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CHLORO(ETHOXYCARBONYL)METHYLENEIMINIUM SALTS - VERSATILE ELECTROPHILIC INTERMEDIATES FOR HETEROCYCLIC SYNTHESIS

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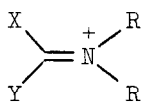
Summary: The preparation of chloro(ethoxycarbonyl)methyleneiminium salts is described. The reaction of these electrophilic salts with various bidentate reagents illustrates their usefulness as intermediates for heterocyclic synthesis.

The electrophilic character and structural diversity of methyleneiminium salts has ensured their prominent position in synthetic chemistry[1]. The parent members of the series (1; X=Y=H) find wide application in Mannich-type reactions[2]. Successive replacement of the methylene hydrogen atoms with chlorine leads to the salts (1; X=Cl, Y=H, Vilsmeir-Haack reagents[3]), and finally to the dichloromethylene salts (1; X=Y=Cl) first characterised and imaginatively exploited by Viehe and his co-workers[4]. We now describe the preparation of further members of the group - the chloro(ethoxycarbonyl)methyleneiminium salts 4 and 5 (SCHEME) and illustrate their use as intermediates for heterocyclic synthesis.

Imidoyl chlorides containing an electron-withdrawing group adjacent to the imine bond are known[5] to be poor electrophiles. In accord with this we find that the imidoyl chloride 2[6] is also a poor electrophile, but only insofar as this refers to its reactivity in the presence of a strong base. Thus with aniline, 2 reacts slowly at room temperature to give 3, but strikingly, in the presence of Et_3N 2 does not react with aniline.



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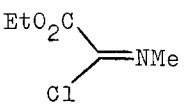

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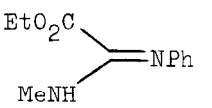

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We conclude that chloride displacement reactions of 2 are facilitated by the intermediacy of the protonated form of the imidoyl chloride[7], i.e. the methyleneiminium salt 4[8]. This conclusion prompted the attempted methylation of 2. The only satisfactory reagent was found to be $MeOSO_2F$[9].

This, on addition (neat) to 2 and following an exothermic reaction, produced a viscous oil containing the salt 5. Although this salt proved too reactive to isolate, the nmr spectrum[10] of the oil, its rapid hydrolysis to give (75%) ethyl N,N-dimethyloxamate, as well as numerous other reactions (SCHEME) confirm its presence.

The polyfunctionality of 4 and 5 prompted an investigation of their potential as intermediates for heterocyclic synthesis. Our findings are illustrated (but by no means limited) by the SCHEME. Following initial nucleophilic attack at the 2-position, cyclisation reactions of 4 and 5 with various bidentate reagents can be summarised:

(1) 2,1-Cyclisation with dinucleophilic reagents to give e.g. 6, 7, 8, 9, 10.

(2) 2,2-Cyclisation with dinucleophilic reagents to give e.g. 11, 12, 13, 16, 21. 2,2-Cyclisation appears more favourable with 5. Thus with 4, phenylenediamine gives exclusively the quinoxalinone 10, whereas 5 affords a 2:1 mixture of the benzimidazole 11 and the quinoxalinone 10.

