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α-CHLORO-ENAMINES—III

SUBSTITUTION AND ELIMINATION REACTIONS ON α-CHLOROENAMINE-β-ACID DERIVATIVES—THE SYNTHESIS OF AN YNAMINE AMIDE AND AN YNAMINE ESTER

R. BUYLE and H. G. VIEHE

Union Carbide European Research Associates, s.a., 95 rue Gatti de Gamond, Brussels 18, Belgium

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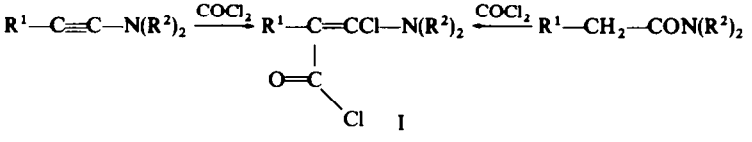
Abstract—Readily accessible β-chloroacyl-α-chloroenamines have two reactive Cl atoms which can be substituted successively with nucleophilic reagents. An ynamine amide and an ynamine ester have been prepared from N,N-diethylchloroacetamide via its β-chloro-β-chloroacyl-α-chloroenamine by chlorine elimination with lithium amalgam.

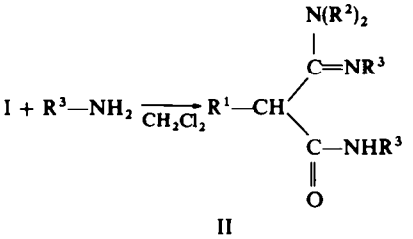
AS REACTIVE derivatives of the malonic acid family, α-chloro-β-chlorocarbonylenamine derivatives (I) can be prepared by reaction of phosgene with ynamines or with acetamide derivatives:[1]



I

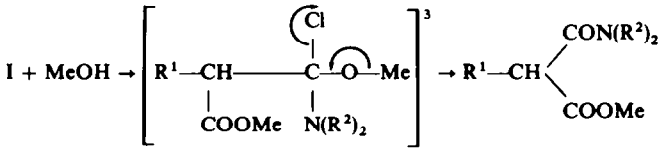
In compounds I, R^2 represents alkyl groups whereas R^1 may vary as described, R^1 being alkyl, aryl or chlorine.

In I, both Cl atoms can be substituted with protic reagents. Thus substituted malonamide-amidines (II) result from aminolysis with primary amines:[2]



II

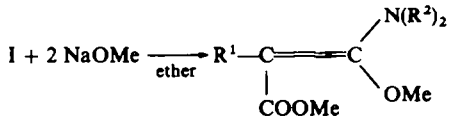
With methanol, derivatives of I form malonic ester-amides[2] (III):



III

III a: R^1 = Cl, R^2 = Et, yield: 82%
b: R^1 = Ph, R^2 = Me, yield: 67%

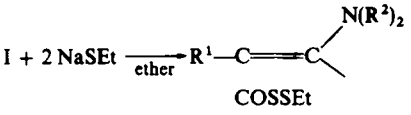
If instead of methanol, two moles of sodium methanolate react with I, the keten-O,N-acetals IV are obtained:



IV

IV a: $R^1 = Me$, $(R^2)_2 = -(CH_2)_5-$, yield: 74%
b: $R^1 = Cl$, $R^2 = Et$, yield: 63%.

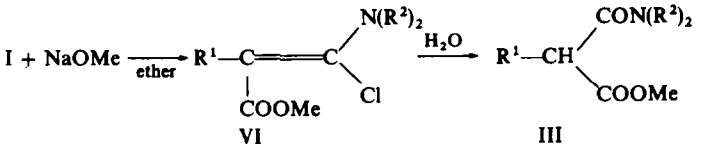
With two moles of sodium ethylthiolate, the corresponding keten-N,S-acetal V is produced from I:



V

V $R^1 = Me$, $(R^2)_2 = -(CH_2)_5-$, yield: 68%.

