A Novel Rearrangement of 3-Arylisoxazol-5(4*H*)-ones: One-Pot Synthesis of New 2,4-Dichloroquinoline-3-carbaldehydes

K. Ashok,*[+] G. Sridevi,[+] Y. Umadevi

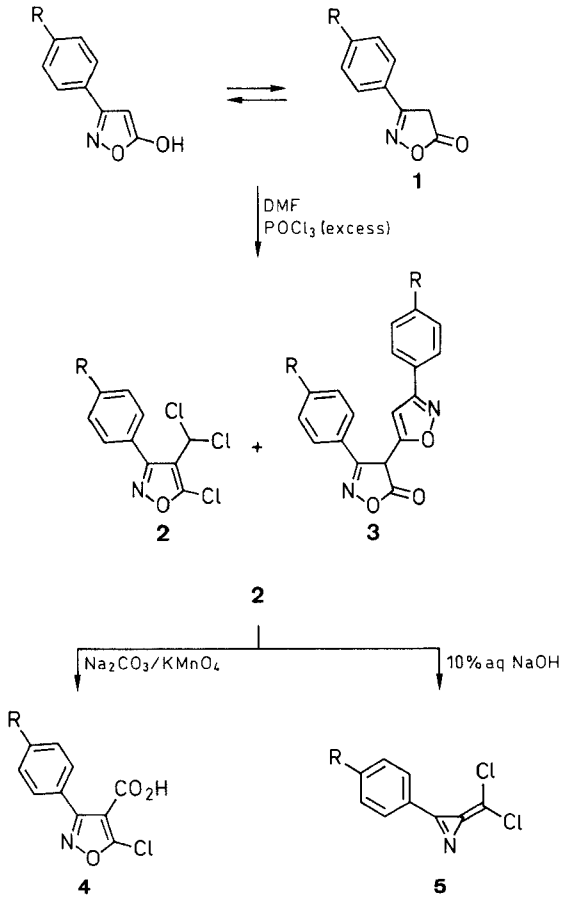
Department of Chemistry, Nizam College, Osmania University, Hyderabad 500001, India

Received 20 January 1992; revised 15 February 1992

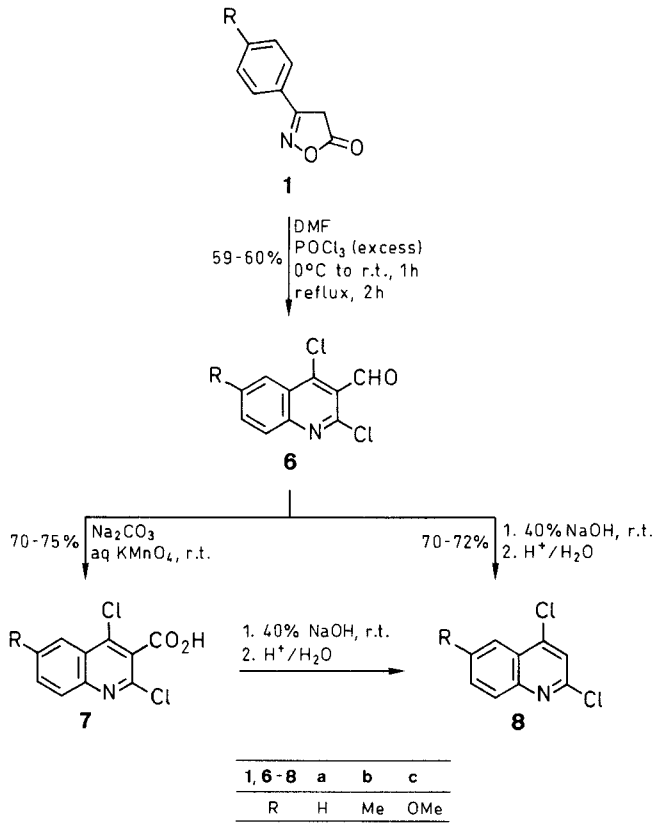
Vilsmeier–Haack reaction, using a specific combination of phosphorus oxychloride and dimethylformamide, on 3-arylisoxazol-5(4*H*)-ones **1** resulted in 2,4-dichloroquinoline-3-carbaldehydes **6** as the major products along with other minor products, through a novel rearrangement. Oxidation of **6** with alkaline potassium permanganate gave 2,4-dichloroquinoline-3-carboxylic acids **7**. Decarbonylation of **6** and decarboxylation of **7** using aqueous sodium hydroxide yielded 2,4-dichloroquinolines **8**. All the compounds were characterised by elemental and spectral analysis.

