A New, Rapid, General Procedure for the Synthesis of Organic Molecules Supported on Methoxy-Polyethylene Glycol (MeOPEG) under Microwave Irradiation Conditions

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The procedure for the precipitation of molecules supported on MeOPEG (molecular mass 5000) and their purification by fractional crystallization has been made easier by use of microwave irradiation. A correct choice of the solvent employed for reaction or purification (DME, THF, 1,2-dichlorobenzene, *i*PrOH, ethylene glycol) allows working with 10 g of MeOPEG-OH, dissolved in 100 mL of solvent, under microwave irradiation conditions and for crystallization to be induced just by removal of the reaction flask from the microwave oven. No additional precipitation solvents are needed, thus reducing the reaction times and the potential hazards of working with large amounts of flammable solvents. The syntheses of several peptides and of a tetrasubstituted pyridine are reported. Large amounts of MeOPEG-OH may be used in this procedure, and so polyethylene glycol assisted organic synthesis can be regarded as a valid preparative technique.

The enormous impact that combinatorial chemistry has had in medicinal and organic chemistry in the last decade has produced a renewed interest in organic synthesis on organic supports, a technique employed for 40 years.[1] Solid-phase organic synthesis (SPOS) has been widely studied and employed for the preparation of libraries of different products,[2] although its use has been limited by several problems.[3] The main problems encountered were difficulties in the reagents reaching the active sites, site-site interactions, limited amounts of product obtained and problems in monitoring the reaction products linked to the support. Another drawback of SPOS is the time required to optimize a synthetic procedure in going from homogeneous to solid phase before automation of the process. One of the possible alternatives to SPOS is the use of a soluble polymer as support.[4] This polymer should be soluble in several organic solvents, so that the linked substrate may react in solution under standard conditions. After completion of the reaction, the polymer-substrate system is precipitated by addition of large quantities of a solvent in which the support is insoluble in order to isolate the compound from the excess of reagents or other by-products. Polyethylene glycol (PEG) and monomethoxypolyethylene glycol (MeOPEG-OH) are the most versatile soluble polymer supports, although other products such as poly(styrene−co-chloromethylstyrene), PEG-stealth stars, and substituted poly(norbornylene)s have recently attracted considerable interest.[5]

Organic molecules linked to polyethylene glycol may be isolated by careful precipitation with dry diethyl ether, hexane, or *tert*-butyl methyl ether. With these solvents, the product obtained is sometimes a slurry precipitate that may contain several impurities. In order to obtain a genuinely crystalline product, further crystallization with EtOH or *i*PrOH is needed. Precipitation with diethyl ether is a time-consuming process. As the recommended ratio is 50 mL of diethyl ether for 1 g of polymer,[6] 500 mL of dry diethyl ether is needed in order to precipitate 10 g of an MeOPEG-grafted molecule (2 mmol, 0.8 g of a final product with 400 molecular mass). The addition of diethyl ether to the reaction mixture must be slow to provide a filterable precipitate. The overall process of precipitation, filtration, and washing of the precipitate may take 6−8 h, with the potential hazard of the use of large quantities of flammable solvents.

We have recently published a communication about the microwave-assisted deprotection of an *N*-Cbz derivative.[7] We also applied this procedure to the deprotection of a Cbz-amino acid linked to MeOPEG-OH and found that these products could be dissolved in relatively small amounts of organic solvents under microwave activation conditions. If the products have a low solubility in that solvent, they may precipitate simply on cooling of the solution when the flask is removed from the microwave apparatus. A correct choice of solvent may thus allow rapid and efficient purification of polyethylene glycol supported compounds without the use of large amounts of precipitating solvents.

