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Synthesis and Some Transformations of Methyl [4-(Oxoacetyl)phenyl]carbamate

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Abstract—The oxidation of methyl (4-acetylphenyl)carbamate with selenium dioxide in dioxane–water (30 : 1) gave methyl [4-(oxoacetyl)phenyl]carbamate whose condensation with ethyl acetoacetate or diethyl malonate and hydrazine hydrate afforded ethyl 3-methyl-6-[4-(methoxycarbonylamino)phenyl]pyridazine-4-carboxylate and methyl {4-[5-(hydrazinecarbonyl)-6-oxo-1,6-dihydropyridazin-3-yl]phenyl}carbamate, respectively. The reaction of methyl [4-(oxoacetyl)phenyl]carbamate with *o*-phenylenediamine in dimethylformamide–ethanol on heating led to the formation of methyl [4-(quinoxalin-2-yl)phenyl]carbamate. Methyl {4-(5,7-dioxo-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)phenyl}carbamate and methyl {4-(5-oxo-7-sulfanylidene-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)phenyl}carbamate were synthesized by reactions of methyl [4-(oxoacetyl)phenyl]carbamate with barbituric and thiobarbituric acids, respectively, and hydrazine hydrate in the presence of zirconyl chloride octahydrate at room temperature.

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Arylglyoxals are important intermediate products in the synthesis of heterocyclic compounds [1–5]. With the goal of obtaining new functionalized hetarylcarbamates as potential prodrugs [6–9], methyl (4-acetylphenyl)carbamate (**1**) was oxidized with selenium dioxide in dioxane–water (30 : 1) according to the procedure described in [10]. We thus isolated methyl [4-(oxoacetyl)phenyl]carbamate (**2**) (Scheme 1). The ^{1}H NMR spectrum of **2** lacked singlet typical of acetyl methyl group, but a new singlet appeared at δ 5.54 ppm due to the CHO proton.

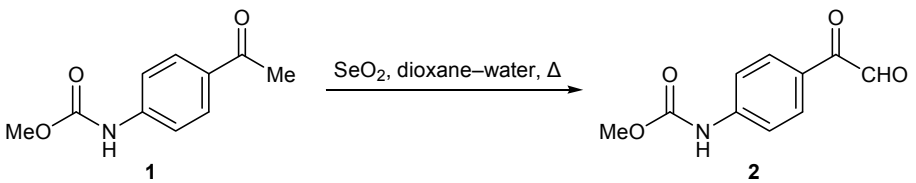
Pyridazine derivatives were found to exhibit anticarcinogenic [11], antitubercular [12], antihypertensive [13], antifungal [14, 15], and antimicrobial activities [16–19]. They also exert rapid systemic effect on plants and are active at very low concentrations. Some pyridazine derivatives are structural analogs of phytohormones [15] present in living cells and responsible for various biochemical transformations [16].

Pyridazine derivatives can be synthesized by condensation of glyoxals with β-keto esters in the presence of hydrazine hydrate [20]. Methyl [4-(oxoacetyl)-phenyl]carbamate (**2**) was brought into three-component condensation with ethyl acetoacetate and hydrazine hydrate at room temperature. The reaction was complete in 1 h, and ethyl 6-[4-(methoxycarbonylamino)phenyl]-3-methylpyridazine-4-carboxylate (**3**) was isolated in 74% yield (Scheme 2). Compound **3** showed in the ^{1}H NMR spectrum singlets at δ 2.38 ppm due to methyl protons and δ 8.56 ppm due to 5-H in the pyridazine ring, as well as other proton signals.

By condensation of **2** with diethyl malonate in pyridine at room temperature and subsequent treatment with hydrazine hydrate we obtained 75% of methyl {4-[5-(hydrazinecarbonyl)-6-oxo-1,6-dihydropyridazin-3-yl]phenyl}carbamate (**4**) (Scheme 3).

