Synthesis of Imidazolidin-4-ones and Their Conversion into 1,4-Benzodiazepin-2-ones

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α-Haloacetanilides Ia-e react with hexamine in ethanol giving the bisimidazolidin-4-one derivatives IIa-e, which hydrolize, in acidic media into the corresponding mono-imidazolidin-4-ones IIIa-e. The compounds IIa-d were converted into 1,4-benzodiazepin-2-ones, under different conditions and in the presence of a variety of agents. The yields were between 50 and 100%.

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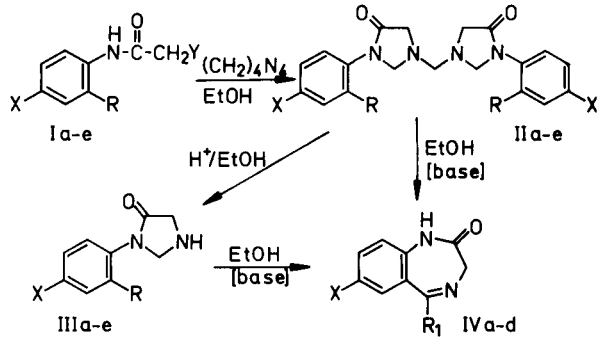
We have developed a very efficient and economical method for preparing 1,4-benzodiazepine derivatives based on the use of -α-haloacetamidobenzophenones substituted in the *p*-position to the acetamido substituent (2-5). Two different mechanisms were postulated for the formation of these products, depending on the state of substitution at the amido-*N*-atom (5). α-Haloacetamidobenzophenones on reaction with an unsubstituted amido nitrogen atom gave two intermediates containing imidazolidin-4-one rings. These were isolated from the reaction mixture and their structures were determined (5). In the case of α-haloacetamidobenzophenones in which the H-atom of the amido group is substituted by other groups, the isolable products were benzodiazepines.

Compounds having structures identical with those of the intermediates isolated from reaction mixtures of the unsubstituted α-haloacetamidobenzophenones were obtained by an independent method (6). These imidazolidin-4-one derivatives were converted to 1,4-benzodiazepin-2-ones by simple refluxing in ethanol.

SCHEME 1.



	X	Y	R	R_1
a	Cl	Cl	PhCO	Ph
b	Cl	Cl	o-ClPhCO	o-ClPh
c	NO_2	Cl	PhCO	Ph
d	Br	Br	o-PyCO	o-Py
e	Cl	Cl	H	—

Table I

Starting Compound	Product	Reaction Solvent and Traping Agent	Melting Point °C	Yield %
IIa	IVa	650 mg ammonium carbonate/absolute ethanol	216-218 (f)	72
IIa	IVa	650 mg ammonium hydroxide/96% ethanol	214-216	53
IIa	IVa	10 ml ammonium hydroxide/absolute ethanol	218-220	100
IIIa	IVa	1 g molecular sieves, 1 mmole triethylamine/absolute ethanol	215-217	76
IIIa	IVa	2 mmoles sodium bicarbonate/absolute ethanol	214-216	58
IIIa	IVa	1 mmole $(CH_2)_6N_4$, 1 mmole methyl iodide/absolute ethanol	214-217	72
IIIa	IVa	ammonium carbonate/96% ethanol	216-218	81
IIIa	IVa	5 ml ammonium hydroxide/96% ethanol	217-219	100
IIb	IVb	10 ml ammonium hydroxide/ethanol	198-200 (g)	82
IIc	IVc	1.0 g ammonium chloride/ethanol	224-225 (h)	85
IIIc	IVc	1.0 g ammonium chloride/ethanol	224-226 (h)	84
IId	IVd	1.0 g ammonium chloride/ethanol	236-238 (i)	95

(f) Lit. (8) mp 215-217°. (g) Lit. (7) mp 199-201°. (h) Lit. (9) mp 224-226°. (i) Lit. (10) mp 237-238.5°.

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Recently, we reinvestigated the synthesis of imidazolidin-4-one derivatives, as well as their conversion to 1,4-benzodiazepin-2-ones, in an attempt to improve the reaction conditions for both. The pathways used are shown in Scheme I.

Thus, the formation of bisimidazolidin-4-one derivatives (II) required no more than the short heating of a haloacetamidobenzophenone (I) and hexamine in ethanol, which resulted in yields of more than 80%. We were able to isolate and purify these compounds. The isolated and purified products (IIa-e) decomposed into monoimidazolidin-4-ones (III) when exposed to dilute hydrochloric acid in a mixture of chloroform and ethanol at room temperature. These products were isolated immediately, either in the form of hydrochlorides, or as free bases after neutralization of the reaction mixture. In this manner, the yields exceeded 80%, and the compounds were pure enough to be used directly in the next step converting them to 1,4-benzodiazepin-2-ones. This conversion occured readily in refluxing ethanol containing such agents as ammonium carbonate, sodium bicarbonate and ammonium chloride or ammonium hydroxide, which are intended to trap the formaldehyde released in the course of the benzodiazepine ring closure.

