An Efficient Synthesis of Δ^1-Pyrrolines and Related Heterocycles *via* the Base Induced Cyclocondensation of α-Ketoimidoyl Chlorides with Electron Deficient Alkenes

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The treatment of α-ketoimidoyl chlorides with amine bases in the presence of a variety of dipolarophiles provides the corresponding Δ^1-pyrroline derivatives in good to moderate yields; these cycloaddition reactions presumably involve acylnitrile ylides as reactive intermediates.

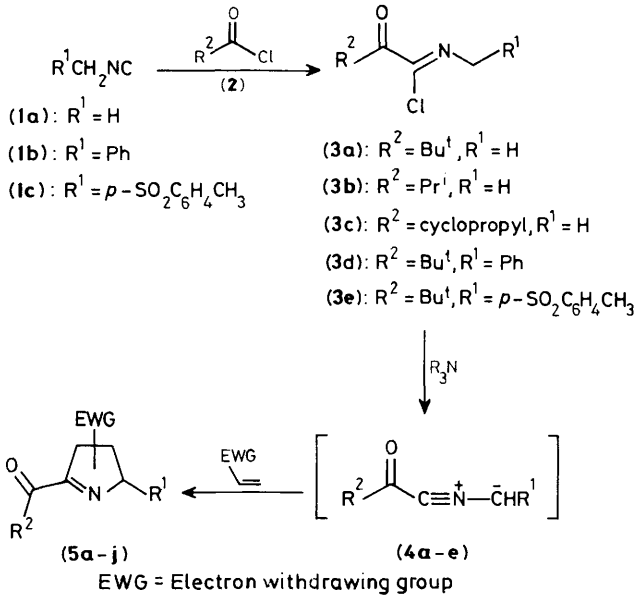
Nitrile ylides[1] and their equivalents[2] have recently been the subject of renewed interest as synthetic intermediates. Although several new, and on occasion exotic, methods have been advanced for the generation of these species,[3] the classical procedure involving the 1,3-dehydrohalogenation of imidoyl chlorides[4] has remained relatively unused.[5] Our interest in the latter method was stimulated by the possibility that α-ketoimidoyl halides derived from the reaction of isonitriles with acyl chlorides would serve as precursors to nitrile ylides and then their cycloadducts (Scheme 1). Here we present results which confirm the viability of this method.

The α-ketoimidoyl chlorides utilised in this investigation were prepared by the reaction of the isonitriles (**1a—c**) with the appropriate acyl chloride (**2**) (1.0 equiv.) in CH_2Cl_2. The isonitriles (**1a** and **b**) were found to react quantitatively with trimethylacetyl chloride over 5—6 hours at room tempera-

Table 1. Cyclocondensation of α-ketoimidoyl chlorides with dipolarophiles.

Imidoyl chloride	Base	Dipolarophile	Products	Yield/ %
(**3a**)	DBU	$MeO_2CCH{=}CH_2$	(**5a**), (**5b**)	46, 17
(**3b**)	DBU	$MeO_2CCH{=}CH_2$	(**5c**), (**5d**)	64, 10
(**3c**)	DBU	$MeO_2CCH{=}CH_2$	(**5e**), (**5f**)	55, 11
(**3d**)	Et_3N	$MeO_2CCHCHCO_2Me$	(**5g**)[a]	46
(**3d**)	Et_3N	$MeO_2CCH{=}CH_2$	(**5h**),[a] (**5i**)[a]	49, 13
(**3a**)	DBU	$PhCOCF_3$	(**6a**), (**6b**)	43, 3
(**3e**)	Et_3N	$MeO_2CCH{=}CH_2$	(**7**)	54

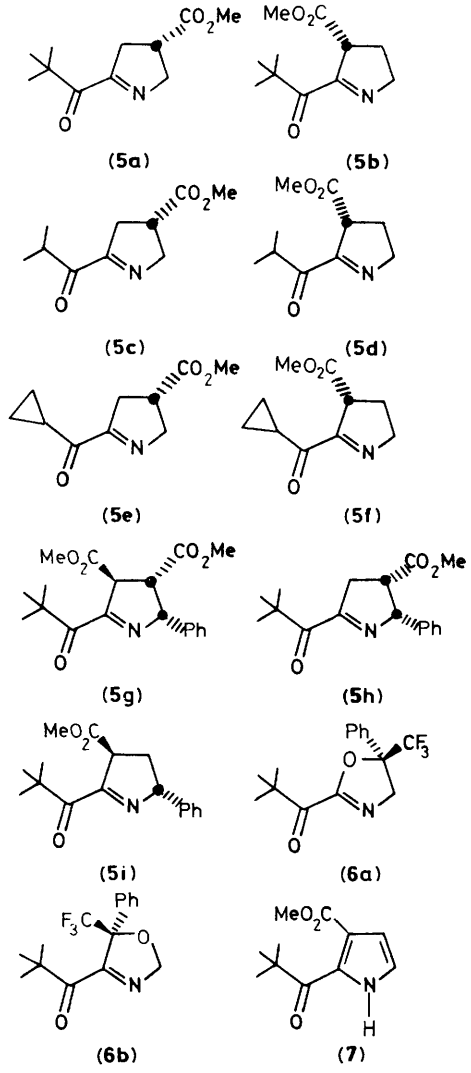
[a] The relative stereochemistry of these cycloadducts was determined by 300 MHz ^1H n.m.r. spectroscopy and single crystal *X*-ray diffraction analysis (Figure 1).



