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New Synthetic Route to the Alkaloid Withasomnine by Ring Transformation of a Functionalized Cyclopropanol via the Parent Pyrrolo[1,2-b]pyrazole

Oleg Kulinkovich*, Nikolai Masalov and Vladimir Tyvorskii

Department of Organic Chemistry, Belarussian State University, Fr. Scorina Av., 4, Minsk 220050, Belarus

and

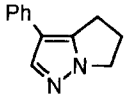
Norbert De Kimpe* and Marian Keppens

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Abstract. Withasomnine has been prepared by rearrangement of 1-(3-chloropropyl)-cyclopropanol into 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole, followed by bromination and [$NiCl_2$(dppp)]-catalyzed phenylation.

The pyrazole alkaloid withasomnine **1** has been isolated from the roots of the Indian medicinal plants *Withania somnifera Dun.*[1] This alkaloid and its 4'-hydroxy derivative were also recently isolated from *Newbouldia leavis*.[2] These plants are used in ethnopharmacological applications, e.g. the treatment of enlarged spleen, migraine, infections and dysentery. Some syntheses of the alkaloid **1** have been published.[3-5]

We report herein on the rearrangement of 1-(3-chloropropyl)cyclopropanol **3** to the parent 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole **7** as a key intermediate in the conversion into the alkaloid withasomnine **1**.



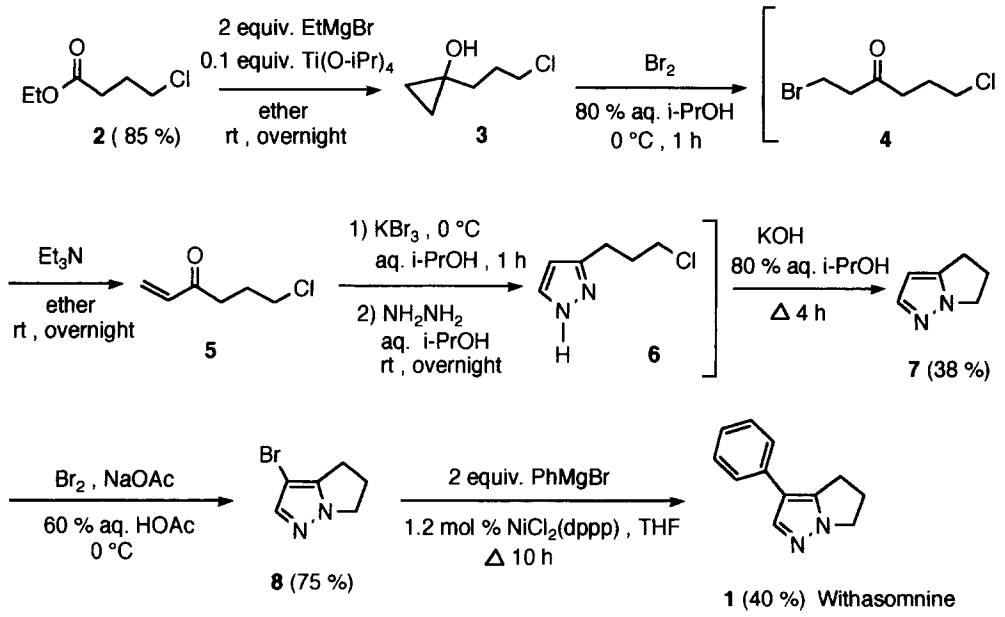
1 Withasomnine

1-(3-Chloropropyl)cyclopropanol **3** was obtained in 85% yield by reaction of ethyl 4-chlorobutyrate **2** with ethylmagnesium bromide in the presence of a catalytic amount of titanium(IV) isopropoxide in ether.[6-8] This cyclopropanol **3** was easily converted (80% yield) into 6-chloro-1-hexen-3-one **5** by reaction with bromine in 80 % aqueous 2-propanol and following 1,2-dehydrobromination of the intermediate β-bromoketone **4** with triethylamine in diethyl ether. The crude vinyl ketone **5** was brominated with potassium perbromide in aqueous 2-propanol and treated with a five-fold excess of hydrazine hydrate at room temperature. 3-(3-Chloropropyl)pyrazole **6** was obtained as the major reaction product and was cyclized by reflux in aqueous 2-propanol in the presence of potassium hydroxide to afford 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole **7**.

When compounds **4-6** were used as intermediates in consecutive reactions without isolation in pure form, the overall yield of the condensed azaheterocycle **7** from cyclopropanol **3** mounted to 38%.

The introduction of a phenyl group in compound **7** to form withasomnine **1** was achieved in two steps. Bromination of pyrazole **7** in 60% aqueous acetic acid in the presence of sodium acetate at 0° C proceeded smoothly giving 3-bromo-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole **8** in 75% yield. The bromopyrazole **8** was coupled with a two-fold excess of phenylmagnesium bromide in refluxing THF solution for 10h under argon

atmosphere in the presence of 1.2 mol% of $[NiCl_2(dppp)]$[9] to give, after the usual workup and column chromatography on alumina (ether-hexane, 10:3), a 40% yield of withasomnine **1**, m.p. 117°C (heptane; lit.[1] m.p. 117-118° C). This coupling reaction led also to the formation of pyrazole **7** as a byproduct, which may be attributable to a metal-halogen exchange reaction between bromide **8** and the Grignard reagent.[9]



This synthetic strategy demonstrates the straightforward conversion of functionalized cyclopropanols into pyrazoles and the subsequent formation of 4H-pyrrolo[1,2-b]pyrazole derivatives as key compounds for the synthesis of withasomnine.

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