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A one-step route to azomethine ylides via chloroiminium salts ☆

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Abstract—A new, one-step procedure for the generation of azomethine ylides, **4** and **20**, via chloroiminium salts, **3** and **19**, is reported. The generation of the azomethine ylides was confirmed by their trapping with dimethyl acetylenedicarboxylate (DMAD) which, upon spontaneous 1,4-dehydrochlorination, gave the corresponding pyrroles **17** and **21**.
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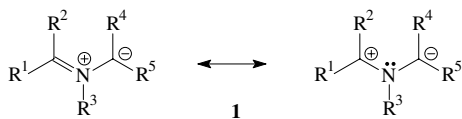
Azomethine ylides **1** are versatile intermediates for the preparation of a wide range of heterocycles through 1,3-dipolar cycloadditions,[1] 1,5-electrocyclisations,[2] or 1,7-electrocyclisations.[3–5] There are many routes to azomethine ylides, including the decarboxylation of iminium salts,[6] the ring-opening of aziridines,[7] and the 1,2-prototropy of α-imino esters.[8]

We wish to describe here a new, one-step route to chloro-substituted 'stabilised' azomethine ylides **4** via chloroiminium salts (amide chlorides) **3** derived from the amides of *N*-aroyl-*N*-methylamino acid esters **2** (Scheme 1), by their reaction with oxalyl chloride.

When amide **2c** ($R^1 = Ph$, $R^2 = Et$) was reacted with $(COCl)_2$ in dry $CHCl_3$ at room temperature, the product of the reaction was an oxazolium salt **5**, presumably formed by the 1,5-electrocyclisation of the azomethine ylide **4**. This oxazolium salt **5** reacted with TMSCN[9] in the presence of CsF in acetonitrile to give the unstable 4-oxazoline **6**, which as its azomethine isomer **7**, could then be trapped with dimethyl acetylenedicarboxylate (DMAD) affording a mixture of the adduct **8** (26% yield) and pyrrole **9** (15%). The adduct **8**, which was obtained as a single diastereoisomer, is unstable and under the reaction conditions can aromatise, via the loss of HCN, to give pyrrole **9** (Scheme 2).[10] The intermediacy of the oxazolium salt **5** was confirmed when the reaction between amide **2c** and oxalyl chloride was performed in an NMR tube in $CDCl_3$. The complete conversion of amide **2c** to oxazolium salt **5** took 6 h at 50 °C.
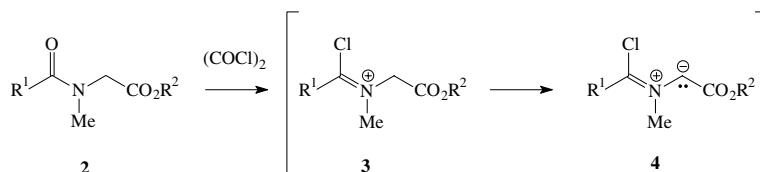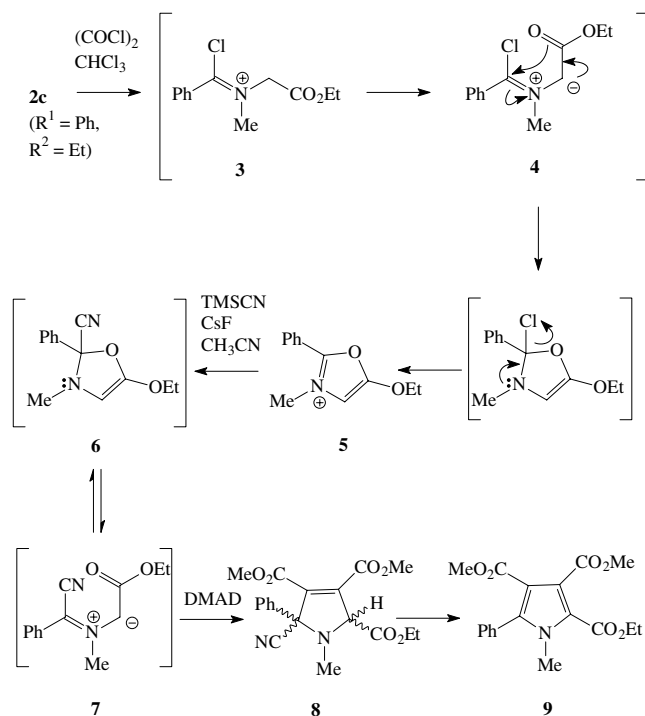

Scheme 1.

