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INTRAMOLECULAR ALKYLATION OF 3-HYDROXYPYRROLE-2-CARBOXYLATES. FORMATION OF 5/5, 5/6, AND 5/7 RING SYSTEMS RELATED TO PYRROLIDINE ALKALOIDS

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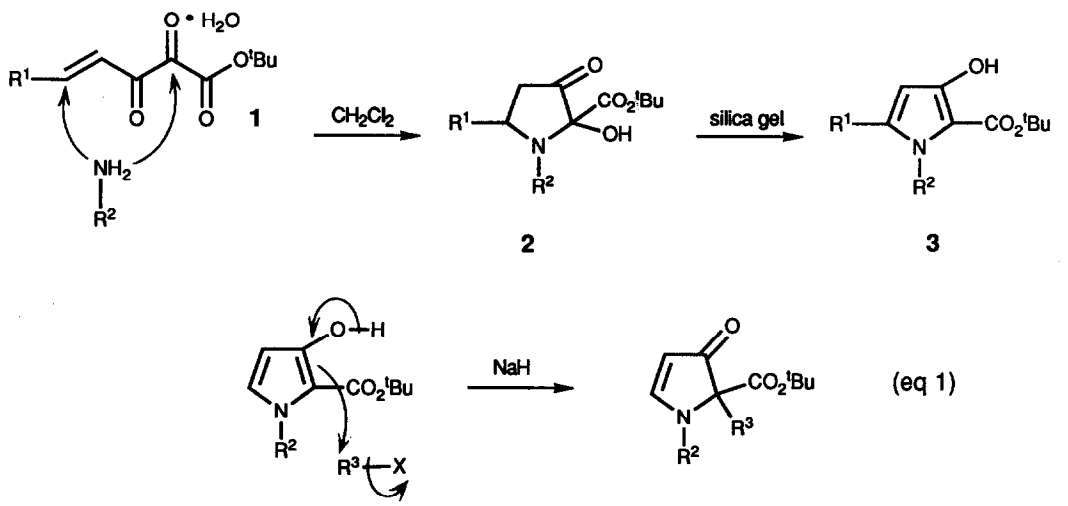
Summary: The intramolecular alkylation of 3-hydroxypyrrole-2-carboxylates **4**, **8**, and **12** leads to fused ring systems found in the pyrrolizidine, indolizidine, and related pyrrolidine alkaloids.

We have recently shown that primary amines undergo reaction with vinyl or alkenyl tricarbonyl ester reagents **1** to form 3-hydroxypyrrole-2-carboxylates by the sequence shown in Scheme 1.[1,2] This direct route to hydroxypyrroles has been utilized in the synthesis of products in the prodigiosin series.[3] In other work, compounds **3**, as analogues of β-keto esters, have been shown to undergo alkylation at the 2-position (eq 1).[4] Our method for forming hydroxypyrroles permits the attachment of residues on the nitrogen atom incorporating leaving groups as in **4**. Alkylation may then take place by intramolecular displacement.

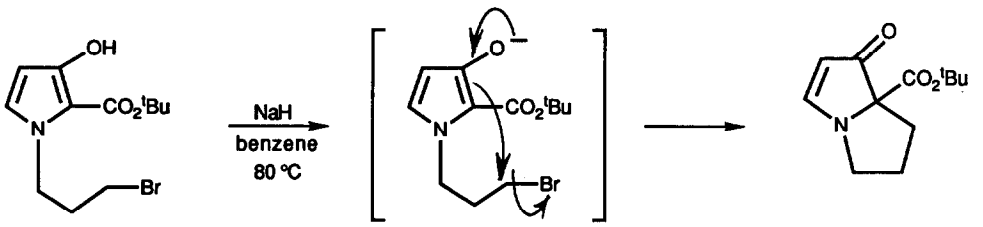
Scheme 1



We now report the use of this method for the formation of 5/5, 5/6, and 5/7 ring systems related to pyrrolidine alkaloids. Schemes 2, 3, and 4 illustrate the use of substituted 3-hydroxypyrrole-2-carboxylates to carry out intramolecular cyclizations. With the opportunity for incorporating functionality in the primary amine component, this method permits flexibility in the substitution pattern of the five, six, or seven-membered ring fused to the pyrrolinone carboxylate moiety. Formation of the 5-5 ring system corresponding to the pyrrolizidines

is illustrated in Scheme 2. In the first step, reaction of **1** (R^1 = H) with 3-bromopropylamine yielded compound **4** (64%).[2] Upon treatment with excess NaH , **4** underwent cyclization by intramolecular alkylation as in **5** to give derivative **6** (88%).[5]

