Low molecular weight MPEG-assisted organic synthesis†

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A toolkit of low molecular weight MPEG-supported coupling agents (^{M}IIDQ, ^{M}EDCI), reagents for the Mitsunobu reaction (^{M}DEAD, ^{M}TPP), an alternative to diazomethane, and scavengers can be used in the solution-phase synthesis of amides, esters and ureas and are easily removed after use by solid-phase extraction (MSPE) using normal silica.

Pharmaceutical drug discovery relies on the rapid synthesis of a large number of potential drug candidates,[1] and this can be done using automation. A major problem for all synthesis, automated or not, is the purification of synthetic intermediates. Solid supports have been widely used to simplify purification,[2] but transfer of methodology from solution phase to heterogeneous systems can be problematic, monitoring of reactions is difficult in solid-phase organic synthesis and resins are expensive, limiting scalability. For these reasons, there has been a drive to develop purification tags which allow solution-phase synthesis but simplify purification.[3,4] *Low molecular weight* or "light" poly(ethylene glycol)-ω-monomethyl ether (MPEG-OH, 8–20 ethylenoxy units, average MW 550) tags are particularly attractive because their derivatives are completely soluble in the normal organic solvents used for reactions and NMR spectroscopy, and have unique chromatographic properties that greatly simplify purification: MPEG derivatives remain attached to silica when eluting with purely aprotic solvents such as DCM or EtOAc.[5] However, they are rapidly eluted in the presence of protic solvents. This allows what we now call MPEG solid-phase extraction (MSPE), where MPEG derivatives are captured on a short silica column and all unPEGylated material is rapidly eluted with EtOAc or DCM.

We suggest that the physicochemical basis for MPEG's behaviour on silica is that MPEG has multiple hydrogen-bond acceptor sites to interact with multiple hydrogen-bond donors on the surface of the silica, but no hydrogen-bond donor sites to interact with aprotic solvents. Although the lone pairs of the carbonyl oxygen atom of ethyl acetate are more Lewis basic than those on the ether oxygen atoms of MPEG and will exchange individual contacts to the silica surface, there is a strong entropic advantage, similar to the chelate effect of multidentate ligands, that means the MPEG is not displaced. On the other hand, when a protic solvent such as methanol is employed, the entropic advantage is overcome by the strong solvation of the MPEG through hydrogen bonding.

MSPE has been exploited only in oligosaccharide synthesis,[5–8] and then only using light-MPEG-tagged starting materials to make light-MPEG-tagged products, before release. However, carrying MPEG-supported material through several synthetic steps has the disadvantage that separation of one MPEG-tagged compound from another can be difficult; this led Ito's group to develop a capture release strategy.[6]

The alternative to tagging the compound of interest is to employ light-MPEG-tagged reagents, catalysts and scavengers in conjunction with MSPE in the synthesis of untagged compounds. This approach has not previously been tried. We now demonstrate light-MPEG-assisted organic synthesis (MPAOS) with a toolkit of light-MPEG-supported reagents, catalysts and scavengers for the production and easy purification of the carboxylic acid derivatives and carbonic acid derivatives which are the mainstay of drug discovery (Fig. 1). This approach is analogous to polymer-assisted solution-phase synthesis,[9] which avoids build up of side products and simplifies monitoring of reactions, but has the problems of heterogeneous reactions.[3,4] MPAOS involves homogeneous reactions, is simple and inexpensive (using only normal silica and solvents), employs reagents whose purity can be easily checked before use, and allows two supported reagents to be used together even when they are required to react with each other. Reagents attached to heavy PEG (MW 2000–20 000) have been used in solution-phase synthesis and removed by precipitation, but their removal relies on insolubility in non-polar solvents and co-precipitation of polar compounds can occur.[3,4] MPAOS avoids this problem as it does not require non-polar solvents; indeed, light-MPEG tagged compounds, which have higher loadings, are soluble even in non-polar solvents. For example, ^{M}TPP, which is the light-MPEG-supported version of triphenylphosphine (TPP), has more than twice the loading of bifunctionalised heavy-PEG TPP,[10] and a 0.2 M solution of ^{M}TPP in diethyl ether or *tert*-butyl methyl ether at 0 °C shows no precipitation. High loading dendritic polyglycerol supported reagents related to those in Fig. 1 have been reported.[11] They are also removed by precipitation from non-polar solvents or by dialysis, and have not been exploited further, except as starting materials to prepare other dendrimers.[12] Recently, a low MW PEG carbodiimide was reported for functionalising nano-particles in water[13] and it might be useful for array synthesis.

