

Synthesis of Spiro[indoline-3,2'-pyrrolidine] Derivatives from β -3-Indolyl Ketone Oximes

Kenichi Tanaka, Yutaka Mori, and Koichi Narasaka*

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

(Received October 6, 2003; CL-030937)

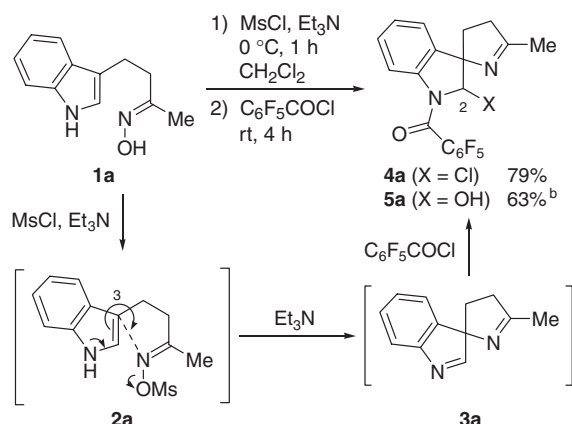
Spiro[indoline-3,2'-pyrrolidine] derivatives were prepared from β -3-indolyl ketone oximes by treatment with methanesulfonyl chloride and triethylamine via the bond formation between 3-position of the indole ring and oxime nitrogen. These diazaspicycles were readily transformed to the corresponding spiro indole derivatives.

Spiro[indoline-3,2'-pyrrolidine] derivatives have received much attention in the development of pharmaceutically active molecules. These diazaspicycles are mostly synthesized by the 1,3-dipolar cycloaddition of azomethine ylides derived from isatins and secondary amines or α -amino acids.¹ Because the dipolarophiles available for the cycloaddition are limited to the activated alkenes, the alternative methods need to be developed for the preparation of a wide variety of the azaspiro indolines. Although the cyclization of 3-(3-aminoalkyl)indoles would be a candidate, there has been reported only one example of such a cyclization by the oxidation of 3-(3-ethylaminopropyl)indole, giving the low yield of the cyclized product.²

Recently, we have developed the intramolecular S_N2 -type reaction at the oxime sp^2 nitrogen to prepare azaheterocycles.³ For the latest instances, cyclic imines and quinolines are synthesized from γ,δ -unsaturated and β -aryl ketone oximes.^{3g,h} Since the reaction of indoles and electrophiles normally takes place at their 3-position,⁴ we expected that spiro[indoline-3,2'-pyrrolidine]s would be obtained from β -3-indolyl ketone oximes by a similar intramolecular S_N2 -type cyclization. In this paper is described this transformation reaction briefly.

β -3-Indolyl ketone oximes were readily prepared by the $SnCl_3$ -catalyzed reaction of indole and enones,^{4c} followed by the oximation⁸ of the resulting ketones. The *syn* and *anti* isomers⁵ of the oximes are separated by column chromatography on silica gel. Thus obtained 4-(3-indolyl)butan-2-one *anti*-oxime **1a** was treated with methanesulfonyl chloride (1.1 molar amounts) and triethylamine (2.2 molar amounts) at 0 °C (Scheme 1). A complex reaction mixture was obtained and the desired indolenine derivative **3a** was not isolated, whereas the same reaction of the *syn* isomer of **1a** gave only the *O*-sulfonylated oxime in 95% yield. As the intramolecular cyclization product, spiro indolenine **3a**, might have been readily hydrolyzed, the isolation of the cyclized product was attempted after the protection of an imino group. When pentafluorobenzoyl chloride⁶ was added to the reaction mixture, spirocyclic 2-chloroindolenine **4a**⁷ was obtained in 79% yield. In addition, quenching the acylation mixture with aqueous sodium bicarbonate in acetone for 20 h yielded the corresponding 2-hydroxy derivative **5a**.⁷

The formation of the diazaspicyclic compounds **4a** and **5a** indicates that the indole ring attacks the oxime nitrogen at the 3-position, affording unstable indolenine derivative **3a**. **4a** was obtained by the *N*-pentafluorobenzoylation of **3a** at the less hindered aldimine nitrogen.

a **1a**:MsCl:Et₃N:C₆F₅COCl = 1:1.1:2.2:1.05.b The reaction mixture was treated with NaHCO₃ (aq.) in acetone for 20 h after the pentafluorobenzoylation.

