Tetrahedron Letters 54 (2013) 6439–6442

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# New one-pot procedure for the synthesis of diprotected amino alcohols from unprotected vinyl aziridines

Giuliana Righi [a,*], Paolo Bovicelli [b], Ilaria Tirotta [c,*]

[a] CNR-ICB Unity of Rome, P.le A. Moro, 5-00185 Rome, Italy
[b] CNR-ICB Unity of Sassari, Traversa La Crucca 3, Baldanica I, 07040 Sassari, Italy
[c] Department of Chemistry, 'Sapienza' University of Rome, P.le A. Moro, 5-00185 Rome, Italy

ARTICLE INFO

*Article history:*
Received 30 June 2013
Revised 7 September 2013
Accepted 13 September 2013
Available online 20 September 2013

*Keywords:*
Vinyl aziridines
Amino alcohols
Acyl derivatives
Ring opening
Oxazolines

ABSTRACT

An unprecedented one-pot reaction that allows the synthesis of diprotected amino alcohols from unprotected vinyl aziridines is reported. The results demonstrate the possibility to use various acyl chlorides in order to obtain differently functionalised fragments. Mechanistic insights are given.



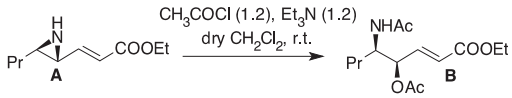
The functionalisation of the aziridine nitrogen with electron-withdrawing groups is a broadly used strategy for the activation of the heterocyclic ring towards nucleophilic attack.

During an attempt in this direction, an unexpected reactivity was observed when particular aziridines were submitted to the usual acylation conditions[1] (Scheme 1): when vinyl aziridine **A** was reacted with 1.2 mmol of $Et_3N$ and 1.2 mmol of $CH_3COCl$ in dry dichloromethane at room temperature, instead of the expected N-protected aziridine, the main product recovered was the diprotected amino-alcohol **B**. NMR studies revealed the complete regio- and stereoselectivity of the reaction, detecting in the crude only one diastereomer with the oxygen in the allylic position was obtained.

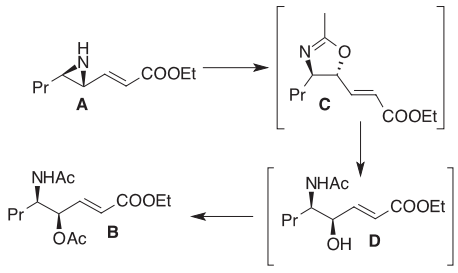
The first mechanistic hypothesis was the formation of an oxazoline **C** that could open to give monoprotected *syn*-amino alcohol **D**, which then could react with acetyl chloride to give **B** (Scheme 2).

*N*-Acyl or *N*-carboxyl vinyl aziridines are known to undergo rearrangements in a wide range of conditions,[2] in particular Cardillo et al.[3] reported a three steps strategy that leads to *syn* monoprotected amino-alcohols. Nonetheless, to the best of our knowledge, there does not seem to be in the literature a thorough study on these peculiar rearrangements nor a one-pot procedure for the formation of diprotected *syn*-amino alcohols from vinyl aziridines.

For these reasons the reaction was investigated in order to verify its reproducibility and scope, to understand its mechanism and the influence that the aziridine functionalisations have on its stereo- and regioselectivity. Therefore three different vinyl aziridines




**Scheme 1.** Unexpected opening reaction.




**Scheme 2.** Proposed mechanism.

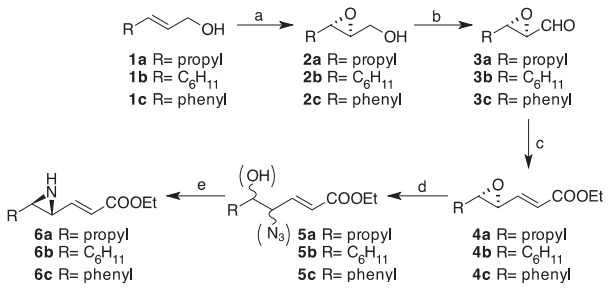
* Corresponding authors at present address: NFMLab-DCMIC 'Giulio Natta' Via L. Mancinelli 7, 20131 Milano, Italy. Tel./fax: +39 02 23994745 (I.T.).
*E-mail address:* ilaria.tirotta@gmail.com (I. Tirotta).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.047