Scheme 2.

Initial attempts to carry out this reaction with the methyl esters of amides **2a–c** in dry chloroform failed so it was decided to monitor the course of the reaction by ^{1}H NMR spectroscopy, which showed that heating the methyl ester **2a** at 50 °C was insufficient, since only the signals of the starting materials were observed, whereas refluxing the solutions led to unexpected results—refluxing amide **2a** with (COCl)$_2$ in dry chloroform gave furanone **16** in 88% yield (Scheme 3).

The structure of furanone **16** was unequivocally established by single crystal X-ray diffraction (Fig. 1).[11]
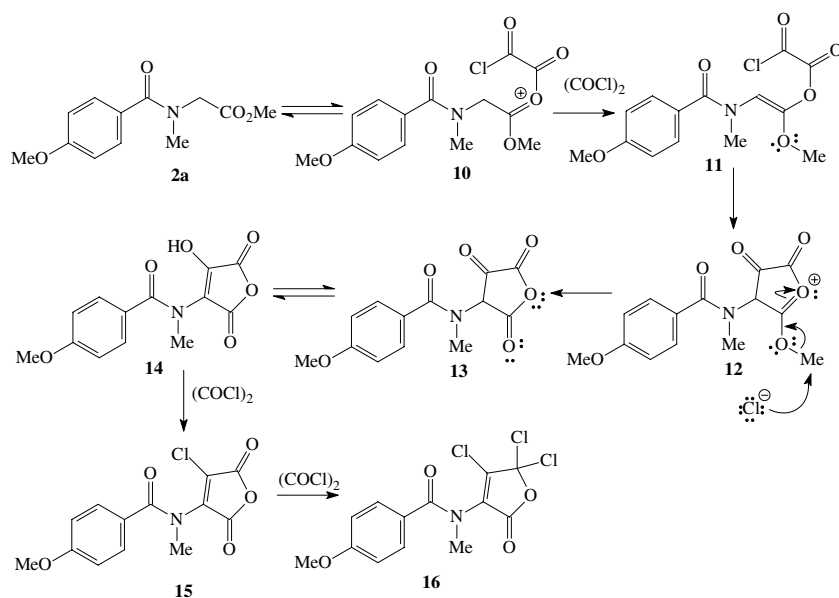
A possible mechanism for the formation of furanone **16** is given in Scheme 3, in which the first step is attack of the ester carbonyl oxygen of **2a** on (COCl)$_2$, followed by the enolisation of the highly acidic methylene group of the oxonium ion **10**. The subsequent intramolecular cyclisation of enol **11** results in another oxonium ion **12**. The loss of methyl chloride leads to the keto-anhydride **13**, the tautomer **14** of which reacts with (COCl)$_2$ affording the disubstituted maleic anhydride **15**. Finally, the reaction between **15** and a third molecule of oxalyl chloride gives furanone **16** (Scheme 3).

In order to prevent this chlorination (Scheme 3), the reactions of the methyl esters of the amides **2** with oxalyl chloride were repeated in dry dichloromethane, in the presence of DMAD, and the pyrrole products **17** of the trapping of the azomethine ylide **4** with DMAD, followed by aromatisation (1,4-dehydrochlorination), were obtained in poor to reasonable yields (Scheme 4 and Table 1).

Next, a series of substituted *N*-aroyl-*N*-methylbenzylamines **18** were prepared and reacted with oxalyl chloride in the presence of DMAD in dry chloroform under reflux, to give the pyrroles **21** (Scheme 5), in moderate yields (Table 2). The structures of the pyrroles **21** were again established by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and high resolution mass spectrometry.

