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Synthesis of Fused Quinolizine Derivatives by Condensation of Cyclic Schiff Bases with β-Keto Esters

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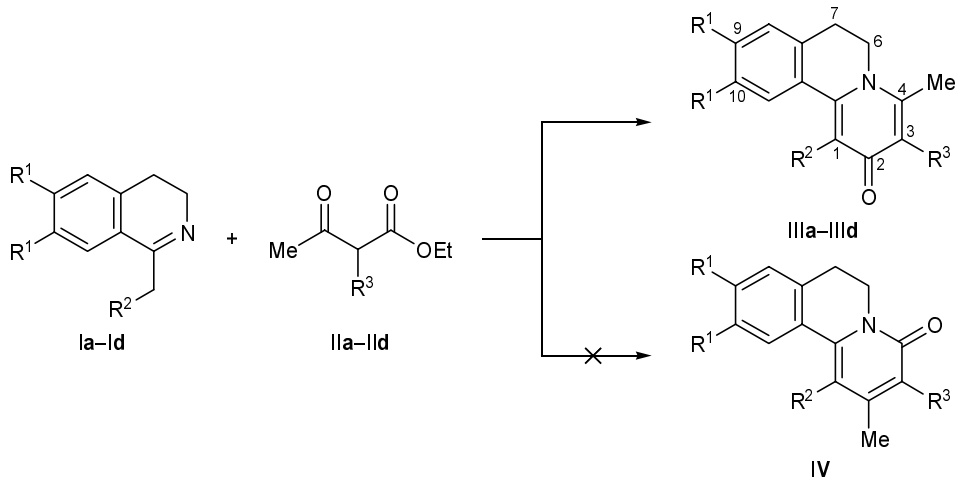
Abstract—A new procedure has been developed for the synthesis of fused nitrogen-containing heterocycles having a bridgehead nitrogen atom via condensation of cyclic Schiff bases with β-keto esters.

Fused nitrogen-containing heterocycles are structural fragments of many natural compounds and are important for various vital processes [1–3]. These compounds are also important for medicine and biotechnology from both theoretical and practical viewpoints [4]. Six-membered nitrogen-containing heterocycles (azines) attract interest as synthons [5] and final products for technical applications, e.g., as dyes [6]. Recent progress in the chemistry of nitrogen-containing heterocycles is largely determined by the development of methods for building up their molecular skeletons [7–9]. Despite a long period of research in this field of heterocyclic chemistry (which has started as early as at the end of the XIXth century [10]), its potential is now far from being exhausted, as follows from the recent achievements [7–9, 11–13]. One of the most fruitful lines includes studies on reactions of Schiff bases with carbonyl, β-dicarbonyl, and β,β'-tricarbonyl compounds and the corresponding enol derivatives [11–13].

While studying approaches to building up fused nitrogen-containing heterocycles via condensation of Schiff bases with derivatives of carbonyl compounds, we discovered a new reaction which may be referred to as Schiff base–β-keto ester cyclocondensation. This reaction makes it possible to append in one step a 4-oxopyridine fragment to a Schiff base and provides a very simple and convenient synthetic route to fused

Scheme 1.



I, **III**, R^1 = H (**a**, **b**), MeO (**c**, **d**); R^2 = H (**a**, **c**), Me (**b**, **d**); **II**, **III**, R^3 = Me (**a**), $PhCH_2$ (**b**), *i*-Bu (**c**), $MeCOCH_2CH_2$ (**d**).

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nitrogen-containing heterocycles having a bridgehead nitrogen atom.

By reaction of Schiff bases **Ia**–**Id** with β-keto esters **IIa**–**IId** on heating in an inert atmosphere (argon, nitrogen) we obtained pyrido[2,1-*a*]isoquinoline derivatives **IIIa**–**IIId** (Scheme 1). The structure of the products was consistent with their spectral parameters. No alternative 2-oxopyridine derivatives **IV** were detected in the reaction mixtures, indicating high regioselectivity of these reactions. The reactions in high-boiling (bp >100°C) organic solvents such as toluene or xylene require a longer time, but the yield and purity of the products change insignificantly.

