Tetrahedron Letters,Vol.24,No.12,pp 1259-1262,1983 0040-4039/83/121259-04$03.00/0
Printed in Great Britain 

# A GENERAL METHOD FOR THE SYNTHESIS OF INDOLES BEARING A VARIETY OF SUBSTITUENTS AT THE β-POSITION, AND ITS APPLICATION TO THE SYNTHESIS OF L-TRYPTOPHAN[1]

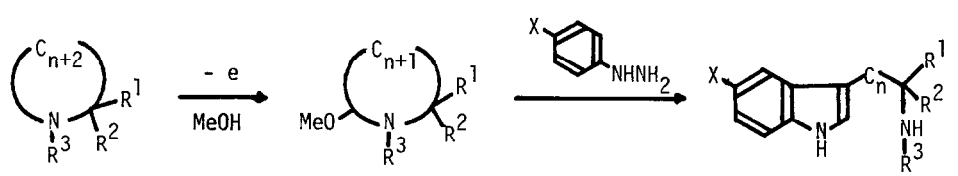
Tatsuya Shono,* Yoshihiro Matsumura, and Takenobu Kanazawa
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, yoshida, Sakyo, Kyoto 606, Japan

A general synthetic method of β-substituted indoles such as indoleacetic acid, tryptamine and L-tryptophan has been exploited utilizing α-methoxylated amides, lactams, a carbamate, and sulfonamides, easily obtainable by an electrochemical method, as key intermediates.

Because of their biological importance, and potentiality as key intermediates in the synthesis of more complicated indole alkaloids, the synthesis of indoles bearing an aminoalkyl or carboxyalkyl group on the β-position has attracted much interest.[2,3] Most of the methods hitherto exploited, however, often require many steps and are not necessarily accepted as convenient general methods.

We report herein a new general and efficient method for the synthesis of indoles substituted with an aminoalkyl group at the β-position. Our process shown in Scheme 1 involves two steps, that is, (i) the anodic preparation[4] of α-methoxylated amides **2a**,**c**,**d**,**h**, lactams **2g**,**i**, a carbamate **2b**, and sulfonamides **2e**,**f**, and (ii) the reaction of **2** with arylhydrazines. Although the synthesis of indoles through the reaction of arylhydrazines with aldehydes has been well known as the Fischer's method,[5] the synthesis of aminoaldehydes being necessarily for the synthesis of **3** is not always facile.[6] Our method clearly shows that the synthesis of equivalents for such aminoaldehydes is easily achievable from cyclic amine derivatives **1** by our anodic method, and that the equivalents work indeed nicely in the reaction with arylhydrazines.

Scheme 1




**1a-i** **2a-i** **3a-m**

The synthesis of tryptamine is described below as a typical example. The anodic oxidation of *N*-benzoylpyrrolidine (**1a**) in methanol yielded the α-methoxylated amide **2a** in 80% yield.

Table I. Isolated Yields (%) of **2a-i** and **3a-m**

| Run | 1 | n | $R^1$ | $R^2$ | $R^3$ | X-⟨⟩-$NHNH_2$ X | α-Methoxylated Compound **2**[a] | β-Substituted Indole **3**[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | 1 | H | H | COPh | H | **2a** (80) | **3a** (76)[c] |
| 2 | **1b** | 1 | H | H | $CO_2CH_3$ | H | **2b** (80) | **3b** (41)[c] |
| 3 | **1c** | 1 | H | H | $COCH_3$ | H | **2c** (45) | **3c** (60)[d] |
| 4 | **1d** | 1 | H | $CO_2CH_3$ | COPh | H | **2d** (94) | **3d** (74)[e] |
| 5 | **1e** | 1 | H | H | Ts | H | **2e** (78) | **3e** (63)[e] |
| 6 | **1f** | 1 | H | $CO_2CH_3$ | Ts | H | **2f** (83) | **3f** (73)[e] |
| 7 | **1g** | 1 | O | | H | H | **2g** (67) | **3g** (40)[e] |
| 8 | **1h** | 2 | H | H | COPh | H | **2h** (97) | **3h** (79)[e] |
| 9 | **1i** | 3 | O | | H | H | **2i** (94) | **3i** (70)[d] |
| 10 | | | **1a** | | | $OCH_3$ | **2a** | **3j** (87)[f] |
| 11 | | | **1d** | | | Br | **2d** | **3k** (40)[g] |
| 12 | | | **1c** | | | $OCH_3$ | **2c** | **3L** (32)[h] |
| 13 | | | **1f** | | | Br | **2f** | **3m** (63)[g] |

[a] Solvent; methanol. Supporting electrolyte; $Et_4NOTs$. Electrodes; carbon rods. Electricity passed; 2.1 - 10 $F$/mol.

[b] The conditions of the reaction of **2** with arylhydrazines; reflux under nitrogen atmosphere for 1.5 - 5 h.

[c] Xylene - $ZnCl_2$ - Arylhydrazines.

[d] AcOEt - Xylene (1 : 2 ) - $ZnCl_2$ - Arylhydrazines.

[e] 1,2-Dichloroethane-1,1,2,2-tetrachloroethane (1 : 1) - $ZnCl_2$ - Arylhydrazines.

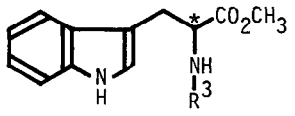
[f] AcOH - EtOH - $H_2O$ (25 : 35 : 40) - Arylhydrazine hydrochlorides.

