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Phenacyl esters as a new photocleavable linker in liquid-phase chemistry

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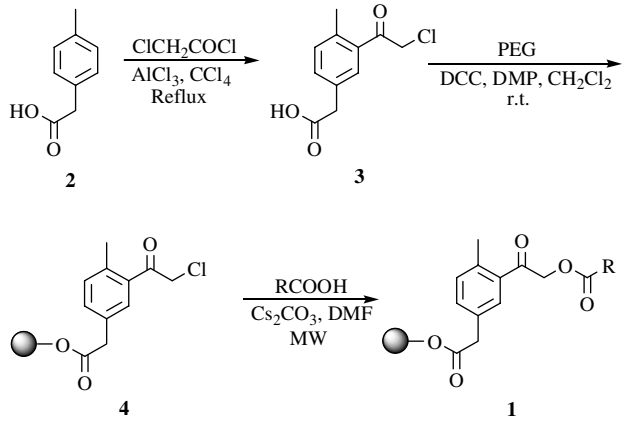
Abstract—PEG-supported 2-methylphenacyl ester as a new photocleavable linker is reported. The photocleavage based on an efficient intramolecular hydrogen abstraction was carried out with 280–366 nm UV irradiation in benzene or methanol to give the corresponding carboxylic acid in high yields and purities. The linker was suitable for aliphatic and aromatic carboxylic acids as well as protected amino acids.

In the last decade, the importance of polymer-supported synthesis of organic molecules has grown dramatically. It is now the main strategy in most of the automated synthesis schemes, for both parallel and combinatorial approaches which are powerful tools in the discovery of new biologically active compounds.[1] The relevant substrate is attached to the polymer support via a linker throughout the synthetic process; essentially, this linker should be robust and withstand a large spectrum of reagents. At the end of the sequence, usually quite harsh conditions, basic or acidic, trigger the release of the modified compound. During the previous years a wide range of linkers, including photolabile linkers, has been developed.[2] The most important advantage of photolabile linkers is their reagent-free cleavage, which allows a release of the library of organic molecules under mild conditions.[3] This detachment is orthogonal to basic, acidic, reductive, and oxidative conditions and therefore affords additional flexibility in the synthesis on polymer support.

Much effort had been directed toward the development of photolabile linkers for ester cleavage.[4] However, most photolabile linkers suffered from the disadvantages of a rather complicated synthesis on the resin and slow cleavage kinetics. Photolabile phenacyl ester linkers were reported to be useful,[5] but this linker was sensitive toward mild nucleophilic reagents and cyclized easily to form diketopiperization.[6]

Recently, Banerjee et al.[7] reported phenacyl ester to be a photoreleasable protecting group for carboxylic acids. Klan et al.[8] found that the direct photolysis of various 2,5-dimethylphenacyl esters in benzene or methanol at 254–366 nm led to the formation of methylindanone and the corresponding carboxylic acids in almost quantitative yields. This work prompted us to investigate the possibility of using the polymer-supported derivatives of 2,5-dimethylphenacyl esters as a photolabile linker. Herein, we disclose our results for this effort.

We selected the soluble polymer polyethylene glycol (PEG) as a support since this polymer has been extensively used in the parallel and combinatorial syntheses of compound libraries.[9] Our work began with the



Scheme 1. Synthesis of the new linker.

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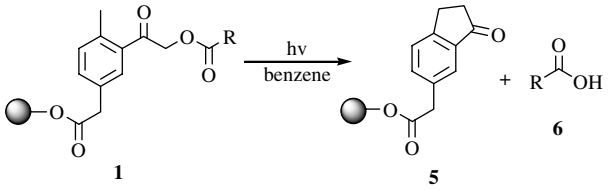
synthesis of linker **1**. As shown in Scheme 1, *p*-methylphenylacetic acid **2** was acylated with chloroacetyl chloride to generate 4-methyl-3-chloroacetylphenylacetic acid **3** in 85% yield.[10] Coupling **3** with commercially available PEG_{4000}, conducted by standard esterification procedures (DCC/DMAP/CH_2Cl_2), yielded the polymer **4**.[11] The subsequent displacement of the chloride with carboxylic acid in the presence of Cs_2CO_3 under microwave irradiation gave 2-methylphenacyl ester linker **1**.[12] The attachment of esters was checked quantitatively by ^1H NMR.

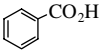
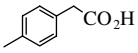
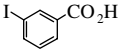
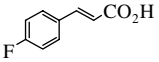
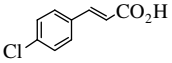
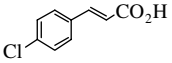
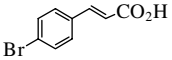
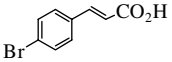
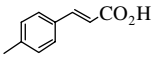
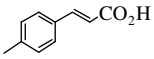
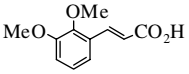
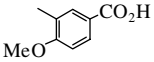
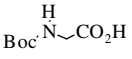
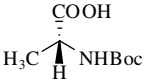
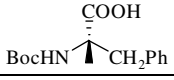


Scheme 2. The photolysis cleavage of the phenacyl ester based linker.