Scheme 1

ture. By way of contrast, toluene-*p*-sulphonylmethyl isocyanide (**1c**) underwent complete reaction with this acyl chloride only after 48 hours at 60 °C. The observed difference in rate can be attributed to the reduced nucleophilicity of the isonitrile moiety of (**1c**) produced by the arylsulphonyl group. The 1,3-dehydrochlorination of the imidoyl halides (**3a—e**) could be readily induced by their exposure to amine bases. For the imidoyl chlorides (**3d** and **e**), triethylamine proved sufficiently basic to promote the extrusion of HCl. However, for the substrates (**3a—c**) the use of the stronger base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was required for dehydrochlorination.

The α-ketonitrile ylides formed in this manner could be trapped with reasonable efficiency by a variety of dipolarophiles with concomitant formation of the corresponding Δ^1-pyrrolines.†‡ A compilation of the results obtained for a number of representative nitrile ylides appear in Table 1.



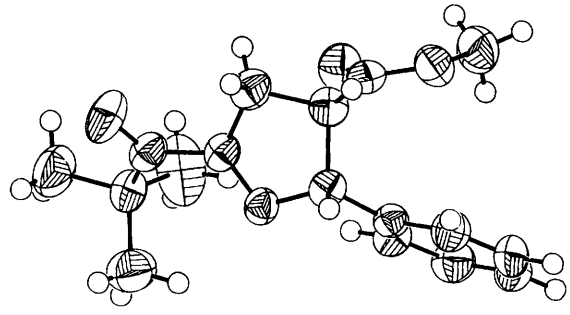


Figure 1. *X*-ray crystal structure of (**5h**).

In experiments intended to establish the concertedness of cycloaddition, efforts were made to intercept the nitrile ylide (**4a**) with dimethyl fumarate and dimethyl maleate.

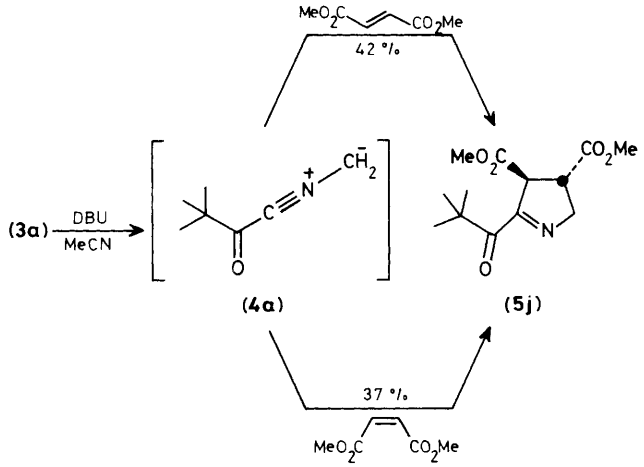
We were initially surprised to discover that the use of either of the above dipolarophiles to intercept the dipole (**4a**) resulted in the formation of a common Δ^1-pyrroline [*e.g.*, (**5j**)]. It was ultimately determined, however, that dimethyl

† Efforts to utilise imidoyl chlorides bearing a methylene group α- to the carbonyl moiety in this method have thus far been unsuccessful.

‡ A representative experimental procedure for the generation and trapping of an acylnitrile ylide is as follows. An oven-dried round-bottomed flask equipped with a nitrogen inlet and a magnetic stirring bar was charged with the dry DBU (167 mg, 1.1 mmol), methyl acrylate (602 mg, 8 mmol), and dry acetonitrile 1.5 ml. The solution was cooled to −10 °C and a solution of the imidoyl chloride (**3a**)[6] (162 mg, 1 mmol) in dry acetonitrile (1 ml) was then added with stirring over 20 min. The mixture was allowed to warm gradually to 0—5 °C with stirring over 5 h whereupon the absence of the imidoyl chloride (**3a**) was revealed by t.l.c. The mixture was diluted with benzene, filtered through Florisil, and the filtrate was concentrated *in vacuo*. The residue was subsequently purified by chromatography on silica gel (5% ethyl acetate–hexane for elution) to provide 98 mg (46%) of the pyrroline (**5a**) and 34 mg (17%) of the pyrroline (**5b**).

