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Photochemical Cleavage and Release of Carboxylic Acids from α-Keto Amides

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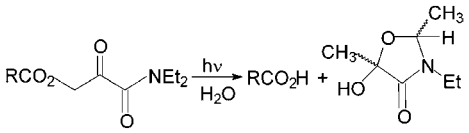
ABSTRACT



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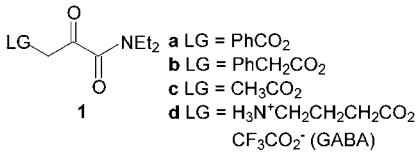
Carboxylate groups incorporated at the position α to the keto carbonyl of α-keto amides 1 were photochemically cleaved in aqueous media to give carboxylic acids in 70–90% yields with quantum yields of 0.3. The cleavage coproducts were diastereomeric hemiacetals 2. Prompt release of acetate and γ-aminobutyrate (GABA) in buffer was observed by difference FT-IR spectroscopy upon 355 nm laser flash photolysis. The time-constant for release of GABA was <30 ms.

Numerous applications exploit photocleavage reactions to deprotect biologically active substrates,[1−3] to release synthetic biooligomers from resin,[4] and for photolithographic patterning of surfaces.[5,6] Such applications largely rely on a few basic types of photocleavable groups such as various derivatives of the *o*-nitrobenzyl group,[7] the benzoin group,[8] and the *p*-hydroxyphenacyl group.[9] Since each type of photocleavable group has specific advantages and limitations for use in a given application, there has continued to be considerable interest in the development of new photocleavable groups, which may offer additional versatility.

In this communication we report on α-keto amides **1a**−**d**, which photochemically release carboxylate leaving groups (LG) that are attached to the position α to the keto carbonyl.



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The impetus for our studies of **1a**−**d** was the possibility that leaving group release could occur via heterolytic cleavage of photogenerated intermediates **3**, since such reactivity was

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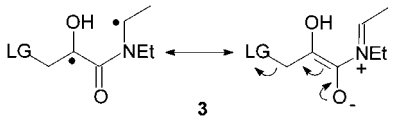
expected to reflect a high degree of zwitterionic character in the intermediates due to charge stabilization by nitrogen and oxygen at the sites shown.[10]



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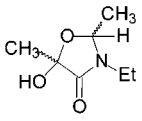
Analogous zwitterionic intermediates had been previously postulated to account for the photochemistry of other α-keto amides.[11,12] Other potentially applicable mechanisms would be solvolytic ionization of the excited state[8a,9] and cleavage to radical pairs that undergo electron transfer.[13]

Photolyses (>300 nm) of α-keto amides **1** in nitrogen-saturated solutions of 50% D_2O in CD_3CN (**1a**,**b**) or air-saturated D_2O containing 25 mM phosphate buffer at pD 5−6 (**1c**,**d**) resulted in the formation of benzoic acid, phenylacetic acid, acetic acid, and GABA, respectively, according to ^1H and ^{13}C NMR spectroscopy of the photolysates.[14,15] In each case, a cleavage coproduct was also formed, which was identified as a ca. 1.5:1 mixture of diastereomeric hemiacetals **2**.[16] The CH_3 group α to the carboxamide group of **2** was labeled with one deuterium. The NMR analyses also showed the presence of minor amounts (<5%) of oxazolidinone **4**.[17]



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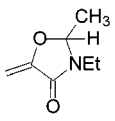

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A preparative direct photolysis of **1a** was conducted in 50% aqueous CH_3CN, and the hemiacetals **2** were isolated by lyophilization of the aqueous phase that remained after repeated extractions with ethyl acetate. To improve the efficiency of the extractions, the two-phase mixture was frozen in dry ice before removing the ethyl acetate phase.

