

The Control of Orientation of Polonovski and the Related Reactions

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A novel base-induced Polonovski-type reaction is described; the regiochemistry of the Polonovski and related reactions can be examined by using 2-methoxytetrahydro-6,12-methanodibenz[*c,f*]azocine *N*-oxide (**1b**) as a probe.

The synthetic utility of the Polonovski reaction¹ has been widely explored and the application of the reaction to the synthesis of the antitumour alkaloid vinblastine is one of the most notable developments.² However, one of the drawbacks of the reaction is the poor predictability of the regiochemistry in the hydrogen abstraction from the α -carbon to the *N*-oxide group. Several factors[†] might be concerned in the regiochemistry of this reaction and the elucidation of one of these

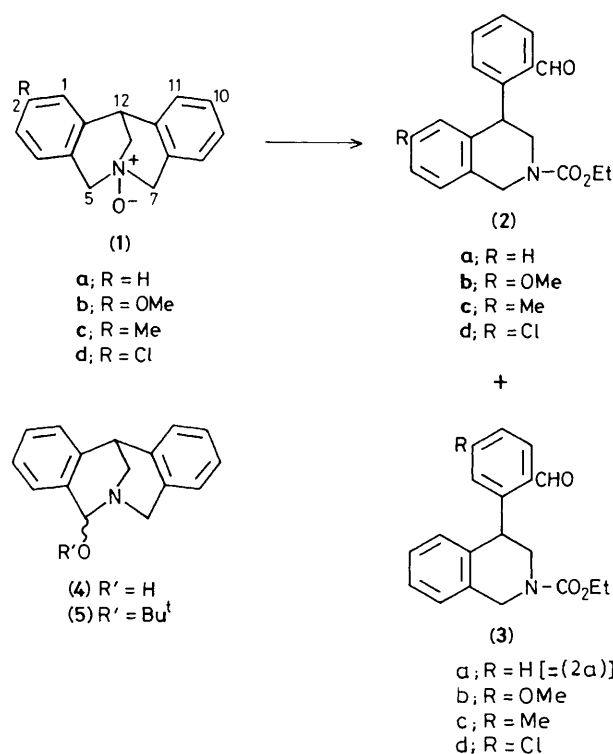
factors would enhance its potential synthetic utility. We are exploring the electronic factors in the orientation of the Polonovski reaction by using tetrahydro-6,12-methanodibenz[*c,f*]azocine *N*-oxides (**1**),³ which have a rigid skeleton well suited stereochemically for examining the regioselectivity: the steric environment around both carbons adjacent to the *N*-oxide of (**1**) being fixed and thus equivalent. We now report novel Polonovski-type reaction of (**1**) with a strong base⁴ such as Bu^tOK in Bu^tOH and the control of the orientation of this and related reactions by applying variable *E2* transition state theory.⁵

Polonovski reaction of (**1a**) (m.p. 231–232 °C) with trifluoroacetic anhydride (1.1 equiv.) followed by treatment with Na₂CO₃ (1 M) afforded (**4**) (m.p. 154–156 °C), which reacted with ethyl chloroformate to give the tetrahydroisoquinoline aldehyde (**2a**) in 95% yield. The structure of (**2a**) was confirmed by its spectroscopic data [*m/z* 309 (*M*⁺); ¹H n.m.r.

[†] The acidity and stereochemistry of hydrogen on the carbon α to the *N*-oxides, the stability of the iminium intermediates, the property of leaving groups on the *N*-oxides, etc. have been discussed; R. T. LaLonde, E. Auer, C. F. Wong, and V. P. Muralidharan, *J. Am. Chem. Soc.*, 1971, **93**, 2501; L. Chevolet, M. Husson, C. Kan-Fan, H. P. Husson, and P. Potier, *Bull. Soc. Chim. Fr.*, 1976, 1222; R. Michelot, *ibid.*, 1969, 4377; P. Mangeney, *Tetrahedron*, 1978, **34**, 1359.

Table 1. Polonovski-type reaction of (1b).

