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Substituent Effects on Competitive Release of Phenols and 1,3-Rearrangement in α-Keto Amide Photochemistry

Chicheng Ma and Mark G. Steinmetz*

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201-1881

mark.steinmetz@marquette.edu

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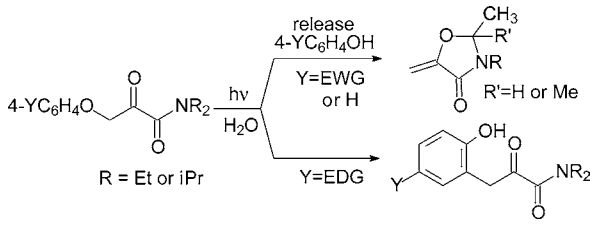
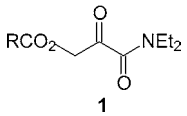
ABSTRACT



Photolysis of α-keto amides bearing 4-YC_6H_4O leaving groups at the position α to the keto group efficiently produces high yields of phenols when Y is an electron-withdrawing group or H. The photoelimination likely involves cleavage of zwitterionic intermediates produced via excited-state hydrogen transfer. When Y is an electron-donating group, competing excited-state ArO–C_α bond scission to radicals occurs, followed by recombination to give 1,3-photorearrangment products.

Photoremovable protecting groups and cage compounds have found widespread use in applications in biological and materials sciences.[1,2] Because relatively few basic types of photochemical cleavage reactions are employed in these applications,[3−6] we have been exploring a new approach for photochemical release of leaving groups that involves cleavage of zwitterionic intermediates. The rapid (<30 ms) and efficient (Φ = ca. 0.3) photoelimination of carboxylate groups from **1** in aqueous solution,[7] for example, is thought



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to involve heterolytic cleavage of zwitterionic intermediates such as **2**, produced upon hydrogen transfer in the excited

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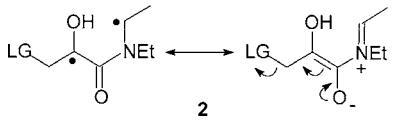
state. Analogous intermediates possessing zwitterionic character have often been postulated to account for the photoreactivity of α-keto amides that lack leaving groups.[8,9]



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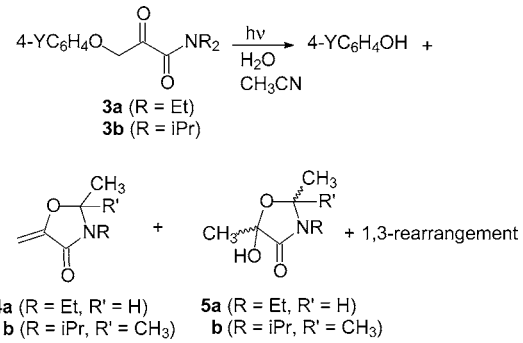
In this paper we show that the photocleavage reaction of α-keto amides can be expanded to include a variety of *para*-substituted phenolic leaving groups in **3a,b** (Scheme 1).

Scheme 1



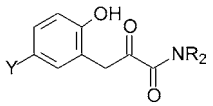
Competing 1,3-photorearrangement of the phenolic group is observed, and the ratio of cleavage to 1,3-rearrangement is controlled by the remote *para* substituent.

Photolyses (>300 nm) of *N*,*N*-diethyl- and *N*,*N*-diisopropyl α-keto amides **3a,b**[10] were conducted in air-saturated solutions of 33% D_2O in CD_3CN. When the *para* substituent Y on the phenolic group 4-YC_6H_4O was an electron-withdrawing group (Y = CN, CF_3) or just H, the major products were the corresponding *para*-substituted phenols and the cleavage coproducts methyleneoxazolidinone **4a,b** and hemiacetal **5a** according to ^1H and ^{13}C NMR analyses of the photolyzates (Scheme 1).[11] The photochemical formation of compound **5b** from the *N*,*N*-diisopropyl amide **3b** was never observed. The major cleavage coproducts **4a,b** were isolated in pure form by silica gel chromatography and fully characterized spectroscopically.[12,13] The highly water-soluble hemiacetal product **5a** was isolated and characterized previously.[7] Substitution by Y = CH_3 or OCH_3 led to progressively lower yields of 4-YC_6H_4OH and **4**, and the formation of 1,3-photorearrangement products **6**[14] was observed. The chemical yields for representative examples are given in Table 1.

