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

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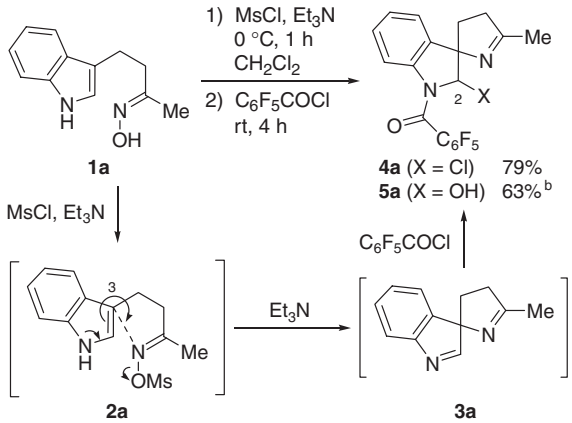
Spiro[indoline-3,2′-pyrrolidine] derivatives were prepared from β-3-indolyl ketone oximes by treatment with methanesulfonyl chloride and triethylamine via the bond formation between 3-position of the indole ring and oxime nitrogen. These diazaspirocycles were readily transformed to the corresponding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

Spiro[indoline-3,2′-pyrrolidine] derivatives have received much attention in the development of pharmaceutically active molecules. These diazaspirocyles are mostly synthesized by the 1,3-dipoloar 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 form 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 $InCl_3$-catalyzed reaction of indole and enones,[4c] followed by the oximation[8] of the resulting ketones. The *syn* and *anti* isomers[5] 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 chloride[6] was added to the reaction mixture, spirocyclic 2-chloroindoline **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 diazaspiro 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.

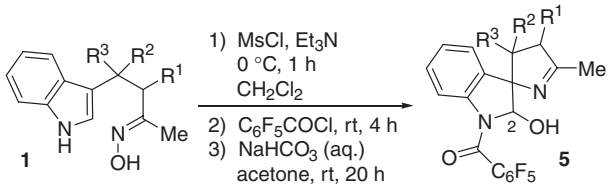


a **1a**:MsCl:Et_3N:C_6F_5COCl = 1:1.1:2.2:1.05.
b The reaction mixture was treated with $NaHCO_3$ (aq.) in acetone for 20 h after the pentafluorobenzoylation.

Scheme 1. Synthesis of diazaspirocycle **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[7] **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]

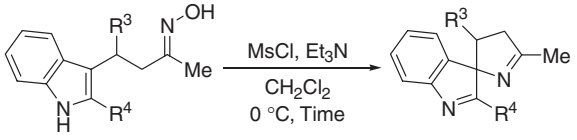


Entry	Oxime	R^1	R^2	R^3	Product (Yield)
1[b]	**1a**	H	H	H	**5a** (63%)
2[c]	**1b**	Me	H	H	**5b** (72%)
3[b]	**1c**	H	Me	Me	**5c** (74%)

a **1**:MsCl:Et_3N:C_6F_5COCl = 1:1.1:2.2:1.05.
b $NaHCO_3$ (aq.) was added 4 h after the addition of C_6F_5COCl.
c $NaHCO_3$ (aq.) was added after the extraction of the product obtained by the treatment of C_6F_5COCl.

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**

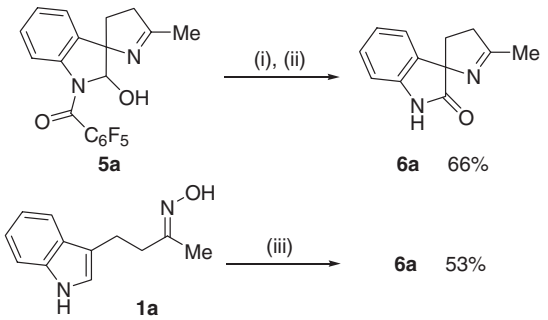


1 **3**

Entry	Oxime	Time	R^3	R^4	Product (Yield)
1	**1d**	1 h	H	Me	**3d** (95%)[b]
2	**1e**	6 h	*t*-BuO_2C	H	**3e** (68%)[b,c]

a **1**:MsCl:Et_3N = 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 acitivity,[1j] 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, CH_2Cl_2; (ii) NaOMe, MeOH, rt, 10 h; (iii) MsCl, $2Et_3N$, 0 °C, 1 h, CH_2Cl_2 then MnO_2 (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′-[2*H*]pyrrole] (**5a**) (75 mg, 63%).

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5 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.
6 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.
7 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.
8 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).

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