Novel Synthetic Method for 3-Aminoindolizine Derivatives from 2-Formyl-1,4-dihydropyridines

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Since 4-aryl-1,4-dihydro-3,5-pyridinedicarboxylates were found to be highly effective calcium antagonists about twenty years ago [1, 2], many dihydropyridines were investigated and have been studied and developed as clinically useful against cardiovascular diseases or hypertension [3, 4]. From this point of view we are interested in preparation and reactions of new 2-substituted 1,4-dihydropyridines.

2-Formyl-1,4-dihydropyridine is readily obtainable from the hydrolysis of 2-dimethoxymethyl-1,4-dihydropyridine, which is prepared by the modified Hantzsch method using three reactants: aldehyde, aminocrotonate, and alkyl 4,4-dimethoxyacetoacetate. It is a very interesting and useful species because of its unique structure and its versatility to functionalized nitrogen-bridged heterocycles. For example, 3-aminoindolizine derivatives, which could not be obtained until now, were synthesized in good yields *via* the Knoevenagel condensation of 2-formyl-1,4-dihydropyridines with 3-phenyl-3-oxopropanenitrile and the following cyclization of the corresponding 2-vinyl-substituted 1,4-dihydropyridine derivatives.

In this paper, we wish to introduce a new procedure for the preparation of some 3-aminoindolizine derivatives *via* the key intermediates, 2-formyl-1,4-dihydropyridines.

2-Formyl-1,4-dihydropyridines *Ia—Ic* (Scheme 1) were prepared as described in papers of *Satoh et al.* [5]. Treatment of 2-formyl-1,4-dihydropyridine derivatives with 3-phenyl-3-oxopropanenitrile and a catalytic amount of piperidine in anhydrous ethanol at room temperature gave the corresponding 2-vinyl-substituted 1,4-dihydropyridine derivatives *IIa—IIc* in 78—90 % yields. Reactions were complete in 3—4 h and products were isolated by crystallization from ethanol at 0 °C. When the reactions were carried out at reflux temperature of ethanol, 3-aminoindolizine derivatives *IIIa—IIIc* were isolated in 72—93 % yields. Compounds *IIa—IIc* are stable at normal conditions ($\theta < 60$ °C), at higher temperature they smoothly cyclize to 3-aminoindolizine derivatives.

The structural elucidation of 2-vinyl-substituted 1,4-dihydropyridines *IIa—IIc* and 3-aminoindolizine derivatives *IIIa—IIIc* was accomplished by NMR and IR spectral analyses. The ^{1}H NMR spectra of 2-vinyl-substituted 1,4-dihydropyridine derivatives *IIa—IIc* showed proton signal at $\delta = 4.8$—5.8, which is characteristic of the proton at C-4 of the 1,4-dihydropyridine ring [6, 7], but is absent in spectra of 3-aminoindolizine derivatives *IIIa—IIIc*. The IR spectra exhibited the presence of cyano group in 2-vinyl-substituted 1,4-dihydropyridine derivatives *IIa—IIc* at $\tilde{\nu} = 2150$—2250 cm^{-1} and its absence in 3-aminoindolizine derivatives *IIIa—IIIc*. The structural assignment was also supported by the ^{13}C NMR spectral data: the presence of cyano group in *IIa—IIc* was indicated by the isolated signal at $\delta = 114$—116.

All new compounds depicted in Scheme 1 were characterized spectroscopically. Data are specified for representative compounds *IIb* and *IIIb*; *IIb*: m.p. = 176—178 °C; ^{1}H NMR spectrum ($DMSO_4$-d_6), δ: 0.95 and 1.15 (d, d, 6H, $CH(C\underline{H}_3)_2$, $J = 6.2$ Hz), 2.22 (s, 3H, C-6—CH_3), 3.67 (s, 3H, OCH_3), 4.75 (m, 1H, $C\underline{H}(CH_3)_2$, $J = 6.2$ Hz), 5.11 (s, 1H, C-4—H), 7.56—8.11 (m, 9H, H_{arom}), 8.12 (s, 1H, =C—H), 8.43 (s, 1H, NH). IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 3348 ν(NH), 2228 ν(CN), 1699 and 1676 ν(C=O), 1651 ν(C=C). For $C_{28}H_{25}N_3O_7$ ($M_r = 515.52$) w_i(calc.): 65.24 % C, 4.89