Alternatively, the bisimidazolidin-4-one derivatives were converted to the corresponding 1,4-benzodiazepines (IV) in a single step on reaction with the above mentioned agents in ethanol at reflux temperature.

A summary of data pertaining to our present experiments is given in Table I. Obviously the best catalysts for conversion of both mono- and bisimidazolidin-4-one derivatives to benzodiazepine derivatives are ammonia and ammonium chloride. The melting points for these products suggest high purity, and due to the excellent yields obtained through the use of this procedure, it is recommended as a method of choice for the synthesis of *N*-(1)-unsubstituted 1,4-benzodiazepin-2-ones.

EXPERIMENTAL

Melting points were determined on a Boetius Mikroheiztisch and are uncorrected. Nmr spectra were recorded on a Perkin Elmer Model R 12 spectrometer with samples dissolved in deuteriochloroform, using tms as an internal standard, unless stated otherwise. Ir spectra were run on a Pye-Unicam Model SP 200 spectromoter using KBr pellets.

The starting comounds Ia-d were synthetized according to previously described procedures (7).

General Procedure for the Synthesis of *N,N*-Methylene-bis-imidazolidin-4-ones IIa-e.

Compounds Ia-d (0.01 mol) and hexamine (0.02 mol) were suspended in 10 ml of 96% ethanol. The suspension was heated for 1 hour at 60°C on a water bath, the temperature was then raised to reflux and refluxing was maintained for 1 to 1.5 hours. The reaction mixture was allowed to cool to room temperature, then 5 ml of ether was added. The resulting precipitate was collected by suction, suspended in 20 ml of ether and suctioned again. This procedure was repeated twice more and the finally obtained precipitate was a pure product (IIa-e).

N,N'-Methylenebis[3-(2-benzoyl-4'-chloro)phenyl]-4-imidasolidinone (IIa).

This compound was obtained in 95% yield, mp 212-214° [lit.[6]., mp 213-215°]; ir (potassium bromide): 3450, 1780, 1670, 1600, 1490, 1430, 1355, 1290, 1256, 1210, 1140, 1110, 960, 900, 830, 800, 750, 700 cm^{-1}; nmr (deuteriochloroform): δ 3.20 (d, 6H), 4.58 (s, 4H), 6.90-8.00 (m, 16H).

Anal. Calcd. for $C_{33}H_{26}Cl_2N_4O_4$ (613.51): C, 64.61; H, 4.27; N, 9.12. Found: C, 64.32; H, 4.52; N, 8.90.

N,N'-Methylenebis[3-(2'-*o*-chlorobenzoyl-4'-chloro)phenyl]-4-imidazolidinone (IIb).

This compound was obtained in 86% yield, mp 218-221°; ir (potassium bromide): 1715, 1675, 1595, 1495, 1415, 1295, 1255, 1050, 980, 820, 810, 755 cm^{-1}; nmr (deuteriochloroform): δ 3.19 (m, 6H), 4.53 (m, 4H), 7.05-7.95 (m, 14H).

Anal. Calcd. for $C_{33}H_{24}Cl_4N_4O_4$ (683.40): C, 58.00; H, 3.69; N, 8.19. Found: C, 58.23, H, 3.44, N, 8.32.

N,N'-Methylenebis[3-(2'-benzoyl-4-nitro)phenyl]-4-imidazolidinone (IIc).

This compound was obtained in 88% yield, mp 201-204°; ir (potassium bromide): 1710, 1675, 1615, 1585, 1530, 1495, 1440, 1340, 1250, 1170, 965, 870, 780 cm^{-1}; nmr (DMSO-d_6): δ 3.27 (s, 6H), 4.60 (s, 4H), 7.20-8.62 (m, 16H).

Anal. Calcd. for $C_{33}H_{26}N_6O_8$ (634.61): C, 62.46; H, 4.13; N, 13.24. Found: C, 62.56; H, 4.10; N, 12.94.

N,N'-Methylenebis[3-(2'-*o*-pyridoyl-4-bromo)phenyl]-4-imidazolidinone (IId).

This compound was obtained in 82% yield, mp 210-212°; ir (potassium bromide) 1710, 1675, 1590, 1490, 1305, 1240, 1005, 815, 795, 755, cm^{-1}; nmr (deuteriochloroform): δ 3.12 (s, 4H), 3.20 (s, 2H), 4.61 (s, 4H), 6.60-8.70 (m, 14H).

Anal. Calcd. for $C_{31}H_{24}Br_2N_6O_4$ (704.41): C, 52.86; H, 3.43; N, 11.93. Found: C, 52.86; H, 3.57; N, 11.64.

