

# Neighboring effect of the lactam functionality in select reactions of 6-azaspiro[4.5]decane-1,7-dione

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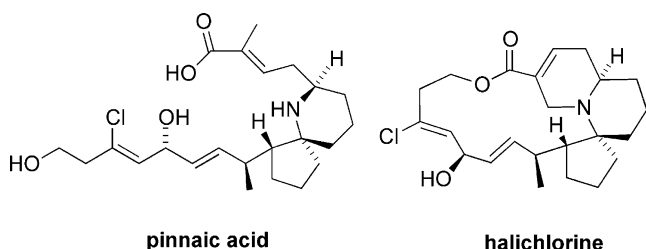
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**Abstract**—The susceptibility of 6-azaspiro[4.5]decane-1,7-dione (**4**) to nucleophilic attack was evaluated. Although steric effects preclude the 1,2-addition of many reagents, more reactive lithium and Grignard species react. Attack from the direction *syn* to the lactam functionality predominates. The acid-catalyzed rearrangement of select products delivered allylic alcohols carrying their double bond at varying distances from the spirocyclic carbon. These designed systems undergo hydrogenation predominantly from that  $\pi$ -surface *syn* to the amide component, the more so when a hydroxyl is proximate to these hetero atoms. The same phenomenon operates when *N*-benzoylated intermediates are hydrolyzed with potassium carbonate in methanol.

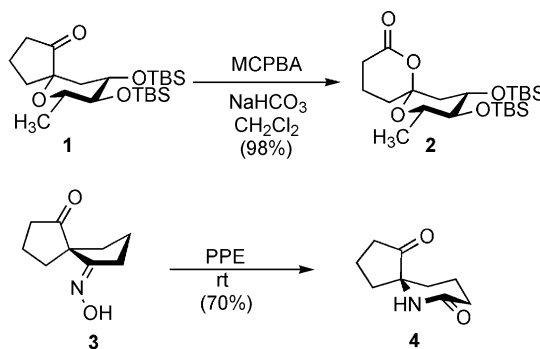
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## 1. Introduction

The structural features peculiar to spirocyclic compounds have fascinated organic chemists for several decades. In carbocyclic systems, great strides have been made since the chemical and chiroptical properties of Fecht's acid<sup>1</sup> and spiro[3.3]hepta-1,5-diene<sup>2</sup> were elucidated in the 1970s. Particularly striking in the intervening years have been the many developments involving the adaptation of new reagents and tactics to bring about spirocyclization events.<sup>3</sup> The elaboration of oxygen- and sulfur-containing analogs has recently been extended to include spirocyclic nucleosides.<sup>4</sup> Nature has contributed to the heightened interest in nitrogen derivatives<sup>5</sup> by serving as the source of bioactive alkaloids such as perhydrohistrionicotoxin,<sup>6</sup> pinnaic acid,<sup>7</sup> and halichlorine.<sup>8</sup>



Despite the advances made in this area, surprisingly little use has been made of stereospecific ring expansion reactions to generate functionalized targets. The Baeyer-Villiger oxidation of **1** to give **2**<sup>9</sup> and the Beckmann rearrangement of **3** to form **4**<sup>10</sup> are illustrative examples. As a consequence, there has been minimal exploration of spiroacetals and keto lactams having these general structural characteristics (Scheme 1). In this report, we detail a selection of reactions to which **4** has been subjected. Functional group compatibility and chemoselectivity are, of course, two ever-present issues. Where relevant and possible, the level of stereocontrol and the preferred direction of reagent approach are established unequivocally. As will be made clear, the amide moiety exerts profound consequences on the stereochemical course of reactions occurring at the neighboring five-membered ring. An example is also provided of reciprocal effects



Scheme 1.

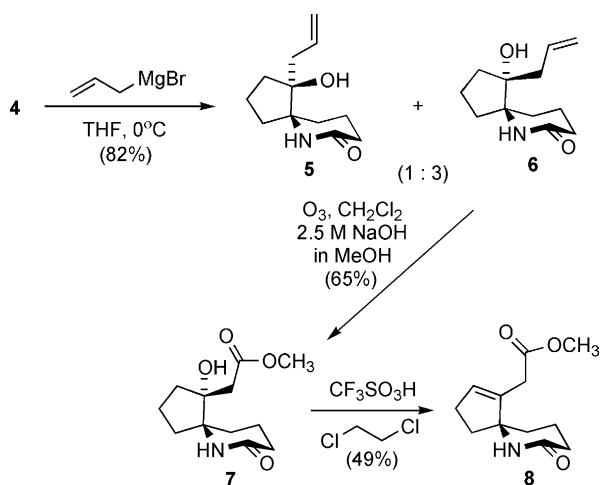
**Keywords:** Spirocycles; Lactams; Carbonyl additions; Rupe rearrangement; Heteroatomic effects.