To explore this possibility, we started to investigate the solubility of MeOPEG-OH (molecular mass 5000) in differ-

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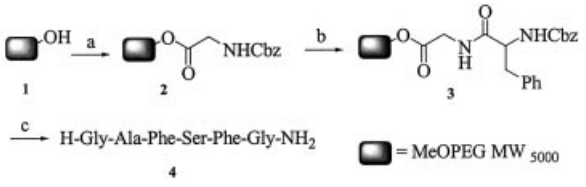
ent solvents under microwave irradiation conditions. We began with the use of a domestic microwave oven under MORE conditions.[8] The representative results were further confirmed by use of a monomode microwave reactor for organic synthesis. The solvents chosen had a range of boiling points from 70 to 198 °C and the experiments were carried out as follows: 1 g of MeOPEG-OH (molecular mass 5000) was mixed with different amounts of solvent and irradiated with microwaves in a sealed pressure tube at low power (60−100 W) until the solid was completely dissolved. The tube was removed from the oven and allowed to cool to room temperature or to 4 °C (refrigerator) until a white solid precipitated. The solid was filtered, washed with dry diethyl ether to remove non-volatile solvents, and dried, and the amount recovered was determined. An analogous procedure was carried out with conventional heating, and the results obtained are listed in Table 1. Several solvents were found to provide better than 90% recovery when microwaves were used. In fact, smaller amounts of solvent were needed for complete dissolution of MeOPEG-supported compounds than for conventional heating, probably due to superheating, allowing higher temperatures to be reached.[9] It is possible to classify these solvents into polar, microwave-sensitive solvents[10] (such as DMF, 1,2-dichlorobenzene, *i*PrOH, or ethylene glycol) or low-polar solvents with low sensitivity to microwave irradiation (such as cyclohexane, toluene, DME, dioxane). The first series of solvents is useful for reactions that are accelerated by heating, the latter for reactions in which heating may be harmful. However, as the dissolved polymer is heated by MW, a constant increment of the temperature occurs when a concentrated solution of any type of polyethylene glycol derivative in any solvent is kept under microwave irradiation conditions.

To develop this new procedure for MeOPEG-supported synthesis, we carried out the synthesis of different peptides and other organic molecules, comparing the results obtained with the classical procedures taken from the literature.[11] In general, we observed that the microwave-assisted syntheses gave better yields and better purities than the classical (on a soluble support) procedure, and in much shorter times. Moreover less solvent was needed to carry out the reactions.

For the synthesis of peptides we decided to link the first amino acid directly to the MeOPEG-OH, and to use Cbz for the α protection of the amino acids and DMTMM as the coupling reagent.[12]

Dicyclohexyl carbodiimide (DCC) was used to link the first amino acid (CbzGlyOH) to MeOPEG-OH (molecular mass 5000). Unfortunately, this reaction must be carried out in pyridine/DMF. All attempts to change the solvent were unsuccessful, and microwave heating also did not give any improvement. Consequently, we employed the smallest amounts possible of pyridine and DMF; at the end of the reaction, the solvents were evaporated under vacuum and the product was crystallized with *i*PrOH by use of microwaves as the heating source.

Compound **2** was obtained in 89% yield. Removal of the Cbz group was performed with $HCOONH_4$ and Pd/C in *i*PrOH under microwave irradiation conditions, taking 10 min to go to completion (Scheme 1). At the end, Pd/C was filtered off and the product was precipitated by cooling of the reaction mixture.[13] The identity of the product was examined by ^1H NMR (disappearance of the benzyl signal at $\delta = 5.2$ ppm). Coupling with CbzPheOH was carried out with DMTMM and DIPEA in DME under microwave irradiation conditions, the solution being maintained at 65 °C for 1 h.[14]



Scheme 1. a) CbzGly−OH, DCC, DMF, Py; b) Pd/C, $HCOONH_4$, *i*PrOH, microwaves, 10 min followed by CbzPheOH, DMTMM, DIPEA, DME, microwaves, 1 h; c) series of deprotections and coupling followed by cleavage with NH_4OH, MeOH, 12 h, room temp.

