Thesis Title A New Method for Synthesis of Pavine Alkaloids: Application to the Synthesis of Natural Argemonine

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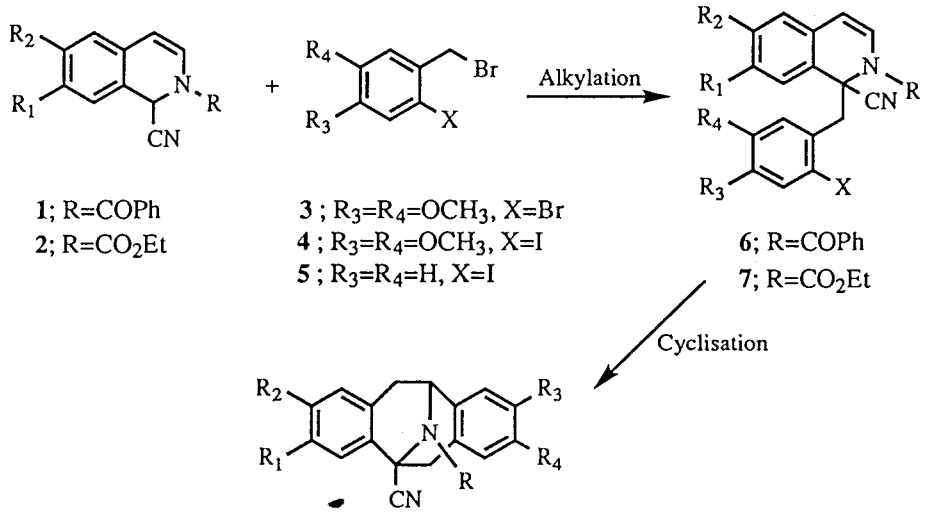
ABSTRACT

Many pavine alkaloids have been previously synthesized, the syntheses mainly involved the Sn/ HCl reduction of papaverine or papaverinium salts including acid catalyzed cyclization of enamine moieties of benzylisoquinolines. In this study a new method for the synthesis of aromatic ring system of pavine alkaloid **8** and **9** was described. The synthetic method involved the intramolecular coupling of isoquinaldonitrile **6** or **7** catalyzed by $Pd(PPh_3)_4$. In addition, the free radical catalyzed cyclization of **6** or **7** by Bu_3SnH/ AIBN was also investigated. The key intermediates **6** and **7** were obtained from the benzylation of Reissert compounds **1** and **2** respectively. In the course of intramolecular pavine ring formation, the effect of halogen and methoxy substituents on the intermediate **6** and **7** was also studied.



1; R=COPh
2; R=CO_2Et

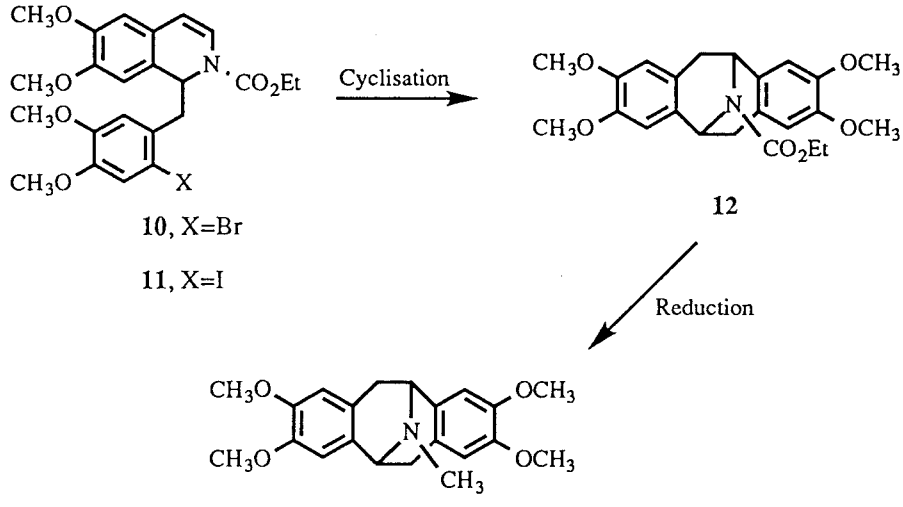
3 ; R_3=R_4=OCH_3, X=Br
4 ; R_3=R_4=OCH_3, X=I
5 ; R_3=R_4=H, X=I

6; R=COPh
7; R=CO_2Et

8; R=COPh
9; R=CO_2Et

R_1=R_2=R_3=R_4=H, OCH_3

Our new method has been applied successfully to the synthesis of natural argemonine alkaloid **13**. The title compound **13** has been achieved by $Pd(PPh_3)_4$ or Bu_3SnH catalyzed intramolecular cyclization of bromo compound **10** (44%) or iodo compound **11** (56%) followed by lithium aluminium hydride reduction of pavine **12**. The starting compounds **10** and **11** were readily prepared from the reaction of 2'-bromo or 2'-iodopapaverine with Bu_3SnH/ CH_2Cl_2 at room temperature, then ethylchloroformate at -78° C and warmed up to room temperature.



10, X=Br

11, X=I

12

Argemonine

13