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SYNTHESES OF 7,8-DIMETHOXY AND 7,8-METHYLENEDIOXY ISOCHROMAN-3-ONES AN EFFICIENT SYNTHESIS OF (±) TETRAHYDROPALMATINE AND (±) CANADINE

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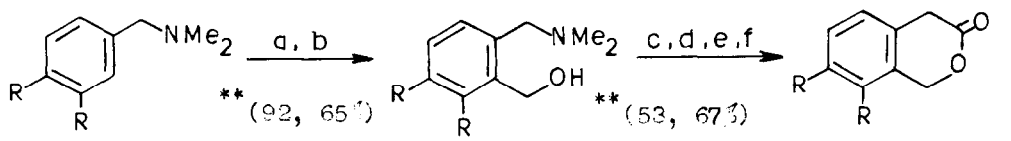
Summary Efficient syntheses of the title compounds, using heteroatom directed lithiation reaction, is described.

Isochroman-3-ones are important synthons. They furnish benzocyclobutenes which can undergo cycloaddition reactions leading to a variety of compounds[1] and also provide efficient route to the berbine alkaloids[1].

Isochroman-3-ones are generally synthesised by methods involving acid catalysed aromatic substitution reactions. For this reason, certain methoxy substituted isochroman-3-ones are not readily synthesised. 7,8-Methylenedioxy isochroman-3-one 2 is not synthesised so far. 7,8-Dimethoxy isochroman-3-one 1 is synthesised only from difficultly available starting materials[2].

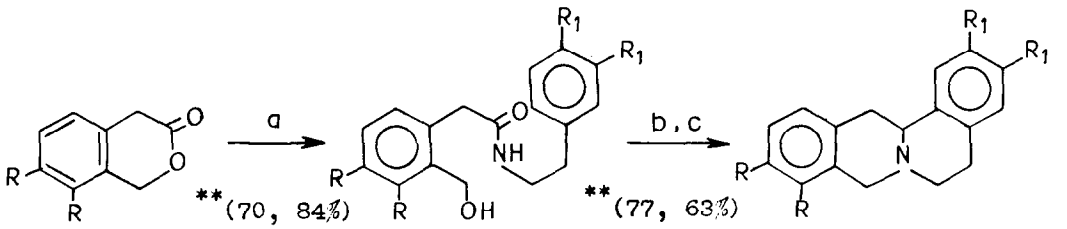
It is now well known that heteroatom directed lithiation reaction[3] can lead to aromatic substitution not favoured in the acid catalysed reaction. Thus for example, we had treated N,N-dimethyl-3-methoxy benzylamine with BuLi followed by ethylene oxide to introduce a hydroxyethyl group at 2-position. The compound was further processed to furnish N,N-dimethyl-5-methoxy tetrahydroisoquinolinium iodide[4]. This feature of lithiation reaction is now used to synthesise both 1 and 2 as shown below.



(a) n-BuLi/ether/0°, 1 h; (b) $(CH_2O)_n$/RT, 15 h;
(c) ClCOOEt/benzene/RT, 5 min; (d) KCN/DMF/RT, 8 h;
(e) KOH/EtOH/reflux, 3 h; (f) $H_3O^{\oplus}$.

1. R = $-OCH_3$
2. R-R = $-O-CH_2-O-$

The ready availability of 1 and 2 has further made it possible to synthesise (±) tetrahydropalmatine 3 and (±) canadine 4. The scheme is as follows :



(a) Homoveratrylamine or Homopiperonylamine/EtOH/RT, 5 h;
(b) $PCl_5/CHCl_3$/RT, 20 min;
(c) $NaBH_4$/MeOH/0° - RT, 45 min.

3. R = R_1 = $-OCH_3$
4. R = $-OCH_3$; R_1-R_1 = $-O\diagdown CH_2$ / $-O\diagup$

In the above sequence use of $PCl_5/CHCl_3$ (at RT) in the Bischler-Napieralski synthesis gives much better yield than $POCl_3$/toluene (at reflux temperature).

Two lithiation routes are known for the synthesis of (±) tetrahydropalmatine. One, where lithiation of (±) laudanosine is the key step[5], proceeds in poor yields. The other, where lithiation of N,N-dimethyl-3,4-dimethoxy benzylamine is the key step[6], has a large number of steps. The acid catalysed method of Kametani[7] is also long and involves protection and deprotection.

The method described above, to our mind, appears to be the most efficient route for obtaining the title compounds.

References

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** The first figure indicates the yield in (±) tetrahydropalmatine series and the second in (±) canadine series.

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