All the MPEG-supported compounds in Fig. 1 were prepared in 1–4 simple steps from MPEG-OH (average MW 550) by adapting preparations of related compounds (see ESI†

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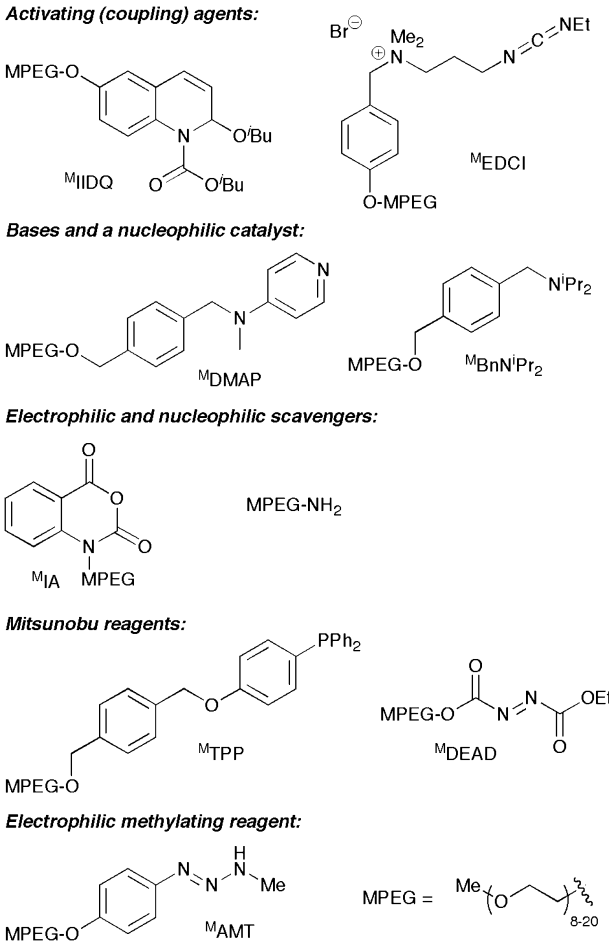
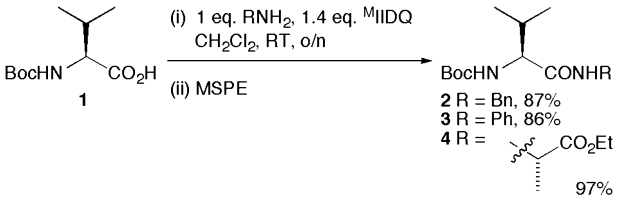


Fig. 1 Light-MPEG-supported reagents for the synthesis of carboxylic acid and carbonic acid derivatives.

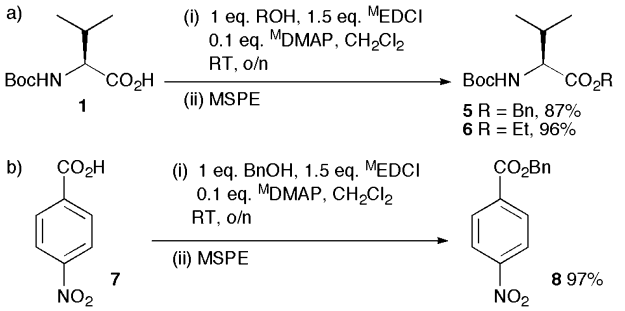
for full details). MPEG-OH is produced industrially from ethylene oxide on a very large scale for cosmetics and household uses (Carbowax^{TM}), and is cheaply available from standard suppliers of fine chemicals. The purity of the synthesized reagents was demonstrated using the methyl signal of the MPEG as an internal reference (δ 3.4) in the ^{1}H NMR spectra. Loadings were determined from the nitrogen or phosphorus content by microanalysis and were in the range 1–1.6 mmol of reagent per gram, depending on the mass of the parent reagent.

Herein, the use of each MPEG-supported compound is illustrated with examples of the preparation of one type of carboxylic acid or carbonic acid derivative. At the end of each reaction, solvent is removed under reduced pressure and then MSPE carried out to remove MPEG-supported material, using 10–14 g of silica for every 1 g of solvent-free unpurified material and eluting the product with ethyl acetate.

The most common way of converting a carboxylic acid into a carboxylic acid derivative is by nucleophilic acyl substitution. Light-MPEG-supported versions of standard activating agents (^{M}IIDQ and ^{M}EDCI), bases and nucleophilic catalysts (^{M}BnN^{i}Pr$_2$ and ^{M}DMAP) can be used in the reaction itself. Alternatively or in combination with these, scavengers (MPEG-NH$_2$[14] and ^{M}IA) can be added after reaction to remove unPEGylated reagents and side products.



Scheme 1 Amide synthesis using an MPEG-supported coupling agent.



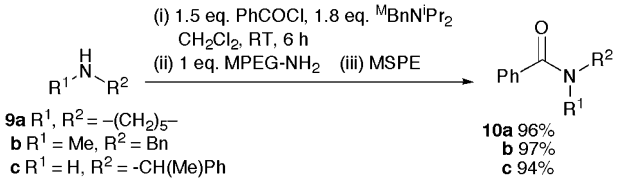
Scheme 2 Ester synthesis using an MPEG-supported coupling agent.

^{M}IIDQ is the MPEG-supported version of 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline,[15–17] an activating agent that generates a mixed anhydride *in situ*. Coupling *N*-Boc-valine **1** with a variety of amines, followed by MSPE, gave the amides **2–4** in good yields and high purity (Scheme 1).

