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THERMOLYTIC RING OPENING OF ACYLOXYBENZOCYCLOBUTENES: AN EFFICIENT ROUTE TO 3-SUBSTITUTED ISOQUINOLINES

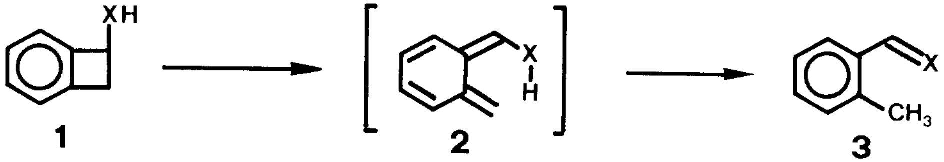
Peter Schiess*, Martine Huys-Francotte and Caspar Vogel

Institut für Organische Chemie der Universität
St. Johanns-Ring 19, CH-4056 Basel, Switzerland.

Summary: Upon flash vacuum pyrolysis acyloxybenzocyclobutenes 4 rearrange through an intramolecular 1,5-acyl shift to 2-formylbenzyl ketones 6 which can be converted to 3-substituted isoquinolines 7.

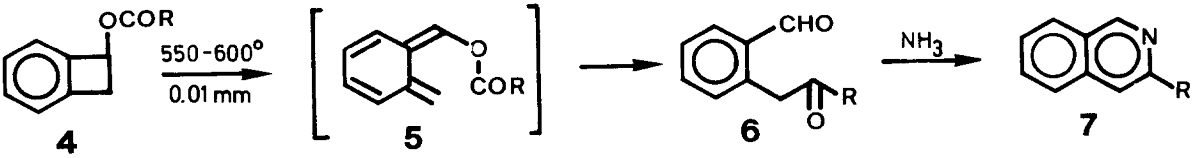
It is well known, that benzocyclobutenes of general structure 1 are thermolabile and rearrange at moderate temperature to unstrained, monocyclic products 3 via their unstable, orthoquinoid valence isomers 2 by way of a sigmatropic 1,5-hydrogen shift reaction (Scheme 1) [1].

Scheme 1



Some time ago we [2] and others [3] have shown that acyl groups can participate in uncatalyzed sigmatropic 1,5-shift reactions at similar rates as hydrogen atoms. Acyloxybenzocyclobutenes 4, therefore, were expected to rearrange via 5 to 2-formylbenzyl ketones 6 (Scheme 2). The experiments reported in the following bear out this expectation.

Scheme 2



Thus, acetoxybenzocyclobutene 4b ($R = CH_3$) upon flash vacuum pyrolysis (FVP)[4] at 540°/0.01 Torr gave the expected ketoaldehyde 6b [5] in high yield. Upon treatment with KOH in methanol 6b was transformed into β-naphthol [6]. With ammonium acetate in methanol according to [7] quantitative conversion of 6b to 3-methylisoquinoline 7b was accomplished.

Conditions typical of FVP methodology [4] (short reaction time, low reactant partial pressure) favouring intramolecular versus intermolecular processes are essential for high yield in the conversion 4b ⟶ 6b. Not surprisingly thermolysis of 4b in condensed phase (neat or as a 10% solution in 1,3-dichlorobenzene at 200°) gave no trace of ketoaldehyde 6b.

Isoquinolines 7 with a variety of substituents R in position 3 were prepared in good yield by the method described above for 7b (see table).

Table Conversion of acyloxybenzocyclobutenes 4 to isoquinolines 7 according to scheme 2 a) b).

	R	**4** b.p./Torr (m.p.)	**7** b.p./Torr (m.p.)	Isolated yield
a	H	50-60°/0.1	55-65°/0.1	90 %
b	CH_3	55-65°/0.1 [8]	(62-63,5°) [9]	84 %
c	$C(CH_3)_3$	100-110°/0.1	80-100°/0.02 [10]	71 %
d	$CH_2C_6H_5$	(38-42°)	(62-64°)	74 %
e	CF_3	50-60°/0.1 [12]	(30-31°)	73 %
f	C_6H_5	(32-34°)	(100-102°) [10]	63 %
g	$4\text{-}NO_2\text{-}C_6H_4$	(117-119°)	(185-189°)	43 %
h	$4\text{-}CH_3O\text{-}C_6H_4$	(124-126°)	(98-100°) [10]	65 %
i	$CH{=}CH{-}CH_3$	80-90°/0.1	(70-71,5°)	25 %
j	$CH_2{-}CH{=}CH_2$	80-90°/0.1	see Scheme 3	
k	$(CH_2)_2CH{=}CH_2$	90-95°/0.1	80-90°/0.05	41 %