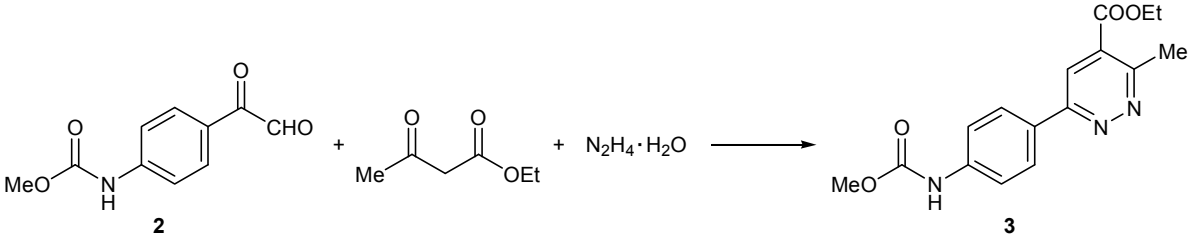
Quinoxaline derivatives are known to possess diverse biological properties; in particular, antibacte-

Scheme 1.

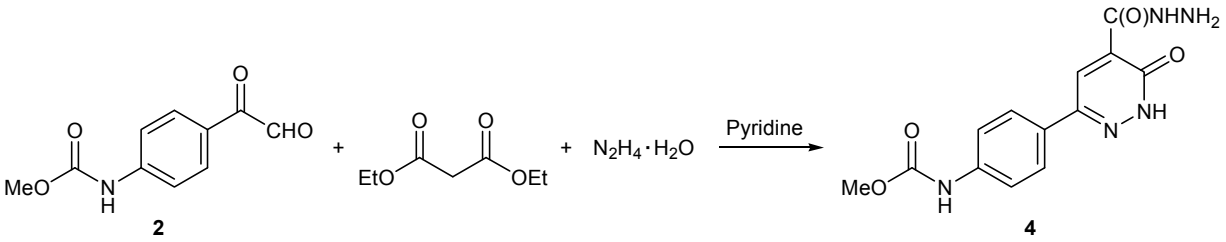


1 **2**

Scheme 2.



Scheme 3.

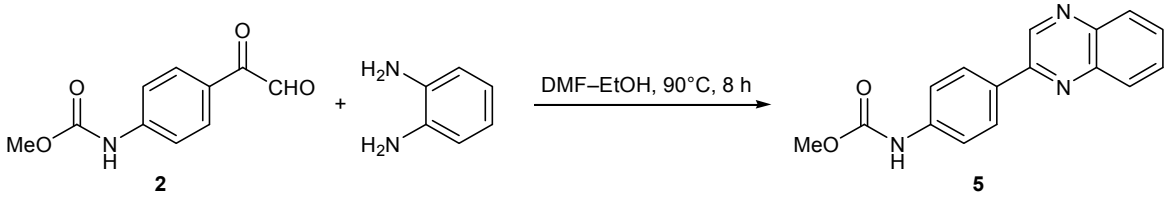


rial, antitumor, cytotoxic, and antiviral agents (including those active against HIV) were found among compounds of this class [21]. Heating of an equimolar mixture of **2** and *o*-phenylenediamine in DMF–EtOH afforded methyl [4-(quinoxalin-2-yl)phenyl]carbamate (**5**) in 89% yield (Scheme 4).

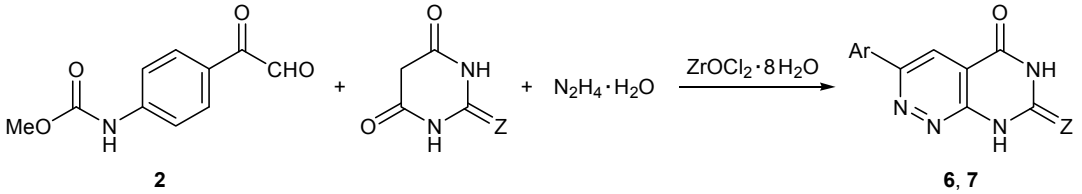
Rimaz et al. [22] previously described the three-component condensation of arylglyoxals with barbituric (thiobarbituric) acid and hydrazine hydrate in the presence of a catalytic amount of zirconyl chloride octahydrate, which afforded pyrimidopyridazine derivatives. We reacted compound **2** with barbituric (thiobarbituric) acid and hydrazine hydrate in the presence of zirconyl chloride octahydrate (Lewis acid) at room temperature and thus obtained methyl {4-(5,7-dioxo-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)-phenyl}carbamate (**6**) and methyl {4-(5-oxo-7-sulfanylidene-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)phenyl}carbamate (**7**) in 74 and 76% yield, respectively (Scheme 5). When the amount of the catalyst exceeded 20 mol %, the reaction was accompanied by side processes. Presumably, coordination of the oxygen atoms of arylglyoxal **2** to the zirconium atom increases electrophilicity of the formyl carbon atom and favors nucleophilic attack of C^5 of barbituric (thiobarbituric) acid, as well as subsequent pyridazine ring closure with participation of hydrazine hydrate.

