

Heterocyclization of Functionalized Heterocumulenes with C,N-, C,O-, and C,S-Binucleophiles: VIII*. Synthesis of Pyrano(chromeno)[3,4-*e*][1,3]oxazines by Condensation of 1-Chloroalkyl Isocyanates with 4-Hydroxy-6-methylpyran-2-one and 4-Hydroxycoumarin

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Abstract—1-Chlorobenzyl isocyanates react with 4-hydroxy-6-methylpyran-2-one and 4-hydroxycoumarin forming 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano(chromeno)[3,4-*e*][1,3]oxazine-2,5-diones. The reaction of 1-aryl-2,2,2-trifluoro-1-chloroethyl isocyanates with the above substrates gives rise to structurally isomeric 2-aryl-2-trifluoromethyl-2,3-dihydro-2*H*,5*H*-pyrano(chromeno)[3,4-*e*][1,3]-oxazine-4,5-diones.

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The heterocyclic system of pyrano(chromeno)-[3,4-*e*][1,3]oxazine is promising both in synthetic and biological aspects. In particular, the intermediate formation of pyrano[3,4-*e*][1,3]oxazine type compounds underlies the design of the synthesis of a macrolide antitumor antibiotic lankacidin C [2, 3]. A number of chromeno[3,4-*e*][1,3]oxazine exhibit a high bactericidal and fungicidal action [4].

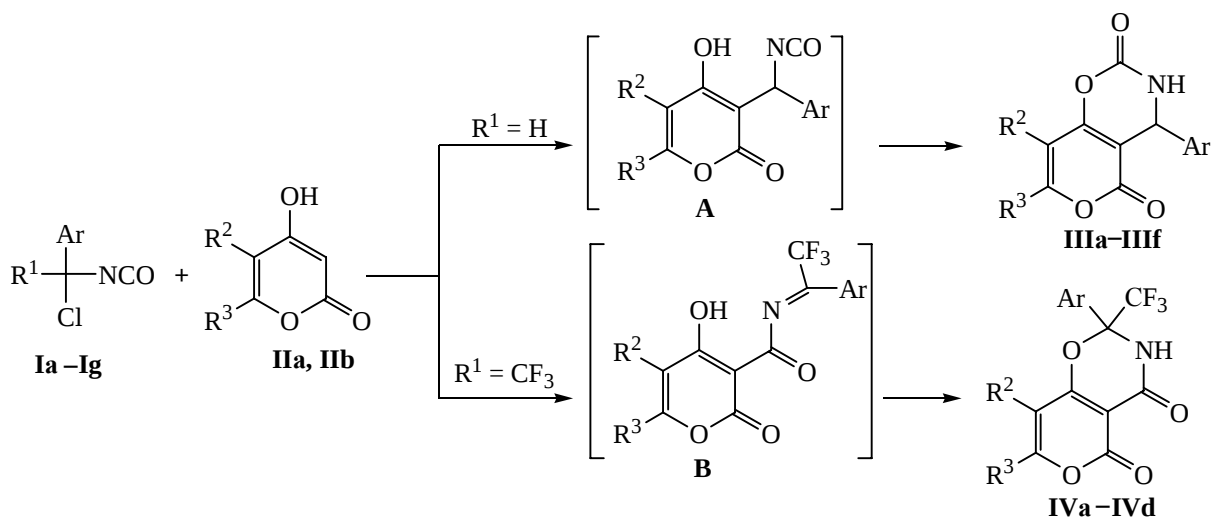
Pyrano[3,4-*e*][1,3]oxazine derivatives are as a rule obtained by reactions of malonyl dichloride with amides [5], nitriles [6], and heterocumulenes. The synthesis of chromeno[3,4-*e*][1,3]oxazine is performed by condensation of 4-hydroxycoumarins with azomethines and aldehydes [4, 8]. The use to this end of a reaction of 2-(3,4-dimethoxyphenyl)chromen-4-one with chloro-sulfonyl isocyanate proved to be less efficient due to the formation of side products, chromenooxathiazines [9].

