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A novel synthesis of 2,3-dihydro-7(1*H*)-indolizinones

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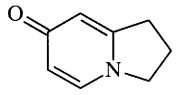
Abstract

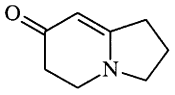
Intramolecular coupling reactions of enynes 2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]acetonitrile (**10**) and ethyl 2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]acetate (**11**), using 9-BBN, catecholborane and alkaline silver nitrate, afforded the 2,3-dihydro-7(1*H*)-indolizinones, 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarbonitrile (**5**) and ethyl 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarboxylate (**6**), respectively.

Keywords: 2,3-dihydro-7(1*H*)-indolizinones; dihydro-ɣ-pyridones; Eschenmoser coupling reaction; enynes; enaminones.

Relatively few methods for constructing 2,3-dihydro-7(1*H*)-indolizinones (**1**) (also referred to as dihydro-ɣ-pyridones) have been reported.[1] Danishefsky reported the synthesis of *iso*-A58365A (**4**), an isomer of the angiotensin converting enzyme inhibitor, A58365A (**3**) by annulation of diazomethylvinylketone with a secondary thiolactam.[1] In contrast, methods for constructing the reduced version of this ring system, namely 2,3,5,6-tetrahydro-7(1*H*)-indolizinone (**2**), abound.[2]



(**1**)



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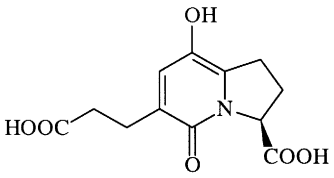
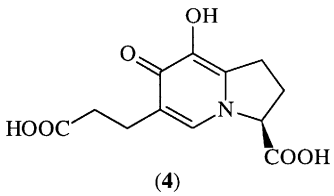


(**3**)



(**4**)

We now report the synthesis of two 2,3-dihydro-7(1*H*)-indolizinones, 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarbonitrile (**5**) and ethyl 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarboxylate (**6**), by means of

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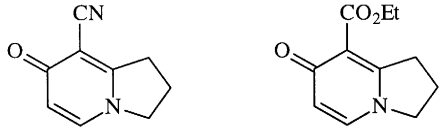
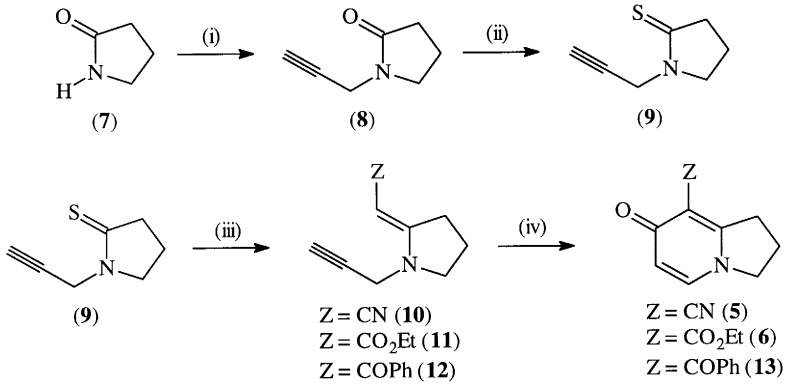
an intramolecular coupling reaction of boranes derived from enynes 2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]acetonitrile (**10**) and ethyl 2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]ethanoate (**11**), respectively.



(**5**) (**6**)

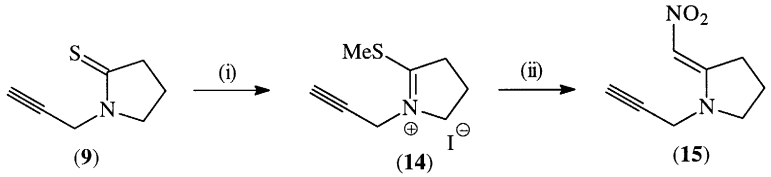
The strategy communicated in this letter represents a new route to this ring system. This strategy is summarised in Scheme 1.



Scheme 1. Reagents and conditions: (i) NaH, propargyl bromide, THF, rt, 85%; (ii) P_2S_5, Na_2CO_3, THF, rt, 87%; (iii) $BrCH_2Z$, CH_3CN, rt, then Et_3N, Ph_3P, rt, 30–74%; (iv) 9-BBN, catecholborane, 0°C, then 2 M aq. KOH, 5 M aq. $AgNO_3$, rt, 12–19%