The structure of compounds **6** and **7** was confirmed by IR and ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra of **6** and **7** we observed a singlet at δ 8.58–8.59 ppm due to 4-H, which is consistent with the data of [22] for structurally related compounds.

Scheme 4.



Scheme 5.



Ar = 4-MeOC(O)NHC$_6$H$_4$; **6**, Z = O; **7**, Z = S.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DRX 500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The ^{13}C NMR spectra were measured on the same instrument at 126 MHz in DMSO-d_6 with complete decoupling from protons. The IR spectra (4000–400 cm^{-1}) were recorded in KBr on an InfraLUM FT-02 spectrometer with Fourier transform. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

Methyl [4-(oxoacetyl)phenyl]carbamate (2). A mixture of 1.11 g (0.01 mol) of selenium dioxide and 6 mL of dioxane containing 0.2 mL of water was stirred at 50–55°C until it became homogeneous, 1.93 g (0.01 mol) of methyl (4-acetylphenyl)carbamate (**1**) was added, and the mixture was stirred for 4 h on heating on a boiling water bath. The hot solution was separated by decanting, and the solvent was removed under reduced pressure. Yield 1.76 g (85%), light yellow crystals, mp 182–183°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 1675, 1710 (C=O), 1610, 1575, 1560 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, NHCO$_2$**Me**), 5.54 s (1H, CHO), 7.28 d (2H, H$_{arom}$, J = 8.5 Hz), 7.96 d (2H, H$_{arom}$, J = 8.5 Hz), 9.58 br.s (1H, N**H**CO$_2$Me). Found, %: C 58.04; H 4.18; N 6.59. $C_{10}H_9NO_4$. Calculated, %: C 57.97; H 4.38; N 6.76.

Ethyl 3-methyl-6-[4-(methoxycarbonylamino)-phenyl]pyridazine-4-carboxylate (3). Hydrazine hydrate (99%), 0.25 mL (5 mmol), was added to a mixture of 0.13 g (1 mmol) of ethyl acetoacetate and 0.207 g (1 mmol) of methyl [4-(oxoacetyl)phenyl]carbamate (**2**) in 5 mL of water. The mixture was stirred for 1 h at room temperature, and the precipitate was filtered off, washed with water (4×10 mL), dried in air, and recrystallized from ethanol. Yield 0.23 g (74%), yellow crystals, mp 125–127°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1710, 1690 (C=O), 1610, 1575, 1565 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH$_2$C**H**$_3$, J = 6.7 Hz), 2.38 s (3H, CH$_3$), 4.41 q (2H, OCH$_2$, J = 6.7 Hz), 3.71 s (3H, OMe), 7.15 d (2H, H$_{arom}$, J = 8.6 Hz), 8.12 d (2H, H$_{arom}$, J = 8.6 Hz), 8.56 s (1H, 5-H) 9.59 br.s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 13.91 (CH$_2$**C**H$_3$), 19.22 (Me), 52.59 (OMe), 59.08 (OCH$_2$), 116.60, 124.59, 124.87, 129.05, 131.56, 134.15, 140.01, 153.33 (C$_{arom}$), 155.14 (NHCO), 167.15 (**C**O$_2$Et). Found, %: C 60.80; H 5.28; N 13.21. $C_{16}H_{17}N_3O_4$. Calculated, %: C 60.94; H 5.43; N 13.33.

Methyl {4-[5-(hydrazinecarbonyl)-6-oxo-1,6-dihydropyridazin-3-yl]phenyl}carbamate (4). A mixture of 0.15 mL (1 mmol) of diethyl malonate and 0.207 g (1 mmol) of compound **2** in 1 mL of pyridine was stirred for 40 min at room temperature, 0.15 mL (3 mmol) of 99% hydrazine hydrate was added, and the mixture was stirred for 30 min and diluted with 5 mL of water. The precipitate was filtered off, dried in air, and recrystallized from methanol. Yield 0.23 g (75%), yellow crystals, mp 165–167°C. IR spectrum, ν, cm^{-1}: 3230–3390 (NH, NH$_2$), 1750, 1720 (C=O), 1620, 1575, 1560 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, OMe), 6.76–6.79 m (2H, NHN**H**$_2$), 7.58 d (2H, H$_{arom}$, J = 7.7 Hz), 7.98 d (2H, H$_{arom}$, J = 7.7 Hz), 8.63 s (1H, 5-H), 9.32 br.s (1H, N**H**NH$_2$), 9.59 br.s (1H, N**H**CO$_2$Me), 12.84 s (1H, 1-H). Found, %: C 51.27; H 4.17; N 22.92. $C_{13}H_{13}N_5O_4$. Calculated, %: C 51.48; H 4.32; N 23.09.

