Ring Cleavage Reactions of 3- and 5-Non-substituted Isoxazoles

A. Alberola*, A. M. González, D. Guerra and F. J. Pulido

Departamento de Química Orgánica de la Universidad de Valladolid y de Investigaciones Químicas del C. S. I. C., Valladolid, Spain

Received July 20, 1981

5-Methylisoxazoles with electron-accepting groups at C-4 (Ia-c) and 2,3-dimethylisoxazolium iodide (II) undergo ring cleavage when treated with organic bases. The nature of the open chain products which were obtained (stable enolates, β-diketones, esters) depends on the group at C-4 and the strength of the base. In some of these processes aromatic aldehydes were used in order to determine the competition between the condensation and the cleavage reaction. The mechanism of the nucleophilic ring cleavage of II is also shown.

J. Heterocyclic Chem., **19**, 1073 (1982).

The acidity of the methyl and methylene groups when attached at the 5-position of an isoxazole nucleus (1,2) determines that 3-substituted 5-methylisoxazoles in the presence of bases behave as generators of carbanions capable of being involved in substitution (3) and addition-elimination (4) processes. Quaternization of the nitrogen atom of 3,5-dimethylisoxazole enhances the ability of the methyl groups to undergo condensation of the aldol, crotonic and Michael type; thus, the reaction of 3,5-dimethylisoxazolium salts with aldehydes in the presence of secondary amines leads to di-condensed products (5). Introduction of unsaturated electron-accepting groups into position 4 also increases the acidity of the 5- and 3-alkyl groups of the isoxazole ring and its salts (6,7). 4-Substituted 2,3,5-trimethylisoxazolium salts undergo hydrogen-deuterium exchange regioselectively in the methyl groups at C-3 and/or C-5 depending on the nature of the group attached at C-4 (7). Reaction of these salts with aldehydes occurs only at the methyl group in which the hydrogen-deuterium exchange takes place (7).

On the other hand, it is well known that the 3- or 5-non-substituted isoxazole derivatives are extremely labile towards the action of nucleophilic agents (8) or in alkaline medium (9). Ring cleavage proceeds under mild conditions to form non-cyclic polyfunctional systems.

In this paper, the differential acidity between the hydrogen atom at C-3 and the methyl group at C-5 of 4-nitro-(Ia), 4-chloro- (Ib) and 4-acetyl-5-methylisoxazole (Ic) is studied. We also extended this work to the study of the differential acidity between the hydrogen atom at C-5 and the methyl group at C-3 of 2,3-dimethylisoxazolium iodide (II).

Results and Discussion.

4-Substituted 5-methylisoxazoles (Ia-c) react with bases (in the presence or absence of oxo compounds) and always lead to open chain products whose nature depends on the base used.

Although 5-methyl groups are activated by electron-accepting groups at C-4, the presence of a nitro group or chlorine atom in this position markedly enhances the acidity of the hydrogen atom attached at C-3 making the isoxazole nucleus of Ia and Ib extremely labile towards cleavage. Thus, Ia and Ib when reacting with piperidine and pyridine lead to the stable enolates IIIa-c, according to the following mechanism previously described (10).

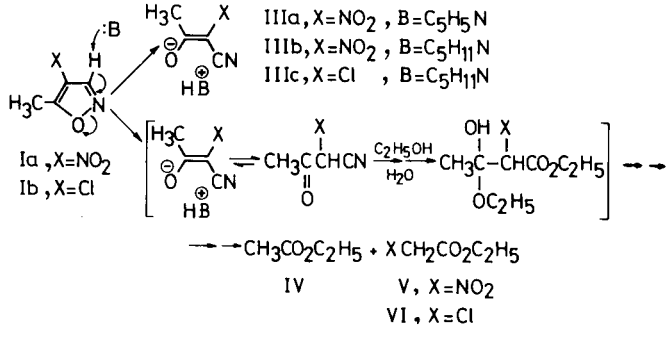

Figure 1

Although ethanol and pyridine are basic enough to cause ring cleavage of Ia and Ib, respectively, they cannot stabilize the resulting enolate which is converted into ethyl acetate (IV) and ethyl nitroacetate (V) or ethyl chloroacetate (VI) *via* a hemiketal intermediate.

