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Mendeleev Commun., 2017, **27**, 172–174
Mendeleev Communications

Synthesis of ethyl 4-(isoxazol-4-yl)-2,4-dioxobutanoates from ethyl 5-aroyl-4-pyrone-2-carboxylates and hydroxylamine

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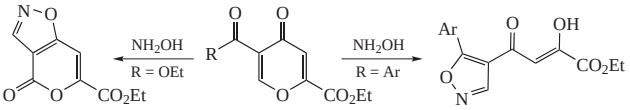
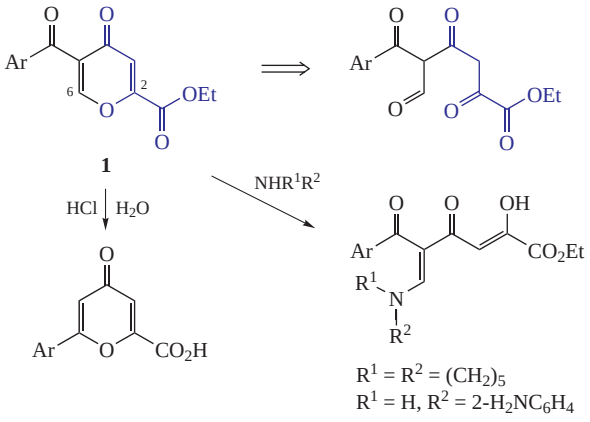
DOI: 10.1016/j.mencom.2017.03.022

Ethyl 5-aroyl-4-pyrone-2-carboxylates react with hydroxylamine in ethanol at –20 °C for 30 days to produce ethyl 4-(5-arylisoxazol-4-yl)-2,4-dioxobutanoates (yields 20–67%). The similar reaction of diethyl 4-pyrone-2,5-dicarboxylate gives ethyl 4-oxo-4*H*-pyrano[3,4-*d*]isoxazole-6-carboxylate in 37% yield.



Currently, researchers pay close attention to derivatives of 2,4-dioxobutanoic acid that show high anti-HIV activity.[1] The modern anti-HIV drugs Raltegravir (2007)[2] and Dolutegravir (2012)[3] belong to this series of compounds. Some recently studied hetaryldioxobutanoic derivatives usually obtained by the Claisen condensation of methyl ketones with diethyl oxalate[4] act as inhibitors of HIV-integrase[5] or as inhibitors of two HIV enzymes, namely, integrase and reverse transferase, simultaneously.[6(a),(b)] In view of this, studies on the further functionalization of dioxobutanoic acids, including those that involve changes in the nature of the heterocyclic substituent, are of current interest.

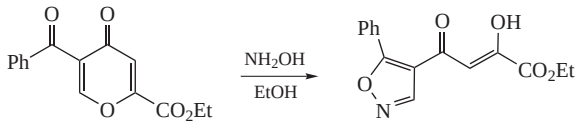
We have recently reported a simple and efficient method for synthesizing ethyl esters of 5-aroyl-4-pyrone-2-carboxylic (5-aroylcomanic) acids **1** by condensation of 1-aryl-2-(dimethylaminomethylidene)butane-1,3-diones (obtained from 1,3-diketones and dimethylformamide dimethyl acetal) with diethyl oxalate in the presence of NaH in THF.[7] These γ-pyrones incorporate five carbonyl groups, two of which are in latent state and appear only after opening of the pyrone ring (Scheme 1). Apart from the dioxobutanoic acid residue, pyrones **1** also contain a 1,3-dicarbonyl residue that can form a heterocyclic system on treatment with a dinucleophile. Unfortunately, data on reactions of this kind were not found in the literature. As to the esters of 5-aroyl-4-pyrone-2-carboxylic acids **1**, it is only known that they are rearranged to 6-aroylcomanic acids in acidic media[7] and react with amines at the C-6 atom with opening of the pyrone ring to give linear 4-aminomethylidene-6-aryl-2,4,6-trioxohexanoates[7,8] (Scheme 1).



