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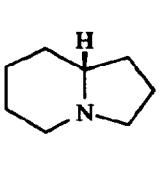
A Simple Route to the Indolizidine Alkaloid Skeleton.

Derek H. R. Barton,* Maria M. M. Araújo Pereira and Dennis K. Taylor.

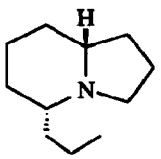
Department of Chemistry, Texas A&M University, College Station
TX 77843-3255, USA.

Abstract: *The Barton-Ester (PTOC) methodology allows for the high yielding synthesis of the indolizidine alkaloid skeleton* ***12*** *starting from readily available (pyrrol-1-yl)acetic acid* ***7****.*

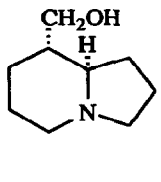
The indolizidine alkaloids constitute a family of compounds based on the parent structure **1**.[1] These compounds which are often toxic, are commonly isolated from the extracts of amphibian skins in minute quantities and exhibit high biological activity.[2] The isolation and enantioselective syntheses of several key indolizidine alkaloids **2-6** have recently been reported.[2b,2c,3,4] We report here a simple and high yielding synthesis of the indolizidine alkaloid skeleton **12**.



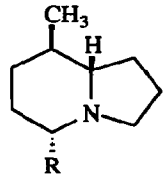
(1)



(2)



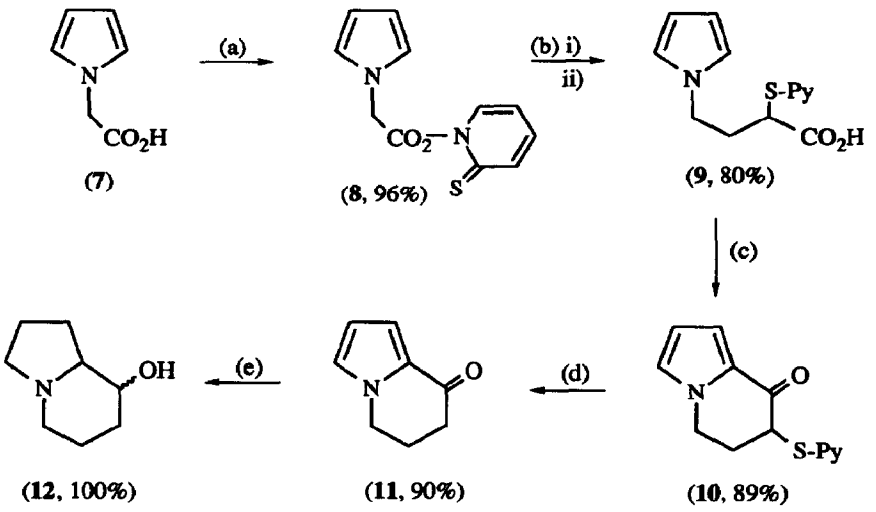
(3)



(4) R = $(CH_2)_3$-CH_3
(5) R = $(CH_2)_3$-CH=CH_2
(6) R = $(CH_2)_3$-C≡CH

Thus, treatment of pyrrol-1-yl acetic acid[5] with DCC and *N*-hydroxypyridine-2-thione in the usual manner[6] afforded the Barton (PTOC) ester **8**[7] in nearly quantitative yield as depicted in Scheme 1. Photolysis of **8** in the presence of excess ethyl acrylate yielded, after workup and subsequent basic hydrolysis, the acid **9**[7] in good yield. Polyphosphoric acid cyclization to **10**[7] followed by reduction employing zinc / acetic acid gave 6,7-dihydro-8(5H)-indolizinone[8] **11** in excellent yield. Catalytic hydrogenation with Pd / C failed to reduce **11**; however hydrogenation over a Rh / Al_2O_3 catalyst[9] afforded the desired indolizidine alkaloid **12** in quantitative yield.

In summary, the Barton-Ester methodology allows for a high yielding synthesis of the indolizidine alkaloid skeleton **12** starting from the readily available acid **7**. Also, preliminary experiments show that the same principle is applicable to the synthesis of substituted indolizidine alkaloids as well as those derived from indole.



(a) *N*-hydroxypyridine-2-thione, DCC, CH_2Cl_2, 25°C; (b) i) ethyl acrylate (10 equiv.), CH_2Cl_2, hν; ii) 20% aq. KOH / MeOH; (c) excess PPA, 16 hr., r.t.; (d) Zn / AcOH, 2.5 hr., r.t.; (e) H_2, 65 psi, 5% Rh / Al_2O_3, 12 hr. r.t.

Scheme 1

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