Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1534–1537
Tetrahedron Letters

Addition of a 3-alkoxy allenylzinc to *N*-acyliminium ions: new entry to propargyl *syn*-1,2-aminoalcohol units

Brindaban Roy, Alejandro Pérez-Luna, Franck Ferreira, Candice Botuha, Fabrice Chemla *

Laboratoire de Chimie Organique, UMR7611, FR2769, Université Pierre et Marie Curie, Case Courrier 183, Tour 44-45 2ème étage, 4 Place Jussieu, 75252 Paris Cedex 05, France

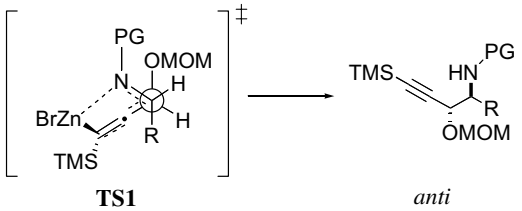
Received 26 November 2007; revised 12 December 2007; accepted 18 December 2007

Abstract

A new addition reaction of a 3-alkoxy allenylzinc reagent to *N*-acyliminiums prepared in situ from imines and acid halides is reported. Unlike addition onto imines or nitrones that affords the trans adducts, acetylenic *syn*-1,2 amino ethers are yielded with good selectivities, thus providing a new entry to propargyl *syn*-1,2-aminoalcohol units.

Acetylenic 1,2-aminoalcohol units are useful building blocks for the synthesis of natural products[1,2] and other biologically interesting compounds.[3–7] Several attractive preparations have been disclosed, including diastereoselective reductions of α-amino ynones,[4,5,7] addition of acetylides onto α-amino aldehydes,[3,7–12] condensations of tin enolates of glycinate onto ynals,[13] ring opening of ethynyl aziridines,[14] additions of 3-alkoxy allenylzincs to α-alkoxy imines[15] and sulfinylimines[16,17] and[2,3]-Wittig rearrangements.[18] However, whereas the preparation of *anti*-aminoalcohols by these methods has proven very efficient and high levels of diastereoselectivity have been generally obtained, access to their *syn* counterpart is hampered by lack of diastereoselectivity except for a few special cases.[4,6,7,9] A rapid general diastereoselective access to acetylenic *syn*-1,2-aminoalcohols is thus still lacking.

As part of our ongoing research on the reactivity of allenylzinc carbenoid reagents,[19–23] we have been interested in the addition of 3-alkoxy allenylzinc reagent **1** to carbon nitrogen double bonds. Both addition to α-alkoxy imines and sulfinylimines have been shown to occur via a six-centre cyclic transition state **TS1** involving activation of the electrophile by the metal, thus affording propargyl *anti*-1,2-amino ethers with very high levels of selectivity (Scheme 1).[15–17] Inspired by reports showing that γ-OMOM allylic stannanes add diastereoselectively to acyclic *N*-acyliminium intermediates via an antiperiplanar transition state to afford allylic *syn*-1,2-amino ethers,[24–26] we reasoned that if reagent **1** would react with such electrophiles through a similar open transition state (vide infra), *syn* amino ethers would be obtained, thus offering a new expeditious route to propargyl *syn*-1,2-aminoalcohols. Moreover, even though there have been several reports on the addition of organometallic reagents to *N*-acyliminium derivatives,[27–29] additions of allenyl-propargyl organometallics have been very scarcely described.[30]



TS1 *anti*

PG = Bn, SOtBu

Scheme 1.

* Corresponding author. Tel.: +33 1 44 27 64 36; fax: +33 1 44 27 75 67.
E-mail address: fchemla@ccr.jussieu.fr (F. Chemla).

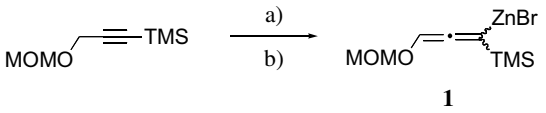
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.102

For the sake of comparison and since no data were available in the literature, we initiated our study by looking at the reaction of **1**,[31] generated in situ by the lithiation of (methoxymethyl) (3-trimethylsilylprop-2-ynyl) ether with *s*BuLi in the presence of TMEDA (Scheme 2), with simple achiral imines **2** and **3** (Scheme 3). Addition in diethyl ether was shown to take place at −50 °C within 2.5 h to give the corresponding *anti*-1,2-amino ethers ***anti*-4** and ***anti*-5** as single isomers. The *anti* stereoselectivity is in accordance with the expected cyclic transition state **TS1** (Scheme 1).

