

A CONVENIENT ACCESS TO 3,4-DISUBSTITUTED ISOQUINOLINES FROM BENZOCYCLOBUTENYL KETOXIMES¹

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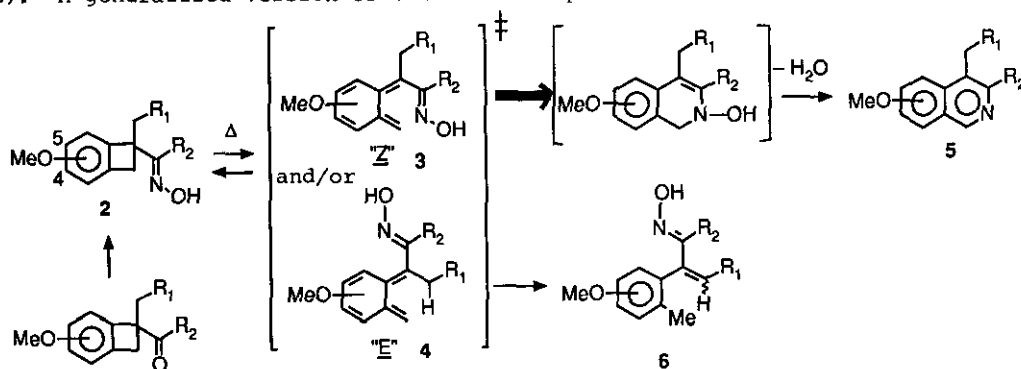
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Abstract — The thermolyses of several benzocyclobutenyl ketoximes (2) proceed *via* a preferential electrocyclic reaction of *Z*-*o*-quinodimethane species (3) to yield 3,4-disubstituted isoquinolines (5).

We have previously reported thermal behaviors of 1,1-disubstituted benzocyclobutenes.² Based on these studies centered on a competition between electrocyclic reaction (ECR) and [1,5]sigmatropic reaction (STR) of *o*-quinodimethane during the thermolysis of 1-acyl(or alkenyl)-1-alkylbenzocyclobutenes, it would be expected that thermolysis of the substrates (2) with an oxime instead of C=O or C=C functionality at C-1 should also proceed preferentially *via* an electrocyclic process of *Z*-*o*-quinodimethane (3) followed by a spontaneous dehydration to give isoquinolines (5). Although a few synthetic examples³ of isoquinolines from benzocyclobutenes by electrocyclic reactions have been reported so far, none of the approaches to 3,4-disubstituted isoquinolines has been discussed from a viewpoint of the competition between ECR and [1,5]STR. Here we wish to report a convenient synthesis of 3,4-disubstituted isoquinolines (5) from benzocyclobutenyl ketoximes (2). A generalized version of the reaction process is shown in Scheme 1.



Scheme 1

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A degassed solution of the crude oxime (2), prepared from the corresponding ketone (1)⁴ with hydroxylamine hydrochloride and sodium acetate, in *o*-dichlorobenzene was heated at 180°C with stirring under an atmosphere of argon. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to afford the isoquinolines (5)⁵ in good to reasonable yields. Representative results are listed in Table 1.

Table 1. Synthesis of isoquinolines (5) by thermolysis of (2)

Run	Substrate (2)			Reaction Time, h	Yield % of 5
	OMe	R ₁	R ₂		
1	C-4	H	Me	3	70
2	5	H	Me	3	67
3	5	Me	Me	5	70
4	5	H	ⁿ Bu	3	58
5	5	CH ₂ Ph	Me	2	79
6	5	H		3	46
7	5	H		2.5	69
8	5	-(CH ₂) ₃ -		10	59+10% of 6
9	5	H		3	26

It should be noted that only in the case of spiro oxime (2: R₁+R₂=(CH₂)₃-) a competitive [1,5]STR⁶ occurred simultaneously with the formation of 6(R₁+R₂=(CH₂)₃-) in 10% yield.

This reaction seems to be useful by the facts that starting oximes are readily available from the corresponding 1-cyanobenzocyclobutenes by standard manipulations and 3,4-disubstituted isoquinolines are not so easy to prepare by the conventional methods.⁷

REFERENCES AND NOTES

1. This paper is dedicated to Sir Derek H. R. Barton, Professor of Texas A & M University, on the occasion of his 70th birthday.
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