The chemical yields of the carboxylic acids produced from direct photolyses of **1a**−**d** with Pyrex-filtered light were 70−90% at high conversions (Table 1). Quantum yields, determined at 310 nm using ferrioxalate actinometry, were 0.31 ± 0.03 and 0.37 ± 0.02 for **1a** and **1b**, respectively, in nitrogen-saturated 50% aqueous acetonitrile. The quantum yields for **1c** were 0.28 ± 0.03 and 0.32 ± 0.03 in air-saturated 50% aqueous acetonitrile and 25 mM phosphate buffer at pH 5.4, respectively. For **1c**, only the quantum yields of disappearance of reactant could be obtained by HPLC analyses of photolysates with 254 nm detection. Nevertheless, these values should equal the efficiency for acetate release, because acetic acid, hemiacetal **2**, and traces of **4** were the only products according to NMR spectroscopy (vide supra). Decarboxylation of a potential acyloxy radical intermediate[13a] was not evidenced by an observed decrease in chemical yield or quantum yield for formation of phenylacetic acid from **1b**.

Table 1. Photochemical Yields of Released Carboxylic Acids and Hemiacetal **2** in 50% D_2O in CD_3CN or D_2O Containing 25 mM Phosphate Buffer at pD 5−6

		yield, %[a,b]		
reactant	additive	unreacted **1**	RCO_2H	**2**
1a	N_2	7	93	88
1a	N_2	11[c]	89[c]	nd[d]
1b	N_2	12	86	66[e]
1c	buffer, air	24	69	77
1d	buffer, air	20	75	83

[a] Yields determined by NMR spectroscopy; runs in buffer used glycine as an internal standard, whereas DMSO was the standard for **1b**. [b] Yields of **4** were <5%. [c] Determined by HPLC analysis using an internal standard and 254 nm UV detection. [d] Not determined. [e] Yield of **4** = 10%.

To determine whether acetate and GABA were released rapidly from **1c**,**d** in pD 6 phosphate buffer (25 mM) in D_2O,

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(14) (a) Photolyses used an air-cooled 450 W medium-pressure mercury lamp inside a Pyrex filter sleeve with each 25 mL sample contained in a quartz tube mounted beside the water-jacketed apparatus. For the NMR studies, 0.5 mL samples of **1a**,**b** in 50% D_2O in CD_3CN and **1c**,**d** in phosphate buffer (25 mM) in D_2O at pD 5−6 were photolyzed for 1−2 h. (b) Quantum yield determinations used a 200 W high-pressure mercury lamp, monochromator, and associated optics as described previously,[14c] with ferrioxalate as the actinometer.[14d] (c) Steinmetz, M. G.; Luo, C.; Liu, C. *J. Org. Chem.* **1999**, *64*, 2057−2065. (d) Hatchard, C. G.; Parker, C. A. *Proc. R. Soc. London* **1956**, *235*, 518.

(15) Photochemical reactants **1a**−**d**, BocGABA derivative **7d**, and compounds **6a** (R = Ph), **6b** (R = $PhCH_2$), **6c** (R = CH_3), and **6d** (R = Boc-$NHCH_2CH_2CH_2$) gave satisfactory C, H, and N elemental analyses. Trifluoroacetate salt **1d** was not analyzed. Slow decomposition of **1d** in pD 5−6 buffer was observed by NMR in the dark with a half-life of 38 h. Samples of **1c** in buffer and **1a**−**c** in 50% D_2O:CD_3CN were stable for days.

(16) Major diastereomer of hemiacetals **2** (undeuterated): ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7 Hz, 3 H), 1.35 (d, J = 5.5 Hz, 3 H), 1.52 (s, 3 H), 3.11 (dq, J = 14, 7 Hz, 1 H), 3.45 (dq, J = 14, 7 Hz, 1 H), 5.30 (q, J = 5.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 12.71, 20.12, 23.52, 34.64, 83.56, 98.38, 169.37. Minor diastereomer of hemiacetals **2**: ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7 Hz, 3 H), 1.44 (d, J = 5.5 Hz, 3 H), 1.47 (s, 3 H), 3.09 (dq, J = 14, 7 Hz, 1 H), 3.51 (dq, J = 14, 7 Hz, 1 H), 5.10 (q, J = 5.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 12.56, 21.34, 22.83, 34.75, 83.93, 98.97, 169.02. These spectra are for hemiacetals **2** that were isolated by careful lyophilization. The presence of some water was unavoidable. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Calcd for 26.3% water content: C, 50.76; H, 8.35; N, 8.46. Found: C, 50.76; H, 8.28; N, 8.66.