The structure of compounds **IIIa**–**IIId** was confirmed by the spectral data. Their IR spectra contained strong absorption bands at 1585–1580 cm^{-1} which, in keeping with the data of [14–16], should be assigned to stretching vibrations of the carbonyl group in the pyridine ring. Medium-intensity and weak bands in the region 1630–1590 cm^{-1} correspond to vibrations of C=C bonds in the pyridine ring [14], and strong bands at 1565–1520 and 1512–1480 cm^{-1} originate from vibrations of aromatic carbon–carbon bonds [17].

The UV spectra of **IIIa**–**IIId** are characterized by the presence of two absorption bands at 257–269 and 281–308 nm, which is consistent with published data [18]. In addition, compounds **IIIc** and **IIId** displayed medium-intensity bands at λ 240 nm due to electron transitions in the methoxy-substituted benzene rings. In the mass spectra of all compounds **III**, we observed peaks from the corresponding molecular ions, $[M + 1]^+$ and $[M - 1]^+$, and fragment ions.

The number and position of signals in the ^{13}C NMR spectra correspond to the assumed structures. The ^1H NMR spectra of **IIIa**–**IIId** contained two-proton triplets from the methylene protons on C^6 and C^7 (δ 3.91–4.09 and 2.90–3.06 ppm, respectively) and three-proton singlets from the 4-methyl groups at δ 2.40–2.46 ppm. The spectra of **IIIc** and **IIId** also contained resonance signals from protons in the methoxy groups on C^9 and C^{10} in the isoquinoline fragment (δ 3.89-3.95 ppm) and other signals.

The structure of compounds **III** was finally confirmed by the NOE spectra [19]. Compound **IIIa** displayed direct and reverse coupling between 11-H (δ 7.75 ppm) and 1-H (δ 6.22 ppm), as well as between 6-H (δ 4.09 ppm) and 4-CH_3 (δ 2.43 ppm). On the other hand, no coupling was observed between protons resonating at δ 6.22 and 2.43 ppm, which could be assigned to structure **IV**. Likewise, compound **IIIb** revealed direct and reverse coupling between 11-H (δ 7.64 ppm) and 1-CH_3 (δ 2.36 ppm) and between 6-H (δ 3.91 ppm) and 4-CH_3 (δ 2.40 ppm). Coupling between protons in the methyl group (δ 2.36 ppm) and methylene unit (δ 4.11 ppm) of the benzyl substituent (which should occur in structure **IV**) was not detected. Thus the above spectral data unambiguously indicate formation of derivatives **III** with the carbonyl group in the γ-position of the pyridine ring rather than α-pyridinone derivatives **IV**.

Pyrido[2,1-*a*]isoquinolines **IIIa**–**IIId** are crystalline substances which melt at a high temperature, as a rule wihtout decomposition. They are moderately soluble in halogenated hydrocarbons and alcohols and poorly soluble in ethers, esters, tetrahydrofuran, dioxane, and water. Compounds **IIIa**–**IIId** crystallized from water-containing solvents mainly as crystal hydrates. The yields of compounds **IIIa**–**IIId** isolated as analytically pure substances were 67–93%; therefore, the described reaction may be recommended as preparative route to fused azines having a bridgehead nitrogen atom.

EXPERIMENTAL

The progress of reactions and the purity of compounds **IIIa**–**IIId** were monitored by TLC on Silufol UV-254 plates using chloroform–methanol (8.5:1.5) as eluent and by gas chromatography–mass spectrometry on an HP 5890/5972 GC–MS system (HP-5MS quartz capillary column, 30 m × 0.25 mm × 0.25 μm; carrier gas helium, flow rate 0.7–1 ml/min; injector temperature 250°C; oven temperature programming from 40 to 300°C at a rate of 6 deg/min; electron impact, 70 eV). The melting points were determined on a Boetius melting point apparatus. The IR spectra were recorded in KBr on a UR-20 spectrometer. The UV spectra were measured on a Specord M-400 spectrophotometer from solutions in ethanol. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-200 instrument at 200 MHz for ^1H and 90.53 MHz for ^{13}C from solutions in $CDCl_3$ using TMS as internal reference.