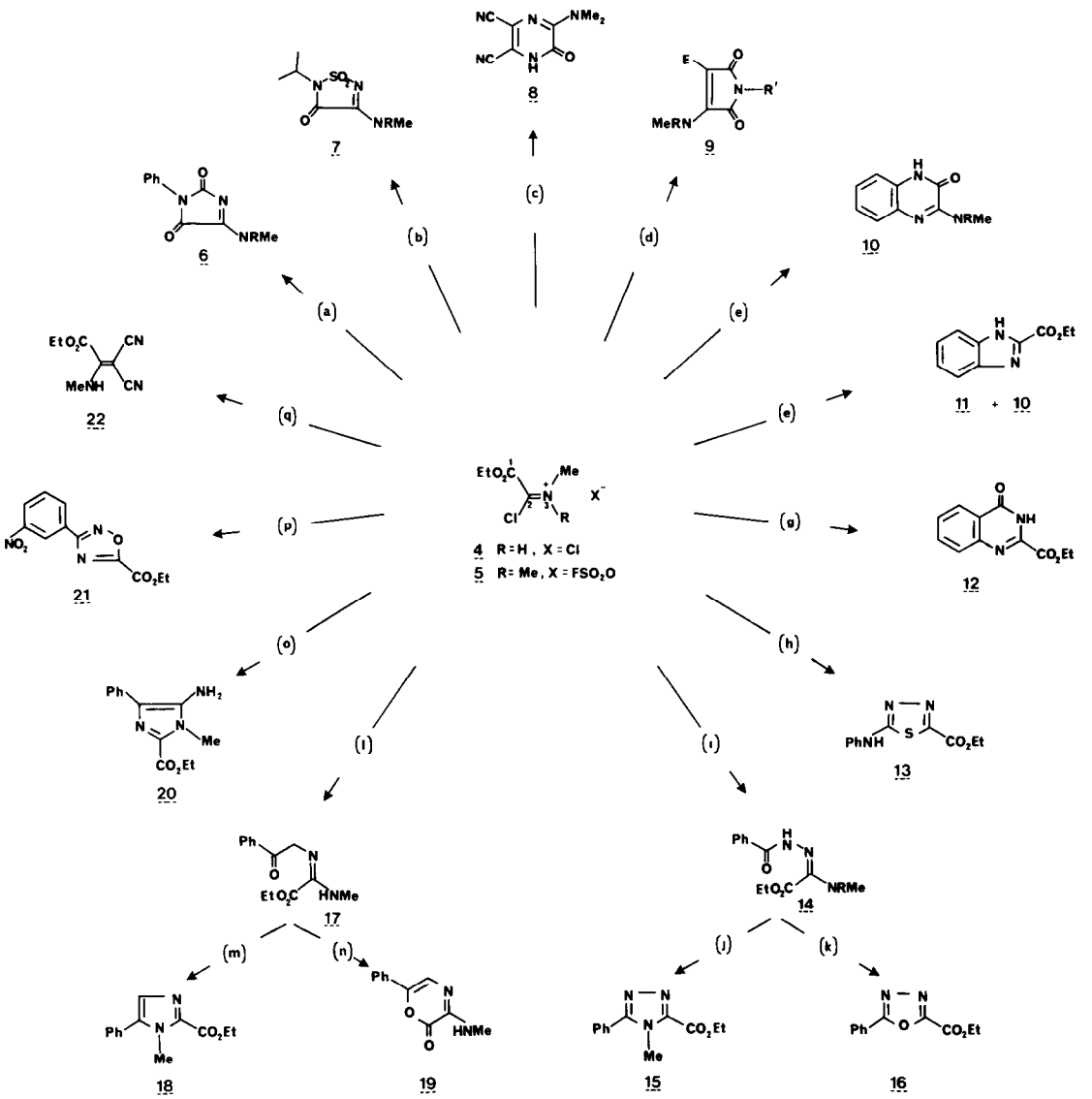
(3) 2,3-Cyclisation (for 4 only) with nucleophiles also containing an electrophilic centre to give e.g. 15, 18, 20.

In certain cases, e.g. 14 and 17, acyclic intermediates can be isolated, and the cyclisation of these brought about in alternative modes to give single products, i.e. 15 or 16, and 18 or 19 respectively.

With carbon-nucleophiles, 4 and 5 behave in a capricious manner. Although 4 reacts with $CH_2(CN)_2$ to give 22, 4 and 5 do not react with malonic esters or with 1,3-diketones. On the other hand, they readily react with appropriately activated amides to afford the maleimides, 9.