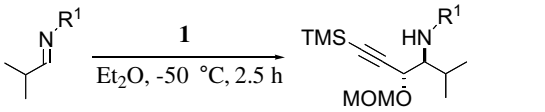
We next turned to the reaction with *N*-acyliminiums. First, paralleling the conditions used for the addition of γ-OMOM allylic stannanes, we attempted to generate electrophile **6** in situ by reaction of the parent hemiaminal **7** with BF_3–Et_2O in a *one-pot* procedure. Reported in CH_2Cl_2, this method was not compatible with our reaction conditions involving Et_2O, and no iminium generation, hence no reaction was observed. We thus decided to generate the *N*-acyliminium species in CH_2Cl_2 prior to addition onto the allenylzinc reagent (Scheme 4, Table 1). Preformation of **6** by reaction of **7** with $TiCl_4$ (method A) led to a complicated mixture of products from which no addition compounds could be isolated (entry 1). On the contrary and to our delight, preformation by reaction of imine **3** with methyl chloroformate (method B)[32] enabled smooth addition of allenylzinc reagent **1** to afford, within 3 h at −50 °C, 1,2-amino ether **8** in 40% yield and as a mixture of two diastereoisomers (*syn*:*anti* = 63:37) (entry 2).

The *syn* relative configuration of the major diastereoisomer was readily determined by comparison with pure ***anti*-8** obtained by reaction of ***anti*-5** with methyl chloroformate (Scheme 5).

Encouraged by the observed reversal of selectivity with respect to the addition onto imines, the influence of several reaction parameters was considered. Using THF as the solvent resulted in a better yield (56%), albeit to the expense of a drop in selectivity (Table 1, entry 3). By contrast, the yield in ether could be increased while keeping the same selectivity by decreasing the amount of TMEDA used to prepare allenylzinc reagent **1** from 1 equiv to 0.1 equiv (entry 4).



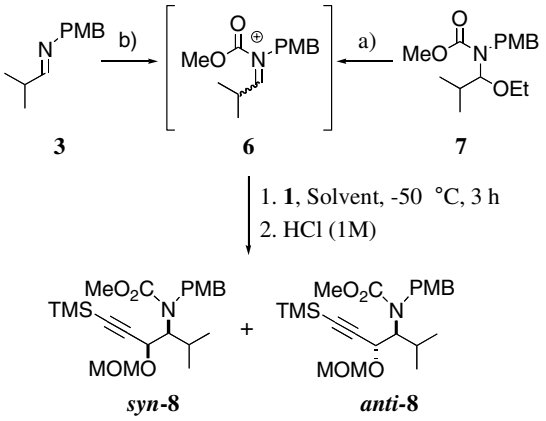
Scheme 2. Reagents and conditions: (a) *s*BuLi, TMEDA (100% or 10%), Et_2O or THF, −80 °C, 1 h.; (b) $ZnBr_2$, −80 °C, 30 min.



R^1 = Bn, **2**
R^1 = PMB, **3**

***anti*-4**, 71 %, d.r. > 98:02
***anti*-5**, 54 %, d.r. > 98:02

Scheme 3.

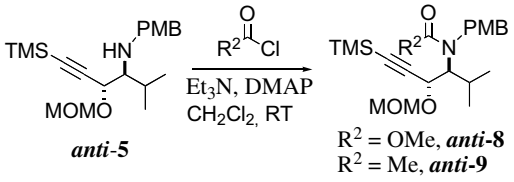


Scheme 4. Reagents and conditions: method A: (a) $TiCl_4$, CH_2Cl_2, −20 °C. Method b: (b) $ClCO_2Me$, CH_2Cl_2, −20 °C.

Table 1
Reaction of allenylzinc reagent **1** with *N*-acyliminium **6**

Entry	Solvent	TMEDA (%)	Method	dr[a] (*syn*:*anti*)	**8**[b] (%)
1	Et_2O	100	A	—	<10
2	Et_2O	100	B	63:37	40
3	THF	100	B	49:51	56
4	Et_2O	10	B	63:37	56

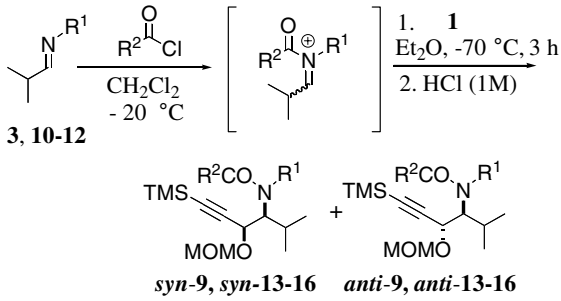
[a] Determined by NMR analysis of the crude material after reduction with $LiAlH_4$ of the carbamate moiety to the corresponding N–Me derivative.
[b] Combined yield of isolated diastereomers after chromatography.