We recently discovered [10] the rules of reaction between cyclic β -diketones and 1-chloroalkyl isocyanates leading to the formation of carbofused 1,3-oxazines, and in this study we applied this reaction to the development of a convenient preparation method for pyrano(chromeno)[3,4-*e*][1,3]oxazine derivatives. It should be noted that despite the structural similarity of

the enol form of cyclic β -diketones and 4-hydroxypyran-2-ones the unambiguous prediction of the regiodirection in the condensation of the latter compounds with 1-chloroalkyl isocyanates was not possible. Moreover, although previously [11] a similarity was observed in the reactions of acetylacetone and dimedone with 1-aryl-2,2,2-trifluoro-1-chloroethyl isocyanates, the reaction of the latter with ethyl acetoacetate was not selective and gave rise to a complex products mixture both of cyclic and acyclic structure.

A comprehensive experimental investigation revealed that the direction of reaction of isocyanates **Ia–Ig** with 4-hydroxypyran-2-one (**IIa**) and 4-hydroxycoumarin (**IIb**) is governed solely by the character of substituent R^1 in the isocyanate molecule. The reaction with 1-chlorobenzyl isocyanates **Ia–Ie** ($R^1 = H$) occurred in toluene at 60°C, did not require the presence of an organic base, and led to the formation of 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano(chromeno)[3,4-*e*][1,3]oxazine-2,5-diones **IIIa–IIIf** in 66–79% yields. 1-Aryl-2,2,2-trifluoro-1-chloroethyl isocyanates **If** and **Ig** reacted with compounds **IIa** and **IIb** in the presence triethylamine and gave in 71–80% yields structurally isomeric 2-aryl-2-trifluoromethyl-2,3-dihydro-4*H*,5*H*-pyrano(chromeno)[3,4-*e*][1,3]oxazine-4,5-diones **IVa–IVd**. Proceeding from these results and the data previously

* For Communication II, see [1].



I, $R^1 = \text{H}$, $\text{Ar} = \text{Ph}$ (**a**), 2- FC_6H_4 (**b**), 3- BrC_6H_4 (**c**), 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**d**), 3,4- $\text{Cl}_2\text{C}_6\text{H}_3$ (**e**); $R^1 = \text{CF}_3$, $\text{Ar} = 4\text{-MeC}_6\text{H}_4$ (**f**), 4- MeOC_6H_4 (**g**); **II**, $R^2 = \text{H}$, $R^3 = \text{Me}$ (**a**); $R^2, R^3 = \text{benzo}$ (**b**); **III**, $R^2 = \text{H}$, $R^3 = \text{Me}$, $\text{Ar} = 3\text{-BrC}_6\text{H}_4$ (**a**), 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**b**), 3,4- $\text{Cl}_2\text{C}_6\text{H}_3$ (**c**); $R^2, R^3 = \text{benzo}$, $\text{Ar} = \text{Ph}$ (**d**), 2- FC_6H_4 (**e**), 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**f**); **IV**, $R^2 = \text{H}$, $R^3 = \text{Me}$, $\text{Ar} = 4\text{-MeC}_6\text{H}_4$ (**a**), 4- $\text{CH}_3\text{OC}_6\text{H}_4$ (**b**); $R^2, R^3 = \text{benzo}$, $\text{Ar} = 4\text{-MeC}_6\text{H}_4$ (**c**), 4- MeOC_6H_4 (**d**).

obtained [10] it may be reliably concluded that 1-chlorobenzyl isocyanates **Ia–Ie** are predominantly prone to the C-alkylation of the 4-hydroxypyran ring giving intermediates **A**. At the same time 1-chloroalkyl isocyanates **If** and **Ig** behave with respect to the same heterocyclic system as C-carbamoylating agents providing in the first stage intermediates of **B** type.