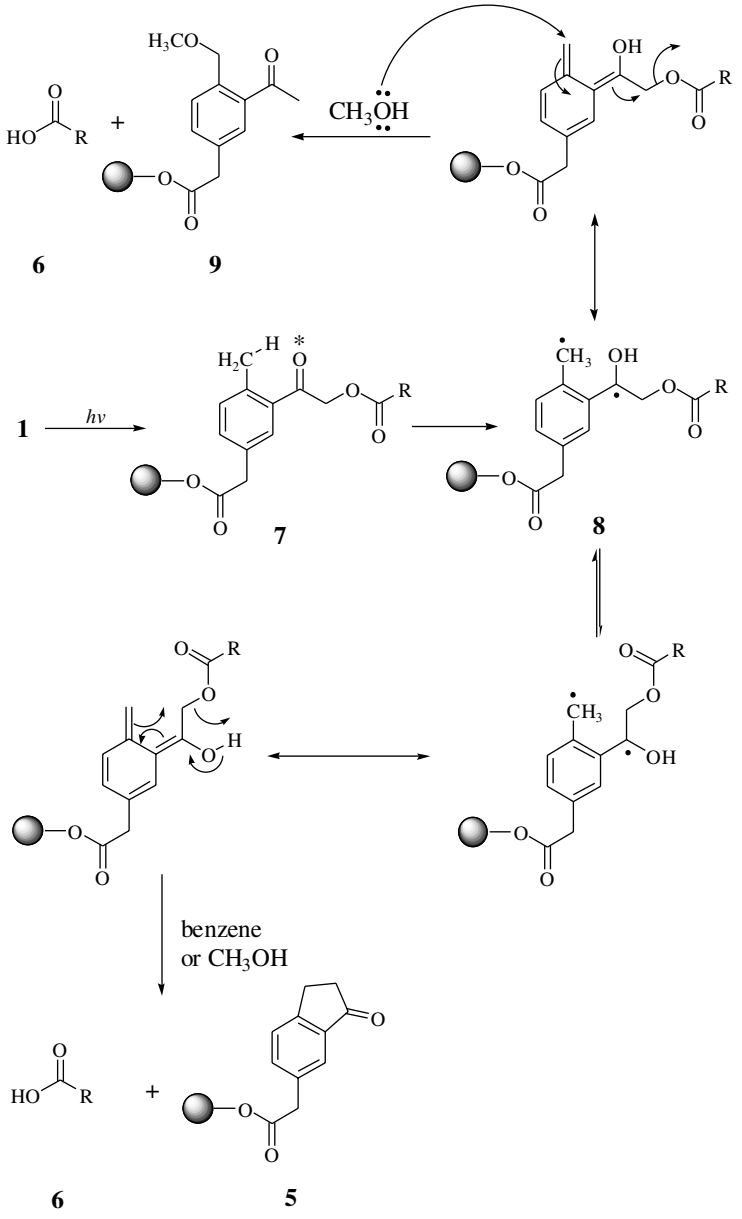
Photolysis of the model linker **1** with high Hg-lamp at 280–366 nm released the corresponding carboxylic acids **6** (Scheme 2) in good yields.[13] The purities of the crude products were always more than 90% (Table 1).

We isolated and analyzed all the significant photo-products. PEG-supported indanone **5** was practically the only photo-product found,[14] in addition to the carboxylic acid, in nonpolar benzene (Scheme 3). This paralleled Klan et al. results obtained by irradiation of 2,5-dimethylphenacyl esters in benzene.[8] The reaction probably proceeded through triplet excited ester **7**

Table 1. Photocleavage of the linker **1** at 280–366 nm

Entry	RCO_2H	Solvent	Time (h)	Yield[a] (%)	Purity[b] (%)
1	CH_3CO_2H	C_6H_6	8	80	91
2		C_6H_6	7	89	94
3		C_6H_6	6	85	95
4		C_6H_6	7	91	95
5		C_6H_6	5	92	92
6		C_6H_6	6	91	94
7		MeOH	6	83	91
8		C_6H_6	6	95	93
9		MeOH	6	87	92
10		C_6H_6	6	96	95
11		MeOH	6	88	93
12		C_6H_6	5	85	94
13		C_6H_6	6	89	95
14		C_6H_6	5.5	73	89
15		C_6H_6	6	78	90
16		C_6H_6	5	80	92

[a] Isolated yield.
[b] Purity of the crude product was determined by GC–MS and HPLC analysis.



Scheme 3. Proposed mechanism for the photocleavage of linker **1**.

and 1,4-biradical **8**, to release the corresponding carboxylic acid in the subsequent step of a possibly concerted rearrangement of the enol. However, photosolvolysis seemed to be a possible pathway when photolysis was accomplished in nucleophilic methanol. Thus, along with indanone **5**, PEG-supported 2-(methoxymethyl)-5-methylacetophenone **9** was also yielded (Scheme 3).

