SYNTHESIS OF 2-PHENYL-4-ACYLOXAZOLIN-5-ONES

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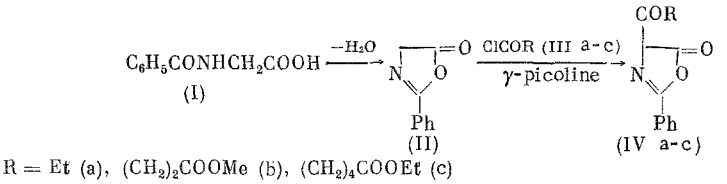
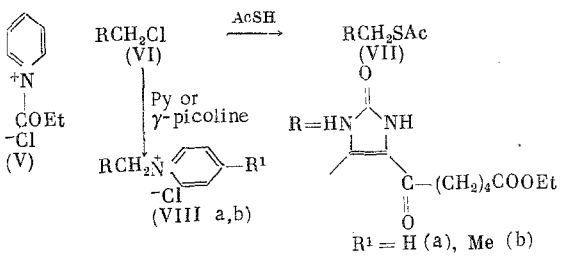
2-Phenyl-4-acyloxazolin-5-ones (PA) are used as intermediates in the synthesis of dihydrosphyngosine, biological precursors of porphyrins, and biotin analogs [1-3]. PA are prepared by the reaction of acid chlorides in γ-picoline with hippuric acid (I) or its azlactonization product, 2-phenyloxazolin-5-one (II) [4]. The major disadvantage in this method for the preparation of PA is low yield.

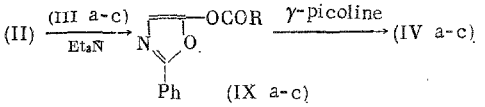


In order to increase the yield of PA, we studied the effect of various polar additives on the yield of 2-phenyl-4-propionyloxazolin-5-one (IVa) obtained in the reaction of excess propionyl chloride (IIIa) with (I) at 0 and 20°C. The following additives were studied: KI, DMSO, DMF, Al_2O_3, CF_3CO_2H, $EtCO_2H$, and Et_4NI. The best effect is obtained for CF_3CO_2H, $EtCO_2H$, and Et_4NI, which give 70-80% yields of (IVa) without significant tar formation. In the absence of these additives or in the presence of KI, DMSO, DMF, or Al_2O_3, the yield of (IVa) is not greater than 50%. Attempts to carry out C-acylation of (II) even in the presence of CF_3CO_2H or Et_4NI gave unsatisfactory results.

It is interesting to note that maximizing the yield of (IVa) requires following a specific order for mixing of the reagents: adding (IIIa) gradually to a solution of (I) in γ-picoline. Mixing in the reverse order gives only small amounts of product (IVa). This effect may be attributed to the participation of (IIIa) itself and not the acylpyridinium ion (V) in the reaction with (I). Similar behavior was also found in our study of the reaction of 4-chloromethyl-5-(δ-carbethoxyvaleryl-imidazolin)2)one [5] with AcSH in γ-picoline or pyridine at 20°C. The nucleophilic substitution product, 4-acetylthiomethyl-5-(δ-carbethoxyvaleryl)imidazolin-2-one (VII), is formed in 65% yield only upon the addition of chloride (VI) to a solution of AcSH in pyridine or γ-picoline. In the case of reversal of the order of mixing, chloride (VI) is converted into pyridinium salts (VIIIa,b), which are incapable of reacting with AcSH under these conditions.



Our finding of reduced electrophilicity for (V) and (VIIIa, b) is not in accord with the concept that halides are activated by their conversion to pyridinium salts [6]



A reduction in the consumption of (IIIa) to 1 mole with retention of the yield of (IVa) is achieved by initially carrying out the O-acylation of (II) in the presence of triethylamine in benzene according to Steglish and Höfle [7] and then

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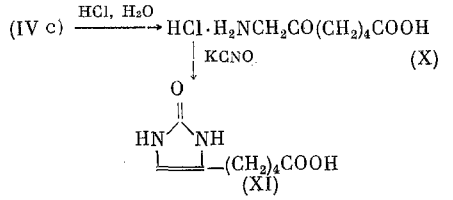
carrying out C-isomerization of the intermediate 2-phenyl-5-propoxyoxazole (IXa) in γ-picoline with added CF_3CO_2H. 4-(β-Carbomethoxypropionyl)- and 4-(δ-carbethoxyvaleryl)-2-)phenyloxazolin-5-ones (IVb, c) are prepared by this method starting with $MeD_2CCH_2CH_2COCl$ (IIIb) and $EtO_2C(CH_2)_4COCl$ (IIIc) and (II) through the intermediate O-acyl-2-phenyloxazolinones (IXb,c) in about 80% yield.



