxamates.

Results and Discussions

With the reasonable assumption that oxygen takes part in the reaction leading to the oxamate **3**, the reaction of **1** with CAN was repeated in an atmosphere of oxygen. In this case, the yield of the oxamate increased to 70%. When the experiment was performed in the absence of oxygen, oxamate formation was not observed; instead, a product identified as a dimer of **1** was isolated. Similar dimerization reactions of 1,3-dicarbonyl compounds have been reported.[14] The reaction requires 2 equiv of CAN, and on using 1 equiv of CAN only half of the starting material was consumed. A number of other acetoacetanilides were subjected to the CAN oxidation under oxygenated conditions, and in all cases the oxamate was obtained in high yields. The results are summarized in Scheme 2.

Scheme 2

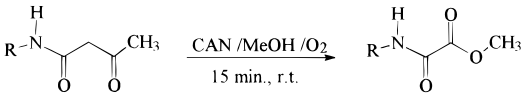


1a R_1=R_2=R_3=H	**3a**(70%)
1b R_1=R_2=H, R_3=CH_3	**3b**(84%)
1c R_1=R_2=H, R_3=OMe	**3c**(78%)
1d R_1=R_2=H, R_3=Cl	**3d**(74%)
1e R_2=R_3=H, R_1=CH_3	**3e**(85%)
1f R_2=R_3=H, R_1=OMe	**3f**(83%)
1g R_2=R_3=H, R_1=CO_2Me	**3g**(70%)
1h R_1=R_3=H, R_2=Br	**3h**(77%)

(i) CAN, MeOH, O_2, r.t, 15 min

It appears that acetoacetamides derived from aliphatic amines are also susceptible to the oxidative transformation. For instance, cyclohexyl acetoacetamide when treated with CAN under the conditions described above transformed smoothly into the oxamate in 88% yield. A similar result was obtained with benzyl acetoacetamide also (Scheme 3). All the new compounds were characterized on the basis of spectral and analytical data.

Scheme 3

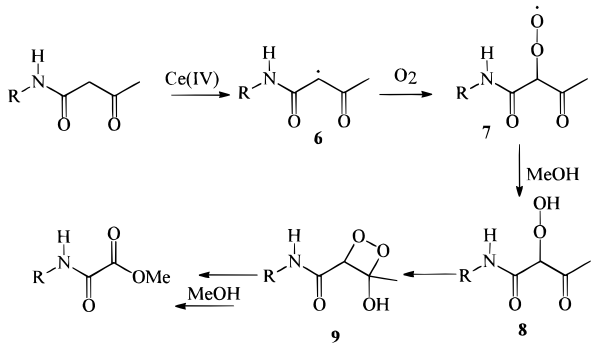


4a	R=Cyclohexyl	**5a (88%)**
4b	R=Benzyl	**5b (83%)**

i) CAN, MeOH, O_2, r.t, 15 min

A mechanistic rationale for the transformation described here may be presented as in Scheme 4. Oxidation

Scheme 4



of the dicarbonyl system by CAN would conceivably lead to the radical **6**. The latter can trap oxygen[15] leading to

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†This paper is dedicated with best regards to Professor Edward Piers on the occasion of his 60th birthday.

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the hydroperoxide **8**, which in turn can yield the dioxetane **9**. Fragmentation of the dioxetane to the aldehyde and oxidation of the latter in methanol can ultimately lead to the oxamate. The peroxy radical **7**, in principle, can abstract a hydrogen from the substrate, thus allowing a catalytic cycle to operate. However, there is no evidence for a catalytic process, and it has been confirmed that 2 equiv of CAN is required for the completion of the reaction. In experiments using less than 2 equiv of CAN, a proportionate amount of substrate remains unchanged. This may be rationalized by invoking the possibility that the peroxy radical is more likely to abstract the C−H proton from methanol, in a process assisted by CAN that is known to form a complex with methanol.[16]

Such oxidative fragmentation of 1,3-dicarbonyl systems is well precedented.[17,18]

The potential application of the reaction as a synthetic method for oxamates is worthy of note. It may be recalled that the existing methods for the synthesis of oxamates, viz., (i) carbonylation of amino alcohols using Pd (II) catalyst,[19] (ii) reaction of amines with oxalyl chloride,[20,21] and (iii) reaction of trichloroacetyl chloride[22] or diisopropyl oxalate,[23] all have certain limitations. It is therefore anticipated that the present method may serve as an alternative in the synthesis of oxamates. It is noteworthy that oxamate functionality is present in a number of therapeutically important compounds.[24,25] In addition, oxamates serve as key intermediates in the synthesis of bioactive 2,3-diketopiperazines.[26]

In conclusion, we have uncovered a facile conversion of acetoacetamides to oxamates that may serve as a convenient alternative to at least some of the conventional procedures for the latter.