1-Alkyl-3,4-dihydroisoquinolines **Ia**–**Id** were synthesized by the Bischler–Napieralski reaction [10, 20] by cyclodehydration of the corresponding phenethylamides with polyphosphoric acid (compounds **Ia** and **Ib**) or phosphoryl chloride (**Ic** and **Id**). Acetoacetates **IIa**–**IIc** were prepared by alkylation of ethyl acetoacetate sodium salt [21]. Compound **IId** was obtained by the Michael addition of ethyl acetoacetate to methyl vinyl ketone [21].

3,4-Dimethyl-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (IIIa). A mixture of 1.45 g (10 mmol) of isoquinoline **Ia** and 2.1 ml (15 mmol) of ethyl 2-methyl-3-oxobutanoate (**IIa**) was heated for 4.5 h at 140–160°C under argon. The mixture was diluted with 70% alcohol and was left overnight at 5°C. The precipitate was filtered off and treated with charcoal (OU-B) in boiling methanol. The mixture was filtered through 7 g of silica gel (5–40 μm, Chemapol), the filtrate was evaporated, and the residue was recrystallized from 70% alcohol to obtain pyrido[2,1-*a*]-isoquinoline **IIIa** as crystal hydrate with one molecule of water (**V**). Attempts to remove crystal water by drying over P_2O_5 under reduced pressure at elevated temperature (80–145°C) resulted in tarring. Yield of **V** 2.26 g (93%), mp 149–154°C. IR spectrum, ν, cm^{-1}: 3550–3200, 3100–2830, 1628, 1585, 1565–1520, 1493, 1349, 1311, 1270, 1252, 1228, 1192, 1180, 1093, 940, 874, 862, 773. UV spectrum, λ_{max}, nm (logε): 269 (4.57), 281 (4.23); λ_{min}, nm (logε): 229.7 (4.01), 269 (4.15). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 s (3H, 3-Me), 1.90 s (2H, H_2O), 2.43 s (3H, 4-Me), 3.06 t (2H, 7-H, *J* = 6.5), 4.09 t (2H, 6-H, *J* = 6.5), 6.22 s (1H, 1-H), 7.24 m (1H, 8-H), 7.41 m (2H, 9-H, 10-H), 7.75 m (1H, 11-H). Found, %: C 73.96; H 7.07; N 5.64. M^+ 225.15. $C_{15}H_{15}NO$. Calculated for $C_{15}H_{15}NO\cdot H_2O$, %: C 74.05; H 7.04; N 5.76. *M* 243.30.

By heating of crystal hydrate **V** for 1.5 h over molecular sieves (4 Å) and subsequent crystallization from anhydrous alcohol we isolated pyrido[2,1-*a*]isoquinoline **IIIa** as weakly colored pale pink prisms with mp 226–227°C. IR spectrum, ν, cm^{-1}: 3100–2820, 1625, 1581, 1550, 1530, 1496, 1334, 1256, 1231, 1191, 875, 864, 784. UV spectrum, λ_{max}, nm (logε): 269.1 (4.56), 280.9 (4.19); λ_{min}, nm (logε): 229.4 (3.98), 269.1 (4.19). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 s (3H, 3-Me), 2.45 s (3H, 4-Me), 3.06 t (2H, 7-H, *J* = 6.0), 4.08 t (2H, 6-H, *J* = 6.0), 6.20 s (1H, 1-H), 7.25 m (1H, 8-H), 7.38 m (2H, 9-H, 10-H), 7.74 m (1H, 11-H). Mass spectrum, *m*/*z* (I_{rel}, %): 226.15 (8.28) $[M + 1]^+$, 225.15 (57.22) $[M]^+$, 224.15 (100) $[M - 1]^+$, 210.10 (2.33), 197.15 (11.32), 196.15 (25.01), 194.15 (5.23), 182.05 (5.74), 181.15 (7.89), 180.15 (9.68), 168.10 (2.14), 167.10 (4.24), 151.95 (2.93), 128 (4.71), 127 (3.31), 115 (11.36), 98.45 (6.77), 97.65 (2.59), 90.25 (4.62), 89.05 (3.37), 83.50 (5.16), 77 (4.60), 76 (2.07), 62.95 (3.34), 52.95 (2.69), 50.95 (3.98). Found, %: C 80.03; H 6.64; N 6.07. $C_{15}H_{15}NO$. Calculated, %: C 79.97; H 6.71; N 6.22. *M* 225.29.