Typical reaction conditions used in this work are given for 6 (R=H), as follows. Dry HCl is passed into a stirred solution of the imidoyl chloride 2 in anhydrous THF until the temperature of the mixture reaches 60°, whereupon phenylurea is added and the mixture stirred until it reaches room temperature. Evaporation of the solvent, neutralisation of the residue with aqueous $NaHCO_3$ and extraction into $CHCl_3$ gives the product. For 6 (R=Me), equimolar proportions of 2 and $MeOSO_2F$[9] are mixed together. Following the exothermic reaction a solution of phenylurea in anhydrous THF is added all at once to the viscous oil, and the mixture then stirred at room temperature for 30 min. Work-up as above gives the product. In certain cases, particularly where reagents insoluble in THF are used (e.g. for 17), we have found it advantageous to perform reactions in the absence of solvent. Catalytic quantities of chloro- or fluorosulphonic acid may be used instead of excess HCl to bring about condensation reactions of 2.

SCHEME[11]



Reagents: a) $PhNHCONH_2$ b) $Me_2CHNHSO_2NH_2$ c) Diamiomaleonitrile
d) ECH_2CONHR' e) o-Phenylenediamine g) Anthranilamide h) $PhNHCSNHNH_2$
i) $PhCONHNH_2$ j) Toluene, reflux k) HCl, toluene l) $PhCOCH_2NH_2.HCl$
m) p-TsOH, toluene, reflux n) Petroleum ether (bp 100-120°), reflux
o) $PhCH(NH_2)CN$ p) m-Nitrobenzamidoxime q) $CH_2(CN)_2$.

References and footnotes

1. For a review see H. Bohme and H. G. Viehe, (E. C. Taylor, Ed.), Advances in Organic Chemistry, 9 (1), Wiley, Interscience, New York (1976).
2. J. Schreiber, H. Maag, N. Hashimoto and E. Eschenmoser, Angew. Chem. Internat. Edit., 10, 330 (1971), and references cited therein.
3. Reference 1, p 225.
4. H. G. Viehe, Angew. Chem. Internat. Edit., 12, 806 (1973).
5. I. Ugi, F. Beck and U. Fetzner, Chem. Ber., 95, 126 (1962).
6. The compound does not appear to have been reported previously. It is readily prepared (76%) by the action of an excess of hot $SOCl_2$ upon $EtO_2CCONHMe$, and has bp 43°/1 mm, n_D^{25} 1.4510, $\delta(CDCl_3)$: 1.4, t, 3H; 3.56, s, 3H; 4.42, q, 2H.
7. A similar dependence upon proton availability has recently been reported for reactions of ethyl cyanoformate and its (putatively) derived imidoyl chloride: Y.Sugiyama, T. Sasaki, and N. Nagato, J. Org. Chem. 43, 4485 (1978).
8. 2 dissolved in $CDCl_3$ containing FSO_3H had δ 1.44, t, 3H; 3.7, d, 3H; 4.42, q, 2H.
9. Methyl fluorosulphonate is a highly toxic reagent; great care must be exercised in its use.
10. $\delta(CDCl_3)$: 1.48, t, 3H; 4.08, s, 3H; 4.18, s, 3H; 4.62, q, 2H.
11. All products gave satisfactory microanalytical and nmr data. Yields (% isolated and recrystallised) and melting points (°C) for the products are: 6, R=H: 60, 229; R=Me: 54, 105; 7, R=H: 67, 195; R=Me: 47, 134; 8, 51,139; 9, E=CN, R=H, R'=H: 50, 275; E=CO_2Et, R=H, R'=Ph: 55, 143; E=COPh, R=H, R'=3-$CF_3C_6H_4$; 70, 124; E=COPh, R=Me, R'=3-$CF_3C_6H_4$: 41, 184; 10, R=H: 71, 238; R=Me: 50, 186; 11: 33, 221; 12: 60, 191; 13: 82, 187; 14, R=H: 56, 160; R=Me: 44, 89; 15: 53, 96; 16: 53, 70; 17: 53, 115; 18: 78, 54; 19: 74, 173; 20: 54, 185; 21: 72, 78; 22: 70, 132.

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