Experimental Section

General Methods. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the external standards. Mass spectra were recorded under EI/HRMS (at 5000 resolution) using an Auto Spec. M mass spectrometer. Column chromatography was performed on silica gel (100−200 mesh). Solvents were distilled prior to use. The CAN used for the reactions was purchased from Aldrich Co. and was used without purification. Substituted acetoacetamides except **1a** and **1g** were prepared from substituted amines.[27] **1a** and **1g** were purchased from E. Merck. Co.

General Procedure for the Preparation of Oxamate (3a). To a solution of **1a** (500 mg, 2.82 mmol) in methanol saturated with oxygen was added an oxygenated solution of CAN (3.86 g, 7.05 mmol) in methanol while the reaction mixture was continuously being purged with oxygen. After 15 min, the reaction mixture was diluted with distilled water, extracted with dichloromethane (3 × 30 mL), washed with saturated brine, and dried over sodium sulfate. The residue obtained after the removal of solvent was chromatographed on a silica gel column to afford a white crystalline solid.

Spectral data of methyl *N*-phenyloxamate[28] (3a): white crystals; recrystallized from CH_2Cl_2−hexane; mp 111−113 °C; IR (KBr) ν_{max} 3351, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.889 (s, 1H, N*H*), 7.660−7.633 (d, 2H, J = 8.1 Hz, Ar*H*), 7.415−7.363 (m, 2H, Ar*H*), 7.229−7.204 (m, 1H, Ar*H*), 3.981 (s, 3H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.449, 153.779, 136.355, 129.166, 125.546, 119.983, 53.953; EIMS *m*/*z* M$^+$ 179.17.

Methyl *N*-(4-methylphenyl)oxamate (3b): white crystals, recrystallized from CH_2Cl_2−hexane; mp 145−147 °C; IR (KBr) ν_{max} 3337, 1729, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.874 (s, 1H, N*H*), 7.542−7.514 (d, 2H, J = 8.3 Hz, Ar*H*), 7.184−7.158 (d, 2H, J = 8 Hz, Ar*H*), 3.954 (s, 3H, OC*H*$_3$), 2.334 (s, 3H, ArC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.523, 153.348, 135.123, 133.817, 129.620, 119.789, 53.753, 20.920. Anal.Calcd for $C_{10}H_{11}NO_3$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.17; H, 5.49; N, 7.2.

Methyl *N*-(4-methoxyphenyl)oxamate (3c): white crystals, recrystallized from CH_2Cl_2−hexane; mp 145−147 °C; IR (KBr) ν_{max} 3353, 3332, 1729, 1697, 1547 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.861 (s, 1H, N*H*), 7.581−7.551 (d, 2H, J = 8.88 Hz, Ar*H*), 6.909−6.879 (d, 2H, J = 8.9 Hz, Ar*H*), 3.946 (s, 3H, OC*H*$_3$), 3.799 (s, 3H, ArOC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.623, 157.184, 153.242, 129.274, 121.369, 114.303, 55.349, 53.827. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.3; N, 6.7. Found: C, 57.51; H, 5.1; N, 6.68.

Methyl *N*-(4-chlorophenyl)oxamate (3d): white crystals, recrystallized from CH_2Cl_2−hexane; mp 164−166 °C; IR (KBr) ν_{max} 3349, 1745, 1690, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.885 (s, 1H, N*H*), 7.622−7.592 (d, 2H, J = 8.8 Hz, Ar*H*), 7.336−7.326 (d, 2H, J = 8.8 Hz, Ar*H*), 3.975 (s, 3H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.303, 153.455, 134.862, 130.794, 129.349, 121.041, 54.068. Anal. Calcd for $C_9H_8NO_3Cl$: C, 50.6; H, 3.77; N, 6.56. Found: C, 50.77; H, 3.56; N 6.53.

