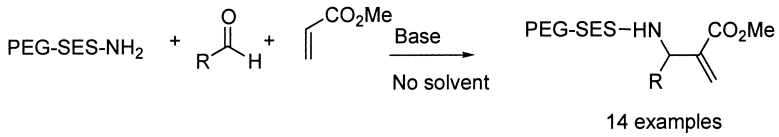
Report

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

Patrice Ribire, Christine Enjalbal, Jean-Louis Aubagnac, Neerja Yadav-Bhatnagar, Jean Martinez, and Frdric Lamaty

J. Comb. Chem., **2004**, 6 (4), 464-467• DOI: 10.1021/cc049966n • Publication Date (Web): 18 May 2004



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

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

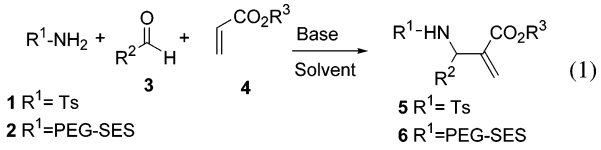
Patrice Ribière,[†] Christine Enjalbal,[†] Jean-Louis Aubagnac,[†] Neerja Yadav-Bhatnagar,[‡] Jean Martinez,[†] and Frédéric Lamaty*,[†]

Laboratoire des Aminoacides, Peptides et Protéines (LAPP), CNRS-Universités Montpellier 1 et 2, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France, and Aventis Pharma, 102, route de Noisy, 93325 Romainville Cedex, France

Received January 27, 2004

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−NH_2[3] or from SES−NSO[4] 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 organometallics[4b,d,8] or enol ethers.[3c,9]

Recently, sulfonyl imines have been involved in an efficient method for the synthesis of β-aminoesters[10] 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, R^1 = 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, R^1 = PEG-SES).



(1)

For this purpose, a novel SES-type linker was prepared[12] and attached to an appropriate PEG polymer.[13] The synthesis of PEG-SES amine **2**, precursor of the imine involved in the aza-Baylis−Hilman, 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**. Bisulfitic transformation[12,15] of the silylated olefin resulted in the formation of sulfonate **11**. Action of PCl_5 provided the corresponding sulfonyl chloride, which was reacted with ammonia gas to yield PEG-SES−NH_2 **2**. At each step, the reaction was monitored by ^{1}H NMR[16], and the product was recovered after precipitation in Et_2O.

Scheme 1

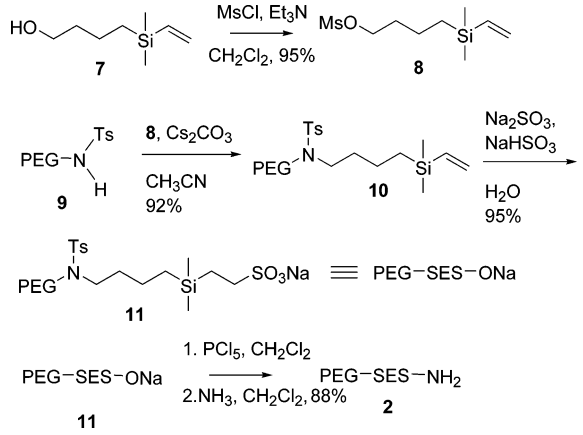


Table 1. Influence of the Solvent on the Conversion to Product (%) at 24 h of Reaction[a]

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).

As a first experiment, PEG-SES−NH_2 **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, R^2 = Ph, R^3 = 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.[11l] 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,[11l] 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 activation[20] 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

* To whom correspondence should be addressed. Fax: +33 (0) 4 67 14 48 66. E-mail: frederic@univ-montp2.fr.
[†] CNRS-Universités Montpellier.
[‡] Aventis Pharma.

