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Feasibility Studies on Amino-[2,3]Wittig Rearrangement. Silyl Triflate-Mediated [2,3]-Sigmatropic Rearrangement of α-Allylamino Esters

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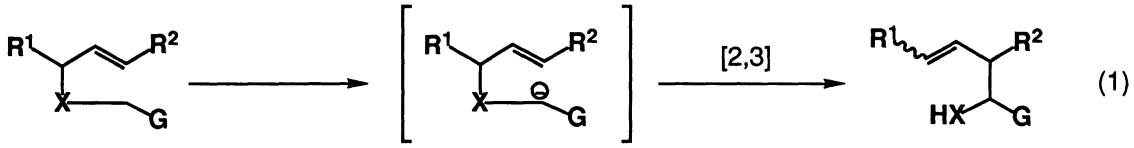
The feasibilities of both the LDA-induced and silyl triflate-mediated [2,3]-sigmatropic rearrangements of α-allylamino esters were studied. While the former enolate rearrangement does not proceed under the usual [2,3]Wittig conditions, the latter rearrangement is shown to proceed via the N-silylated ylide to provide the formal amino-[2,3]Wittig product with a high diastereoselectivity.

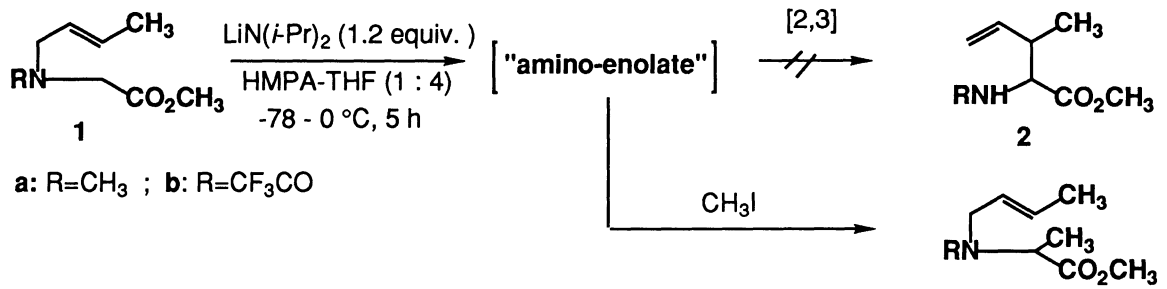
As a general reaction type, the [2,3]Wittig rearrangement (**A** → **B** in Eq. 1) has currently found wide application in organic synthesis.[1] However, no studies have been reported on its amino version, termed "amino-[2,3]Wittig rearrangement" (**C** → **D**),[2] except for the single example of N-benzyl-β-vinyl-β-lactams.[3,4] In an effort to further expand the synthetic scope of the [2,3]Wittig technology, we now disclose the results of feasibility studies on the [2,3]-sigmatropic rearrangements of the α-allylamino esters **1** which might produce the α-amino acid derivatives **2** of synthetic interest.



(1)

A, X=O
C, X=NR
B, X=O
D, X=NR

First, we studied the rearrangement of the α-crotylamino ester **1a**[5] under the usual enolate [2,3]Wittig condition [6] (Scheme 1). Rather unexpectedly, any rearrangement product **2a** was not detected in the resulting mixture (GLC and NMR assay). Instead, however, trapping the resulting mixture with iodomethane gave the



1

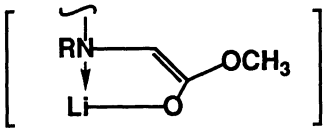
a: R=CH_3 ; **b:** R=CF_3CO

2

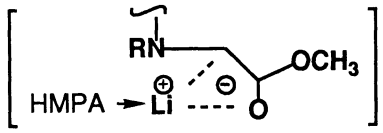
Scheme 1.

