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SYNTHESIS OF 1-SUBSTITUTED 5-ACETYL (ETHOXYCARBONYL)-2,3-DIHYDROPYRAZOLO-[3,4-*b*]PYRIDIN-3-ONES

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1-Substituted 5-aminopyrazol-3-ones react selectively with ethoxymethylidene β-dicarbonyl compounds (3-ethoxymethylidene-2,4-pentanedione, diethyl 2-ethoxymethylidenemalonate, and ethyl 2-ethoxymethylideneacetoacetate) with the formation of dihydropyrazolylaminomethylidene β-dicarbonyl derivatives, which undergo thermal intramolecular cyclization to 5-functionalized dihydropyrazolo[3,4-b]pyridin-3-ones.

Keywords: 5-acetyl-4-methyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-ones, 1-substituted 5-aminopyrazol-3-ones, ethyl 4-hydroxy-3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylate, ethoxymethylidene-β-dicarbonyl compounds.

The interest in derivatives of pyrazolo[3,4-*b*]pyridine-5-carboxylic acid is due to their valuable biological properties. Substances with antiherpetic [1], antimitotic [2], antiarrhythmic [3], anti-inflammatory [4], and anxiolytic [5] activity have been found among them. Thermal intramolecular cyclization of the products from condensation of 5-aminopyrazoles with diethyl 2-ethoxymethylidenemalonate is used for their synthesis [3, 6-12] and allows, as a rule, to obtain condensed systems with an ethoxycarbonyl substituent in the pyridine ring. The use of 5-aminopyrazol-3-ones as binucleophilic component [13, 14] in a reaction of such a type may prove rather useful for the preparation of derivatives additionally functionalized in the pyrazole ring. Here it should be noted that 1-substituted 5-aminopyrazol-3-ones have not been studied before in such transformations. For this reason, it seemed expedient to investigate the reaction of 1-substituted 5-aminopyrazol-3-ones **1a-e** with a series of ethoxymethylidene β-dicarbonyl compounds: 3-ethoxymethyl-idene-2,4-pentanedione (**2a**), diethyl 2-ethoxymethylidenemalonate (**2b**), and ethyl 2-ethoxymethylidene-acetoacetate (**2c**).

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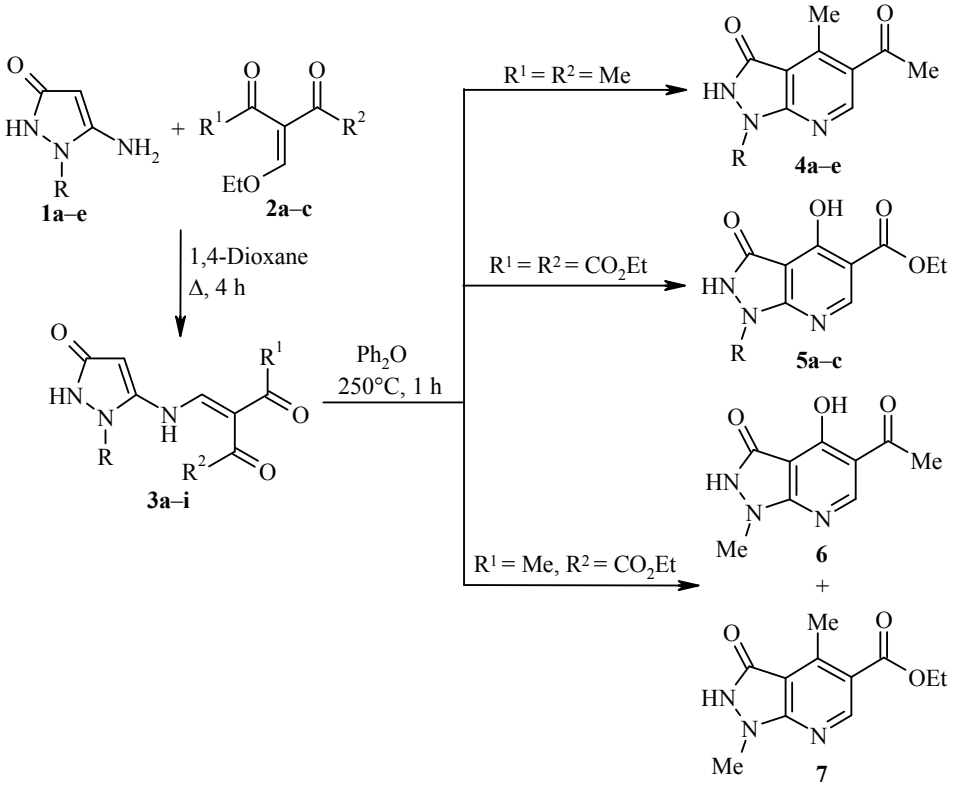
It was found that compounds **1a-e** react with ethoxymethylidene derivatives **2a-c** in refluxing dioxane with the formation of the condensation products **3a-i**, which are high-melting crystalline substances (yields 49-80%). The ^{1}H NMR spectra of compounds **3a-i** are characterized by singlets for the H-4 protons of the pyrazolone ring at 5.52-6.13 ppm and by doublets of the NH and =CH group protons of the exocyclic enamine fragment at 10.62-12.77 and 7.96-8.18 ppm respectively, with spin-spin coupling constants of 11-12 Hz.