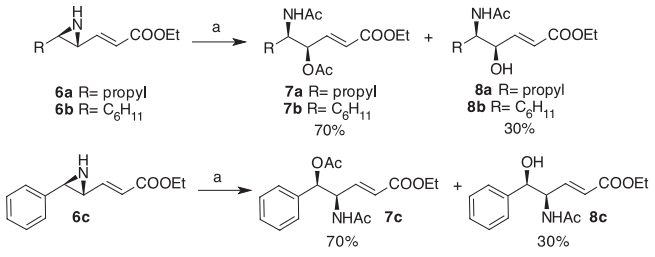
were prepared: the R group was changed in order to evaluate the influence that its steric hindrance and electronic effects have on the reaction. In addition, to investigate the possibility of a broader scope, different acyl chlorides were chosen: $CH_3COCl$, $CH_3(CH_2)_8COCl$ (interesting for its long alkyl chain, which is found in many natural products), and PhCOCl (interesting for the possible effects of the phenyl group on the reaction).

All the substrates were easily and in fairly good yield prepared starting from the corresponding allylic alcohols **1a–c**[4] (Scheme 3).

An epoxydation reaction[5] followed by an oxidation of the hydroxyl groups afforded epoxy aldehydes **3a–c**. A subsequent Horner–Emmons reaction[6] yielded α,β-unsaturated epoxy esters **4a–c**, the oxirane ring of which was then regio-selectively and stereospecifically opened, using a methodology recently developed by our group,[7] to afford azidoalcohols **5a–c**, which were finally converted into the corresponding aziridines **6a–c** via a well-known procedure.[8]




**Scheme 3.** Reagents and conditions: (a) *m*-CPBA, $CH_2Cl_2$, 0 °C, 3 h (85–90%); (b) TEMPO, IBDA, $CH_2Cl_2$, rt 2 h or $Py/SO_3$, DMSO, $Et_3N$, $CH_2Cl_2$, rt 2 h (70–80%); (c) LiOH, TEPA, THF, 70 °C, 2 h (85–95%); (d) $BF_3OEt_2$, $TMSN_3$, $CH_2Cl_2$, rt 1 h (95%); (e) $PPh_3$, acetonitrile, rt −70 °C, o/n (90%).




**Scheme 4.** Reagents and conditions: (a) $Et_3N$ (1.2 equiv), $CH_3COCl$ (1.2 equiv), dry $CH_2Cl_2$, rt 3–5 h (50% overall).

When all substrates were submitted to the same conditions used the first time the reaction failed to prove reproducible and very unsatisfactory yields were obtained (50% overall) (Scheme 4).

Besides the formation of the diprotected amino alcohol, there always was a significant amount of monoprotected derivative (30%). Moreover, compound **6c** led to derivatives **7c** and **8c** both characterised by the presence of the O-protected group in the benzylic position instead of the allylic one. The reaction proved to be regioselective nonetheless, and the regioselectivity seemed to be driven by the peculiar reactivity of the allylic position for compounds **6a** and **6b**, whereas for compound **6c** the benzylic position proved to be more reactive than the allylic one. The recovery of monoprotected derivatives **8a**, **8b**, and **8c** could be explained by the insufficient amount of acetyl chloride in the reaction media. Another possible explanation would be that not all the oxazoline is opened during the reaction, but a small part opens during the work-up, hence leading to the monoprotected derivative.

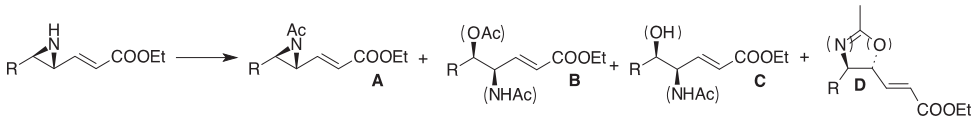
Therefore the reaction conditions were varied in order to identify the best suitable ones for the synthesis of diprotected derivatives and the results are summarised in Table 1.

When the aziridines were reacted with 1.2 equiv of $CH_3COCl$ and $Et_3N$ as well as when the equivalents were doubled (Entries 1 and 2), the amount of diprotected amino alcohol and monoprotected derivative were, on average, 70–100% for the former and 0–30% for the latter, with an overall yield of 50%. It is also important to note that in some cases it was possible to identify the oxazoline in the reaction crude and to isolate it in very small amount after purification. In both cases (Entries 1 and 2) the reaction led to a complex mixture of products, failing to prove reproducible and to give reasonable yields of the desired diacylated compound.

