Synthesis of Imidazolin-2-ones by Rearrangement of *N*-Carbamoyliminium Salts derived from 4-Hydroxyimidazolidin-2-ones

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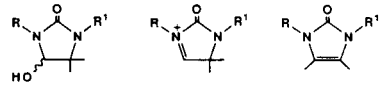
Received February 6, 1989

The action of trifluoroacetic acid on 4-hydroxyimidazolidin-2-ones **9a,b,c** induces the formation of *N*-carbamoyliminium salts **10a,b,c** which rearrange to imidazolin-2-ones **11a,b,c**. The reactions proceed in high yield at ambient temperatures.

J. Heterocyclic Chem., **26**, 1523 (1989).

In an earlier publication [1] we reported the synthesis of 4-hydroxyimidazolidin-2-ones **1**. Previous workers have used compounds of this type to generate *N*-carbamoyliminium salts **2** which have proven to be versatile intermediates for the construction of annelated systems by intramolecular cyclisation reactions [2]. Transformations of these ionic species involving rearrangement to imidazolin-2-ones **3** appear to have received little attention and reported examples [3] relate to 3-alkyl substituents **3a**. Of interest to this laboratory are procedures for synthesizing cyclic ureas containing aromatic substituents. This paper examines the application of 3-aryl-4-hydroxyimidazolidin-2-ones **1b** to the formation and subsequent rearrangement of *N*-aryliminium intermediates **2b** to provide 3-arylimidazolin-2-ones **3b**.

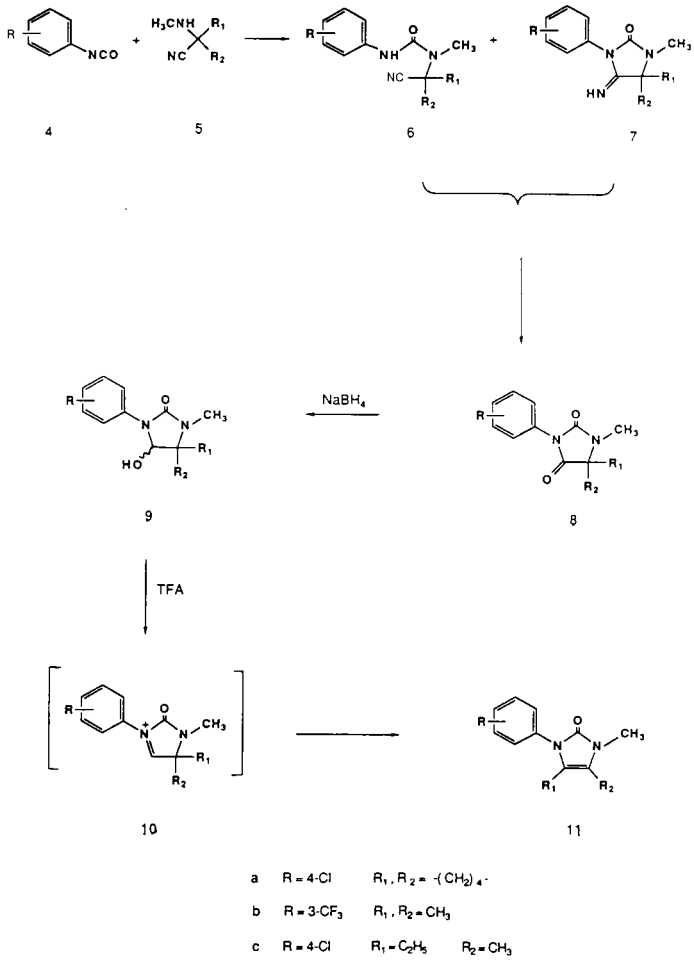


1 2 3

a R = alkyl
b R = aryl

The starting materials **9a,b,c** for this study were readily prepared. Reactions of the appropriate isocyanates **4** and nitriles **5** at ambient temperature furnished two-component mixtures which were presumed to consist of the ureas **6a,b,c** and their cyclic derivatives **7a,b,c**. The imino derivatives **7a** and **7c** were identified as the sole reaction products formed after prolonged refluxing. Acid hydrolysis of the binary mixtures yielded the corresponding hydantoins **8a,b,c** which were cleanly reduced with sodium borohydride to 4-hydroxyimidazolidin-2-ones **9a,b,c**.