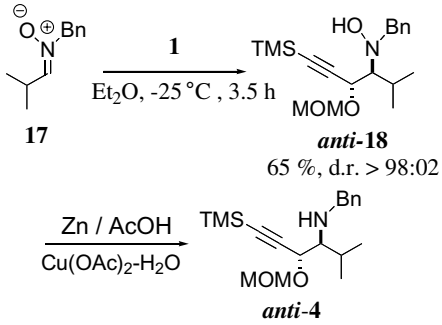
Scheme 5.

Next, addition onto different types of acyliminiums was considered (Scheme 6). Under the same reaction conditions, allenylzinc condensation also took place onto iminiums formed from imine **3** and acyl chlorides to afford 1,2 amino-alcohols **9**, **13** in reasonable yields as a mixture of two diastereoisomers (Table 2). Here again, as confirmed by comparison with acylated pure *anti*-1,2-amino ether ***anti*-9** obtained by acylation of ***anti*-5** (Scheme 5), the *syn*-isomers were the major ones. Whereas benzoyl chloride (Table 2, entry 2) gave similar levels of selectivity as methyl chloroformate, the use of acetyl chloride enabled a significant enhancement (entry 1). The imine nitrogen substituent had little impact on the reaction stereochemical outcome since reactions starting with *N*-allyl-, *N*-propyl-, or *N*-cyclohexyl- imines **10**–**12** afforded the corresponding adducts **14**–**16** with comparable selectivities as those obtained starting from imine **3** bearing a PMB group (entries 3–5 vs 1).

The observed stereochemical outcome of the addition, comparable to that of γ-OMOM allylic stannanes to *N*-acyliminiums derived from imine **2**,[24–26] is consistent with a preferred antiperiplanar acyclic transition state **TS2**



Scheme 6.



Scheme 8.

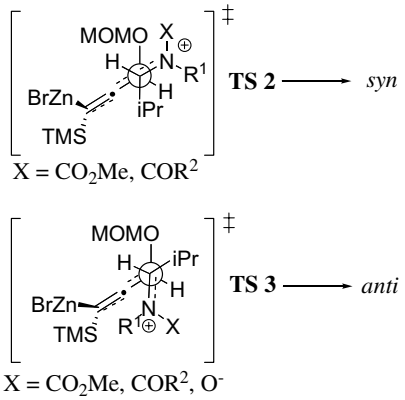
Table 2
Reaction of allenylzinc reagent **1** with *N*-acyliminiums generated by reaction of imines **3**, **10**–**12** with acyl chlorides

Entry	Imine	R^1	R^2	Product	dr[a] (*syn*:*anti*)	Yield[b] (%)
1	**3**	PMB	Me	**9**	74:26	53
2	**3**	PMB	Ph	**13**	61:39	31
3	**10**	allyl	Me	**14**	73:27	53
4	**11**	propyl	Me	**15**	72:28	70
5	**12**	Cy	Me	**16**	70:30	96

[a] Determined by NMR analysis of the crude material.
[b] Combined yield of isolated diastereomers after chromatography.

affording the *syn* adducts, and a less favourable synclinal acyclic transition state **TS3** affording the *anti* adducts (Scheme 7).

Nevertheless, the observed influence of the acylating reagent on the diastereoselectivity is rather intriguing as it seems that a more electron-withdrawing acyl group leads to better *syn* selectivity. This very simplistic analysis is of course complicated by possible differences in *E*/*Z* preferences of the intermediate acyliminium ion.[27,28] To shed some light on this issue, we sought to use nitrones, which are known to be stereochemically well defined, as electrophiles.[33,34] Moreover, reports of additions of allenyl-propargyl organometallics to nitrones are rare.[35–38] We were thus glad to see that addition of allenyl zinc reagent **1** took place at −25 °C within 3.5 h to afford, after hydrolysis, hydroxylamine **18** in 60% yield as a single diastereoisomer (Scheme 8). As evidenced by comparison with the corresponding amine ***anti*-4** after reductive N–O bond cleavage, the *anti*-1,2-hydroxylamino ether was obtained. Accordingly, and much to our surprise, allenyl zinc reagent **1** adds to nitrone **17** exclusively via a synclinal transition state **TS3** and not through an antiperiplanar one. Initially unforeseen, this result seems to fit the overall trend according to which an antiperiplanar transition state (affording the *syn* amino alcohol) is favoured with a stronger electron-withdrawing imine activating group (acetyl (*syn*:*anti* = 75:25) > carbomethoxy (*syn*:*anti* = 63:37) ≈ benzoyl (*syn*:*anti* = 61:39) > oxygen (*syn*:*anti* = 0:100)).



Scheme 7.

