A thermally-induced, tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition approach to carbocyclic spirooxindoles

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Abstract
The synthesis of C3-carbocyclic spirooxindoles was realized by way of an intramolecular [2 + 2] cycloaddition reaction between a vinylidene indolin-2-one and an alkyne. The cycloaddition reaction occurs selectively with the distal double bond of the allene, is tolerant of a phenyl and trimethylsilyl group on the terminus of the alkyne, and can be used to access bicyclo[4.2.0]octadienes and bicyclo[5.2.0]nonadienes. The allene precursors are not observed, but are likely intermediates of an infrequently encountered thermal [3,3]-sigmatropic rearrangement of a propargylic acetate.

Introduction
Spirooxindoles are structural motifs containing a heterocycle or carbocycle at the C3 position of an oxindole. Particularly well known are the pyrrolidinyl-spirooxindoles 1 which have been classified as a privileged motif due to their presence in a large number of heterocyclic alkaloids (Figure 1) [1]. Spirotryprostatin B (2) is just one example of many natural products from this class exhibiting interesting biological activity [2]. Compounds possessing a carbocycle at the C3 position of the oxindole, such as 3, are less common and spirooxindoles containing a four carbon spirocycle are rare. One notable natural product containing this basic skeleton is welwitindoline A isonitrile (4); a compound that has recently captured the attention of the synthetic community [3,4].

Spirocyclobutanes-1,3'-indolin]-2'-ones (3, n = 0) have previously been prepared but the synthetic approach is mostly limited to simple spirocyclobutanes that are accessed via alklylation chemistry [5]. Alternatively, more structurally complex spirocyclobutanes have been obtained from homodimerization reactions of allenes or alkenes [6,7]. However, neither of these...


Figure 1: Heterocyclic and carbocyclic spirooxindoles.

approaches provides an enabling strategy for accessing the densely functionalized and unsymmetrical molecular architectures of many of the natural products possessing this oxindoline core. We anticipated that access to this class of compounds utilizing chemistry developed in our laboratories would provide an expansion of substructures within this chemical space, thus enhancing the discovery of new biological probes and pharmaceuticals [8].

We recently disclosed a thermal [2 + 2] cycloaddition reaction of allene-yynes to provide a variety of alkylidene cyclobutenes in good yields [9-18]. Notable features of this reaction were the stability of the resulting alkylidene cyclobutenes, the regioselectivity for reaction of the distal double bond of the allene, and ready cyclization of substrates possessing heteroatom tethers to give heterocyclic structures (Scheme 1) [19-26]. Inspired by the unique skeleton of welwitindolinone A, the feasibility of this method for the preparation of spirooxindole alkaloids was investigated. The preliminary results of this study are reported herein.

Results and Discussion

To begin the investigation, the first challenge was the preparation of a functionalized vinylidene indolin-2-one 5 (Figure 2). There is only one report of this allene substructure in the literature and it was not particularly well suited for the incorporation of additional functionality [6]. Scattered reports of propargylic acetates thermally rearranging to allenyl acetates exist, thus, it was reasoned that the allene moiety of 5 could be obtained by way of a thermal [3,3]-sigmatropic rearrangement of the propargyl acetate 6 to give compound 5 where R² = OAc (Figure 2) [27].

Preparation of propargyl acetate 9a was accomplished by the addition of the lithium acetylide of 8 to N-methyl isatin (7) followed by acetylation of the resulting propargyl alcohol. Heating propargyl acetate 9a to 225 °C in 1,2-dichlorobenzene in the microwave for 30 min gave the spirooxindole 10a in 60% yield (Scheme 2). Structural confirmation of 10a was
Table 1: Synthesis of spirooxindoles.

| Entry | R^1  | R^2  | n   | Solvent\(^a\) | Temp  | Time | Product | Yield |
|-------|------|------|-----|-------------|-------|------|---------|-------|
| 1     | Me   | Ph   | 1   | 1,2-dichlorobenzene | 225 °C | 30 min | 10a     | 60%   |
| 2     | Me   | TMS  | 1   | 1,2-dichlorobenzene | 225 °C | 50 min | 10b     | 50%   |
| 3     | Me   | H    | 1   | 1,2-dichlorobenzene | 225 °C | 50 min | 10c     | 0%    |
| 4     | SEM  | Ph   | 1   | 1,2-dichlorobenzene | 225 °C | 60 min | 10d     | 61%   |
| 5     | MOM  | Ph   | 1   | 1,2-dichlorobenzene | 225 °C | 60 min | 10e     | 57%   |
| 6     | MOM  | Ph   | 2   | N-methylpyrrolidinone | 250 °C | 10 min | 10e     | 61%   |
| 7     | MOM  | Ph   | 1   | N-methylpyrrolidinone | 250 °C | 5 min  | 10f     | 48%   |

\(^a\)In our original report, the most successful solvent system for the cycloaddition was toluene doped with an ionic liquid (0.3 M). However, we have moved away from this solvent system because subsequent to that study, two sample solutions (out of hundreds), that were allowed to age for an hour prior to microwave irradiation, immediately exploded upon irradiation. Oliver Kappe has made similar observations when using ionic liquids in the presence of ethylene gas in the microwave. Kappe demonstrated that the explosion is due to the ionic liquid initiating an exothermic polymerization reaction [28]. We suspect that the ionic liquid initiated a polymerization reaction of the allene-ynes when allowed to stand prior to irradiation.
Experimental

Spirooxindole (10a) Propargyl acetate 9 (30 mg, 0.081 mmol) was dissolved in 1,2-dichlorobenzene (1.62 mL) in a 0.5–2 mL Biotage™ microwave vial. The vial was capped and the solution irradiated in the microwave for 30 min at 225 °C. The reaction mixture was diluted with hexane (2 mL) and applied to a silica gel column. The column was eluted with hexanes (100 mL) and then with 25% ethyl acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to provide 18 mg of spirooxindole 10a as a brown oil in 60% yield.

Supporting Information

General methods, experimental and spectral data are provided for all new compounds in the Supporting Information.

Supporting Information File 1 General methods, experimental and spectral data. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-33-S1.pdf]

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