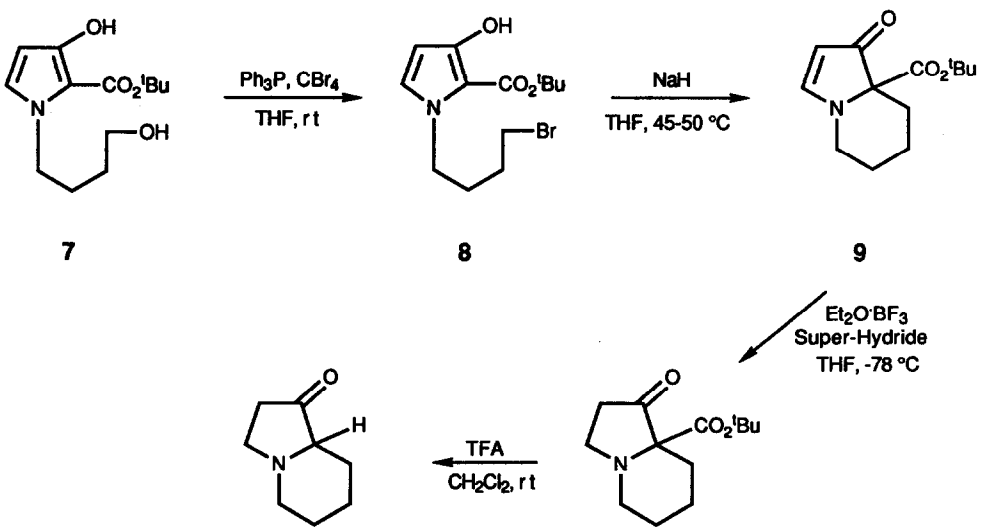
Scheme 2



4 **5** **6**

To prepare indolizidine derivatives, a primary amine separated from the leaving group by a four-carbon chain was needed. Thus, reaction between 4-amino-1-butanol and the vinyl tricarbonyl ester **1** (R^1 = H) provided the desired hydroxypyrrole **7** (64%). Selective conversion of the primary alcohol **7** to the bromide **8** was achieved using triphenylphosphine and carbon tetrabromide (81%) (Scheme 3).[6] When **8** was treated with excess NaH, cyclization took place to give the indolizidine derivative **9** (88%). The vinylogous amide **9** could be