Azlactones (IVa) and (IVb) were identified by direct comparison with known samples [3, 8]. The structure of azlactone (IVc) was confirmed by acid cleavage to the hydrochloride salt of ε-keto-ζ-aminoenanthic acid (X) and the subsequent conversion of (X) to 4-(4'-carboxybutyl)imidazolin-2-one (XI) by the action of KCNO according to our previous procedure [1].

EXPERIMENTAL

The UV spectra were taken in ethanol on a Specord UV-VIS spectrometer. The IR spectra were taken as KBr pellets on a UR-20 spectrometer. The PMR spectra were taken on a Varian DA-60-IL spectrometer with HMDS as internal standard. Thin-layer chromatography was carried out on Silufol UV-254 (UV and iodine vapor detection).

2-Phenyl-4-propionyloxazolin-5-one (IVa). A sample of 2 ml propionyl chloride (IIIa) was added gradually with stirring to a solution of 0.9 g hippuric acid (I) and 0.5 ml CF_3CO_2H in 10 ml dry γ-picoline. The mixture was stirred for an additional 5 h at 0°C, diluted with water, and acidified with 1:1 HCl. The precipitate was filtered off, washed with water, and dissolved in 5% KOH. The filtrate was acidified with 1:1 HCl and the precipitate formed was filtered off, washed again with water, and dried in the air to yield 0.9 g (82%) (IVa) with mp 193-195°C (dec.), R_f 0.72 (ethyl acetate, EA). IR spectrum: 1455, 1500, 1555, 1570, 1780, 2600 cm^{-1}. The same indices were found for a known sample of (IVa) [8]. The yields of (IVa) were 80-81% when carrying out the reaction of 0.9 g (I) with 1.5 ml (IIIa) in the presence of 1 ml CF_3CO_2H, 1 ml $EtCO_2H$, or 2 g Et_4NI in 10 ml γ-picoline at 20°C for 15 h.

A sample of 2.5 ml Et_3N was added gradually with stirring to a solution of 1.4 g 2-phenyloxazolin-5-one (II) [9] and 1 ml (IIIa) in 45 ml benzene and maintained for 1 h at 20°C. The precipitate was removed by filtration. The filtrate was evaporated in vacuum. The residue was an oil containing 2-phenyl-5-propoxyoxazole (IXa) which underwent hydrolysis with 1:1 HCl at 20°C for 12 h to give a mixture of hippuric and propionic acids.

A solution of 0.3 ml CF_3CO_2H in 8 ml γ-picoline was added gradually with stirring and ice cooling to unpurified (IXa) obtained from 1.4 g (II). The mixture was stirred for an additional 20 h at 0°C and treated with dilute HCl and ice. The precipitate was removed by filtration, washed with water, and reprecipitated from a basic solution using dilute HCl to yield 1.3 g (70%) (IVa) with mp 193-195°C (dec.), R_f 0.72 (EA).

2-Phenyl-4-(β-carbomethoxyvaleryl)oxazolin-5-one (IVb). A yield of 3.5 g (79%) (IVb) with mp 176-178°C and R_f 0.64 (EA) was prepared by analogy to the above procedure from 2.4 g (II) and 2.3 g of the acid chloride of the monomethyl ester of succinic acid (IIIb). IR spectrum: 1487, 1560, 1730, 1778 cm^{-1}. The same indices were found for an authentic sample of (IVb) [3].

2-Phenyl-4-(δ-carbethoxyvaleryl)oxazolin-5-one (IVc). A yield of 16.9 g (76%) (IVc) with mp 110-112°C (from EA) and R_f 0.74 (EA) was obtained by analogy to the above procedure from 11.3 g (II) and 14.7 g of the acid chloride of the monoethyl ester of adipic acid (IIIc). IR spectrum: 1490, 1555, 1730, 1775 cm^{-1}. PMR spectrum ($CDCl_3$, δ, ppm): 1.18 t (CH_3), 1.72 m (CH_2CH_2), 2.31 m (CH_2), 2.75 m (CH_2), 4.07 q (OCH_2), 7.41 m, 7.90 m (aromatic ring). Found: C, 64.14; H, 6.08; N, 4.49%. Calculated for $C_{17}H_{19}O_5N$: C, 64.34; H, 6.04; N, 4.41%.