When heated in diphenyl ether at 250°C for 1 h, the compounds **3a-e** undergo intramolecular cyclo-condensation with the formation of 5-acetyl-4-methyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-ones **4a-e** with yields of 52-65%. Under analogous conditions, compounds **3f-h** are converted into ethyl 4-hydroxy-3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylates **5a-c** with somewhat smaller yields (43-50%). In the case of compound **3i**, obtained by the reaction of 5-aminopyrazol-3-one **1a** with the unsymmetrical ethoxymethylidene derivative **2c**, thermal cyclization takes place nonselectively and leads to a mixture of 5-acetyl-4-hydroxy-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **6** and ethyl 4-methyl-3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylate **7**, which are formed in a ratio of 5:1, according to the chromato-mass spectroscopy data. It was possible to separate compounds **6** and **7** by preparative liquid chromatography.

The formation of the dihydropyrazolo[3,4-*b*]pyridine ring in all types of compounds **4-7** is confirmed by the presence of singlets for the H-6 protons at 8.69-9.01 ppm in their ^{1}H NMR spectra and of signals for the C-4 atoms in the region of 135-148 ppm (for compounds **4** and **7**) and 166-171 ppm (for compounds **5** and **6**), for C-5 in the region of 105-110 ppm (for compounds **5** and **6**), 117 ppm (for compound **7**), and 125-127 ppm (for compound **4**), and also for C-6 in the region of 146-153 ppm in their ^{13}C NMR spectra.



1a R = Me, **1b** R = Ph, **1c** R = 4-FC_6H_4, **1d** R = 4-ClC_6H_4, **1e** R = Bn; **2a** $R^1 = R^2$ = Me, **2b** $R^1 = R^2$ = OEt, **2c** R^1 = Me, R^2 = OEt; **3a** R = $R^1 = R^2$ = Me; **3b** R = Ph, $R^1 = R^2$ = Me; **3c** R = 4-FC_6H_4, $R^1 = R^2$ = Me; **3d** R = 4-ClC_6H_4, $R^1 = R^2$ = Me; **3e** R = Bn, $R^1 = R^2$ = Me; **3f** R = Me, $R^1 = R^2$ = OEt; **3g** R = Ph, $R^1 = R^2$ = OEt; **3h** R = 4-FC_6H_4, $R^1 = R^2$ = OEt; **3i** R = R^1 = Me, R^2 = OEt; **4a** R = Me, **4b** R = Ph, **4c** R = 4-FC_6H_4, **4d** R = 4-ClC_6H_4, **4e** R = Bn; **5a** R = Me, **5b** R = Ph, **5c** R = 4-FC_6H_4