3a (52%) ; **3b** (71%)

α-methylated product **3a** in 52% yield.[7] These observations indicate that the amino-enolate thus generated even in HMPA-THF is not capable of undergoing the [2,3]-sigmatropic shift, in sharp contrast to the high [2,3]Wittig reactivity of the oxy-enolate counterpart.[6] This failure may be attributed to the fully chelated structure (**E**, R=CH_3) that cannot serve as the migrating terminus for the [2,3]-shift.[6,8] Next, a similar rearrangement of the trifluoroacetamide **1b**[5] was examined with the hope that the enolate terminus would tend to take the solvent-separated structure (**F**, R=$COCF_3$) that is favorable for the [2,3]-shift.[6] Unfortunately, again, any rearrangement product was not obtained, but **3b** was obtained via trapping the resulting mixture with iodomethane. Thus, it might be concluded that the [2,3]-sigmatropic reactivities of the amino-enolate termini concerned are much lower than that of the oxy-enolate terminus. The elucidation of mechanistic grounds for the reactivity difference must await more detailed studies on the structure and reactivity of amino-enolate species.

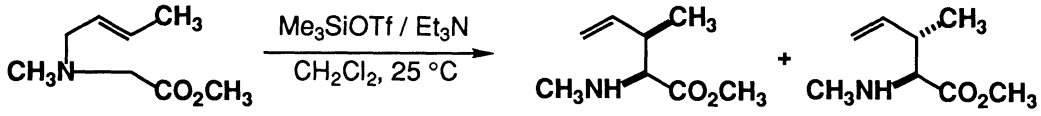


E



F

Furthermore, the applicability of the silyl triflate-mediated procedure[9] to the rearrangement of **1a** was examined. We found that the rearrangement was best achieved by adding trimethylsilyl triflate (5.0 equiv.) to a mixture of **1a** and triethylamine (4.0 equiv.) in dichloromethane at 0 °C and stirring the mixture at 25 °C for 24 h to afford, after hydrolysis, the [2,3]-shifted product **2a**[10] in 69% GLC yield with a high erythro-selectivity (Eq. 2).[11] The diastereomeric ratio was determined by capillary GLC, and the stereochemistry of these products

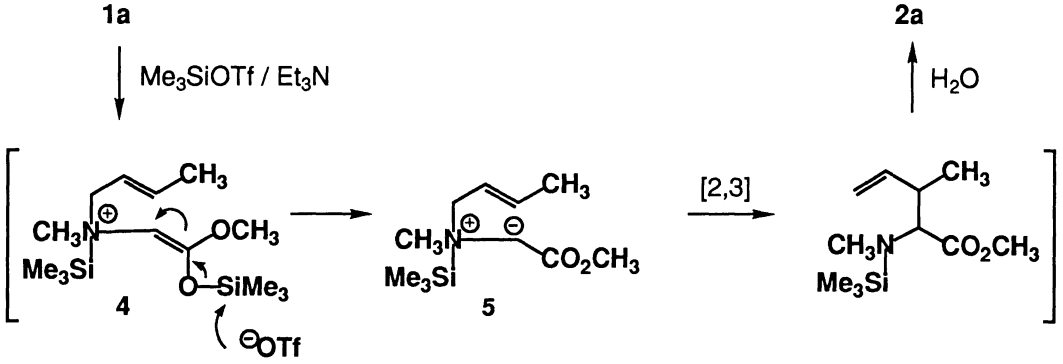


(2)