Scheme 1

In this work, we were the first to study the reaction of ethyl 5-aroylcomanoates **1** with hydroxylamine using ethyl 5-benzoylcomanoate **1a** as the model substrate. Initially, we used hydroxylamine hydrochloride and hydroacetate in ethanol at room temperature, but these reactions gave complex mixtures of products. The reaction with free hydroxylamine at 0–20 °C for 2 h really afforded the expected isoxazole **2a** in only 15% yield, however, the yield could be raised to 46% by performing the reaction in an EtOH–THF mixture at –20 °C for 30 days (THF was used to improve the solubility of the starting pyrone) (Scheme 2).†

It should be noted that the literature[9] contains only data on the reactions of 2,6-disubstituted 4-pyrones with hydroxylamine to give mainly oximes, pyridones or pyridine 1-oxides. The formation of isoxazoline and isoxazole derivatives was observed only in the case of 2-(2-furyl)-6-phenyl-4-pyrone.[9(e)]



1a **2a**

Solvent	*T*/°C	*t*/days	Yield (%)
EtOH	0→20	1 h	15
EtOH–THF	–20	10	25
EtOH–THF	–20	14	39
EtOH–THF	–20	30	46

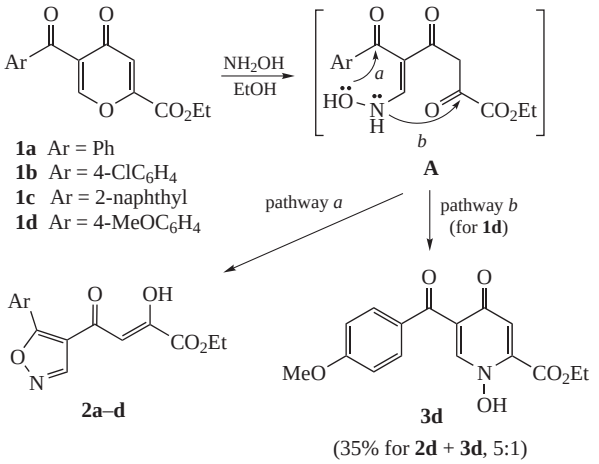
Scheme 2

† IR spectra were recorded on a PerkinElmer Spectrum BX-II instrument with ATR accessory. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 or $CDCl_3$, with TMS and residual solvent peaks as internal standard.

General procedure for the synthesis of ethyl 4-(isoxazol-4-yl)-2,4-dioxobutanoates **2**. A mixture of NH_2OH·HCl (0.087 g, 1.25 mmol) and KOH (0.062 g, 1.11 mmol) was stirred in EtOH (2 ml) at 20 °C for 30 min. The precipitate of KCl was filtered off and washed with 1 ml EtOH, then cold solution of pyrone **1** (0.73 mmol) in THF (1 ml for **1a** or 2–3 ml for **1b**,**c**) was added to the filtrate cooled to –20 °C. The reaction mixture was kept at –20 °C for 30 days. The resulting residue was filtered, washed with 1 ml cold EtOH and, if necessary, recrystallized from EtOH.

Having the optimum conditions for the oximation of pyrones **1** in hand, we performed this reaction with 5-aroylcomanoates **1b**–**d** and obtained compounds **2a**–**d** in 20–66% yields (Scheme 3).† A small admixture of the corresponding pyridone **3** was sometimes detected in unpurified products. It could be easily removed by recrystallization from EtOH. The reaction with 4-methoxybenzoylpyrone **1d** gave a mixture of isoxazole **2d** and pyridone **3d** in 5 : 1 ratio and in 35% total yield. Isoxazole **2d** was isolated in 20% yield by additional recrystallization from EtOH. Pyridone **3d** was also obtained pure, though in a low yield (16%), by keeping pyrone **1d** with excess hydroxylamine (2.3 equiv.). It is important to note that no bis-isoxazole, the product of addition of a second hydroxylamine molecule to the 1,3-dicarbonyl moiety of molecule **2d**, was formed in this case.