3-Benzyl-1,4-dimethyl-6,7-dihydro-2*H*-pyrido-[2,1-*a*]isoquinolin-2-one (IIIb). A mixture of 0.8 g (5 mmol) of isoquinoline **Ib** and 1.6 ml (7.5 mmol) of 2-benzyl-3-oxobutanoate (**IIb**) was heated for 8.5 h at 160–180°C under argon. The mixture was dissolved in chloroform and subjected to flash chromatography [22] on 10 g of silica gel (5–40 μm, Chemapol) using chloroform–methanol (8.5:1.5) as eluent. The eluate was evaporated, and the residue was dried at 110°C under reduced pressure over P_2O_5 and recrystallized from anhydrous alcohol to obtain pyrido[2,1-*a*]isoquinoline **IIIb** as pale yellow crystals. Yield 1.2 g (75.9%), mp 146–148°C. IR spectrum, ν, cm^{-1}: 3100–2830, 1620–1600, 1580, 1560–1540, 1500–1480, 1454, 1425, 1376, 1257, 1184, 770, 750, 740, 704. UV spectrum, λ_{max}, nm (logε): 208 (4.58), 257.2 (4.60), 285.4 (4.20); λ_{min}, nm (logε): 233.1 (4.10), 271.4 (4.17). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 s (3H, 1-Me), 2.40 s (3H, 4-Me), 2.94 t (2H, 7-H, *J* = 6.0), 3.91 t (2H, 6-H, *J* = 6.0), 4.11 s (2H, 14-H), 7.18 m (1H, 8-H), 7.24–7.44 m (5H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 7.64 m (1H, 11-H). Found, %: C 83.67; H 6.65; N 4.36. $[M]^+$ 315. $C_{22}H_{21}NO$. Calculated, %: C 83.78; H 6.71; N 4.44. *M* 315.41.

3-Isobutyl-9,10-dimethoxy-4-methyl-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one (IIIc). A mixture of 1.03 g (5 mmol) of isoquinoline **Ic** and 1.12 g (6 mmol) of 2-isobutyl-3-oxobutanoate (**IIc**) was heated for 7 h at 140–160°C under argon. The mixture was diluted with chloroform and passed through 9 g of silica gel using chloroform–methanol (9.5:0.5) as eluent. The eluate was evaporated, and the residue was recrystallized twice from chloroform–diethyl ether (2:3) and dried for 72 h in a vacuum desiccator over P_2O_5. Pyrido[2,1-*a*]isoquinoline **IIIc** was isolated as colorless prisms. Yield 1.3 g (79.3%), mp 226–228°C. IR spectrum, ν, cm^{-1}: 3050–2820, 1615, 1600, 1580, 1554, 1505, 1477, 1460–1440, 1380, 1350, 1337, 1315, 1296, 1280–1255, 1248, 1218, 1178, 1160, 1137, 1100, 1060, 1024, 985, 882, 870–850, 827, 780. UV spectrum, λ_{max}, nm (logε): 220 (3.99), 240.8 (4.05), 263.9 (4.09), 314.3 (3.96); λ_{min}, nm (logε): 238.9 (3.91), 249.4 (3.94), 292 (3.83). ^{1}H NMR spectrum, δ, ppm, (*J* Hz): 0.97 d (6H, 15-H, 16-H, *J* = 7.0), 1.90 m (1H, 14-H, *J* = 7.0), 2.44 s (3H, 4-CH_3), 2.58 d (2H, 13-H, *J* = 7.0), 2.98 t (2H, 7-H, *J* = 6.0), 3.93 s (3H, OMe), 3.95 s (3H, OMe), 4.05 t (2H, 6-H, *J* = 6.0), 6.72 s (1H, 1-H), 6.78 s (1H, 8-H), 7.21 s (1H, 11-H). Found, %: C 73.41; H 7.63; N 4.16. $[M]^+$ 327. $C_{20}H_{25}NO_3$. Calculated, %: C 73.37; H 7.70; N 4.28. *M* 327.42.

