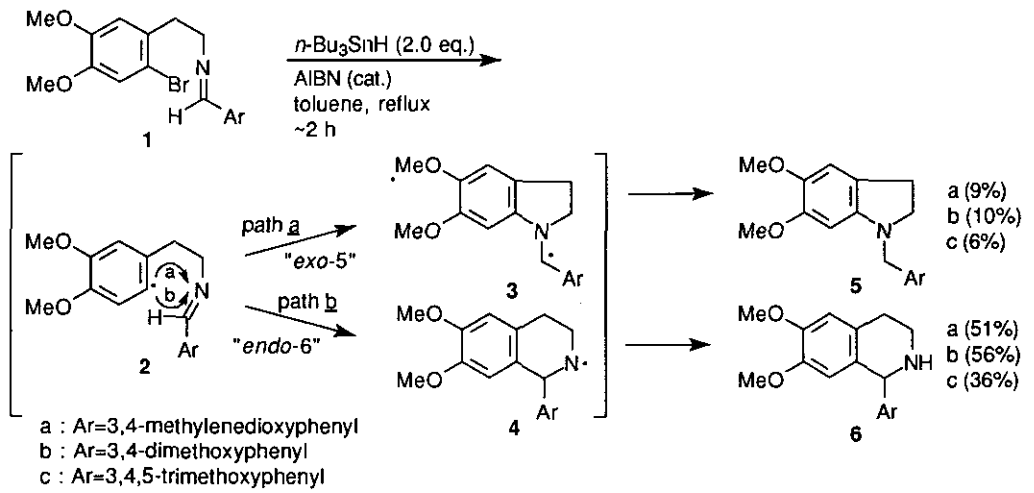
INDOLINE FORMATION BY REGIOSELECTIVE ARYL RADICAL CYCLIZATION TO AZOMETHINE BOND

Seiichi Takano,* Mahito Suzuki, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract —— Aryl radical-initiated cyclization of the ketimines derived from acetophenone and benzophenone occurred exclusively at the nitrogen end of the azomethine bond in an *exo*-5 mode to yield the corresponding indoline derivatives.

As we have demonstrated in a synthesis of the 1-phenylisoquinoline alkaloids,[1] an aryl radical-initiated cyclization[2] of the aldimines (**1**) occurs preferentially at the carbon end of the azomethine bond in an *endo*-6 mode (path b) rather than at the nitrogen end in an *exo*-5 mode (path a) leading to the isoquinolines (**6**)

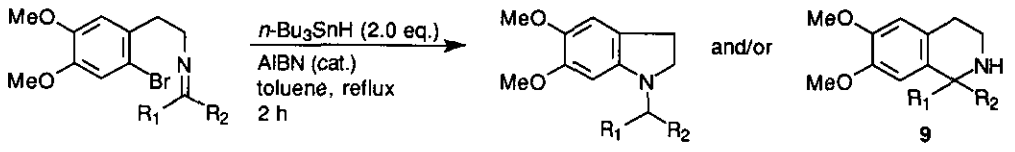


Scheme 1

Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

accompanied by a minor amount of the indoline derivatives (**5**) (**Scheme 1**). Although the observed regiochemical outcome did not seem to be in accord with the Baldwin's rule,[3] it has recently been reasonably rationalized by a kinetic study carried out by Tomaszewski and Warkentin.[4] In this paper we describe an attemption to inverse the regioselectivity of this aryl radical-initiated cyclization to an azomethine bond by using ketimines as substrates.

Because ketimines reside an extra substituent on the azomethine carbon, it can be expected that the cyclization would be forced to take place at the nitrogen end of the azomethine bond in an *exo*-5 mode to giving rise to indoline derivatives selectively even though it is kinetically disfavored.[4] We, therefore, examined the aryl radical-initiated cyclization using the ketimines, prepared from 2-(2-bromo-4,5-dimethoxyphenyl)ethylamine[5] and aliphatic and aromatic ketones, in comparison with the aldimines, prepared from the same amine and aliphatic and aromatic aldehydes (**Scheme 2**).



7 **8** **9**

a : R_1=*n*-Bn, R_2=H; b : R_1=*tert*-Bu, R_2=H; c : R_1, R_2= $-(CH_2)_5-$; d : R_1=Ph, R_2=H; e : R_1=Ph, R_2=Me; f : R_1=R_2=Ph; g : R_1, R_2=$(2\text{-}C_6H_4)_2$

Scheme 2

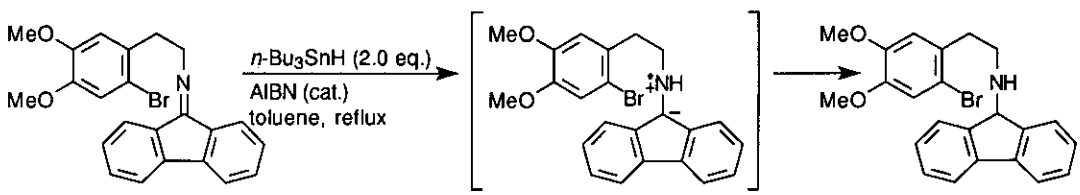
Table 1 Reaction of Imine (**7**) with Tri-*n*-butyltin Hydride

	imine (**7**)					
Entry		R_1	R_2	indoline (**8**) (%)	isoquinoline (**9**) (%)	
1	(a)	*n*-Bu	H	0		0
2	(b)	*t*-Bu	H	0		0[a]
3	(c)	$-(CH_2)_5-$		0		0
4	(d)	C_6H_5	H	(d) 2.0	(d)	21.1
5	(e)	C_6H_5	Me	(e) 10.5		0
6	(f)	C_6H_5	C_6H_5	(f) 58.7		0
7	(g)	$-(2\text{-}C_6H_4)_2-$		0		0[b]

a. Debrominated imine was obtained in 47.9% yield.
b. The secondary amine (**11**) was obtained in 53.4% yield.