Scheme 1. Synthesis of diazaspicyclic **4a** and **5a** from *anti*-oxime **1a**.^a

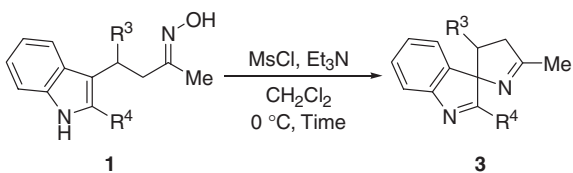
Some examples for the transformation of β -3-indolyl ketone oxime to spiro[indoline-3,2'-pyrrolidine] derivatives are shown in Table 1. Oximes **1b** and **1c** having alkyl substituents at the α - or β -position gave the 2-hydroxy cyclized products **5b** and **5c** in moderate yields, respectively (Entries 2 and 3).

Table 1. Transformation of 4-(3-indolyl)butan-2-one oximes **1** to spiro-cyclic 2-hydroxyindolines **5**^a

Entry	Oxime	R ¹	R ²	R ³	Product (Yield)
1 ^b	1a	H	H	H	5a (63%)
2 ^c	1b	Me	H	H	5b (72%)
3 ^b	1c	H	Me	Me	5c (74%)

a **1**:MsCl:Et₃N:C₆F₅COCl = 1:1.1:2.2:1.05.b NaHCO₃ (aq.) was added 4 h after the addition of C₆F₅COCl.c NaHCO₃ (aq.) was added after the extraction of the product obtained by the treatment of C₆F₅COCl.

When β -(2-methyl-3-indolyl) ketone oxime **1d** was treated with methanesulfonyl chloride and triethylamine, the cyclization also proceeded smoothly to yield azaspirocyclic indolenine **3d**, which was stable enough to be isolated in 95% yield by a column chromatography on Florisil (Table 2, Entry 1). Also in a similar cyclization of oxime **1e** having a *tert*-butoxycarbonyl group at the β -position of the oxime, 68% yield of the corresponding bisimine **3e**⁷ was obtained (Table 2, Entry 2).

Table 2. Conversion of 4-(3-indolyl)butan-2-one oximes **1** to spiroindolenine **3**


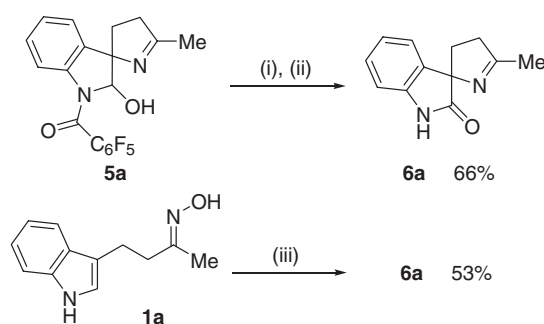
Entry	Oxime	Time	R ³	R ⁴	Product (Yield)
1	1d	1 h	H	Me	3d (95%) ^b
2	1e	6 h	<i>t</i> -BuO ₂ C	H	3e (68%) ^{b,c}

a 1:MsCl:Et₃N = 1:1.1:2.2.

b Isolated by column chromatography on Florisil.

c NMR yield (anthracene as an internal standard).

Spiro[pyrrolidine-2,3'-oxindole] derivatives are reported to have a antimicrobial and antifungal activity,^{ij} and were readily obtained from diazaspirocycles **5**. As shown in Scheme 2, treatment of **5a** with Dess–Martin periodinane and the successive removal of *N*-pentafluorobenzoyl group resulted in the formation of oxindole **6a**. In addition, it is noteworthy that **6a** was synthesized from oxime **1a** in one-pot procedure. After oxime **1a** was treated with methanesulfonyl chloride and triethylamine, excess manganese dioxide was added to the mixture, yielding **6a** in 53% yield.



Reagents: (i) Dess–Martin periodinane, CH₂Cl₂; (ii) NaOMe, MeOH, rt, 10 h; (iii) MsCl, 2Et₃N, 0 °C, 1 h, CH₂Cl₂ then MnO₂ (15 molar amounts), rt, overnight.

Scheme 2. Synthesis of spiro[pyrrolidine-2,3'-oxindole] derivative **6a** from **1a** or **5a**.

General experimental procedure is as follows (Scheme 1): To a dichloromethane (3 mL) solution of 4-(3-indolyl)butan-2-one oxime (**1a**) (0.30 mmol) and triethylamine (0.65 mmol) was added methanesulfonyl chloride (0.33 mmol) at 0 °C. After 1 h at 0 °C, the reaction mixture was treated with a dichloromethane (2 mL) solution of pentafluorobenzoyl chloride (0.31 mmol) and was stirred at room temperature for 4 h, followed by the addition of aqueous sodium bicarbonate and acetone. After 20 h with stirring, the organic materials were extracted with dichloromethane and dried over sodium sulfate. The solvent was removed in vacuo, and the crude products were purified by thin-layer chromatography (silica gel deactivated with triethylamine, hexane:ethyl acetate = 1:2) to afford 3',4'-dihydro-2-hydroxy-5'-methyl-1-pentafluorobenzoylspiro[indoline-3,2'-[2H]pyrrole] (**5a**) (75 mg, 63%).

