

Preparation of 1,3-Diaryl-2-imidazolidinones

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In connection with our work on insect chemosterilants (2) related to imidazolidinone (3), it was necessary to consider several approaches to the synthesis of 1,3-diaryl-2-imidazolidinones. Although several reviews of imidazole chemistry (4,5) indicate the condensation of *N,N'*-disubstituted ethylenediamines with phosgene to be quite general, examples of this reaction involving diaryl substituents, both in our hands and in the literature reports, invariably provided 2-imidazolidinones in less than 10% yield.

Other reported preparations of 1,3-diphenyl-2-imidazolidinone (IIa) involve the reaction of substituted malonic esters with *N,N'*-diphenylethylenediamine (6), the condensation of 1,3-diphenyl-2-thiourea with ethylene oxide (7) and, the reaction of chloral with *N,N'*-diphenylethylenediamine followed by expulsion of chloroform and oxidation (8). 2-(Phenylimino)-3-phenyl-1,3-oxazolidine is reported to undergo rearrangement into IIa (9). Finally, Mitsunobu, *et al.* (10) have described isolating 1,3-diaryl-2-imidazolidinones as one of several products arising from the reaction of bis(2-anilinoethyl)ethyl phosphite with aryl isocyanates.

All of the above approaches to II are characterized by low yields and/or rather inaccessible starting materials. Furthermore, with the exception of the last method, none of the syntheses is readily adaptable to the preparation of imidazolidinones bearing dissimilar aryl groups.

Therefore, we decided to investigate the cyclization of (2-haloethyl)urea derivatives as a route to the desired imidazolidinones. First utilized by Gabriel in 1895 to prepare 1-phenyl-2-imidazolidinone (11), this reaction has appeared intermittently in the literature since then (12), and has recently been observed to occur with several 1-(2-chloroethyl)urea candidates tested for anticoplastic activity (13).

By means of previously described procedures, *N*-(2-hydroxyethyl) derivatives of aniline, *p*-anisidine, *p*-anisole and *p*-chloroaniline were prepared (14), and converted to their 2-chloroethyl analogs (15). The reaction of these substituted anilines with various aryl isocyanates in benzene solution provided 1-(2-chloroethyl)-1,3-diarylurea derivatives (Table I). Warming the ureas in ethanolic sodium hydroxide produced the required 2-imidazolidinones in fair to good yields (Table II).

In order to help rule out the possibility of the (2-chloroethyl)ureas having cyclized to phenylimino-oxazolidines, IIa was oxidized with chromic acid to 1,3-diphenylhydantoin (1 hour reaction time) and to 1,3-diphenylimidazolidinetrione (12 hours reaction time).

EXPERIMENTAL

N-(2-Hydroxyethyl)anilines.

The procedure of Adams and Segar (14) was used to prepare previously described *N*-(2-hydroxyethyl)-*p*-toluidine, m.p. 43-44° (14); *N*-(2-hydroxyethyl)-*p*-anisidine, m.p. 41-42° (16); and *p*-chloro-*N*-(2-hydroxyethyl)aniline, m.p. 77-78° (14) from (2-chloroethyl)chloroformate and the corresponding anilines.

N-(2-Chloroethyl)anilines.

N-(2-Hydroxyethyl)aniline derivatives were converted to their hydrochloride salts and allowed to react with phosphorus oxychloride as described by Tipson (15) to provide: *N*-(2-chloroethyl)aniline hydrochloride, m.p. 156-158° (15); *N*-(2-chloroethyl)-*p*-toluidine hydrochloride, m.p. 160-162° (17); *N*-(2-chloroethyl)-*p*-anisidine hydrochloride, m.p. 150-152° (17); and *p*-chloro-*N*-(2-chloroethyl)aniline hydrochloride, m.p. 149-153°.

Anal. Calcd. for C₈H₉Cl₂N·HCl: C, 42.42; H, 4.45. Found: C, 42.18; H, 4.43.

1-(2-Chloroethyl)-1,3-diarylureas (Table I).

General Procedure.

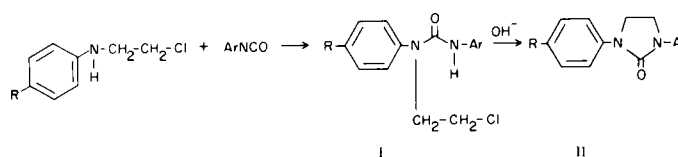
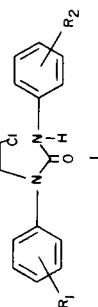


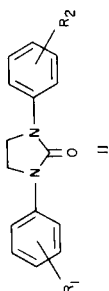
TABLE I
1-(2-Chloroethyl)-1,3-diaryllureas



