

## Synthesis of Isoquinolines from Azidocinnamates; the Effect of Iodine

Deirdre M. B. Hickey, Christopher J. Moody, and Charles W. Rees

Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, U.K.

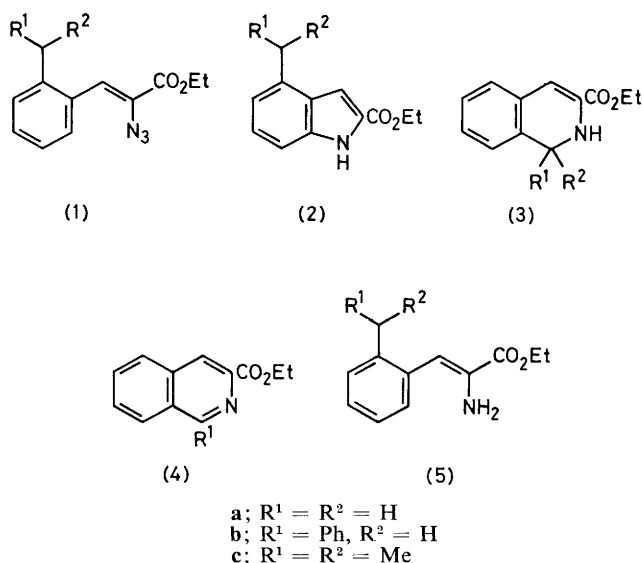
Iodine has a marked catalytic effect on the thermolysis of azidocinnamates; indoles, isoquinolines, 1,2-dihydroisoquinolines, or enamines are isolated depending on the conditions.

We have recently reported a simple synthesis of isoquinolines under neutral conditions which involves the mild thermal decomposition of azidocinnamates in which both *ortho*-positions are occupied by alkyl groups.<sup>1</sup> In contrast, mono-*ortho*-substituted azidocinnamates (e.g. **1a**) are known to give indoles (e.g. **2a**) in high yield on heating.<sup>2</sup> We now report that iodine has an unexpected effect on this latter reaction, and that isoquinolines can be formed at the expense of indoles.

Ethyl azidoacetate was condensed with 2-benzylbenzaldehyde under the usual conditions<sup>1,3</sup> to give the azidocinnamate (**1b**) (65%), m.p. 61–62 °C.† Decomposition of (**1b**) in boiling toluene under nitrogen for 2.5 h gave the indole (**2b**) (40%), m.p. 164–165 °C, as the major product, and the 1,2-dihydroisoquinoline (**3b**) (25%), m.p. 102–103 °C. However, when the decomposition of (**1b**) was repeated in boiling toluene (2.5 h) in the presence of a catalytic amount of iodine ( $\leq 10$  mol %), the product ratio was markedly changed, and the isoquinoline (**4b**), m.p. 100–101 °C, was the major product (40%), with the yield of the indole (**2b**) reduced to less than 10%. No 1,2-dihydroisoquinoline (**3b**)‡ was isolated although another product which was formed was identified as the enamine (**5b**) (30%), characterised as its *N*-acetyl derivative, m.p. 145–146 °C.

It seemed likely that the enamine (**5b**) was being formed from an intermediate nitrene by hydrogen abstraction from the 1,2-dihydroisoquinoline. Therefore, an attempt was made to suppress enamine formation and to increase the yield of isoquinoline by performing the decomposition in the presence of more iodine (1 mol. equiv.), as oxidant, and potassium acetate. Enamine formation was totally suppressed under these conditions, though the yield of isoquinoline was increased only to 50%.

The vinyl azide (**6**), prepared from fluorene-1-carbaldehyde, behaved similarly on thermolysis. Refluxing in xylene (1 h) gave the indole (**7**) (90%), and the isoquinoline (**8**) (5%). A catalytic amount of iodine (10 mol %) reduced the yield of



the indole (**7**) to 50%, though the yield of isoquinoline (**8**) was only doubled. Increasing the amount of iodine (1 mol. equiv.) raised the yield of (**8**) to 20%.