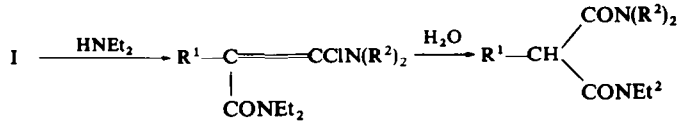
In all these reactions the two Cl atoms are substituted but their relative reactivity with only one mole of substitution reagent was examined. It was found that compound I reacts selectively with the Cl atom of the CO group. Thus with sodium methanolate the chloroenamine VI can be isolated where hydrolysis to the amidester III proves the formulated structure:



VI III

VI $R^1 = Cl$, $R^2 = Et$, yield: 72%.

As expected, the analogous chloroenamine amides VII are obtained with diethylamine. Hydrolysis of VII produces the malondiamide VIII:

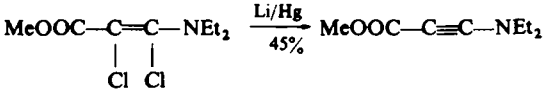


VII VIII

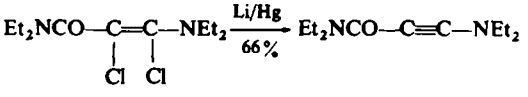
VII and VIII a: $R^1 = Me$, $(R^2)_2 = -(CH_2)_5-$
b: $R^1 = Cl$, $R^2 = Et$

The two reactive Cl atoms in I, react with difunctional protic reagents yielding heterocyclic compounds (described in Part IV of this series) and since the carbonyl chlorine is more reactive in comparison with the Cl in α-position to the nitrogen, the structure of the hetereocyclic compounds derived from I and dissymetric reagents can be deduced.

The compounds VI and VIIb derived from I (R^1 = Cl) undergo facile Cl elimination with magnesium or better with lithium amalgam in THF and form the ynamine ester (IX) and the ynamine amide (X).

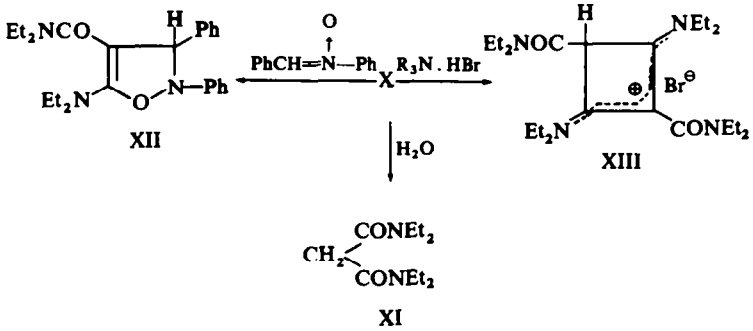


VI IX



VIIb X

The structure of X follows from the characteristic IR spectrum (C≡C at 2165 cm^{-1}) and the simple NMR data. Further support for this structure results from the formulated reactions. Thus X hydrolyses readily (0·1N HCl) to bis-N,N-diethylmalonamide (XI) and reacts with acids or better with their ammonium salts (cyclodimerization[4]) yielding cyclobutenecyanines (XIII), whereas with benzanilid-N-oxide, 1,3-cycloaddition[5] to the isoxazoline takes place.



XII XIII

XI

Similarly, the sensitive ynamine ester IX can be characterized spectroscopically and chemically as described recently by independent syntheses.[6]

EXPERIMENTAL*

Reaction of α-chloro-β-chlorocarbonyl enamines (I) *with methanol*

Malonic amide III was obtained by dissolving 0·1 mole of I in 75 ml MeOH. The excess MeOH was removed *in vacuo*. Distillation or recrystallization of the residue gave malonic ester-amide III.

* With W. Rennerts and J. Eloy.

Methyl-N,N-diethylcarbamyl chloroacetate (IIIa); yield: 82%; b.p. 92–94° ($5 \cdot 10^{-3}$ mm); recrystallization from ether–hexane, m.p. 52°. (Found: C, 46·20; H, 6·76; Cl, 17·11; N, 6·89. Calc. for $C_8H_{14}ClNO_3$: C, 46·23; H, 6·75; Cl, 17·12; N, 6·75%).

Methyl-α-N,N-dimethylcarbamyl phenylacetate (IIIb); yield: 67%; recrystallization from EtOAc, m.p.: 114°. (Found: C, 64·93; H, 6·64; N, 6·48; O, 21·91. Calc. for $C_{12}H_{15}NO_3$: C, 65·18; H, 6·78; N, 6·33; O, 21·71%).