Thiolactam **9** was prepared in two steps from 2-pyrrolidinone (**7**). The first step involved alkylation of 2-pyrrolidinone (**7**) with propargyl bromide. 1-(2-Propynyl)tetrahydro-2*H*-pyrrol-2-one (**8**) was obtained in a satisfactory 85% yield. Thionation of this substrate using a mixture of phosphorus pentasulfide and sodium carbonate[3] afforded 1-(2-propynyl)tetrahydro-2*H*-pyrrole-2-thione (**9**) in 87% yield. The key enaminones (**10**, **11** and **12**) were prepared by Eschenmoser sulfide contraction[4] of thiolactam (**9**) with bromoacetonitrile, ethyl bromoacetate and phenacyl bromide, respectively. 2-[1-(2-Propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]acetonitrile (**10**), ethyl 2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]ethanoate (**11**) and 1-phenyl-2-[1-(2-propynyl)tetrahydro-2*H*-pyrrol-2-ylidene]-1-ethanone (**12**) were obtained in 74, 30 and 60% yield, respectively. The enaminones were obtained as predominantly one geometric isomer based on GC evidence of the material before column chromatography. Comparison of ^{1}H NMR data with literature values showed that these compounds were obtained as the *E*-isomers (vide infra). The preferred geometry of these types of enaminones appears to depend on whether the nitrogen atom is secondary or tertiary. Secondary enaminones have been shown to exist in the *cis-s-cis* configuration which allows intramolecular hydrogen bonding resulting in a very stable six-membered ring.[5,6] Tertiary enaminones were shown to exist in the *trans-s-trans* conformation by Michael.[7] This was demonstrated by the anisotropic deshielding effect that the carbonyl oxygen atom of vinylogous urethanes has, due to its spatial proximity, on the hydrogen atom at C-3 of the pyrrolidine ring.

A related vinylogous nitramine (**15**) was prepared in 43% yield according to the route shown in Scheme 2. This involved methylation of thiolactam (**9**) on sulfur followed by condensation of the resulting methylthioiminium salt (**14**) with nitromethane.

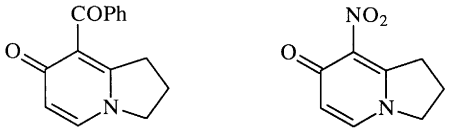


Scheme 2. Reagents and conditions: (i) CH_3I, $CHCl_3$; (ii) CH_3NO_2, K_2CO_3, DMF, 43%

Brown and Coleman communicated a route to acetylenic organoboranes and alcohols by chemoselective hydroboration of double bonds in the presence of triple bonds by 9-BBN.[8] It is known that 9-BBN is exceptionally sluggish in the hydroboration of terminal alkynes relative to other dialkylboranes.[8] In addition, hydroboration of acetylenes with 9-BBN is slow compared to hydroboration of structurally similar olefins. Brown et al. reported the very ready coupling of hydroborated olefins in situ by silver nitrate in the presence of alkali.[9,10] Catecholborane is known to be far less reactive than dialkylboranes[11,12] but is well known to monohydroborate alkynes to form the corresponding alkeneboronic esters.[13] Consideration of these facts prompted our investigation to assess whether the above methodology could be used to cyclise enynes **10**–**12** and **15**.

The cyclisation reactions were effected by adding catecholborane followed by 9-BBN to the enynes in THF at 0°C and subsequent treatment with 5 M aqueous silver nitrate and 2 M aqueous sodium hydroxide solution.[14] The cyclisation reaction failed if only catecholborane or 9-BBN was used. In this manner, 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarbonitrile (**5**) and ethyl 7-oxo-1,2,3,7-tetrahydro-8-indolizinecarboxylate (**6**) were synthesised in 19 and 12% yield, respectively.[15] Little appears to be known of the behaviour of enaminones and related compounds toward hydroboration and merits further investigation. Based on the literature precedent presented (vide supra), it appears reasonable to assume that the carbon–carbon double bond and triple bond are hydroborated with 9-BBN and catecholborane, respectively. The cyclisation reaction then presumably results from alkaline silver nitrate mediated intramolecular coupling of the derived alkylborane and vinylborane.

The cyclisation reaction is clearly dependent on the nature of the electron-withdrawing group *Z* (Scheme 1). Vinylogous enaminone **12** and nitramine **15** failed to give cyclised products **16** and **17** under the given reaction conditions.



In summary, we have developed a new method for the synthesis of the 2,3-dihydro-7(1*H*)-indolizinone ring system. These compounds are attractive intermediates for the preparation of more complex natural products. Attempts to extend the methodology to 6,7,8,9-tetrahydro-2*H*-quinolizin-2-ones are in progress.

Acknowledgements

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14. Typical experimental procedure: A stirred solution of the enyne (100–150 mg) in dry THF (5–10 cm^3) was cooled to 0°C and then treated with 9-BBN (1 mol equivalent, 0.5 M solution in THF). After 120 minutes catecholborane (1 mol equivalent, 1.0 M solution in THF) was added at 0°C and the resulting mixture stirred for 60 min and allowed to warm to ambient temperature. An aqueous potassium hydroxide solution (2 M, 2 mol equivalents) was added at 0°C followed by an aqueous silver nitrate solution (5 M, 2 mol equivalents). The resulting mixture was allowed to warm to ambient temperature and stirred for 60 min. The reaction mixture was diluted with water and the organic material extracted with ethyl acetate (5×10 ml). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 50–60% ethyl acetate/hexane) to afford the desired products in yields of 12–19%.
15. All new compounds were characterised spectroscopically and by high resolution mass spectrometry.