When the ninhydrin test − carried out on the solid obtained by removal of a sample of the reaction mixture, cooling down and filtering − showed that no more free amine was present, the flask was removed from the microwave and the dipeptide CbzGlyPhe supported on MeOPEG was reco-

Table 1. Solubility and recovery of 1 g of MeOPEG-OH in different solvents under low power (100 W) microwave irradiation

Solvent, b.p.	Dielectric loss tangent[a]	Solubility of 1 g of MeOPEG-OH under MW conditions (temp.), recovery	Solubility of 1 g of MeOPEG-OH with conventional heating (temp.), recovery
*t*BuOMe, 55 °C	0.025	10 mL (50 °C), 90%	10 mL (55 °C), 90%
THF, 66 °C	0.030	10 mL (40 °C), 85%	10 mL (40 °C), 85%
DME, 84−86 °C	n.r.	10 mL (50 °C), 97%	20 mL (85 °C), 90%
Dioxane, 101 °C	n.r.	10 mL (50 °C), 90%	20 mL (80 °C), 80%
Toluene, 110 °C	< 0.010	10 mL (40 °C), 98%	10 mL (110 °C), 90%
Cyclohexane, 81 °C	< 0.010	10 mL (40 °C), 98%	40 mL (80 °C), 95%
*i*PrOH, 81−83 °C	0.799	10 mL (95 °C), 98%	30 mL (80 °C), 70%
$ClCH_2CH_2Cl$, 81−84 °C	0.127	10 mL (98 °C), 95%	20 mL (80 °C), 80%
$HOCH_2CH_2OH$, 196−198 °C	1.350	10 mL (225 °C), 86%	15 mL (190 °C), 60%
DMF, 153 °C	0.161	4 mL (70 °C), 66%	5 mL (140 °C), 60%
1,2-$Cl_2C_6H_4$, 179−180 °C	0.589	10 mL (190 °C), 96%	25 mL (180 °C), 80%

[a] Taken from ref.[10]

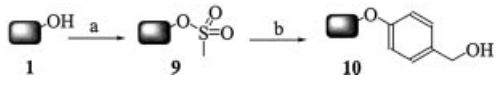
Table 2. Peptides prepared starting from 15 g of compound **1**

Sequence[a]	ESI-MS	Amino acid analysis	Amount isolated (yield)
H-Gly-Ala-Phe-Ser-Phe-Gly-NH_2 (**4**)	584.8	Gly, 1.79; Ala, 0.98; Phe, 1.77; Ser, 1.00	0.82 g (47%)
H-Ile-Ala-Val-Gly-NH_2 (**5**)	358.4	Ile, 1.00; Ala, 0.96; Val, 1.01; Gly, 0.89	0.69 g (65%)
H-Hys-Ile-Hys-Gly-NH_2 (**6**)	464.5	Ile, 1.00; Hys, 1.68; Gly, 0.98	0.83 g (60%)
H-Lys-Pro-Gly-Phe-Gly-NH_2 (**7**)	504.2	Lys, 1.00; Pro, 0.79; Phe, 0.90; Gly, 1.80	0.80 g (53%)
H-Tyr-Gly-Gly-Phe-Leu-NH_2 (**8**)	554.6	Tyr, 0.87; Gly, 1.79; Leu, 1.00; Phe, 0.95	0.84 g (51%)

[a] All building blocks were protected as Cbz at the α-nitrogen atom. The following side chain functionalized amino acids were used: Cbz−His(Boc)−OH; Cbz−Lys(Boc)−OH. The Boc group was removed with *i*PrOH/TFA/Et_3SiH (8.00:2.85:0.15) before cleavage. Tyr and Ser were used without protection of the OH group.

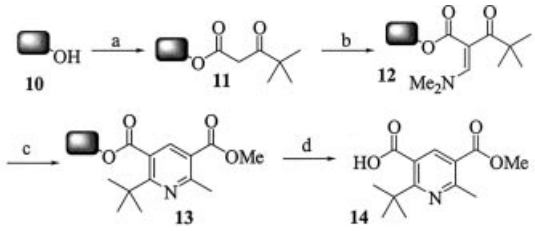
vered by cooling of the flask and filtering of the precipitate. The other amino acids were inserted by the same procedure of deprotection by transfer hydrogenation and coupling with DMTMM/DIPEA with CbzSerOH, CbzAlaOH, and CbzGlyOH. At the end, the hexapeptide **4** (in the terminal carboxyamide form) was removed by aminolysis with NH_4OH and MeOH.[15] The deprotection and coupling process for any amino acid inserted required 3−4 h, so the pentapeptide could be obtained in shorter times than needed for all the procedures employing liquid supports reported in the literature. Peptides **4**−**8** prepared by this procedure are listed in Table 2. The products were analysed by use of an amino acid analyser and possible racemization investigated after hydrolysis of the crude peptide with 6 N HCl and HPLC analysis on a chiral column.