Interestingly, when aziridines **6a** and **6b** (R = propyl, cyclohexyl) were reacted with an excess of $Et_3N$ (entry 3) it was possible to recover the oxazoline as the only product even after purification of the reaction crude, even though only in small amounts (40% yield). However, these data are not reproducible: performing the reaction on compound **6c** (R = phenyl) only the correspondent protected aziridine was detected in the reaction crude. This has led to the conclusion that the reaction evolves through very labile equilibria that are difficult to control so much to obtain only one of the intermediates. What seemed more plausible was the possibility to drive the reaction towards the last product, the diprotected amino alcohol.

Finally, when all three aziridines were reacted with 3 equiv of $CH_3COCl$ and only 1 equiv of $Et_3N$ (entry 4), the diprotected derivative was recovered in a very satisfactory yield (70%). Therefore

**Table 1**
Different reaction conditions for the acetyl chloride mediated ring-opening[15]: results



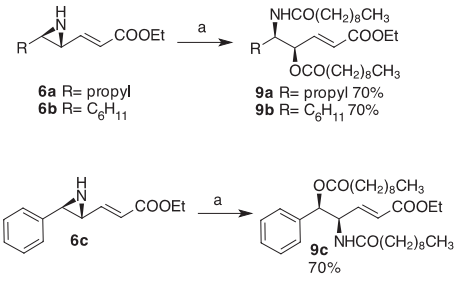

| Entry | $CH_3COCl$ (equiv) | $Et_3N$ (equiv) | Solvent | Overall yield (%) | A (%) | B (%) | C (%) | D (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.2 | 1.2 | Dry $CH_2Cl_2$ | 50 | — | 70–100 | 0–30 | Traces |
| 2 | 2.4 | 2.4 | Dry $CH_2Cl_2$ | 50 | — | 70–100 | 0–30 | Traces |
| 3 | 1.6 | 2 | Dry $CH_2Cl_2$ | | Variable results | | | |
| 4 | 3 | 1 | Dry $CH_2Cl_2$ | 70 | — | >95 | — | Traces |

these conditions were identified as the most suitable for our purposes and used with the other acyl chlorides chosen for the study.

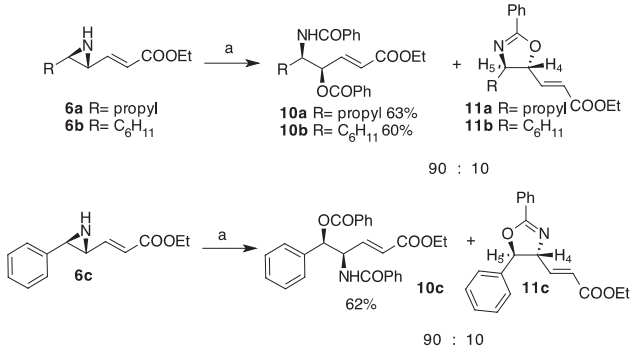
In light of these findings, we believe that, when the reaction media is sufficiently acidic, oxazoline C (see Scheme 2) is directly converted into the diprotected compound B (Table 1, entry 4). However, when this is not the case, part of it stays intact and then gets cleaved during work-up leading to the monoprotected compound D (Table 1, Entries 1 and 2).

Performing the reactions on all three substrates, using 3 equiv of decanoyl chloride and 1 equiv of $Et_3N$, the expected diprotected derivatives (**9a–c**) were recovered in, on average, 70% yield (Scheme 5).

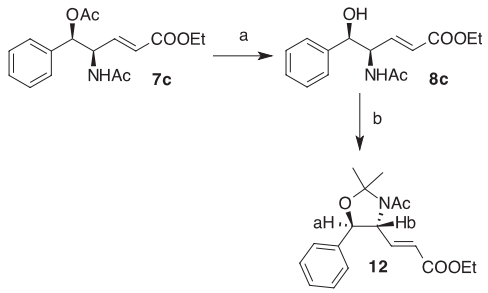
The reactions with benzoyl chloride required 4 equiv of chloride and 1 equiv of $Et_3N$ in order to obtain diprotected derivatives **10a–c** in a 60% yield alongside with small amounts of the corresponding oxazolines in a 90:10 ratio (Scheme 6). In these cases the amount of oxazoline recovered was higher than what was previously observed and this can be explained by the stabilisation given to the molecule by the phenyl group. The *trans* stereochemistry for oxazolines **11a–11c** was assigned by comparison with the literature value of the coupling constants $J_{4,5}$[9] and allowed a first confirmation of the proposed mechanism.