Methyl [4-(quinoxalin-2-yl)phenyl]carbamate (5). A mixture of 0.108 g (1 mmol) of *o*-phenylenediamine, 0.207 g (1 mmol) of methyl [4-(oxoacetyl)-phenyl]carbamate (**2**), 1 mL of dimethylformamide, and 3 mL of ethanol was heated for 8 h at 90°C. The mixture was cooled, and the precipitate was filtered off, washed with cold ethanol (5 mL), and recrystallized from ethanol. Yield 0.22 g (79%), colorless crystals, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 1710 (C=O), 1620, 1570, 1560 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, OMe), 7.53–7.75 m (5H, H$_{arom}$), 7.97–8.03 m (2H, H$_{arom}$), 8.47 s (1H, H$_{arom}$), 9.35 s (1H, 3-H), 9.58 br.s (1H, NH). Found, %: C 68.56; H 4.52; N 14.88. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.05.

Methyl {4-(5,7-dioxo-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)phenyl}carbamate (6). A mixture of 0.207 g (1 mmol) of methyl [4-(oxoacetyl)phenyl]carbamate (**2**), 0.128 g (1 mmol) of barbituric acid, 0.2 mL (4 mmol) of 99% hydrazine hydrate, and 0.064 g (0.2 mmol) of zirconyl chloride octahydrate in 7 mL of water was stirred for 30 min at room temperature. The precipitate was filtered off, washed with water (30 mL), dried in air, and recrystallized from methanol. Yield 0.23 g (72%), gray–green crystals, mp 310–312°C (decomp.). IR spectrum, ν, cm^{-1}: 3220–3400 (NH), 1750, 1710 (C=O), 1610, 1570, 1565 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, OMe), 7.11 d (2H, H$_{arom}$, J = 8.4 Hz), 7.98 d (2H, H$_{arom}$, J = 8.4 Hz), 8.59 s (1H, 4-H), 9.54 br.s (1H, N**H**CO$_2$Me), 11.32 s (1H, NH), 14.07 s (1H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 52.45 (OMe),

109.21, 118.36, 123.63, 127.78, 129.61, 135.13, 137.61, 152.10 (C_{arom}), 154.96 (NH**C**O_2Me), 160.17, 163.65 (C=O). Found, %: C 53.49; H 3.36; N 22.08. $C_{14}H_{11}N_5O_4$. Calculated, %: C 53.68; H 3.54; N 22.36.

Methyl {4-(5-oxo-7-sulfanylidene-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazin-3-yl)phenyl}-carbamate (7) was synthesized in a similar way from 0.207 g (1 mmol) of compound (**2**), 0.144 g (1 mmol) of thiobarbituric acid, and 0.2 mL (4 mmol) of 99% hydrazine hydrate in the presence of 0.064 g (0.2 mmol) of zirconyl chloride octahydrate. Yield 0.22 g (68%), yellow crystals, mp 287–289°C (decomp.). IR spectrum, ν, cm^{-1}: 3210–3400 (NH), 1750, 1720 (C=O), 1610, 1575, 1565 (C=C_{arom}), 1126 (C=S). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, OMe), 7.13 d (2H, H_{arom}, J = 8.7 Hz), 7.98 d (2H, H_{arom}, J = 8.7 Hz), 8.59 s (1H, 4-H), 9.54 br.s (1H, N**H**CO_2Me), 11.42 s (1H, NHCO), 13.82 br.s (1H, NHCS). ^{13}C NMR spectrum, δ_C, ppm: 52.45 (OMe), 109.1, 119.31, 127.13, 131.14, 134.84, 135.25, 139.32, 151.42, 152.26 (NH**C**O_2Me), 160.14 (C=O), 160.41 (C=S). Found, %: C 50.92; H 3.14; N 21.05. $C_{14}H_{11}N_5O_3S$. Calculated, %: C 51.06; H 3.37; N 21.27.

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