The Vilsmeier–Haack reaction on heterocyclic compounds as well as their synthesis using this reaction has been widely studied.[1-3] Reinvestigation of the Vilsmeier–Haack reaction on 3-phenylisoxazol-5(4*H*)-one[4] (**1a**) by Anderson revealed some discrepancies such as the absence of formation of the reported[5] trichloroisoxazole **2**, bisisoxazole **3** and the azirine **5** in the reaction (Scheme 1). This prompted us to repeat the reaction in order to throw light on these structures and surprisingly we observed the formation of the hitherto unreported 2,4-dichloroquinoline-3-carbaldehydes **6** which serve as useful reactive intermediates for the preparation of angular and linear quinoline-fused heterocycles such as furano- and pyranoquinoline alkaloids. Considering that incorporation of a formyl group at C-3 position of the quinoline ring by electrophilic substitution reaction is difficult, the present method provides a synthetically useful route for the preparation of **6** and analogues, under easily accessible conditions.

When 3-phenylisoxazol-5(4*H*)-one[6] (**1a**) suspended in dimethylformamide was allowed to react with an excess of phosphorus oxychloride at 0 °C, followed by raising the temperature of the reaction mixture slowly up to 80 °C on a water bath, two compounds were obtained with mp 119 °C (**A**) and mp 275 °C (**B**). Compound **A** was insoluble in alkali and did not give any ferric chloride colouration for 5-OH of **1a**. IR (KBr) spectrum of this compound demonstrated a carbonyl absorption at ν = 1700 cm^{-1} (CHO) and this was confirmed by usual chemical tests. Inspection of ^1H NMR ($CDCl_3$ DMSO-d_6) revealed a singlet at δ = 10.50 for an aldehydic proton and a multiplet at δ = 7.55–8.35 integrating for four aromatic protons which clearly tells that one carbon atom of phenyl group of the original isoxazole ring system **1a** has been attacked leading to the formation of benzo-fused system. In the mass spectrum, the peak at highest mass



Scheme 1



Scheme 2

Downloaded by: York University libraries. Copyrighted material.

was observed at $m/z = 225$ and revealed a two chlorine pattern (p:p + 2:p + 4 = 9:6:1). The high resolution mass spectrum determined the molecular composition as $C_{10}H_5Cl_2NO$. This data coupled with analytical information suggested the product **A** to be 2,4-dichloroquinoline-3-carbaldehyde (**6a**) (Scheme 2). The structure of **6a** was further confirmed by ^{13}C NMR spectrum analysis and the following chemical reactions.