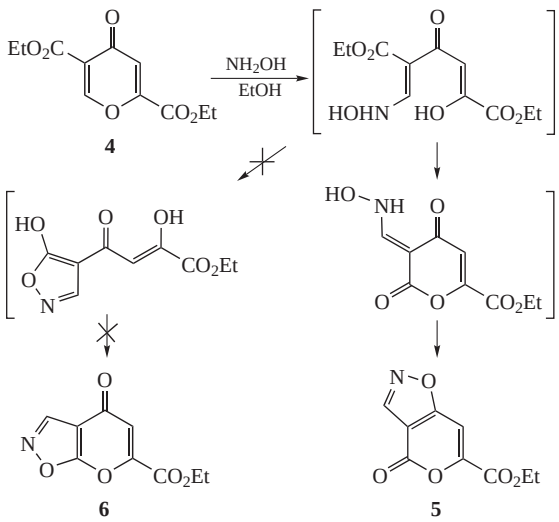
The structure of isoxazoles **2a**–**d** was determined from elemental analysis and ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of these compounds in DMSO-d_6 contained singlets of =CH protons of the diketone moiety and the isoxazole ring at δ 6.82–6.88 and 9.23–9.37, respectively. The mobile proton involved in the formation of the intramolecular hydrogen bond is not observed in DMSO-d_6 solution due to a considerable broadening but manifests itself in $CDCl_3$ in low field at δ 14.6–15.0 as a broadened singlet; the isoxazole proton in $CDCl_3$ is shifted upfield by ~0.7 ppm (δ 8.64 for compound **2d**). The regiochemistry of isoxazoles **2** was confirmed by comparison with the chemical shifts ($CDCl_3$) of the protons of the isoxazole ring in 5-phenylisoxazole-4-carboxylic esters (δ 8.63)[10] and in 3-phenylisoxazole-4-carboxylic acid (δ 8.28).[11] These data allow us to unambiguously assign products **2** to 5-phenylisoxazole-4-carboxylic derivatives.



Scheme 3

The possible mechanism of formation of compounds **2** involves the hydroxylamine attack at the C-6 atom of the pyrone ring followed by ring opening and formation of intermediate **A**, which can undergo cyclization by two pathways to give either isoxazole **2** (pathway *a*) or pyridone **3** (pathway *b*). Though the formation of pyridones is typical of the chemistry of γ-pyrones with N-nucleophiles,[9,12] the formation of isoxazoles **2** in our case can be explained by the existence of an aroyl substituent at 5-position and its favourable location with respect to the hydroxylamino group in intermediate **A**. Incorporation of an electron-donating MeO group in the benzene ring decreases the electrophilicity of the aroyl carbonyl, which favors the competing formation of pyridone **3d** (see Scheme 3).

Unlike 5-aroylcomanoates **1**, the reaction of diethyl 4-pyrone-2,5-dicarboxylate (diethyl isochelidonate)[13] **4** with free hydroxylamine in a EtOH–THF system at –20 °C for one month affords ethyl 4-oxo-4*H*-pyrano[3,4-*d*]isoxazole-6-carboxylate **5** in 37% yield (Scheme 4).‡ The ^{1}H NMR spectrum of this compound in



Scheme 4

Ethyl (Z)-2-hydroxy-4-oxo-4-(5-phenylisoxazol-4-yl)but-2-enoate **2a**. Yield 0.101 g (46%), white crystals, mp 110–112 °C. ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, 3H, Me, *J* 7.1 Hz), 4.31 (q, 2H, CH_2, *J* 7.1 Hz), 6.86 (s, 1H, =CH), 7.75–7.79 (m, 3H, Ph), 7.98 (d, 2H, H-2 and H-6 from Ph, *J* 7.3 Hz), 9.30 (s, 1H, $=CH_{isoxazole}$), the OH proton was not observed due to broadening. IR (ATR, ν/cm^{-1}): 3109, 1720, 1587, 1565, 1475, 1284, 770. Found (%): C, 59.64; H, 4.35; N, 4.85. Calc. for $C_{15}H_{13}NO_5 \cdot 0.75\,H_2O$ (%): C, 59.90; H, 4.86; N, 4.66.