4-(9,10-Dimethoxy-1,4-dimethyl-2-oxo-6,7-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-3-yl)-2-butanone (IIId). A mixture of 1.1 g (5 mmol) of isoquino-

line **Id** and 1.2 g (6 mmol) of ester **IId** in 10 ml of toluene was heated for 27 h under reflux in an argon atmosphere. The mixture was evaporated, the residue was dissolved in chloroform, and the solution was subjected to flash chromatography on 15 g of silica gel (5–40 μm) using chloroform–methanol (9.5:0.5) as eluent. The eluate was evaporated, and the residue was recrystallized twice from chloroform–diethyl ether (2:3) and dried for 72 h under reduced pressure over P_2O_5. Pyrido[2,1-*a*]isoquinoline **IIId** was isolated as colorless crystals. Yield 1.19 g (66.7%), mp 161–163°C. IR spectrum, ν, cm^{-1}: 3050–2820, 1715, 1620–1590, 1580, 1555–1535, 1512–1495, 1486, 1455, 1435, 1385–1355, 1286, 1260, 1143, 1074, 785, 774, 754. UV spectrum, λ_{max}, nm (log ε): 212.3 (4.36), 239.3 (4.40), 260 (4.35), 308.1 (4.25); λ_{min}, nm (log ε): 208.5 (4.36), 225.8 (4.28), 250 (4.24), 278 (4.09). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 s (3H, 15-H), 2.36 s (3H, 1-Me), 2.46 s (3H, 4-Me), 2.72–2.98 m (6H, 7-H, 12-H, 13-H), 3.89 s (3H, OMe), 3.94 t (2H, 6-H, *J* = 6.0), 3.95 s (3H, OMe), 6.76 s (1H, 8-H), 7.15 s (1H, 11-H). Mass spectrum, *m*/*z* (I_{rel}, %): 356.3 (3.47) $[M + 1]^+$, 355.3 (14.85) $[M]^+$, 354.3 (4.87) $[M - 1]^+$, 340.3 (7.24), 338.3 (3.06), 314.25 (2.72), 313.25 (22), 312.25 (100), 310.2 (2.71), 298.3 (5.81), 297.2 (4.83), 296.2 (17.59), 294.2 (2.08), 284.25 (2.35), 282.15 (3.99), 280.15 (3.18), 270.25 (4.92), 268.25 (4.98), 266.2 (2.66), 255.2 (2.05), 254.2 (9.22), 252.2 (3.8), 240.15 (2.42), 239.15 (2), 238.15 (5.26), 226.15 (4.08), 225.15 (2.06), 224.15 (4.31), 212.1 (4.39), 211.1 (2.31), 210.1 (4.29), 208.1 (92.24), 207.1 (2.44), 196.05 (3.5), 194.15 (2.28), 182.15 (2.75), 180.05 (2.04), 168.1 (2.56), 167.1 (2.05), 156.1 (12.8), 154.05 (2.12), 141.05 (2.15), 134.65 (9.41), 133.45 (2.28), 128 (3.39), 127 (2.92), 115 (5.11), 111.5 (2.01), 102.95 (2.18), 90.85 (2.58), 77 (3.57), 65 (2.48), 52.95 (2.69). Found, %: C 70.83; H 6.97; N 3.79. $C_{21}H_{25}NO_4$. Calculated, %: C 70.96; H 7.09; N 3.94. *M* 355.43.

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