The behaviour of 4-acetyl-5-methylisoxazole (Ic) is perceptibly different from that which the analogous 4-nitro and 4-chloro derivatives show. The polar effect of the acetyl group (σ = 0.28) (11), smaller than those of the nitro group (σ = 0.65) (11), and the chlorine atom (σ = 0.46) (11), determines that the hydrogen atom at C-3 of Ic is much less acid than the same atom of Ia and Ib. Since the acetyl group at C-4 increases, in little extent, the acidity of the 5-methyl group, the hydrogen at C-3 and the methyl group of the acetyl group of Ic must posses a comparable acidity. Thus, in the presence of strong bases such as dilute sodium hydroxide Ic is converted into the sodium enolate VIIa, which is easily cyclized to 4-cyano-3,5-dimethylisoxazole (VIII) when treated with hydroxylamine hydrochloride. On the other hand, the reaction of Ic with piperidine in the presence of benzaldehyde leads to the piperidinium enolate VIIb and a cinnamoylisoxazole intermediate, which undergoes ring cleavage and further reaction with benzaldehyde to give 3-cyano-6-phenyl-5-hexene-2,4-dione (IX) and 4-cyano-1,7-diphenyl-1,6-heptadiene-3,5-dione (X).

Although this cinnamoylisoxazole intermediate could not be isolated, the former scheme has been sufficiently

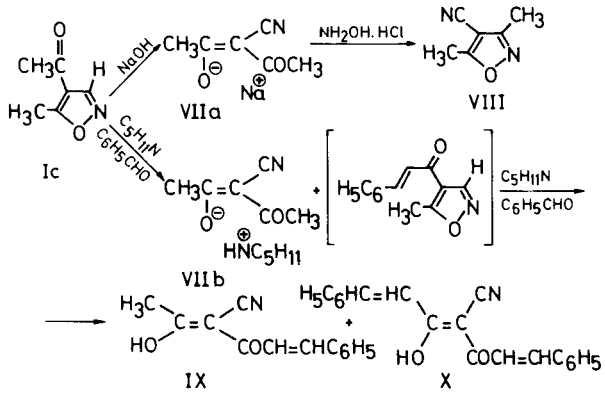

Figure 2

proven by the fact that VIIb under the same conditions fails to react with benzaldehyde whereas the 4-acetyl-3,5-dimethylisoxazole (XI) (which is not easily cleaved by the action of bases) yields 4-cinnamoyl-3,5-dimethylisoxazole (XII) when treated with benzaldehyde in the presence of sodium ethoxide.

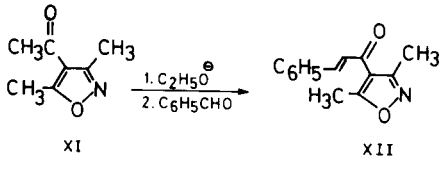

Figure 3

The lower basicity of pyridine does not permit condensation of Ic with benzaldehyde. Instead of this, ring cleavage is observed after the reaction is refluxed in ethanol for 5 hours. The resulting pyridinium enolate which is not stable, condenses with benzaldehyde to yield 3-cyano-4-phenyl-3-buten-2-one (XIII). Formation of XIII involves alcoholysis of the cyano-β-diketone intermediate resulting from the above condensation, and further elimination. The identification of cyanoacetylacetone (XIV) and ethyl acetate (IV) (gc) corroborates the following scheme.

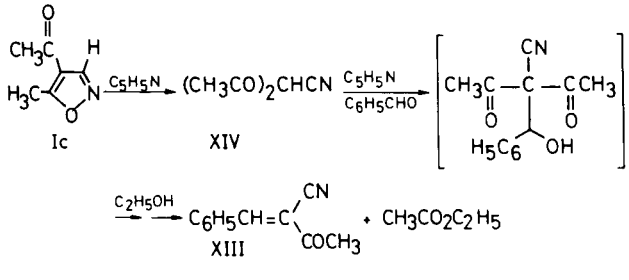

Figure 4

The reaction of 2,3-dimethylisoxazolium iodide (II) with pyridine or piperidine in ethanol solution leads only to ethyl acetoacetate (XV) and its *N*-methylimine (XVI); the presence of aromatic aldehydes does not affect the final results. Consequently, the acidity of the hydrogen atom at C-5 is higher than that of the 3-methyl group. The mechanism of the nucleophilic cleavage of 3-non-substituted isoxazolium salts seems to proceed with preliminary removal of the proton from the unsubstituted carbon atom by the nucleophile followed by neutralization of the negative charge of the resulting isoxazolyl anion which causes cleavage of the N-O bond and formation of a ketene intermediate (non-isolable). This intermediate spontaneously adds ethanol to give XVI which is partially hydrolized to XV.