**Scheme 5.** Reagents and conditions: (a) decanoyl chloride (3 equiv), $Et_3N$ (1 equiv), dry $CH_2Cl_2$, rt, 2–5 h.




**Scheme 6.** Reagents and conditions: (a) benzoyl chloride (4 equiv), $Et_3N$ (1 equiv), dry $CH_2Cl_2$, rt, 2 h.




**Scheme 7.** Reagents and conditions: (a) $Na_2CO_3$, MeOH, rt, o/n (70%); (b) CSA, DMP, $CH_2Cl_2$, rt, o/n (40%).

To confirm the stereochemical assignment of all products obtained, compound **7c** was converted into the corresponding oxazolidine **12** (Scheme 7), via a selective deprotection[10] of the hydroxyl moiety, followed by an intramolecular cyclisation. Oxazolidines are characterised by a peculiar value for the coupling constants $J_{4,5}$:[11] the approximate value is 5 Hz for *trans* oxazolidines and 0 Hz for *cis* ones. Compound **12** proved to be a *trans* oxazolidine, thus confirming the hypothesised *syn* stereochemistry for both the mono and the diprotected derivatives. This also corroborates our proposed mechanism, however ongoing studies will allow us to have a more thorough understanding of it.

To the best of our knowledge this is the first one-pot procedure reported for the synthesis of diprotected amino alcohols from vinyl aziridines. The data collected showed the complete regio- and stereoselectivity of the reaction: in all cases only the *syn* diastereomer was recovered, characterised by the O-protected group in the allylic position for compounds with R = propyl and cyclohexyl, and in the benzylic position for the compound with R = phenyl. The steric hindrance of the R group does not influence the reaction at all; the influence exerted by the phenyl group can be ascribed to the particular reactivity of the benzylic position, which proved to be sensibly more reactive than the allylic one. Regarding the group on the double bond, we believe its role is crucial and its electron withdrawing nature essential for the regioselectivity of the reaction, as we have already observed in previous work on similar compounds.[12] The reaction performed with 3 or 4 equiv of acyl chloride and 1 equiv of triethylamine proved to be reproducible and applicable to different substrates and acyl chlorides. It is fast (2–5 h), fairly clean, and leads with good yields (60–70%) to unsaturated diprotected amino alcohols, useful precursors of a wide range of biologically active compounds. For example, they are used as readily available precursors in the preparation of (*E*)-alkene dipeptide isosteres, frequently employed in SAR (structure–activity relationship) studies for the close resemblance with the three-dimensional structure of the amide bond.[13,14] Studies in this directions are currently undergoing in our laboratories and will allow the broadening of the reaction scope.

## Acknowledgements

We thank MIUR (Ministry of University and Research, Rome) for partial financial support (PRIN 2010–2011: Design and stereoselective synthesis of compounds active towards protein targets involved in viral and tumoral pathologies).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.047.

## References and notes

1. Toshimitsu, A.; Aoai, T.; Owada, H.; Uemura, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 4727–4733.
2. (a) Lindstrom, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94–98; (b) Brichacek, M.; NavarroVillalobos, M.; Plichta, A.; Njardarson, J. T. *Org. Lett.* **2011**, *13*, 1110–1113; (c) Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385–8386; (d) Foglia, T. A.; Gregory, L. M.; Maerker, G. *J. Org. Chem.* **1970**, *35*, 3779–3785; (e) Nabeya, A.; Shigemoto, T.; Iwakura, Y. *J. Org. Chem.* **1975**, *40*, 3536–3539.
3. (a) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Tetrahedron Lett.* **1999**, *40*, 8261–8264; (b) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Eur. J. Org. Chem.* **2000**, *13*, 2489–2494; (c) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574–8583.

