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Allenylmethylsilanes as Nucleophiles in *N*-Acyliminium Ion Chemistry

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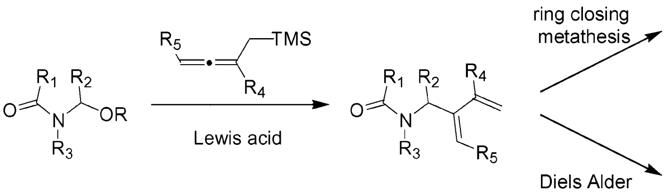
ABSTRACT



Treatment of a variety of *N*-acyliminium ion precursors with 2,3-butadienyl(trimethyl)silane and related allenes in the presence of $BF_3 \cdot OEt_2$ provides good yields of *N*-protected 2-(aminomethyl)-substituted 1,3-dienes, which prove to be useful substrates for subsequent Diels–Alder and alkene metathesis reactions.

An important C−C bond forming reaction for the construction of nitrogen-containing molecules is the addition of carbon nucleophiles to *N*-acyliminium intermediates.[1] Silicon-containing π-nucleophiles have proven particularly useful in this process, as the silyl function both enhances the reactivity and controls the regioselectivity of the π-nucleophile.[2] Thus, the employment of allylsilanes, allenylsilanes, and silyl enol ethers leads to the introduction of allyl, propargyl, and 2-oxoalkyl groups, respectively, onto the iminium carbon atom.[1]

Yet another type of silicon-containing nucleophiles are the (allenylmethyl)silanes,[3] which have been used in reactions with aldehydes and acetals[4] and also in [2 + 2]-cycloadditions.[5] To the best of our knowledge, 2,3-butadienyl(trimethyl)silane and analogues thereof have not been used as nucleophiles with *N*-acyliminium ions.[6]

In this communication we report the reaction of allenylmethylsilanes **3** and analogous structures with a range of *N*,*O*-(hemi)acetals **1** via the *N*-acyliminium ion intermediate **2** to form the 2-substituted dienes **4** (Scheme 1).[7] We also report on the versatility of the products **4** by showing preliminary results of Diels−Alder and alkene metathesis reactions.

Our preparation of allenylmethylsilane **3a** is a modification of the procedure described by Goré.[3a] On treatment of propargyl tosylate (**5a**) with trimethylsilyl-methylmagnesium chloride in diethyl ether in the presence of CuCN and LiCl

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[1] For a recent reviews, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082.

[2] Review: Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57−575.

[3] For syntheses of allenylmethylsilanes, see: (a) Montury, M.; Psaume, B.; Goré, J. *Tetrahedron Lett.* **1980**, *21*, 163−166. (b) Kleijn, H.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 5143−5148. (c) Pornet, J. *J. Organomet. Chem.* **1988**, *340*, 273−282. (d) Harada, T.; Osada, A.; Oku, A. *Tetrahedron Lett.* **1995**, *36*, 723−724. (e) Creary, X.; Jiang, Z.; Butchko, M.; McLean, K. *Tetrahedron Lett.* **1996**, *37*, 579−582. (f) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377−11390. (g) Lahrech, M.; Hacini, S.; Parrain, J.-L.; Santelli, M. *Tetrahedron Lett.* **1997**, *38*, 3395−3398. (h) Tseng, H.-R.; Lee, C.-F.; Yang, L.-M.; Luh, T.-Y. *J. Org. Chem.* **1999**, *64*, 8582−8587. (i) Maruyama, Y.; Yoshiuchi, K.; Ozawa, F. *J. Organomet. Chem.* **2000**, *609*, 130−136.

[4] (a) For a recent review, see: Hatakeyama, S. *J. Synth. Org. Chem. Jpn* **1997**, *55*, 793−802. (b) Luo, M.; Matsui, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett.* **2000**, *41*, 4401−4402.

[5] (a) Colvin, E. W.; König, W. A.; Loreto, M. A.; Rowden, J. Y.; Tommasini, I. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2405−2408. (b) Hojo, M.; Murakami, C.; Nakamura, S.; Hosomi, A. *Chem. Lett.* **1998**, 331−332.

[6] For reactions of allenes with *N*-acyliminium ions, see: Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2000**, *65*, 8317−8325 and references therein.

[7] For a comparable synthesis of 1,3-dienes with an amide substituent at the 1-position of the diene, see: Takacs, J. M.; Weidner, J. J. *J. Org. Chem.* **1994**, *59*, 6480−6483.

