Pergamon

Tetrahedron Letters 39 (1998) 4757–4760

TETRAHEDRON LETTERS

A Short Synthesis of (±)-Alloyohimbane *via* a Thioisomünchnone Based Intramolecular Dipolar-Cycloaddition Reaction

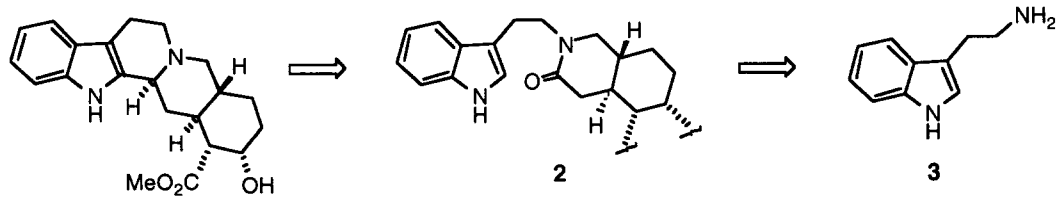
*Todd M. Heidelbaugh, Bing Liu and Albert Padwa**
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received 14 April 1998; accepted 22 April 1998

Abstract: Thioisomünchnone dipoles were generated by the reaction of bromoalkenoyl chlorides with thioamides. The intramolecular dipolar-cycloaddition reaction was used for a short synthesis of the yohimbanoid alkaloid (±)-alloyohimbane.

Polycyclic nitrogen containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active drugs.[1,2] Members of the yohimbane alkaloid family possess a characteristic pentacyclic indole ring system and generally exhibit a wide range of important pharmacological properties.[3] Construction of the core indolo[2,3-*a*]quinolizidine skeleton found in yohimbine (**1**) has presented a formidable challange to synthetic organic chemistry and several elegant methods have been developed to achieve this goal.[4-7] Key synthetic elements in some of these approaches have included Diels-Alder cycloaddition,[8] radical cyclization,[9] Oxy-Cope[10] and amino-Claisen rearrangements,[11] and photocyclization pathways.[12] A particularly viable strategy that has been extensively utilized for the construction of the polycyclic framework of the yohimbane alkaloids is to assemble appropriately functionalized derivatives of indoloquinolizidine and to elaborate them further into different target compounds (Scheme I).[4-7]

Scheme I



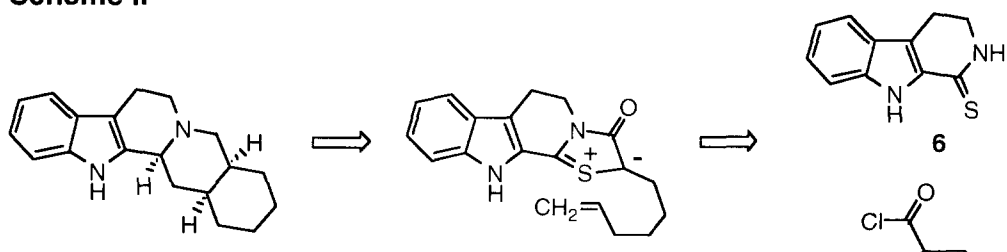
Yohimbine (**1**) **2** **3**

Our interest in yohimbinoid alkaloid syntheses was prompted by the desire to explore thioisomünchnone dipolar-cycloaddition chemistry[13] as a key strategy for the assembly of these alkaloids. The approach we had in mind (Scheme II) was based on our previous success involving the reaction of 2-substituted thiolactams with bromoacetyl chloride as a method to generate anhydro-4-hydroxy-1,3-thiazolium hydroxides (thioisomünchnones).[14] We envisioned that dipole **5**, derived from

0040-4039/98/$19.00
PII: S0040-4039(98)00901-0

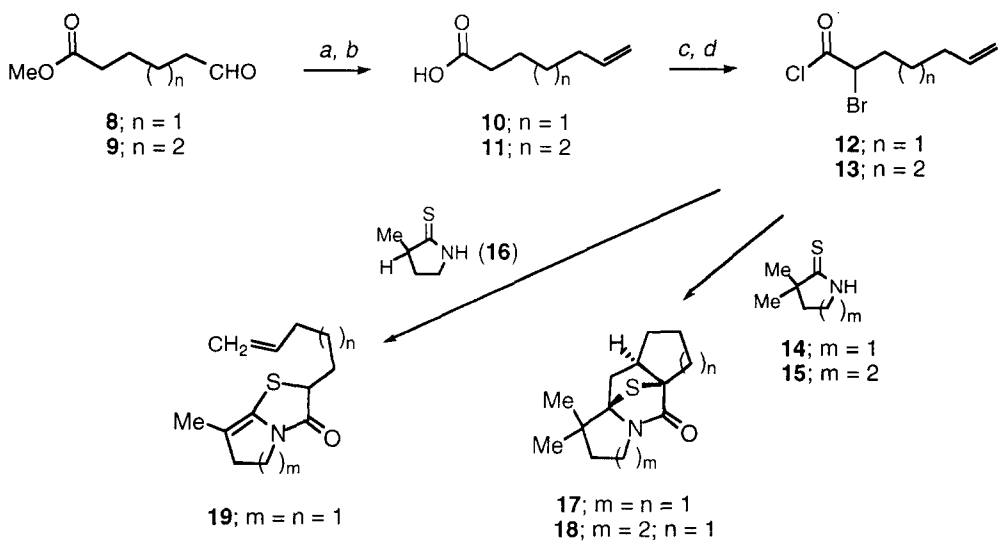
the reaction of thioamide **6** and bromoacid chloride **7**, would readily undergo intramolecular dipolar-cycloaddition. Removal of the sulfur atom from the resulting cycloadduct (*vide infra*) followed by amide reduction should lead to alloyohimbane (**4**).[15]