4. For the substrates with R = cyclohexyl the appropriate alcohol **1b** is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde. A Horner–Emmons reaction, followed by a reduction of the ester using DIBAL, led to alcohol **1b** with an overall yield of 97%.
5. For the purposes of this work it is not mandatory to have optically active compounds, all the molecules are intended as racemates and the stereochemistry is only reported as the relative one.
6. Bonadies, F.; Scettri, A.; Di Campli, C. *Tetrahedron Lett.* **1996**, *37*, 1899–1900.
7. Righi, G.; Salvati Manni, L.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett.* **2011**, *52*, 3895–3896.
8. Legters, J.; Thijs, L.; Zwanemburg, B. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*, 1–15.
9. Matsushima, Y.; Kino, J. *Tetrahedron Lett.* **2006**, *47*, 8777–8780. and references therein cited.
10. Devijver, C.; Salmoun, M.; Daloze, D.; Braekman, J. C.; De Weerdt, W. H.; De Kluijver, M. J.; Gomez, R. *J. Nat. Prod.* **2000**, *63*, 978–980.
11. Cui, P.; McCalmont, W. F.; Tomsig, J. L.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem.* **2008**, *16*, 2212–2225.
12. Righi, G.; Bovicelli, P.; Tirotta, I. *Synthesis* **2012**, *44*, 3202–3208.
13. Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875–4886.
14. Tamamura, H.; Hiramatsu, K.; Ueda, S.; Wang, Z.; Kusano, S.; Terakubo, S.; Trent, J. O.; Peiper, S. C.; Yamamoto, N.; Nakashima, H. *J. Med. Chem.* **2005**, *48*, 380–3914.
15. *General procedure for the acyl chloride mediated ring-opening reactions*: 1 mmol of the appropriate substrate was dissolved in 1 ml of dry dichloromethane and the solution cooled to 0 °C. $Et_3N$ (1 mmol, 0.17 ml) and the appropriate acyl chloride (3 mmol) were added drop-wise and the mixture left stirring at room temperature until complete consumption of the substrate (TLC monitoring). The reaction mixture was diluted with dichloromethane, washed with ice cold water and neutralised with a saturated solution of $NaHCO_3$, the organic layer was dried over $Na_2SO_4$ and the solvent removed in vacuo to leave the crude, which was purified by flash chromatography. (4*R**,5*R**, *E*)-ethyl 5-(*N*-acetyl)amino-4-acetoxy-oct-2-enoate (**7a**): pale yellow oil (200 mg, 70%); IR (neat): 3320, 2980, 1716, 1640, 1250 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$): 6.81 (1H, dd, *J* = 5.1, 15.8 Hz, CH=CHCO), 5.91 (1H, dd, *J* = 1.6, 15.8 Hz, CHCO), 5.49 (1H, ddd, *J* = 1.6, 5.1, 5.3 Hz, CH-OAc), 5.4 (1H, d, *J* = 9.9 Hz, NH), 4.31–4.08 (3H, m, $COCH_2CH_3$ + CHNAc), 2.14 (3H, s, $COCH_3$), 1.99 (3H, s, $COCH_3$), 1.53–1.15 (7H, m, $COCH_2CH_3$ + $CH_2CH_2CH_3$), 0.89 (3H, t, *J* = 7.1 Hz, $CH_2CH_2CH_3$); $\delta_C$ (75 MHz $CDCl_3$): 170.1, 169.9, 165.7, 142.5, 123.3, 73.7, 60.8, 51.1, 33.9, 23.3, 20.9, 19.2, 14.3, 13.9; HRMS (ES Q-TOF): $[M+H]^+$, found 286.1659. $C_{14}H_{23}NO_5$ requires 286.1654. (4*R**,5*R**, *E*)-ethyl 4-(*N*-acetyl)amino-5-hydroxy-5-phenyl pent-2-enoate (**8c**): yellow oil (30 mg, 10%); IR (neat): 3444, 2986, 1715, 1656, 1190 $cm^{-1}$; $\delta_H$ (300 MHz $CDCl_3$): 7.62–7.22 (5H, m, Ph); 6.94 (1H, dd, *J* = 8.4, 17.6 Hz, CH=CHCO), 5.95 (1H, dd, *J* = 1.7, 17.6 Hz, CHCO), 5.87 (1H, d, *J* = 8.8 Hz, NH), 5.22 (1H, dddd, *J* = 1.7, 4.6, 8.4, 8.8 Hz, CH-NHAc), 5.11 (1H, d, *J* = 4.6 Hz, CHOH), 4.18 (2H, q, *J* = 7.2 Hz, $COCH_2CH_3$), 2.5 (1H, br s, OH), 1.99 (3H, s, $COCH_3$), 1.2 (3H, t, *J* = 7.2 Hz, $COCH_2CH_3$); $\delta_C$ (75 MHz $CDCl_3$): 169.9; 165.6; 143,2; 136.1, 128.7; 128.5; 126.7, 123.1; 70.6; 60.5, 53.9; 22.7; 13.9; HRMS (ES Q-TOF): $[M+H]^+$, found 278.1396. $C_{15}H_{19}NO_4$ requires 278.1392.