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Synthesis of Pyridines from 1,2,4-Triazines under High Pressure

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Abstract—A procedure has been proposed for the synthesis of pyridines from 1,2,4-triazine derivatives and bicyclo[2.2.1]hepta-2,5-diene under high pressure in the presence of lithium perchlorate as catalyst.

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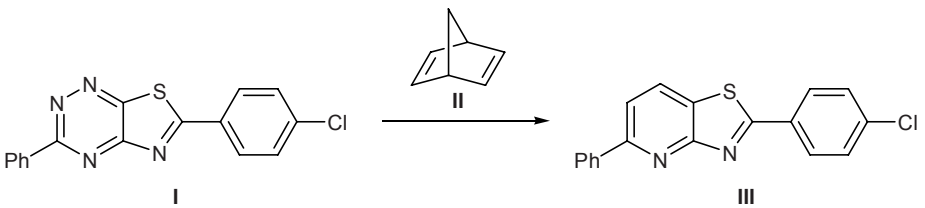
Pyridine derivatives, including fused heterocyclic compounds containing a pyridine ring, constitute a number of natural substances and are widely used in the synthesis of various biologically active compounds [1–5]. Synthesis and studies on the properties of new pyridine derivatives may be regarded as a promising line in the design of effective medical agents. Therefore, development of new approaches to previously inaccessible pyridine derivatives attracts considerable interest.

Among the existing methods for the preparation of pyridine compounds, transformations of 1,2,4-triazine ring into pyridine by the action of alkenes and alkynes are challenging. Specifically, the use of fused 1,2,4-triazines, which have become accessible via tandem S_N^H reactions [6–8], attracts interest. In fact, 1,2,4-triazine ring can be readily modified with nucleophiles, including difunctional ones, and subsequent reactions of fused 1,2,4-triazines could lead to polyfunctional pyridine derivatives which are difficult to obtain by other methods [9].

It is known that electron-deficient 1,2,4-triazines smoothly react with electron-rich dienophiles [10–13]. In keeping with published data [14] and our own results [15–18], application of high pressure is effective in the synthesis of many heterocyclic systems. While studying the cycloaddition of bicyclo[2.2.1]-hepta-2,5-diene to thiazolo[4,5-*e*][1,2,4]triazine, we previously showed that such reactions cannot be accomplished under atmospheric pressure [19]. We also found that the reaction of 6-(4-chlorophenyl)-3-phenyl-[1,3]thiazolo[4,5-*e*][1,2,4]triazine (**I**) with bicyclo-[2.2.1]hepta-2,5-diene (**II**) at a pressure of 1000 MPa gives the corresponding pyridine derivative **III** in 44% yield (Scheme 1). In the present communication we demonstrate that the reaction is general and that the procedure can be extended to a wide series of 1,2,4-triazines.

With a view to develop a new general method of synthesis of pyridine derivatives, we examined reactions of bicyclo[2.2.1]hepta-2,5-diene (**II**) with both 1,2,4-triazines and fused systems based thereon. The

Scheme 1.



I **III**

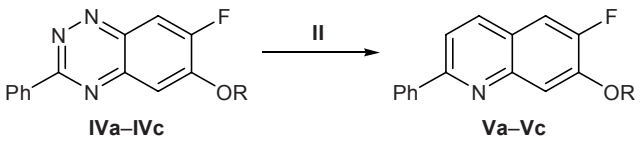
Table 1. Reaction conditions and yields of 2-(4-chlorophenyl)-5-phenyl[1,3]thiazolo[4,5-*b*]pyridine (**III**) from 6-(4-chlorophenyl)-3-phenyl[1,3]thiazolo[4,5-*e*][1,2,4]triazine (**I**) and bicyclo[2.2.1]hepta-2,5-diene (**II**)

Temperature, °C	Pressure, MPa	Solvent	Catalyst	Yield of **III**, %	Unreacted **I**, %
100	1000	CH_2Cl_2	–	44	56
100	1500	CH_2Cl_2	–	95	5
150	500	CH_2Cl_2	–	45	55
150	1000	CH_2Cl_2	–	86	14
100	500	Et_2O	$LiClO_4$	15	85
150	500	Et_2O	$LiClO_4$	98	–
150	500	CH_2Cl_2	$SnOBu_2$	50	22
150	500	MeCN	$SnOBu_2$	42	13
150	500	MeCN	–	–	94
150	500	Et_2O	$BF_3 \cdot Et_2O$	Tarring	

effects of various factors (pressure, catalyst, solvent, reaction time) on the cycloaddition of compound **II** to 1,2,4-triazines were estimated. High-pressure reactions were carried out in Teflon ampules using a setup described in [20].