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## 2. Results and discussion

The determination of  $S_N2$  solvolysis rates, which showed neopentyl systems to react at a level  $10^{-5}$  that exhibited by the corresponding ethyl derivative,<sup>11</sup> provided a proper forum for appreciating the strong deceleration effect of alkyl substitution proximal to a reaction center.<sup>12</sup> In a similar manner, the tetrahedral mechanism for substitution at a carbonyl carbon is equally slowed or blocked completely when steric crowding is elevated.<sup>13</sup> The pronounced deceleration associated with both processes is adequate to render such substrates synthetically useless in most cases. These consequences can be expected to complicate the chemistry of **4**, although in more subtle ways. With regard to the diastereotopic faces of the ketone carbonyl group in this spirocycle, one is *syn* to a polymethylene chain while the other is flanked by the nitrogen atom that is part of the lactam functionality. Depending on the basicity of the reagent to which **4** is being subjected, deprotonation may operate at N, chelation may become an operational factor, and other forms of complexation could play a role in making matters more mechanistically complex. The extent to which the title compound is sensitive to one or more of these phenomena is certain to impact upon its reactivity and to offer intriguing opportunities for control of stereoselectivity during nucleophilic capture when operational.

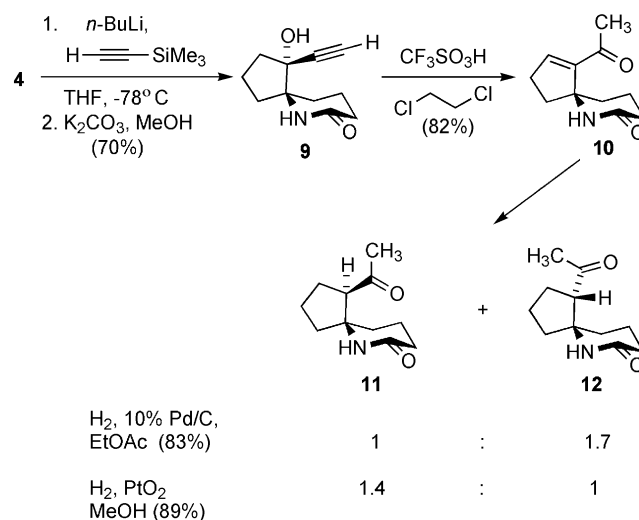
In line with the points of emphasis made above, **4** proved to be totally unreactive to such well-known transformations as the Horner-Wadsworth-Emmons,<sup>14</sup> Wittig,<sup>15</sup> Reformatsky,<sup>16</sup> and Peterson reactions.<sup>17</sup> When we uncovered the comparative inertness of **4** toward lithium ynolates such as  $H_3C-C\equiv O^-Li^+$ ,<sup>18</sup> it was quite apparent that recourse needed to be made to more reactive organometallic reagents. To this end, **4** was admixed at 0 °C with 3 equiv of allylmagnesium bromide in THF. In this instance, the diastereomeric carbinols **5** and **6** were formed in a 1:3 ratio and a combined yield of 82% (Scheme 2). The ease of chromatographic separation of **5** from **6** facilitated the stereochemical assignments which were made by analogy to **9** (see below) and concluded that the preferred trajectory of attack was from that direction *syn* to the amide linkage. Attempts to gain further confirmation by NOE methods proved inclusive. However, this product partitioning is of no



Scheme 2.

consequence if dehydration is ultimately contemplated. For example, ozonolysis of **6** in the presence of methanolic sodium hydroxide<sup>19</sup> results in smooth conversion to hydroxy ester **7**. Alternate involvement of the **5/6** mixture gave rise to a diastereomeric mixture with comparable efficiency. Subsequent treatment of **7** with triflic acid in 1,2-dichloroethane<sup>20</sup> provided  $\beta,\gamma$ -unsaturated ester **8** with a minimum of Wagner-Meerwein rearrangement products.

Next to be considered was the possibility of introducing an acetylide side chain for the purpose of implementing a subsequent Rupe rearrangement.<sup>21</sup> Admixture of **4** with an excess of lithiated trimethylsilylacetylene resulted in a rapid reaction at  $-78$  °C and gave rise to a single carbinol, the stereochemistry of which was assumed to be as shown in Scheme 3 as a result of the reduced size of the sp<sup>2</sup>-hybridized nucleophile. Following application of the conventional protodesilylation protocol,<sup>22</sup> the action of potassium carbonate in methanol on this adduct furnished **9**, the three-dimensional features of which were unequivocally established by X-ray crystallographic analysis. The isomerization of **9** under the standard conditions of sulfuric acid–acetic acid at the reflux temperature<sup>23</sup> gave **10**, although only in an average yield of 25%. An extended search for an improved way to accomplish this transformation was rewarded with the discovery that modest quantities of triflic acid (ca. 5 equiv) in 1,2-dichloroethane at rt promotes rapid and efficient conversion to the  $\alpha,\beta$ -unsaturated keto lactam **10** (82%).



Scheme 3.

Interestingly, the stereochemical outcome of the hydrogenation of **10** at 1 atm proved to be catalyst dependent. When recourse was made to 10% palladium on charcoal in ethyl acetate, **11** and **12** were produced in a 1:1.7 ratio (Scheme 3). When the alternative use of platinum oxide in methanol or ethyl acetate was screened, diastereomer **11** now predominated. Accordingly, either dihydro product can be generated as the major constituent simply by switching the catalyst system.

Our ability to separate **11** from **12** by chromatographic means allowed for proper assessment of their equilibrium

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