N-Carbamoyliminium ion formation, followed by rearrangement, was initiated with trifluoroacetic acid at room temperature. The spiro compound **9a** formed the tetrahydrobenzimidazolone **11a** almost immediately in quantitative yield. The gem-dimethyl analogue **9b** gave the expected dimethylimidazolone **11b** in 96% yield after one week. From the 5-ethyl-5-methyl precursor **9c**, two isomeric products **11c** and **12** appeared possible depending on

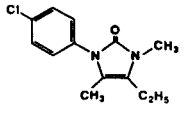


4 5 6 7 9 8 10 11

a R = 4-Cl $R_1, R_2 = -(CH_2)_4-$
b R = 3-CF_3 $R_1, R_2 = CH_3$
c R = 4-Cl $R_1 = C_2H_5$ $R_2 = CH_3$

which 5-alkyl substituent in the ion **10c** migrated to the electron-deficient centre. In the event, the exclusive formation of **11c**, quantitatively after a few hours, indicated total preference for transpostion of the ethyl group, a result which suggests that the migratory aptitude of the higher alkyl outweighs any tendency to form the most highly stabilised carbonium ion **13** [4]. The identity of the rearrangement product **11c** was established by nOe experiments. Irradiating the 1-methyl signal enhanced the reso-

nance of the 5-methyl substituent and had no effect on the multiplets of the ethyl group. Irradiating the methylene signal increased the peak-heights of the aromatic protons (particularly ortho) which did not respond to an irradiation of the 5-methyl resonance. Interestingly, there was no significant interaction between the 4- and 5-alkyl groups.



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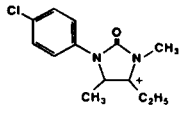

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In conclusion, this brief study has demonstrated that 5,5-dialkyl substituted 3-aryl-4-hydroxyimidazolidin-2-ones are suitable precursors for *N*-aryl-*N*-carbamoyliminium salts which transform readily, with the likelihood of high regiospecificity, to 4,5-dialkyl substituted 3-arylimidazolin-2-ones.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra (ir) were run on a Pye Unicam SP 1100 spectrophotometer using potassium chloride discs. The symbol b denotes a broad absorption. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R-32 or a Bruker WM300. Chemical shifts are in parts per million (δ) relative to TMS, and coupling constants (J values) are in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Elemental analyses were performed on a Carlo Erba Elemental Analyser Model 1102.

General Procedure for Synthesizing Hydantoins **8a,b,c**.

A solution consisting of 0.1 mole of the appropriate isocyanate **4** and 100 ml of ether was stirred in a bath of ice-water and treated dropwise with 0.1 mole of the requisite aminonitrile **5**. The solid which separated was filtered after 30 minutes and shown by thin layer chromatography to be a mixture of two compounds. The solid was boiled under reflux for 1 hour in a solution of 150 ml of 20% hydrochloric acid and 30 ml of ethanol. After dilution with 200 ml of water, the product was extracted with dichloromethane. The extracts were dried and the solvent removed under vacuum leaving a solid residue which was recrystallized.

The spiro hydanotion **8a** was obtained from 4-chlorophenylisocyanate and 1-cyano-1-methylaminocyclopentane in 78% yield after recrystallization from propan-2-ol, mp 97-99°; ir: ν C=O 1765, 1720 (b) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.65-2.25 (m, 8H), 2.91 (s, 3H), 7.35 (m, 4H).