With the aim of generalizing this procedure, we applied the microwave-assisted technique to the synthesis of organic molecules such as the tetrasubstituted pyridine **14**, based on Knoevenagel and Hantzsch condensation chemistry,[16] by use of MeOPEG with the acid-sensitive linker **10**.[17] Thus, MeOPEG-OH was first transformed in the corresponding mesylate **9** (Scheme 2). This reaction was carried out in DME under microwave irradiation conditions at approximately 60 °C in the presence of MsCl (2 equiv.) and DIPEA (3 equiv.). After 1 h, the MeOPEG-OH had been completely converted into the corresponding mesylate. The flask was removed from the microwave, the solid was filtered off on Celite, and the warm solution was left to cool to room temperature to give mesylate **1** in 95% yield.[18] The next step, the formation of the phenyl ether with 4-hydroxybenzyl alcohol in the presence of Cs_2CO_3, is a reaction reported to need 16−48 h to go to completion.[6] We looked for a microwave-active solvent that might accelerate the process and found that if the reaction was carried out in ethylene glycol (previously dried with 4 Å molecular sieves) under microwave irradiation conditions, product **10** could be obtained after 10 min irradiation at 100 W (sealed tube at 195 °C), affording MeOPEG bearing the Wang-type linker **10** in 92% yield.



Scheme 2. a) MsCl, DIPEA, DME, 60 °C (microwave irradiation) 1 h; b) 4-hydroxybenzyl alcohol, Cs_2CO_3, ethylene glycol, 195 °C (microwave irradiation), 10 min

Compound **10** was treated with methyl 4,4-dimethyl-3-oxapentanoate in 1,2-dichlorobenzene under microwave activation conditions. After 10 min at 170 °C, the acetoacetylation[19] had gone to completion to give compound **11**, which was recovered after the solution had been cooled to 0 °C (Scheme 3). The solid was subsequently treated with neat dimethylformamide dimethylacetal under microwave irradiation conditions to give compound **12**, which was isolated after evaporation of the excess of dimethylformamide dimethylacetal and crystallization from *i*PrOH. Hantzsch-type cyclization was carried out with methyl aminocrotonate in 1,2-dichlorobenzene and proceeded quantitatively at 170 °C for 5 min to give the corresponding MeOPEG-supported tetrasubstituted pyridine **13**. Cleavage from the support was carried out with TFA/*i*PrOH/Et_3SiH (1:1:0.1) for 2 min under MW irradiation conditions.[20] After filtration and washing of the solid obtained with *i*PrOH after cooling, the collected solvents were evaporated and product **14** was isolated in 65% overall yield by crystallization from diethyl ether.



Scheme 3. a) 4,4-Dimethyl-3-oxopentanoate , 1,2-dichlorobenzene, 170 °C (microwave irradiation), 10 min; b) DMF/DMA, 100 °C (microwave irradiation), 10 min; c) methyl aminocrotonate, 1,2-dichlorobenzene, 170 °C (microwave irradiation), 10 min; d) TFA, Et_3SiH, *i*PrOH

In order to compare our method with the method employing a PEG melt as the (liquid) support,[21] we tried to use this procedure in the preparation of pyridine **14**. From **10**, acetoacetylation did not occur properly (unchanged **10** remained after more that 15 min of irradiation and with use of a large excess of the β-oxo ester). No differences were observed in the transformation of **9** into **10**, whereas the Hantzsch-type cyclization again did not work.