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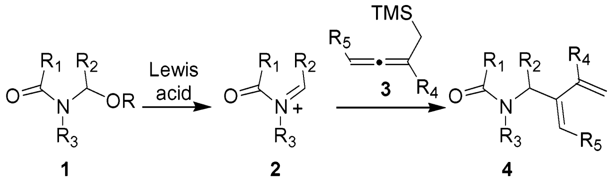
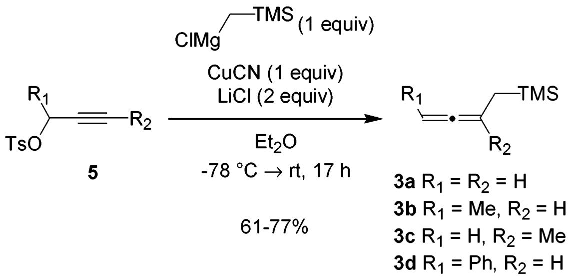
Scheme 1



the product was obtained in 65% yield on a 16 g scale (Scheme 2). Three substituted analogues **3b**−**d**[8] were synthesized in a similar manner starting from the corresponding substituted propargyl tosylates (synthesized by tosylation of the corresponding alcohols) in 61−77% yield. As allenylmethylsilane **3b** is a chiral allene, we were interested to know whether its axial chirality would be transferred in the *N*-acyliminium ion reaction. Optically active allene **3b** ($[\alpha]_D = -11.1$, *c* 1.31, $CHCl_3$) was synthesized in the usual way (see Scheme 2) from the tosylate of commercially available enantiopure (*S*)-but-3-yn-2-ol.[9] The ee of the product appeared to be only ca. 70% as determined by a well-known NMR method.[10]

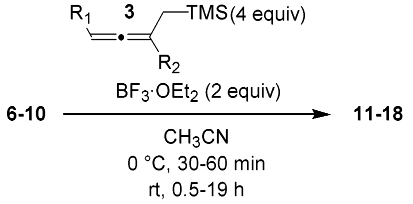
Scheme 2

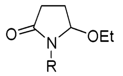
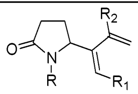
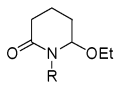
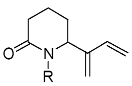
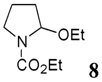
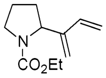
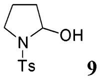
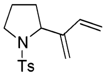
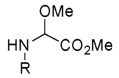
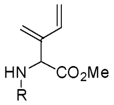


Allene **3a** was then used as π-nucleophile in the reaction with a range of different *N*-acyliminium ion precursors (see Table 1). Precursors **6a**−**f** and **7a,b** were obtained from the corresponding imides by successive *N*-alkylation, $NaBH_4$ reduction, and acidic ethanolysis, according to well-known procedures.[11] Likewise, **8**[12] and **9**[13] were prepared via reduction of *N*-substituted lactams. The methoxyglycine derivatives **10a,b** were synthesized via coupling of the appropriate carbamate with methyl glyoxylate methyl hemiacetal followed by methanolysis.[14]

Initially CH_2Cl_2 was chosen as solvent to effect the *N*-acyliminium ion reaction between allene **3a** (4 equiv) and precursor **6b** in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) as the Lewis acid. This reaction did not go to completion even after 17 h, and only 16% of the expected dienelactam **11b** was isolated. However, when carried out in acetonitrile the reaction was finished in 4 h in a satisfactory yield of 69%.

Table 1.



entry	precursor	allene	time (h)	product	yield (%)[a]
					
1	**6a** R = H	**3a**	1.5	**11a**	74
2	**6a** R = H	**3b**	1.5	**12**	84
3	**6a** R = H	**3c**	3	**13**	85
4	**6a** R = H	**3d**	1	**14**	65
5	**6b** R = Bn	**3a**	4	**11b**	69
6	**6c** R = All	**3a**	1.5	**11c**	63
7	**6d** R = 3-butenyl	**3a**	19	**11d**	42[b]
8	**6e** R = 4-pentenyl	**3a**	2	**11e**	74
9	**6f** R = 5-hexenyl	**3a**	2	**11f**	72
					
10	**7a** R = H	**3a**	6.5	**15a**	87
11	**7b** R = All	**3a**	17	**15b**	68[c]
12	 **8**	**3a**	2	 **16**	49
13	 **9**	**3a**	0.5	 **17**	74
					
14	**10a** R = Cbz	**3a**	2	**18a**	88
15	**10b** R = Fmoc	**3a**	1	**18b**	75

[a] Isolated yields after column chromatography. [b] Using 10 equiv of nucleophile and 5 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2. [c] Using 10 equiv of nucleophile and 5 equiv of $BF_3{\cdot}OEt_2$.

