Pergamon

Tetrahedron Letters 43 (2002) 1453–1456

TETRAHEDRON LETTERS

A convenient procedure for the preparation of α-aminoallenes using a three-component reaction of aldehyde, carbamate and propargylsilane

Manuella Billet, Angèle Schoenfelder, Philippe Klotz and André Mann*

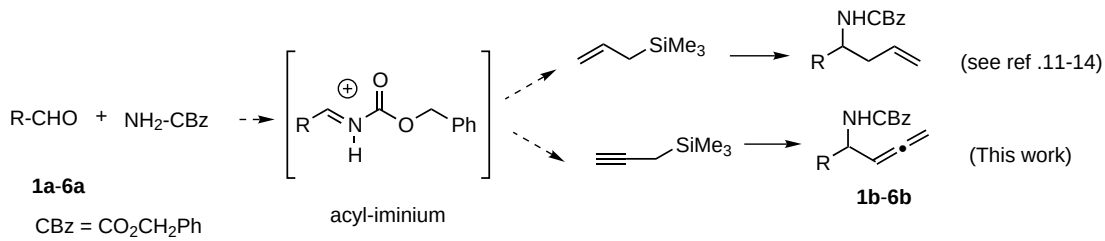
Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081, 74 route du Rhin, BP 24 F-67401 Illkirch, France

Received 9 November 2001; accepted 4 January 2002

Abstract—A three-component reaction is described using an aldehyde, a carbamate and trimethylpropargylsilane in the presence of a Lewis acid for the production in moderate to good yield of α-allenyl amines. The reaction is applicable to aromatic or aliphatic aldehydes. The obtained α-aminoallenes are transformed into Δ^3-pyrrolidines or amino acids by using the reactivity of the cumulene function.

The search for rapid and 'low tech' procedures for the construction of functionalized compounds from commercial sources is a stimulating trend in the daily practice of organic chemistry.[1–3] One way to approach this objective is to use multi-component reactions, such as the ones developed in the past by Ugi,[4] Passerini,[5] Bignelli,[6] or recently by Petasis.[7] The obvious advantages of these processes are the production of molecular diversity from cheap reaction partners. As we were involved in the utilization of silicon reagents for the preparation of azaheterocycles,[8,9] we and others have made use of a three-component reaction for the preparation of homoallylamines. Indeed a mixture of an aldehyde, an allylsilane and a carbamate in the presence of a Lewis acid furnished homoallylamines in excellent yields.[10–14] A transient acyliminium ion is supposed to be the reactive species in this reaction. As both propargyl- and allylsilanes react via an SE2′ process in the presence of electrophiles, we decided to experiment with the behavior by using propargylsilane in place of allylsilane in the above three-component reaction. We speculated that if, as expected, γ-attack would occur on the intermediate acyliminium,[15] this new three-component mixture would offer a direct access to α-aminoallenes (Scheme 1).

Allenylamines are not only valuable functionalized intermediates for organic synthesis (see below), but have also been identified as potent irreversible substrates for pyridoxal-phosphate dependent enzymes.[16,17] Usually α-allenylamines are obtained by a tedious elaboration from the corresponding propargylamine using Crabbe's procedure,[18–20] but to the best of our knowledge no general one-step process has been reported. In this letter we report our preliminary results on a new synthesis of α-aminoallenes using a three-component reaction, and their transformation into Δ^3-pyrrolidines or amino acids. In a first experiment, trimethylpropargylsilane, benzyl carbamate and benzaldehyde (**1a**) were



Scheme 1. Three-component reactions with allyl- and propargylsilane.

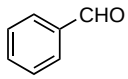
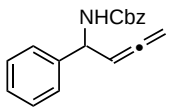
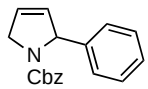
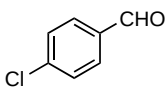
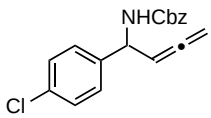
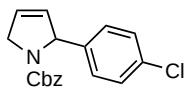
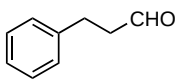
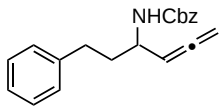
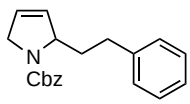
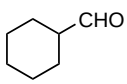
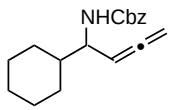
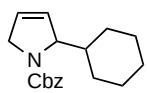
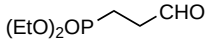
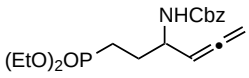
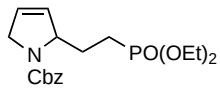
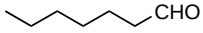
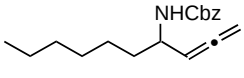
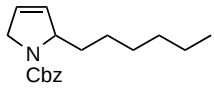
* Corresponding author. Tel.: +33 (0)3 90 24 42 27; fax: +33 (0)3 90 24 43 10; e-mail: andre.mann@pharma.u-strasbg.fr

