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A Simple and General Synthesis of 4-Oxo-4,5,6,7-Tetrahydroindoles *via* a Novel Intramolecular 1,3-Dipolar Cycloaddition Approach

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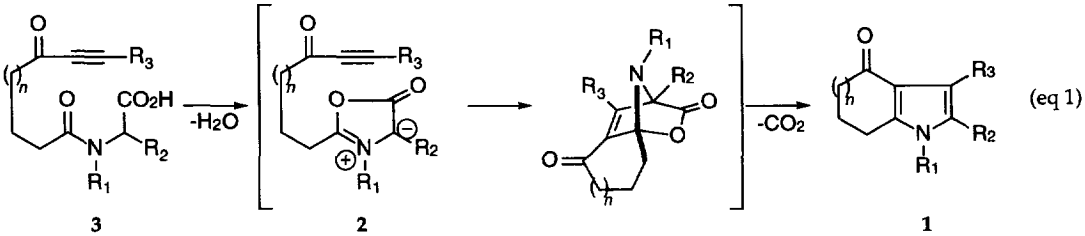
*Summary: A general synthesis of 4-keto-4,5,6,7-tetrahydroindoles **6-12** has been achieved in two steps using a new intramolecular 1,3-dipolar cycloaddition approach in moderate yields (45-60%). The potential of this methodology is demonstrated by the synthesis of a mitomycin skeleton (**15**) and a topoisomerase-1 inhibitor skeleton (**17**).* Copyright © 1996 Elsevier Science Ltd

1,3-Dipolar cycloadditions of münchnones developed by Huisgen[1-3] constitute a widely employed synthetic strategy to a large variety of heterocyclic systems. The reaction utilizes a dehydrative cyclization of an *N*-acylated amino acid to give a 1,3-dipole, such as **2**, which then reacts with acetylenic dipolarophiles yielding pyrroles upon loss of CO_2. Our interest was to develop a simple and versatile intramolecular approach to the synthesis of 4-oxygenated indoles and indoloquinones since these structural units are present in biologically important alkaloids and mitomycins, respectively.[4-7] We imagined the 4-oxygenated indoles could be derived from the corresponding ketopyrroles **1**, which in turn could be formed *via* a new intramolecular 1,3-dipolar cycloaddition approach from **3** (eq 1). It is interesting to note that our approach is complementary to the Jacobi *bis*-heteroannulation approach to furans,[8] and Wuonola's imidazole Diels-Alder approach.[9]

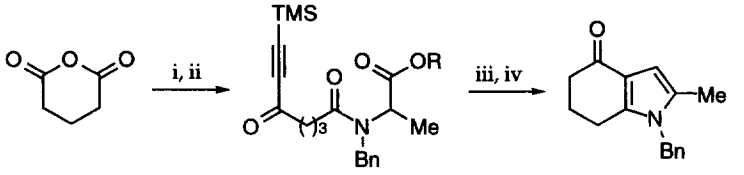


3 **2** **1**

We report here a successful realization of this strategy, which to our knowledge is the first example of such an intramolecular cycloaddition reaction to afford 4-oxo-4,5,6,7-tetrahydroindoles.[10] Thus, glutaric anhydride (**4**) was treated with *bis*-(trimethysilyl)acetylene[11] in the presence of $AlCl_3$ to afford 7-trimethysilyl-5-oxo-hept-6-ynoic acid in 98% yield (eq 2). This acid was then condensed with *N*-benzylalanine methyl ester hydrochloride in presence of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)[12] to furnish *N*-benzyl-*N*-(7-trimethysilyl-5-oxo-hept-6-yn-1-oyl)-alanine methyl ester (**5a**) in 83% yield. The ester **5a** reacted with lithium iodide in EtOAc[13] to provide the cyclization substrate *N*-benzyl-*N*-(7-trimethysilyl-5-oxo-hept-6-yn-1-oyl)-alanine (**5b**) in 78% yield after purification. Acid **5b** was then heated in Ac_2O at 70-80 °C for 45 min, and the temperature was slowly raised to 125 °C (3 h), whereupon workup gave a dark brown product. The crude NMR and TLC showed a single product, which was purified by chromatography and characterized as 4-oxo-2-methyl-4,5,6,7-tetrahydroindole (**6**, 68%).[14] Alternatively, the reaction could also be conducted in one pot without purification of the intermediate acid **5b** to give pyrrole **6** in 52% overall yield (for two steps). The trimethylsilyl group was

cleaved during the cycloaddition step, but it was possible to isolate and characterize the corresponding 3-trimethylsilyl pyrrole. Cycloaddition with TMS substitution appears to be slighly more facile than compared with the parent (H) acetylenic substrate.[15]

The cycloaddition reaction is indeed very general as evidenced by the synthesis of variety of tetrahydroindoles from the corresponding readily available amino acid methyl esters. Thus, a variety of amino acids including



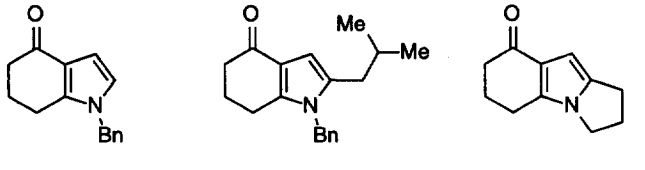
(eq 2)

