SYNTHESIS OF 4-IMIDAZOLIN-2-ONES

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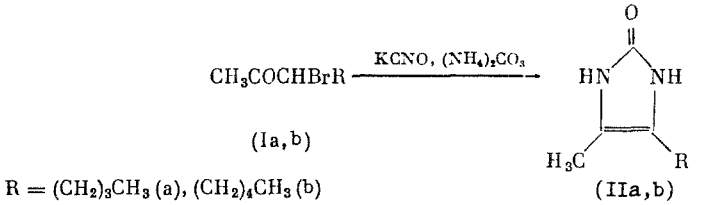
The reaction of α-bromoketones with $CO(NH_2)_2$ and $AcONH_4$ in aqueous acetic acid gave substituted 4-imidazolin-2-ones.

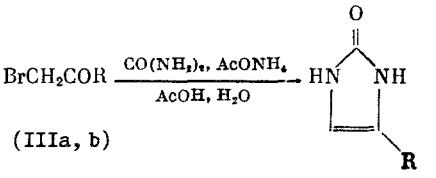
In previous work [1], we have shown that 3-bromo-2-alkanones (Ia) and (Ib) undergo cyclocondensation with KCNO and $(NH_4)_2CO_3$ in aqueous DMF to give 4-alkyl-5-methyl-4-imidazolin-2-ones (IIa) and (IIb) [1].



(Ia,b) (IIa,b)

R = $(CH_2)_3CH_3$ (a), $(CH_2)_4CH_3$ (b)

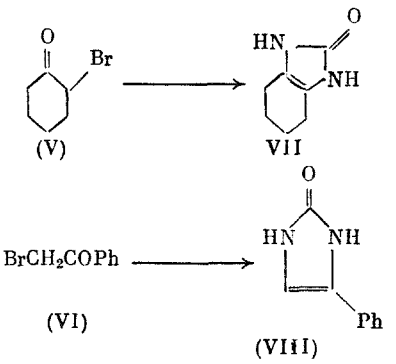
Attempts to extend this method to 1-bromo-2-alkanones proved unsuccessful. We have established that the $CO(NH_2)_2$–$AcONH_4$–AcOH–H_2O system may be used for the conversion of 1-bromo-2-alkanones into 4-alkyl-4-imidazolin-2-ones.



(IIIa, b) (IVa, b)

R = $(CH_2)_4CH_3$ (a), $(CH_2)_5CH_3$ (b)

For example, the reactions of 1-bromo-2-heptanone (IIIa) and 1-bromo-2-octanone (IIIb) with $CO(NH_2)_2$ and $AcONH_4$ in aqueous acetic acid at reflux gave 4-pentyl- and 4-hexyl-4-imidazoline-2-ones (IVa) and (IVb) in 50-55% yield. Analogously, 2-bromocyclohexanone (V) and α-bromoacetophenone (VI) gave 4,5-tetramethylene-4-imidazolin-2-one (VII) in 65% yield and 4-phenyl-4-imidazolin-2-one (VIII) in 75% yield.



(V) VII

(VI) (VIII)

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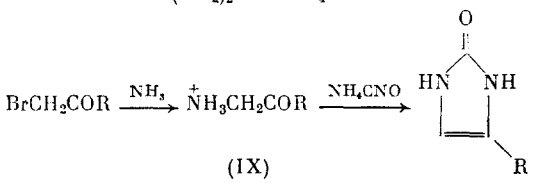
We may assume that the conversion of α-bromoketones (IIIa), (IIIb), (V), and (VI) to imidazolin-2-ones proceeds through an intermediate nucleophilic substitution of the bromine atom by an amino group and subsequent cyclocondensation of the α-aminoketones (IX) with ammonium cyanate obtained from urea.

$$AcONH_4 \longrightarrow AcOH + NH_3$$
$$CO(NH_2)_2 \longrightarrow NH_4CNO$$



(IX)

This scheme is supported by the capacity of the hydrochloride salt of α-aminoacetophenone, $PhCOCH_2NH_2 \cdot HCl$ to convert smoothly to 4-phenyl-4-imidazolin-2-one (VIII) under the conditions for the formation of 4-imidazolin-2-ones (IVa), (IVb), (VII), and (VIII) from α-bromoketones (IIIa), (IIIb), (V), and (VI).