We also examined the stability of the (R=*p*-$MeC_6H_4CH{=}CH$) linker toward different reagents. The model linker **1h** was treated under various reaction conditions for 1–2 h. Afterward, the linker were washed, dried, and subjected to photolysis. Stability toward typical TFA deprotection conditions widely used in peptide synthesis schemes was examined by incubating **1h** with TFA/CH_2Cl_2 for 1 h at room temperature. We were gratified to find that the linker was stable, which would make it possible to deprotect the groups sensitive to acids or bases before photocleavage. Yields of the photocleavage were compared with results of the photolysis of untreated polymer **1h** and given in Table 2.

In summary, we have developed a new photolabile linker system based on PEG-supported 2-methylphenacyl

Table 2. Stability of the linker **1h** toward different reagents

Entry	Reaction conditions	Yield[a] (%)
1	TFA/CH_2Cl_2, rt	95
2	$BF_3{\cdot}Et_2O/CH_2Cl_2$, rt	93
3	Et_3N/acetone, rt	91
4	NaI/DMF, 80 °C	98
5	DBU/PhMe, 80 °C	90
6	NaO^{t}Bu/THF, rt	97

[a] Yield of photolysis compared to yield of photolysis of untreated linker.

esters. The linker was selectively cleaved by 280–366 nm UV irradiation with a short reaction time. Desired carboxylic acids were obtained in high yields and purities. The linker was compatible with many reagents and reaction conditions. Further investigations in the utility of this linker in combinatorial chemistry are currently underway.

Acknowledgments

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10. Procedure for the preparation of 3-chloroacetyl-4-methyl phenylacetic acid **3**: to a solution of *p*-methylphenylacetic acid **2** (0.1 mol) in carbon tetrachloride (150 mL) was added anhydrous aluminum chloride (0.35 mol) three times under stirring. Then the chloroacetyl chloride was added dropwise at such a rate that the temperature never rose above 5 °C. After refluxing for 4 h, the mixture was poured into 1 M hydrochloric acid (200 mL) and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$. To the water layer was added hydrochloric acid until the solution showed acidity, and then extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/hexane 1:3) afforded **3** (19.2 g, 85 mmol, 85%) as yellow crystals: mp 116–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.68 (s, 2H), 4.64 (s, 2H), 7.27 (d, J = 10.8 Hz, 1H), 7.36 (d, J = 7.9, 1H), 7.53 (s, 1H) ppm. MS (ESI): m/z 225 ($[M+Na]^+$).
11. Procedure for the preparation of polymer **4**: to a solution of PEG_{4000} (2 g) in CH_2Cl_2 (15 mL) was added **3** (4 mmol), dicyclohexylcarbodiimide (4 mmol) and 4-dimethylaminopyridine (1 mmol). After stirring for 24 h at 40 °C, the solution was filtrated. The filtrate was concentrated, dissolved in *i*-PrOH (80 mL), and cooled at 0 °C for 2 h. The resulting crystals were collected by filtration and washed with *i*-PrOH and ether. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.24 (s, 2H), 3.61–3.67 (m, PEG), 4.23–4.25 (t, 2H, PEGOCH$_2$C**H**$_2$OCO), 4.63 (s, 2H), 7.22 (d, J = 10 Hz, 1H), 7.32 (d, J = 10 Hz, 1H), 7.53 (s, 1H) ppm.
12. General procedure for the preparation of PEG-bound esters **1**. To a suspension of **4** (500 mg) in DMF (5 mL) was added the corresponding acid (1 mmol) and Cs_2CO_3 (0.75 mmol). The vessel was placed inside the cavity of the microwave synthesizer, heated to reflux at 250 W power for 10 min, and then cooled to room temperature. Ether was added to deposit the resulting linker **1**. The crystals were collected by filtration and washed with ether. All products give satisfactory ^{1}H NMR data. For compound **1g** (R=*p*-BrC_6H_4CH=CH): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.60–3.68 (m, PEG), 3.71 (s, 2H), 4.25–4.27 (t, 2H, PEGOCH$_2$C**H**$_2$OCO), 5.32 (s, 2H), 6.58 (d, J = 15 Hz, 1H), 7.24 (d, 1H), 7.36 (d, J = 10 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 7.73 (d, J = 16 Hz, 1H) ppm.
13. Typical procedure for the photocleavage of the model linker **1**: a solution of linker **1** (100 mg) in benzene (20 mL) was irradiated in a quartz immersion well reactor using a 200 W Xenon Short Arc lamp (USHIO INC. JAPAN) between 280 nm and 366 nm (filter, UV-340, sh) for 5–8 h. Irradiation was stopped when conversation reached at least 90% (GC). Analyses were performed using TLC, GC–MS, and HPLC–MS techniques.
14. For compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64–2.68 (m, 2H), 3.07 (t, J = 5.9 Hz, 2H), 3.64–3.68 (m, PEG), 3.71 (s, 2H), 4.25–4.27 (br s, 2H, PEGOCH$_2$C**H**$_2$OCO), 7.34 (d, J = 7.9 Hz, 1H), 7.39 (dd, J = 1.5, 7.9 Hz, 1H), 7.54 (s, 1H) ppm.