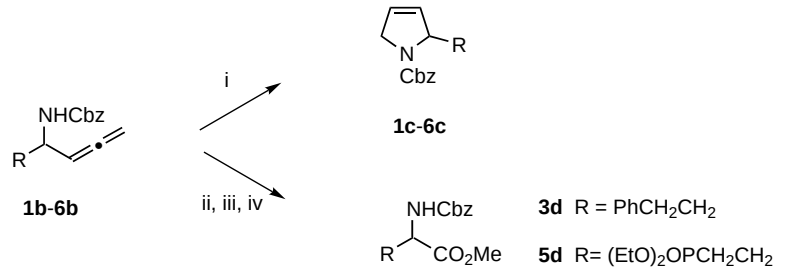
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00056-4

mixed in acetonitrile at 0°C, $BF_3{\cdot}OEt_2$ was added dropwise; after 30 min reaction time at 0°C, a TLC control revealed that all the starting material was consumed. Indeed a fast reaction took place, the new compound formed was isolated by column chromatography on silica gel, and the ^1H (300 MHz) and ^{13}C (50 MHz) NMR spectra exhibited the characteristic signals for an allenyl group.[21,22] A small amount of the corresponding propargyl adduct could also be isolated. However, we found that if the reaction time is shortened to 10 min, this by-product was not detected. This result which is not unexpected at all, but has never been observed constitutes a fast and good yielding process for the obtention of α-aminoallen. It is noteworthy that no traces of the corresponding allenyl or propargyl alcohols were detected, suggesting that the propargylsilane reacts faster with the iminium than with the corresponding aldehyde. Fortunately the formation of water during the initial step of the reaction (iminium step) does not interfere at all with the subsequent electrophilic substitution step. These two observations have already been made in the three-component reaction with allylsilane. However, as propargylsilanes are generally reported to be less reactive as the allylsilanes,[23] these results were not obvious at all and constituted good surprises. In order to check for the generality of the reaction, several aliphatic or aromatic aldehydes were submitted to the three-component reaction. We report our results in Table 1. The reaction proceeds with either kind of aldehyde (the yields were not optimized). It seems that the reaction gave slightly better yields with aliphatic rather than aromatic aldehydes (compare entries 1–2 with 3–6). Anyway, the merits of this reaction for the preparation of α-aminoallenes are the following: the aldehyde substrates are commercially available, benzylcarbamate is a cheap nitrogen equivalent and the reaction conditions are easy to implement. Our finding is a good example of what a 'low-tech' chemical transformation can be. Finally we describe a very easy way to transform various aldehydes (**1a**–**6a**) to α-aminoallenes (**1b**–**6b**).

Next we turn our interest to the transformation of the allenes (**1b**–**6b**). The unique chemistry of the propa-1,2-

Table 1. Results from aldehydes (**1a**–**6a**) in the three-component reaction, and their transformation in pyrrolidines

Entry	Aldehyde	amino-allene	pyrrolidine
1	 **1a**	 **1b** (63%)	 **1c** (80%)
2	 **2a**	 **2b** (68%)	 **2c** (73%)
3	 **3a**	 **3b** (69%)	 **3c** (79%)
4	 **4a**	 **4b** (74%)	 **4c** (79%)
5	 **5a**	 **5b** (77%)	 **5c** (84%)
6	 **6a**	 **6b** (82%)	 **6c** (69%)



Scheme 2. *Reagents and conditions*: (i) $AgBF_4$, CH_2Cl_2, rt, 12 h; (ii) O_3, CH_2Cl_2, Me_2S; (iii) PCD then (iv) CH_2N_2.

dienyl system is amenable to a variety of useful structures. For instance it has been reported that activation with Lewis acids produces an intramolecular cyclization of the allene, a hydroamination, which yields the corresponding pyrrolidines.[24] When we tried that heterocyclization in the presence of $AgBF_4$ in CH_3CN on allenes **1b–6b**, we obtained with excellent yields the corresponding pyrrolidines **1c–6c**.[25–28] The synthetic potentialities of these pyrrolidines towards the obtention of polycondensed azaheterocycles are very large.[29]

Other chemical transformations of allenes are of interest, for instance the ozonolysis of the cumulene system. This reaction first reported by Favorskii has been used by Corey in the synthesis of α-hydroxyaldehydes.[28] We decided to extend this sequence to the synthesis of amino acids in the following way: allenes **3b** and **5b** were submitted to ozonolysis in the usual way and the aldehydes obtained were directly oxidized to the corresponding acids with PDC (Scheme 2). The crude was treated by diazomethane to get the fully protected α-amino acids **3d** and **5d**. Both compounds were obtained, in 60–65% yields. Interestingly, compound **5d** is the fully protected (±) AP5 (2-amino-5-phosphonopentanoic acid) a potent ligand for the metabotropic glutamate receptor.[30]

Thus, in this work we have presented a rapid access to α-aminoallenes in a one-pot procedure making use of a three-component reaction. The reaction conditions are mild, easy to perform and applicable to many aldehydes. We believe that this improvement in the synthesis of aminoallenes, together with the transformation of the cumulene function should encourage the utilization of aminoallenes in organic synthesis.