TABLE 1. The Physicochemical Characteristics of Compounds **3a-i**, **4a-e**, **5a-c**, **6**, and **7**

Compound	Empirical formula	Found, % / Calculated, %			Mp*, °C	Yield, %
		C	H	N		
3a	$C_{10}H_{13}N_3O_3$	53.60 / 53.81	5.75 / 5.87	18.80 / 18.82	224-225	78
3b	$C_{15}H_{15}N_3O_3$	62.98 / 63.15	5.18 / 5.30	14.66 / 14.73	223-224	65
3c	$C_{15}H_{14}FN_3O_3$	59.55 / 59.40	4.59 / 4.65	13.98 / 13.85	211-212	78
3d	$C_{15}H_{14}ClN_3O_3$	55.95 / 56.35	4.32 / 4.41	13.05 / 13.14	239-240	75
3e	$C_{16}H_{17}N_3O_3$	64.04 / 64.20	5.65 / 5.72	14.11 / 14.04	193-194	72
3f	$C_{12}H_{17}N_3O_5$	51.01 / 50.88	5.93 / 6.05	15.00 / 14.83	195-196	80
3g	$C_{17}H_{19}N_3O_5$	59.37 / 59.12	5.57 / 5.55	12.29 / 12.17	228-229	49
3h	$C_{17}H_{18}FN_3O_5$	56.28 / 56.50	5.10 / 4.99	11.49 / 11.56	210-211	52
3i	$C_{11}H_{15}N_3O_4$	52.29 / 52.17	6.06 / 5.97	16.61 / 16.59	194-195	80
4a	$C_{10}H_{11}N_3O_2$	58.40 / 58.53	5.47 / 5.40	20.50 / 20.48	224-225	58
4b	$C_{15}H_{13}N_3O_2$	67.12 / 67.41	4.98 / 4.90	15.80 / 15.72	237-238	59
4c	$C_{15}H_{12}FN_3O_2$	62.89 / 63.15	4.09 / 4.24	14.81 / 14.73	245-246	65
4d	$C_{15}H_{12}ClN_3O_2$	59.51 / 59.71	4.00 / 4.01	14.04 / 13.93	244-246	59
4e	$C_{16}H_{15}N_3O_2$	67.99 / 68.31	5.27 / 5.37	15.03 / 14.94	204-205	52
5a	$C_{10}H_{11}N_3O_4$	50.32 / 50.63	4.46 / 4.67	17.59 / 17.71	217-218	43
5b	$C_{15}H_{13}N_3O_4$	60.22 / 60.20	4.30 / 4.38	14.13 / 14.04	212-213	47
5c	$C_{15}H_{12}FN_3O_4$	56.50 / 56.79	3.92 / 3.81	13.31 / 13.24	213-215	50
6	$C_9H_9N_3O_3$	52.32 / 52.17	4.30 / 4.38	20.40 / 20.28	211-212	21
7	$C_{11}H_{13}N_3O_3$	55.95 / 56.16	5.43 / 5.57	17.89 / 17.86	193-194	5

*Solvents for recrystallization: dioxane (compounds **3a**,**c**,**d**,**f-i**, **5c**), MeOH (compound **3b**), EtOH (compounds **3e**, **4e**) DMF (compound **4a**), and AcOH (compounds **4b-d**, **5a**,**b**).

The experimental results indicate that the structure of the electrophilic component (the ethoxymethylidene β-dicarbonyl compounds **2a-c**) has practically no effect on the yields of the primary condensation products **3a-i**. The thermal transformation of the latter is controlled by the substituents R^1 and R^2 and, in the case where they are non-equivalent, is accompanied by nonselective occurrence of the process and by low yields of the products **6** and **7**.

Thus, we have proposed an effective method for the synthesis of new 5-acetyl(ethoxycarbonyl)-dihydropyrazolo[3,4-*b*]pyridin-3-ones based on the cyclocondensation of 1-substituted 5-aminopyrazol-3-ones with 2-ethoxymethylidene derivatives of acetylacetone and malonic ester.