The yields of 2-(4-chlorophenyl)-5-phenyl[1,3]thiazolo[4,5-*b*]pyridine (**III**) formed in the reaction of 6-(4-chlorophenyl)-3-phenyl[1,3]thiazolo[4,5-*e*][1,2,4]triazine (**I**) with bicyclo[2.2.1]hepta-2,5-diene (**II**) under different conditions are given in Table 1. It is seen that the use of $BF_3 \cdot Et_2O$ as catalyst promotes tarring of the reaction mixture. Dibutyltin oxide showed no appreciable catalytic activity, though it was successfully used by us previously to catalyze cycloaddition processes [15]. The most effective catalyst was lithium perchlorate which is frequently used as catalyst in Diels–Alder reactions [16]; in our case, it allowed us to reduce the pressure from 1500 to 500 MPa, the yield of **III** remaining comparable. Lower pressure made it possible to increase the reaction volume. The reaction volume under a pressure ranging from 1000 to 1500 MPa usually does not exceed a few milliliters, while at a pressure of 500 MPa the reaction volume can be increased up to 500 ml. Thus lithium perchlorate as catalyst ensured preparation of required amounts of the target pyridine derivative.

Scheme 2.



IVa–IVc **Va–Vc**

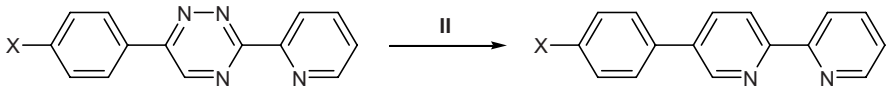
R = Me (**a**), Et (**b**), *i*-Bu (**c**).

The proposed procedure was successfully extended to fluorine-containing 1,2,4-benzotriazines **IVa**–**IVc**. These compounds reacted with bicyclo[2.2.1]hepta-2,5-diene (**II**) to give the corresponding substituted quinolines **Va**–**Vc** (Scheme 2).

Table 2 contains the conditions of the reaction of 6-ethoxy-7-fluoro-3-phenyl-1,2,4-benzotriazine (**IVb**) with bicyclo[2.2.1]hepta-2,5-diene (**II**) and the yields of 7-ethoxy-6-fluoro-2-phenylquinoline (**Vb**) thus formed. The data in Table 2 indicate that lithium perchlorate also facilitates formation of quinoline **Vb** and that the reactivity of benzotriazines **IV** toward bicyclo[2.2.1]hepta-2,5-diene (**II**) is lower than the reactivity of thiazolotriazine **I**. Presumably, compounds **IV** are less electron-deficient than **I**. Under the optimal conditions ensuring 98% yield of thiazolopyridine **III** (lithium perchlorate, 500 MPa, 150°C, 6 h), the yield of quinoline **Vb** was as poor as 12%. The reactions with benzotriazines **IV** required more severe conditions, namely higher pressure and longer reaction time. When the reactions of compounds **IVa** and **IVc** with bicyclo[2.2.1]hepta-2,5-diene (**II**) were carried out in the presence of lithium perchlorate at a pressure of 1000 MPa at 165°C, the yields of quinolines **Va** and **Vc** in 48 h attained 80–90%.

The structure of quinolines **Va**–**Vc** was proved by the NMR and mass spectra and elemental analyses. In the ^{1}H NMR spectra of **Va**–**Vc**, the 3-H proton in the quinoline ring resonated as a doublet at δ 7.76–7.78 ppm with a vicinal coupling constant ^3J of 8.6 Hz, which is typical of *ortho* protons. The 4-H signal in the spectrum of **Vc** appeared at δ 8.08 ppm (^3J = 8.6 Hz) separately from signals of the phenyl protons. The

Scheme 3.



VIa, **VIb** **VIIa**, **VIIb**

X = Cl (**a**), MeO (**b**).

mass spectra of **Va**–**Vc** contained the molecular ion peaks.

The high-pressure procedure implying the use of lithium perchlorate as catalyst was also effective in reactions with nonfused triazines. The reactions of triazines **VIa** and **VIb** with bicyclo[2.2.1]hepta-2,5-diene (**II**) at 1000 MPa (100°C) in 1 h gave 92–96% of the corresponding pyridines **VIIa** and **VIIb** (Scheme 3). Pyridines **VIIa** and **VIIb** were synthesized previously in comparable yields by heating compounds **VIa** and **VIb** in boiling xylene for 10 h [21].