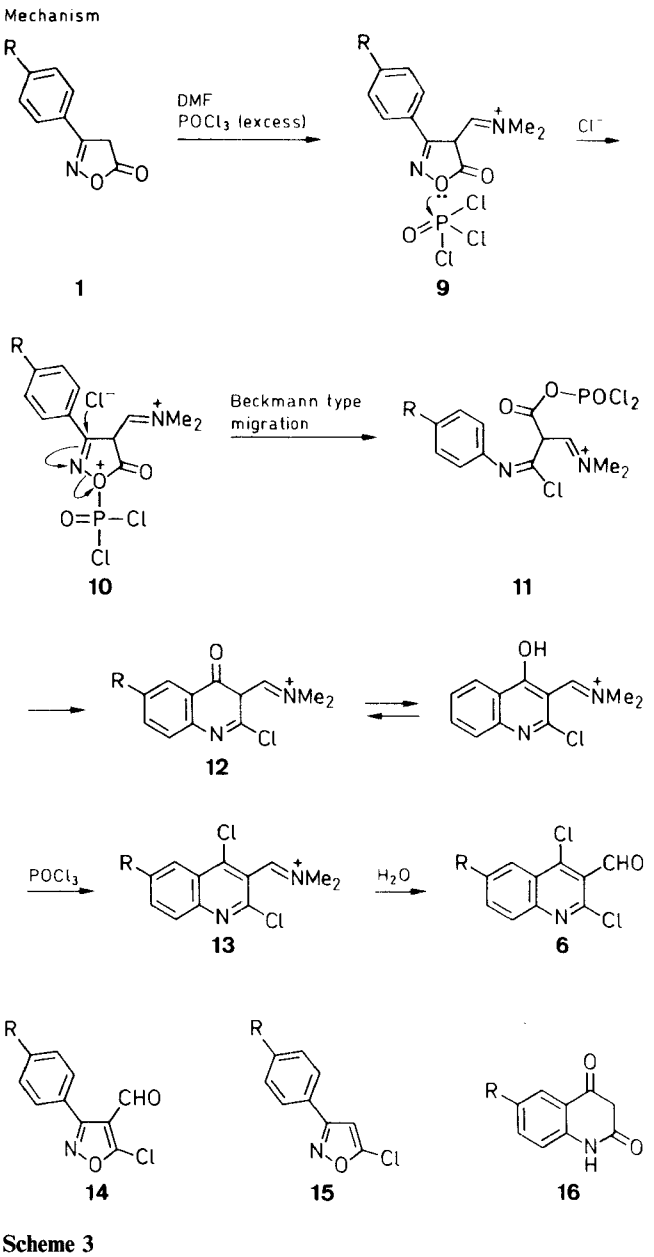
Treatment of **6a** with 40% sodium hydroxide gave a compound which showed lack of carbonyl absorption in the IR (KBr) spectrum. Its ^1H NMR recorded a multiplet at $\delta = 7.30-8.10$ for aromatic protons. Molecular ion was recorded at $m/z = 197$ in its mass spectrum. This compound has been assigned the 2,4-dichloroquinoline (**8a**) structure based on the spectral data and confirmed by independent synthesis of authentic sample from methyl anthranilate.[7] Though the reaction conditions are those of a Cannizzaro reaction, only decarbonylation of **6a** occurred, without the formation of the corresponding alcohol and acid, possibly due to the presence of the electron withdrawing chlorines at C-2 and C-4 of **6a** as observed in the case of 2,6-dichlorobenzaldehyde.[8]

Oxidation of **6a** with alkaline potassium permanganate gave hitherto unreported 2,4-dichloroquinoline-3-carboxylic acid (**7a**) and subsequent treatment of this acid with 40% sodium hydroxide in turn yielded the dichloro compound **8a**. It may be noted that ethyl 2,4-dihydroxyquinoline-3-carboxylate on treatment with 40% sodium hydroxide is reported to yield 2,4-dihydroxyquinoline directly.[7]

The decarbonylation product from **6a** and decarboxylation product from **7a** were identical in all respects (superimposable IR spectrum). These reactions proved the structure of **6a** beyond any doubt. Since the compounds **7a** and **8a** of this paper (Scheme 2) and the product "**4a**" and "**5a**" obtained from "**2a**" (Scheme 1) are identical by spectral means, the chloro acid, "**4a**", and azirine "**5a**" reported in the original article[5] must be 2,4-dichloroquinoline-3-carboxylic acid (**7a**) and 2,4-dichloroquinoline (**8a**), respectively. The earlier erroneous structural assignments may be ascribed to improper examination and interpretation of the observed spectral data.

The transformation of isoxazolone **1a** to quinoline **6a** is envisaged to involve the initial formation of 4-(dimethyliminomethyl)-3-phenylisoxazol-5(4*H*)-one chloride (**9**) which then undergoes heterolytic ring fission of N–O bond of isoxazole ring and simultaneous phenyl group migration to electron deficient nitrogen (Beckmann type) and attack of chloride ion on the carbocation of **10** to form **11**. Subsequent nucleophilic attack of phenyl ring of **11** on carboxylic carbon leads to the formation of **12** which gives 2,4-dichloro-3-(dimethyliminomethyl)quinoline chloride (**13**) and this **13** ultimately forms **6** on aqueous workup. The mechanism was proposed on the basis of the following observations (Scheme 3).

