

The Neber Route to Substituted Indoles

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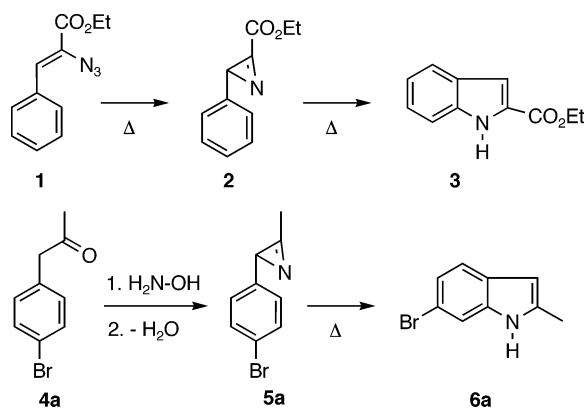
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Indoles are ubiquitous components both of physiologically active natural products and of important pharmaceuticals.¹ Progress in the development of indole chemistry depends on the development of efficient synthetic routes to a variety of substitution 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 synthesis² 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**.

Scheme 1



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 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.

Table 1. Indoles from α -Aryl Ketones

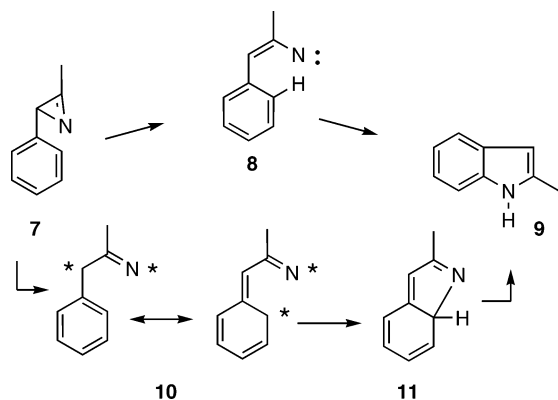
α -Aryl Ketone	Azirine ^a Yield (%)	Temp °C (Time - h)	Indole	Yield (%)
1 	5a 78 ^b	170 (18)		88
2 	5b 70 ^b	170 (13)		86
3 	5c ^c 91 ^d	150 (16)		89 ^e
4 	5d 78 ^b	170 (18)		84
5 	- ^e	40 (1)		41 ^f

^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**.

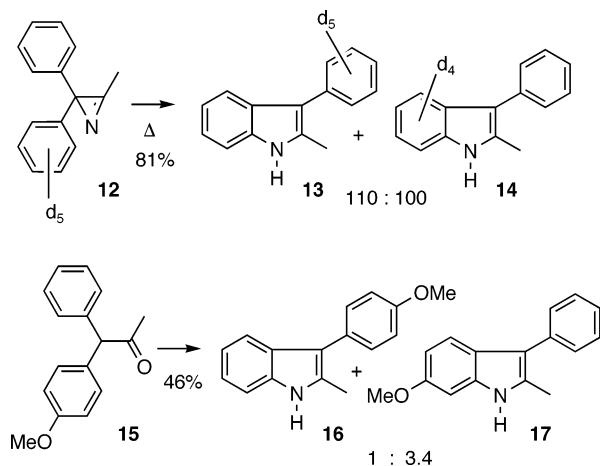
We were curious as to the mechanism of the azirine to indole rearrangement. Following the literature,^{4a} we expected (Scheme 2) that the rate-determining step would be cleavage of the C–N single bond. There were, then, two limiting mechanisms: formation of the nitrene **8** followed by insertion into 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

Scheme 2



Scheme 3



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 50 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.

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Supporting Information Available: Experimental details and spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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