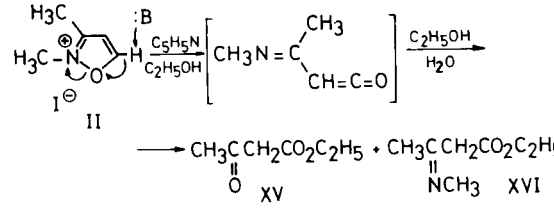

Figure 5

EXPERIMENTAL

Melting points are uncorrected. 4-Nitro-5-methylisoxazole (12), 4-chloro-5-methylisoxazole (13), 4-acetyl-5-methylisoxazole (14), 3-methylisoxazole (15) and 3,5-dimethyl-4-acetylisoxazole (16) were prepared by established procedures. 2,3-Dimethylisoxazolium iodide, mp 174-176°, was prepared by treating 3-methylisoxazole with methyl iodide according to the literature method (17). The infrared spectra were recorded for nujol mulls in the case of solids or for thin films in the case of liquids, using a Pye Unicam SP-1100 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 analytical nmr spectrometer with tetramethylsilane as an internal standard. Solvents and reagents were purified by conventional methods. Gas-liquid chromatography was performed on a Hewlett Packard 5710 gas chromatograph.

Reaction of Ia with Bases.

To a solution of 1.8 g (14 mmoles) of Ia in 5 ml of ethanol was added dropwise 14 mmoles of pyridine or piperidine with stirring at −5° and the mixture was allowed to stand at below 0° for 3 minutes. After evaporation of the ethanol at room temperature, the residue was collected, washed with ether and recrystallized from chloroform to give 2.8 g (98%) of IIIa or 2.9 g (98%) of IIIb. The ionic structures of IIIa and IIIb have been elucidated through their physical and spectroscopic characteristics.

1-Nitro-1-cyanoacetone Pyridinium Salt (IIIa).

This compound was obtained as colorless needles, mp 103-104°; ir (nujol): 2750-2450 (broad), 2235, 1640, 1600, 1505, 760, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, CH_3, 3H), 7.65 (m, β-pyridinium ion protons, 2H), 8.15 (m, γ-pyridinium ion proton, 1H), 8.4 (m, α-pyridinium ion protons, 2H), 12.6 (s, $^+$N-H, 1H); IIIa does not vaporize in the mass spectrometer; however it decomposes on heating in the instrument to release the free amine and the 1-cyano-1-nitro-2-hydroxypropene. The mass spectrum of IIIa showed ions at 128 (M^+, 100), 129 (M + 1, 5.5), 111 (M-17, 10), 43 (8) corresponding to the 1-cyano-1-nitro-2-hydroxypropene, and ions at 79 (M^+, 100), 52 (M-27, 12) corresponding to pyridine.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.34; N, 20.28. Found: C, 52.26; H, 4.40; N, 20.17.

1-Nitro-1-cyanoacetone Piperidinium Salt (IIIb).

This compound was obtained as colorless prisms, mp 68-69°; ir (nujol): 3100 (broad), 2235, 1640, 1490 cm^{-1}; nmr (deuteriochloroform): δ 1.8 (m, β- and γ-piperidinium ion protons, 6H), 2.2 (s, CH_3, 3H), 3.25 (m, α-piperidinium ion protons, 4H), 6.2 (s, $^+NH_2$, 2H); ms: 128 (M^+, 100), 129 (M + 1, 5.5), 111 (M-17, 10), 43 (8) and ions at 85 (M^+, 100), 70 (M-15, 33) corresponding to piperidine.

Anal. Calcd. for $C_9H_{15}N_3O_3$: C, 50.70; H, 7.04; N, 19.71. Found: C, 50.65; H, 6.95; N, 19.83.

A solution of 1.8 g (14 mmoles) of Ia in 5 ml of 95% aqueous ethanol was refluxed for 4 hours. Evaporation of the solvent yielded 0.82 g (44%) of ethyl nitroacetate (V). Ethyl acetate (IV) was also identified (gc) from the original solution.

Reaction of Ia with Benzaldehyde.

When the above reactions were carried out in the presence of benzaldehyde, enolates IIIa and IIIb were obtained in minor yields along with polymeric materials. No condensation products were isolated.

Reaction of Ib with Bases.