An alternative scheme entailing the nucleophilic substitution of the bromine atom by an acetoxy group by the action of the acetate anion with subsequent cyclocondensation of the intermediate α-acetoxyketones with $CO(NH_2)_2$ appears less likely since $PhCOCH_2OAc$ [2] and $CO(NH_2)_2$ in acetic acid in the presence of ammonia form only traces of 4-phenyl-4-imidazolin-2-one (VIII).

1-Bromo-2-alkanones (IIIa) and (IIIb) with a ~10% impurity of 3-bromo isomers (Ia) and (Ib) as well as 2-bromocyclohexanone (V) were obtained by the selective bromination of the corresponding ketones in a mixture of $CO(NH_2)_2$ and acetic acid.

Since 3-bromoalkanones (Ia) and (Ib) are incapable of giving imidazolinones (IIa) and (IIb) under our conditions, traces of these compounds in 1-bromoketones (IIIa) and (IIIb) does not hinder the separation of pure (IVa) and (IVb).

The application of the same reagents (AcOH and $CO(NH_2)_2$) for the bromination of 2-alkanones and the heterocyclization of 1-bromo-2-alkanones permit us to convert 2-alkanones to 4-alkyl-4-imidazolin-2-ones (IVa) and (IVb) in the same flask without the separation of intermediates (IIIa) and (IIIb).

Imidazolinones (IVa), (IVb), (VII), and (VIII) were identified by PMR spectroscopy and comparison with authentic samples.

EXPERIMENTAL

The PMR spectra were taken on Varian 60-IL and Tesla BS-497 spectrometers using HMDS as the internal standard. The thin-layer chromatography was carried out on Silufol UV-254 plates. The spots were developed by iodine vapor and, in the case of imidazolin-2-ones, also by $FeCl_3$.

4-Pentyl-4-imidazolin-2-one (IVa). A sample of 1.6 ml (31.4 mmoles) Br_2 was added with stirring to a mixture of 3.6 ml (25.9 mmoles) 2-heptanone and 5 g (83.3 mmoles) $CO(NH_2)_2$ in 10 ml glacial acetic acid upon ice cooling. This mixture was stirred for an additional 1 h at 15-18°C and then for 20 h at 20°C, diluted with water, and extracted with methylene chloride. The extract was dried over $MgSO_4$ and evaporated. The residue was distilled in vacuum to give 3.5 g (70%) 1-bromo-2-heptanone (IIIa), bp 113-117°C (25 mm), n_D^{17} 1.4670. PMR spectrum in CCl_4 (δ, ppm): 0.81 m (CH_3), 1.30 m [$(CH_2)_3$], 2.30 s ($CH_3COCHBr$), 2.75 t (CH_2CO, J = 7 Hz), 3.75 s ($COCH_2Br$) [3].

The integral intensities of the signals at 2.30 and 3.75 ppm indicate that (IIIa) contains about 10% 3-bromo-2-heptanone (Ia). Bromination of 2-heptanone in methanol in the presence of $CO(NH_2)_2$ according to our previous procedure [3] led to an 82:18 mixture of (IIIa) and (Ia) in 55% yield.

a. A sample of 5 ml 30% aqueous ammonia was added gradually with stirring to a mixture of 1.2 g (6.2 mmoles) (IIIa) and 4 g (66.7 mmoles) $CO(NH_2)_2$ in 10 ml glacial acetic acid, heated at reflux for 5 h, and partially evaporated in vacuum. The residue was diluted with water and left overnight. The precipitate was filtered off, washed with water and ether, and dried in the air to give 0.48 g (50%) (IVa), mp 177-179°C (1:1 EtOH–H_2O), R_f 0.55 (3:0.5

EA–EtOH). PMR spectrum in CF_3CO_2H (δ, ppm): 0.93 t (CH_3, J = 5 Hz), 1.32 m [$(CH_2)_3$], 2.43 t (CH_2, J = 7 Hz), 6.30 br.s (HC=) [4].

Imidazolinone (IVa) could not be obtained from bromoketone (IIIa) and $CO(NH_2)_2$ in the absence of $AcONH_4$.

b. A sample of 0.8 ml (15.7 mmoles) Br_2 was added with stirring to a mixture of 1.8 ml (12.95 mmoles) 2-heptanone and 12 g (199.8 mmoles) $CO(NH_2)_2$ in 24 ml glacial acetic acid upon ice cooling and stirred for an additional 0.5 h at 15-18°C and then for 20 h at 20°C. A sample of 15 ml 30% aqueous ammonia was added to the reaction mixture, heated at reflux for 5 h, diluted with water, and left overnight at 20°C. The precipitate was filtered off, washed with water and ether, and dried in the air to give 0.75 g (38%) (IVa), mp 177-179°C (1:1 EtOH–H_2O).