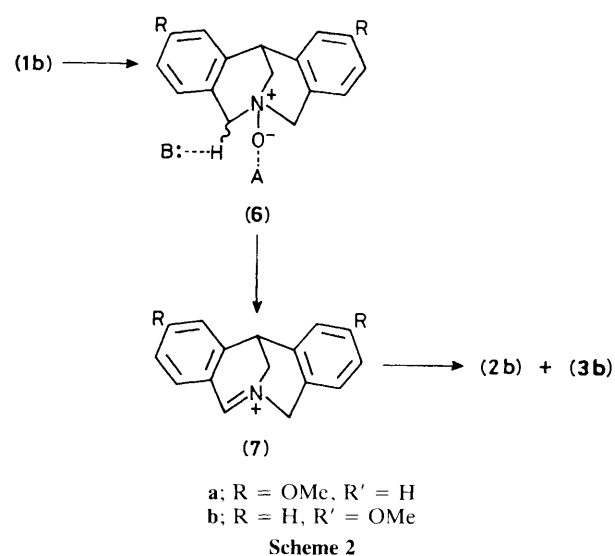
Entry	Reagent	Molar equiv.	Solvent	Temp. (°C)	Time (h)	Yield (2b) + (3b) (%)	Ratio (2b) : (3b)
1	Me ₃ COK	5	Me ₃ COH	150	2	80	8 : 1
2	(MeCO) ₂ O	10	CH ₂ Cl ₂	r.t. ^a	12	75	2 : 1
3	(CF ₃ CO) ₂ O	1.1	CH ₂ Cl ₂	0	1	95	1 : 1
4	(CF ₃ SO ₂) ₂ O	1.1	CH ₂ Cl ₂	0	0.5	89	1 : 5
5	(MeCO) ₂ O	1.1	Et ₃ N CH ₂ Cl ₂	r.t.	1	71	3 : 1
6	MeCOCl	1.1	CH ₂ Cl ₂	r.t.	4	92	1 : 1
7	<i>p</i> -MeC ₆ H ₄ SO ₂ Cl	1.1	CH ₂ Cl ₂	r.t.	15	63	1 : 1.3
8	CF ₃ SO ₂ Cl	1.1	CH ₂ Cl ₂	r.t.	1	25	1 : 1.8

^a r.t. = room temperature.**Scheme 1**

δ (CDCl₃) 3.74 (1H, dd, *J* 14.0 and 4.0 Hz), 4.07 (1H, dd, *J* 14.0 and 4.0 Hz), 4.55 (1H, d, *J* 17.0 Hz), 5.05 (1H, d, *J* 17.0 Hz), 5.33 (1H, t, *J* 4.0 Hz), 10.27 (1H, s); ν (neat) 1685 cm⁻¹ (broad, split). On the other hand, heating (1a) with Bu^tOK (5 equiv.) in Bu^tOH in a sealed tube (150 °C) gave the 5-*t*-butoxy derivative (5)‡ in 85% yield, which on subsequent treatment with HCl (2 M) provided (4). Reaction of (5) with Na₂CO₃ (1 M)–ClCO₂Et afforded (2a) quantitatively. (See Scheme 1.)

In order to examine the orientation of Polonovski and related reactions, an asymmetrically substituted *N*-oxide (1b) was chosen. Reactions of (1b) (m.p. 221–222 °C) with several reagents followed by treatment with Na₂CO₃ (1 M)–ClCO₂Et were carried out and the regioisomeric ratios of the products

‡ Spectroscopic data (5): *m/z* 293 (*M*⁺); ¹H n.m.r. δ (CDCl₃) 1.44 (9H, s), 3.22 (1H, d, *J* 13 Hz), 3.67 (1H, s), 3.72 (1H, d, *J* 13 Hz), 4.00 (1H, d, *J* 18 Hz), 4.59 (1H, d, *J* 18 Hz), 5.17 (1H, s). The formation of (5) can be elucidated by the addition of Bu^tO⁻ or Bu^tOH to a strained iminium ion such as (7).

**Table 2.** Polonovski-type reaction of (1c) and (1d).

Reagent	Ratio (2c) : (3c) (Total yield %)	Ratio (2d) : (3d) (Total yield %)
Me ₃ COK	3 : 1 (86)	1 : 3 (76)
(CF ₃ CO) ₂ O	1.8 : 1 (85)	1 : 1.7 (95)
(CF ₃ SO ₂) ₂ O	1 : 1 (76)	1 : 1.2 (80)

(2b) : (3b) were determined by g.l.c. The reaction conditions and the results are shown in Table 1, and notable regiochemical trends are observed in the Polonovski reactions (entries 1–4). The observed regiochemistry may be rationalized (Scheme 2) by applying the variable *E2* transition state theory to the elimination of both H and OA in (6) leading to the iminium intermediate (7).§ Thus, a stronger base (Et₃N) > AcO⁻ > Cl⁻ leads to an increase in the carbanion character (*Elcb* like) at the transition state (6a), so it favours the formation of (2b) [via the thermodynamically less stable (7a)] (entries 2, 5, 6). A better leaving group (CF₃SO₃⁻ > *p*-MeC₆H₄SO₃⁻ > AcO⁻) which shifts the transition state (6b) to an *El*-like

§ For the possibility of the presence of transient species such as (7) see: A. Greenberg and J. F. Liebman, 'Strained Organic Molecules,' ed. H. H. Wasserman, Academic Press, New York, 1978, p. 117, 320, and references cited therein.

direction, favours the formation of (**3b**) [*via* the more stable (**7b**)] (entries 6,7,8). As a whole, the results in entries 1—4 indicate the general trend toward an increasing proportion of (**2b**) as the base is stronger and the leaving group becomes less effective. Furthermore, other asymmetrically substituted *N*-oxides, (**1c**) and (**1d**), were subjected to the Polonovski reactions and the expected results were obtained (Table 2).

In conclusion, the prediction and control of the orientation of the Polonovski and related reactions are possible, and the application of this novel Polonovski-type reaction as a key step in the synthesis of natural products is described in the accompanying communication.

Received, 21st August 1984; Com. 1206

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