This we have developed a general procedure for the synthesis of pyridine derivatives by high-pressure reaction of the corresponding 1,2,4-triazines with bicyclo[2.2.1]hepta-2,5-diene in the presence of lithium perchlorate.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer from solutions in DMSO-d_6. The mass spectra (electron impact, 70 eV) were obtained on a Kratos instrument with direct sample admission into the ion source. The melting points were measured on a Boetius hot stage and were not corrected. The progress of reactions was monitored by TLC on Silufol UV-254 plates using petroleum ether–ethyl acetate (1:2) as eluent. Column chromatography was performed on silica gel (0.060–0.200 mm) from Acros Organics.

2-(4-Chlorophenyl)-5-phenyl[1,3]thiazolo[4,5-*b*]-pyridine (III). A Teflon ampule was charged with a mixture of 405 mg (4.4 mmol) of bicyclo[2.2.1]-hepta-2,5-diene (**II**), 100 mg (0.31 mmol) of 6-(4-chlorophenyl)-3-phenyl[1,3]thiazolo[4,5-*e*]-[1,2,4]triazine (**I**), and 170 mg (1.7 mmol) of lithium perchlorate in 10 ml of diethyl ether, and the mixture was kept for 6 h at 500 MPa on heating to 150°C. The mixture was then applied to a column charged with silica gel, and the column was eluted with hexane–ethyl acetate (3:1). A fraction containing compound **III** was collected, the solvent was removed under reduced pressure, and the residue was recrystallized from hexane. Yield 96 mg (97%), colorless crystals, mp 234–235°C. ^{1}H NMR spectrum, δ, ppm: 7.52 m (5H, H_{arom}), 7.83 d (1H, pyridine, J = 8.4 Hz), 8.20 m (4H, H_{arom}), 8.32 d (1H, pyridine, J = 8.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 117.47, 126.63, 126.95, 128.47, 128.57, 128.99, 129.19, 131.25, 132.21, 136.55, 138.08, 155.35, 163.94, 169.43. Mass spectrum, m/z (I_{rel}, %): 324 (36) $[M + 2]^+$, 323 (30) $[M + 1]^+$, 322 (100) $[M]^+$, 185 (63), 158 (10), 153 (31), 141 (33), 115 (32), 106 (14), 77 (20), 43 (25). Found, %: C 67.01; H 3.39; N 8.70; S 9.96. $C_{18}H_{11}ClN_2S$. Calculated, %: C 66.97; H 3.43; N 8.68; S 9.93. M 322.81.

Compounds **Va**–**Vc**, **VIIa**, and **VIIb** were synthesized in a similar way.

6-Fluoro-7-methoxy-2-phenylquinoline (Va). The reaction mixture was heated for 10 h at 170°C at a pressure of 1000 MPa. Yield 68 mg (90%), colorless

Table 2. Reaction conditions and yields of 7-ethoxy-6-fluoro-2-phenylquinoline (**Vb**) from 6-ethoxy-7-fluoro-3-phenyl-1,2,4-benzotriazine (**IVb**) and bicyclo[2.2.1]hepta-2,5-diene (**II**)

Temperature, °C	Pressure, MPa	Solvent	Reaction time, h	Catalyst	Yield of **Vb**, %	Unreacted **IVb**, %
110	0.1	PhMe	48	–	–	98
150	500	Et_2O	6	$LiClO_4$	12	86
160	500	Et_2O	12	$LiClO_4$	28	70
150	1000	Et_2O	12	$LiClO_4$	61	36
165	1000	Et_2O	48	$LiClO_4$	92	–
160	1500	Et_2O	9	$LiClO_4$	63	35

crystals, mp 118–120°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 4.08 s (3H, OCH_3), 7.40–7.55 m (4H, H_{arom}), 7.60 d (1H, 5-H, J = 8.2 Hz), 7.78 d (1H, 3-H, J = 8.6 Hz), 8.06–8.16 m (3H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 56.24, 110.19, 110.92, 111.30, 117.69, 121.74, 121.92, 127.43, 128.89, 129.30, 135.73, 139.63, 146.44, 149.77, 150.78, 151.06, 154.78, 157.01. Mass spectrum, m/z (I_{rel}, %): 254 (18) $[M + 1]^+$, 253 (100) $[M]^+$, 238 (13), 222 (6), 210 (23), 209 (21), 183 (8), 149 (6), 127 (7), 43 (12). Found, %: C 75.81; H 4.73; F 7.46; N 5.54. $C_{16}H_{12}FNO$. Calculated, %: C 75.88; H 4.78; F 7.50; N 5.53. M 253.28 .