In conclusion, we have shown that allenyl zinc reagent **1** adds to *N*-acyliminium ions to afford propargyl *syn*-1,2-amino ethers in good yields and reasonable selectivities affording a new straightforward entry to propargyl *syn*-1,2-aminoalcohols. Addition to nitrones also takes place but affords exclusively the *anti*-aminoethers. Both reactions are believed to take place through acyclic transition states (antiperiplanar and synclinal, respectively) showing that preventing the addition to take place through a close transition state does not ensure high levels of *syn* selectivity. An antiperiplanar transition state seems to be favoured over a synclinal one with stronger electrophiles. The reasons for this behaviour are not yet fully understood and are currently under study in our laboratory. They will be reported in due course.

Acknowledgement

Boyscast fellowship (to B.R.) is gratefully acknowledged.

References and notes

1. Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705.
2. Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358.
3. Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772.
4. Alemany, C.; Bach, J.; Farràs, J.; Garcia, J. *Org. Lett.* **1999**, *1*, 1831.
5. Dondoni, A.; Perrone, D.; Turturici, E. *J. Org. Chem.* **1999**, *64*, 5557.
6. Lee, B. W.; Lee, J. H.; Jang, K. C.; Kang, J. E.; Kim, J. H.; Park, K.-M.; Park, K. H. *Tetrahedron Lett.* **2003**, *44*, 5905.
7. Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **2006**, *47*, 5317.
8. Henegan, M.; Procter, G. *Synlett* **1992**, 489.
9. D'Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 9631.

10. Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron: Asymmetry* **1998**, *9*, 1427.
11. Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2979.
12. Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett.* **2001**, *3*, 2269.
13. Gridley, J. J.; Coogan, M. P.; Knight, D. W.; Malik, K. M. A.; Sharland, C. M.; Singkhonrat, J.; Williams, S. *Chem. Commun.* **2003**, 2550.
14. Palais, L.; Chemla, F.; Ferreira, F. *Synlett* **2006**, 1039.
15. Poisson, J.-F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889.
16. Chemla, F.; Ferreira, F. *Synlett* **2006**, 2613.
17. Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235.
18. Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245.
19. Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A.; Roy, B. *New J. Chem.* **2007**, *31*, 1552.
20. Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269.
21. Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244.
22. Ferreira, F.; Denichoux, A.; Chemla, F.; Bejjani, J. *Synlett* **2004**, 2051.
23. Chemla, F.; Ferreira, F. *Synlett* **2004**, 983.
24. Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310.
25. Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 953.
26. Chevallier, F.; Beaudet, I.; Le Grognec, E.; Toupet, L.; Quintard, J.-P. *Tetrahedron Lett.* **2004**, *45*, 761.
27. Speckamp, W. N.; Hiemstra, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 2, p 1047.
28. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
29. For a selected example involving an organozinc reagent see: Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497.
30. For examples involving allenyl/propargylsilanes, see: Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1984**, *25*, 3115; Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014; Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233; Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805; for examples involving allenylstannanes, see: Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103.
31. *Typical procedure for the addition of 3-alkoxy allenylzinc 1 onto imines, N-acyliminiums and nitrones*: Under a nitrogen atmosphere, at −80 °C, to a stirred Et_2O (40 mL) solution of methoxymethyl ether of 3-trimethylsilyl-2-propyn-1-ol (0.688 g, 4 mmol) and TMEDA (0.06 mL, 0.4 mmol) was added dropwise *sec*-BuLi (1.3 M in hexane, 2.92 mL, 4 mmol). The resulting clear orange mixture was stirred for 1 h at −80 °C and then $ZnBr_2$ (1 M in Et_2O, 4.4 mL, 4.4 mmol) was added. The resulting white slurry of allenylzinc **1** was stirred at −80 °C for an additional 30 min before a CH_2Cl_2 (8 ml) solution of the appropriate electrophile (2.0 mmol) was added. The temperature was allowed to raise to the reaction temperature and the mixture allowed to stirred for the reaction time. The reaction was quenched with NH_4Cl/NH_3 (2:1) (30 mL). EtOAc (30 mL) was added, and the layers were separated, the aqueous one being extracted twice with EtOAc (20 mL). The combined organics were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient of eluent 0–20% EtOAc in cyclohexane) to lead to the desired adduct.
32. *Typical procedure for the preparation of N-acyliminiums by method B* : Imine (2.0 mmol) is dissolved in dry CH_2Cl_2 (8 mL) and the solution is cooled to −25 °C. Acyl chloride (2.2 mmol) is added dropwise and the mixture is stirred for 1 h at −20 °C. The solution is cooled at −50 °C prior to addition onto the allenylzinc reagent.
33. Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
34. Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442.
35. Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. *Tetrahedron Lett.* **2003**, *44*, 6755.
36. Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632.
37. Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353.
38. Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153.