Reaction of α-chloro-β-chlorocarbonyl enamines (I) *with sodium methanolate*

(a) *Keten-O, N-acetal derivatives* IV. To a suspension of 12 g (0·2 mole) NaOMe in 400 ml ether, 0·1 mole of I in 100 ml ether was added and the mixture stirred at 25° for 10 hr. The ppt of NaCl was separated and the organic phase evaporated under reduced press. Distillation of the residue gave IV.

α-Methyl-β-methoxy-β-piperidino acrylic acid methyl ester (IVa): yield, 74%; b.p. 104–106° (0·5 mm), $\lambda(cm^{-1})$ 1678, 1587, 1562 on the pure liquid. (Found: C, 61·50; H, 8·67; N, 6·25. Calc. for $C_{11}H_{19}NO_3$: C, 61·98; H, 8·92; N, 6·57%).

α-Chloro-β-methoxy-β-N,N-diethylamino acrylic acid methyl ester (IVb): yield, 63%; b.p. 82–84° (0·01 mm), $\lambda(cm^{-1})$ 1671, 1562, 1550 on the pure liquid. (Found: C, 48·67; H, 7·99; Cl, 16·47; N, 6·01. Calc. for $C_9H_{16}ClNO_3$: C, 48·70; H, 7·23; Cl, 16·05; N, 6·33%).

(b) *α,β-Dichloro-β-diethylamino acrylic acid methyl ester* (VI). To a suspension of 6 g (0·1 mole) NaOMe in 250 ml ether, 23 g (0·1 mole) of α,β-dichloro-β-diethylamino-acrylyl chloride in 100 ml of ether was added and the mixture stirred at 25° for 10 hr. The ppt of NaCl was separated and the organic phase evaporated under reduced press. The ester VI distilled at 64–66° at a press of 0·01 mm and 16·3 g (72% by weight) of α,β-dichloro-β-diethylamino acrylic acid methyl ester was obtained; $\lambda(cm^{-1})$ 1695, 1561 on the pure liquid. (Found: C, 42·55; H, 5·38; N, 6·44. Calc. for $C_8H_{13}Cl_2NO_2$: C, 42·40; H, 5·70; N, 6·20%).

Hydrolysis of VI yielded IIIa.

Reaction of α-chloro-β-chlorocarbonyl enamines (I) *with sodium ethylthiolate*

Keten-N,S-acetal derivatives V. A suspension of 16·8 g (0·2 mole) sodium ethylthiolate in 150 ml THF was treated with 22·2 g (0·1 mole) α-methyl-β-chloro-β-piperidino acrylyl chloride in 150 ml THF. The mixture was stirred for 10 hr at 25°. After removal of the ppt, the solvent was evaporated at reduced press. Distillation of the residue gave 18·6 g (68%) of V, b.p. 170–171° (4 mm); $\lambda(cm^{-1})$ 1621, 1494 on the pure liquid. (Found: C, 57·26; H, 8·69; N, 5·02; S, 23·52. Calc. for $C_{13}H_{23}NOS_2$: C, 57·15; H, 8·43; N, 5·15; S, 23·41%).

Reaction of α-chloro-β-chlorocarbonyl enamines (I) *with diethylamine*

To a soln containing 0·05 mole of I in 50 ml ether 7·3 g (0·1 mole) Et_2NH in 50 ml ether was added during 15 mins with stirring and cooling in an ice bath. The ppt of Et_2NH_2Cl was filtered off and the organic phase evaporated under reduced press. Distillation of the residue gave VII and hydrolysis of VII yielded VIII.

N,N-diethyl-α-methyl-β-chloro-β-piperidino acrylamide (VIIa); yield: 59%; b.p. 112–114° (0·05 m); $\lambda(cm^{-1})$: 1645, 1440 on the pure liquid. (Found: C, 60·89; H, 9·18; N, 11·04. Calc. for $C_{13}H_{23}ClN_2O$: C, 60·35; H, 8·89; N, 10·84%).

