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UNUSUAL REACTIVITY OF AZOMETHINE YLIDES DUE TO ELECTRONIC EFFECTS: A NOVEL ROUTE TO 5-ALKYLIDENE-3-OXAZOLINES+

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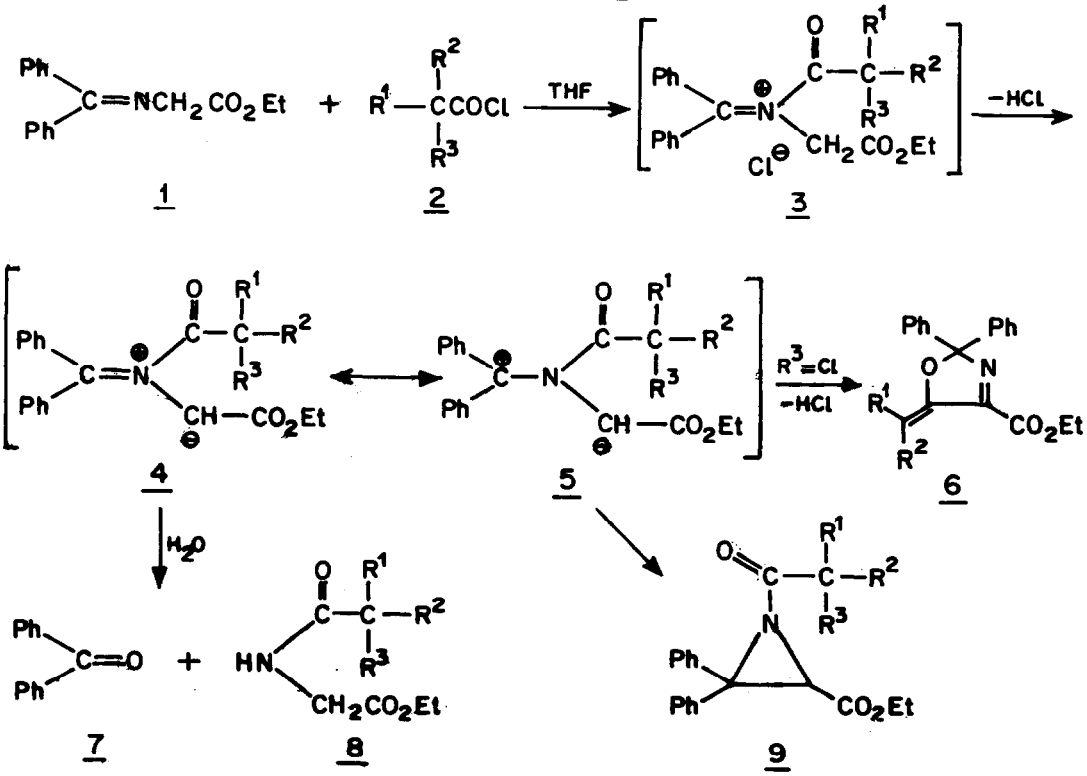
Abstract: The reaction of α-chloroacyl chlorides with glycine Schiff bases affords 3-oxazolines.

Recently we reported the first neighbouring aryl group directed cyclization of azomethine ylides leading to N-acylaziridines.[1] Azomethine ylides have received considerable attention because of their ready accessibility and synthetic potential.[2] Little attention has been devoted so far to the electronic effects of remote polar groups on azomethine ylides, although they are well documented on the reactivity of functional groups in general.[3] We have now studied the reaction of α-chloroacyl chlorides **2** with Schiff base **1** to evolve the effect of neighbouring chlorine group. Surprisingly, we found that rather a novel reaction occurred resulting in the formation of 5-alkylidene-3-oxazolines **6** (Scheme1).