Anal. Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.32; H, 5.42; N, 10.05. Found: C, 59.90; H, 5.33; N, 9.62.

The gem-dimethyl analogue **8b** was prepared from 3-trifluoromethylisocyanate and 2-cyano-2-methylaminopropane in 53% yield after recrystallization from ethyl acetate/60-80 petroleum ether, mp 99-101°; ir: ν C=O 1770, 1725, 1705 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 6H), 2.91 (s, 3H), 7.45-7.81 (m, 4H).

Anal. Calcd. for $C_{13}H_{13}F_3N_2O_2$: C, 54.54; H, 4.58; N, 9.79. Found: C, 54.67; H, 4.47; N, 9.67.

The 5-ethyl-5-methyl hydantoin **8c** was obtained from 4-chlorophenylisocyanate and 2-cyano-2-methylaminobutane in 46% yield, recrystallised from ethyl acetate/60-80 petroleum ether, mp 59-61°; ir: ν C=O 1765, 1715 (b) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.71-0.88 (m, 3H), 1.43 (s, 3H), 1.58-2.05 (m, 2H), 2.91 (s, 3H), 7.37 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.52; H, 5.54; N, 10.62.

3-(4-Chlorophenyl)-4-imino-1-methyl-1,3-diazaspirononan-2-one **7a**.

The two-component mixture from the reaction of 4-chlorophenylisocyanate and 1-cyano-1-methylaminocyclopentane was boiled under reflux in ethyl acetate for 6 hours. The solvent was removed under vacuum and the residual solid recrystallized from ethyl actate/60-80 petroleum ether, mp 103-105°; ir: ν NH 3240, C=O 1725, C=N 1655 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.75-2.35 (m, 8H), 2.96 (s, 3H), 6.80-7.20 (b, 1H, exchanges with deuterium oxide), 7.25-7.55 (m, 4H).

Anal. Calcd. for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81; N, 15.13. Found: C, 60.13; H, 5.52; N, 14.84.

5-Ethyl-1,5-dimethyl-4-imino-3-(4-chlorophenyl)imidazolidin-2-one **7c**.

The mixture obtained from the reaction of 4-chlorophenylisocyanate and 2-cyano-2-methylaminobutane was refluxed in ethyl acetate for 3 hours. After removing the solvent, the residual solid crystallized from ethyl acetate/60-80 petroleum ether, mp 113-115°; ir: ν NH 3270, C=O 1725, C=N 1655 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.78-0.95 (m, 3H), 1.52 (s, 3H), 1.71-2.05 (m, 2H), 2.42 (s, 3H), 6.95-7.35 (1H, exchanges with deuterium oxide), 7.23-7.55 (m, 4H).

Anal. Calcd. for $C_{13}H_{16}ClN_3O$: C, 58.75; H, 6.07; N, 15.81. Found: C, 58.36; H, 6.07; N, 15.43.

General Procedure for the Synthesis of Hydroxyimidazolidin-2-ones **9a,b,c**.

To 0.03 mole of the appropriate hydantoin **8a,b,c** in 50 ml of ethanol was added 0.31 g of sodium borohydride. The suspension was stirred at room temperature for 6 hours and then a further 0.31 g of the hydride was added. After the reaction was complete (tlc), the solvent was removed under vacuum. The residue was dissolved in dichloromethane, washed with water and dried. After removing the solvent, there remained a solid residue which crystallized from ethyl acetate/60-80 petroleum ether.

The reduction of **8a** took 24 hours to complete and afforded the cyclopentyl derivative **9a** in 73% yield mp 140-143°; ir: ν OH 3240 (b), C=O 1680 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.35-1.90 (m, 8H), 2.36 (s, 3H), 4.86 (d, 1H, collapses to a singlet on addition of deuterium oxide), 5.37 (d, 1H, exchanges with deuterium oxide), 7.13-7.66 (m, 4H).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.95; H, 6.25; N, 9.61.