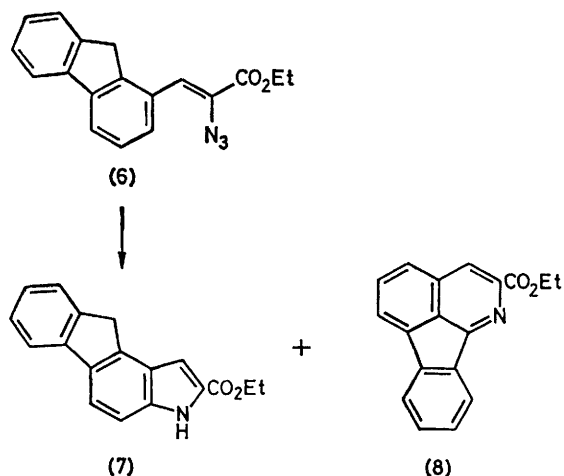
Iodine had a similar effect on the decomposition of the azidocinnamate (**1a**) with only an *ortho*-methyl group. Whereas thermolysis in boiling toluene gave exclusively the indole (**2a**) (97%) as previously reported,<sup>2</sup> thermolysis in toluene in the presence of iodine§ reduced the yield of the indole (**2a**) to 30%, and gave the isoquinoline (**4a**) (20%), picrate m.p. 156–158 °C (lit.,<sup>4</sup> 157 °C), and the enamine (**5a**) (15%). Increasing the amount of iodine suppressed enamine formation, and increased the yield of the isoquinoline (**4a**) (30%).

Thermolysis of the *o*-isopropyl-azidocinnamate (**1c**) followed a similar pattern in that the indole (**2c**) was the major product (65%) in boiling xylene alone, but in the presence of

† Satisfactory analyses and spectral data were obtained for all new compounds.

‡ 1,2-Dihydroisoquinoline (**3b**) was recovered unchanged after being heated in toluene (2 h), but was dehydrogenated rapidly by iodine at room temperature.

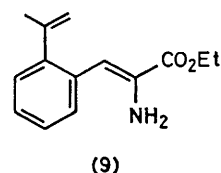
§ Thermolysis in boiling 1-iodopropane (102 °C), in the absence of iodine, gave exactly the same result as in toluene, suggesting that iodine was not acting simply as a heavy atom.



iodine the yield of indole was reduced in favour of the dihydroisoquinoline (3c). However, in this case the situation is complicated by formation of the enamine (9) by intramolecular abstraction of hydrogen from the isopropyl group (*cf.* ref. 5).

Decomposition of vinyl azides is expected to proceed with loss of nitrogen to give azirines.<sup>1,2,5</sup> Indeed, when the azide (1a) was heated for only 1 h in toluene, the corresponding azirine was isolated (50%), together with the indole (2a) (50%). Subsequent thermolysis of the azirine with and without iodine gave results very similar to those obtained starting from the azide.

The fate of the vinyl nitrene derived by thermal ring opening of the azirine is thus different in the absence and presence of iodine. In the absence of iodine the singlet nitrene can undergo



electrocyclic ring closure to give indoles and some direct insertion to give 1,2-dihydroisoquinolines, and hence isoquinolines. In the presence of catalytic amounts of iodine more insertion occurs and enamines (5) are now formed suggesting the intermediacy of a triplet or radical species which efficiently abstracts hydrogen from the dihydroisoquinoline. Indeed, in the presence of iodine and the good hydrogen donor, hydroquinone, enamines (5) are formed in high yield. In the absence of iodine there is no abstraction of hydrogen from hydroquinone.

The simplest explanation of our observations is that in the absence of iodine only singlet nitrene products are formed, but in its presence typical triplet or radical processes supervene.

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## References

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