Similar conditions appeared successful for the other *N*-acyliminium precursors **6**−**10** to provide the expected dienelactam products in yields ranging from 42% to 88% (Table 1). The products were somewhat air-sensitive oils that should be kept under nitrogen. In two cases a slightly different procedure was applied. For precursor **7b** (entry 11) the standard conditions resulted in only 34% yield of the diene product **15b**, together with 14% of the piperinone resulting from ethanol elimination from **7b**. On using a larger excess of both the nucleophile (10 equiv) and the Lewis acid (5 equiv) the yield was doubled to 68%, without observing the elimination product. In the case of precursor **6d** (entry 7) the standard conditions furnished none of the desired diene, but instead the unsaturated *N*-substituent caused *N*-acyliminium cyclization with incorporation of acetonitrile furnishing bicyclic imidate **19** (Figure 1). When this reaction

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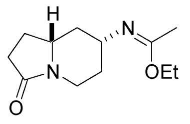
[8] Colvin, E. W.; Monteith, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1230−1232.

[9] Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726−3730.

[10] Mannschreck, A.; Munninger, W.; Burgemeister, T.; Goré, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399−408.



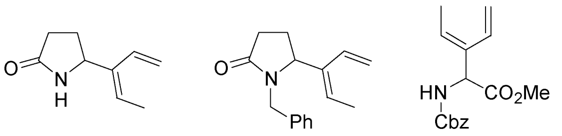
19

Figure 1. Bicyclic imidate from **6d**.

was carried out in CH_2Cl_2 with a larger excess of both nucleophile (10 equiv) and Lewis acid (5 equiv) the cyclization was prevented and the diene **11d** was formed in a moderate yield (42%). The protected methoxyglycines **10** showed excellent reactivity to allene **3a**, providing protected butadienylglycines **18** in good yields. To the best of our knowledge this special α-amino acid has not been synthesized before. It was reported to occur in a natural γ-glutamyldipeptide.[15]

The reactions of the substituted nucleophiles **3b−d** with *N*-acyliminium ion precursor **6a** resulted in formation of the 1,2-disubstituted dienyllactams **12−14** in 65−85% yield. Diene **12** was formed as the pure *E*-isomer as shown by a ^{1}H NMR NOE experiment, whereas **14** was a 1:1 mixture of geometric isomers.

Subjection of the *N*-acyliminium ion precursors **6a,b** and **10a** to the optically active allene **3b** resulted in ee's up to 21% for the products (Figure 2). Although the extent of transmission of axial chirality to the new stereocenter is rather poor (30% at the most, corrected for the ee of starting allene), the present work is the first demonstration of this phenomenon in a S_E2' reaction of a chiral allene.



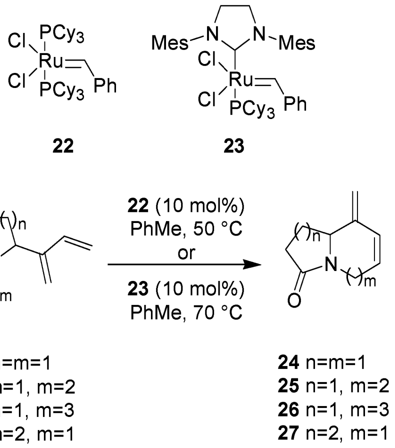
12 79%, 21 % ee **20** 84 %, 14 % ee **21** 85 %, 10 % ee

Figure 2. Enantioenriched products from reactions of optically active allene **3b** (ee 70%). The ee's were determined by using the chiral shift reagent Eu(hfc)$_3$ in ^{1}H NMR.

After successful formation of a range of 1,3-dienylamides we briefly explored the potential applications of these molecules. The ring-closing metathesis reaction[16,17] of systems with a terminal alkene in the *N*-substituent was first investigated.

The trienes **11c,d** and **15b** were subjected to Grubbs' catalyst **22**, resulting in the formation of the six-membered ring products **24** and **27** in moderate to high yields. For successful closure of the compounds **11d,e** the 2nd generation Grubbs' catalyst (**23**) was required, giving the seven- and eight-membered ring products **25** and **26**, respectively, in high yields (Scheme 3, entries 3 and 4). As could be expected from a literature precedent,[18] only the least substituted double bond of the 1,3-diene system reacted to produce compounds **24−27**, which possess an exocyclic methylene.

Scheme 3[a]



entry	precursor	catalyst	yield (%)[a]
1	**11c**	**22**	85
2	**11d**	**22**	<18
3	**11d**	**23**	86
4	**11e**	**23**	45
5	**15b**	**22**	62

[a] Isolated yields after column chromatography.