4-(4'-Carboxybutyl)imidazolin-2-one (XI). A mixture of 1.6 g (IVc) and 25 ml 1:1 HCl was heated at reflux for 3 h and then cooled to 20°C. Benzoic acid was removed by filtration and the filtrate was heated at reflux for 1 h with activated charcoal, and evaporated in vacuum to yield 0.79 g of the hydrochloride salt of ε-keto-ζ-aminoenanthic acid (X) which was used in the next step without additional purification. For this purpose, (X) was dissolved in 11 ml water, and KCNO was added to give pH ~7. The mixture was maintained for 24 h at 20°C and then acidified with dil. HCl. The precipitate was removed by filtration, washed with water, and dried in the

air to yield 0.72 g (76%) (XI) with mp 239-241°C (from ethanol) and R_f 0.47 (1 :4 ethanol−EA). PMR spectrum (CF_3CO_2H, δ, ppm): 1.35 m (CH_2CH_2), 2.20 m ($CH_2C=C$, CH_2CO), 6.13 s (HC=C). Found: C, 51.56; H, 6.64; N, 14.55%. Calculated for $C_8H_{12}O_3N_2 \cdot 0.1H_2O$: C, 51.49; H, 6.62; N, 15.00%.

4-Acetylthiomethyl-5-(carbethoxyvaleryl)imidazolin-2-one (VII). A sample of 0.3 g 4-chloromethyl-5-(δ-carbethoxyvaleryl)imidazolin-2-one (VI) [10] was added to a solution of 0.11 ml AcSH in 4 ml dry pyridine, stirred for 3 h at 20°C, diluted with 15 ml water, acidified with dil. HCl to pH ~ 1, and then maintained for 3 h at 0°C. The precipitate was removed by filtration, washed with water, and dried in the air to yield 0.22 g (65%) (VII) with mp 110-111°C and R_f 0.25 (EA). The sample of (VII) did not give a depressed mixed melting point with an authentic sample [11].

4-(Pyridinium-1'-methyl)-5-(δ-carbethoxyvaleryl)imidazolin-2-one Chloride (VIIIa). A sample of 0.3 g (VI) was added to 0.4 ml dry pyridine and maintained for 4 h at 20°C. The precipitate was filtered off, washed with pyridine and then with ether to yield 0.28 g (44%) (VIIIa) with mp 165-167°C and R_f 0.56 (7 :2 :1 i-PrOH−NH_4OH−H_2O). UV spectrum: λ_{max} 260, 310 nm. PMR spectrum (CF_3CO_2H, δ, ppm): 1.17 t (CH_3), 1.65 m (CH_2CH_2), 2.37 m ($CH_2CO_2C_2H_5$), 2.80 m (CH_2CO), 4.12 q (OCH_2), 6.00 s (CH_2N), 7.93 m (pyridine ring). Found: C, 51.10; H, 6.32; N, 11.29; Cl, 9.82%. Calculated for $C_{17}H_{12}ClN_3O_4$: C, 55.51; H, 6.03; N, 11.42; Cl, 9.64%.

4-(γ-Picolinium-1'-methyl)-5-(δ-carbethoxyvaleryl)imidazolin-2-one Chloride (VIIIb). A sample of 0.65 g (55%) (VIIIb) with mp 166-167°C and R_f 0.57 (7 :2 :1 i-PrOH−NH_4OH−H_2O) was obtained by analogy to the above procedure from 0.9 g (VI) and 5 ml γ-picoline at 20°C for 30 min. UV spectrum: λ_{max} 256, 305 nm. PMR spectrum (CF_3CO_2H, δ, ppm): 1.00 t (CH_3), 1.60 m (CH_2CH_2), 2.20 m (CH_2CO_2Et), 2.33 s (CH_3), 2.50 m (CH_3CO), 3.86 q (CH_2O), 5.60 s (CH_2), 7.44 m, 8.44 m (γ-picoline ring). Found: C, 53.53; H, 6.49; N, 11.04; Cl, 8.97%. Calculated for $C_{18}H_{25}ClN_3O_4$: C, 54.07; H, 6.55; N, 10.51; Cl, 8.87%.

Thioacetate (VII) was not formed by the action of AcSH on salt (VIIIa) or (VIIIb) in pyridine or γ-picoline, respectively, at 20°C for 3 h.

CONCLUSIONS

1. A positive effect was found for trifluoroacetic acid, pripionic acid, and tetraethylammonium iodide on the formation of 2-phenyl-4-propionyloxazolin-5-one from propionyl chloride and hippuric acid in γ-picoline.

2. A preparative method was developed for the synthesis of 2-phenyl-4-acyloxazolin-5-ones using acid chlorides in benzene with subsequent O→C isomerization of the intermediate 2-phenyl-5-acyloxyoxazoles in γ-picoline in the presence of trifluoroacetic acid.

3. Reduced electrophilicity was found for N-acylpyridinium salts and 4-(pyridinium-1'-methyl)-5-δ-carbethoxyvaleryl)imidazolin-2-one.

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