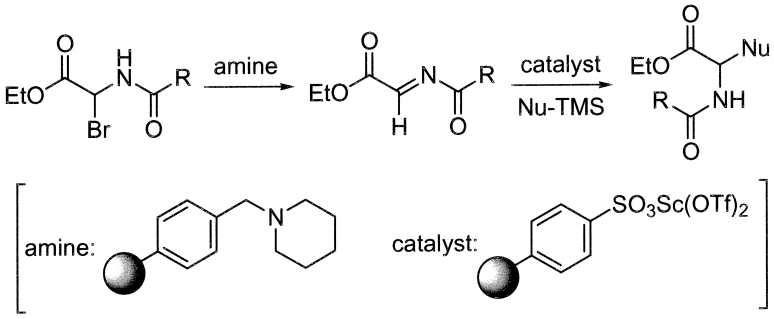
JOURNAL OF combinatorial CHEMISTRY

Report

Direct Formation of N-Acylated Amino Acid Derivatives via Nucleophilic Addition to *N*-Acylimino Esters Using a Polymer-Supported Amine and Scandium Triflate

Sh Kobayashi, Hidetoshi Kitagawa, and Ryosuke Matsubara

J. Comb. Chem., **2001**, 3 (5), 401-403• DOI: 10.1021/cc010009c • Publication Date (Web): 07 July 2001



More About This Article

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

- Supporting Information
- Links to the 1 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

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

JOURNAL OF combinatorial CHEMISTRY

Volume 3, Number 5 September/October 2001

Reports

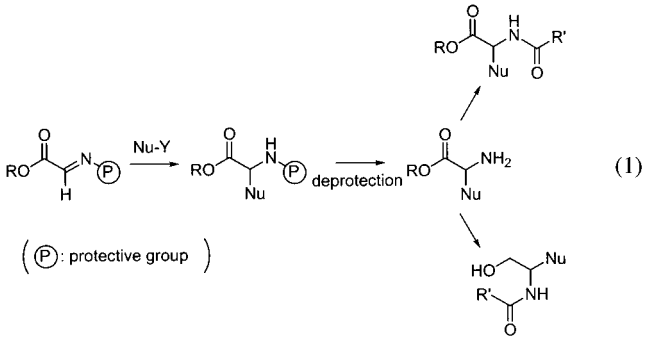
Direct Formation of N-Acylated Amino Acid Derivatives via Nucleophilic Addition to *N*-Acylimino Esters Using a Polymer-Supported Amine and Scandium Triflate

Shū Kobayashi,* Hidetoshi Kitagawa, and Ryosuke Matsubara

Graduate School of Pharmaceutical Sciences, The University of Tokyo and CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyou-ku, Tokyo, 113-0033, Japan

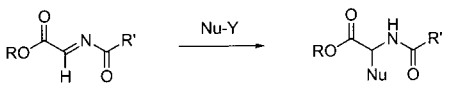
Received February 28, 2001

N-Acylated amino acid derivatives are often observed in biologically important compounds such as peptides,[1] ceramides,[2] etc. The use of α-imino esters provides a convenient method for the preparation of N-acylated amino acid derivatives (eq 1). After nucleophilic addition to α-imino esters,



(1)

the protective groups of the amino moieties are removed, and then the amino groups are acylated.[3] More conveniently, reactions of *N*-acylimino esters would give N-acylated amino acid derivatives directly (eq 2).[4] However, *N*-acylimino esters



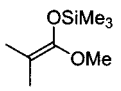
(2)

are unstable and their use in organic synthesis has been rather limited. In this paper, we describe a new method for the preparation of N-acylated amino acid derivatives via nucleophilic addition to *N*-acylimino esters using polymer-supported amine and scandium catalysts. The method is simple and provides a convenient way for the preparation of N-acylated amino acid derivatives.

We chose α-bromoglycine derivatives (**1a**−**d**) as the starting material.[5] Ethyl *N*-benzoyl-2-bromoglycine (**1a**) was treated with triethylamine to give highly active *N*-acylimino ester in situ.[6] Subsequently, the addition of silyl enol ether **2a** in the presence of a catalytic amount of $Sc(OTf)_3$[7] afforded the desired adduct (**3a**).

