A CONVENIENT ACCESS TO 3,4-DISUBSTITUTED ISOQUINOLINES FROM BENZOCYCLOBUTENYL KETOXIMES[1]

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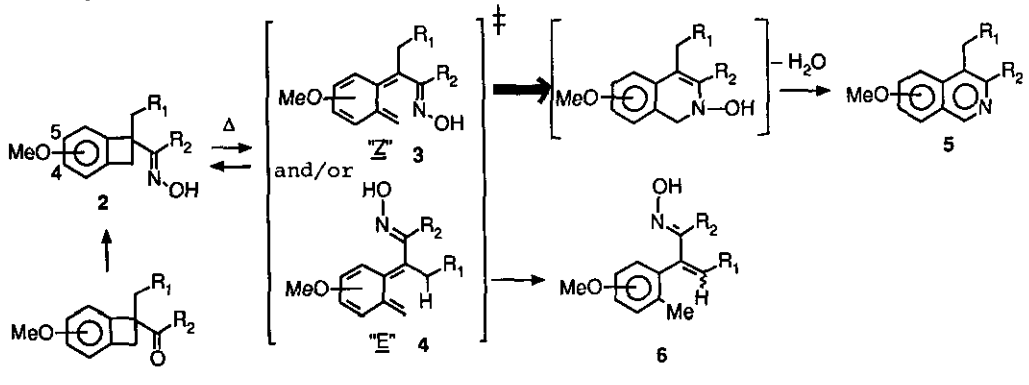
Abstract —— *The thermolyses of several* benzocyclobutenyl ketoximes (2) proceed via a preferential electrocyclic reaction of Z-o-quinodimethane species (3) to yield 3,4-disubstituted isoquinolines (5).

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 examples[3] 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

† *Deceased October 11, 1988.*

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**)

		Substrate (**2**)		Reaction	Yield %
Run	OMe	R_1	R_2	Time, h	of **5**
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_2Ph	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**: $R_1+R_2=-(CH_2)_3-$) a competitive [1,5]STR[6] occurred simultaneously with the formation of **6**($R_1+R_2=-(CH_2)_3-$) 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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5. All new compounds exhibited satisfactory spectroscopic and analytical (combustion and/or high-resolution mass spectral) data consistent with the structures shown.
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