Selected spectroscopic data for (**5a**): ^{1}H n.m.r. (200 MHz, $CDCl_3$–Me_4Si) δ 1.26 (9H, s, Me_3C), 2.98—3.29 (3H, m, CH and CH_2), 3.67 (3H, s, CH_3O), 4.30 (2H, m, CH_2); ^{13}C n.m.r. (75.46 MHz, $CDCl_3$) δ 26.72, 39.84, 39.98, 44.16, 52.17, 66.01, 170.86, 174.53, 204.83; I.r. (Film) cm^{-1} 1724 (CO_2CH_3), 1670 (CO), 1620 (C=N).

Selected spectroscopic data for (**5b**): ^{1}H n.m.r. (200 MHz, $CDCl_3$–Me_4Si) δ 1.32 (9H, s, Me_3C), 2.07 (1H, m, CH), 2.24 (1H, m, CH), 3.69 (3H, s, CH_3O), 4.01 (1H, m, CH), 4.21 (2H, m, CH_2); ^{13}C n.m.r. (75.46 MHz, $CDCl_3$) δ 26.78, 27.19, 29.69, 44.09, 52.20, 62.50; I.r. (Film) cm^{-1}: 1745 (CO_2CH_3), 1680 (CO), 1620 (C=N). Satisfactory analytical data were obtained for both compounds.



maleate is rapidly and quantitatively isomerised to the corresponding fumarate ester prior to cycloaddition by DBU at 0 °C.

The possibility that acylnitrile ylides generated from α-ketoimidoyl chlorides in the above manner might serve as addends in intramolecular cycloadditions was explored in the following way. Acylation of the isonitrile (**8**)§ with trimethylacetyl chloride afforded the α-ketoimidoyl chloride (**9**) in quantitative yield. Slow adddition of (**9**) to a solution of *N*,*N*-di-isopropylethylamine (1.25 equiv.) in MeCN at 40 °C furnished the tetrahydroindole (**11**) in 27% yield. That the intermediate ylide (**10**) could be competitively intercepted by activated dipolarophiles was demonstrated by its generation in the presence of methyl acrylate (10 equiv., MeCN, Et_3N). In this instance, the pyrroline (**12**) was formed as the predominant cycloadduct in 32% yield.

Additional applications of acylnitrile ylides to problems of synthetic interest will be reported in due course.

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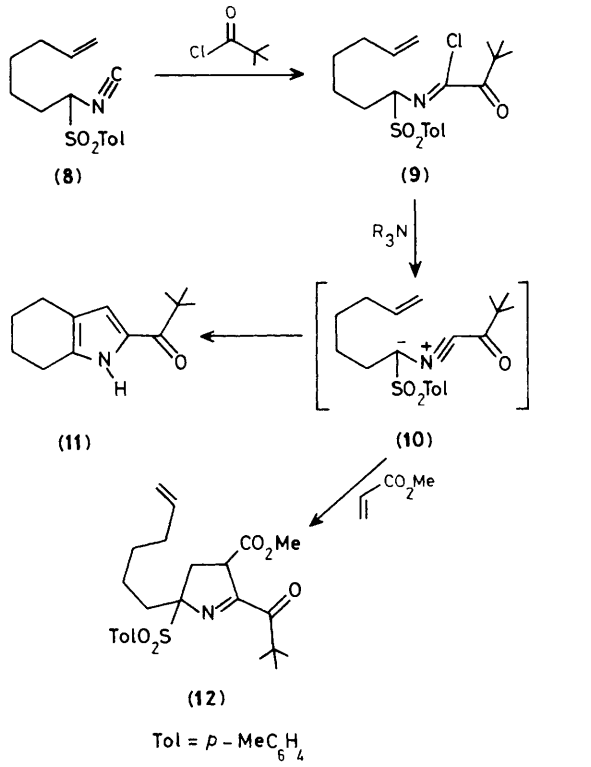

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§ The isonitrile (**8**) was prepared in 73% yield by the sequential lithiation of tosylmethyl isocyanide [lithium diisopropylamide (LDA), tetrahydrofuran (THF)] followed by alkylation of the resultant anion with 6-bromohex-1-ene.

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