Tetrahedron Letters 50 (2009) 1447–1449

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Entry to nitrogen-containing heterocycles by based-promoted heterocyclization on allenylamides of L-α-aminoacids

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ARTICLE INFO

Article history:
Received 20 November 2008
Revised 22 December 2008
Accepted 13 January 2009
Available online 19 January 2009

Keywords:
Allenes
Heterocyclization
Hydroamination
Microwave irradiation
Imidazolidinones
Pyrazinones
Pyrroles

ABSTRACT

Allenylamides of Boc-protected α-aminoacids easily gave in basic medium heterocyclic products arising from attack of the NH group on the inside C–C double bond of the 1,2-diene moiety, namely imidazolidinones, pyrazinones, and a pyrrole compound. The microwave-assisted heterocyclization occurred cleanly at C-β of the allenyl group with formation of pyrazin-2-ones having an endo- or exocyclic double bond.

The construction of nitrogen heterocycles is an important goal in organic synthesis due to their occurrence in many natural substances as well as synthetic pharmaceuticals.[1] Among the wide range of substrates utilized as starting materials to this aim, allenes constitute an interesting class of organic compounds with peculiar chemical reactivity, having two cumulated double bonds.[2]

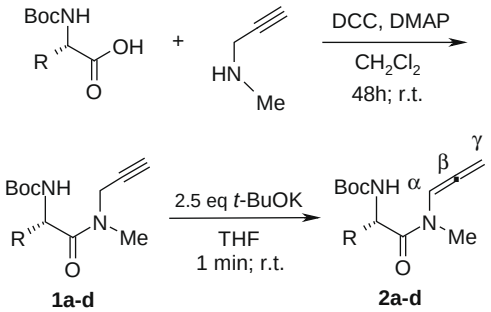
Intramolecular reactions of allenes may be achieved when the substrate contains a nucleophilic moiety in a suitable position. Among them, base-promoted reactions have been extensively studied as a route to hetero- and carbocycle systems by using nitrogen,[3] oxygen[4], or carbon[5] nucleophiles. Transition metal-catalyzed cyclization processes of allenes are also known.[6]

Within our research line on the development of novel methods to build nitrogenated heterocycles, some years ago we considered the behavior of amino- and sulfonylallenes as dipolarophiles in 1,3-dipolar cycloadditions.[7] On continuing our interest in synthesis and transformations of functionalized allenes, we have turned our attention toward *N*-allenyl amides. In this Letter we describe the cyclization reactions of allenylamides derived from α-aminoacids.

As precursors for the allene derivatives **2**, we first synthesized propargylamides **1** starting from *N*-Boc-protected L-α-aminoacids and methylpropargylamine by treatment with DCC (1.2 equiv) and 4-(dimethylamino)pyridine (0.02 equiv) in dichloromethane at room temperature (Scheme 1). The isomerization of **1**, induced by means of *t*-BuOK (2.5 equiv) in anhydrous THF, gave rise to allenylamides **2** in near quantitative yields.[8]

While previously reported aminoallenes were revealed prone to the formation of an internal C–C triple bond,[7a] compounds **2a–d** showed high stability making possible their storage for a long time.

The outcome of the allene formation was strongly dependent on the reaction time. The exposure to the base for only one minute



a: R = *i*-Pr, **1**: 95%, **2**: 98%
b: R = i-Bu, 1: 96%, 2: 92%
c: R = Bn, **1**: 94%, **2**: 95%
d: R = Ph, 1: 97%, 2: 95%

Scheme 1. Preparation of allenylamides **2a–d** from natural α-aminoacids.