Although the microwave reactor was equipped with a magnetic stirrer, the viscosity of the MeOPEG melt, with a molecular mass of 5000, may prevent rapid and complete diffusion of the reagents. Nevertheless, when the "melt"

method is used, the solidified PEG must be crystallized from *i*PrOH or other solvents at the end of the reaction, so there are no advantages over our procedure.

In conclusion, we have demonstrated that, with a correct choice of solvent, it is possible to decrease the time needed to carry out organic reactions on PEG-supported molecules. The absence of the typical precipitation steps drastically reduces overall reaction times and removes the need for the use of large amounts of potentially dangerous solvents. With this procedure, larger amounts of PEG may be used, and so PEG-assisted organic synthesis can function as a valid preparative technique.

Experimental Section

General: MeOPEG-OH 5000 was purchased from Fluka AG and dried by melting at 80 °C under vacuum (1 Torr) for 30 min. The yields of the PEG-supported molecules were determined by weight, by assuming that the PEG fragment had a molecular mass of 5000 Da. The purities of these compounds were determined by ^{1}H NMR analysis at 300 or 200 MHz in $CDCl_3$ with presaturation of the PEG signals at $\delta = 3.6$ ppm. Amino acid analyses were carried out after hydrolysis of the sample with HCl (6 N) containing 0.1% of phenol in sealed tubes under microwave activation conditions, as reported in the literature.[22] Quantitative and chiral amino acid analyses were performed with a Biotronik (now Biochrom Ltd) LC 5001 amino acid analyser. The chiral column employed was a Crownpack CR(+), 150 × 4 mm (Dancel Chem. Ind., Tokyo). The reactions under microwave activation conditions were carried out in a household apparatus or in a Prolabo Synthwave 402 monomode microwave reactor. The different procedures are described below.

Heating in a Domestic Oven:[10] Reactions were carried out in a sealed pressure tube (Aldrich Chemical Techware). The tube was placed inside the oven, together with a beaker filled with water. The sample was irradiated at 100 W for 1 min, the oven was then opened, and the hot water contained in the beaker was changed. After 1 min resting time, the operations of 1 min of irradiation followed by 1 min of resting and water change were repeated until the reaction had gone to completion. When a low microwave-active solvent (such as DME or toluene) was employed, the sample could be irradiated without resting until the water in the beaker started to boil. The irradiation was then stopped and the water was changed. To ensure that the temperature of the solvent does not rise too much, the volume of water used must be at least 3 times that of the organic solvent.

Heating in a Monomode Reactor: In the monomode reactor the reaction can be carried out in a sealed flask, the limits of the temperature (not the power) being set inside the flask. With microwave-active solvents the temperature chosen was around the boiling point of the solvent, whereas with low active solvents it was possible to keep the temperature of the flask at 40−60 °C for relatively long times (20−30 min). The dissolved polyethylene glycol is in any case microwave-sensitive, so the temperature rises as soon as the irradiation is kept constant. To monitor the progress of the reaction, 1 mL of the hot solution was taken, cooled to precipitate the MeOPEG-supported compound and filtered, and the product was analysed by ^{1}H NMR, FT-IR, or colorimetric tests.

Loading of the First Amino Acid. Product 2: Cbz-Gly-OH (2.96 g, 14.2 mmol) was dissolved in dry pyridine (40 mL) and cooled to 0 °C. DCC (1.74 g, 8.49 mmol) was added to this solution, and the mixture was stirred at 0 °C for 1 h. The solution was filtered under N_2, and the pyridine solution was added to MeOPEG-OH (**1**, 15.0 g, approx. 3 mmol), dissolved in dry DMF (20 mL). DMAP (0.47 g, 3.6 mmol) was added and the solution was stirred at room temperature for 2 d. At the end, the solvent was evaporated under high vacuum and the residue was crystallized twice from hot *i*PrOH (150 mL each) to give product **2** (14.50 g, 94% yield). ^{1}H NMR ($CDCl_3$): $\delta = 3.98$ (t-like, 2 H, $PEGCH_2$-OCO), 4.35 (s, 2 H, CH_2Gly), 5.18 (s, 2 H), 6.03 (s, 1 H), 7.20−7.40 (m, 5 H) ppm.