Table 1. Yields of Photoproducts in 33% D_2O in CD_3CN[a]

	yield, %			
reactant	unreacted **3**	ArOH	**4**	**6**
3a, Y = CN	0	98	47[b]	0
3a, Y = H	41	52[c]	43	0
3a, Y = OCH_3	22	<5	<5	64
3b, Y = CN	17	76	79	0
3b, Y = H	40	59	60	0
3b, Y = OCH_3	22	<5	<5	74

[a] Yields determined by NMR spectroscopy with DMSO as standard. [b] Yield of **5a** was 31%. [c] Yields determined by HPLC analysis using an internal standard and 254 nm UV detection.



6a (R = Et)
b (R = iPr)

It is noteworthy that no deuterium is incorporated from the D_2O into the terminal position of the methylene group of **4a,b**, whereas in **5a**, the corresponding CH_3 group becomes monodeuterated. The absence of deuterium in **4** indicates that an enol-keto tautomerization does not occur prior to its formation. Instead, we suspect that the cyclization to **4** is assisted by deprotonation of the enol **7** by *para*-substituted phenolate anion in an initially formed ion pair (Scheme 2).

Product ratios and yields further suggest that as the basicity of the *para*-substituted phenolate leaving group decreases, the deprotonation and cyclization to **4** becomes sufficiently slow such that tautomerization of **7** to **8** can compete in the case of the *N*,*N*-diethyl derivative to give monodeuterated

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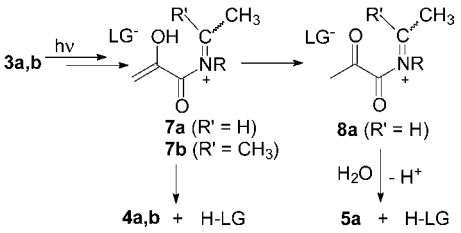
(11) Photolyses used an air-cooled 450-W medium-pressure mercury lamp equipped with a Pyrex filter sleeve. The air-saturated solutions were mounted externally beside the lamp in NMR tubes or 30-mL Pyrex tubes.

(12) Solutions of the reactants in air-saturated aqueous acetonitrile showed no evidence of hydrolysis or other reactions for periods of at least 1 week.

(13) (a) Compound **4a**: ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.49 (d, J = 5.4 Hz, 3 H), 3.21 (dq, J = 14, 7 Hz, 1 H), 3.69 (dq, J = 14, 7 Hz, 1 H), 4.56 (d, J = 2.4 Hz, 1 H), 4.90 (d, J = 2.4 Hz, 1 H), 5.44 (q, J = 5.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 13.25, 20.98, 35.18, 86.20, 86.89, 150.85, 160.72. (b) Compound **4b**: ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 6.6 Hz, 6 H), 1.53 (s, 6 H), 3.47 (sept, J = 6.6 Hz, 1 H), 4.46 (d, J = 2.1 Hz, 1 H), 4.83 (d, J = 2.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.73, 27.07, 46.53, 85.05, 95.32, 150.16, 159.70.

