Tetrahedron Letters 52 (2011) 1151–1153

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 4-aminoguaiazulene and its δ-lactam derivatives

Alexandros Kiriazis, Ingo B. Aumüller, Jari Yli-Kauhaluoma *

Division of Pharmaceutical Chemistry, Faculty of Pharmacy, PO Box 56 (Viikinkaari 5 E), FI-00014 University of Helsinki, Finland

ARTICLE INFO

Article history:
Received 19 November 2010
Revised 16 December 2010
Accepted 4 January 2011
Available online 13 January 2011

Keywords:
Azulene
Conjugation
Amine
Heterocycle
Lactam

ABSTRACT

A method for nitrogen insertion into guaiazulene hydrocarbons is developed. A one-pot reaction of 7-isopropyl-1-methylazulene-4-carboxylic acid, diphenylphosphoryl azide, and an alcohol (MeOH, ^{t}BuOH or BnOH) affords the corresponding carbamates. Deprotection of benzyl (7-isopropyl-1-methylazulen-4-yl)carbamate under basic conditions gave 4-aminoguaiazulene, which undergoes ring annulation reactions with 1,2-dicarbonyl reagents to yield tricyclic δ-lactams.

The present synthetic study details the chemical modification of azulene[1] based hydrocarbons belonging to the sesquiterpene class of natural products. Guaiazulene (**1**), an azulene derivative, is found in Nature as a constituent of pigments in mushrooms, guaiac wood oil, and some marine invertebrates, and currently, these natural resources also serve as its commercial sources. Guaiazulene is an FDA-approved cosmetic color additive and has potential applications as an anti-ulcer drug.

In our previous studies, we developed a one-pot transformation of azulene derivatives into complex tricyclic heptafulvenes and, subsequently, into tropones under mild reaction conditions.[2] Guaiazulene (**1**) was found to undergo electrophilic substitution reactions (S_E) with doubly activated 1,2-dicarbonyl compounds to yield 1′-hydroxyalkyl azulenes. After isolation, these azulenes were treated with the base to furnish new tricyclic azulene derivatives that possessed a fused six-membered ring containing various substituents.

As part of our ongoing studies to modify the guaiazulene structure, we became interested in introducing a heteroatom into this structure. This modification would be especially interesting as nitrogen-substituted azulene derivatives are scarcely documented in the literature. Herein, we focus on the insertion of nitrogen into the 4-position of the guaiazulene seven-membered ring. This approach offered the possibility of synthesizing a number of new heterocyclic azulene derivatives. Previously, Hamajima et al. reported the synthesis of 3-aminoguaiazulene, where the amino group is attached to the five-membered ring.[3] Modification of the 4-position of guaiazulene is feasible due to the enhanced acidity of the C–H bond in its methyl group, a procedure that reflects a common strategy in the field of azulene chemistry.[4]

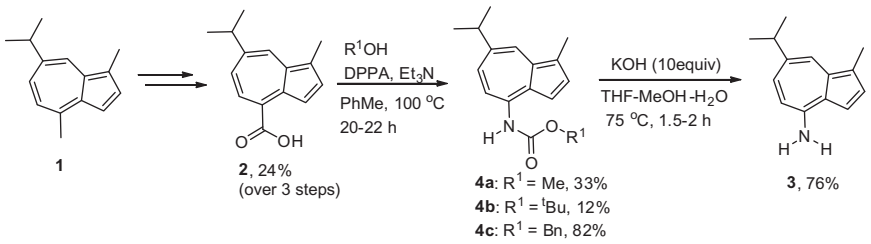
We have previously utilized this strategy for the three-step synthesis of 7-isopropyl-1-methylazulene-4-carboxylic acid (**2**)[5] starting from **1**. This crystalline and stable aryl carboxylic acid **2** was prepared and used as a starting material for our syntheses.