Methyl *N*-(2-methylphenyl)oxamate (3e): white crystals, recrystallized from CH_2Cl_2−hexane; mp 76−78 °C; IR (KBr) ν_{max} 3382, 1716, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.83 (s, 1H, N*H*), 8.019−7.993 (d, 1H, J = 7.86 Hz, Ar*H*), 7.279−7.204 (m, 2H, Ar*H*), 7.151−7.128 (d, 1H, J = 7.05 Hz, Ar*H*), 3.977 (s, 3H, OC*H*$_3$), 2.328 (s, 3H, ArOC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.765, 153.565, 134.427, 130.690, 128.307, 127.182, 126.000, 121.792, 54.036, and 17.596; HRMS calcd for $C_{10}H_{11}NO_3$ 193.073893, found 193.075254; EIMS M$^+$ + 1 194 (5), M$^+$ 193 (45).

Methyl *N*-(2-methoxyphenyl)oxamate (3f): white crystals, recrystallized from CH_2Cl_2−hexane; mp 72−74 °C; IR (KBr) ν_{max} 3391, 1785, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 9.483 (s, 1H, N*H*), 8.420−8.390 (dd, 1H, J = 7.9 Hz, J = 1.1 Hz Ar*H*), 7.135−7.109 (m, 1H, Ar*H*), 7.025−6.999 (m, 1H, Ar*H*), 6.934−6.907 (d, 1H, J = 8 Hz, Ar*H*), 3.97 (s, 3H, OC*H*$_3$), 3.923 (s, 3H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.352, 153.429, 148.490, 126.037, 125.374, 121.107, 119.973, 110.146, 55.813, 53.925; EIMS M$^+$ + 1 210 (38) M$^+$ 209 (100). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 56.99; H, 5.32; N, 6.08.

Methyl *N*-(2-carbomethoxyphenyl)oxamate (3g): white crystals, recrystallized from CH_2Cl_2−hexane; mp 150−152 °C; IR KBr ν_{max} 3259, 1729, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 12.591 (s, 1H, N*H*), 8.761−8.733 (d, 1H, J = 8.25 Hz, Ar*H*),

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8.098−8.068 (dd, 1H, J = 1.2, 7.9 Hz, Ar*H*), 7.637−7.581 (m, 1H, Ar*H*), 7.218−7.165 (m, 1H, Ar*H*), 4.00 (s, 3H, OCH_3), 3.985 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 168.067, 161.060, 154.335, 139.638, 134.708, 131.086, 123.993, 120.593, 116.221, 53.858, 52.592. Anal. Calcd for $C_9H_8NO_5$: C, 55.7; H, 4.67; N, 5.9. Found: C, 55.69; H, 4.71; N, 6.04.

Methyl *N*-(3-bromophenyl)oxamate (3h): white crystals, recrystallized from CH_2Cl_2−hexane; mp 110−111 °C; IR (KBr) ν_{max} 3337, 1729, 1706, cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 8.881 (s, 1H, N*H*), 7.850 (s, 1H, Ar*H*), 7.610−7.584 (d, 1H, J = 7.7 Hz, Ar*H*), 7.335−7.214 (m, 2H, Ar*H*), 3.794 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.319, 153.591, 137.640, 130.643, 128.729, 123.008, 122.895, 118.420, 104.907,54.205; LRMS M$^+$ + 2 259 (80), M$^+$ 257 (77); HRMS (EI) calcd for $C_9H_8NO_3Br$ 258.966708, found 258.966958.

Methyl *N*-cyclohexyloxamate (5a): white crystals, recrystallized from CH_2Cl_2−hexane; mp 77−79 °C; IR (KBr) ν_{max} 3267, 2935, 2854, 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 6.963 (s, 1H, N*H*), 3.894 (s, 3H, OCH_3), 3.843−3.744 (m, 1H, >C*H*NH), 1.969−1.930 (m, 2H, CH_2), 1.774−1.629 (m, 3H, CH_2), 1.461−1.340 (m, 2H, CH_2), 1.293−1.138 (m, 3H, CH_2); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.555, 155.211, 53.491, 48.901, 32.657, 25.447, 24.720; HRMS calcd for $C_9H_{15}NO_3$ 185.105194, found 185.106430; M$^+$ 185 (2.3).

Methyl *N*-benzyloxamate (5b): white crystals, recrystallized from CH_2Cl_2−hexane; mp 116−118 °C; IR (KBr) ν_{max} 3270, 2952, 1738, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 7.395 (s, 1H, N*H*), 7.371−7.265 (m, 5H, Ar*H*), 4.522−4.502 (d, 2H, J = 6 Hz, CH_2NH), 3.890 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$−CCl_4, v/v, 3:1) δ 161.120, 156.070, 136.728, 128.874, 127.960, 53.409, 43.956.

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Supporting Information Available: Copies of carbon NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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