N,N'-Methylenebis[3-(4-chlorophenyl)]-4-imidazolidinone (IIe).

This compound was obtained in quantitive yield, mp 215-216°; ir (potassium bromide): 1695, 1605, 1510, 1440, 1410, 1345, 1210, 1130, 1095, 1085, 1010, 890, 840, 820 cm^{-1}; nmr (deuteriochloroform): δ 3.58 (m, 6H), 4.68 (m, 4H), 7.17-7.70 (m, 8H).

Anal. Calcd. for $C_{19}H_{18}Cl_2N_4O_2$: 56.31; H, 4.48; N, 17.49. Found: 56.61; H, 4.37; N, 17.76.

General Procedure for the Synthesis of 3-Substitutedimidazolidin-4-ones (IIIa-IIIe).

The appropriate starting compound (IIa-e) (0.3 mmoles) was dissolved in a mixture of 7 ml of chloroform and 6 ml of 96% ethanol. To this solution, 1 ml of concentrated hydrochloric acid was added, and the reaction mixture was stirred at room temperature for 15 minutes. Afterwards, the organic solvent mixture was evaporated and the residue was treated three times with 7 ml of benzene to remove water. The wax-like material was dissolved in acetone and then ether was added dropwise until crystallization. The crystals obtained were collected by suction and dried.

3-(2'-Benzoyl-4'-chlorphenyl)-4-imidazolidinone Hydrochloride (IIIa).

This compound was obtained in 95% yield, m.p. 177-179° [lit. (5) mp 159-160° (162-183°)]; ir (deuteriochloroform): 3450, 3000-2000 multiplet, 1725, 1655, 1590, 1480, 1465, 1400, 1330, 1290, 1245, 1195, 1000, 970, 865, 805, 780 cm^{-1}; nmr (DMSO-d_6): δ 3.67 (s, 2H), 5.02 (s, 2H), 6.70 (s, 1H), 7.17-8.63 (m, 8H).

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O_2$ (337.21): C, 56.99; H, 4.18; N, 8.31. Found: C, 56.71; H, 4.32; N, 8.14.

3-(2'-*o*-Chlorobenzoyl-4'-chlorophenyl)-4-imidazolidinone Hydrochloride (IIIb).

This compound was obtained in 83% yield, mp 149-150°; ir (potassium bromide): 3450, 1708, 1670, 1490, 1335, 1290, 1265, 1210, 1140, 1110, 960, 900, 830, 800, 750, 700 cm^{-1}; nmr (deuteriomethanol): δ 3.90 (s, 2H),

5.20 (s, 2H), 7.30-7.90 (m, 7H).

Anal. Calcd. for $C_{16}H_{13}Cl_3N_2O_2$ (371.65): C, 51.71; H, 3.53; N, 7.54. Found: C, 51.43; H, 3.99; N, 7.72.

3-(2'-Benzoyl-4'-nitrophenyl-4-imidazolidinone Hydrochloride (IIIc).

This compound was obtained in 81% yield, mp 184-186°; ir (potassium bromide): 3500, 1740, 1670, 1615, 1535, 1340, 1330 cm^{-1}; nmr (DMSO-d_6): δ 3.05 (s, 2H), 4.62 (s, 2H), 7.20-8.60 (m, 8H).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_4$ (347.76): C, 55.26; H. 4, 06; n, 12.08. Found: C, 54.98; H, 4.15; N, 11.89.

3-(2'-*o*-Pyridoyl-4'-bromphenyl)-4-imidazolidinone Dihydrochloride (IIId).

This compound was not isolated in its pure form; ir (potassium bromide): 3450, 1700, 1670, 1580, 1480, 1435, 1300, 1280, 1236, 1000, 950, 810, 785, 745 cm^{-1}.

3-(4'-Chlorophenyl)-4-imidazolidinone (IIIe).

The free base was obtained after neutralisation of hydrochloride with ammonia, yield 100%, mp (base) 125-127°; ir (potassium bromide): 3370, 1695, 1605, 1510, 1440, 1410, 1345, 1210, 1130, 1095, 1085, 1010, 885, 840, 820, 775 cm^{-1}; nmr (DMSO-d_6): δ 3.30 (s, 2H), 3.37 (s, 1H), 4.57 (s, 2H), 7.06-7.67 (m, 4H).

Anal. Calcd. for $C_9H_9ClN_2O$ (196.63): C, 54.98; H, 4.61; N, 14.25. Found: C, 55.00; H, 4.95; N, 14.55.

General Procedure for the Conversion of Compounds II and III to 1,4-Benzodiazepin-2-ones.

Compound II or III (1.0 mmole) was suspended in 25 ml of obsolute ethanol, the traping agent was added (see Table I) and the mixture was refluxed for 6 to 12 hours. The reaction mixture was brought to dryness, and the residue was crystallized from ether. The relevant data are listed in Table I.

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