Synthesis of α-Carbolines from β-(3-Indolyl) Ketone *O*-2,4-Dinitrophenyloximes

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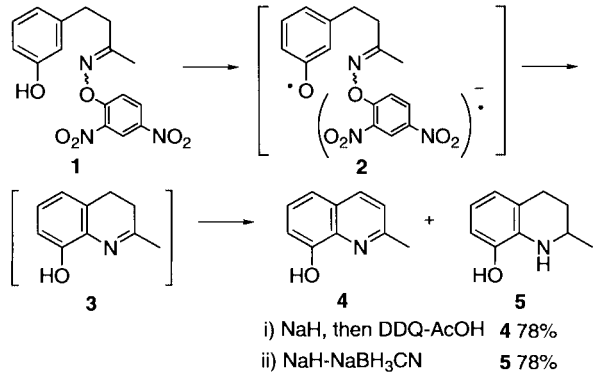
α-Carbolines are synthesized from β-(3-indolyl) ketone *O*-2,4-dinitrophenyloximes by the treatment with sodium hydride and sodium cyanoborohydride.

α-Carbolines have been received much attention due to their pharmacological activities, such as cytostatic and antitumor activity.[1] Much effort has been devoted to develop the preparative methods.[2] One of the representative strategies for the construction of α-carboline skeleton is the bond formation between C(4a)–C(4b) by the Graebe–Ullmann reaction[2] or the Fischer reaction.[2] These methods, however, exhibit low regioselectivity for constructing substituted indole moieties. Another representative method is pyridine ring formation starting from unstable 2-aminoindoles.[2] Some other approaches have been developed to overcome the drawbacks of these traditional methods; intramolecular Diels–Alder reaction of pyrazinone[3a] and 2-aminopyrimidine derivatives,[3b] intramolecular cross-coupling of 2-boryl(2-bromopyridyl)aniline,[3c] and 6π electron cyclization of indolyl 2-isocyanate intermediates.[3d] In this article, we would like to report a convenient method for the synthesis of α-carbolines by the cyclization of readily available β-(3-indolyl) ketone *O*-2,4-dinitrophenyloximes.[4]

Recently we have reported a preparative method of 8-qunolinols from 2-(*m*-hydroxyphenyl)ethyl ketone *O*-2,4-dinitrophenyloximes by electron transfer process.[5] For example, the treatment of 4-(*m*-hydroxyphenyl)butan-2-one *O*-2,4-dinitrophenyloxime (**1**) with sodium hydride and then with 2,3-dichloro-4,5-dicyano-*p*-benzoquinone (DDQ) yields 2-methyl-8-quinolinol (**4**). The tetrahydro derivative **5** is also prepared by the reaction with sodium hydride and sodium cyanoborohydride as shown in Scheme 1. In these reactions, single electron transfer occurs from phenolate moiety and/or NaH–$NaBH_3CN$ to 2,4-dinitrophenyl group, giving anion radical intermediates such as **2**. Then the nitrogen–oxygen bond of the aryloxyimino group cleaves with elimination of 2,4-dinitrophenolate and the cyclization occurs simultaneously to give 3,4-dihydro-8-quinolinol **3**.



Scheme 1. Synthesis of 8-quinolinol **4** and 1,2,3,4-tetrahydroquinolin-8-ol **5**.

Based on these findings, it was expected that β-(3-indolyl) ketone *O*-2,4-dinitrophenyloximes **6** might cyclize to α-dihydrocarbolines via similar anion radical intermediates. The cyclization of 4-(3-indolyl)butan-2-one 2,4-dinitrophenyloxime (**6a**)[4] did not proceed unexpectedly by the treatment with sodium hydride, whereas α-carboline **7a** was obtained in 40% yield when the reaction was carried out under the coexistence of 3,4-methylenedioxyphenol (sesamol)[6] (Table 1, entries 1 and 2) without tetrahydro-α-carboline. To prepare tetrahydro-α-carboline, the reaction was carried out under the combined use of NaH and $NaBH_3CN$. The reaction proceeded more smoothly, however, tetrahydro-α-carboline could not be obtained but **7a** was isolated in 60% yield (Table 1, entry 3)[7] with small amount of side products.[8] No cyclization occurred by the use of $NaBH_3CN$ in the absence of NaH and **6a** was almost recovered.

Although the mechanism is not explained clearly, the reaction may be initiated by the one electron reduction of the 2,4-dinitrophenyl moiety of **6a** with NaH–$NaBH_3CN$, as the synergistic effect of NaH and alcoholate was reported in a similar reduction of benzophenone.[9] The cyclization proceeds with elimination of dinitrophenolate to give α-dihydrocarboline, which is readily oxidized to α-carboline **7a** during the isolation.

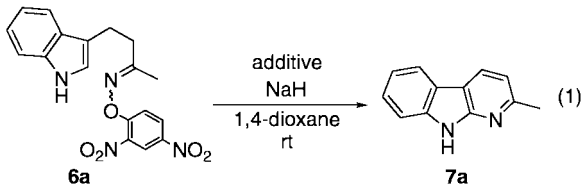
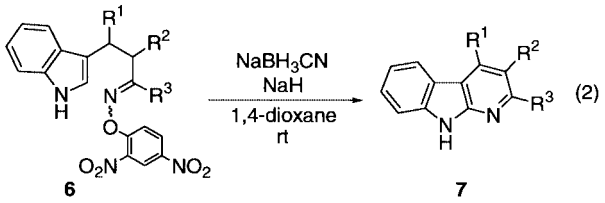


