APPRAOCHES TO THE TOTAL SYNTHESIS OF AMARYLIDACEAE ALKALOIDS. ALTERNATIVE PREPARATIONS OF 5-SUBSTITUTED 2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINES

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Abstract - The preparation of several 5-substituted 2,3,4,5-tetrahydro-1H-2-benzazepines of general structure B, versatile synths for the total synthesis of Amaryllidaceae alkaloids, is described.

As part of our research program dealing with the synthesis of Amaryllidaceae alkaloids\(^1\) we have recently completed the total synthesis of (±)-elwesine\(^2\) (1) and (±)-lycoramine\(^3\) (2), two representative members of the series, starting from common cinnamoylitrile precursors A (Scheme I). Along the lines of our synthetic strategy, a second common target was soon envisaged, namely, the 5-substituted 2,3,4,5-tetrahydro-1H-2-benzazepine B.

![Scheme I](image-url)

We now report two alternative methods for the preparation of tetrahydrobenzazepines\(^*\) of general structure B. Our first approach to the synthesis of type-B compounds stems from the well-known\(^4\) preparation of 4-arylbutanoic acids by carboxylation of the organometallic intermediate formed in the titanium tetrachloride-catalyzed Grignard transfer reaction between alkylmagnesium halides (ie., n-propylmagnesium bromide) and the appropriate terminal olefins.

In this manner, safrrole (3), readily generates in 63% yield the 4-(3,4-methylenedioxyphenyl)butanoic acid (4), mp 67-69°C (lit.\(^*\) mp 67-69°C). Next, formation of the basic hydroazepine nucleus was
carried out under our usual conditions.\textsuperscript{18} Namely, initial treatment of acid 4 with ethyl chloroformate in the presence of triethylamine\textsuperscript{7} (Scheme II) furnished the mixed anhydride 5, which without isolation was allowed to react with sodium azide in wet acetone. The resulting (crude) acyl azide 6 was then heated to reflux in toluene for 2.5 h to yield isocyanate 7 ($\nu_{\text{max}}$ 2270 cm\textsuperscript{-1}). Finally, treatment of 7 with neat polyphosphoric acid (PPA) at room temperature produced the highly crystalline seven-membered ring lactam 8, mp 127-129°C (EtOAc-hex), in 52% overall yield.\textsuperscript{8}

\textbf{Scheme II}

\begin{align*}
3 & \rightarrow 4 \\
\text{CO}_2\text{CO}_2\text{Et} & \text{CO}_2\text{N} & \text{NCO} \\
5, \, z = & \text{CO}_2\text{CO}_2\text{Et} & \text{CO}_2\text{N} \\
6, \, z = & \text{CO}_2\text{N} & \text{NCO} \\
8, \, R = & H & R = Me \\
9, \, R = & Me & \text{Me} \\
10 & & \\
\end{align*}

In order to introduce the necessary functional handle at the 5-position, we proceeded next to protect the nitrogen function. Straightforward N-alkylation with methyl iodide/sodium hydride in dry tetrahydrofuran (THF) afforded the N-methyl lactam 9, mp 93-94°C (EtOAc-hex), in 96% yield. Photo-oxidation of 9 in the presence of N-bromosuccinimide (NBS) and anhydrous calcium carbonate\textsuperscript{9} furnished the desired 5-oxo derivative 10, mp 133-135°C (EtOAc-hex), in 89% yield. (Scheme II).

From our previous work\textsuperscript{3} on the synthesis of the galanthamine-like Amaryllidaceae alkaloids,\textsuperscript{10} it can be seen that hydrobenzazepinedione\textsuperscript{11,12} 10 is in fact a versatile and now readily available advanced intermediate.

On the other hand, the readily available alkyl aryl acetates are amenable substrates for the elaboration of various type-B hydrobenzazepines. The series has been elaborated with both the methyl 3,4-dimethoxy-(11a) and 3,4-methylenedioxyphenylacetates (11b). Thus, reaction of ester 11a\textsuperscript{13} with acrylonitrile under Triton B catalysis affords (Scheme III) cyanoester 12a, mp 63-64°C (EtOAc-hex), in 72% yield. The ester grouping was chemospecifically\textsuperscript{14} reduced to the primary alcohol 13a (92% yield) by using a small excess of lithium borohydride in THF at room temperature, followed by protection as the corresponding benzyl ether (84%; benzyl chloride/NaH in a 9:1 mixture of THF-dimethylformamide).
Scheme III