The structure of synthesized compounds **IIIa–IIIc** and **IVa–IVd** was confirmed by IR, ^1H , ^{13}C , and ^{19}F NMR spectra. In the IR spectra of pyrano(chromeno)oxazine-2,5-diones **IIIa–IIIc** the absorption bands of $\text{C}=\text{O}$ groups are observed in the region 1760–1770 and 1720–1730 cm^{-1} indicating the presence of the urethane fragment in the structure of the molecule. In the spectra of the structurally isomeric pyrano(chromeno)oxazine-4,5-diones **IVa–IVd** alongside the absorption bands of the carbonyls in the pyran (coumarin) ring absorption bands are also observed in the region 1670–1680 cm^{-1} corresponding to the $\text{C}=\text{O}$ group of the amide fragment of the heterocyclic system. NH group of all compounds mentioned give rise to absorption in the region 3100–3400 cm^{-1} . In the ^1H NMR spectra of compounds **IIIa–IIIc** doublets of protons H^4 and NH are observed at 5.24–5.57 and 8.92–9.19 ppm respectively with coupling constants 2.0–2.4 Hz. The fluorine signals of the trifluoromethyl groups in compounds **IVa–IVd** are observed in the region $-80.70 \div -81.33$ ppm. ^{13}C NMR spectra were also measured for compounds **IIIc**, **IIId** and **IVb**, **IVc**. We found that the signals of C^4 atoms of

pyrano(chromeno)oxazines of type **III** appeared in a characteristic region 51.8–53.2 ppm, and the spectra of pyrano(chromeno)oxazines of type **IV** were characterized by the presence of quartet signals from C^2 atoms ($^2J_{\text{C-F}}$ 28–35 Hz) and quartets from carbon atoms of the CF_3 group ($^1J_{\text{C-F}}$ 283–286 Hz) in the regions 89–90 and 120.3–121.4 ppm respectively reliably confirming their structures [10].

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from samples pelletized with KBr. ^1H , ^{13}C , and ^{19}F NMR spectra were registered from solutions in $\text{DMSO}-d_6$ on a spectrometer Varian-Gemini (299.95, 75.4, and 282.2 MHz respectively), internal references TMS (^1H , ^{13}C), CCl_3F (^{19}F). 1-Chlorobenzyl isocyanates **Ia–Ie** [12] and aryl-2,2,2-trifluoro-1-chloroethyl isocyanates **If** and **Ig** [13] were obtained by published procedures.

4-Aryl-3,4-dihydro-2H,5H-pyrano(chromeno)-[3,4-e][1,3]oxazine-2,5-diones IIIa–IIIc. To a solution of 5 mmol of isocyanate **Ia–Ie** in 20 ml of anhydrous toluene was added 5 mmol of compound **IIa** or **IIb**. The reaction mixture was stirred for 4 h at 60°C, cooled, the precipitate formed was filtered off, washed with toluene, dried, and recrystallized from ethanol.

4-(Bromophenyl)-7-methyl-3,4-dihydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,5-dione (IIIa). Yield 66%, mp 225–227°C. IR spectrum, cm^{-1} : 3300, 3250 (NH),

1760, 1730 (C=O). ^1H NMR spectrum, δ , ppm: 2.25 s (3H, CH_3), 5.24 d (1H, CH, J 2.0 Hz), 6.31 s (1H, CH), 7.31–7.34 m (2H_{arom}), 7.47–7.49 m (2H_{arom}), 8.92 d (1H, NH, J 2.0 Hz). Found, %: C 49.78; H 3.05; N 4.10. $\text{C}_{14}\text{H}_{10}\text{BrNO}_4$. Calculated, %: C 50.03; H 3.00; N 4.17.

7-Methyl-4-(4-nitrophenyl)-3,4-dihydro-2H,5H-pyrano[3,4-*e*][1,3]oxazine-2,5-dione (IIIb). Yield 70%, mp 154–156°C. IR spectrum, cm^{-1} : 3310, 3220 (NH), 1760, 1720 (C=O). ^1H NMR spectrum, δ , ppm: 2.25 s (3H, CH_3), 5.41 d (1H, CH, J 2.4 Hz), 6.31 s (1H, CH), 7.61 d (2H_{arom} , J 9.0 Hz), 8.22 d (2H_{arom} , J 9.0 Hz), 9.02 d (1H, NH, J 2.4 Hz). Found, %: C 55.76; H 3.27; N 9.21. $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_6$. Calculated, %: C 55.64; H 3.33; N 9.27.