Compound I	R ₁	R ₂	Recryst. Solvent (a)	M.p., °C	Yield, %	Formula	Calculated, %	Found, %	Notes
							C	H	N
a	H	H	A	71-72	71	C ₁₅ H ₁₅ ClN ₂ O	65.57	5.50	10.20
b	H	2-OC ₂ H ₅	A	89-91	90	C ₁₇ H ₁₉ ClN ₂ O ₂	64.05	6.01	8.79
c	H	3-CH ₃	A	100-101	75	C ₁₆ H ₁₇ ClN ₂ O	66.55	5.93	9.70
d	H	4-Cl	B	85-86	78	C ₁₅ H ₁₄ Cl ₂ N ₂ O	58.27	4.56	9.06
e	H	3,4-Cl ₂	B	74-74.5	99	C ₁₅ H ₁₃ Cl ₃ N ₂ O	52.43	3.81	8.15
f	H	3-NO ₂	C	92-93	90	C ₁₅ H ₁₄ ClN ₃ O ₃	56.35	4.41	13.14
g	4-CH ₃	3,4-Cl ₂	D	109-110	64	C ₁₆ H ₁₅ Cl ₃ N ₂ O	53.73	4.23	7.83
h	4-CH ₃	4-NO ₂	D	138.5-139.5	62	C ₁₆ H ₁₆ ClN ₃ O ₃	57.58	4.83	12.59
i	4-Cl	2-OC ₂ H ₅	D	104-104.5	71	C ₁₇ H ₁₈ Cl ₂ N ₂ O ₂	57.80	5.14	7.93
j	4-Cl	3-NO ₂	D	144-146	75	C ₁₅ H ₁₃ Cl ₂ N ₃ O ₃	50.87	3.70	11.86
k	4-OCH ₃	3-NO ₂	D	146-147	78	C ₁₆ H ₁₆ ClN ₃ O ₄	54.94	4.61	12.01
l	4-OCH ₃	3,4-Cl ₂	D	111-112.5	70	C ₁₆ H ₁₅ Cl ₃ N ₂ O ₂	51.43	4.05	7.50

(a) A, cyclohexane; B, methanol; C, benzene; D, ethanol.

TABLE II
1,3-Diaryl-2-imidazolidinones



Compound II	R ₁	R ₂	Recryst. Solvent (a)	M.p., °C	Yield, %	Formula	Calculated, % C H N	Found, % C H N
a	H	H	A	218.5-219.5 (b)	46	C ₁₅ H ₁₄ N ₂ O	72.32 6.43 9.92	72.57 6.26 9.97
b	H	2-OC ₂ H ₅	B	81-83	79	C ₁₇ H ₁₈ N ₂ O ₂	76.16 6.39 11.10	75.95 6.30 10.95
c	H	3-CH ₃	C	143-144	69	C ₁₆ H ₁₆ N ₂ O	66.06 4.80 10.27	66.20 4.88 10.20
d	H	4-Cl	C	205-207	53	C ₁₅ H ₁₃ ClN ₂ O	58.65 3.94 9.10	58.84 3.98 9.17
e	H	3,4-Cl ₂	A	163-164	79	C ₁₅ H ₁₂ Cl ₂ N ₂ O	63.60 4.63 14.83	63.81 4.58 14.86
f	H	3-NO ₂	D	172-174	73	C ₁₅ H ₁₃ N ₃ O ₃	59.83 4.39 8.72	59.98 4.44 8.82
g	4-CH ₃	3,4-Cl ₂	A	190-191	84	C ₁₆ H ₁₄ Cl ₂ N ₂ O	64.64 5.09 14.13	64.84 5.06 14.33
h	4-CH ₃	4-NO ₂	D	200-203	79	C ₁₆ H ₁₅ N ₃ O ₃	64.46 5.41 8.84	64.62 5.52 8.92
i	4-Cl	2-OC ₂ H ₅	B	105-107	65	C ₁₇ H ₁₇ ClN ₂ O ₂	56.70 3.81 13.19	56.87 3.76 13.22
j	4-Cl	3-NO ₂	A	158-158.5	80	C ₁₅ H ₁₂ ClN ₃ O ₃	61.34 4.83 13.41	61.06 4.66 13.17
k	4-OCH ₃	3-NO ₂	A	163-165	72	C ₁₆ H ₁₅ N ₃ O ₄	56.99 4.18 8.31	57.20 4.11 8.27
l	4-OCH ₃	3,4-Cl ₂	D	194-196	56	C ₁₆ H ₁₄ Cl ₂ N ₂ O ₂		

(a) A, acetonitrile; B, aqueous methanol; C, ethanol; D, dimethylformamide. (b) Reported (6) m.p. 216-217° C.

Dry (sodium sulfate) 10% benzene solutions of *N*-(2-chloroethyl)aniline (prepared from the hydrochloride derivative in the usual way) and an equimolar amount of substituted phenyl isocyanate were combined and refluxed for 4 hours. The solvent was removed *in vacuo* and the residue was recrystallized.

1,3-Diaryl-2-imidazolidinones (Table II).

General Procedure.

To a solution of 1-(2-chloroethyl)-1,3-diarylurea (10 mmoles) in 95% ethanol (25 ml.) was added 1 ml. of 10*N* sodium hydroxide. After refluxing for 15 minutes, the solution was concentrated *in vacuo* to about ½ its original volume, chilled, and the product obtained by filtration.

1,3-Diphenylhydantoin.

To a solution of 1,3-diphenyl-2-imidazolidinone (1.0 g., 4 mmoles) in purified acetone (30 ml.) was added 10 ml. of Jones reagent (18). After refluxing for 1 hour the reaction was poured onto ice and the almost colorless crystals were collected by filtration. Recrystallization from ethanol provided 0.82 g. (77%) of 1,3-diphenylhydantoin, m.p. 130°; mixed m.p. with authentic sample (19) produced no depression.

1,3-Diphenylimidazolidinetrione.

The reaction of Jones' reagent with 1,3-diphenyl-2-imidazolidinone was repeated exactly as in the previous example but the time of heating was extended to 12 hours. Working up the reaction as described above afforded 1,3-diphenylimidazolidinetrione that was recrystallized twice from ethanol to give 0.45 g. (40%) of colorless flakes, m.p. 202°; mixed m.p. with authentic material (20) produced no depression.

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