This work was supported by the Grant-in-Aid for Scientific Research on Priority Areas (A) No. 412 “Exploitation of Multi-Element Cyclic Molecules” and the Grant-in-Aid for The 21st Century COE Program for Frontiers in Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

- a) H. Aridill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatangul, and S. Kanajun, *J. Chem. Soc., Chem. Commun.*, **1986**, 602. b) H. Aridill, M. J. R. Dorrity, R. Grigg, M.-S. Leon-Ming, J. F. Malone, V. Sridharan, and S. Thianpatangul, *Tetrahedron*, **46**, 6433 (1990). c) T. Coulter, R. Grigg, J. F. Malone, and V. Sridharan, *Tetrahedron Lett.*, **32**, 5417 (1991). d) D. Fokas, W. J. Ryan, D. S. Casebier, and D. L. Coffen, *Tetrahedron Lett.*, **39**, 2235 (1998). e) V. Nair, K. C. Sheela, N. P. Path, and G. K. Eigendorf, *Tetrahedron Lett.*, **41**, 6217 (2000). f) V. Nair, K. C. Sheela, and N. P. Rath, *Chem. Lett.*, **2000**, 980. g) A. A. Raj and R. Raghunathan, *Tetrahedron*, **57**, 10293 (2001). h) S. El-Ahl Abel-Aziz, *Heteroat. Chem.*, **13**, 324 (2002). i) A. K. Ganguly, N. Seah, V. Popov, C. H. Wang, R. Kuang, A. K. Saksena, B. N. Prammanik, T. M. Chan, and A. T. McPhail, *Tetrahedron Lett.*, **43**, 8981 (2002). j) A. A. Raj, R. Raghunathan, M. R. SrideviKumari, and N. Raman, *Bioorg. Med. Chem.*, **11**, 407 (2003).
- M. J. Kornet and A. P. Thio, *J. Med. Chem.*, **19**, 892 (1976).
- a) H. Kusama, Y. Yamashita, and K. Narasaka, *Chem. Lett.*, **1995**, 4. b) H. Kusama, K. Uchiyama, Y. Yamashita, and K. Narasaka, *Chem. Lett.*, **1995**, 715. c) H. Kusama, Y. Yamashita, K. Uchiyama, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **70**, 965 (1997). d) S. Mori, K. Uchiyama, Y. Hayashi, K. Narasaka, and E. Nakamura, *Chem. Lett.*, **1998**, 111. e) K. Uchiyama, M. Yoshida, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, **1998**, 607. f) M. Yoshida, K. Uchiyama, and K. Narasaka, *Heterocycles*, **52**, 681 (2000). g) M. Yoshida, M. Kitamura, and K. Narasaka, *Chem. Lett.*, **2002**, 144. h) M. Kitamura, T. Kikuchi, M. Yoshida, and K. Narasaka, *Synthesis*, **2003**, in press.
- For some recent examples, see: a) T. Okauchi, M. Itonaga, T. Minami, T. Owa, K. Kitoh, and H. Yoshino, *Org. Lett.*, **2**, 1485 (2000). b) K. B. Jensen, J. Thorhauge, R. G. Hazell, and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, **40**, 160 (2001). c) J. S. Yadav, S. Abraham, B. V. S. Reddy, and G. Sabitha, *Synthesis*, **2001**, 2165. d) M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, and A. Umani-Ronchi, *J. Org. Chem.*, **67**, 3700 (2002). e) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, and J. Wu, *J. Am. Chem. Soc.*, **125**, 10780 (2003).
- In this manuscript, *syn* and *anti* isomer of oxime derivatives are defined when the hydroxy group on the oxime nitrogen is oriented *syn* and *anti* to the nucleophilic moiety, respectively.
- Trapping of the **3a** with other electrophiles such as acetyl chloride, trifluoroacetic anhydride, benzyloxycarbonyl chloride, and *p*-toluenesulfonyl chloride gave the complex mixture of products.
- Compound **4a**, **5b**, and **3e** were obtained as a mixture of two diastereomers, while compound **5a** and **5c** were obtained as a single diastereomer. The stereochemistry of **5a–c** has not been determined.
- Yields of the oximes **1a–e**: **1a**, 95% (*anti:syn* = 3:1). **1b**, 92% (*anti:syn* = 3:1). **1c**, 96% (*anti:syn* = 4:1). **1d**, 95% (*anti:syn* = 3:1). **1e**, 95% (*anti:syn* = 7:2).