Scheme II



The successful implementation of this approach relied on the synthesis of the requisite bromoacid chloride. Aldehydo-esters **8** and **9** were first prepared by the Schreiber ozonolysis protocol.[16] These compounds were converted to carboxylic acids **10** and **11** in good yield using a standard Wittig reaction followed by alkaline saponification. Treatment of **10** and **11** with 2 equiv of LDA followed by sequential

Scheme III

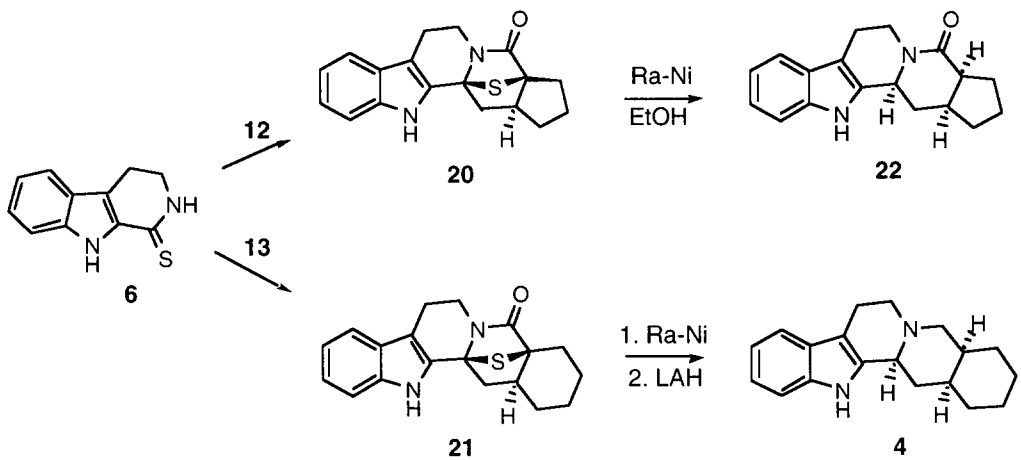


Reagents: (a) $Ph_3P{=}CH_2$; (b) KOH/MeOH; (c) LDA/CBr_4; (d) $(COCl)_2$

reaction with carbon tetrabromide and then oxalyl chloride according to the Snider procedure[17] delivered the desired bromoacid chlorides **12** and **13** in 76% and 61% yield, respectively. Reaction of thioamides **14** and **15** with bromoacid chloride **12** and triethylamine (1.5 equiv) in toluene at 110 °C resulted in the formation of cycloadducts **17** and **18** in 67% and 74% yield, respectively. The depicted stereochemistry is the result of *endo* cycloaddition with regard to the dipole. This assignment is based on our related work dealing with intramolecular isomünchnone cycloaddition chemistry, for which X-ray crystallographic analysis had been performed.[18] When a hydrogen atom is present in the α-position of the thioamide (*i.e.*, **16**), the initially formed *N*-acyl iminium ion undergoes proton loss to produce the *S,N*-acetal **19** at a faster rate than thioisomünchnone formation.

The facility with which polycyclic *N*-heterocycles could be assembled from simple thioamides prompted us to use the above methodology for the preparation of alloyohimbane **4**. Treatment of the unprotected thiocarboline **6** with bromoacid chlorides **12** and **13** afforded cycloadducts **20** and **21** in 62% and 75% yield, respectively (Scheme IV). Raney-Ni reduction of **20** gave the pentacyclic analog **22** in 85% yield as the major diastereomer. A short synthesis of alloyohimbane **4** was achieved in 24% yield by subjecting cycloadduct **21** to the Raney-Ni conditions followed by further reduction using LAH.

Scheme IV



In conclusion, this study has demonstrated that the intramolecular dipolar-cycloaddition reaction of thioisomünchnones represents a highly efficient method for the synthesis of polycyclic *N*-heterocycles. We have achieved a short, straightforward synthesis of (±)-alloyohimbane, and the method should be amenable to the synthesis of other members of the yohimbane alkaloid family.

Acknowledgment: We gratefully acknowledge support of this work by the National Institutes of Health (CA-26750). We wish to thank Mr. Bassem M. El. Daieef for some experimental assistance.

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