The key reaction in the preparation of amine **3** was the use of the modified Curtius–Schmidt rearrangement.[6] Carboxylic acid **2** was first converted into the corresponding isocyanate via an acyl azide intermediate using diphenylphosphoryl azide (DPPA).[7] A one-pot reaction in the presence of triethylamine and an alcohol (methanol, *tert*-butanol or benzyl alcohol) gave carbamates **4a–c** in variable yields (Scheme 1). For example, when methanol and *tert*-butanol were used, the yields were only moderate (12–33%). However, in the case of benzyl alcohol the reaction proceeded well, and benzyl (7-isopropyl-1-methylazulen-4-yl)carbamate (**4c**) was isolated in 82% yield after silica gel column chromatography.

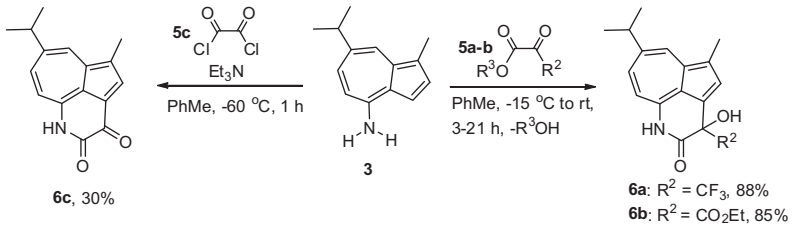
Subsequent deprotection of Cbz-protected amine **4c** turned out to be challenging, as standard methods, such as catalytic hydrogenation or acid hydrolysis with HBr, suffered from the participation of the azulene moiety in numerous side reactions. Removal of benzyl carbamate was achieved in the presence of potassium hydroxide in an aqueous solution of THF and MeOH. When compound **4c** was heated with KOH in THF–MeOH–H_2O, the color of the reaction mixture changed quickly from blue to deep purple. The hydrolysis was complete in 1–1.5 h (TLC monitoring) and 7-isopropyl-1-methylazulen-4-amine (**3**) was isolated in good yield (76%) after column chromatography on silica gel. Amine **3** was found to be relatively stable when stored under an inert atmosphere in a refrigerated toluene solution (concentration approx. 0.10 mM).

* Corresponding author. Tel.: +358 9 191 59170; fax: +358 9 191 59556.
E-mail address: Jari.yli-kauhaluoma@helsinki.fi (J. Yli-Kauhaluoma).

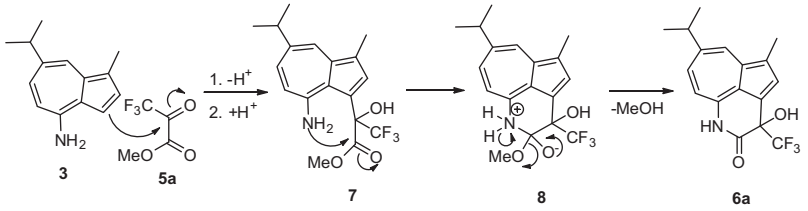
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.01.016



Scheme 1. The synthesis of 4-aminoguaiazulene (**3**) from guaiazulene (**1**) via carboxylic acid **2**.[5]



Scheme 2. Cyclization of 4-aminoguaiazulene (**3**) to give δ-lactams **6a–c**.



Scheme 3. Proposed reaction mechanism for the formation of δ-lactam **6a**.

In agreement with our previous work,[2] 7-isopropyl-1-methylazulen-4-amine (**3**) reacted with various 1,2-dicarbonyl compounds **5a–c** (Scheme 2). The cascade reactions between **3** and **5a–c** produced δ-lactams **6a–c** under mild reaction conditions without the need for a catalyst.