1. Involvement of intermediacy of 5-chloro-3-phenylisoxazole-4-carbaldehyde[4] (**14a**) or 5-chloro-3-phenylisoxazole[9a,b] (**15a**) was ruled out as their treatment with phosphorus oxychloride/dimethylformamide under the same conditions failed to furnish **6a**.



Scheme 3

2. Vilsmeier–Haack reaction on quinoline-2,4-(1*H*,3*H*)-dione[7] (**16**) did not give **6** ruling out the participation of **16** as a possible intermediate from **1**.

The above reactions also reveal that the Beckmann type migration must have taken place after formylation of the isoxazole ring of **1a** leading to the formation of **6a**.

Except for the carbonyl absorption, not reported in the IR spectrum of "**2a**",[5] the spectral data and melting points of all the products, derived from "**2a**"[5] have been reproduced by us as reported in the original article.[5] At this stage we have thus been able to correct the reported[5] structures, (i) the trichloro compound "**2a**", corrected to 2,4-dichloroquinoline-3-carbaldehyde (**6a**) (ii) 5-chloro-3-phenylisoxazole-4-carboxylic acid, "**4a**", corrected to 2,4-dichloroquinoline-3-carboxylic acid (**7a**) and (iii) the

Downloaded by: York University libraries. Copyrighted material.

dichloroazirine, "**5a**", corrected to 2,4-dichloroquinoline (**8a**). Characterisation of compound **B** is in progress.

In conclusion it may be said that the reaction of 3-arylisoxazol-5(4*H*)-ones **1** with phosphorus oxychloride/dimethylformamide is extremely sensitive to experimental conditions and if the prescribed conditions are strictly followed, it serves as a useful synthetic method for the preparation of hitherto unknown 6-(un)substituted 2,4-dichloroquinoline-3-carbaldehydes **6**. The reason for the inability to reproduce[4] the reported[5] results by Anderson may be due to the difference in the experimental conditions. The present reaction thus represents a novel interesting rearrangement of an isoxazole to a quinoline carbaldehyde under Vilsmeier–Haack reaction conditions.

Melting points were determined in open glass capillaries on a tempo melting point apparatus and are uncorrected. IR spectra in KBr (ν_{max} in cm^{-1}) were recorded on a Shimadzu-435 IR spectrophotometer and ^1H NMR and ^{13}C NMR spectra on Jeol FX-90 Q MHz NMR spectrometer (with TMS as internal standard). Mass spectra were recorded on a VG micromass 7070H at 70 eV. The compounds were checked for their homogeneity by TLC on silica gel-G. Satisfactory microanalysis obtained for **6a–c, 7a–c, 8a**: C ± 0.18, H ± 0.06, N ± 0.29.

Synthesis of 6-(Un)substituted 2,4-Dichloroquinoline-3-carbaldehydes 6; General Procedure:

3-Arylisoxazol-5(4*H*)-one **1** (0.012 mol) was mixed with DMF (2 mL, 0.026 mol) and kept at 0 °C. To this, $POCl_3$ (5 mL, 0.053 mol) was added dropwise with constant stirring during 0.5 h. After the addition was over, the mixture was kept at r.t. for 0.5 h and then heated on water-bath for 2 h. After allowing it to stand for 2 h at r.t. the mixture was poured over crushed ice with vigorous stirring and the product separated was filtered and washed with aq $NaHCO_3$ (2%). The crude product was subjected to chromatographic purification over a column of silica gel, eluting with petroleum ether/benzene (1:1) mixture to give pure **6**.

Note: All these compounds are strong skin irritants.

6a: Yield: 59% (1.33 g from 1.93 g of **1a**) mp 119 °C.

IR (KBr): ν = 2950 (CH), 1700 (C=O), 1600 cm^{-1} (C=N).

^1H NMR ($CDCl_3$/DMSO-d_6): δ = 7.50–8.00 (m, 3H, 5-H, 6-H, 7-H), 8.40 (d, 1H, 8-H), 10.50 (s, 1H, CHO).

^{13}C NMR (DMSO-d_6): δ = 188.70 (CHO), 148.80 (C-2), 121.10 (C-3), 134.30 (C-4), 126.10 (C-5), 128.60 (C-6), 129.60 (C-7, C-8) 125.18 (C-4a), 145.20 (C-8a)

MS: *m/z* (%) = 229 (P + 4, 10), 227 (P + 2, 64), 226 (61), 225 (M^+, 100), 224 (72), 196 (24), 189 (34), 161 (36), 154 (34), 126 (12), 76 (16).