TABLE 2. The IR and ^{1}H NMR Spectra of Compounds **3a-i**, **4a-e**, **5a-c**, **6**, and **7**

Compound	IR spectrum*, $\nu_{C=O}$, cm^{-1}	^{1}H NMR, δ, ppm (*J*, Hz)
3a	1625	2.36 (3H, s, CH_3); 2.40 (3H, s, CH_3); 3.53 (3H, s, CH_3); 5.77 (1H, s, H-4); 8.09 (1H, d, *J* = 11.6, =CH); 9.84 (1H, s, NH); 12.57 (1H, d, *J* = 11.2, NH)
3b	1630	2.33 (3H, s, CH_3); 2.51 (3H, s, CH_3); 6.11 (1H, s, H-4); 7.46-7.62 (5H, m, H Ph); 8.05 (1H, d, *J* = 11.3, =CH); 10.37 (1H, s, NH); 12.76 (1H, d, *J* = 11.6, NH)
3c	1625	2.32 (3H, s, CH_3); 2.33 (3H, s, CH_3); 6.12 (1H, s, H-4); 7.40-7.57 (4H, m, H Ar); 8.18 (1H, d, *J* = 12.0, =CH); 10.37 (1H, br. s, NH); 12.76 (1H, d, *J* = 11.2, NH)
3d	1640	2.33 (3H, s, CH_3); 2.34 (3H, s, CH_3); 6.13 (1H, s, H-4); 7.42-7.56 (4H, m, H Ar); 8.17 (1H, d, *J* = 9.2, =CH); 10.36 (1H, br. s, NH); 12.77 (1H, d, *J* = 8.4, NH)
3e	1625	2.29 (3H, s, CH_3); 2.37 (3H, s, CH_3); 5.09 (2H, s, CH_2Ph); 5.87 (1H, s, H-4); 7.16-7.37 (5H, m, H Ph); 8.11 (1H, d, *J* = 12.0, =CH); 10.02 (1H, br. s, NH); 12.73 (1H, d, *J* = 11.6, NH)
3f	1695	1.20-1.27 (6H, m, $2CH_2C\underline{H}_3$); 3.49 (3H, s, CH_3); 4.11-4.19 (4H, m, $2C\underline{H}_2CH_3$); 5.52 (1H, s, H-4); 7.96 (1H, d, *J* = 11.7, =CH); 9.85 (1H, br. s, NH); 10.39 (1H, br. s, NH)
3g	1685	1.16-1.24 (6H, m, $2CH_2C\underline{H}_3$); 4.08-4.12 (4H, m, $2C\underline{H}_2CH_3$); 5.89 (1H, s, H-4); 7.39-7.51 (5H, m, H Ph); 8.07(1H, d, *J* = 12.4, =CH); 10.31 (1H, s, NH); 10.70 (1H, d, *J* = 14.4, NH)
3h	1640, 1690	1.15-1.22 (6H, m, $2CH_2C\underline{H}_3$); 4.07-4.15 (4H, m, $2C\underline{H}_2CH_3$); 5.87 (1H, s, H-4); 7.37-7.55 (4H, m, H Ar); 8.67 (1H, d, *J* = 11.2, =CH); 10.33 (1H, br. s, NH); 10.62 (1H, d, *J* = 12.0, NH)
3i	1700	1.24 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.43 (3H, s, CH_3); 3.57 (3H, s, CH_3); 4.15 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 5.62 (1H, s, H-4); 8.07 (1H, d, *J* = 11.6, =CH); 9.81 (1H, s, NH); 12.57 (1H, br. s, NH)
4a	1670	2.61 (3H, s, CH_3); 2.81 (3H, s, CH_3); 3.80 (3H, s, CH_3); 8.88 (1H, s, H-6); 11.44 (1H, br. s, NH)
4b	1678	2.65 (3H, s, CH_3); 2.86 (3H, s, CH_3); 7.52-8.21 (5H, m, H Ph); 9.01 (1H, s, H-6); 12.10 (1H, br. s, NH)
4c	1685	2.64 (3H, s, CH_3); 2.83 (3H, s, CH_3); 7.35-8.18 (4H, m, H Ar); 8.98 (1H, s, H-6); 12.12 (1H, br. s, NH)
4d	1680	2.64 (3H, s, CH_3); 2.82 (3H, s, CH_3); 7.56-8.22 (4H, m, H Ar); 8.98 (1H, s, H-6); 12.15 (1H, br. s, NH)
4e	1675	2.63 (3H, s, CH_3); 2.82 (3H, s, CH_3); 5.43 (2H, s, CH_2Ph); 7.16-7.37 (5H, m, H Ph); 8.98 (1H, s, H-6); 11.57 (1H, br. s, NH)
5a	1672	1.37 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 3.78 (3H, s, CH_3); 4.40 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 8.69 (1H, s, H-6); 11.24 (1H, br. s, NH); 12.06 (1H, br. s, OH)
5b	1660	1.09 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.40 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.50-8.12 (5H, m, H Ph); 8.77 (1H, s, H-6); 11.82 (1H, br. s, NH); 11.99 (1H, br. s, OH)
5c	1670	1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.38 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.99-7.35 (4H, m, H Ar); 8.74 (1H, s, H-6); 11.90 (1H, br. s, NH); 11.96 (1H, br. s, OH)
6	1655	2.66 (3H, s, CH_3); 3.77 (3H, s, CH_3); 8.79 (1H, br. s, H-6); 11.29 (1H, br. s, NH)*[2]
7	1710	1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.86 (3H, s, CH_3); 3.80 (3H, s, CH_3); 4.30 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 8.82 (1H, s, H-6); 11.45 (1H, br. s, NH)