Ethyl (Z)-4-[5-(4-chlorophenyl)isoxazol-4-yl]-2-hydroxy-4-oxobut-2-enoate **2b**. Yield 0.155 g (66%), white crystals, mp 138–140 °C. ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, Me, *J* 7.1 Hz), 4.31 (q, 2H, CH_2, *J* 7.1 Hz), 6.88 (s, 1H, =CH), 7.59 (d, 2H, H-3 and H-5 from Ar, *J* 8.6 Hz), 8.01 (d, 2H, H-2 and H-6 from Ar, *J* 8.6 Hz), 9.36 (s, 1H, $=CH_{isoxazole}$), the OH proton was not observed due to broadening. ^{13}C NMR (DMSO-d_6) δ: 13.8, 62.2, 101.6, 115.3, 124.7, 128.9, 131.0, 136.9, 151.4, 161.4, 165.2, 170.0, 185.0. IR (ATR, ν/cm^{-1}): 3470, 3105, 2999, 1717, 1670, 1606, 1582, 1262, 827. Found (%): C, 56.08; H, 3.74; N, 4.32. Calc. for $C_{15}H_{12}ClNO_5$ (%): C, 56.00; H, 3.76; N, 4.35.

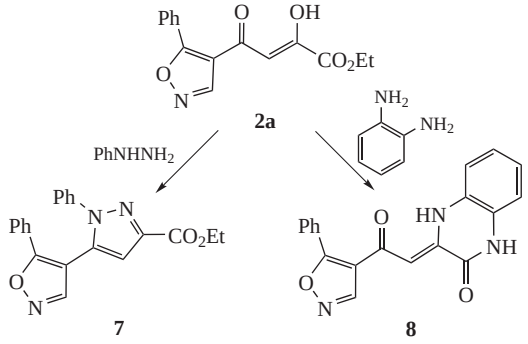
Ethyl (Z)-2-hydroxy-4-[5-(naphthalen-2-yl)isoxazol-4-yl]-4-oxobut-2-enoate **2c**. Yield 0.158 g (64%), yellow crystals, mp 132–133 °C. ^{1}H NMR (DMSO-d_6) δ: 1.26 (t, 3H, Me, *J* 7.1 Hz), 4.27 (q, 2H, CH_2, *J* 7.1 Hz), 6.88 (s, 1H, =CH), 7.61 (t, $1H_{naphthalene}$, *J* 7.0 Hz), 7.65 (t, $1H_{naphthalene}$, *J* 6.8 Hz), 7.94–8.02 (m, $2H_{naphthalene}$), 8.05 (d, $2H_{naphthalene}$, *J* 8.4 Hz), 8.63 (s, 1H, H-$1_{naphthalene}$), 9.35 (s, 1H, $=CH_{isoxazole}$), the OH proton was not observed due to broadening. ^{13}C NMR (DMSO-d_6) δ: 13.7, 62.1, 101.6, 115.3, 123.2, 125.1, 127.1, 127.7, 128.3, 128.4, 129.0, 130.0, 132.1, 134.1, 151.4, 161.4, 165.2, 171.2, 185.1. IR (ATR, ν/cm^{-1}): 3111, 1720, 1630, 1575, 1284, 779. Found (%): C, 67.56; H, 4.42; N, 3.85. Calc. for $C_{19}H_{15}NO_5$ (%): C, 67.65; H, 4.48; N, 4.15.