[g] AcOH - Arylhydrazine hydrochlorides.

[h] AcOH - $H_2O$ (25 : 75) - Arylhydrazine hydrochlorides.

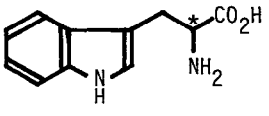
Refluxing a solution of **2a** (2 mmol) and phenylhydrazine (2.4 mmol) in xylene (15 ml) in the presence of anhydrous zinc chloride (2.4 mmol) for 1.5 h afforded **3a** (76%), which was easily converted by hydrolysis with sodium hydroxide in aqueous ethylene glycol to tryptamine in 82% yield. Results are summarized in Table I.

Furthermore, this method is applicable to the preparation of L-tryptophan[3e] from L-proline without losing the optical purity of L-proline (eq. 1). Thus, **3d** and **3f** were prepared from **1d** and **1f** in the yields shown in Table I, respectively. The conversion of **3f** to L-tryptophan was achieved by the electrochemical reduction[7] of **3f** in methanol containing $Me_4NCl$ followed by hydrolysis of the resulting amino ester (52% overall yield), whereas the hydrolysis of **3d** with aqueous potassium hydroxide resulted in the formation of racemic tryptophan[3d] in 70% yield.



**3d**, $R^3$ = COPh
**3f**, $R^3$ = Ts

**3f** → 1) $Me_4NCl$, + 2e; MeOH, Pb cathode, Pt anode; 2) $^-OH$



L-tryptophan
52%
$[\alpha]_D^{20}$ -33.5° ($H_2O$)
optical purity, 95%

(1)

As exemplified by the successful synthesis of a variety of important indoles such as tryptamine, indoleacetic acid amide (**3g**),[8] indolebutyric acid amide (**3i**),[8b] L-tryptophan[3e] and melatonine (**3L**),[9] this method possesses high potentiality in the synthesis of β-substituted indoles.

Acknowledgment. T.S. wishes to thank the Yamada Science Foundation for supporting this work, and Y.M. wishes to thank the Ministry of Education, Science, and Culture, Japan, for Grant-in-Aid for Scientific Research (B) (No. 57470066).

## References and Notes

(1) Electroorganic Chemistry. 69.

(2) Some of the typical reviews;

(a) J. P. Kutney, "The Total Synthesis of Natural Products", ed. by J. ApSimon, Wiley-Interscience, New York (1977), Vol. 3, p. 274.

(b) "Indoles", ed. by W. J. Houlihan, Wiley-Interscience, New York (1972), Parts 1 and 2, and (1979), Part 3.

(3) Some of the recent synthesis of indoles;

(a) M. Mori, K. Chiba, and Y. Ban, *Tetrahedron Lett.*, **1977**, 1037.

(b) Y. Ito, K. Kobayashi, and T. Saegusa, *J. Org. Chem.*, **44**, 2030 (1979).

(c) J. T. Carlock, J. S. Bradshaw, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **42**, 1883 (1977).
(d) U. Hengartner, A. D. Batcho, J. F. Blout, W. Leimgruber, M. E. Larscheid, and J. W. Scott, *J. Org. Chem.*, **44**, 3748 (1979).
(e) U. Hengartner, D. Valentine, Jr., K. K. Johnson, M. E. Larscheid, F. Pigott, F. Scheidl, J. W. Scott, R. C. Sun, J. M. Townsend, and T. H. Williams, *J. Org. Chem.*, **44**, 3741 (1979).
(f) Y. Ito, K. Kobayashi, and T. Saegusa, *Tetrahedron Lett.*, **1979**, 1039.
(g) I. Fleming and M. Woolias, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 829.
(h) H. Person, M. D. A. Pardo, and A. Founcaud, *Tetrahedron Lett.*, **21**, 281 (1980).
(i) J. KöKösi, I. Herwecz, G. Szász, and Z. Mészáros, *Tetrahedron Lett.*, **22**, 4861 (1981).
(4) (a) S. D. Ross, M. Finkelstein, and R. C. Peterson, *J. Org. Chem.*, **31**, 133 (1966).
(b) T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, **97**, 4264 (1975).
(c) M. Mitzlaff, K. Warning, and H. Jensen, *Justus Liebigs Ann. Chem.*, **1978**, 1713.
(d) L. Eberson, J. Hlavaty, L. Jönson, K. Nyberg, R. Servin, H. Sternerup, and L. -G. Wistrand, *Acta Chem. Scand.*, **B33**, 133 (1979).
(e) T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S.-i. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, **104** (1982), in press.
(5) B. Robinson, *Chem. Rev.*, **69**, 227 (1969).
(6) O. A. Moe, and D. T. Warner, *J. Am. Chem. Soc.*, **70**, 2765 (1948).
(7) (a) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 3462 (1965).
(b) T. Iwasaki, K. Matsumoto, M. Matsuoka, T. Takahashi, K. Okumura, *Bull. Chem. Soc. Jpn.*, **46**, 852 (1973).
(8) (a) H. Feichtinger, *Chem. Ber.*, **95**, 2238 (1962).
(b) D. G. Crosby, J. B. Boyd, and H. E. Johnson, *J. Org. Chem.*, **25**, 1826 (1960).
(9) J. Szmuskzovicz, W. C. Anthony, and R. V. Heinzelman, *J. Org. Chem.*, **25**, 857 (1960).

(Received in Japan 11 December 1982)