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REACTIONS OF BENZOYLHETEROAROYLMETHANES WITH HYDROXYLAMINE HYDROCHLORIDE

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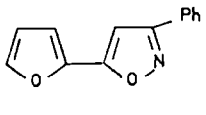
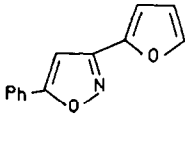
Abstract—Benzoyl-2-furoylmethane reacts with hydroxylamine hydrochloride to give predominantly 5-(2-furyl)-3-phenylisoxazole and not as reported in the literature 3-(2-furyl)-5-phenylisoxazole. Benzoyl-2-thenoylmethane and benzoylpicolinoylmethane afforded 3-phenyl-5-(2-thienyl)isoxazole and 5-phenyl-3-(2-pyridyl)isoxazole respectively.

3,5-Disubstituted isoxazoles are obtained in good yield from reactions of β-diketones with hydroxylamine hydrochloride.[1,2] 3-Aryl-5-phenylisoxazoles are obtained from *p*-substituted dibenzoylmethanes possessing −I−R substituents, whereas diketones having +I+R substituents give only 5-aryl-3-phenylisoxazoles. Mixtures of both isomeric isoxazoles are obtained from diketones with −I+R substituents.[3] The report by Musante and Berretti[4] that benzoyl-2-furoylmethane leads to 3-(2-furyl)-5-phenylisoxazole seems somewhat at variance with the above results and hence it was decided to reinvestigate the reaction of this diketone with hydroxylamine hydrochloride and also the analogous reactions of benzoyl-2-thenoylmethane and benzoylpicolinoylmethane.

The product from the reaction of benzoyl-2-furoylmethane with hydroxylamine hydrochloride on examination by TLC was shown to consist of two components, which were separated by column chromatography. These compounds were the two possible isomeric isoxazoles obtained in a ratio of 4:1. The mass spectra of the major and minor components were consistent with the structures being 5-(2-furyl)-3-phenylisoxazole (**1**) and 3-(2-furyl)-5-phenylisoxazole (**2**) respectively. Prominent peaks in the mass spectra of these isoxazoles corresponded to the 2-FurCO$^+$ and PhCO$^+$ ions respectively. (The base peaks of 3-aryl-5-phenyl- and 5-aryl-3-phenyl-isoxazoles are PhCO$^+$ and ArCO$^+$ respectively.)[5]



(1)



(2)

Confirmation of the structures of these isoxazoles was obtained by their oxidation to 3-phenylisoxazole-5-carboxylic acid and 5-phenylisoxazole-3-carboxylic acid respectively.

The physical constants of these acids were in agreement with the published values and their mass spectra were also consistent with these structures. The melting point of the mixture of carboxylic acids obtained by oxidation of the mixture of isomeric isoxazoles was very similar to that of 5-phenylisoxazole-3-carboxylic acid thus leading to the confusion in the literature.

Reactions of benzoyl-2-thenoylmethane and benzoylpicolinoylmethane with hydroxylamine afforded 3-phenyl-5-(2-thienyl)isoxazole and 5-phenyl-3-(2-pyridyl)isoxazole respectively as the sole products. Their structures were established from their mass spectral behaviour. These structures are in accord with the postulate that reaction initially occurs at the more negative carbon atom of the diketone.[3]

EXPERIMENTAL

Benzoyl-2-furoylmethane,[6] benzoyl-2-thenoylmethane[6] and benzoylpicolinoylmethane[7] were prepared by standard lit. procedures and had m.ps 65°, 78–79° and 89° respectively.

Formation of isoxazoles from β-diketones. A soln of the diketone (0.01 mol) in MeOH (60 ml) was added to a soln of hydroxylamine hydrochloride (1.4 g 0.02 mol) in water and the mixture refluxed until the product separated out (1–2 hr). The isoxazole was filtered off from the cooled mixture and crystallised from light petroleum (b.p. 40–60°).

Benzoyl-2-thenoylmethane gave *3-phenyl-5-(2-thienyl)-isoxazole* as buff needles (70%), m.p. 95–96° (Found: C, 68.5; H, 3.8; N, 6.2. $C_{13}H_9NOS$ requires: C, 68.8; H, 3.9; N, 6.2%): *m/e* 227 (100%, M^+), 111 (80%, $C_4H_3S{\cdot}CO^+$), 83 (57%, $C_4H_3S^+$).

Benzoylpicolinoylmethane gave *5-phenyl-3-(2-pyridyl)-isoxazole* as colourless crystals (63%), m.p. 88–89° (Found: C, 75.4; H, 4.4; N, 12.3. $C_{14}H_{10}N_2O$ requires: C, 75.6; H, 4.5; N, 12.6%): *m/e* 222 (100%, M^+), 105 (40%, PhCO$^+$), 77 (80%, Ph$^+$).

Benzoyl-2-furoylmethane gave a mixture of 5-(2-furyl)-3-phenylisoxazole and 3-(2-furyl)-5-phenylisoxazole as cream crystals (80%), m.p. 80–81° (lit.,[4] 81°). TLC using 9:1 hexane:ether as eluant showed that the product was a mixture of two compounds. Chromatography of this mixture (1.5 g) on an alumina column using 9:1 hexane:ether as eluant gave *5-(2-furyl)-3-phenylisoxazole* (1.2 g). This was crystallized as colourless needles from aq. MeOH, m.p. 76–77° (Found: C, 74.0; H, 4.2; N, 6.6. $C_{13}H_9NO_2$ requires: C, 73.9; H, 4.3; N, 6.6%), *m/e* 211 (100%, M^+) 103 (10%PhCN$^+$), 95 (70%, $C_4H_3O{\cdot}CO^+$) 67 (80%, $C_4H_3O^+$). Further elution with the same solvent gave *3-(2-furyl)-5-phenylisoxazole* (0.3 g) which was crystallized from aq. MeOH as colourless needles, m.p. 95° (Found: C, 74.2; H, 4.55; N, 6.6. $C_{13}H_9NO_2$ requires: C, 74.0; H, 4.3; N, 6.6%): *m/e* 211 (100%, M^+), 105 (57%, PhCO$^+$), 77 (95%, Ph$^+$).

Oxidation of 2-furyl-phenylisoxazoles. A soln of the mixture of isoxazoles (1.0 g), as prepared from the benzoyl-2-furoylmethane, in acetone (60 ml) was added to a soln of $KMnO_4$ (5 g) in water and the mixture was refluxed for 15 min. The acetone was distilled off and the soln was then made acid by addition of 2M H_2SO_4 (5 ml). SO_2 was passed through the soln to clear it. White crystals of the isoxazole carboxylic acids were obtained and filtered off and crystallized from water, m.p. 158–162° (lit.,[4] 163°) (0.6 g, 70%).

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Oxidation of 5-(2-furyl)-3-phenylisoxazole gave colourless needles of 3-phenylisoxazole-5-carboxylic acid (72%), m.p. 178° (lit.,[8] 178°): *m/e* 189 (100%, M^+), 144 (59%, $[M\text{-}H_2O\text{-}H]^+$), 116 (35%, $[M\text{-}CO\text{-}COOH]^+$) 103 (12% $PhCN^+$).

Oxidation of 3-(2-furyl)-5-phenylisoxazole gave colourless needles of 5-phenylisoxazole-3-carboxylic acid (67%), m.p. 163° (lit.,[9] 163°): *m/e* 189 (67%, M^+), 144 (41%, $[M\text{-}CO_2\text{-}H]^+$), 105 (100%, $PhCO^+$), 77 (23%, Ph^+).

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