As before, formation of pyrrole **21** is proposed to proceed through formation of the chloroiminium salt **19**, which is subsequently deprotonated, affording azomethine ylide **20**. This 1,3-dipole is stabilised by delocalisation of the negative charge into the aromatic ring of the benzyl function. The subsequent cycloaddition with DMAD leads to pyrrole **21** after 1,4-dehydrochlorination (Scheme 5). The delocalisation of the negative charge depends upon the substituent (R^2) in the *para*-position of the benzyl function in the initial amide **18**
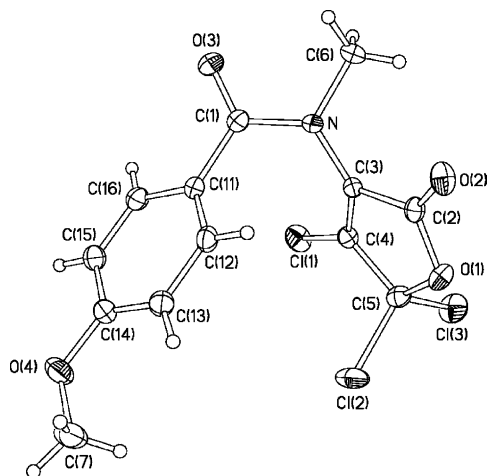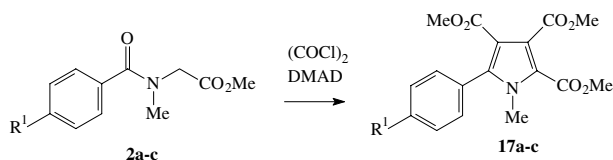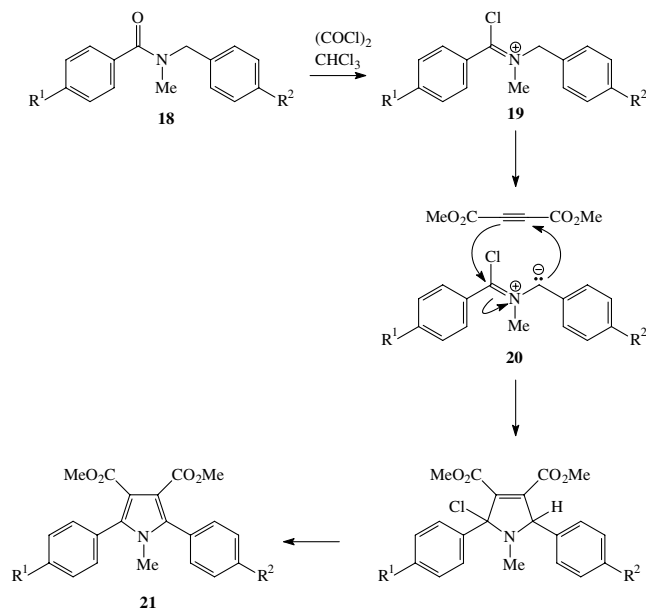

Scheme 3.

Figure 1. Single crystal X-ray structure of furanone **16** (50% thermal ellipsoids).

Scheme 4.

Table 1. Yields of pyrroles **17** from amides **2** ($R^2 = Me$)

Entry	R^1	% Yield (RT)	% Yield (reflux)
a	p-CH$_3$OC$_6$H$_4$	15	26
b	p-O$_2$NC$_6$H$_4$	21	64
c	Ph	12	28

Scheme 5.

Table 2. Yields of pyrroles **21** from amides **18**

Entry	R^1	R^2	% Yield
a	H	NO$_2$	31
b	NO$_2$	NO$_2$	29
c	MeO	NO$_2$	29
d	H	Cl	17
e	H	H	11

and the expected stability of the azomethine ylides **20** correlates with the yields of the pyrroles. A substituent in the *para*-position of the benzoyl group (R^1) does not appear to influence the yield of the pyrroles **21**. One possible explanation of this fact is that resonance structure **20a** is a stronger contributor to the electronic distribution in the azomethine ylide than resonance structure **20b**.
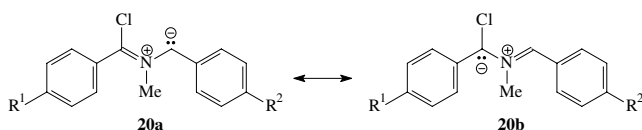
Once again, it was found that the polarity of the solvent has an impact on the yield of the pyrrole. For example, performing the reaction of amide **18a** with oxalyl chloride in dry DCM afforded the pyrrole **21a** in an improved yield of 47%. This may be due to either the deprotonation step in the suggested mechanism (see Scheme 5) being more favourable in more polar solvents, or the azomethine ylide being stabilised by better solvation by the dichloromethane.