The gem-dimethyl reduction product **9b** was obtained in 78% yield after a reaction time of 24 hours, 139-141°; ir: ν OH 3290 (b), C=O 1685 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.06 (s, 3H), 1.18 (s, 3H), 2.24 (s, 3H), 4.91 (d, 1H, collapses to singlet on addition of deuterium oxide), 5.27 (d, 1H, exchanges with deuterium oxide), 7.13-8.07 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}F_3N_2O_2$: C, 54.16; H, 5.25; N, 9.72. Found: C, 53.85; H, 5.19; N, 9.45.

The conversion of **8c** to **9c** required 3 days for completion,

yield 53%, mp 153-155°; ir: ν OH 3210 (b), C=O 1675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95-1.18 (m, 3H), 1.23-2.15 (m, 2H), 2.37 (s, 3H), 4.98 (d, 1H, collapses to a singlet on addition of deuterium oxide), 5.27 (d, 1H, exchanges with deuterium oxide), 7.12-7.65 (m, 4H).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_2$: C, 58.10; H, 6.38; N, 10.42. Found: C, 58.00; H, 6.42; N, 10.35.

Synthesis of Imidazolin-2-ones **11a,b,c.**

A solution of 25 ml of trifluoroacetic acid and 0.0125 mole of the appropriate hydantoin **9a,b,c** was stored at room temperature until all starting material had disappeared (tlc). The solution was poured on ice-water and the product extracted with dichloromethane. The extracts were washed successively with sodium bicarbonate solution and water. The dried organic solution was evaporated under vacuum affording a chromatographically pure residual solid.

This procedure gave the benzimidazolone **11a** in 98% yield from **9a** after 30 minutes. Recrystallization from ethyl acetate/60-80 petroleum ether provided colourless needles, mp 91-94°; ir: ν C=O 1690, C=C 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60-2.00 (m, 4H), 2.17-2.50 (m, 4H), 3.18 (s, 3H), 7.34 (m, 4H).

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 63.84; H, 5.38; N, 10.30.

The dimethylimidazolin-2-one **11b** formed in 96% yield from **9b** after 1 week. Recrystallization from ethyl acetate/60-80 petroleum ether gave colourless crystals, mp 87-90°; ir: ν C=O 1690, C=C 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.88 (s, 3H), 2.20 (s, 3H), 3.19 (s, 3H), 7.51 (m, 4H).

Anal. Calcd. for $C_{13}H_{13}F_3N_2O$: C, 57.77; H, 4.85; N, 10.37. Found: C, 57.74; H, 5.01; N, 10.09.

The 4-ethyl-5-methylimidazolin-2-one **11c** was obtained in 96% yield from **8c** after 2 hours. Recrystallization from ethyl acetate/60-80 petroleum ether provided colourless needles, mp 92-94°; ir: ν C=O 1685, C=C 1655 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.74 (t, 3H), 1.98 (s, 3H), 2.28 (q, 2H), 3.15 (s, 3H), 7.11-7.42 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.03; N, 11.17. Found: C, 62.55; H, 6.08; N, 10.74.

Acknowledgements.

I would like to thank Dr. A. A. S. Bright for his contribution in elucidating the structure of **11c** and the Directors of Chesterford Park Research Station for allowing this work to be published.

REFERENCES AND NOTES

[1] T. L. Hough, I. R. Hough and R. W. Pannell, *J. Heterocyclic Chem.*, **23**, 1125 (1986).

[2] See Zeng-Kun Liao and H. Kohn, *J. Org. Chem.*, **50**, 1884 (1985) and references cited therein.

[3] H. Kohn and Zeng-Kun Liao, *J. Org. Chem.*, **47**, 2787 (1982).

[3] For a discussion on the migratory aptitude of alkyl groups in carbonium ions see J. March, "Advanced Organic Chemistry", John Wiley and Sons, Inc, New York, 1985, p 949.