Photodecarboxylative Additions of α-Thioalkyl-Substituted Carboxylates to Alkyl Phenylglyoxylates

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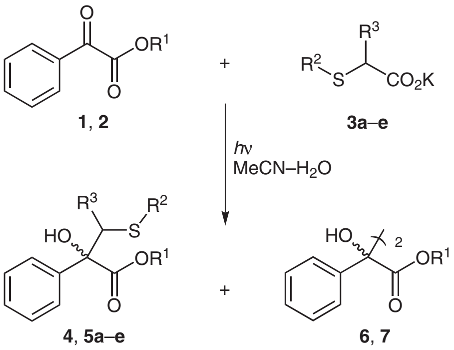
Received 25 May 2010

Abstract: Irradiations of alkyl phenylglyoxylates with sulfur-containing carboxylates yielded the corresponding photodecarboxylative addition products in moderate to good yields of 26–58%. Reductive photodimerization competed with decarboxylative addition in all cases. The reaction protocol was successfully transferred to a microreactor. With potassium 2-(methylsulfanyl)propionate, photoadditions gave diastereomeric mixtures with low selectivity for the *like*-isomer.

Key words: photodecarboxylation, phenylglyoxolates, photochemistry, photoinduced electron transfer, microreactor

The photochemistry of phenylglyoxylates and phenylglyoxylamides has been intensively studied over the last decades.[1–5] Among the many transformations examined are, for example, Norrish,[1] Paternò–Büchi,[2] photoreduction,[3] and photocyclization reactions.[4] For the related phthalimide chromophore, we have recently developed the photodecarboxylative addition of carboxylates as a versatile alkylation method and alternative to Grignard additions.[6] The procedure utilizes easily accessible carboxylic acid salts and has been scaled up using a 308 nm excimer system.[7] We therefore became interested in applying the photodecarboxylation protocol to simple alkyl phenylglyoxylates and α-thioalkyl-substituted carboxylates. Five sulfur-containing carboxylates **3a**–**e** were thus irradiated at 350 nm in aqueous acetonitrile in the presence of either methyl or ethyl phenylglyoxylate (**1** and **2**, Scheme 1).[8]



Scheme 1 Photoreaction of **1**/**2** with sulfur-containing carboxylates **3a**–**e**

In all cases, the desired alkylation products **4a**–**e** and **5a**–**e** were obtained as main products together with the corresponding reductive dimerization product **6** and **7** (Table 1). Isolation by column chromatography furnished products **4** and **5** in moderate to good yields of 26–58%. Irradiation of **1** in the presence of 10 equivalents of **3a** did not prevent the formation of the undesired dimerization product **6** and effectively the same ratio of **4a**/**6** (76:24) was obtained. Likewise, irradiations of the **1**/**3a** pair at 300 nm in either aqueous acetonitrile or aqueous acetone gave no improvements in terms of yields or selectivities.

The simple reaction protocol was furthermore applied to ‘microphotochemistry’.[9] A commercially available microreactor (dwell device, mikroglas), which was placed under a UV panel (Luzchem) fitted with 5 UVA lamps, was chosen (Figure 1).[10] The synthesis of **4a** was again used as a model. Using a residence time of one hour, a **4a**/**6** mixture of 76:24 was isolated.

Figure 1 Microreactor (dwell device, mikroglas) under a UV exposure panel (Luzchem)

The diastereoselectivity of the reaction was furthermore studied for the branched potassium 2-(methylsulfanyl)propionate **8** (Scheme 2, Table 2). In both cases, the diastereomeric ratio was determined by integration of baseline-separated signals in the ^{1}H NMR spectra of the crude product as 1:1.1 in favor of the *like*-diastereomer.[11] The photoaddition products were isolated in good yields of 55% (**9**) and 51% (**10**).

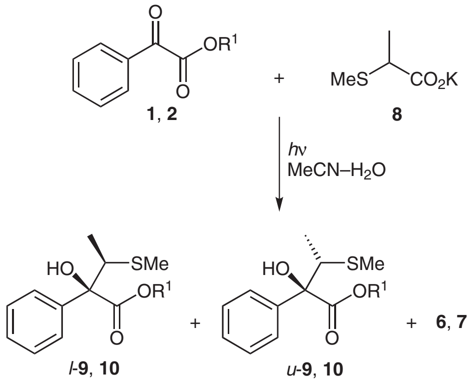
In order to demonstrate the superiority of the photodecarboxylation protocol, **1** was irradiated in dry acetonitrile in the presence of 5 equivalents of 1,3-dithiane (**11**). Compound **11** is advantageous over other thioethers since it is a solid and thus easier to work with. After exhaustive irradiation of 22 hours, a 20:80 mixture of **4e** and **6** was obtained. Purification by column chromatography furnished the desired addition product **4e** in a low yield of 16%.