Nucleophile (**2**)

2a: R = H
2b: R = OMe
2c: R = Cl

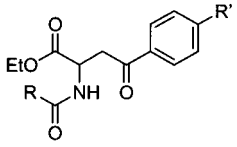


2d

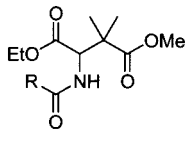
2e

2f

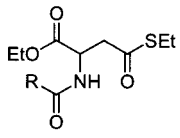
Product (**3**)



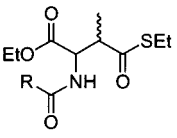
3a: R = Ph, R' = H
3b: R = Ph, R' = OMe
3c: R = Ph, R' = Cl
3f: R = Me, R' = OMe
3g: R = $(CH_2)_{10}CH_3$, R' = OMe
3k: R = OEt, R' = OMe



3d: R = Ph
3h: R = $(CH_2)_{10}CH_3$
3l: R = OEt



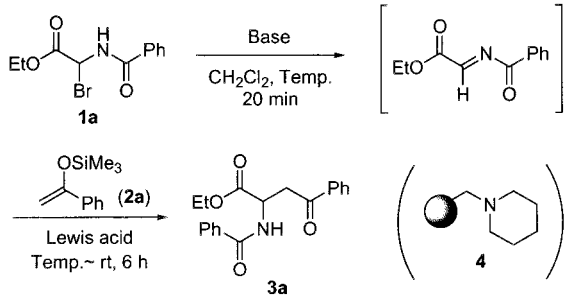
3e: R = Ph
3i: R = $(CH_2)_{10}CH_3$



3j: R = $(CH_2)_{10}CH_3$ (dr = 65 : 35)
3m: R = OEt (dr = 55 : 45)

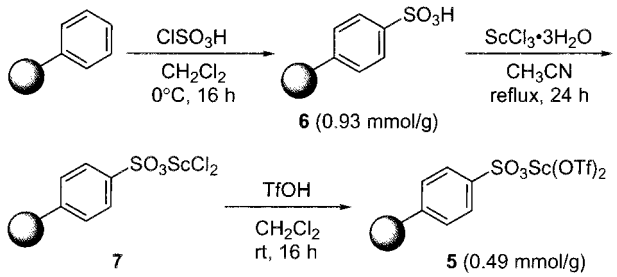
10.1021/cc010009c CCC: $20.00
Published on Web 07/07/2001

Table 1. Mannich-Type Reaction of *N*-Acyliminoacetates with Silyl Enol Ether (**2a**)



entry	base (equiv)	Lewis acid (mol %)	**2a** (equiv)	temp, °C	yield, %
1	Et_3N (1.2)	$Sc(OTf)_3$ (20)	3.0	−78	71
2	Et_3N (1.2)	$Sc(OTf)_3$ (20)	3.0	0	40
3	Et_3N (1.2)	$Sc(OTf)_3$ (10)	1.2	−78	33
4	**4** (1.5)	**5** (5)	3.0	−78	76
5	**4** (1.5)	**5** (5)	3.0	0	84
6	**4** (1.5)	**5** (1)	1.2	0	79

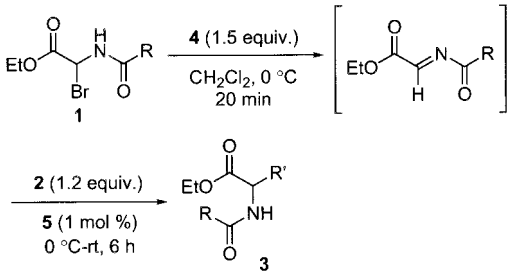
Scheme 1. Synthesis of Polymer-Supported Scandium Catalyst (**5**)



Several reaction conditions were examined, and the results are summarized in Table 1. In the case of using 20 mol % of $Sc(OTf)_3$ as the catalyst, the reaction proceeded to give **3a** in 71% yield (entry 1). When the amounts of the catalyst and the silyl enol ether were reduced, the yield of **3a** was decreased (entry 3). It was assumed that the catalytic activity of $Sc(OTf)_3$ was somewhat depressed by the coordination of a slight excess of Et_3N. We then decided to use a polymer-supported reagent and catalyst. Commercially available piperidinomethylpolystylene **4** and polymer-supported scandium catalyst **5** were selected.[8] Polymer-supported scandium catalyst (**5**) was synthesized from Merrifield resin according to the modified method shown in our previous report (Scheme 1).[9] The sulfonation of polystyrene (1% divinylbenzene cross-linked) with $ClSO_3H$ gave polymer-supported sulfonic acid (**6**). The loading level of **6** was determined to be 0.93 mmol/g by the acid−base titration.[10] The treatment of **6** with $ScCl_3 \cdot 6H_2O$ gave polymer-supported scandium chloride (**7**). Finally, **7** was treated with trifluoromethanesulfonic acid to afford scandium triflate **5**. The loading of **5** was determined by the amount of ash in the elemental analysis.