(17) Oxazolidinone **4**: ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7 Hz, 3 H), 1.47 (d, J = 5.5 Hz, 3 H), 3.22 (dq, J = 14, 7 Hz, 1 H), 3.69 (dq, J = 14, 7 Hz, 1 H), 4.56 (d, J = 2 Hz, 1 H), 4.90 (d, J = 2 Hz, 1 H), 5.45 (q, J = 5.5 Hz, 1 H).

355 nm laser photolyses were monitored directly by difference FT-IR spectroscopy using the system described previously.[7a] The difference spectra represent the difference between the spectra obtained after photolysis and the spectrum before photolysis. In the case of **1c**, one laser shot resulted in the prompt appearance of a 1560 cm^{-1} feature, which corresponded to the asymmetric carboxylate vibration of the released acetate (Figure 1). This feature increased with

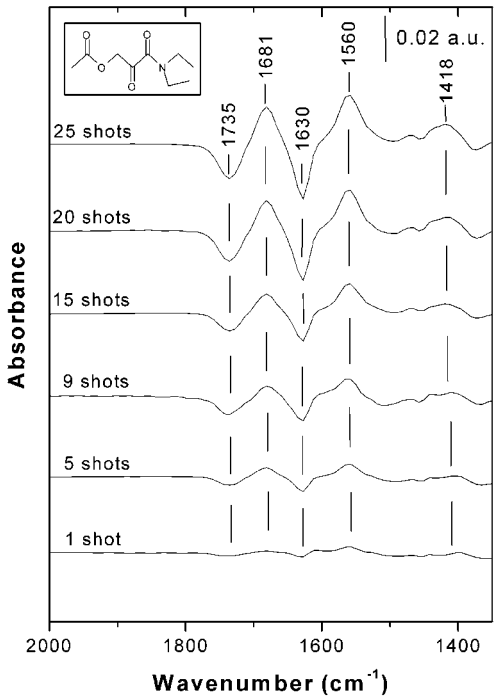


Figure 1. Difference FT-IR spectra obtained for a series of 355 nm laser flash photolyses of 0.18 M **1c** in 25 mM phosphate buffer.

additional laser shots, along with a 1681 cm^{-1} feature, which was confirmed by FT-IR spectroscopy to be due to formation of hemiacetals **2**. The negative features in the difference FT-IR spectrum at 1735 cm^{-1} and 1630 cm^{-1} resulted from photolytic depletion of the reactant **1c**. However, the time constant for the release of the acetate could not be determined, because of the low intensity of absorption of the acetate produced after a single laser pulse.

For the trifluoroacetate salt of "caged" GABA derivative **1d** (LG = $H_3N^+CH_2CH_2CH_2CO_2$), the FT-IR difference spectra showed a prominent feature at 1564 cm^{-1} after one laser shot. This feature, which could be assigned to the asymmetric carboxylate vibration of the released GABA, was of sufficient intensity that its time evolution could be followed using the rapid-scan technique. The time constant for photolytic release of the GABA was determined to be 30 ± 5 ms (Figure 2).[7a] Since this time constant is at the lower limit of the time resolution of the rapid-scan method, work is underway to synthesize the large quantities of the caged GABA **1d** needed for determination of the time constant on the microsecond time scale by the step-scan technique, which requires a flowing sample.