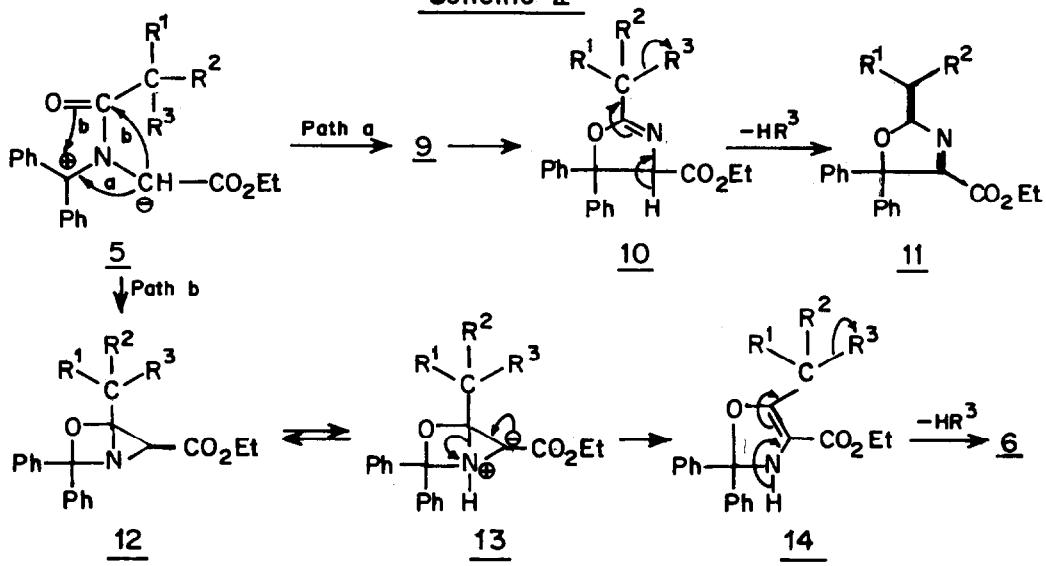
Scheme-1



This letter describes the importance of electronic effects in this unusual transformation (5→6) and reports a convenient method for the synthesis of 3-oxazolines.

Reaction of trichloroacetyl chloride **2a** with glycine Schiff base **1**[1] in THF furnished 3-oxazoline **6a** as a sole product (87%, entry 1, Table).[4-6] The structure of the new oxazoline **6a** was established on the basis of relevant spectral data, including characteristic oxazoline carbon signals at δ 115.40 (s, C-2), 147.93 (s, C-5), and 153.32 (s, C-4) in ^{13}C-NMR spectrum[5] and a single crystal X-ray analysis[7]. Although the formation of both regio-isomers **6** and **11** is possible, as outlined in Scheme-2, the deshielded sp^3 and shielded sp^2 carbon signal at δ 115.40 and 147.93 respectively, exclude structure **11** for the product.[8] This surprising result together with the limited methods for 3-oxazoline synthesis[9] suggested a further study with different acyl chlorides to establish the generality of the process. Indeed, treatment of **1** with several α-chloroacyl chlorides **2** (entries 1-4 & 7) under analogous reaction conditions afforded **6** (67-87%, Table).

Scheme-2



The mechanism invoked to explain the formation of aziridines (path **a**) involving the influence of a neighbouring aryl group[1] is not adequate for the present case, although a chlorine atom is known to stabilise the carbocation via a 5-membered transition state.[10] Thus, neither the aziridines **9** nor **11** via **10**[11] were detected in the reaction products. Alternatively, the formation of oxazoline **6** could be rationalized by the inductive effect of chlorine group.

According to FMO theory,[12] azomethine ylides generally prefer to react with electron deficient dipolarophiles because such a pair of addends possesses a narrow dipole HOMO-dipolarophile LUMO gap. The α-chlorine group in **5** (R^3 = Cl), formed by reaction of α-chloro acyl chlorides with **1** enhances the dipolarophilic activity of the carbonyl function due to its electron-withdrawing inductive effect.[13,14] Thus, the reactive electron-deficient

Table: Reaction of Schiff base 1 with acid chlorides 2[4]

Entry	Substituents			Product[5]	m.p.(°C)	Yield(%)
	R^1	R^2	R^3			
1	Cl	Cl	Cl	**6a**	114	87
2	H	Cl	Cl	**6b**	56	84
3	H	H	Cl	**6c**[6]	-	67
4	CH_3	H	Cl	**6d**[6]	-	70
5	CH_3	H	H	**8a**[1]	50-51	83
6	$ClCH_2$	H	H	**8b**	66	83
7	Ph	H	Cl	**6e**	161	82
8	Ph	H	H	**9**[1]	105	75

carbonyl dipolarophile in **5** may prefer intramolecular [3+2]cycloaddition (path **b**, Scheme 2) compared to the formation of N-acylglycinates with propanoyl chloride (entry 5) *via* hydrolysis of **3** (Scheme 1). The bicyclic intermediate **12** possibly rearranges *via* **13** and **14** to furnish 3-oxazolines **6** (Scheme 2).

The chlorine group in β-position is less effective in activating the carbonyl moiety,[13] as is clear from the formation of N-acylglycinate **8b** with 2-chloropropanoyl chloride (entry 6) *via* hydrolysis of **4**. Further, the observation of 3-oxazoline **6e** as the exclusive product with α-aryl-α-chloroacyl chloride (entry 7) compared to N-acylaziridine **9** with α-arylacyl chloride (entry 8) reveals the dominance of inductive effect over neighbouring group effect.