11a,b → 12a,b → 13a,b

14a,b → 15a,b

16a,b

18a

17a

Series  
- a, 3,4-(OMe)₂  
- b, 3,4-(OCH₂O)
Next, basic hydrolysis (40% NaOH in refluxing ethanol) of the nitrile grouping produced the oily acid 15a in 81% yield. Transformation of the latter into urethane 16a was carried out as before by means of a one-pot Curtius rearrangement,16a,7 with final methanolysis of the resulting (crude) isocyanate. The expected urethane 16a was isolated as a thick colorless oil in 74% yield. Finally, the missing one-carbon unit was introduced via a modified two-step Tscherniac-Einhorn reaction.15 Namely, hydroxymethylation of 16a (formaldehyde, 25% NaOH, dioxane, room temperature, 15h) proceeded uneventfully in 92% yield. The 1H-nmr spectrum (CDCl3, 90 MHz) of the oily N-methylol derivative 17a showed a broad singlet (2H) at 4.70 ppm for the N-CH2OH grouping. The formation of the desired complete hydrobenzazepine skeleton of 16a was carried out next, in nearly quantitative yield, by simply heating 17a with a catalytic amount of p-toluenesulfonic acid in benzene (Dean-Stark trap).16 The overall yield of this sequence is 30.7%. Alternatively, methyl 3,4-methylenedioxyphenylacetate17 (11b) was reacted with acrylonitrile to produce the oily cyano ester 12b in 74% yield. As before, lithium borohydride reduction to 13b (94%), followed by benzyl ether formation (77%) afforded nitrile 14b as a colorless oil. Basic hydrolysis (40% NaOH, EtOH, reflux, 8h) furnished acid 15b, mp 103-105°C (EtOAc-hex), in 88% yield after column chromatography on silica gel. Curtius rearrangement, followed by methanolysis of the intermediate isocyanate gave urethane 16b, as a thick colorless oil, in 75% overall yield. Finally, the desired hydrobenzazepine 18b was prepared by a modification of our original cyclization conditions. Namely, direct treatment of 15b with excess chloromethyl methyl ether (as the one-carbon source) and 57% hydriodic acid in glacial acetic acid18 at 5°C produces 18b19 as a colorless oil in 82% yield.20 The overall yield for this sequence is 29%.

Full account of this work and its application in the total synthesis of other Amaryllidaceae alkaloids will be reported elsewhere.
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REFERENCES

8. All new compounds were adequately characterized by spectral methods (IR, 'H-nmr, MS) and, whenever possible, gave satisfactory combustion analytical data and/or high resolution molecular weight determination.
15. For previous examples of the modified Tscherniac-Einhorn reaction in the total synthesis of
Amaryllidaceae alkaloids, see references 2 and 3. For recent reviews of the aromatic \( \alpha \)-amidoalkylation reaction, see H. E. Zaugq, *Synthesis*, 1984, 85, 181.

16. 18a: Colorless oil; \( \text{ir (neat)} v_{\text{max}} \) 3020, 2960, 2880, 1710, 1600, 1525 cm\(^{-1}\); \( ^1H\)-nmr (CDCl\(_3\)) \( \delta \) 7.32 (s, 5H, Ph), 6.70 (s, 2H, C\(_6\)-H and C\(_9\)-H), 4.53 (s, 2H, -OCH\(_2\)Ph), 4.35 (bs, 2H, C\(_1\)-H\(_2\)), 3.83 and 3.80 (s, 6H, 2xOCH\(_3\)), 3.61 (s, 3H, -COOCH\(_3\)), 3.68-3.53 (m, 3H, C\(_5\)-H and -CH\(_2\)-OCH\(_2\)Ph), 3.20 (m, 2H, C\(_1\)-H\(_2\)), 1.90 ppm (m, 2H, C\(_3\)-H\(_2\)).


19. 18b: Colorless oil; \( \text{ir (neat)} v_{\text{max}} \) 3030, 2950, 2890, 1700, 1250 cm\(^{-1}\); \( ^1H\)-nmr (CCl\(_4\)) \( \delta \) 7.17 (s, 5H, Ph), 6.50 (m, 2H, C\(_6\)-H and C\(_9\)-H), 5.70 (s, 2H, -OCH\(_2\)O-), 4.47 (s, 2H, -OCH\(_2\)Ph), 4.2 (bs, 2H, C\(_1\)-H\(_2\)), 3.53 (s, 3H, -COOCH\(_3\)), 3.67 - 3.2 (m, 3H, C\(_5\)-H and -CH\(_2\)-OCH\(_2\)Ph), 3.10 (m, 2H C\(_3\)-H\(_2\)), 1.7 ppm (m, 2H, C\(_4\)-H\(_2\)).

20. A few practical limitations of this reaction have been found. It works best for acid-stable protected derivatives of the primary hydroxyl group (ie., acetates, alkyl ethers), but fails completely for the free hydroxyl compound or for acid-labile protecting groups (ie., THP ethers). Otherwise, it constitutes a viable alternative to the two-step Tscherniac-Einhorn \( \alpha \)-amidoalkylation reaction.

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