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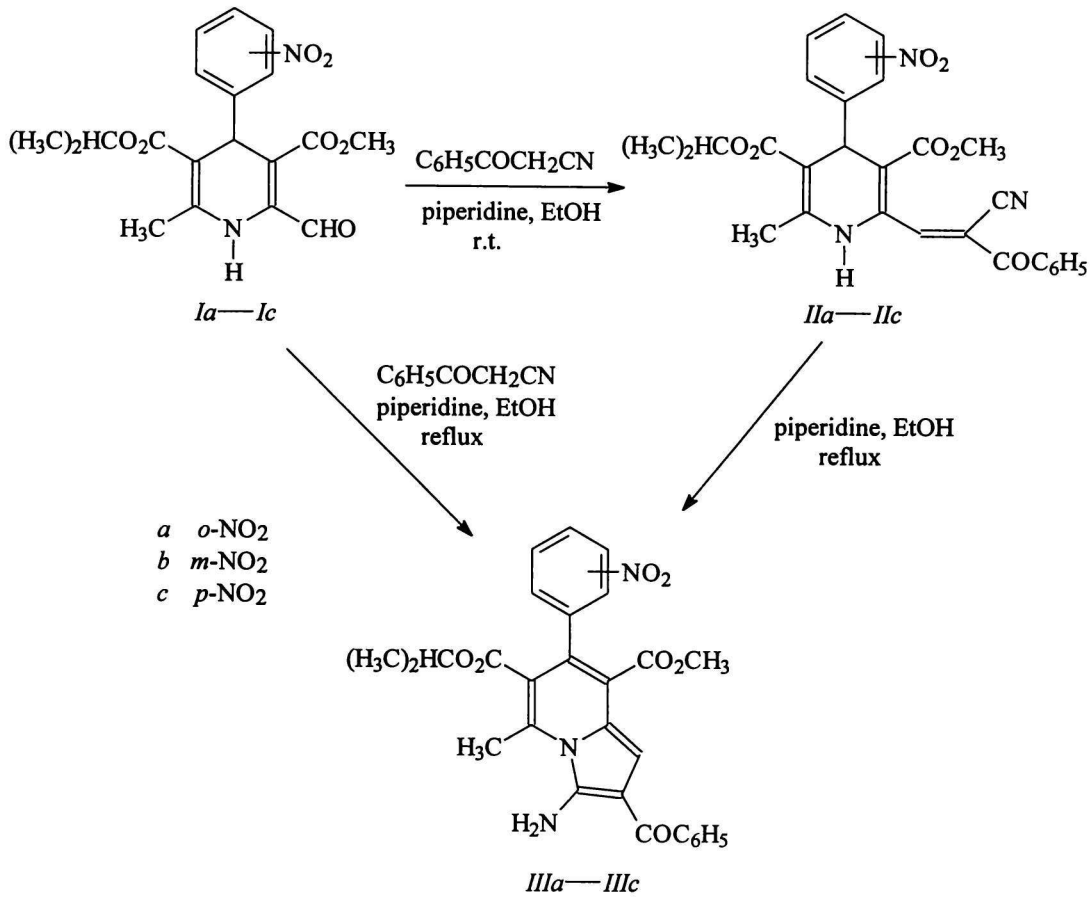

Scheme 1

% H, 8.15 % N; w_i(found): 65.32 % C, 5.09 % H, 8.16 % N. *IIIb*: m.p. = 158—160 °C, ^{1}H NMR spectrum (500 MHz, $CDCl_3$, TMS), δ: 0.96 (d, 6H, $(C\underline{H}_3)_2CH$, J = 6.3 Hz), 2.94 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 4.80 (m, 1H, $(CH_3)_2C\underline{H}$, J = 6.3 Hz), 6.71 (s, 1H, C-1—H), 7.27—8.14 (m, 9H, H_{arom}), IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 3501 ν(NH), 1728 and 1717 ν(C=O), 1620 ν(C=C). For $C_{28}H_{25}N_3O_7$ (M_r = 515.52) w_i(calc.): 65.24 % C, 4.89 % H, 8.15 % N; w_i(found): 65.48 % C, 4.99 % H, 8.23 % N.

In summary, we developed a novel synthetic method for 3-aminoindolizine derivatives from 2-formyl-1,4-dihydropyridines. Our work to elucidate the reaction mechanism is in progress.

REFERENCES

1. Bossert, F. and Vater, W., *Naturwissenschaften 58*, 578 (1971).
2. Goldmann, S. and Stoltefuss, J. *Angew. Chem., Int. Ed. 20*, 762 (1991).
3. Towart, R. and Wehinger, E., *Arzneim.-Forsch. 32* (I), 338 (1982).
4. Tamazawa, T., Arima, H., Kojima, T. Isomura, Y., Okuda, M., Fujita, S., Furaya, T., Takenaka, T., Inagaki, O., and Terai, M., *J. Med. Chem. 29*, 2304 (1986).
5. Satoh, Y., Ichihashi, M., and Okumura, K., *Chem. Pharm. Bull. 39*, 3189 (1991).
6. Collie, J. N., *Liebigs Ann. Chem. 226*, 294 (1884).
7. Marchalín, Š. and Kuthan, J. *Collect. Czech. Chem. Commun. 48*, 3123 (1983).

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