In conclusion, it appears that the polar effect can exercise a large degree of control on reaction compared to neighbouring group effect. Further, these studies provide a convenient method for the synthesis of 3-oxazolines.

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+NCL Communication No. 4824

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4. **General Procedure:** To a solution of ethyl N-(diphenylmethylene)glycinate (3.74 mmol) in dry THF (5 ml) at 0°C was added a solution of acyl chloride (4.62 mmol) in THF (5 ml). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 to 2.0 hr. After the usual work up, the products were purified by flash chromatography on silica gel using an appropriate mixture of n-hexane/ethyl acetate as eluent.

5. The unoptimised yields refer to isolated products. All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and satisfactory elemental analysis. Selected spectroscopic details of oxazolines: **6a**: ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 1.36 (t, 3H), 4.44 (q, 2H), 7.12-7.80 (m, 10H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 13.57(q), 62.82(t), 103.35 (s, =$\underline{C}Cl_2$), 115.40(s, C-2), 125.96, 128.26, 128.57, 139.06, 147.93 (s, C-5), 153.32 (s, C-4), 161.42(s); IR (Nujol): 3060, 2920, 2850, 1740, 1640, 1610, 1580, 1490, 1450 cm^{-1}; Mass m/e (%) 379(M^+ +4, 4),377 (M^+ +2, 25), 375(M^+, 38), 265(25), 219(28), 192(47), 165(100), 105(10), 77(12). **6b**: ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.37(t, 3H), 4.40 (q, 2H), 6.55(s, 1H), 7.26-7.88 (m, 10H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 98.55 (d, =$\underline{C}HCl$), 113.89 (s, C-2), 151.34 (s, C-5), 152.30 (s, C-4), 159.27(s); IR ($CHCl_3$) 1730, 1660, 1600 cm^{-1}; Mass m/e (%) 343 (M^+ +2, 7), 341 (M^+, 21). **6c**: ^{1}H-NMR ($CDCl_3$, 90MHz) δ 1.42 (t, 3H), 4.44 (q, 2H), 4.97 (d, J = 2Hz, 1H), 5.17 (d, J = 2Hz, 1H), 7.22-7.91 (m, 10H); ^{13}C-NMR ($CDCl_3$, 90MHz) δ 88.49(t, =$\underline{C}H_2$), 108.40(s, C-2), 155.53(s, C-5), 156.85(s, C-4), 160.6(s); IR (Neat) 1730, 1660, 1600 cm^{-1}; Mass m/e (%) 307 (M^+, 17). **6d**: ^{1}H-NMR ($CDCl_3$, 80MHz) δ 1.32(t, 3H), 1.86(d, 3H), 4.40(q, 2H), 5.64(q, 1H), 7.20-7.96(m, 10H); ^{13}C-NMR ($CDCl_3$, 90MHz) δ 11.06 (q, =$CH\underline{C}H_3$), 101.76(d, =$\underline{C}HCH_3$), 111.50(s, C-2), 151.32(s, C-5), 154.42 (s, C-4), 160.61(s); IR (Neat) 1730, 1660, 1600 cm^{-1}; Mass m/e (%) 321 (M^+, 48). **6e**: ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.42(t, 3H), 4.44(q, 2H), 6.62(s, 1H), 7.20-7.91(m, 15H); ^{13}C-NMR ($CDCl_3$, 300MHz) δ 106.24 (d, =$\underline{C}HPh$), 114.17(s, C-2), 149.62 (s, C-5), 155.42(s, C-4), 160.47(s); IR ($CHCl_3$) 1730, 1640, 1600 cm^{-1}; Mass m/e (%) 383 (M^+, 62).

6. Oxazolines **6c** and **6d** are unstable gummy liquids and dimerises even at 0°C as indicated by mass spectra.

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8. The C-5 ($\underline{sp}^3$) and C-2 ($\underline{sp}^2$) of **11** would appear at ca. 90 and 160 ppm respectively. For ^{13}C-NMR spectra of substituted oxazolidines and oxazoles, see: F. Orsini, F. Pelizzoni, M. Forte, R. Destro and P. Gariboldi, Tetrahedron, **44**, 519 (1988); H. Hiemstra, H. A. Houwing, O. Possel and M. van Lensen, Can. J. Chem., **57**, 3168 (1979).

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