6b: Yield: 59% (1.41 g from 2.1 g of **1b**) mp 120 °C.

IR (KBr): ν = 2960 (CH), 1700 (C=O), 1600 cm^{-1} (C=N).

^1H NMR ($CDCl_3$): δ = 2.40 (s, 3H, CH_3), 7.50–7.90 (m, 2H, 5-H, 7-H), 8.00 (d, 1H, 8-H); 10.48 (s, 1H, CHO)

^{13}C NMR (DMSO-d_6): δ = 20.756 (CH_3), 187.938 (CHO), 145.465 (C-2), 123.037 (C-3), 135.497 (C-4), 124.228 (C-5, C-7), 124.012 (C-6), 127.696 (C-8), 127.696 (C-4a), 139.072 (C-8a).

MS: *m/z* (%) = 243 (P + 4, 10), 241 (P + 2, 69), 240 (68), 239 (M^+, 100), 238 (70), 210 (20), 203 (28), 175 (28), 168 (48), 140 (40), 114 (15), 113 (14).

6c: Yield: 60% (1.53 g from 2.29 g of **1c**) mp 152 °C.

IR (KBr): ν = 2950 (CH), 1695 (C=O), 1620 cm^{-1} (C=N).

^1H NMR ($CDCl_3$/DMSO-d_6): δ = 4.00 (s, 3H, OCH_3), 7.50–7.70 (m, 2H, 5-H, 7-H), 7.98 (d, 1H, 8-H), 10.50 (s, 1H, CHO).

^{13}C NMR (DMSO-d_6): δ = 55.535 (OCH_3), 188.046 (CHO), 142.973 (C-2), 120.018 (C-3), 129.754 (C-4), 102.667 (C-5, C-7), 159.008 (C-6), 125.420 (C-8, C-4a), 112.310 (C-8a).

MS: *m/z* (%) = 259 (P + 4, 11), 257 (P + 2, 68), 256 (68), 255 (M^+, 100), 254 (80), 226 (18), 219 (25), 191 (25), 184 (40), 156 (42), 130 (20).

6-(Un)substituted 2-4-Dichloroquinoline-3-carboxylic Acids (7); General Procedure:

To **6** (0.01 mol) in cold aq Na_2CO_3 (10%, 5 mL), aq $KMnO_4$ (10%) was added dropwise at r.t., until the colour persists with constant stirring. The mixture was filtered and the filtrate was acidified by adding dil. HCl carefully. The precipitated acid **7** was filtered and recrystallised from H_2O.

7a: Yield: 70% (1.69 g from 2.26 g of **6a**) mp 168 °C (dec).

IR (KBr): ν = 2700–3300 (OH), 1700 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 7.46–8.26 (m, 4H_{arom}), 12.30 (s, 1H, CO_2H).

MS: *m/z* (%) = 245 (P + 4, 12), 243 (P + 2, 72), 242 (P + 1, 12), 241 (M^+, 100), 224 (60), 206 (6), 197 (6), 196 (16), 161 (25), 126 (11).

7b: Yield: 73% (1.87 g from 2.4 g of **6b**) mp 202 °C (dec).

IR (KBr): ν = 2710–3300 (OH), 1700 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 2.65 (s, 3H, CH_3), 7.50–8.00 (m, 3H_{arom}), 12.28 (s, 1H, CO_2H).

MS: *m/z* (%) = 259 (P + 4, 12), 257 (P + 2, 71), 256 (P + 1, 14), 255 (M^+, 100), 238 (55), 210 (20), 175 (22), 140 (15).

7c: Yield: 75% (2.04 g from 2.56 g of **6c**) mp 228 °C (dec).

IR (KBr): ν = 2720–3320 (OH), 1700 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 3.98 (s, 3H, OCH_3), 7.51 (m, 2H, 5-H, 7-H), 7.90 (d, 1H, 8-H), 12.30 (s, 1H, CO_2H).

