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Synthesis of isoquinolines by irradiation of 1-methoxy-2-azabuta-1,3-dienes in a neutral medium

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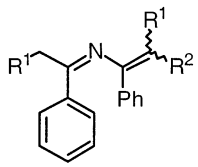
Abstract—We describe, for the first time, the photocyclization of 2-azadienes in a neutral medium. The reaction leads to the formation of isoquinolines.

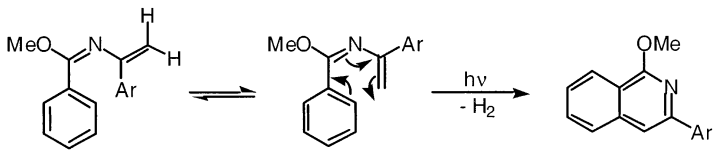
We have previously reported the preparation of substituted quinolines[1,2] and pyridines[3] by the irradiation of 4-amino-1-azabuta-1,3-dienes. Our methodology implies building a six-membered ring through a photocyclization process. Interestingly, irradiation in neutral[1] or acidic[2,3] medium led to different products. After completing our study on such 1-azadienes, we focused our interest on the photocyclization of 2-azabuta-1,3-dienes. In this case, this reaction could lead to the formation of isoquinolines, an important skeleton in many substances with biological activity or industrial applications.[4] However, despite the high versatility of 2-azabutadienes in synthetic procedures,[5] only a few examples of light-induced cyclization of protonated 2-azabutadienes[6] are described and no study in a neutral medium has been reported. The fact that the photochemical behavior of 1-azabutadienes varies depending on the reaction conditions prompted us to investigate the irradiation of non-protonated 2-azabuta-1,3-dienes. We wish to report here our preliminary results on this field.

Firstly, we prepared some appropriate 2-azadienes **1** (by dimerization of imines)[7] that could lead to an electrocyclic ring closure (Fig. 1). Based on ultraviolet absorption data of **1a** (methanol: $\lambda = 208$, 246 and 305 nm, $\varepsilon \approx 25000$, 19000 and 760 M^{-1} cm^{-1}, respectively), we carried out its irradiation in methanol or THF (10^{-2} M solution) using a 125 W medium-pressure mercury lamp through quartz both with and without tetrafluoroboric acid (1.1 equiv.). The reaction was monitored by ^1H NMR spectroscopy. Complete



1a $R^1 = Me$, $R^2 = H$
1b $R^1 = Et$, $R^2 = H$
1c $R^1 = Ph$, $R^2 = H$
1d $R^1 = Ph$, $R^2 = Cl$

Figure 1.



1e Ar = Ph
1f Ar = *p*-Me-C_6H_4
1g Ar = *p*-MeO-C_6H_4

2e (63%)
2f (38%)
2g (45%)

Scheme 1.

Keywords: azadienes; cyclization; isoquinolines; photochemistry.

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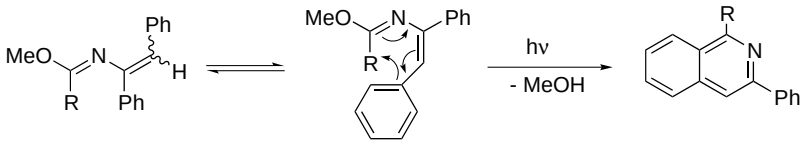

1h R = Ph
1i R = Me

2h (69%)
2i (38%)

Scheme 2.

consumption of the starting material occurred after 6–7 h. Unfortunately, the reaction led to the formation of polymeric material instead of the expected isoquinoline derivatives. The same results were obtained for **1b** and **1c**. In order to increase the photoreactivity of the starting 2-azadienes, we carried out the preparation of the chlorinated compound **1d** (by reaction of 2-azadiene **1c** with *N*-chlorosuccinimide)[1b,8] but, after irradiation in THF (10^{-2} M) through quartz, **1d** did not suffer any appreciable change after 10 h.

Then, we prepared some 2-azadienes bearing a methoxy group by reaction of Fischer carbene complexes with 2-azirines.[9] The absorption spectrum of 1-methoxy-1,3-diphenyl-2-aza-1,3-butadiene **1e** showed bands at 225, 256 and 345 nm ($\varepsilon \approx 10100$, 5800 and 350 M^{-1} cm^{-1}, respectively). The irradiation of **1e** yielded a new product, which was purified by column chromatography (silica gel, hexane/Et_2O, 1:1) and identified as 1-methoxy-3-phenylisoquinoline **2e** by its spectroscopic data (^1H and ^{13}C NMR) and mass spectrometry (Scheme 1). The best results were obtained by irradiation through quartz of a 10^{-3} M solution in hexane with a 400 W medium-pressure mercury lamp for 5 h. Likewise, isoquinolines **2f** and **2g** were obtained by irradiation of 2-azadienes **1f** and **1g**, respectively, for 8 h. In order to explain these results, we propose an initial six π-electron photoannelation process with formation of a cyclic structure that loses molecular hydrogen under irradiation,[10] thus giving the corresponding isoquinoline.

Interestingly, when the 1-methoxy-2-azadiene bears a phenyl group at the 4-position, this group was involved in the cyclization. Thus, irradiation of 1-methoxy-1,3,4-triphenyl-2-aza-1,3-butadiene **1h**[9] for 8 h gave the 1,4-diphenylisoquinoline **2h** after loss of methanol (Scheme 2). This result may be explained by the fact that methanol is easier to remove than molecular hydrogen. This fact allows the substitution by an alkyl group in the 1-position and, thus, **1i**[9] gave 1-methyl-4-phenylisoquinoline **2i** after 1 h of irradiation.

In summary, we have described, for the first time, the photoannelation of 1-methoxy-2-azadienes to give isoquinolines in a neutral medium. Further studies to elucidate the mechanism and to extend the scope of this reaction are in progress.

Typical procedure for the irradiation of 2-azadienes 1e–i. A 10^{-3} M solution of the corresponding 2-azadiene in hexane was bubbled with argon and irradiated through Pyrex, at room temperature under an Ar atmosphere, using a medium-pressure mercury lamp (400 W) until complete consumption of the starting material (monitored by ^1H NMR spectroscopy). The solvent was evaporated under reduced pressure and the resulting isoquinoline was separated and/or purified by column chromatography (silica gel, hexane/Et_2O, 1:1).

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