*The absorption of the OH and NH groups appears in the form of difficult to identify broad bands in the region of 3200-3450 cm^{-1}.

*[2]The proton of the OH group does not appear on account of deuterium exchange with water present in the solvent.

TABLE 3. The ^{13}C NMR Spectra of Compounds **4a-e**, **5a-c**, **6**, and **7**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
4a	16.8 (4-CH_3); 30.4 (CH_3); 33.2 (1-CH_3); 105.4 (C-3a); 125.5 (C-5); 147.1 (C-4); 150.8 (C-7a); 152.6 (C-6); 155.7 (C-3); 199.2 (C=O)
4b	16.6 (4-CH_3); 30.5 (CH_3); 108.0 (C-3a); 120.0 (C Ar); 125.2 (C-5); 127.1 (C Ar); 129.5 (C Ar); 139.5 (C-4); 147.1 (C-7a); 150.3 (C Ar); 152.7 (C-6); 157.1 (C-3); 199.2 (C=O)
4c	16.5 (4-CH_3); 30.4 (CH_3); 107.8 (C-3a); 116.2 (d, $^2J_{C-F}$ = 24, C-3',5'); 121.6 (d, $^3J_{C-F}$ = 10, C-2',6'); 126.9 (C-5); 135.9 (C-4); 147.2 (C-7a); 150.0 (C-1'); 152.7 (C-6); 157.0 (C-3); 159.5 (d, $^1J_{C-F}$ = 241, C-4'); 199.0 (C=O)
4d	16.5 (4-CH_3); 30.4 (CH_3); 108.2 (C-3a); 121.1 (C Ar); 127.2 (C-5), 129.4 (C Ar); 138.3 (C-4); 144.1 (C Ar); 148.4 (C-7a); 150.3 (C Ar); 152.7 (C-6); 157.2 (C-3); 199.1 (C=O)
4e	16.8 (4-CH_3); 30.5 (CH_3); 49.6 (CH_2); 105.6 (C-3a); 125.9 (C-5); 128.0 (C Ar); 128.0 (C Ar); 129.0 (C Ar); 137.9 (C-4); 147.2 (C-7a); 150.8 (C Ar); 152.8 (C-6); 156.1 (C-3); 190.2 (C=O)
5a*	12.3 ($CH_2\underline{C}H_3$); 34.9 (1-CH_3); 65.0 ($\underline{C}H_2CH_3$); 99.6 (C-3a); 105.6 (C-5); 143.6 (C-7a); 146.2 (C-6); 157.3 (C-3); 167.5 (C=O); 171.7 (C-4)
5b*	12.3 ($CH_2\underline{C}H_3$); 65.0 ($\underline{C}H_2CH_3$); 98.9 (C-3a); 104.9 (C-5); 125.0 (C Ar); 130.9 (C Ar); 132.1 (C Ar); 132.6 (C Ar); 142.8 (C-7a); 146.1 (C-6); 157.7 (C-3); 167.6 (C=O); 171.5 (C-4)
5c*	12.3 ($CH_2\underline{C}H_3$); 65.1 ($\underline{C}H_2CH_3$); 99.7 (C-3a); 105.7 (C-5); 118.0 (d, $^2J_{C-F}$ = 24, C-3',5'); 128.0 (d, $^3J_{C-F}$ = 10, C-2',6'); 128.6 (C-1'); 143.3 (C-7a); 146.1 (C-6); 157.3 (C-3); 164.8 (d, $^1J_{C-F}$ = 255, C-4');167.5 (C=O); 171.7 (C-4)
6	27.4 (CH_3); 33.6 (1-CH_3); 94.8 (C-3a); 110.8 (C-5); 150.5 (C-7a); 153.8 (C-6); 155.1 (C-3); 166.7 (C-4); 204.0 (C=O)
7	14.7 ($CH_2\underline{C}H_3$); 16.5 (4-CH_3); 33.3 (1-CH_3); 60.9 ($\underline{C}H_2CH_3$); 105.0 (C-3a); 117.3 (C-5); 148.3 (C-4); 151.1 (C-7a); 152.2 (C-6); 155.4 (C-3); 166.3 (C=O)