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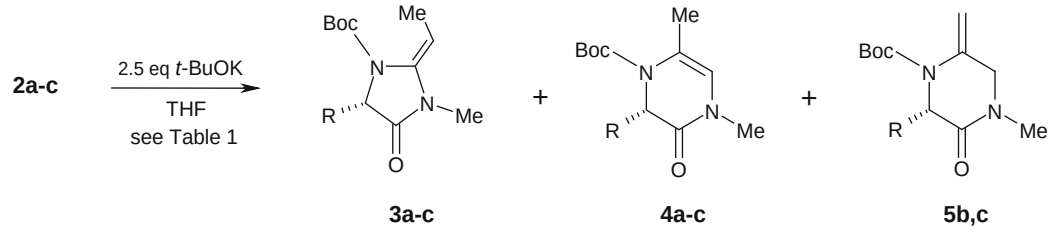
doi:10.1016/j.tetlet.2009.01.074



Scheme 2. Heterocyclization of allenylamides **2a**–**c**.

Table 1
Nitrogen-containing heterocycles produced via Scheme 2

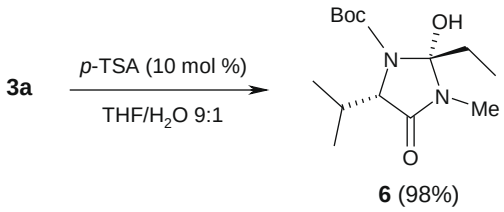
Entry	R	Conditions	Yield%		
			3	**4**	**5**
a	*i*-Pr	rt, 4 h	32	29	—
a	*i*-Pr	MW irradiation, 30 min	—	95	—
b	*i*-Bu	rt, 4 h	9	28	25
b	*i*-Bu	MW irradiation, 30 min	—	89	—
c	Bn	rt, 4 h	8	36	27
c	Bn	MW irradiation, 30 min	—	72	—

promoted a clean formation of the allenyl products, while a longer exposure to the base gave rise to complex mixtures of five- or six-membered heterocyclic products arising from intramolecular attack of the aminogroup on the carbon–carbon double bond.

With this evidence in hand, we tried to identify efficient conditions for synthetically useful heterocyclization procedure and we selected allene **2a** to this purpose. The cleanest reaction, with limited formation of tarry products, was accomplished in the presence of *t*-BuOK (2.5 equiv) in THF at room temperature for 4 h. Under these conditions, we obtained the optically active 2-ethylydenimidazolidin-4-one **3a** and 5-methyl-3,4-dihydro-pyrazin-2-one **4a** in 32% and 29%, respectively (Scheme 2, Table 1).[9] The *Z*-configuration of compound **3a** is consistent with the observed mutual NOE enhancements between the *N*-methyl group and the vinyl hydrogen atom (3.3% and 5.8%). HPLC analysis with chiral column of **3a** and **4a**, achieved in comparison to a sample of racemic mixture, proved an enantiomeric purity better than 99.5%.[10]

The formation of the observed products can be rationalized as follows. While the 1,4-diazine ring is resulted from the nucleophilic attack of the Boc-protected amine to the C-β of the allene group, the formation of the endiamine five-membered product is brought by an isomerization of the double bond of the first-generated cyclization product on the C-α.

Compound **3a** was smoothly and quantitatively transformed into 2-ethyl-2-hydroxy-imidazolidin-4-one **6**[11] by acid-catalyzed addition of water to the carbon–carbon double bond (Scheme 3). This process, which involves generation of a new stereocenter in 2-position of the imidazolidinone ring, gave only one diastereoisomer and its absolute configuration was identified by X-ray diffractometric analysis to be 2*R*,5*S* (Fig. 1).[12]



Scheme 3. Transformation of imidazolidinone **3a**.