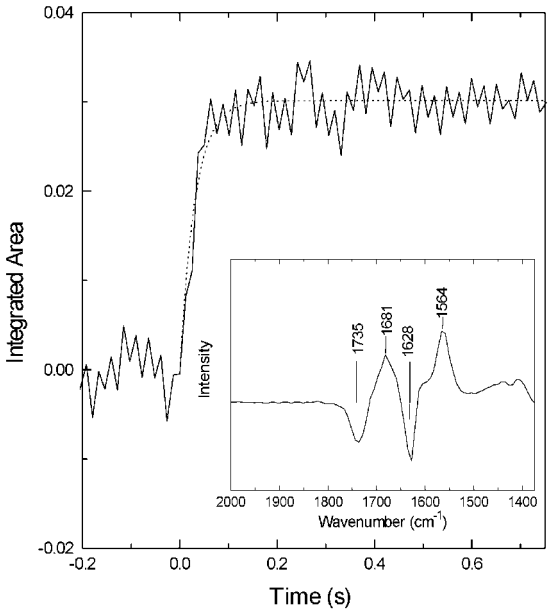
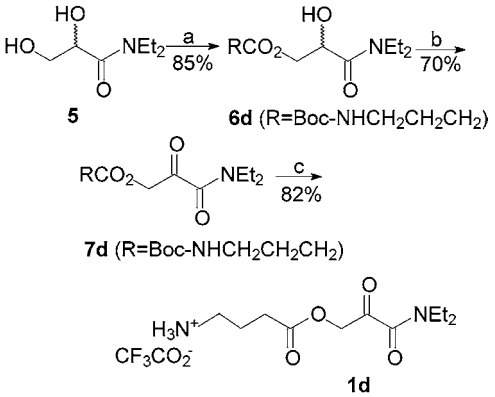


Figure 2. Time evolution of the difference feature at 1564 cm^{-1} (area integrated between 1540 and 1600 cm^{-1}) in the FTIR difference spectrum (inset) for pulsed laser photolysis of **1d**. The increase in intensity of the feature at 1564 cm^{-1} could be well represented with a single exponential (dotted line) with a time constant of 30 ± 5 ms.

GABA derivative **1d** was synthesized by DCC coupling of diol **5** with *N*-Boc-γ-aminobutyric acid, PCC oxidation of secondary alcohol **6d**, and deprotection of **7d** using TFA (Scheme 1). Sephadex LH-20 chromatography and lyophilization then gave the trifluoroacetate salt of **1d**. The synthesis of acetate **1c** in 45% overall yield followed a similar route, whereas for **1a** and **1b**, diol **5** was instead acylated using benzoic anhydride or phenylacetyl chloride followed by oxidation to give 25 and 52% overall yields of these keto amides after two steps.

Scheme 1



(a) Boc-$NHCH_2CH_2CH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt;
(b) PCC, CH_2Cl_2, rt; (c) TFA, CH_2Cl_2, rt

In conclusion, our experimental results are the first to demonstrate photorelease of leaving groups from α-keto amides. Carboxylates are released efficiently in high chemical yields upon exposure to $\lambda > 300$ nm light, and the efficiencies are comparable to those of other photoremovable protecting groups for carboxylates.[1,2] The photorelease of GABA occurs on the sub-30 ms time scale. The quantum yields are similar for a variety of carboxylate leaving groups in aqueous acetonitrile and buffer, which is consistent with a mechanism involving release of carboxylates via cleavage of photogenerated zwitterionic intermediates. Nevertheless, further work is needed to elucidate the mechanism of the photocleavages, to determine the release time of GABA on a shorter time scale and to explore the photorelease of other functional groups from α-keto amides.

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Supporting Information Available: FT-IR spectra of **1c**,**d**, hemiacetals **2**, acetate, and γ-aminobutyrate (GABA) in 25 mM phosphate buffer, ^{1}H and ^{13}C NMR data for **1a**−**d**, and ^{1}H and ^{13}C NMR spectra of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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