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The Neber Route to Substituted Indoles

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Abstract

Two complementary procedures have been developed for the conversion of the oximes of α -aryl ketones to azirines. On heating, the azirines rearrange smoothly to the corresponding indoles. The overall transformation offers a versatile route to indoles, complementary to the Fischer indole synthesis.

Indoles are ubiquitous components both of physiologically-active natural products and of important pharmaceuticals.¹ Progress in the development of indole chemistry depends on the development of efficient synthetic routes to a variety of substitution patterns. We report what appears to be a general indole synthesis starting from *alkyl*-substituted benzene derivatives. This approach is complementary to the Fischer indole synthesis,² that starts with an *aminated* benzene ring, and to other existing methods for indole construction from *disubstituted* aromatics.³ The reduction to practice of this route⁴ to indoles opens a new expanse of pharmaceutical space for exploration.

We took as our lead the observation that the only existing approach to the preparation of indoles that started from an alkyl-substituted benzene, the pyrolysis of α -azido cinnamates (Scheme 1), was known^{4b} to proceed by way of the intermediate azirine **2**. We reasoned that α -aryl azirines such as **5a**, available by Neber reaction^{5,6} of the oximes derived from α -aryl ketones such as **4a**, could also undergo thermolytic rearrangement to give the indole.^{4,8}

The challenge proved to be the efficient conversion of the oxime derived from the α -aryl ketone to the azirine.⁷ Activation of the oxime OH with a leaving group is an invitation to competing Beckmann rearrangement and/or Beckmann fragmentation. We eventually developed two complementary procedures (Table 1) for effecting this transformation. For monoaryl acyclic ketones such as **4a**, exposure of the oxime to MsCl and Et₃N at 20 °C followed by the addition of DBU led smoothly to the azirine. For the diaryl ketone **4c** and the cyclic ketone **4e**, an alternative procedure, Mitsunobu cyclization of the oxime with DIAD/Bu₃P or Ph₃P, was more satisfactory. We were pleased to observe that each of the azirines in Table 1 was stable to chromatographic purification and to storage. The thermal rearrangement to the indole (sealed tube, *o*-xylene) worked smoothly for each of the azirines. The temperature for the rearrangement ranged from 170 °C (entry 1) down to less

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than 40 °C (entry 5). In the latter case, the azirine could not be isolated, because it rearranged to the indole as it was formed.

We were curious as to the mechanism of the azirine to indole rearrangement. Following the literature,^{4a} we expected (Scheme 2) that the rate-determining step would be cleavage of the C-N single bond. There were, then, two limiting mechanisms: formation of the nitrene **8** followed by insertion into the Ar-H σ bond to give **9**, or π participation from the aromatic ring to give **10**, which would reorganize to **11** and then **9**.

To probe this question, we carried out two additional cyclizations, of **12**, and of the intermediate unstable azirine derived from **15** (Scheme 3). We reasoned that the σ insertion (intermediate **8**) would lead to a substantial isotope effect. In fact, there was only a very minor isotope effect ($\leq 10\%$, ^1H NMR integration) in the formation of **13** and **14**.¹⁰

There was still the formal possibility that the nitrene **8** (Scheme 2) was cyclizing much more quickly than it could rotate. To assess this, we rearranged the azirine derived from **15**. In fact, there was a significant preference for insertion into the more electron-rich aromatic ring, to give **17**, suggesting that the cyclization is proceeding by way of the π mechanism. The observed preference for **17** may be of some preparative utility.

The cyclodehydration of the oximes of α -aryl ketones to indoles, sought for at least fifty years,⁸ has now been reduced to practice. We expect that this approach will be particularly useful for the preparation of indoles having highly-substituted benzene rings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Indoles from α -Aryl Ketones

α -Aryl Ketone	Azirine ^a Yield (%)	Temp °C (Time - h)	Indole	Yield (%)
<p>1</p> <p>4a</p>	<p>5a 78^b</p>	170 (18)	<p>6a</p>	88
<p>2</p> <p>4b</p>	<p>5b 70^b</p>	170 (13)	<p>6b</p>	86
<p>3</p> <p>4c</p>	<p>5c 91^d</p>	150 (16)	<p>6c</p>	89 ^c
<p>4</p> <p>4d</p>	<p>5d 78^b</p>	170 (18)	<p>6d</p>	84

α -Aryl Ketone	Azirine ^a Yield (%)	Temp °C (Time - h)	Indole	Yield (%)
^e	40 (1)		41 ^f

^a) Yield of azirine from ketone.

^b) Crude oxime to azirine by MsCl; DBU.

^c) Previously reported in ref. 9.

^d) Crude oxime to azirine by DIAD/Bu₃P.

^e) Crude oxime to azirine by DIAD/Ph₃P.

^f) Yield of indole from ketone **4e**.