1a

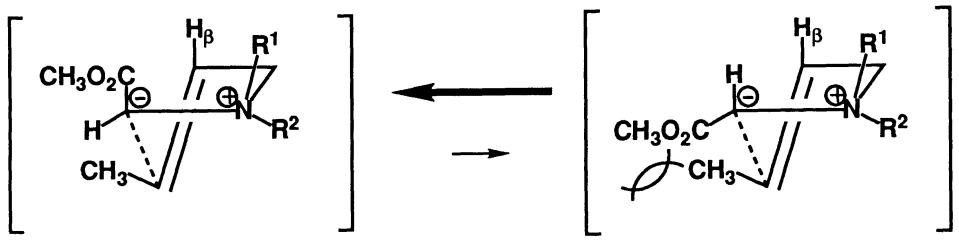
erythro **-2a** (81 : *threo* **-2a** 19)

was assigned through GLC comparisons of their hydrogenation products with an authentic threo-isomer derived from L-isoleucine.[12] In analogy with the mechanism advanced for the silyl triflate-mediated rearrangement of α-allyloxy esters,[9] the present rearrangement is likely to involve the Sommelet-type [2,3]-shift[13] of the N-silylated ylide **5** generated in situ from the silylammonium species **4** (Scheme 2).



Scheme 2.

The observed erythro-preference is reasonably interpreted as the result that the conformation **G** is sterically more favorable than **H** since the pseudo-1,3-diaxial repulsion of Hβ ↔ CO_2CH_3 in **G** is smaller than the gauche repulsion of CH_3 ↔ CO_2CH_3 in **H**.[9,14]



In summary, this work has demonstrated that the LDA-induced rearrangement of α-allylamino esters does not proceed under the usual enolate conditions, but the silyl triflate-mediated rearrangement proceeds via the N-silylated ylide to provide the formal amino-[2,3]Wittig product with a high erythro-selectivity. Further works are in progress on the amino-[2,3]Wittig rearrangement of other substrates in different ways.

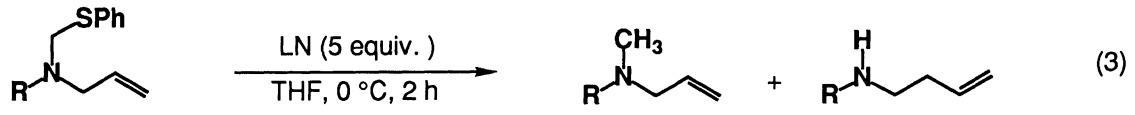
References

1) For a review, see: T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).

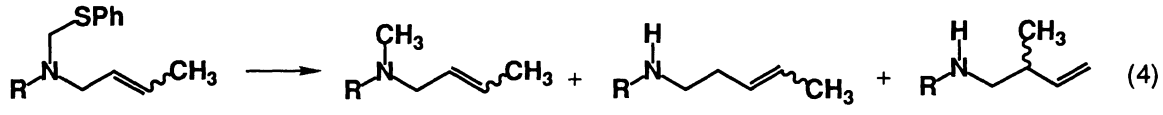
2) A frontier orbital consideration tells us that the amino-[2,3]-shift should proceed with greater facility than the usual oxy-[2,3]-shift, since the HOMO level of an amino-carbanion is much higher in energy than that of an oxy-carbanion in general, thus making the interaction between the HOMO(carbanion) and LUMO(allyl) more effective: I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," John Wiley & Sons, London (1976).

3) T. Durst, R. V. D. Elzen, and M. J. LeBelle, *J. Am. Chem. Soc.*, **94**, 9261 (1972).

4) Quite recently, Broka and Shen have reported that the reductive desulfurization of the N,S-acetal **6** with lithium naphthalenide (LN) gives rise to the reduction product **7** and the rearrangement product **8** (Eq. 3): C. A. Broka and T. Shen, *J. Am. Chem. Soc.*, **111**, 2981 (1989). Although they have claimed **8** as the amino-[2,3]Wittig product, this was proved not to be the case by our own experiment where **9** was employed as the substrate with a regiochemical marker. We found that a similar reductive desulfurization of **9** did not afford any [2,3]-shifted product **12**, instead giving a 4 : 1 mixture of the reduction product **10** and the [1,2]-shifted product **11** in 66% combined yield (Eq. 4).