SYNLETT 2010, No. 15, pp 2240–2243
Advanced online publication: 12.08.2010
DOI: 10.1055/s-0030-1258032; Art ID: D12810ST

Table 1 Product Compositions and Experimental Details for Photoadditions of **1**/**2** with **3a**–**e**

Glyoxylate	R^1	Carboxylate	R^2	R^3	Time (h)	Product composition (%)[a]		Yield (%)[b]
						4/5	**6/7**	**4/5**
1	Me	**3a**	Me	H	1	77	23	37
1	Me	**3b**	Et	H	2	88	12	50
1	Me	**3c**	Ph	H	2	90	10	53
1	Me	**3d**	Bn	H	3	81	19	58
1	Me	**3e**	$(CH_2)_3S$		4	66	34	27
2	Et	**3a**	Me	H	2	85	15	44
2	Et	**3b**	Et	H	2	65	35	44
2	Et	**3c**	Ph	H	2	77	23	43
2	Et	**3d**	Bn	H	2	67	33	36
2	Et	**3e**	$(CH_2)_3S$		4	65	35	26

[a] Determined by 1H NMR spectroscopy of the crude reaction mixture.
[b] Isolated yield.

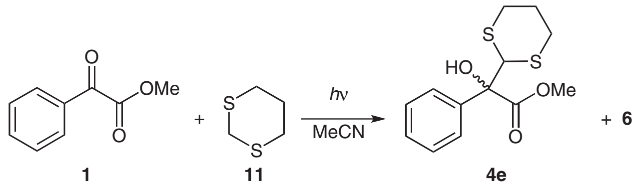


Scheme 2 Addition of potassium 2-(methylsulfanyl)propionate **8** to **1**/**2**

Table 2 Product Compositions and Experimental Details for Photoadditions of **1**/**2** with **8**

Glyoxylate	R^1	Time (h)	Product composition[a]			Yield (%)[b]
			9/10	**6/7**	*l*/*u*	**9/10**
1	Me	4	80	20	1.1:1	55
2	Et	4	60	40	1.1:1	51

[a] Determined by ^1H NMR spectroscopy of the crude reaction mixture.
[b] Isolated yield.

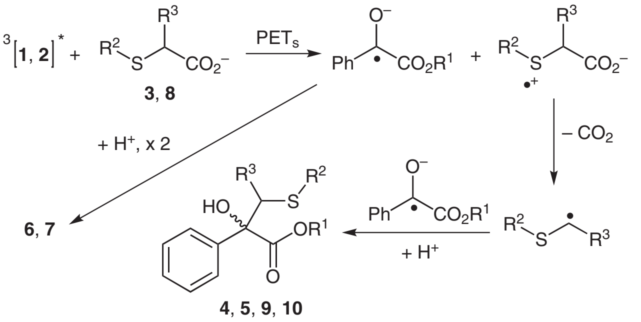


Scheme 3 Photoreaction of **1** with 1,3-dithiane **11**

The general mechanistic scenario for photodecarboxylative additions of α-thioalkyl-substituted carboxylates to alkyl phenylglyoxylates is depicted in Scheme 3. Based on the available electrochemical and spectroscopic data of simple phenylglyoxylates, the limiting maximum oxidation potential for an exergonic photoinduced electron transfer has been established to 1.7 V (vs. SCE).[4b,12] Due to the low oxidation potential of thioethers (for Me_2S: $E_{Ox} = 1.23$ V vs. SCE[13]) vs. carboxylates (for $MeCO_2^-$: calcd $E_{Ox} = 1.54$ V in MeCN vs. SCE[14]), electron transfer to the triplet excited phenylglyoxylates is expected to occur predominately from the sulfur atom. Subsequent α-decarboxylation of the thioether radical cation gives the corresponding carbon-centered radical. Carbon bond formation and protonation furnishes the addition products **4**, **5**, **9**, and **10**, respectively (Scheme 4). Consequently, the mechanism parallels that of the related phthalimide system.[15]

Alternatively, the alkyl phenylglyoxylate radical anions dimerize to the reduction products **6** and **7**. Similar competitive scenarios have been reported for other hydrogen and electron donors.[3] The differences in yields and selectivities when changing from the methyl ester **1** to the ethyl ester **2** suggest that intramolecular H abstraction may compete with photodecarboxylation.[1]

In comparison with simple thioethers (as **11**),[16] the decarboxylation pathway (using **3e**) is much more efficient and chemoselective. Hence, the carboxylate group in α-position to the thioether functions as a powerful activating group for PET reactions. Furthermore, addition occurs exclusively at the carbon that carries the directing carboxylate function. For thioethers themselves, competing nonproductive electron and proton back-transfer reduces the overall efficiency for addition.[9,15a] In addition, asym-



Scheme 4 Mechanistic scenario

metrically substituted thioethers commonly give mixtures of regioisomers.[17]

In conclusion, α-thioalkyl-substituted carboxylates undergo photodecarboxylative addition to alkyl phenylglyoxylates. Conversion rates, isolated yields and selectivities were higher compared to reactions with simple thioethers. The easy procedure was suitable for adaptation in 'microphotochemistry'.