(14) (a) Compound **6a** (Y = OCH_3): ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H), 1.11 (t, J = 7.2 Hz, 3 H), 3.27 (q, J = 7.2 Hz, 2 H), 3.36 (q, J = 7.2 Hz, 2 H), 3.74 (s, 3 H), 3.95 (s, 2 H), 6.68 (d, J = 3.0 Hz, 1 H), 6.74 (dd, J = 3.0, 8.7 Hz, 1 H), 6.81 (d, J = 8.7 Hz, 1 H), 7.46 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 12.70, 14.79, 41.12, 42.73, 42.90, 56.07, 115.14, 116.33, 119.46, 120.45, 148.86, 153.98, 166.34, 196.39. (b) Compound **6b** (Y = OCH_3): ^1H NMR ($CDCl_3$) δ 0.99 (d, J = 6.9 Hz, 6 H), 1.32 (d, J = 6.9 Hz, 6H), 3.38 (sept, J = 6.9 Hz, 1 H), 3.74 (s, 3 H), 3.76 (sept, J = 6.9 Hz, 1 H), 3.91 (s, 2 H), 6.66 (d, J = 3.0 Hz, 1 H), 6.76 (dd, J = 3.0, 8.7 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.02 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.08, 20.68, 42.45, 46.73, 50.49, 56.00, 115.21, 116.22, 119.96, 120.47, 148.71, 154.15, 168.15, 196.51.

Scheme 2



hemiacetal **5a** as an accompanying cleavage coproduct. Cleavage coproducts **5a** predominate when the leaving groups are weakly basic carboxylate anions.[7]

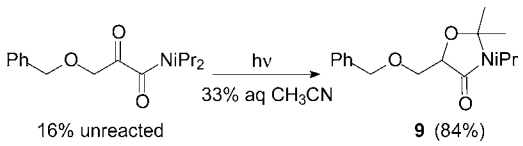
Table 2. Quantum Yields for Photolyses of **3a,b** with Various *para* Substituents, Y[a,b]

reactant;	Φ		reactant;	Φ	
3a, Y	ArOH	**6a**[c]	**3b**, Y	ArOH	**6b**[c]
CN	0.30	0	CN	0.30	0
CF_3	0.30	0	H	0.23	0
H	0.26	0	CH_3	0.15	0.10
CH_3	0.16	0.13	OCH_3	0.07	0.19
OCH_3	0.07	0.26			
$-(CH_2)_4-$[d]	0.05	0.19			

[a] High-pressure mercury lamp (200 W), monochromator, and optical bench apparatus used with ferrioxalate as actinometer at 310 nm; see ref 15. [b] HPLC analyses with internal standard used to quantify **3a,b** and 4-Y-C_6H_4OH. [c] Taken as $\Phi_{dis} - \Phi_{phenol}$ where Φ_{dis} is the disappearance quantum yield and Φ_{ArOH} is the quantum yield for 4-Y-C_6H_4OH (ArOH). [d] Y,Z = $(CH_2)_4$ in 3,4-Y,Z-C_6H_3OH.

The quantum yields (Table 2)[15] show that the elimination of substituted phenols 4-YC_6H_4OH is an efficient photoreaction when Y is a *para* electron-withdrawing group (EWG) or H but that the efficiencies strongly decrease in going to *para* electron-donating groups, (EDG, Y = CH_3, OCH_3 and Y,Z = $(CH_2)_4$ in 3,4-Y,Z-C_6H_3OH). For a mechanism involving intermediates such as **2** one would expect that as the elimination of the leaving group becomes less efficient, cyclization to form oxazolidinone or β-lactam products should[8,9] become increasingly important. Such a cyclization to form **9** (Scheme 3),[16] however, is only observed when the leaving group is as basic as an alkoxide, but not for **3a,b** (Y = CH_3, OCH_3), despite the reduced efficiencies for elimination to give 4-$CH_3C_6H_4OH$. The quantum yields for formation of

Scheme 3



the *para*-substituted phenols (Table 2) thus are not governed by leaving group ability of the phenolate anion in intermediates such as **2**. The reduced efficiencies for phenol formation with Y = EDG coincides with the emergence of 1,3-photorearrangment to give products **6** as an important, even predominant photoprocess that competes with the excited-state hydrogen transfer reaction leading to the phenols.