To a solution of 1.6 g (14 mmoles) of Ib in 5 ml of ethanol was added 14 mmoles of piperidine with stirring at 0° and the mixture was allowed to stand at this temperature for 3 minutes. Work-up as described for Ia gave 2.6 g (93%) of white crystals of 1-chloro-1-cyanoacetone piperidinium salt (IIIc), mp 85° (from chloroform); ir (nujol): 3000-2550 (broad), 2205, 1630, 620 cm^{-1}; nmr (deuteriochloroform): δ 1.8 (m, β- and γ-piperidinium ion protons, 6H), 2.0 (s, CH_3, 3H), 3.25 (m, α-piperidinium ion protons, 4H), 7.8 (s, $^+NH_2$, 2H). The ms of IIIc had peaks at 119 (M + 2, 35), 118 (M + 1, 5), 117 (M^+, 100), 82 (M-35, 20), 43 (10) corresponding to the 1-chloro-1-cyano-2-hydroxypropene as well as the ions corresponding to the piperidine.

Anal. Calcd. for $C_9H_{15}ClN_2O$: C, 53.33; H, 7.41; N, 13.83. Found: C, 53.46; H, 7.45; N, 13.69.

Reaction of 1.6 g (14 mmoles) of Ib with pyridine instead of piperidine in 5 ml of refluxing 95% aqueous ethanol (5 hours) yielded after evaporation of the solvent 0.43 g (25%) of ethyl chloroacetate (VI). Ethyl acetate (IV) was also identified (gc) from the original solution.

Reaction of Ic with Sodium Hydroxide. Synthesis of 4-Cyano-3,5-dimethylisoxazole (VIII).

Compound Ic (4.1 g, 33 mmoles) was dissolved in 5 ml of ethanol and this mixture was added to an ethanolic solution of 1.32 g (33 mmoles) of sodium hydroxide which was cooled in ice. The white powder that precipitated was filtered and washed with ethanol to give 3.82 g (79%) of cyanoacetylacetone sodium salt (VIIa), infusible below 350°; ir (nujol): 2230, 1650 cm^{-1}; nmr (deuterium oxide): δ 2.1 (s, methyl groups, 6H).

A mixture of 3.83 g (26 mmoles) of VIIa and 2.78 g (40 mmoles) of hydroxylamine hydrochloride in 6 ml of water was refluxed for 6 hours. The cooled mixture was extracted with ether and the organic layer dried over anhydrous calcium sulfate. Evaporation of the solvent left a viscous oil which was distilled (30°/1.5 mm) to give 2.10 g (66%) of 4-cyano-3,5-dimethylisoxazole (VIII), white plates, mp 46° (lit (18) 43-44°); ir (nujol): 2240, 1630 cm^{-1}; nmr (carbon tetrachloride): δ 2.35 (s, CH_3-3, 3H), 2.6 (s, CH_3-5, 3H).

Reaction of Ic with Benzaldehyde.

a) In Piperidine.

Benzaldehyde (4.25 g, 40 mmoles) dissolved in 10 ml of ethanol was added to a mixture of 5 g (40 mmoles) of Ic and 1.7 g (20 mmoles) of piperidine in 10 ml of ethanol. The mixture was stirred at 40° for 4 hours, then cooled. Yellow crystals from the ethanolic solution were collected, recrystallized from methanol and proven to be 4-cyano-1,7-diphenyl-1,6-heptadien-3,5-dione (X), yield 6.65 g (55%). After evaporation of the ethanol the solid residue was extracted twice with 3 ml of water. The water-insoluble residue was filtered off, washed with water, dried, recrystallized from chloroform and proven to be 3-cyano-6-phenyl-5-hexene-2,4-dione (XI); yield 1.3 g (15%). The aqueous extract was evaporated to dryness *in vacuo* at room temperature. This left white crystals that were recrystallized from chloroform and proven to be cyanoacetylacetone piperidinium salt (VIIb), yield 2.1 g (25%). When the above reaction was heated under reflux for 8 hours the only product isolated was X, yield 9 g (75%). The identification of these compounds were achieved in the following way.

Cyanoacetylacetone Piperidinium Salt (VIIb).