4-(3,4-Dibromophenyl)-7-methyl-3,4-dihydro-2H,5H-pyrano[3,4-*e*][1,3]oxazine-2,5-dione (IIIc). Yield 73%, mp 230–233°C. IR spectrum, cm^{-1} : 3300, 3200 (NH), 1770, 1730 (C=O). ^1H NMR spectrum, δ , ppm: 2.25 s (3H, CH_3), 5.28 d (1H, CH, J 2.4 Hz), 6.32 s (1H, CH), 7.29 d (1H_{arom} , J 9.6 Hz), 7.53–7.58 m (2H_{arom}), 8.93 d (1H, NH, J 2.4 Hz). ^{13}C NMR spectrum, δ , ppm: 19.39, 51.84, 97.54, 98.21, 127.37, 129.38, 130.76, 131.00, 141.95, 146.00, 160.23, 160.26, 164.38. Found, %: C 51.39; H 2.88; N 4.34. $\text{C}_{14}\text{H}_9\text{Cl}_2\text{NO}_4$. Calculated, %: C 51.56; H 2.78; N 4.29.

4-Phenyl-3,4-dihydro-2H,5H-chromeno[3,4-*e*][1,3]oxazine-2,5-dione (IIId). Yield 75%, mp 250–252°C. IR spectrum, cm^{-1} : 3400 (NH), 1760, 1720 (C=O). ^1H NMR spectrum, δ , ppm: 5.41 d (1H, CH, J 2.0 Hz), 7.33–7.47 m (7H_{arom}), 7.70 t (1H_{arom} , J 6.4 Hz), 7.85 d (1H_{arom} , J 6.4 Hz), 8.98 d (1H, NH, J 2.0 Hz). ^{13}C NMR spectrum, δ , ppm: 53.23, 102.04, 112.75, 116.52, 122.41, 124.77, 127.07, 128.21, 128.59, 133.11, 140.84, 146.05, 152.59, 154.99, 158.51. Found, %: C 69.55; H 3.73; N 4.83. $\text{C}_{17}\text{H}_{11}\text{NO}_4$. Calculated, %: C 69.62; H 3.78; N 4.78.

4-(2-Fluorophenyl)-3,4-dihydro-2H,5H-chromeno[3,4-*e*][1,3]oxazine-2,5-dione (IIIf). Yield 67%, mp 227–229°C. IR spectrum, cm^{-1} : 3320 (NH), 1760, 1730 (C=O). ^1H NMR spectrum, δ , ppm: 5.54 d (1H, CH, J 2.0 Hz), 7.12–7.22 m (2H_{arom}), 7.38–7.51 m (4H_{arom}), 7.70 t (1H_{arom} , J 7.5 Hz), 7.91 d (1H_{arom} , J 7.5 Hz), 9.05 d (1H, NH, J 2.0 Hz). Found, %: C 65.84; H 3.15; N 4.67. $\text{C}_{17}\text{H}_{10}\text{FNO}_4$. Calculated, %: C 65.60; H 3.24; N 4.50.

4-(4-Nitrophenyl)-3,4-dihydro-2H,5H-chromeno[3,4-*e*][1,3]oxazine-2,5-dione (IIIIf). Yield 72%, mp 234–236°C. IR spectrum, cm^{-1} : 3320 (NH), 1760, 1720 (C=O). ^1H NMR spectrum, δ , ppm: 5.57 d

(1H, CH, J 2.2 Hz), 7.40–7.49 m (2H_{arom}), 7.69–7.74 m (3H_{arom}), 7.89 d (1H_{arom} , J 7.8 Hz), 8.20 d (2H_{arom} , J 8.7 Hz), 9.19 d (1H, NH, J 2.2 Hz). Found, %: C 60.20; H 3.09; N 8.22. $\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_6$. Calculated, %: C 60.36; H 2.98; N 8.28.

2-Aryl-2-trifluoromethyl-2,3-dihydro-4H,5H-pyrano(chromeno)[3,4-*e*][1,3]oxazine-4,5-diones IVa–IVd. To a solution of 5 mmol of isocyanate **If** or **Ig** in 20 ml of anhydrous toluene was added 5 mmol of compound **IIa** or **IIb** and then at stirring within 0.5 h was added 0.7 ml (5 mmol) of triethylamine in 10 ml of anhydrous toluene. The reaction mixture was stirred at room temperature for 6 h, the precipitate formed was filtered off, washed with water, dried, and recrystallized from ethanol.