Cbz Removal. General Procedure: Product **2** (14.00 g, 2.73 mmol) was dissolved in *i*PrOH (140 mL) under microwave irradiation conditions. $HCOONH_4$ (0.63 g, 10 mmol) and Pd/C (10%, 100 mg) were added to this solution, and the mixture was heated under microwave irradiation conditions for 3 min. The hot solution was passed through Celite to remove the solid and allowed to cool to room temperature. The solid was filtered, and washed with cold *i*PrOH (approximately 100 mL) and dry diethyl ether (50 mL). A ninhydrin test on the solid was positive. In the NMR spectrum the singlet of the benzylic position of Cbz at $\delta = 5.1-5.3$ ppm was absent.

Coupling with DMTMM. General Procedure: The NH_2-free peptide supported on MeOPEG (10 g) was dissolved in DME (10 mL for each gram of polymer) under microwave irradiation conditions. The Cbz-amino acid (3 equiv.) was added to this solution, followed by DMTMM (2 equiv.) and NMM (2 equiv.). The mixture was stirred for at least 2 h under microwave irradiation conditions (1 min of irradiation at 100 W every 15 min, 60 °C as the internal highest temperature recorded by the instrument). A sample of the solution was taken, filtered, and cooled to 4 °C. The solid was separated, and the ninhydrin test was carried out on that solid. If the test was positive the reaction mixture was stirred for an additional period until the test on the withdrawn solid was negative. Additional DMTTM and amino acid can be added if required. If the coupling would not go to completion, the partially unchanged compound could be separated by precipitation on cooling, filtered, and subjected to a second reaction cycle. When the test was negative, the solution was warmed under microwave irradiation conditions for 1 min, the solid was rapidly filtered off on Celite, and the solution was cooled to 4 °C. The formed solid was filtered and crystallized from hot *i*PrOH (100 mL under microwave irradiation conditions). The product was analysed by ^{1}H NMR spectroscopy. Alternatively a small amount of the product was cleaved from the support (see below) and analysed by ESI-MS.

Cleavage of Peptide 4 from MeOPEG. General Procedure: The product of the couplings (approximately 9−10 g) was dissolved in a mixture of NH_4OH/H_2O/MeOH (5:2:3, 100 mL), and this was stirred at room temp. for 12 h. The solvent was evaporated to approximately 40 mL under vacuum, and the flask was cooled. Product **4** was precipitated by slow addition of acetone. The residue obtained (approximately 1.5 g) was finally taken up in water (10 mL, sonication was required for complete solubilization) and extracted with $CHCl_3$ (3 × 20 mL). Peptide **4** was finally obtained by lyophilization of the aqueous phase (0.82 g, approximately 47% yield) and was characterized by ESI-MS and amino acid analysis. Analyses of peptides prepared by this method are reported in Table 2.

Synthesis of Mesylate 9: MeOPEG-OH (molecular mass 5000) (15.0 g, approx. 3 mmol) was dispersed in DME (150 mL). The solid was dissolved by heating the system at 40−50 °C under microwave irradiation conditions for 3 min. MsCl (0.7 g, 6.1 mmol) was

added to this solution, followed by DIPEA (1.16 g, 9 mmol). The mixture was stirred at approximately 60 °C for 1 h under microwave irradiation conditions. The flask was removed from the oven and allowed to cool to room temperature. After 30 min, a precipitate had formed. The solid was separated by filtration and washed with DME and diethyl ether. The solid was dissolved in *i*PrOH (150 mL) under microwave irradiation conditions and the solution allowed to cool to room temperature. The crystallized solid was filtered, washed several times with dry diethyl ether (50 mL each) and dried under vacuum to give mesylate **9** (15 g, 98% yield). ^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3 H, CH_3-Ms), 4.31 (t-like, 2 H, $PEGCH_2$-OMs) ppm.