This compound was obtained as colorless cubes, mp 83-85°; ir (nujol): 3000-2460 (broad), 2205, 1650 cm^{-1}; nmr (deuteriochloroform): δ 1.7 (m, β- and γ-piperidinium ion protons, 6H), 2.0 (s, methyl groups, 6H), 3.1 (m, α-piperidinium ion protons, 4H), 8.5 (s, $^+NH_2$, 2H); ms: 125 (M^+, 11), 43 (100) (cyanoacetylacetone) and the ions corresponding to piperidine.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.85; H, 8.57; N, 13.33. Found: C, 62.80; H, 8.51; N, 13.29.

3-Cyano-6-phenyl-5-hexene-2,4-dione (IX).

This compound was obtained as yellowish needles, mp 130-131° (lit (19) 130°); ir (nujol): 2225, 1640, 1605, 980, 770, 695 cm^{-1}; nmr (deuteriochloroform): δ 2.45 (s, CH_3, 3H), 6.9 (d, J = 16 Hz, olefinic proton attached at C-5, 1H), 7.2-7.6 (m, aromatic protons, 5H), 7.65 (d, J = 16 Hz, olefinic proton attached at C-6, 1H), 16.4 (s, OH, 1H); ms: 213 (M^+, 58.5), 214 (M + 1, 8.5), 212 (M - 1, 23.4), 198 (M - 15, 18.2), 195 (M - 18, 20.7), 180 (M - 33, 31.2), 170 (M - 43, 83), 136 (M - 77, 21), 131 (M - 82, 91), 103 (M - 110, 75.4), 77 (52), 43 (100).

4-Cyano-1,7-diphenyl-1,6-heptadiene-3,5-dione (X).

This compound was obtained as yellow needles, mp 233-235° (ethanol); ir (nujol): 2220, 1630, 1625, 1580, 985, 760, 690 cm^{-1}; nmr (deuteriochloroform): δ 7.05 (d, J = 15 Hz, olefinic protons attached at C-2 and C-6, 2H), 7.15-7.55 (m, aromtic protons, 10H), 7.70 (d, J = 15 Hz, olefinic protons attached at C-1 and C-7, 2H), 19.6 (s, OH, 1H); ms: 301 (M^+, 53.8), 302 (M + 1, 13.1), 284 (M - 17, 11.5), 283 (M - 18, 31), 282 (M - 19, 54), 224 (M - 77, 17.2), 180 (M - 121, 27), 170 (M - 131, 42.4), 131 (100), 103 (65.2), 77 (23.1).

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.73; H, 4.98; N, 4.65. Found: C, 79.80; H, 5.00; N, 4.45.

b) In Pyridine.

Benzaldehyde (4.25 g, 40 mmoles) dissolved in 10 ml of ethanol was added to a mixture of 1.6 g (20 mmoles) of pyridine and 5.0 g (40 mmoles) of Ic in 10 ml of ethanol and the reaction mixture was refluxed for 5 hours. The reaction was followed by gc and ethyl acetate was identified from the original solution. Evaporation of the ethanol left a residue which was distilled under reduced pressure and led to a 1st fraction (30-42°/2 mm) consisting of a mixture (gc) of benzaldehyde, Ic and cyanoacetylacetone (XIV) (each compound identified by comparison with authentic sample) and a 2nd fraction (55-60°/2 mm) that was proven to be XIII; yield 1.37 g (20%).

3-Cyano-4-phenyl-3-buten-2-one (XIII).

This compound was obtained as white plates, mp 81-83° (lit (20) 83°) from chloroform-carbon tetrachloride; ir (nujol): 2220, 1710, 1595, 1580, 1370, 770, 695 cm^{-1}; nmr (deuteriochloroform): δ 2.5 (s, CH_3, 3H), 7.3 (m, m- and p-aromatic protons, 3H), 7.75 (m, o-aromaic protons, 2H), 7.9 (s, olefinic proton, 1H); ms: 171 (M^+, 90.6), 172 (M + 1, 9.3), 170 (M - 1, 100), 156 (M - 15, 37.5), 129 (M - 42, 37.5), 128 (M - 43, 34), 102 (M - 69, 25), 101 (M - 70, 16.2), 77 (17.3), 43 (7).

Reaction of 4-Acetyl-3,5-dimethylisoxazole (XI) with Benzaldehyde.