The 1,3-photorearrangement products **6** observed for Y = CH_3 and Y = OCH_3 can be seen as being formed via bond homolysis to give a phenoxyl radical and an α-keto radical followed by recombination of the caged radical pair. Analogous excited state homolytic cleavages are typically observed upon photolysis of α-(*p*-methoxyphenoxy)acetophenone[17] and α-(*p*-methoxyphenoxy)acetone and related *para*-substituted derivatives bearing EDGs.[18] Rate constants for the cleavages are known to be 10^7-10^9 and correlate with σ^+ constants of the phenoxyl *para* substituents.[17a] Quantum yields observed for **6** (Table 2) follow this trend. Thus, **6** is produced efficiently for those 4-YC_6H_4O groups that have EDG such as Y = CH_3 and OCH_3. This is consistent with known[19] ArO−C bond weakening by *para* electron donors and the substantial ArO−C bond strengthening for *para* EWGs.

In 355 nm laser flash photolyses experiments with argon-saturated solutions of **3a** (Y = CH_3) and **3b** (Y = OCH_3) we detect *para*-substituted phenoxyl radicals of cage escape. These radicals give rise to very long-lived transient absorptions at 400−410 nm, which are identical to the absorptions observed for the independently generated radicals using benzophenone with the *para*-substituted phenols as quenchers. On the other hand, laser flash photolyses of **3a** (Y = H) gave no detectable phenoxyl radicals, although we could readily detect these long-lived free radicals in laser flash photolysis experiments with benzophenone and phenol. The rise times of the transient absorptions observed showed that the phenoxyl radicals were formed within the duration of the laser pulse (ca. 10 ns), suggesting that the radical cleavages occur directly in the excited state, which would agree with precedent.[17,18]

The picture that emerges from the foregoing work is that the ArO−C_α bond scission to radicals, which produces **6**, and the hydrogen transfer, which gives intermediates such as **2** and ultimately the substituted phenols, compete with

(15) (a) The detailed procedures used for quantum yield determinations[15b] and ferrioxalate actinometry[15c] were described previously. (b) Steinmetz, M. G.; Luo, C.; Liu, G. *J. Org. Chem.* **1999**, *64*, 2057−2065. (c) Hatchard, C. G.; Parker, C. A. *Proc. R. Soc. London* **1956**, *235*, 518.

(16) (a) Yields were determined by ^{1}H NMR spectroscopy with DMSO as standard; only traces of benzaldehyde from Norrish Type II photoreaction were detected. (b) Oxazolidinone **9**: ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 7.2 Hz, 3 H), 1.44 (s, 3 H), 1.45 (d, J = 7.2 Hz, 3 H), 1.49 (s, 3 H), 3.36 (sept, J = 7.2 Hz, 1 H), 3.69(dd, J = 5.1, 10.5 Hz, 1 H), 3.77 (dd, J = 2.4, 10.5 Hz, 1 H), 4.39 (dd, J = 2.4, 5.1 Hz, 1 H), 4.55 (d, J = 12.3 Hz, 1 H), 4.63 (d, J = 12.3 Hz, 1 H) 7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 20.21, 20.50, 27.13, 27.51, 49.08, 70.31, 70.57, 76.80, 95.22, 127.55, 127.60, 128.31, 138.09, 168.14.

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each other in the excited state.[20] A remote *para* substituent that is an EDG sufficiently weakens the ArO−C_α bond such that homolysis becomes an important or even predominant photoprocess. Otherwise, the photoreactivity is dominated by hydrogen transfer and formation of phenolic products.

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Supporting Information Available: Adsorption spectra and kinetics curves for *p*-methoxyphenoxyl and *p*-methylphenoxyl radicals produced in nanosecond laser flash photolysis experiments with **3b** (Y = OCH_3) and **3a** (Y = CH_3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) According to the data in Table 2 the disappearance quantum yields Φ_{dis} are insensitive to competition by excited-state ArO−C_α homolysis with hydrogen abstraction. Two factors could be responsible: (1) the caged radical pairs regenerate the starting α-keto amides in addition to forming **6**, and (2) the homolysis rate contributes to the total rate of excited-state decay.