When polymer-supported amine **4** and catalyst **5** were used, the yields were improved significantly even in the case where the amounts of the catalyst and the silyl enol ether were decreased (entries 4−6). As expected, no interaction between the polymer-supported amine and the scandium catalyst occurred, and thus, the catalytic activity of the scandium was not depressed by the coordination of the amine. In addition, workup procedures became very simple by using the polymer-supported amine and catalyst; only filtration gave the desired products, and this procedure is suitable for the preparation of a library.

Table 2. Mannich-Type Reaction of *N*-Acyliminoacetates with Various Nucleophiles



entry	substrate	Nu−Y	product	yield, %
1	**1a**: R = Ph	**2a**	**3a**	79
2		**2b**	**3b**	85
3		**2c**	**3c**	76[a]
4		**2d**	**3d**	91
5		**2e**	**3e**	86
6	**1b**: R = Me	**2b**	**3f**	74
7	**1c**: R = $(CH_2)_{10}CH_3$	**2b**	**3g**	86
8		**2d**	**3h**	75
9		**2e**	**3i**	79
10		**2f**	**3j**	82
11	**1d**: R = OEt	**2b**	**3k**	71
12		**2d**	**3l**	90
13		**2f**	**3m**	76

[a] The reaction was performed for 12 h.

Other substrates were investigated, and the results are summarized in Table 2. The reactions of several silyl enolates proceeded smoothly to afford the corresponding adducts in high yields. In the reactions of substrates having a long-chain acyl group (**1c**) or a carbamate group (**1d**), the reaction also proceeded in high yields.

A typical experimental procedure is described for the reaction of **1a** with **2a**. To a solution of **1a** (28.6 mg, 0.10 mmol) in dichloromethane (1.5 mL) was added **4** (3.63 mmol/g, 41.3 mg, 0.15 mmol) at 0 °C. After the solution was stirred for 20 min, **2a** (23.1 mg, 0.12 mmol) in dichloromethane (1.0 mL) and **5** (0.49 mmol/g, 2.1 mg, 1.0 mol %) were added to the reaction mixture. The mixture was stirred for 6 h at room temperature and filtered. After the resins were washed with dichloromethane, 0.2 N HCl in dichloromethane (1.0 mL) was added to the filtrate. After being stirred for 5 min at room temperature, the mixture was evaporated to dryness. The crude product was purified by flash column chromatography on silica gel to afford **3a** (25.6 mg, 79%).

In summary, a convenient method for the preparation of N-acylated amino acid derivatives has been developed. The method is based on nucleophilic addition to in-situ-prepared *N*-acylimino esters using a polymer-supported amine and scandium salt. The procedure is very simple, and the direct formation of N-acylated amino acid derivatives has been achieved. Further studies on the synthesis of biologically important compounds as well as on an asymmetric version of this method are in progress.

Supporting Information Available. Experimental procedure for the preparation of **1a**−**d** and **3a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298−1307. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Wälchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582−2588. (c) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243−2266. (d) von Döhren, H.; Keller, U.; Vater, J.; Zocher, R. *Chem. Rev.* **1997**, *97*, 2675−2705.

(2) For reviews see the following. (a) Dickson, R. C. *Annu. Rev. Biochem.* **1998**, *67*, 27−48. (b) Kolter, T.; Sandhoff, K *Angew. Chem., Int. Ed.* **1999**, *38*, 1532−1568.

(3) (a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. (b) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168−2169. (c) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504−3506.

(4) (a) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W. Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693−1701. (b) Münster, P.; Steglich, W. *Synthesis* **1987**, 223−225. (c) Bretschneider, T.; Miltz, W.; Münster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403−5414. (d) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114−4116. For a review of *N*-acyliminium ions and related intermediates, see the following. (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

(5) For the preparation of *N*-acyl-α-bromoglycine ethyl esters, see the following. Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599−609.

(6) For other methods for the preparations of *N*-acylimino esters, see the following. (a) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4607−4610. (b) Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron Lett.* **1995**, *36*, 861−864.

(7) (a) Kobayashi, S. *Eur. J. Org. Chem.*, **1999**, 15−27. (b) Kobayashi, S. *Synlett* **1994**, 689−701.

(8) For a review see the following. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195.

(9) (a) Nagayama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 567−569. See also the following. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256−2257. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977−8978. (d) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron Lett.* **1996**, *37*, 9221−9224. (e) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985−2986.

(10) The acid−base titration procedure is described below. To a suspension of **6** (54.8 mg) in H_2O−EtOH (1/1, 20 mL) was added an aqueous NaOH solution (0.1001 N, 3.0 mL). After the mixture was stirred for 3 h, a 0.04% solution of phenolphthalein in EtOH (0.10 mL) was added to the suspension as an indicator. The solution was titrated with an aqueous HCl solution (0.0999 N, 2.60 mL) with stirring. The loading level of **6** was determined to be 0.93 mmol/g.

CC010009C