To a solution of sodium methoxide prepared from 0.4 g of sodium and 20 ml of methanol was added a mixture of 1.4 g (13 mmoles) of benzaldehyde and 1.8 g (13 mmoles) of XI and the reaction mixture was refluxed by stirring for 2 minutes. The mixture was kept at 0° overnight and the precipitated crystals were recrystallized from ethanol to give 2.42 g (82%) of 4-cinnamoyl-3,5-dimethylisoxazole (XII), white crystals,

mp 96-98° (ethanol); ir (nujol): 1665, 1615, 1580, 990, 760, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.45 (s, CH_3-3, 3H), 2.6 (s, CH_3-5, 3H), 6.9 (d, J = 16 Hz, olefinic proton attached at the α-position of cinnamoyl group, 1H), 7.0-7.3 (m, aromatic protons, 5H), 7.5 (d, J = 16 Hz, olefinic proton attached at the β-position of cinnamoyl group, 1H); ms 227 (M^+, 44.7), 228 (M + 1, 6.2), 226 (M − 1, 41.2), 212 (M − 15, 7), 199 (M − 28, 5), 184 (M − 43, 17.1), 170 (M − 57, 10), 156 (M − 71, 7), 131 (M − 96, 23.4), 124 (M − 103, 12.8), 103 (39.7), 82 (25.9), 77 (40.7), 43 (100).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found: C, 74.17; H, 5.67; N, 6.25.

Reaction of II with Bases.

Compound II (1.87 g, 8.3 mmoles) dissolved in 5 ml of 95% aqueous ethanol was treated with 0.8 g (10 mmoles) of pyridine or 0.85 g (10 mmoles) of piperidine and the reaction mixture was refluxed for 3 hours. After evaporation of ethanol the crude product consisting of ethyl acetoacetate (XV) and its *N*-methylimine (XVI) was submitted to gas chromatographic analysis. Each component was identified by the authentic sample. Compound XVI was prepared by the literature method (21). Analytical gc was carried out using a stainless steel column (3 mm × 4 m); liquid phase Dexil-300 on Chromosorb Q, 130°, nitrogen, 35 ml/minute, injection 250°; ethyl acetoacetate (XV): 40%, t_R = 3 minutes; ethyl β-(*N*-methylimino)-*n*-butyrate (XVI): 60%, t_R = 8.8 minutes.

REFERENCES AND NOTES

(1) N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocyclic Chem.*, **2**, 365 (1963).

(2) B. J. Wakefield and D. J. Wright, *ibid.*, **25**, 147 (1979).

(3) C. Kashima, Y. Yamamoto and Y. Tsuda, *J. Org. Chem.*, **40**, 526 (1975).

(4) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).

(5) W. Lampe and J. Smolinska, *Rocz. Chem.*, **28**, 163 (1954); *Bull. Acad. Pol. Sci.*, **6**, 481 (1958).

(6) G. Renzi, V. Dal Piaz and S. Pinzauti, *Gazz. Chim. Ital.*, **99**, 753 (1969).

(7) A. Alberola, A. M. González and F. J. Pulido, in press.

(8) R. B. Woodward and R. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961) and references (1) and (2).

(9) R. P. Barnes, "Heterocyclic Compounds", Vol 5, R. C. Elderfield, ed, John Wiley and Sons, New York, 1952 and references (1) and (2).

(10) A. De Munno, V. Bertini and F. Lucchesini, *J. Chem. Soc., Perkin Trans. II*, 1121 (1977).

(11) R. A. Y. Jones, "Physical and Mechanistic Organic Chemistry", Cambridge University Press, Cambridge, 1979, p 57.

(12) C. Musante, *Gazz. Chim. Ital.*, **76**, 131 (1946).

(13) A. Quilico and R. Justoni, *Rend. Ist. Lomb. Sci.*, **69**, 587 (1936).

(14) P. Vita-Finzi and P. L. Carmella, *Ann. Chim. Ital.*, **55**, 1233 (1965).

(15) G. Soula, German Patent 1,958,252 (1971); *Chem. Abstr.*, **75**, 63763v (1971).

(16) A. Padwa, E. Chem and A. Ku, *J. Am. Chem. Soc.*, **97**, 6484 (1975).

(17) W. Lampe and J. Smolinska, *Rocz. Chem.*, **28**, 163 (1954).

(18) E. Bernary and M. Rosenfeld, *Chem. Ber.*, **55**, 3425 (1922).

(19) C. H. Eugster, L. Leichner and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).

(20) N. K. Kochetkov, S. D. Sokolov and V. M. Luboshnikova, *Zh. Obshch. Khim.*, **32**, 1778 (1962).

(21) A. Korschun and P. Roll, *Bull. Soc. Chim. France*, **33**, 1106 (1923).