MS: *m/z* (%) = 275 (P + 4, 13), 273 (P + 2, 78), 272 (P + 1, 14), 271 (M^+; 100), 254 (50), 226 (22), 191 (25).

6-(Un)substituted 2,4-Dichloroquinolines 8; General Procedure:

Method A. *Decarbonylation of* **6**: Compound **6** (0.01 mol) in aq NaOH (40%), 10 mL) was stirred for an hour at r.t. and the mixture diluted with H_2O and neutralised with dil. HCl. The solid that separated was filtered and extracted with petroleum ether, and purified over a column of silica gel, eluting with petroleum ether/benzene (4:1) to give pure **8**.

Method B. *Decarboxylation of* **7**: 2,4-Dichloroquinoline-3-carboxylic acid **7** (0.01 mol) in aq NaOH (40%, 10 mL) was stirred for 1 h at r.t. and was neutralised with dil. HCl. The product that separated was purified according to the procedure given for Method A.

8a: Yield: 70% (1.38 g from 2.26 g of **6a**) mp 68 °C (Lit.[7], 68 °C):

IR (KBr): ν = 1605 cm^{-1} (C=N).

^1H NMR ($CDCl_3$): δ = 7.40–8.10 (m, H_{arom}).

MS: *m/z* (%) = 201 (P + 4, 10), 199 (P + 2, 65), 198 (9), 197 (M^+, 90), 162 (100), 127 (58), 101 (28), 100 (36), 76 (50).

8b: Yield: 72% (1.52 g from 2.4 g of **6b**) mp 95 °C (Lit.[10], 94–95 °C).

IR (KBr): ν = 1605 cm^{-1} (C=N).

^1H NMR ($CDCl_3$): δ = 2.60 (s, 3H, CH_3), 7.42–8.20 (m, 4H_{arom}).

8c: Yield: 72% (1.64 g from 2.56 g of **6c**) mp 174 °C (Lit.[10], 175 °C).

IR (KBr): ν = 1605 cm^{-1} (C=N).

^1H NMR ($CDCl_3$): δ = 3.97 (s, 3H, OCH_3), 7.33–7.52 (m, 3H, 3-H, 5-H, 7-H), 7.95 (d, 1H, 8-H).

We are (KA and GS) thankful to CSIR, New Delhi, India for awarding research fellowship. Authors also wish to thank Prof. G.S. Krishna Rao, Department of Organic Chemistry, Indian Institute of Science, Bangalore (India) for his helpful discussions and Prof. P.K. Saiprakash, Head, Department of Chemistry, Osmania University, Hyderabad for his encouragement. Our thanks are also due to the Director. I.I.C.T., Hyderabad, and the Director CDRI, Lucknow for providing mass and NMR spectra.

Downloaded by: York University libraries. Copyrighted material.

+ Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India.

(1) Kantlehner, W. *Adv. Org. Chem.* **1976** *9(2)*, 5.
(2) Meth-Cohn, O.; Tarnowski, B. *Adv. Heterocycl. Chem.* **1982**, *31*, 207.
(3) Jutz, C. *Adv. Org. Chem.* **1976**, *9(1)*, 225.
(4) Anderson, D.J. *J. Org. Chem.* **1986**, *51*, 945.
(5) Kallury, R.K.M.R.; Devi, P.S.U. *Tetrahedron Lett.* **1977**, 3655.
(6) Fitton, A.O.; Smalley, R.K. *Practical Heterocyclic Chemsitry*, Academic: New York, N.Y. 10003, 1968; p 29.
(7) Buchmann, F.J.; Hamilton, C.S. *J. Am. Chem. Soc.* **1942**, *64*, 1358.
(8) Lock, G. *Chem. Ber.* **1933**, *66*, 1527.
(9) (a) Adembri, G.; Tedeschi, P. *Estralto Boll. Sci. Fac. Chim. Ind. Bologna.* **1965**, *23*, 203; *Chem. Abstr.* **1965**, *63*, 13234.
(b) Michetich, R.G.; Chin, C.G. *Can. J. Chem.* **1970**, *48*, 1371.
(10) Shah, V.R.; Bose, J.L.; Shah, R.C. *J. Sci. Ind. Res.* **1960**, *19 B*, 176.

Downloaded by: York University libraries. Copyrighted material.