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Preparation of Poly(Ethylene Glycol) Sulfonamide: Synthesis of N-Supported β -Aminoesters via the Aza-Baylis–Hillman Reaction

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The 2-trimethyl silyl ethylsulfonyl (or SES) group is a valuable protecting group of amines in organic synthesis.¹ It can be cleaved by fluoride-promoted β -elimination. The SES-activated imines generated either from the corresponding sulfinyl chloride,² SES–NH₂³ or from SES–NSO⁴ are promising synthetic intermediates, since they can be involved in various reactions for the construction of more complex molecules, such as Diels–Alder^{4a,5} or [3 + 2] cycloadditions,^{3b} aziridination,^{3a,6} reduction,^{4c,7} and addition of organo-metallics^{4b,d,8} or enol ethers.^{3c,9}

Recently, sulfonyl imines have been involved in an efficient method for the synthesis of β -aminoesters¹⁰ via the so-called aza-Baylis–Hillman reaction.¹¹ An in situ preparation of the imine starting from tosylamine **1** has been described^{11d–g}, and subsequent reaction with acrylate **4** provided the amino ester (eq 1, R¹ = Ts). To our knowledge, such a reaction with an easily removable sulfonyl protection is unprecedented. We now report the first nitrogen-anchored polymer-supported aza-Baylis–Hillman reaction (eq 1, R¹ = PEG–SES).

For this purpose, a novel SES-type linker was prepared¹² and attached to an appropriate PEG polymer.¹³ The synthesis of PEG–SES amine **2**, precursor of the imine involved in the aza-Baylis–Hillman, is described in Scheme 1.

Tosylated PEG diamine **9** was reacted with the mesylate **8** (obtained from the known alcohol **7**¹⁴) in the presence of a base to give **10**. Bisulfite transformation^{12,15} of the

Scheme 1

Table 1. Influence of the Solvent on the Conversion to Product (%) at 24 h of Reaction^a

R ²	THF	dioxane	no solvent
phenyl	100	100	100 (3)
3,5-dimethoxyphenyl	93	95	100 (12)
2-isobutyl	33	65	100 (12)

^a When the reaction is faster, the reaction time is given in brackets (in hours).

silylated olefin resulted in the formation of sulfonate **11**. Action of PCl₅ provided the corresponding sulfonyl chloride, which was reacted with ammonia gas to yield PEG–SES–NH₂ **2**. At each step, the reaction was monitored by ¹H NMR¹⁶, and the product was recovered after precipitation in Et₂O.

As a first experiment, PEG–SES–NH₂ **2** was reacted with methyl acrylate and benzaldehyde in the presence of DABCO in dioxane to provide the expected amino ester with a complete conversion and in good yield as the sole product (eq 1, R² = Ph, R³ = Me). THF as solvent was also tried, but the reaction still needed 24 h to reach completion (Table 1). Since the Baylis–Hillman reaction is known to be slowed by dilution with a solvent, we performed the reaction in the absence of solvent.¹¹ⁱ In that case, reaction time was dramatically reduced since 100% conversion into the final product was obtained within only 3 h at 70 °C in the case of benzaldehyde. Furthermore, the reaction conditions presented herein were also tested for aldehydes that are known to react slowly,¹¹ⁱ such as a deactivated aromatic aldehyde (3,5-dimethoxybenzaldehyde) and an aliphatic aldehyde (isovaleraldehyde) (Table 1). In both cases, when a solvent was present, full conversion could not be obtained within 24 h. In sharp contrast, in the absence of solvent, the reaction was complete within 12 h. Switching the base from DABCO to quinuclidine did not significantly modify the reaction rate. Microwave activation²⁰ was also investigated and provided results similar to those of conventional heating, but with a shorter reaction time (30–40 min).

The presence of a polymeric support provides the possibility of employing a large excess of reactants that is easily

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Figure 1. Examples of amino esters obtained by reaction of aza-Baylis–Hillman in the absence of solvent.

Scheme 2

removed after precipitation by filtration and washing. Consequently, the reaction, including the in situ imine formation, was driven to completion by the large excess of reactants (20 equiv) (Scheme 2). Moreover, one possible competing process is the concomitant formation of the β -hydroxy ester via a direct Baylis–Hillman reaction between methyl acrylate and benzaldehyde.^{11f} Since the polymer is connected to the nitrogen atom of the starting material, only the nitrogen containing-products were isolated upon precipitation, whereas the hydroxyester side-product was eliminated by filtration and washing. This resulted in the isolation of the β -amino ester as the sole product (Scheme 2). An alternative to this supported synthesis would have been to anchor acrylate **4** via an ester bond to the polymer.^{11e,17} But the preferred sulfonyl connection to nitrogen has further advantages. First, an ester bond is more prone to cleavage

in basic medium, especially with the possible presence of moisture associated with an oxophilic polymer, which would result in the loss of the product.¹⁸ Second, one can envisage a supported reaction with other Michael acceptors than acrylate.^{11f,19}

This aza-Baylis–Hillman represents one more example of a PEG-supported reaction that can be performed in the absence of solvent. Indeed, we have shown recently that PEG-supported molecules could participate in reactions, such as phase-transfer catalyzed alkylation²⁰ or ring-closing metathesis,²¹ under solvent-free conditions. A PEG-supported molecule such as **2** is solid at room temperature but melts at the reaction temperature, providing a solvent-like environment for the reaction.

This three-component aza-Baylis–Hillman reaction was performed in parallel with various aldehydes. Figure 1 shows the diversity of synthesized unsaturated β -aminoesters.

The substituents and their different positions on the aromatic ring of the aryl aldehyde were varied. Hetero-aromatic aldehydes can also take part in this reaction to yield unsaturated β -aminoesters, such as **6d**, **6h**, and **6l**. Although the use of other aliphatic aldehydes has not been investigated, the preparation of **6n** shows that such and maybe other unreactive aldehydes could be considered. Interestingly, the nonprotected 3-hydroxy benzaldehyde could react in good yield. Direct release from the polymer (CsF, Ac₂O) resulted in the cleavage but with the concomitant formation of the corresponding acetate.

The unsaturated β -aminoesters **6a–n** are valuable synthons, since they own various functionalities that can be used in further reactions.²² As a proof of concept, we tested the hydrogenation/cleavage sequence on four of the unsaturated β -aminoesters (**6a–d**). Since the hydrogenation with classical conditions (H₂, Pd/C, or Pd(OH)₂) was very slow, this reaction was performed with H₂ in the presence of

Table 2. Examples of Aminoesters Obtained by Hydrogenation Followed by Cleavage from the Polymer

	R ²	% yield	
		12	13
a	phenyl	92	25
b	4-methoxycarbonylphenyl	88	26
c	3,5-dimethoxyphenyl	91	34
d	2-furyl	86	34

Wilkinson's catalyst to yield **12a–d** with excellent conversion (eq 2).

Release from the polymer support was performed by action of fluoride ions, followed by trapping with acetic anhydride, to yield the acetylated aminoesters **13a–d**. Results for the syntheses of β -amino esters, including cleavage from the polymer, are presented in Table 2. The yields are rather modest, but the purity is high without further purification.

In summary, we have developed a new sulfonyl linker and presented the first examples of the N-supported aza-Baylis–Hillman reaction for the parallel synthesis of β -aminoesters. It is worth noting that the absence of solvent accelerates the reaction. Further transformation (hydrogenation) has been efficiently performed, and preliminary results with regard to the cleavage/deprotection step have been presented. Extension of this chemistry is currently underway in our laboratory.

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