Scheme 3

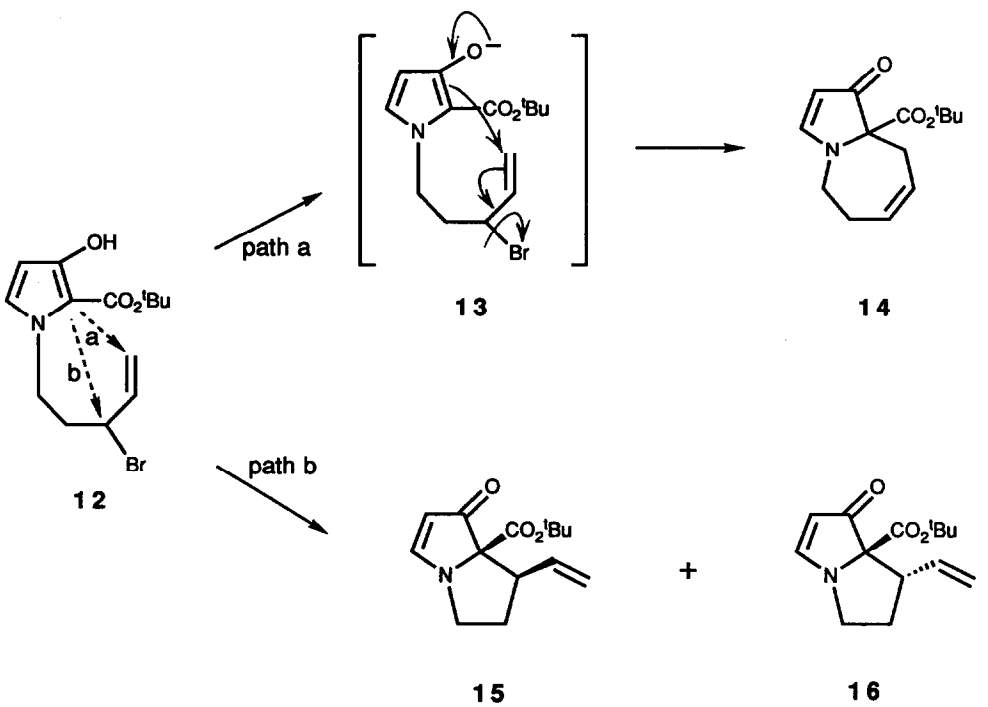


7 **8** **9** **10** **11**

reduced at -78 °C with Super-Hydride in the presence of $Et_2O{\cdot}BF_3$ to give **10** (79%), which upon exposure to excess anhydrous TFA, underwent decarboxylation to give the known indolizidine **11** (76%).[7] This method provides an efficient and direct entry to functionalized indolizidines depending upon the substitution pattern of the primary amine fragment.[8,9]

With hydroxypyrrole **12**,[10,11] two possibilities exist for intramolecular alkylation as shown in Scheme 4. We found that when **12** was treated with NaH, the alkylation proceeded mainly via a S_N2' displacement as in **13** to afford the bicyclic compound **14** (66%). As by-products, the pyrrolizidine derivatives **15** and **16** were also obtained (24%, 1:1 ratio of **15** to **16**). The 5,7-fused ring systems in **14** is found in a number of naturally occurring homoerythrina[12] and stemona alkaloids.[13]

Scheme 4



In summary, the intramolecular alkylation of 3-hydroxypyrrole-2-carboxylates leads to bicyclic systems of potential interest in pyrrolidine alkaloid synthesis. Future work will focus on the application of this methodology to the synthesis of natural products.

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5 All new compounds gave satisfactory ^{1}H NMR, IR, MS, high-resolution MS and/or elemental analyses.

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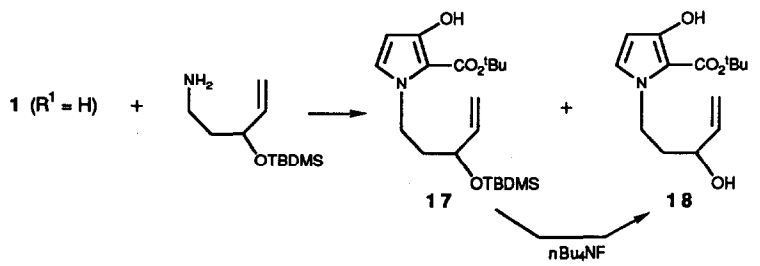
8 We are currently pursuing a synthesis of the indolizidine alkaloid, slaframine, using the primary amine $NH_2CH_2CH(OTBDMS)CH_2CH_2OH$.

9 For an iminium ion route to the indolizidines involving the reaction of **1** (R^1 = H) with amines containing multiple donor sites see: Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701.

10 Hydroxypyrrole **12** was prepared as follows: 5-amino-3-t-butyldimethylsilyloxypentene[10] was reacted with the vinyl tricarbonyl reagent **1** (R^1 = H) to give the hydroxypyrrole[2] as a mixture of TBDMS-protected **17** (55%) and desilylated product **18** (12%). The TBDMS group was readily removed with tetrabutylammonium fluoride (99%), and the resulting alcohol **18** converted to the bromide **12** using carbon tetrabromide and triphenylphosphine (91%).



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