Thus, the imines (**7**), prepared by condensation of the amine with the ketones as well as with the aldehydes, were treated with tri-*n*-butyltin hydride (2 equiv.) in toluene (ca. 1% concentration) in the presence 2,2'-azobisisobutyronitrile (AIBN) (10 mol%) at refluxing temperature under argon for 2 h and the products were separated by silica gel column chromatography (**Table 1**). As appeared, the ketimine (**7c**) as well as the aldimines (**7a,b**), obtained from both aliphatic aldehydes and ketone, did not afford any cyclization products (Entries 1~3). Because of instability of the reaction products under the work-up conditions, we could not isolate these reaction products except for the debrominated imine (**7b**: Br=H) from **7b**, but reductive debromination occurred in every case.

On the other hand, both of the aromatic ketimines (**7e~g**) and the aromatic aldimine (**7d**), except the fluorenonimine (**7g**), furnished the cyclization products in fair to moderate yields. As expected the ketimines (**7e,f**) afforded the indolines (**8e,f**), exclusively, without formation of the isoquinolines (Entries 5 and 6), while the aldimine (**7d**) generated a 1:10 mixture of the indoline (**8d**) and the isoquinoline (**9d**) (Entry 4). Although optimization must be necessary, the observed regiochemical outcome is noteworthy from the synthetic point of view, because a variety of indolines bearing readily removable *N*-substituent can be accessible by the aryl radical-initiated cyclization *via* aromatic ketimines. The generation of the secondary amine (**11**) from the fluorenonimine (**7g**) was also interesting though it did not furnish the expected indolenine (Entry 7). This may be rationalized by assuming the radical anion intermediate (**10**) whose stability owing to aromaticity of the fluorenyl moiety leads preferential generation of the amine (**11**) leaving the halogen atom intact (**Scheme 3**).

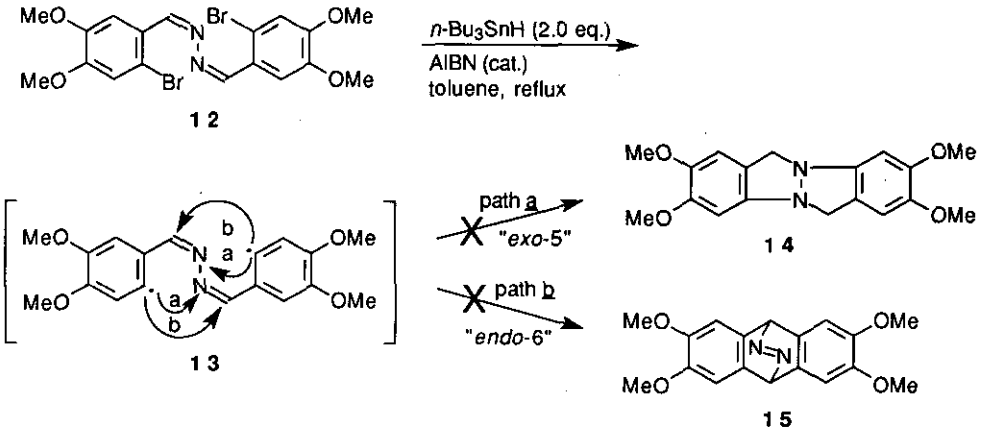


7g **10** **11**

Scheme 3

In order to know the prefered regiochemistry in the radical cyclization, we also examined the reaction using the symmetric bis-hydrazone substrate (**12**) which would allow cyclization either in an *exo*-5-nitrogen mode (path a) or in an *endo*-6-carbon mode (path b) *via* the symmetric bis-radical intermediate (**13**) to give the interesting

heterocycle (**14**) or (**15**). However, the reaction did not take place in an expected way which furnished the debromination product (**12**: Br=H) instead in 57.4% yield (**Scheme 4**).



Scheme 4

REFERENCES

1. S. Takano, M. Suzuki, A. Kijima, and K. Ogasawara, *Chemistry Lett.*, 1990, 315. See also, *ibid.*, *Tetrahedron Lett.*, 1990, **31**, 2315; S. Takano, M. Suzuki, and K. Ogasawara, *Heterocycles*, 1990, **31**, 1151.

2. Pertinent reviews and monographs for the radical reaction: A. L. J. Beckwith, *Tetrahedron*, 1982, **37**, 3073; B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 753 and 1985, **24**, 553; B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds,' Pergamon Press, Oxford, 1986; W. P. Neuman, *Synthesis*, 1987, 665; D. P. Curran, *ibid.*, 1988, 417, 489; D. P. Curran, In 'Comprehensive Organic Synthesis,' eds. by B. M. Trost, I. Fleming, and M. F. Semmelhack, Pergamon Press, Oxford, 1991, **4**, 715; C. P. Jasperse, D. P. Curran, and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237.

3. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

4. M. J. Tomaszewski and J. Warkentin, *Tetrahedron Lett.*, 1992, **33**, 2123.

5. J. Harley-Mason, *J. Chem. Soc.*, 1953, 200.

Received, 19th May, 1993