4 5 a, R = Me b, R = H (Bn = CH_2Ph) 6

i. $AlCl_3$, CH_2Cl_2, TMS—≡—TMS, 98%
ii. BnNHCH(Me)CO_2Me, CDMT, NMM, 83%
iii. Li-I, EtOAc, Δx, 75%
iv. Ac_2O, 70 °C → 125 °, 68%

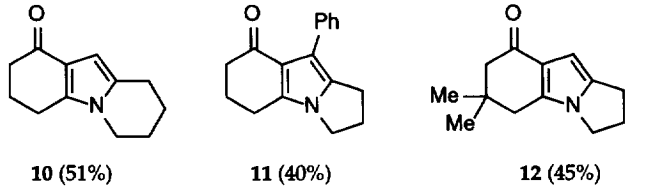
glycine (→ **7**), alanine (→ **6**), leucine (→ **8**), proline (→ **9**) and pipecolinate (→ **10**) were incorporated into the corresponding tetrahydroindoles in fairly good yield. The cycloaddition was also compatible with phenyl substitution on the acetylene (→ **11**) and dimethyl groups in the side chain (→ **12**) (Table).

Table. The yields represent an average of duplicate runs.



7 (47%) **8** (60%)

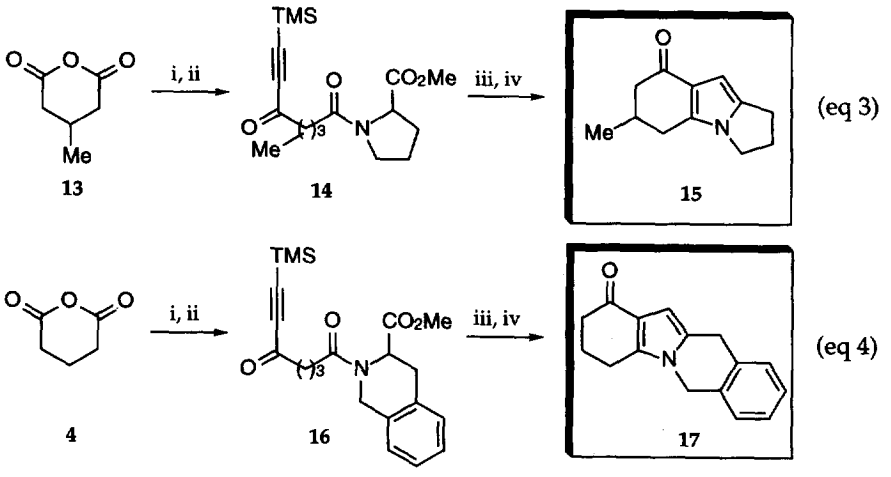
9 (45%)



10 (51%) **11** (40%) **12** (45%)

The application of this methodology was further demonstrated through synthesis of a mitomycin skeleton **15** (eq 3). The key substrate, **14**, was prepared in two steps from commercially available 3-methylglutaric anhydride (**13**), and was converted to **15** in two steps with an overall yield of 48%. Similarly a convergent synthesis of camptothecin skeleton **17** was accomplished from **16** in 46% yield (eq 4).

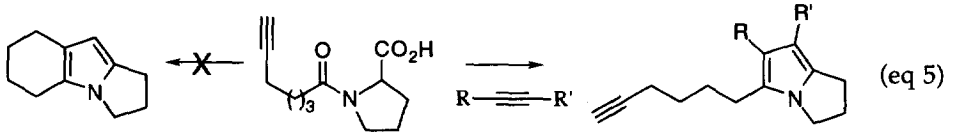
Other salient features of the transformation warrant further comment. It appears that under these thermal conditions, the presence of an electrophilic acetylenic bond is essential for success of intramolecular 1,3-dipolar cycloaddition to give tetrahydroindoles. For example, substrate **18** upon heating with Ac_2O did not afford any



i. $AlCl_3$, CH_2Cl_2, TMS—≡—TMS
ii. amino ester, CDMT, NMM

iii. Li-I, EtOAc, Δx
iv. Ac_2O, 70 °C → 125 °

tetrahydroindole **19**, but in the presence of added dimethylacetylene dicarboxylate gave a product characterized as dimethyl 2,3-dihydro-5-(5-hexyne)-1H-pyrrolizine-6,7-dicarboxylate (**20**) in 85% isolated yield (eq 3). Similarly, the addition of ethyl propiolate gave **21** in 56% yield (mixture of regioisomers, 1:2 ratio).



19 18

20, R = R' = CO_2Me
21, R = H, R = CO_2Et (1:2)

Furthermore, a variety of *N*-protecting groups (methyl, benzyl, p-methoxybenzyl, and 4-nitrophenethyl) were tolerated in the cycloaddition reaction. It was found that the *N*-methyl analogue of **5** gave the lowest yield (30%), whereas the 4-nitrophenethyl derivative gave the highest yield (60%) of the corresponding tetrahydroindoles. Efforts are currently underway to further optimize the yields by employing other protecting groups.

In summary a general synthesis of functionalized 4-oxo-4,5,6,7-tetrahydroindoles using a new approach has been developed, and efforts are currently underway to optimize the reaction, with application to naturally occurring and pharmacologically interesting indole and indoloquinone intermediates. The previously unknown and inaccessible[16] acetylenic precursors were prepared in a mild manner from commercially available starting materials.

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