Hydrolysis of VIIa yielded VIIIa, b.p. 106–108° (0·02 mm). (Found: C, 64·61; H, 10·07; N, 12·05. Calc. for $C_{13}H_{24}N_2O_2$: C, 65·00; H, 10·00; N, 11·70%).

N,N-diethyl-α,β-dichloro-β-diethylamino acrylamide VIIb, yield: 68%; b.p. 99–101° (0·1 mm); $\lambda(cm^{-1})$ 1645, 1458, 1430 on the pure liquid. (Found: C, 49·22; H, 7·40; N, 10·60. Calc. for $C_{11}H_{20}Cl_2N_2O$: C, 49·50; H, 7·48; N, 10·47%).

Hydrolysis of VIIb yielded VIIIb; recrystallization from hexane m.p. 88°. (Found: C, 53·20; H, 8·45; Cl, 14·55; N, 11·17. Calc. for $C_{11}H_{21}ClN_2O_2$: C, 53·13; H, 8·45; Cl, 14·29; N, 11·26%).

Preparation of 3-diethylamino-propiolic acid methyl ester IX

A mixture of 4·5 g (0·02 mole) VI, 50 ml THF and 130 g 0·5% LiHg was heated during 15 min at the boiling point. After cooling, the organic phase was separated and evaporated under reduced press. The ynamine IX distilled at 66–68° at a press of 0·01 mm, 1·4 g (45% by weight) of ynamine was obtained; $\lambda(cm^{-1})$ 2165, 1695 on the pure liquid; NMR (τ, TMS) 6·33/S/3H; 6·91/M/4H; 8·77/M/6H in $CDCl_3$. (Found: N, 8·23. Calc. for $C_8H_{13}NO_2$: N, 9·00%).

Hydrolysis of IX with 0·1 N HCl yielded the expected N,N-diethyl monoamide-monomethyl ester of malonic acid. The IR spectrum was essentially identical with that of an authentic sample.

Preparation of N,N-*diethyl*-3-*diethylamino propiolamide* X

A mixture of 5·3 g (0·02 mole) of VIIb, 50 ml THF and 130 g 0·5% LiHg was heated for 15 min at the boiling point. After cooling, the organic phase was separated and evaporated under reduced press. The ynamine-amide X distilled at 102–104° at a press of 0·05 mm, yielding 2·6 g (66% by weight) of N,N-diethyl-3-diethylamino propiolamide; $\lambda(cm^{-1})$ 2170, 1612 on the pure liquid. (Found: N, 14·01. Calc. for $C_{11}H_{20}N_2O$: N, 14·28%).

Reactions of the ynamine-amide X.

(a) *Hydrolysis.* The ynamine-amide X treated with 0·1N HCl yielded XI. The IR spectrum was identical with that of a sample prepared by reaction of diethylamine with malonyl dichloride.

(b) *With benzanilid-*N-*oxide.* A mixture of 2 g (0·01 mole) of X, 2 g (0·01 mole) benzanilid-N-oxide and 10 ml toluene was heated for 20 min at 100°. After cooling, the solvent was evaporated under reduced press. Recrystallization of the residue from hexane, yielded 2·9 g (75% by weight) of XII, m.p. 140°. (Found: C, 72·90; H, 7·99; N, 10·70; O, 8·34. Calc. for $C_{24}H_{31}N_3O_2$: C, 73·26; H, 7·89; N, 10·69; O, 8·16%).

(c) *With* N,N-*dimethylaniline hydrobromide.* To a soln containing 2 g (0·01 mole) of X in 50 ml CH_2Cl_2 1 g (0·005 mole) N,N-dimethylaniline hydrobromide in 50 ml CH_2Cl_2 was added dropwise with stirring. The solvent was evaporated under reduced press and recrystallization of the residue from an acetone–ether gave 1·4 g (59% by weight) of XIII, m.p. 140°; UV: λ, 295 mμ; ε_{295}, 30,000. (Found: C, 54·14; H, 8·60; Br, 16·36; N, 12·25; O, 6·57. Calc. for $C_{22}H_{41}BrN_4O_2$: C, 55·81; H, 8·67; Br, 16·92; N, 11·84; O, 6·76%).

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