Acknowledgment

This research project was financially supported by Science Foundation Ireland (SFI, 07/RFP/CHEF817 and 06/RFP/CHO028), the Environmental Protection Agency (EPA, 2008-ET-MS-2-S2) and the Department of Environment, Heritage and Local Government (DEHLG, 2008-S-ET-2). The authors would like to thank Dr. Andreas Freitag (mikroglas chemtech) for technical advice and support.

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(8) **General Procedure for Irradiation**
The alkyl phenylglyoxylate (1.5 mmol) was dissolved in MeCN (50 mL). A solution of the potassium carboxylate (4.5 mmol) in H_2O (50 mL) was added, and the mixture was irradiated (Rayonet Photochemical Reactor RPR-200; $\lambda = 350 \pm 30$ nm) at 15–20 °C in a Pyrex tube ($\lambda \geq 300$ nm) while purging with a slow stream of nitrogen. The progress of the reaction was monitored by TLC analysis or by passing the departing gas stream through a sat. $Ba(OH)_2$ solution until precipitation of $BaCO_3$ had ceased. Most of the MeCN was evaporated, and the remaining solution was extracted with EtOAc (4×25 mL). The combined organic layers were washed with 5% $NaHCO_3$ (1×25 mL) and brine (1×25 mL), dried over $MgSO_4$, and evaporated. The products were purified by flash column chromatography (eluent: *n*-hexane–EtOAc = 5:1).
Selected Physical and Spectral Data for the Product Methyl-2-(1,3-dithian-2-yl)-2-hydroxy-2-phenylacetate (4e)
Yellowish solid, mp 104–106 °C. $R_f = 0.39$ (SiO_2, *n*-hexane–EtOAc = 5:1). ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 1.84$ (m, 2 H, CH_2), 2.40–2.46 (m, 1 H, SCH_2), 2.56–2.62 (m, 1 H, SCH_2), 3.02–3.09 (m, 1 H, SCH_2), 3.19–3.26 (m, 1 H, SCH_2), 3.61 (s, 3 H, OCH_3), 4.48 (s, 1 H, CH), 5.14 (s, 1 H, OH), 7.14–7.24 (br m, 3 H, H_{arom}), 7.56 (dd, $^3J = 8.4$ Hz, $^4J = 1.6$ Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.1$ (t, 1 C, CH_2), 28.0 (t, 1 C, SCH_2), 28.3 (t, 1 C, SCH_2), 50.4 (d, 1 C, CH), 53.9 (q, 1 C, OCH_3), 85.1 (s, 1 C, COH), 126.0 (d, 2 C, CH_{arom}), 128.3 (d, 1 C, CH_{arom}), 128.4 (d, 2 C, CH_{arom}), 139.1 (s, 1 C, Cq_{arom}), 173.8 (s, 1 C, C=O) ppm. IR (KBr): $\nu = 3490$, 2953, 2925, 2892, 1725, 1239,

733, 692 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 284 (<1) [M$^+$], 119 (100) [M$^+$ – H_2O], 105 (12), 91 (4), 77 (14), 45 (5).

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(10) The dwell-reactor is made out of Foturan glass ($\lambda \geq 300$ nm) and has a total path length of 1.15 m (20 turns) on a 118 mm × 73 mm aperture. The reactor consisted of a(bottom) serpentine reaction channel 0.5 × 2 mm (D × W), with a second(top), heat-exchanging channel through which water is passed in order to control the reactor temperature. The degassed reaction mixture (20 mL)[8] was pumped through the reaction channel via a syringe pump and collected in a test tube.

(11) The assignment was based on the NMR data of the corresponding phthalimide analogues, see: (a) Griesbeck, A. G.; Oelgemöller, M.; Lex, J.; Haeuseler, A.; Schmittel, M. *Eur. J. Org. Chem.* **2001**, 1831. (b) Peters, K.; Peters, E.-M.; Oelgemöller, M.; Cho, J.-M.; Griesbeck, A. G. *Z. Krist. NCS* **2000**, *215*, 37.

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(16) Irradiation of **2** in benzene and in the presence of 5 equiv of Me$_2$S gave the corresponding addition product **5a** in a yield of 35%. Selectivity (**7** vs. **5a**) was determined as 60:40. Similar results were obtained with 1,3-dithiolane.[3a]

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