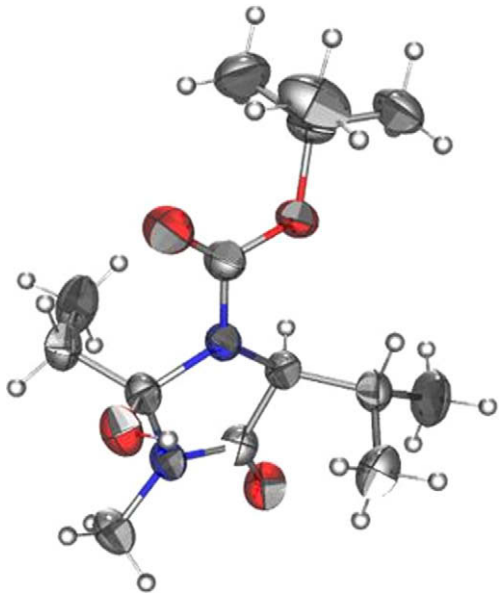


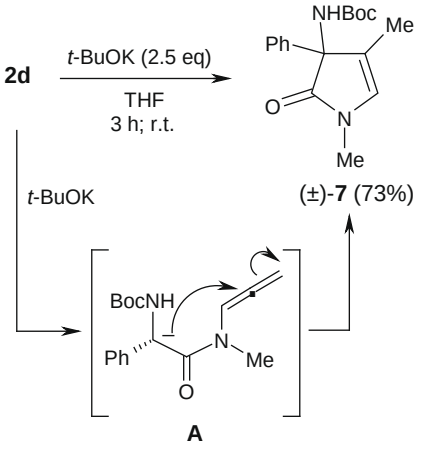
Figure 1. Ortep drawing (at 30% probability level) of the molecular structure of compound **6**, highlighting the *2R,5S* absolute configuration. C, gray; H, light gray; N, blue; O, red.

Heterocyclization also occurred with allenes **2b,c** according to a more regioselective process. Despite their structures strictly related to **2a**, different ratios of five- and six-membered products were achieved. In fact, only small amounts of imidazolidinones **3b,c** (9% and 8%, respectively) were obtained, while pyrazinones **4b,c** were the major products besides their isomers **5b**,**c**, so indicating preference for the C-β attack by the nucleophilic nitrogen.

However, the reactions just described, carried out at room temperature, furnished the heterocyclic products in moderate yields (see Table 1). Improved yields could not be achieved by refluxing the solution due to the thermal decomposition of the substrates. Hence, due to the ability of microwave irradiation to accelerate several organic reactions,[13] the heterocyclization processes were tested in a microwave reactor. Under these conditions, the reactions occurred cleanly in shorter times and higher yields giving exclusively the six-membered ring products **4**.[14]

It must be said that when the propargylamides **1a–c** were submitted to a prolonged treatment in the presence of *t*-BuOK in order to promote directly the heterocyclization process, complex mixtures with a high amount of tarry material were obtained.

Interestingly, a different behavior was observed for the allene **2d**, arising from L-phenylglycine. In this case, the treatment with *t*-BuOK at room temperature gave rise to the formation of only one product, whose analytical and spectroscopic data accorded with structure **7**[15] (Scheme 4).



Scheme 4. Heterocyclization of allenylamide **2d**.

The observed outcome can be due to the higher acidity of the benzylic α-aminoacidic hydrogen of **2d** with respect to **2a–c**. Consequently, in the presence of *t*-BuOK, the deprotonation of carbon atom instead of the Boc-protected aminogroup is operative, followed by the nucleophilic attack of the carbanion species **A** on the sp-carbon. Such a mechanism well justifies the obtainment of the pyrrolyl product in racemic form.

In conclusion, we have developed a simple procedure for building monocyclic five- and six-membered nitrogenated heterocycles from new allenylamides of L-α-aminoacids under base conditions. The moderate yields of the reactions performed at ambient temperature could be significantly increased by applying microwave activation. Further investigations, mainly based on the use of transition metals, are in progress in order to achieve more selective reactions and differently substituted products.

Acknowledgments

The authors gratefully acknowledge the Ministero dell'Università e della Ricerca for financial support and for the PhD fellowships to S.S. (Progetto Giovani 2004) and M.R. (Progetto Giovani 2006).