Ethyl (Z)-2-hydroxy-4-[5-(4-methoxyphenyl)isoxazol-4-yl]-4-oxobut-2-enoate **2d**. The resulting precipitate was a mixture of compounds **2d**:**3d** = 5 : 1. It was recrystallized from EtOH to give 0.046 g of **2d** (20%), yellow crystals, mp 106–107 °C. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, Me, *J* 7.1 Hz), 3.89 (s, 3H, MeO), 4.37 (q, 2H, CH_2, *J* 7.1 Hz), 6.71 (s, 1H, =CH), 7.04 (d, 2H, H-3 and H-5 from Ar, *J* 9.0 Hz), 8.01 (d, 2H, H-2 and H-6 from Ar, *J* 9.0 Hz), 8.64 (s, 1H, $=CH_{isoxazole}$), 14.6–15.0 (s, 1H, OH). ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, Me, *J* 7.1 Hz), 3.89 (s, 3H, MeO), 4.31 (q, 2H, CH_2, *J* 7.1 Hz), 6.86 (s, 1H, =CH), 7.07 (d, 2H, H-3 and H-5 from Ar, *J* 8.8 Hz), 8.01 (d, 2H, H-2 and H-6 from Ar, *J* 8.8 Hz), 9.23 (s, 1H, $=CH_{isoxazole}$), the OH proton was not observed due to broadening. ^{13}C NMR (DMSO-d_6) δ: 13.8, 55.5, 62.1, 101.6, 114.0, 114.3, 118.0, 131.0, 151.4, 161.4, 162.2, 164.9, 171.2, 185.6. IR (ATR, ν/cm^{-1}): 3113, 2935, 2836, 1719, 1609, 1575, 1257, 1177, 779. Found (%): C, 60.24; H, 4.55; N, 4.35. Calc. for $C_{16}H_{15}NO_6$ (%): C, 60.57; H, 4.77; N, 4.41.

‡ *Ethyl 4-oxo-4*H*-pyrano[3,4-*d*]isoxazole-6-carboxylate* **5**. This compound was obtained from diethyl isochelidonate **4**. Additional quantity of compound **5** was isolated from filtrate and recrystallized from EtOH. Yield 0.062 g (37%), a yellow solid, mp 174–176 °C. ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, 3H, Me, *J* 7.1 Hz), 4.34 (q, 2H, CH_2, *J* 7.1 Hz), 7.76 (s, 1H, =CH), 8.72 (s, 1H, $=CH_{isoxazole}$). ^{13}C NMR (DMSO-d_6) δ: 13.9, 61.9, 116.5, 118.7, 138.4, 140.3, 160.6, 161.3, 161.5. IR (ATR, ν/cm^{-1}): 3232, 3065, 3006, 1694, 1554, 1209, 788. Found (%): C 47.37; H, 3.72; N, 6.09. Calc. for $C_9H_7NO_5 \cdot H_2O$ (%): C, 47.58; H, 3.99; N, 6.17.

DMSO-d_6 contains, aside from the ester group protons, two singlet signals at δ 7.76 and 8.72. The choice in favor of structure **5** is based on the ^{13}C NMR spectrum which contains three low-field signals of carbonyl groups in the range of δ 160.6–161.5 allowing product **5** to be assigned to 2-pyrones[14] rather than 4-pyrones. It should also be noted that, according to literature data,[15] the ^{13}C NMR spectra of 4-oxo-4*H*-pyrano[2,3-*c*]pyrazoles of type **6** (potent alternative products) contain a characteristic signal of the carbonyl group of the γ-pyrone ring in the region of δ 173.2–176.7 (DMSO-d_6).

Since isoxazoles **2** herein obtained are derivatives of acylpyruvic acid, they can be used to synthesize various heterocyclic ensembles.[16] In fact, refluxing isoxazole **2a** with phenylhydrazonium hydrochloride in ethanol for 1 h gave isoxazolylpyrazole **7** in 72% yield, while the similar reaction with *o*-phenylenediamine led to quinoxalinone **8** in 81% yield (Scheme 5).



Scheme 5

In summary, we were the first to perform the reaction of 5-acylcomanoates with hydroxylamine giving promising isoxazolyldioxobutanoates which were converted into heterocyclic ensembles with an isoxazole moiety. In the case of diethyl isochelidonate, the reaction occurred in a different manner and resulted in ethyl 4-oxo-4*H*-pyrano[3,4-*d*]isoxazole-6-carboxylate. We are going to continue the development of methods for incorporation of a dioxobutanoic acid moiety into organic compounds of various classes using 4-pyrone-2-carboxylic acids in our laboratory.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2017.03.022.

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Received: 28th July 2016; Com. 16/5013