7-Ethoxy-6-fluoro-2-phenylquinoline (Vb). Yield 66 mg (87%), colorless crystals, mp 112–114°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.59 t (3H, CH_3, J = 7.0 Hz), 4.23 q (2H, OCH_2, J = 7.0 Hz), 7.40–7.55 m (4H, H_{arom}), 7.58 d (1H, 5-H, J = 8.2 Hz), 7.78 d (1H, 3-H, J = 8.5 Hz), 8.05–8.17 m (3H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.63, 64.80, 110.92, 111.29, 117.63, 127.48, 128.92, 129.28, 135.71, 135.82, 139.78, 146.54, 149.99, 150.18, 150.47, 154.99, 157.06. Mass spectrum, m/z (I_{rel}, %): 268 (8) $[M + 1]^+$, 267 (48) $[M]^+$, 239 (95), 238 (100), 222 (18), 209 (16), 190 (17), 149 (11), 97 (10), 83 (8), 77 (10), 55 (13), 43 (35). Found, %: C 76.41; H 5.29; F 7.04; N 5.17. $C_{17}H_{14}FNO$. Calculated, %: C 76.39; H 5.28; F 7.11; N 5.24. M 267.31.

6-Fluoro-7-(2-methylpropoxy)-2-phenylquinoline (Vc). Yield 58 mg (81%), colorless crystals, mp 65–67°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.11 d (6H, CH_3, J = 6.7 Hz), 2.37 m (1H, CH, J = 6.7 Hz), 3.98 d (2H, OCH_2, J = 6.7 Hz), 7.40–7.54 m (4H, H_{arom}), 7.58 d (1H, 5-H, J = 8.2 Hz), 7.76 d (1H, 3-H, J = 8.6 Hz), 8.08 d (1H, 2-H, J = 8.6 Hz), 8.12 d (2H, H_{arom}, J = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.24, 28.08, 75.41, 110.90, 111.20, 117.49, 127.42, 128.86, 129.23, 135.63, 135.74, 139.72, 146.48, 150.01, 150.41, 150.69, 155.01, 156.89. Mass spectrum, m/z (I_{rel}, %): 295 (15) $[M]^+$, 239 (68), 238 (18), 203 (100), 202 (55), 149 (13), 101 (13), 84 (24), 71 (26), 57 (66), 43 (27). Found, %: C 77.17; H 6.09; F 6.32; N 4.69. $C_{19}H_{18}FNO$. Calculated, %: C 77.27; H 6.14; F 6.43; N 4.74. M 295.36.

5-(4-Chlorophenyl)-2,2′-bipyridine (VIIa). The reaction mixture was heated for 1 h at 110°C under a pressure of 1000 MPa. Yield 81 mg (96%), colorless crystals, mp 148–149.5°C (from MeOH). ^{1}H NMR spectrum, δ, ppm: 7.29 m (1H, pyridine), 7.42 d (2H, H_{arom}, J = 8.4 Hz), 7.63 d (2H, H_{arom}, J = 8.4 Hz), 7.85 m (1H, pyridine), 8.02 d (1H, 3-H, J = 8.3 Hz), 8.51 m (2H, 4-H, pyridine), 8.72 d (1H, pyridine, J = 4.5 Hz), 8.91 s (1H, 6-H). Mass spectrum, m/z (I_{rel}, %): 268 (35) $[M + 2]^+$, 267 (28) $[M + 1]^+$, 266 (100) $[M]^+$, 240 (8), 238 (25), 231 (6), 229 (15), 204 (18), 149 (21), 102 (12), 78 (9), 58 (13), 44 (27). Found, %: C 72.10; H 4.13; Cl 13.32; N 10.49. $C_{16}H_{11}ClN_2$. Calculated, %: C 72.05; H 4.16; Cl 13.29; N 10.50. M 266.73.

5-(4-Methoxyphenyl)-2,2′-bypiridine (VIIb). Yield 78 mg (92%), colorless crystals, mp 124–126°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H, OMe), 7.04 d (2H, H_{arom}, J = 8.7 Hz), 7.32 m (1H, pyridine), 7.62 d (2H, H_{arom}, J = 8.7 Hz), 7.84 m (1H, pyridine), 8.00 d (1H, 3-H, J = 8.3 Hz), 8.44 m (2H, 4-H, pyridine), 8.71 d (1H, pyridine, J = 4.5 Hz), 8.89 s (1H, 6-H). Mass spectrum, m/z (I_{rel}, %): 263 (23) $[M + 1]^+$, 262 (100) $[M]^+$, 248 (23), 247 (51), 220 (10), 219 (31), 192 (10), 191 (12), 149 (8), 78 (9), 58 (7), 43 (17). Found, %: C 77.91; H 5.36; N 10.69. $C_{16}H_{11}ClN_2$. Calculated, %: C 77.84; H 5.38; N 10.68. M 262.31.

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