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TETRAHYDROPYRIDONES VIA INTRAMOLECULAR UREIDOMERCURATION

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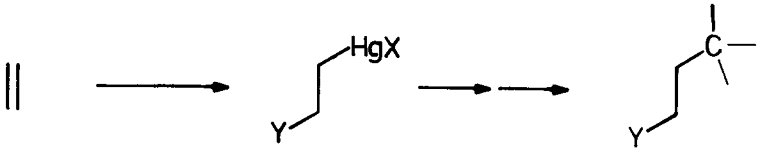
Summary: A four-step synthesis of δ-coniceine utilizes sequential ureidomercuration and reductive coupling of the mercurial.

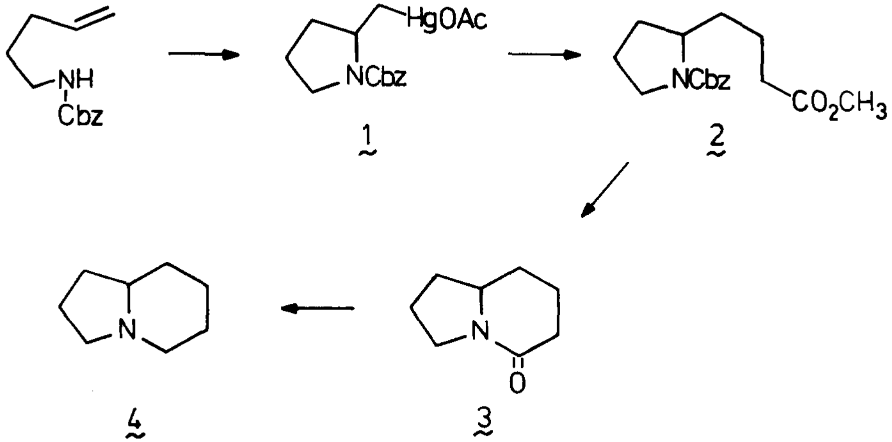
The hetero-mercuration of double bonds is a process of considerable potentiality in synthesis.[1,2.3] In such reactions the mercury attacks in a Markownikoff sense with high positional definition. The organo-mercury bond is sufficiently covalent to allow for the survival of a hetero substituent on the adjacent carbon atom - a property not widely shared by more polarized organometallic systems. While the weakly reactive organo-mercury bond resists direct attack by typical carbon electrophiles,[1-3] upon suitable "activation" a variety of such carbon-carbon bond-forming processes may be actuated. Thus, in net terms, the sequence shown in equation (1) corresponds to "hetero-carbonation" of a double bond.



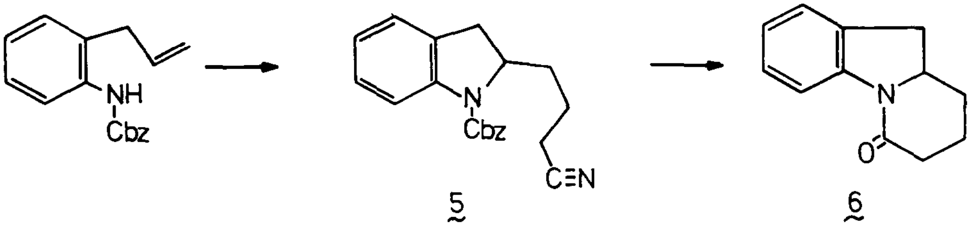
(1)

The most widely employed regimen for "activation" of mercurials has been transmetalation. The full range of compatibility of various transmetalation schemes with particular hetero-atoms awaits more definition.[4] Another activation method, elegantly and systematically developed by Giese and co-workers with a range of mercurials, involves reductive coupling with various derivatives of acrylic acid.[5] We have been examining the applicability of this chemistry to some synthetic problems.[6a] Below, we report a synthesis of fused tetrahydro-pyridones by a very simple three-step sequence. The sequence involves: (i) intramolecular ureidomercuration, (ii) reductive coupling and (iii) de-protection of the amine, resulting in formation of the δ-lactam. This sort of simply executed chemistry could well prove to be adaptable to the synthesis of a host of alkaloids and other classes of natural products.[6b,c]

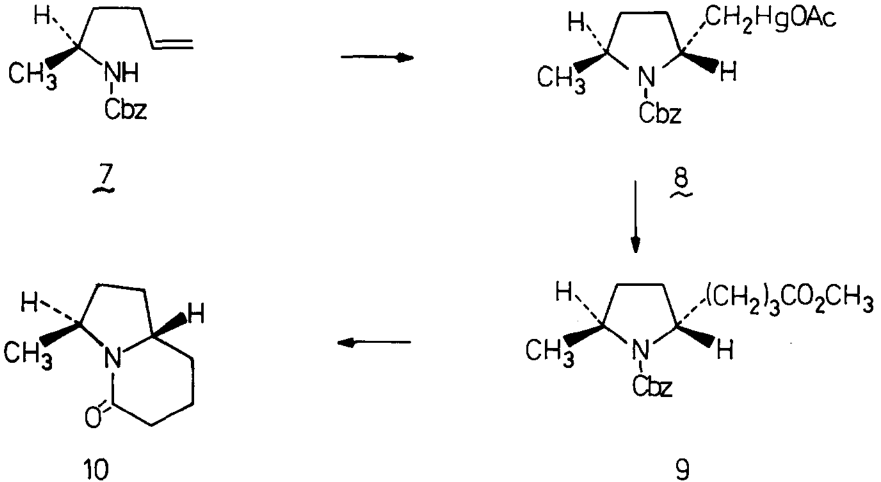
We illustrate this synthetic approach in the context of a four-step synthesis of δ-coniceine. Reaction of N-Cbz-5-amino-1-pentene with mercuric acetate gave a crude mercurial formulated as **1**. Reaction of **1** with sodium trimethoxyborohydride in dichloromethane containing a two-fold excess of methyl acrylate afforded a 64% overall yield of **2**.^{7a,b} Hydrogenolysis of **2** afforded a difficulty characterizable amino ester, which on warming gave a 93% yield of the previously reported^{8} lactam, **3**. The latter was converted (LiAlH$_4$-THF-rt) to δ-coniceine^{9} (**4**), characterized as its picrate, mp. 229-231°C (lit^{9} 230-231°C).



In a similar way treatment of N-Cbz-o-allylaniline with mercuric acetate in THF followed by reaction of the crude mercurial with sodium cyanoborohydride in the presence of 1:1 acrylonitrile: dichloromethane gave a 79% yield of **5**.^{7a} Reaction of **5** with 5:1/AcOH:conc.HCl at 100° for 9 hr. followed by neutralization and chromatography gave a 71% yield of the benzo[b]-indolizidinone **6**.^{7a} This type of transformation could be helpful in the construction of a variety of indolic alkaloids.



It was of further interest to examine a case where the ureidomercuration addressed an issue of sterochemistry. Reaction of **7** with mercuric acetate according to the procedure recently described by Harding[10] afforded **8**. This compound, when submitted to reductive coupling ($NaBH_4$; methyl acrylate/dichloromethane), gave a 41% yield of **9**.[7a] Hydrogenolysis of **9** (H_2;Pd/C; ethanol) followed by thermolysis of the resultant amino ester afforded an 85% yield of **10**.[7a]



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

These findings form the basis of some new strategies, which are designed to simplify the synthesis of challenging natural products. The pursuit of these goals is one of the current concerns of our laboratory.

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9. See M. F. Garst, J. N. Bonfiglio and J. Marks, ibid **47** 1495 (1982) and references therein.

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