References

1. Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288–2337.
2. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366–374.
3. Posner, G. *Chem. Rev.* **1986**, *86*, 831–844.
4. Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728 and references cited therein.
5. Armstrong, R.; Combs, A.; Tempest, P.; Brown, S.; Keating, T. *Acc. Chem. Res.* **1996**, *29*, 123 and references cited therein.
6. Hu, E.; Sidler, D.; Dolling, U. *J. Org. Chem.* **1998**, *63*, 3454–3457 and references cited therein.
7. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.
8. Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958–959.
9. Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 6087–6091.
10. Meester, W. J. N.; Rutjes, F. P. J. T.; Hemkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601–1604.
11. Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997–1000.
12. Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674–2675.
13. Roux, M.; Santelli, M.; Parrain, J. L. *Org. Lett.* **2000**, *2*, 1701–1704.
14. Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 631–634.
15. Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1984**, *25*, 3115–3118.
16. Casara, P.; Jund, K.; Bey, P. *Tetrahedron Lett.* **1984**, *25*, 1891–1894.
17. McCarthy, J. R.; Barney, C. L.; Matthews, D. P.; Bargar, T. M. *Tetrahedron Lett.* **1987**, *28*, 2207–2210.
18. Crabbe, P.; Fillion, D.; André, D.; Luche, J. L. *Chem. Commun.* **1979**, 859–860.
19. Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley and Sons: New York, 1984.
20. Dieter, R. K.; Nice, L. E. *Tetrahedron Lett.* **1999**, *40*, 4293–4296 and references cited therein.
21. Typical experimental procedure for the preparation of **1b–6b**. A mixture of aldehyde (1 equiv.), benzyl carbamate (1 equiv.) and trimethyl-propargylsilane (1 equiv.) was prepared in CH_3CN (5 mL) under nitrogen. Then $BF_3{\cdot}OEt_2$ (1 equiv. as a commercial solution in ether) was added dropwise at 0°C. The reaction mixture was quenched 10 min later with $NaHCO_3$ (5 mL of a saturated aqueous solution). The organic material was extracted with Et_2O (2×10 mL), washed with saturated brine (5 mL) and concentrated in vacuo to a residue that was purified by chromatography on silica gel eluting with Hex/Et_2O: 1/9.
22. Physical data for **3b**: $R_f = 0.53$ (Hex/Et_2O: 1/9); ^1H NMR (300 MHz) $\delta = 1.85$–1.97 (m, 2H), 2.66 (m, 2H), 4.18–4.22 (m, 1H), 4.80 (dd, $J = 2.7$ and 6.6 Hz, 2H), 5.08 (s, 2H), 5.24 (q, $J = 6.6$ Hz, 1H), 6.42 (d, $J = 7.6$ Hz, 1H), 7.19–7.31 (m, 10H). ^{13}C NMR (75 MHz) $\delta = 32.5$, 37.3, 49.8, 66.0, 77.0, 93.15, 126.1, 128.1, 128.7, 128.8, 137.9, 142.3, 156.1, 207.8.

23. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192.
24. Schierlé, K.; Vahle, R.; Steckhan, E. *Eur. J. Org. Chem.* **1998**, 509–514 and references cited therein.
25. Amombo, M. O.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871–1874.
26. Typical procedure for the preparation of pyrrolidines **1c**–**6c**. The aminoallene (1 equiv.) is dissolved in CH_2Cl_2 and $AgBF_4$ (1 equiv.) is added at once to the mixture; stirring was continued overnight and then the solvent evaporated in vacuo. The residue was immediately purified by chromatography on silica gel eluting with Hex/Et_2O: 1/9.
27. Physical data for **3c**: ^{1}H NMR (300 MHz) $\delta = 1.19$–1.27 (m, 2H), 1.63–1.79 (m, 2H), 4.03–4.10 (dd, $J = 6.0$ and 6.0 Hz, 2H), 5.01–5.13 (m, 2H), 5.48–5.64 (m, 2H), 5.76–5.79 (d, $J = 7.9$ Hz, 2H), 7.32–7.39 (m, 10H). ^{13}C NMR (50 MHz) $\delta = 32.1$, 35.3, 48.6, 58.2, 69.9, 125.2, 126.3, 127.4, 128.3, 128.4, 128.7, 129.5, 137.3, 141.0, 156.0.
28. Corey, E. J.; Jones, G. B. *Tetrahedron Lett.* **1991**, *32*, 5713–5716.
29. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579–8629 (a review on indolizidines).
30. For a recent review, see: Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.