In summary, azomethine ylides **4** and **20** (derived from *N*-aroyl-*N*-methylamino acid esters **2** or *N*-aroyl-*N*-methylbenzylamines **18**) can be prepared in a simple one-step procedure, via chloroiminium salts, **3** and **19**, and trapped with DMAD to give pyrroles, **17** and **21**. Excessive heating of this reaction leads to unexpected products. For example, the amino acid methyl ester **2a** reacted with oxalyl chloride in the absence of DMAD to give the novel trichlorofuranone **16**.

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10. **8** White solid (0.052 g, 26%), mp 112–113 °C (found: MH^+ 373.139, calcd for $C_{19}H_{21}N_2O_6$: MH^+, 373.139); ν_{max} (KBr)/cm^{-1} 1741 and 1711 (ester C=O); δ_H (300 MHz; CDCl$_3$) 1.36 (3H, t, *J* 7.1, C*H$_3$*CH$_2$), 2.45 (3H, s, NC*H$_3$*), 3.64 (3H, s, 4-CO$_2$C*H$_3$*), 3.86 (3H, s, 3-CO$_2$C*H$_3$*), 4.27–4.40 (2H, m, OC*H$_2$*CH$_3$), 4.97 (1H, s, 2-H), 7.41–7.43 (3H, m, Ar-H), 7.58–7.61 (2H, m, Ar-H); δ_C (75 MHz; CDCl$_3$) 14.7 (*C*$_3$CH$_2$), 31.7 (N*C$_3$*), 53.0 (CH$_3$, 4-CO$_2$*C$_3$*), 53.3 (CH$_3$, 3-CO$_2$*C$_3$*), 62.5 (O*C$_2$*CH$_3$), 72.3 (CH, C-2), 75.0 (quat, C-5), 115.5 (quat, *C*N), 127.4 (2×CH), 129.2 (2×CH), 130.1 (CH), 135.3 (quat, C-1′), 139.0 (quat, C-3), 139.5 (quat, C-4), 161.5 (quat, C=O), 162.4 (quat, C=O), 168.0 (quat, C=O). The configuration of **8** has not been established. **9** White solid (0.028 g, 15%), mp 117–118 °C (found: MH^+ 346.129, calcd for $C_{18}H_{20}NO_6$: MH^+, 346.1285); δ_H (270 MHz; CDCl$_3$) 1.35 (3H, t, *J* 7.1, C*H$_3$*CH$_2$), 3.60 (3H, s, OC*H$_3$*), 3.66 (3H, s, NC*H$_3$*), 3.95 (3H, s, OC*H$_3$*), 4.31 (2H, q, *J* 7.1, OC*H$_2$*CH$_3$), 7.28–7.31 (2H, m, Ar-H), 7.45–7.50 (3H, m, Ar-H); δ_C (75 MHz; CDCl$_3$) 14.5 (*C*H$_3$CH$_2$), 34.9 (N*C*H$_3$), 51.8 (O*C*H$_3$), 53.1 (O*C*H$_3$), 61.4 (O*C*H$_2$CH$_3$), 112.0 (quat, C-3 or C-4), 120.6 (quat, C-2), 126.0 (quat, C-3 or C-4), 128.7 (2×CH), 129.8 (CH), 130.3 (quat, C-1′), 130.7 (2×CH), 143.6 (quat, C-5), 160.3 (quat, C=O), 163.4 (quat, C=O), 167.2 (quat, C=O).

11. $C_{13}H_{10}Cl_3NO_4$, $M = 350.57$, monoclinic, $a = 7.3651(3)$, $b = 20.2855(10)$, $c = 10.1981(5)$ Å, $\beta = 103.019(3)°$, $V = 1484.5(1)$ Å^3, $T = 120(2)$ K, colourless crystal ($0.42 \times 0.28 \times 0.15$ mm), space group $P2_1/n$ (no 14), $Z = 4$, $\mu = 0.63$ mm^{-1}. Reflections, 20,080 in number (4328 independent, $R_{int} = 0.031$) with 60° were measured on a CCD area detector and corrected for absorption. The structure was solved by direct methods and refined on F^2 of all data by full-matrix least squares (non-H atoms in anisotropic, H in isotropic approximation) to $R = 0.034$ [3820 reflections with $I > 2\sigma(I)$] and $wR(F^2) = 0.092$ (all data), using SHELXL-97 software. Full structural data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-221744.