6 (R= *n*-C_7H_{15}) **7** (1 : **8** 4)



9 (R= *n*-C_7H_{15}) **10** **11** **12**

5) The substrate of **1a** (95% *E*) was prepared via reaction of N-methyl glycine methyl ester with crotyl chloride (95% *E*), and **1b** (95% *E*) was obtained from glycine methyl ester hydrochloride by trifluoroacetylation followed by allylation with crotyl chloride (95% *E*) following Oppolzer's procedures: W. Oppolzer and H. Andres, *Helv. Chem. Acta.*, **62**, 2282 (1979). ^{1}H NMR ($CDCl_3$), **1a**: δ 1.72 (d, J=4.5 Hz, 3H), 2.38 (s, 3H), 3.12 (d, J=6.0 Hz, 2H), 3.27 (s, 2H), 3.77 (s, 3H), 5.35-5.95 (m, 2H); **1b**: δ 1.77 (d, J=6.0 Hz, 3H), 3.80 (d, J=2.1 Hz, 3H), 3.98-4.44 (m, 4H), 5.23-6.08 (m, 2H).

6) O. Takahashi, T. Saka, K. Mikami, and T. Nakai, *Chem. Lett.*, **1986**, 1599. It should be noted that the use of the solvent containing hexamethylphosphoramide (HMPA) is essential for effecting the ester enolate [2,3]Wittig rearrangement.

7) ^{1}H NMR ($CDCl_3$), **3a**: δ 1.27 (d, J=7.5 Hz, 3H), 1.68 (d, J=5.7 Hz, 3H), 2.26 (s, 3H), 3.07 (d, J=5.7 Hz, 2H), 3.46 (q, J=7.5 Hz, 1H), 3.69 (s, 3H), 5.35-5.87 (m, 2H); **3b**: δ 1.53 (d, J=7.5 Hz, 3H), 1.74 (d, J=5.7 Hz, 3H), 3.72 (s, 3H), 4.09 (d, J=7.5 Hz, 2H), 4.25 (q, J=7.5 Hz, 1H), 5.30-6.10 (m, 2H).

8) O. Takahashi, T. Maeda, K. Mikami, and T. Nakai, *Chem. Lett.* **1986**, 1355.

9) K. Mikami, O. Takahashi, T. Tabei, and T. Nakai, *Tetrahedron Lett.*, **27**, 4511 (1986).

10) ^{1}H NMR ($CDCl_3$), **2a**: δ 1.07 (d, J=7.5 Hz, 3H), 1.73 (s, 1H), 2.15-2.63 (m, 1H), 2.37 (s, 3H), 3.24-3.40 (m, 1H), 3.73 (s, 3H), 5.03-5.32 (m, 2H), 5.63-6.09 (m, 1H). GLC (XE-30, 3 m, 80 °C), t_R=16.1 min for erythro-**2a** and 17.5 min for threo-**2a**.

11) A large excess of the triflate was required for completion. The use of TMSOTf (2.4 equiv.) and Et_3N (2.2 equiv.), for instance, afforded only 15% isolated yield of **2a**, along with 33% recovery of **1a**.

12) GLC (XE-30, 3 m, 80 °C), t_R=16.5 min for the erythro-isomer and 17.3 min for the threo-isomer. ^{1}H NMR ($CDCl_3$), the authentic threo-isomer: δ 0.77-1.00 (m, 6H), 1.03-1.96 (m, 4H), 2.43 (s, 3H), 3.07 (d, J=6.0 Hz, 1H), 3.77 (s, 3H).

13) For a review on the Sommelet rearrangement, see: S. H. Pine, *Org. React.*, **18**, 403 (1970). For a recent example of the [2,3]-sigmatropic shift of N-ylides, see: K. Honda, S. Inoue, and K. Sato, *J. Am. Chem. Soc.*, **112**, 1999 (1990).

14) For a general discussion of the transition state model for the [2,3]-sigmatropic rearrangement, see: Ref. 1 and K. Mikami, Y. Kishi, and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983).

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