*The ^{13}C NMR spectra were recorded in CF_3COOH.

EXPERIMENTAL

The IR spectra were recorded in pellets with KBr on a UR-20 instrument. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz respectively) with TMS as internal standard. Elemental analysis was performed on a Perkin Elmer CHN Analyzer. The melting points were determined on a Kofler bench and were not corrected. Preparative liquid chromatography was conducted on a Combi Flash Companion instrument with a two-wave UV detector with detection at 235 and 254 nm; RediSep 12g column, sorbent silica gel 40-60 μm, pore diameter 60 Å; flow rate 30 ml/min; stepwise gradient elution.

The starting compounds were synthesized by the methods in [13] (compound **1a**) and [14] (compounds **1b-e**).

3-{[(2-Alkyl(aryl)-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)amino]methylidene}pentane-2,4-diones 3a-e, Diethyl {[(2-Alkyl(aryl)-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)amino]methylidene}propanedioates 3f-h, Ethyl 3-Oxo-2-{[(2-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-3-yl)amino]methylidene}butanoate (3i) (General Method). A mixture of compound **1a-e** (5 mmol) and compound **2a-c** (5 mmol) in 1,4-dioxane (12 ml) was refluxed for 4 h. After cooling, the precipitate was filtered off. The filtrate was evaporated, the residue was crystallized with the addition of EtOH (6-8 ml), and the crystals that formed were mixed with the first portion of the precipitate and recrystallized.

5-Acetyl-1-alkyl(aryl)-4-methyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-ones 4a-e, Ethyl 1-Alkyl-(aryl)-4-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates 5a-c, 5-Acetyl-4-hydroxy-1-methyl-1,2-dihydro-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (6), and Ethyl 1,4-Dimethyl-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (7) (General Method). A mixture of compound **3a-i** (1.5 mmol)

and diphenyl ether (5 ml) was heated with stirring at a bath temperature of 250°C for 1 h. After cooling, hexane (25 ml) was added to the reaction mixture, the mixture was thoroughly mixed, and the precipitate was filtered off. Compounds **4a-e** and **5a-c** were recrystallized, and compounds **6** and **7** were isolated by preparative chromatography (eluent $CHCl_3$–MeCN, 3:1 and 7:3 respectively).

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