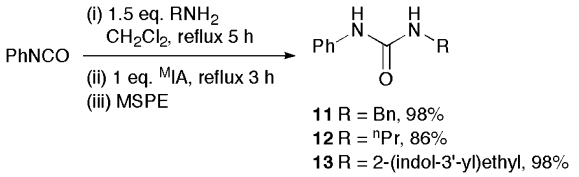
Carbodiimides are also common activating agents in the formation of carboxylic acid derivatives,[15] so MPEG-supported EDCI was used in conjunction with a supported version of the nucleophilic catalyst DMAP to convert *N*-Boc-valine **1** into esters **5** and **6**, and *p*-nitrobenzoic acid **7** into benzyl ester **8** (Scheme 2). Again the products were isolated in high yields and excellent purity following MSPE.

An alternative to the use of supported reagents is to employ supported scavengers. MPEG-supported benzyldiisopropylamine was used in the reaction of amines **9a–c** with an excess of benzoyl chloride, when reaction was complete MPEG-NH$_2$ was added to scavenge unreacted acid chloride (Scheme 3). All MPEG-supported compounds were removed by MSPE giving the pure amides **10a–c** following evaporation of solvent. Similarly, the electrophilic scavenger ^{M}IA (the MPEG-supported version of isatoic anhydride[18]) was added at the end of reactions between phenyl isocyanate and various amines, used in excess, to give good yields of pure ureas **11–13** following MSPE (Scheme 4).

Although nucleophilic acyl substitution is the most common way of making esters, nucleophilic substitution of a good leaving group by a carboxylate anion is also frequently used.



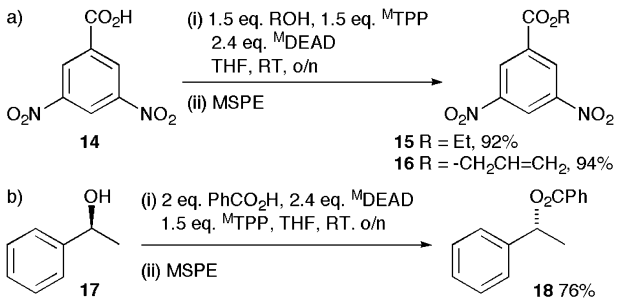
Scheme 3 Amide synthesis using an MPEG-supported base and nucleophilic scavenger.



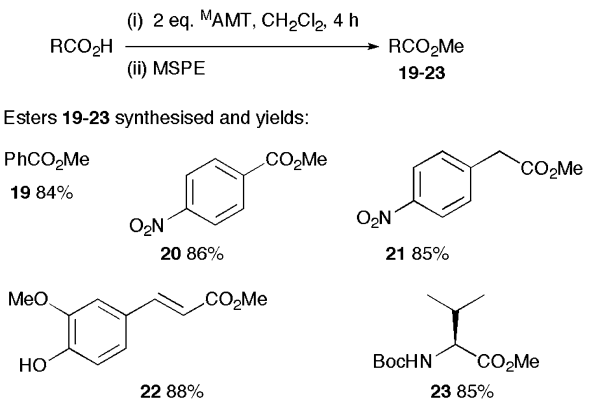
Scheme 4 Urea synthesis using an MPEG-supported electrophilic scavenger.

The Mitsunobu reaction is particularly important.[19] It uses the combination of TPP and diethyl azadicarboxylate (DEAD) to convert an alcohol into a triphenylphosphine oxide (TPPO) leaving group while simultaneously generating a nucleophilic anion from a weak acid. Unfortunately, the TPPO and reduced DEAD produced by the reaction are often difficult to remove from the desired product by chromatography. On the other hand, our MPEG-supported versions of these reagents ^{M}TPP and ^{M}DEAD and the side products produced from them are easily removed by MSPE, so that carboxylic acid **14** is converted into esters **15** and **16** in high yield, and similarly alcohol **17** gives ester **18** in high purity following MSPE (and an alkaline aqueous wash in the case of ester **18**, Scheme 5).

Finally, 1,3-arylmethyltriazenes are alternative reagents to diazomethane for the mild methylation of carboxylic acids.[20] The MPEG-version of this reagent ^{M}AMT methylates a range of acids to give methyl esters **19–23** in good yield and high purity following MSPE (Scheme 6).



Scheme 5 Mitsunobu reactions using MPEG-supported reagents.



Scheme 6 Methylation of carboxylic acids using MPEG-supported arylmethyltriazene.

In summary, we have demonstrated light-MPEG-assisted organic synthesis (MPAOS) for the first time, as a new and inexpensive way of simplifying solution phase synthesis using only standard glassware and normal silica. We have simultaneously provided a whole toolkit of supported reagents for the preparation of esters, amides and ureas. MPAOS should be easy to automate, and the light-MPEG toolkit should greatly facilitate the synthesis of arrays of compounds for drug discovery.

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