4-Hexyl-4-imidazolin-2-one (IVb). By analogy to (IIIa), the bromination of 4 ml (25.58 mmoles) 2-octanone, 1.6 ml (31.4 mmoles) Br_2 in a mixture of 5 g (83.3 mmoles) $CO(NH_2)_2$ and 10 ml acetic acid gave 4.5 g (85%) 1-bromo-2-octanone (IIIb), bp 120-123°C (25 mm), n_D^{17} 1.4690. PMR spectrum in CCl_4 (δ, ppm): 0.81 m (CH_3), 1.25 m [$(CH_2)_4$], 2.29 s ($CH_3COCHBr$), 2.53 t (CH_2CO, J = 7 Hz), 3.76 s ($COCH_2Br$) [3]. The integral intensities of the signals at 2.29 and 3.76 ppm indicated that (IIIb) contained ~10% 3-bromo-2-octanone (Ib) as an impurity.

The bromination of 2-octanone in methanol in the presence of $CO(NH_2)_2$ according to our previous procedure [3] led to an 82:18 mixture of (IIIa) and (IIIb) in 50% yield.

By analogy to (IVa) (procedure *a*), 1 g (4.82 mmoles) 1-bromo-2-octanone (IIIb), 4 g (66.6 mmoles) $CO(NH_2)_2$, and 5 ml 30% aqueous ammonia in 8 ml acetic acid gave 0.45 g (55%) (IVb), mp 176-178°C (1:1 EtOH–H_2O) [4], R_f 0.66 (3:0.5 EA–EtOH). PMR spectrum in CF_3CO_2H (δ, ppm): 0.92 t (CH_3, J = 4 Hz), 1.30 m [$(CH_2)_4$], 2.43 t (CH_2, J = 7 Hz), 6.33 s (HC=) [5].

By analogy to (IVa) (procedure *b*), 2 ml (12.8 mmoles) 2-octanone, 0.8 ml (15.7 mmoles) Br_2, 12 g (199.8 mmoles) $CO(NH_2)_2$, and 15 ml 30% aqueous ammonia in 24 ml acetic acid gave 0.95 g (44%) (IVb), mp 176-178°C (1:1 EtOH–H_2O).

4,5-Tetramethylene-4-imidazolin-2-one (VII). By analogy to (IIIa), 2 g (20.4 mmoles) cyclohexanone and 1.1 ml (21.58 mmoles) Br_2 in a mixture of 2 g (33.3 mmoles) $CO(NH_2)_2$ and 10 ml acetic acid maintained at 18-20°C for 0.5 h gave 2.5 g (70%) 2-bromocyclohexanone (V), bp 115-118°C (23 mm), n_D^{20} 1.5130. PMR spectrum in CCl_4 (δ, ppm): 1.85 m [$(CH_2)_3$], 2.14 m (CH_2CO), 4.32 t (CHBr, J = 4 Hz) [5].

By analogy to (IVa), 1.8 g (10.1 mmoles) 2-bromocyclohexanone, 4 g (66.6 mmoles) $CO(NH_2)_2$, and 4 ml 30% aqueous ammonia in 16 ml acetic acid gave 0.9 g (65%) (VII), dec. 337-340°C (from EtOH) [6], R_f 0.70 (1:1 EA–EtOH). PMR spectrum in CF_3CO_2H (δ, ppm): 1.32 br.s (CH_2CH_2), 2.54 s ($2CH_2$) [6].

4-Phenyl-4-imidazolin-2-one (VIII). By analogy to (IVa), 1 g (5.02 mmoles) α-bromoacetophenone, 4 g (66.6 mmoles) $CO(NH_2)_2$, and 6 ml 30% aqueous ammonia in 16 ml acetic acid upon heating at reflux for 3 h gave 0.6 g (75%) (VIII), dec. ~300°C (EtOH) [7], R_f 0.65 (2:0.5 EA–EtOH). PMR spectrum in CF_3CO_2H (δ, ppm): 6.53 m (HC=), 7.05 m (aromatic ring).

Analogously to (IVa), 0.6 g (3.5 mmoles) hydrochloride salt of α-aminoacetophenone (X) [7], 2 g (33.3 mmoles) $CO(NH_2)_2$, and 3 ml 30% aqueous ammonia in 8 ml acetic acid gave 0.5 g (89%) (VIII), dec. ~300°C (EtOH).

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