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9. *Procedure for cyclization of* **2a**: A solution of **2a** (100 mg, 0.4 mmol) and *t*-BuOK (112 mg, 1.0 mmol) in THF (8 mL) was stirred for 4 h at room temperature. The solution was filtered off through a short silica gel path (hexane/AcOEt 4:1 as eluent), and the solvent was evaporated under reduced pressure affording **3a** (32 mg, 32%) and **4a** (29 mg, 29%).
Compound **3a**. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.51 (s, 9H), 1.71 (d, J = 7.1 Hz, 3H), 2.26 (dqq, J = 3.5 Hz, 6.9 Hz, 6.9 Hz, 1H), 2.96 (s, 3H), 4.26 (d, J = 3.5 Hz, 1H), 4.44 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3 (q), 17.3 (q), 19.2 (q), 26.2 (q), 28.6 (q), 32.8 (d), 66.7 (d), 82.3 (s), 89.2 (d), 138.6 (s), 152.7 (s), 170.5 (s). IR (Nujol): 1685, 1710 cm^{-1}. $[\alpha]_D^{23}$ +3.7 (c 0.03, $CHCl_3$).
Compound **4a**. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 1.47 (s, 9H), 1.83 (m, 1H), 2.06 (s, 3H), 3.02 (s, 3H), 4.34 (m, 1H), 5.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0 (q), 19.4 (d), 28.3 (q), 28.6 (q), 33.2 (q), 63.8 (d), 81.8 (s), 117.8 (d), 119.7 (s), 153.4 (s), 166.1 (s). IR (Nujol): 1684, 1706 cm^{-1}. $[\alpha]_D^{23}$ +103.0 (c 0.70, $CHCl_3$).
10. The enantiopurity was determined by HPLC (OD-H column, 4.6 × 250 mm, mobile phase of 70/30 hexane/EtOH, flow rate 1.0 mL/min) with a detector at 231 nm.
11. *Compound* **6**: Mp 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (X part of ABX_3 system, J = 7.5 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.52 (s, 9H), 2.07 (A part of ABX_3 system, J = 14.9 Hz, 7.5 Hz, 1H), 2.28 (m, 1H), 2.51 (B part of ABX_3 system, J = 14.9 Hz, 7.5 Hz, 1H), 2.87 (s, 3H), 3.97 (d, J = 4.1 Hz, 1H), 4.58 (s br, 1H, missing after deuteriation). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8 (q), 17.5 (q), 20.2 (d), 24.8 (q), 28.7 (q), 30.9 (t), 31.5 (d), 63.6 (d), 82.4 (s), 100.6 (s), 154.7 (s), 170.6 (s). IR (Nujol): 1680, 1709, 3380 cm^{-1}. $[\alpha]_D^{23}$ +7.1 (c 0.03, $CHCl_3$).
12. *X-ray crystallography for* **6**: triclinic, space group $P\bar{1}$, a = 5.917(3) Å, b = 9.257(2) Å, c = 14.909(4) Å, α = 88.56(2)°, β = 84.26(3)°, γ = 84.60(2)°, V = 808.8(5) Å^3, Z = 2, $F(000)$ = 312, ρ = 1.176 g cm^{-3}, μ(Mo–Kα) = 0.086 mm^{-1}. The R, wR figures of merit reached final values of 0.043, 0.111 for the 2270 observed reflections ($I > 2\sigma(I)$), and 0.059, 0.119 for all of the 2913 unique reflections, 182 parameters. Goodness of fit, highest peak, and deepest hole reached final values of 1.049, 0.195 e Å^{-3} and −0.216 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 709855. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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14. *Procedure for cyclization of* **2a** *under microwave irradiation:* A solution of **2a** (100 mg, 0.4 mmol) and *t*-BuOK (112 mg, 1.0 mmol) in THF (5 mL) was heated for 30 min at 50 °C and 250 Watt in a CEM Discover microwave reactor. The solution was filtered off through a short silica gel path (hexane/AcOEt 4:1 as eluent), and the solvent was evaporated under reduced pressure affording **4a** as a colorless oil (95 mg, 95%).
15. *Compound* **7**. Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.74 (d, J = 1.6 Hz, 3H), 3.01 (s, 3H), 5.24 (s br, 1H, missing after deuteriation), 6.24 (q, J = 1.6 Hz, 1H), 7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9 (q), 24.3 (q), 29.8 (q), 68.1 (s), 80.8 (s), 119.6 (s), 126.2 (d), 129.0 (d), 129.3 (d), 129.5 (d), 137.5 (s), 154.4 (s), 177.8 (s). IR (Nujol): 1697, 1712 cm^{-1}.