Table 1. Cyclization of 2,4-dinitrophenyloxime **6a**

Entry	Additive	Yeild/%
1	none	0
2	sesamol	40
3	$NaBH_3CN$	60

The transformation of some β-(3-indolyl) ketone *O*-2,4-dinitrophenyloxime derivatives **6** was attempted and the results are listed in Table 2. β-Substituted ketone *O*-2,4-dinitrophenyloxime **6b** was transformed to 2,4-dimethyl-α-carboline **7b** in 45% yield. Although α-substituted ketone oximes readily undergo the Beckmann rearrangement, oxime **6c** cyclized to give 9*H*-2,3-dimethylpyrido[2,3-*b*]indole (**7c**) in 45% yield without the Beckmann product.[10] As a model reaction toward the synthesis of 2-amino-α-carboline[11] which has high mutagenic activity toward *Salmonella typhimurium* was examined

the cyclization of 2,4-dinitrophenyloxime of α-keto ester. That is, 9*H*-2-ethoxycarbonylpyrido[2,3-*b*]indole (**7d**) was obtained from 2-*O*-2,4-dinitrophenyloxyimino-4-(3-indolyl)butanoic acid ethyl ester (**6d**) in 72% yield.



6 **7**

Table 2. Preparation of α-carbolines **7**

Oxime	R^1	R^2	R^3	Yield/%	α-Carboline
6a	H	H	CH_3	60	**7a**
6b	CH_3	H	CH_3	45	**7b**
6c	H	CH_3	CH_3	45	**7c**
6d	H	H	$CO_2C_2H_5$	72	**7d**

General experimental procedure is as follows (Table 2, entry 1): To a 1,4-dioxane (10 mL) suspension of sodium hydride (10 mmol) and sodium cyanoborohydride (5.0 mmol), was added a 1,4-dioxane (10 mL) solution of 4-(3-indolyl)butan-2-one *O*-2,4-dinitrophenyloxime (**6a**) (1.0 mmol) at room temperature. After the mixture was stirred for 12 h at room temperature, the reaction was quenched by adding water and the organic materials were extracted with diethyl ether and dried over potassium carbonate. After the solvent was removed in vacuo, the crude products were purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1) to afford 9*H*-2-methylpyrido[2,3-*b*]indole (**7a**) (0.60 mmol, 60%).

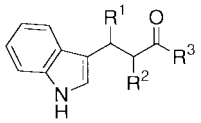
References and Notes

1 a) A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut, and C. Francisco, *J. Nat. Prod.*, **57**, 528 (1994). b) T. P. Blackburn, D. Bolton, I. T. Forbes, C. N. Johnson, R. T. Martin, D. R. Thomas, M. Thompson, and N. Upton, *Bioorg. Med. Chem. Lett.*, **4**, 279 (1994). c) C. Moquin-Pattey and M. Guyot, *Tetrahedron*, **45**, 3445 (1989).

2 A review article for the preparation of α-carbolines: A. A. Semenov and V. V. Tolstikhina, *Chem. Heterocycl. Compd. (English transl.)*, **1984**, 345.

3 a) A. Tahri, K. J. Buysens, E. V. Van der Eycken, D. M. Vandenberghe, and G. J. Hoornaert, *Tetrahedron*, **54**, 13211 (1998). b) W. A. W. Stolle, A. T. M. Marcelis, A. Koetsier, and H. C. van der Plas, *Tetrahedron*, **45**, 6511 (1989). c) P. Rocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron*, **49**, 49 (1993). d) S. Achab, M. Guyot, and P. Potier, *Tetrahedron Lett.*, **36**, 2615 (1995).

4 Preparation of the starting materials: The *O*-2,4-dinitrophenyloximes **6** were synthesized from the corresponding β-(3-indolyl) ketones **6'** by the reported procedure; M. J. Miller and G. M. Loudon, *J. Org. Chem.*, **40**, 126 (1975). Ketones **6a'** and **6b'** were prepared by the reported procedure; J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957). β-Substituted ketone **6c'** was prepared by aldol condensation of 3-indolecarbaldehyde and acetone followed by 1,4-addition of methylcuprate. Keto ester **6d'** was prepared by the reported procedure; D. G. Hangauer, Jr., *Tetrahedron Lett.*, **22**, 2439 (1981).



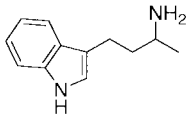
6'

5 a) K. Uchiyama, Y. Hayashi, and K. Narasaka, *Synlett*, **1997**, 445. b) A. Ono, K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem Lett.*, **1998**, 437. c) K. Uchiyama, A. Ono, Y. Hayashi, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **71**, 2945 (1998).

6 K. Uchiyama, Y. Hayashi, and K. Narasaka, *Chem. Lett.*, **1998**, 1261.

7 In the preparation of 8-quinolinols, **4** and **5**, the cyclization is also accelerated by the combined use of NaH and $NaBH_3CN$ as compared to the treatment with NaH alone.

8 Side products are about 10% of ketone **6a'** and a trace amount of amine **8a**.



8a

9 P. Caubere, *Angew. Chem., Int. Ed. Engl.*, **22**, 599 (1983).

10 a) K. I. Kuchkova, A. A. Semenov, and I. V. Terent'eva, *Khim. Geterotsikl. Soedin.*, **1970**, 197. b) K. I. Kuchkova, E. P. Styngach, F. Sh. Rivilis, N. M. Frolova, and A. A. Semenov, *Khim. Geterotsikl. Soedin.*, **1976**, 386.

11 D. Yoshida, T. Matsumoto, R. Yoshimura, and T. Matsuzaki, *Biochem. Biophys. Res. Commun.*, **83**, 915 (1978).