The usefulness of the 1,3-dienylamides for further chemistry was also apparent from their reactivity in the Diels−Alder reaction. We selected product **11b** as an example substrate and performed intermolecular Diels−Alder reactions of this diene with maleic anhydride (**28**) and *N*-methylmaleimide (**29**). As expected, these reactions proceeded smoothly at 120 °C in xylene to furnish the cycloaddition products **30** and **31** as a 1:1 mixture of diastereomers (Scheme 4).

We then turned our attention to the more interesting intramolecular variant, which would be a type 2 Diels−Alder

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(11) (a) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163−172. (b) See also: Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1985**, *41*, 4367−4416 and references therein.

(12) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231−1232.

(13) Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537−9544.

(14) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863−866. An optimized procedure was used according to: Van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6083−6085.

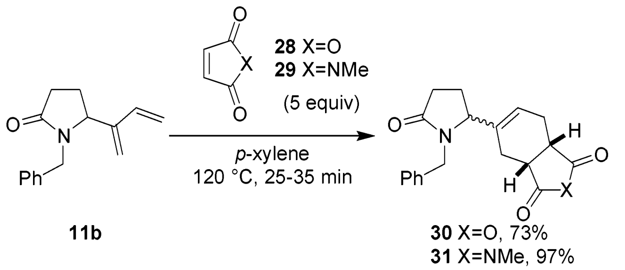
(15) Campos, L.; Marlier, M.; Dardenne, G.; Casimir, J. *Phytochemistry* **1983**, *22*, 2507−2508.

(16) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236−3253.

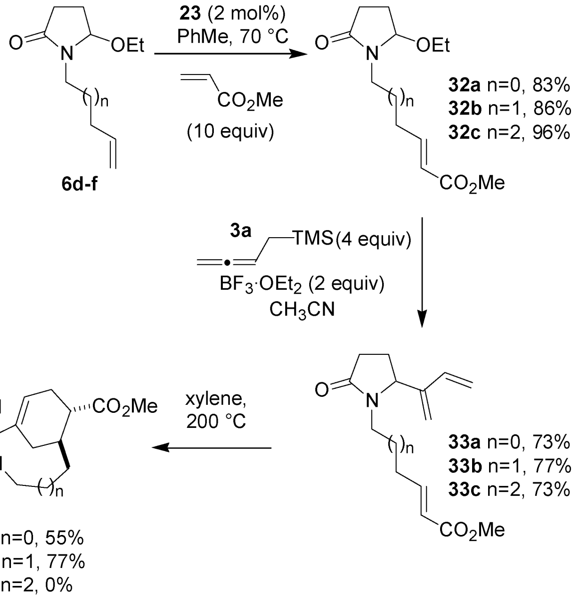
(17) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695−1701.

(18) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310−7318.

Scheme 4



Scheme 5



process leading to bridged systems.[19] For the synthesis of the appropriate Diels–Alder precursors, the *N*,*O*-acetals **6d–f** were subjected to a cross-metathesis reaction with methyl acrylate (10 equiv) in the presence of catalyst **23**. In this way the activated alkenes **32a–c** were obtained in high yields. Subjection of **32a–c** to the standard *N*-acyliminium ion conditions provided the Diels Alder precursors **33a–c** in good yield. Heating of these compounds in xylene in a sealed tube at 200 °C induced the cycloaddition reaction to give the bridged systems **34a** and **34b** as single diastereomers (Scheme 5). The assignment of the stereochemistry is suggested by a computational comparison[20] with the alternative diastereomer, which appeared higher in energy (4.5 kcal/mol for **34a** and 12.9 kcal/mol for **34b**). Precursor **33c** failed to give cycloaddition.

In conclusion, we have shown that the use of allenylmethylsilane (**3a**) as nucleophile in *N*-acyliminium ion reactions leads to amides containing the 1,3-diene moiety in moderate to high yields. Substituted allenylmethylsilanes (**3b–d**) react equally well and are able to transfer axial chirality, although the levels of asymmetric induction are poor. The products are versatile substrates, not only for subsequent ring-closing metathesis and Diels–Alder reactions, but conceivably for several other useful synthetic processes.

Acknowledgment. This research has been financially supported by the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO).

Supporting Information Available: General procedures for the *N*-acyliminium ion, metathesis, and Diels–Alder reactions and full characterization data for compounds **3a–d**, **11–21**, **24–27**, and **30–34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For a recent review, see: Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820–849.

(20) Spartan was used for the computation, employing the Single Point Energy, Molecular Mechanics, MMFF method.