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[a033]

Synthesis of 1-vinyl isoquinolines and isoindolines by cyclization of acyliminium ions derived from allenamides

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Abstract

A new approach to 1-vinyl isoquinolines and isoindolines using as the key step the acid catalyzed cyclization of allenamides via an acyliminium ion intermediate has been achieved.

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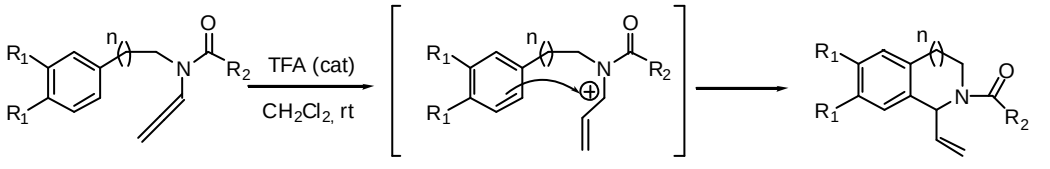
Introduction

Allenamide chemistry[1] has received a lot of attention in the very last years.[2] Recently the reactivity of this type of compounds was explored in transition-metal catalyzed cyclization,[3] [2+2] and inverse demand [4+2] cycloadditions,[4] and other cyclization reactions.[5] Due to allylic stabilization of the resulting intermediates, these electron-deficient allenamines are highly reactive towards nucleophilic, electrophilic, and even radical addition[6] at the central *sp* carbon atom.

Results and discussion

In this communication we describe a new cyclization reaction based on the formation of an acyliminium ion[7] by treatment of an appropriate allenamide with trifluoroacetic acid. Treatment of allenamides **1**[8] with a catalytic amount of TFA (10% mol) in dichloromethane at room temperature afforded the vinyl substituted heterocyclic compounds **3** in moderate to good yields. This cyclization should proceed through mechanism presented in Scheme 1, i.e, protonation of the allenamides **1** to give the acyliminium ions **2**, which suffer then electrophylic aromatic substitution. The mild conditions in which these reactions take place can be undoubtedly attributed to the allylic nature of the intermediate cations **2**.

Scheme 1



1 **2** **3**

Table 1. Acid catalyzed cyclization of allenamides **1a-1e.**

Compound	n	R_1	R_2	% Yield of 3
a	0	MeO	H	22
b	1	MeO	H	67
c	1	H	H	-
d	1	MeO	2-I-Phenyl	78
e	2	MeO	H	-

In the case of benzylallenamide **1a** indoline **3a** is obtained in low yield (22 %). Much better yield was observed for phenethyl compounds **1b** and **1d**, 67 % and 78 % respectively. The presence of an electron rich aromatic ring was found necessary for the reaction to take place since allenamide **1c** did not deliver any cyclization product even under forced conditions (50% mol TFA, DMF, 70 ºC). Treatment of the homologous compound **1e** did not produce any cyclised product under the standard reaction conditions; we rose the temperature to 60 ºC but only the secondary amide derived from hydrolysis was observed. Accordingly with the experimental results, DFT *ab initio* computations showed that 6-membered ring formation (entries b, c and d) are nearly free of stereoelectronic constraints due to proper alignment of reactive centers.

In resume, allenamides can be used as precursors of acyliminium ions under very mild conditions, to prepare either 1-vinyl isoindolines or isoquinolines. These last compounds could serve as intermediates for a new approach to the skeleton of naturally occurring methylene protoberberines, which is under study.

Acknowledgements

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References and Notes

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[8] Allenamides **1a-e** were prepared by condensation of appropriate secondary amides with propargyl bromide (KOtBu/DMSO) and subsequent base-catalyzed isomerization of the resulting propargylamide in the reaction medium.