Synthesis of the Benzyl Alcohol 10: Mesylate **9** (15 g, approx. 2.94 mmol) was mixed with ethylene glycol (150 mL), together with 4-hydroxybenzyl alcohol (1.09 g, 8.82 mmol) and Cs_2CO_4 (2.87 g, 8.82 mmol). The mixture was heated under microwave irradiation conditions for 10 min (225 °C internal temperature recorded by the instrument). The flask was removed from the oven, the solid was rapidly filtered off, and the solution was allowed to cool to room temperature and put into a refrigerator. After 30 min, a solid had formed. After addition of *i*PrOH (50 mL), the solid was filtered, washed with diethyl ether, and crystallized from *i*PrOH (100 mL) under microwave irradiation conditions to give product **10** (14.5 g, 96% yield). ^{1}H NMR ($CDCl_3$): δ = 3.98 (t-like, 2 H, $PEGCH_2$-OAr), 4.20 (s, 2 H, $ArCH_2OH$), 6.98 (d, *J* = 8 Hz, 2 H), 7.29 (d, *J* = 8 Hz, 2 H) ppm.

MeOPEG-Bound β-Oxo Ester 11: Compound **10** (10 g, approx. 1.94 mmol) was dissolved in 1,2-dichlorobenzene (50 mL) together with methyl 4,4-dimethyl-3-oxopentanoate (1.22 g, 7.76 mmol). The solution was heated at approx. 170 °C for 7 min. The mixture was cooled to 4 °C and the solid formed was separated by filtration. The solid was crystallized from hot *i*PrOH to give compound **11** (10 g, 94%). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, *t*Bu), 3.40 (s, 2 H) 3.98 (t-like, 2 H, $PEGCH_2OAr$), 4.58 (s, 2 H), 7.00 (d, *J* = 8 Hz, 2 H), 7.30 (d, *J* = 8 Hz, 2 H) ppm.

MeOPEG-Bound Enone 12: Compound **11** (10 g, approx. 1.82 mmol) was dissolved in dimethylformamide dimethylacetal (15 mL) and the flask was irradiated at 100 W for 10 min (100 °C). The solvent was evaporated and the crude solid was crystallized from hot *i*PrOH to give compound **12** (10 g, approx. 96% yield). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, tBu), 2.42 and 2.48 (two s, 6 H), 3.98 (t-like, 2 H, $PEGCH_2OAr$), 4.68 (s, 2 H), 6.77 (s, 1 H), 7.00 (d, *J* = 8 Hz, 2 H), 7.30 (d, *J* = 8 Hz, 2 H) ppm.

2-*tert*-Butyl-5-(methoxycarbonyl)-6-methylnicotinic Acid (14): Compound **12** (10 g, approx. 1.82 mmol) was dissolved in 1,2-dichlorobenzene (50 mL) together with methyl aminocrotonate (0.65 g, 5.65 mmol), and the solution was heated at 100 W for 10 min (approx. 170 °C). The solution was cooled to 4 °C and the solid was collected by filtration and crystallized from hot *i*PrOH. The solid (**13**) was dissolved in a mixture of *i*PrOH/TFA/Et_3SiH (8.00:2.85:0.15, 100 mL) and irradiated at 100 W for 2 min. The flask was cooled and the precipitate was filtered and washed several times with *i*PrOH and THF. The solutions were collected and the solvents were evaporated to give a solid that was washed several times with diethyl ether to give compound **14** as the pyridinium trifluoroacetate (0.43 g, 65% yield). An analytical sample was obtained after short path chromatography on silica gel, eluting with acetone/MeOH/Et_3N (9:0.9:0.1). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H), 2.02 (s, 3 H), 3.97 (s, 3 H), 7.96 (s, 1 H), 10.11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.3, 28.9, 34.7, 50.1, 127.4, 127.9, 138.7, 156.8, 159.9, 168.2, 171.7 ppm. ESI/MS: *m*/*z* = 252.6 [M^+ + 1]. $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.66, H 6.76, N 5.55.

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