7-Methyl-2-(4-methylphenyl)-2-trifluoromethyl-2,3-dihydro-4H,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (IVa). Yield 77%, mp 215–217°C. IR spectrum, cm^{-1} : 3300 (NH), 1760, 1680 (C=O). ^1H NMR spectrum, δ , ppm: 2.26 s (3H, CH_3), 2.34 s (3H, CH_3), 6.48 s (1H, CH), 7.28 d (2H_{arom} , J 8.4 Hz), 7.48 d (2H_{arom} , J 8.4 Hz), 10.10 s (1H, NH). ^{19}F , δ , ppm: –81.31. Found, %: C 56.81; H 3.59; N 4.10. $\text{C}_{16}\text{H}_{12}\text{F}_3\text{NO}_4$. Calculated, %: C 56.64; H 3.57; N 4.13.

7-Methyl-2-(4-methoxyphenyl)-2-trifluoromethyl-2,3-dihydro-4H,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (IVb). Yield 80%, mp 184–186°C. IR spectrum, cm^{-1} : 3310 (NH), 1760, 1670 (C=O). ^1H NMR spectrum, δ , ppm: 2.27 s (3H, CH_3), 3.79 s (3H, CH_3), 6.46 s (1H, CH), 7.00 d (2H_{arom} , J 8.7 Hz), 7.52 d (2H_{arom} , J 8.7 Hz), 10.06 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 20.19, 55.27, 89.71 q (C^2 , J 28.7 Hz), 94.26, 98.23, 114.23, 120.34 q (CF_3 , J 286.2 Hz), 124.48, 128.35, 156.18, 157.64, 160.97, 169.49, 170.53. ^{19}F NMR spectrum, δ , ppm: –81.33. Found, %: C 54.23; H 3.36; N 4.07. $\text{C}_{16}\text{H}_{12}\text{F}_3\text{NO}_5$. Calculated, %: C 54.09; H 3.40; N 3.94.

2-(4-Methylphenyl)-2-trifluoromethyl-2,3-dihydro-4H,5H-chromeno[3,4-*e*][1,3]oxazine-4,5-dione (IVc). Yield 75%, mp 218–220°C. IR spectrum, cm^{-1} : 3220, 3100 (NH), 1760, 1680 (C=O). ^1H NMR spectrum, δ , ppm: 2.32 s (3H, CH_3), 7.26 d (2H_{arom} , J 8.4 Hz), 7.38 d (1H_{arom} , J 8.4 Hz), 7.49 t (1H_{arom} , J 7.2 Hz), 7.57 d (2H_{arom} , J 8.4 Hz), 7.82 t (1H_{arom} , J 7.2 Hz), 8.07 d (1H_{arom} , J 8.4 Hz), 10.39 s (1H, NH). ^{13}C NMR spectrum, δ , ppm: 20.67, 90.30 q (C^2 , J 35.0 Hz), 97.58, 112.38, 116.85, 121.44 q (CF_3 , J 283.7 Hz), 124.10, 125.18, 126.60, 128.85, 129.58, 129.79, 136.19, 141.13, 154.70, 157.31, 164.75. ^{19}F NMR spectrum, δ , ppm: –80.70. Found, %: C 60.63; H 3.18;

N 3.75. $C_{19}H_{12}F_3NO_4$. Calculated, %: C 60.81; H 3.22; N 3.73.

2-(4-Methoxyphenyl)-2-trifluoromethyl-2,3-dihydro-4H,5H-chromeno[3,4-e][1,3]oxazine-4,5-dione (IVd). Yield 71%, mp 190–192°C. IR spectrum, cm^{-1} : 3300, 3150 (NH), 1760, 1680 (C=O). 1H NMR spectrum, δ , ppm: 3.77 s (3H, CH_3), 6.99 d ($2H_{arom}$, J 8.7 Hz), 7.38 d ($1H_{arom}$, J 8.7 Hz), 7.50 t ($1H_{arom}$, J 8.1 Hz), 7.59 d ($2H_{arom}$, J 8.7 Hz), 7.83 t ($1H_{arom}$, J 8.1 Hz), 8.10 d ($1H_{arom}$, J 8.7 Hz), 10.40 s (1H, NH). ^{19}F , δ , ppm: –81.26. Found, %: C 58.29; H 3.11; N 3.64. $C_{19}H_{12}F_3NO_5$. Calculated, %: C 58.32; H 3.09; N 3.58.

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