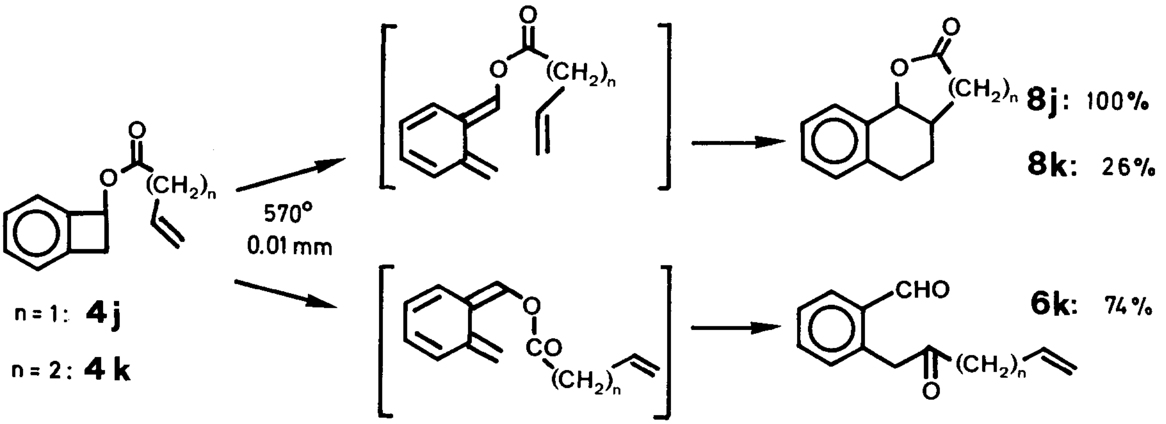
a) *Except for the conversion* 4b ⟶ 7b *which has been carried out on a 30 g-*scale the reactions reported in this table have been performed with samples of 0.5 - 1 g of ester 4 and reaction conditions have not been optimized.

b) All new compounds have been characterized by elemental analysis and full spectral data.

Two limitations of the pyrolytic transformation 4 → 6 shall be outlined:

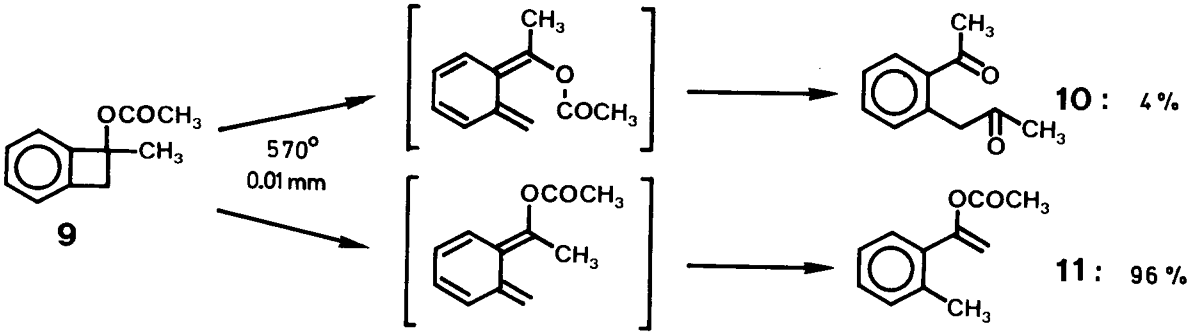
1. With esters 4j and 4k, derived from unsaturated acids, intramolecular cycloaddition [1] competes with acyl migration. Thus 4j yields no ketoaldehyde 6j but only γ-lactone 8j as a mixture of stereoisomers [13]. From 4k a 3 : 1 mixture of 6k and δ-lactone 8k (trans isomer only) [14] is formed. It seems likely that the competing isomerisation pathways leading to 6 and 8 originate from stereoisomeric forms of the ortho-quinoid valence isomers of the starting esters 4j and 4k as indicated in Scheme 3.

Scheme 3



2. From tertiary esters such as 9 only a small amount of acyl migration product 10 (quantitatively transformed into 1,3-dimethylisoquinoline upon treatment with ammonia) is obtained. The major product is enol acetate 11, formed through hydrogen migration via the E-form of the reactive ortho-quinodimethane intermediate (see Scheme 4).

Scheme 4



Benzocyclobutenone, the precursor of 4a - 4k (through LiAlH$_4$-reduction and esterification) is readily obtained by FVP of toluic acid chloride [15]. The synthesis of 3-substituted isoquinolines 7 from inexpensive starting materials (o-toluic acid, aromatic or aliphatic acid RCOOH, ammonia and LiAlH$_4$) described in this communication involves two pyrolytic reaction steps. It thus demonstrates the usefulness of FVP-methodology in preparative organic chemistry.

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[13] 8j, cis-isomer: 70%, mp. 103-104°; ^{1}H-NMR (CDCl$_3$): δ 5,4 d, 1 H, J = 6 Hz.
trans-isomer: 30%, mp. 136-137°; ^{1}H-NMR (CDCl$_3$): δ 4,9 d, 1 H, J = 9 Hz.

[14] 8k, trans-isomer: mp. 138-141°; ^{1}H-NMR (CDCl$_3$): δ 5,1 d, 1 H, J = 8,3 Hz.

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