10.1021/cc049966n CCC: $27.50
Published on Web 05/18/2004

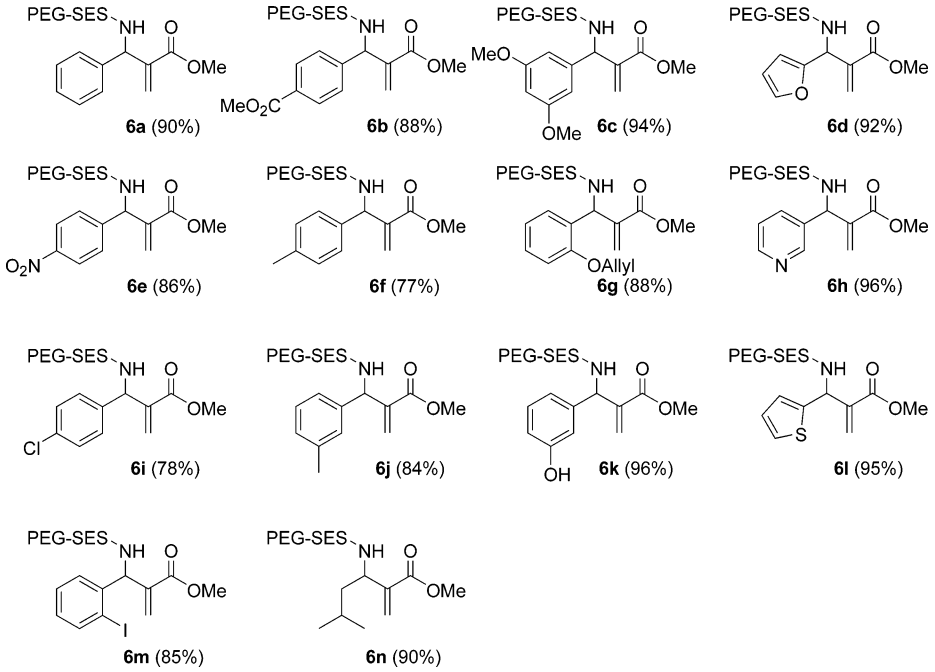
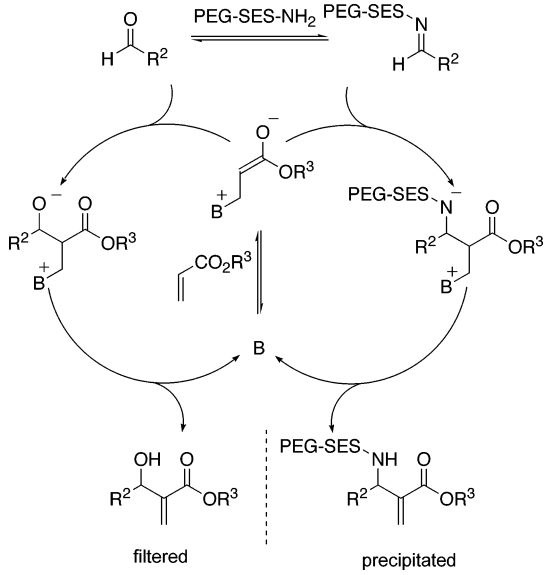


Figure 1. Examples of amino esters obtained by reaction of aza-Baylis−Hillman in the absence of solvent.

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 alkylation[20] 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.

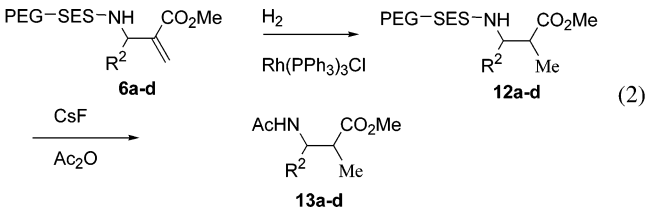
The substituents and their different positions on the aromatic ring of the arylic aldehyde were varied. Heteroaromatic aldehydes can also take part in this reaction to yield unsaturated β-aminoesters, such as **6d**, **6h**, and **6l**. Although the use of other aliphatic aldehydes has not been investigated, 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, Ac_2O) 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 (H_2, Pd/C, or $Pd(OH)_2$) was very slow, this reaction was performed with H_2 in the presence of

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

		% yield	
	R^2	**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).



(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.

Acknowledgment. We thank the CNRS and the MENRT for financial support. P.R. thanks Aventis Pharma for a fellowship.

Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. ^{1}H NMR spectra of compounds **6a**−**n**, **12a**−**d**, and **13a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Weinreb, S. M.; Ralbovsky, J. L. In *Hanbook of Reagents for Organic Synthesis, Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. J., Eds.; Wiley: Chichester, 1999; p 425−427. (b) In *Protective Groups in Organic Synthesis*; 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; Wiley: New York, 1999; p 612. (c) Kocienski, P. J. In *Protecting Groups*; Enders, D., Noyori, R., Trost, B. M., Eds.; Thieme: Stuttgart; New York, 2000, p 215−216.

(2) Artman, G. D.; Bartolozzi, A.; Franck, R. W.; Weinreb, S. M. *Synlett* **2001**, 232−233.

(3) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368−8369. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031−5041. (c) Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J., III.; Lectka, T. *Tetrahedron* **1999**, *55*, 8869−8882.

(4) (a) Sisko, J.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3037−3040. (b) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393−395. (c) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 3475−3482. (d) Schleusner, M.; Gais, H.-J.; Koep, S.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 7789−7800.

(5) Li, B.; Franck, R. W.; Capozzi, G.; Menichetti, S.; Nativi, C. *Org. Lett.* **1999**, *1*, 111−113.

(6) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *120*, 361−362. (b) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587−1589. (c) Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635−1643. (d) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433−1436. (e) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335−2344.

(7) (a) Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 4143−4145. (b) Ward, D. E.; Gai, Y.; Kaller, B. F. *J. Org. Chem.* **1996**, *61*, 5498−5505.

(8) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.

(9) (a) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III.; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168−2169. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67−77.

(10) (a) *Enantioselective synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035

(11) (a) Perlmutter, P.; Chin, C. T. *Tetrahedron Lett.* **1984**, *25*, 5951−5952. (b) Kuendig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413−14. (c) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696−701. (d) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731−2732. (e) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729−2730. (f) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2001**, *66*, 6498−6501. (g) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329−2334. For the use of chiral sulfinimines, see: (h) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577−1581. (i) Shi, M.; Xu, Y. M. *Tetrahedron: Asymmetry* **2002**, *13*, 1195−1200. For the use of diphenylphosphinamide, see: (j) Shi, M.; Zhao, G.-L. *Tetrahedron Lett.* **2002**, *43*, 9171−9174. For reviews on the Baylis−Hillman reaction, see: (k) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (l) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (m) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, 103, 811−891.

(12) For the synthesis of a related but more fragile linker, see: Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2002**, 2308−2316.

(13) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546−54.

(14) (a) Kricheldorf, H. R.; Moerber, G.; Regel, W. *Synthesis* **1981**, *5*, 383−384. (b) Kirpichenko, S.; Tolstikova, L.; Suslova, E.; Albanov, A.; Voronkov, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *106*, 47−54.

(15) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, ***27***, 2099−2102.

(16) Each compound supported on PEG has been characterized by ^{1}H, ^{13}C NMR.

(17) (a) Richter, H.; Walk, T.; Hoeltzel, A.; Jung, G. *J. Org. Chem.* **1999**, *64*, 1362−1365. (b) Räcker, R.; Döring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932−6939.
(18) Lakshmipathi, P.; Crevisy, C.; Gree, R. *J. Comb. Chem.* **2002**, *4*, 612−621.
(19) For examples, see: (a) Genski, T.; Taylor, R. J. K. *Tetrahedron Lett.* **2002**, *43*, 3573−3576. (b) Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393−5395. (c) Jauch, J. *Eur. J. Org. Chem.* **2001**, 473−476. (d) Keck, G. E.; Welch, D., S. *Org. Lett.* **2002**, *4*, 3687−90.
(20) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **2000**, *41*, 6371−6375.
(21) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787−6790.
(22) (a) Kündig, E. P.; Xu, L.-H.; Romanens, P. *Tetrahedron Lett.* **1995**, *36*, 4047−50. (b) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 319−21. (c) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213−1220. (d) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737−3740. (e) Lee, H. J.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **1999**, *40*, 4363−4366. (f) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett.* **1998**, *39*, 6223−6226. For reactions on close structures, see, for example: (g) Huck, J.; Receveur, J.-M.; Roumestant, M.-L.; Martinez, J. *Synlett* **2001**, 1467−1469. (h) Huck, J.; Duru, C.; Roumestant, M. L.; Martinez, J. *Synthesis* **2003**, 2165−2168. (i) Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Organometallics* **2003**, *22*, 2426−2435.

CC049966N