The one-pot reaction between azulenyl amine **3** and methyl 3,3,3-trifluoropyruvate (**5a**) proceeded efficiently and yielded δ-lactam **6a** in 88% yield after purification by column chromatography. Theoretically, this reaction could have led to two regioisomeric products, but only one product was isolated. The azulenyl amine reacts in a similar fashion to that reported for the pure hydrocarbon guaiazulene,[2] as rationalized in Scheme 3. The high nucleophilicity of the electron-rich 3-position ensures that electrophilic substitution of this carbon atom is the predominant reaction between **3** and **5a** to yield **7**. This is followed by a ring closure to furnish **8**. Finally, the elimination of methanol produces δ-lactam **6a**. The regioselectivity is further explained by the high electrophilicity of the central carbon atom of the doubly activated dicarbonyl reagent.

The reaction with diethyl ketomalonate (**5b**) is comparable to that of **5a** (Scheme 2). Reaction of amine **3** at room temperature for 21 h yielded the corresponding lactam **6b** in 85% isolated yield after purification by column chromatography. In contrast, these types of cyclizations do not run smoothly with carbonyl reagents that are not additionally activated, such as ethyl pyruvate, 2,3-butanedione, and ethyl glyoxylate. In these cases, we were unable to obtain any lactam product. However, other very reactive dicarbonyl reagents can be successfully employed, demonstrating that a broader structure variety is accessible by analogous reaction procedures. For example, we found that a rapid reaction occurs between amine **3** and oxalyl chloride (**5c**) (Scheme 2). When the reaction temperature was as low as −60 °C and an excess of the tertiary base (Et_3N) was used, δ-lactam **6c** was obtained in moderate (30%) yield after purification. In contrast to the α-hydroxy lactams **6a** and **6b**, product (**6c**) contains a different functional group and is an α-ketolactam.

In summary, we have developed a method for the synthesis of Cbz-protected aminoazulene **4c** via a Curtius–Schmidt rearrangement. Deprotection under basic conditions gave the surprisingly stable 7-isopropyl-1-methylazulen-4-amine (**3**), which was found to undergo a cascade reaction with 1,2-dicarbonyl electrophiles to produce a new six-membered ring fused to the azulene aromatic system. These cyclization products were isolated and characterized as tricyclic δ-lactams **6a–c**. Further work is being conducted in an effort to expand the scope of the reaction and to investigate the biological properties of these compounds as potential inhibitors of protein kinases.[8]

Acknowledgments

We thank the Graduate School of Pharmaceutical Research and the European Commission (Contract No. LSHB-CT-2004-503467) for financial support.

Supplementary data

Supplementary data (experimental procedures, compound characterization data, and ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.016.

References and notes

1. Plattner, P. A.; Pfau, A. S. *Helv. Chim. Acta* **1937**, *20*, 224–232.
2. Aumüller, I. B.; Yli-Kauhaluoma, J. *Org. Lett.* **2009**, *11*, 5363–5365.
3. (a) Hamajima, R.; Iwano, K.; Okuda, H. *Yakugaku Zasshi* **1978**, *98*, 1101–1107; (b) Hamajima, R.; Nishimura, H.; Kojima, K. *Yakugaku Zasshi* **1981**, *101*, 1048–1052.
4. (a) Neidlein, R.; Kramer, W. *Helv. Chim. Acta* **1982**, *65*, 280–285; (b) Neidlein, R.; Kramer, W.; Krotz, R. *Arch. Pharm.* **1984**, *317*, 984–995; (c) Gibson, W. K.; Leaver, D.; Roff, J. E.; Cumming, C. W. *J. Chem. Soc., Chem. Commun.* **1967**, 214–215; (d) Aumüller, I.; Lindhorst, T. K. *Eur. J. Org. Chem.* **2006**, 1103–1108.
5. Aumüller, I. Ph.D. Dissertation, University of Kiel, Germany, 2002.
6. Curtius, T. *Chem. Ber.* **1890**, *23*, 3023.
7. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205; (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
8. Some of the azulenes synthesized were preliminarily tested against a panel of serine/threonine kinases, which belong to the CAMK (calcium/calmodulin-regulated kinases) family of kinases. Further work to characterize these bioactivities is now in progress in our collaborators' laboratory.