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The Neber Route to Substituted Indoles

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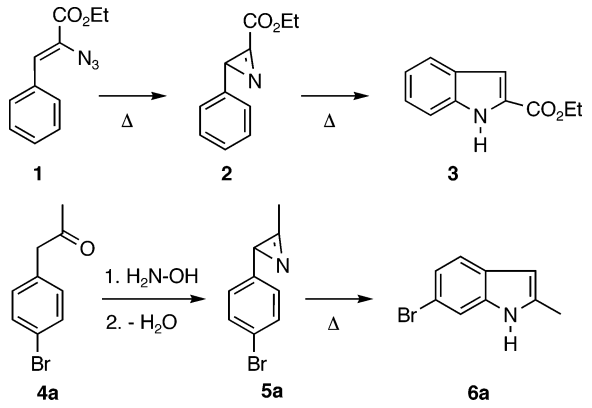
Indoles are ubiquitous components both of physiologically active natural products and of important pharmaceuticals.[1] Progress in the development of indole chemistry depends on the development of efficient synthetic routes to a variety of substitution patterns. We report what appears to be a general indole synthesis starting from *alkyl*-substituted benzene derivatives. This approach is complementary to the Fischer indole 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 route[4] 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**.

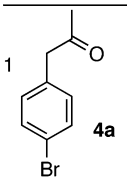
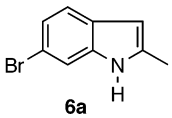
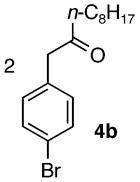
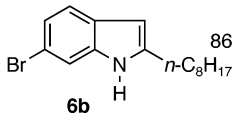
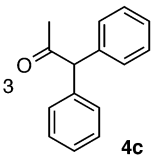
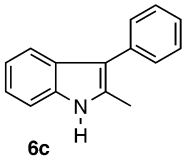
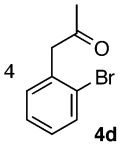
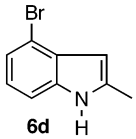
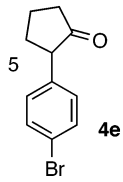
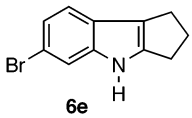
Scheme 1



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 Et_3N 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/Bu_3P or Ph_3P, 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	 **4a**	**5a** 78[b]	170 (18)	 **6a**	88
2	 **4b**	**5b** 70[b]	170 (13)	 **6b**	86
3	 **4c**	**5c**[c] 91[d]	150 (16)	 **6c**	89[c]
4	 **4d**	**5d** 78[b]	170 (18)	 **6d**	84
5	 **4e**	- [e]	40 (1)	 **6e**	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/Bu_3P. [e] Crude oxime to azirine by DIAD/Ph_3P. [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

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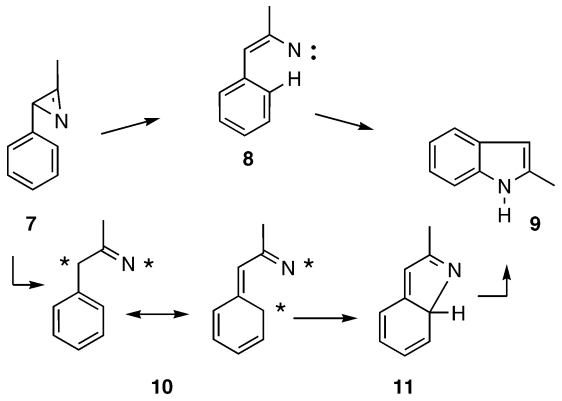
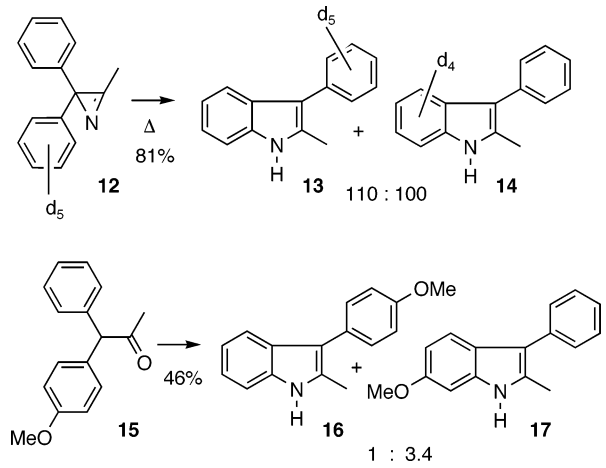
Scheme 2



Scheme 3



minor isotope effect (≤10%, ^{1}H 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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