Synthesis and Properties of Cyclic Keto Alkenylammonium Salts

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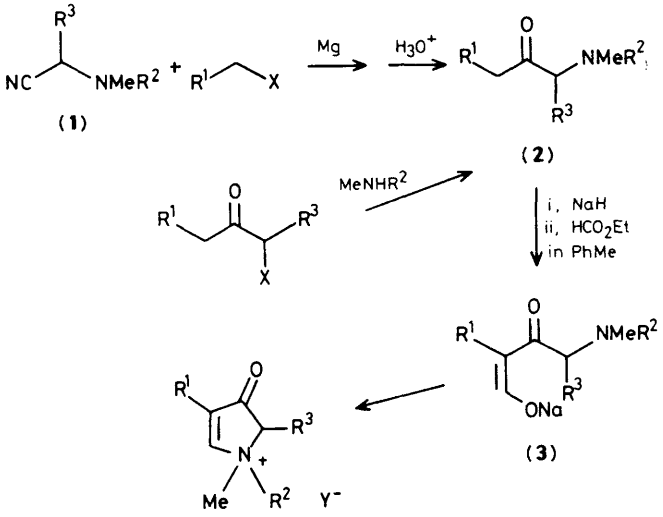
The cyclic keto alkenylammonium salts (**4**)—(**8**) have been prepared by a short, general route and their acidic and electrophilic properties examined.

For some time now, we have been interested in the synthesis and reactivity of alkenylammonium salts.[1] We now report a short and efficient synthesis of cyclic examples of these interesting compounds, *e.g.*, (**4**)—(**8**) (Scheme 1).

The starting α-aminoketones (**2**) were prepared in one of two ways, depending upon the substitution pattern desired. The simplest method involved reaction of an amine with the appropriate α-halogenoketone, resulting in good yields (52—100%) of the desired α-aminoketones. When regiospecific formation of the desired α-halogenoketones was expected to be difficult, an alternative strategy was employed. This involved reaction of dimethylaminoacetonitrile with a Grignard reagent,[2] which, after hydrolysis, gave α-aminoketones (**2**; R^2 = Me) in moderate yields (48—86%). When α-substituted α-aminoketones were desired (**2**; $R^3 \neq H$), the former approach was required, because reaction of substituted aminoacetonitriles (**1**; $R^3 \neq H$) with Grignard reagents produced tertiary amines in which the Grignard reagent had displaced cyanide.

The aminoketones (**2**) were treated with sodium hydride (1 equiv.) and ethyl formate (4 equiv.) in dry toluene[3] and the resulting sodium salts (**3**) precipitated by addition of ether (see



Ts = *p*-$MeC_6H_4SO_2$; Ms = $MeSO_2$

Scheme 1. See text for conversion of (**3**) into (**4**).

Table 1). When methyl ketones (**2**; R^1 = H) were employed, only 1 equiv. of ethyl formate could be used since an excess of this reagent failed to produce any of the desired product. [It was found, however, that reduction of the amount of ethyl formate to 1 equiv. in reactions of (**2**; $R^1 \neq H$) resulted in significantly lower yields.] In each case, only one isomer of (**3**) was isolated, which was assumed to be the *Z*-isomer, owing to expected chelation of the sodium cation by the ketoenolate.

Conversion of enolate salts (**3**) into cyclic alkenylammonium salts could be effected by treatment with toluene-*p*-sulphonyl chloride, which gave the tosylate salts (**4**). The presumed intermediate vinyl tosylates were never isolated but rather were converted directly into (**4**) by internal addition–elimination.†

Other methods of effecting ring closure were also investigated. For example, treatment of (**3a**) with methanesulphonyl chloride or diethyl chlorophosphate gave the corresponding alkenylammonium salts (**5a**) and (**6a**) respectively, although the yields were somewhat lower than those obtained for the tosylates. Although treatment of (**3a**) with 48% tetrafluoroboric acid did not yield the analogous tetrafluoroborate salt (**7a**), this compound could be obtained in quantitative yield by stirring an acetonitrile suspension of the tosylate salt (**4a**) with an excess of sodium tetrafluoroborate. These tetrafluoroborate salts were considerably more soluble in solvents such as acetonitile and acetone than their tosylate counterparts.

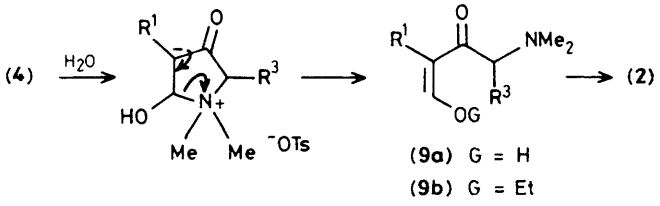
Alternatively, solutions of (**3a**) in acetic anhydride, when treated at room temperature with 1 equiv. of either 48% tetrafluoroboric acid or 70% perchloric acid yielded the corresponding salts (**7a**) and (**8a**) in 27 and 60% yield, respectively. Similarly, treatment of (**3f**) with tetrafluoroboric acid in acetic anhydride gave (**7f**) in 29% yield.

It is interesting to point out that the cyclization of (**3**) to give (**4**) is a formal violation of Baldwin's rules for ring closure.[4] The first step of the addition–elimination mechanism for cyclization involves attack of the lone pair of the tertiary amine on the β carbon of the β-tosyloxy enone,‡ a 5-*endo-trig* process, disfavoured by Baldwin's rules.§

A characteristic of the cyclic salts (**4**) that is not exhibited by their acyclic counterparts is a pronounced acidity of the protons at C-2, these protons being exchanged rapidly in deuterium oxide. Exchange of protons α to quaternized amines has been demonstrated previously[5] and it is believed that the carbonyl group at C-3 is enhancing this effect. Approximate half-lives determined by n.m.r. spectroscopy were < 1 h for compounds (**4a—d**). Although the exact values varied somewhat from sample to sample, the exchange of (**4a**) was consistently found to be the most rapid, with a typical half-life being ~10 min. It is suspected that traces of sodium

Table 1. Preparation of (**3**) and (**4**).

				% Isolated yield	
	R^1	R^2	R^3	(**3**)	(**4**)
a	Ph	Me	H	85	60
b	Me	Me	H	100	73
c	Et	Me	H	95	51
d	Me	Me	Me	77	88
e	H	Ph	H	66	0
f	H	Me	H	55	41
g	H	Me	Ph	47	58
h	H	$PhCH_2$	H	33	0

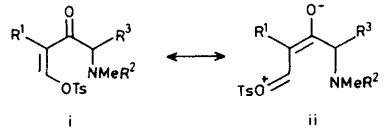


Scheme 2

† In a typical procedure, (**3a**) (17.8 mmol) was suspended in dry acetonitrile (500 ml). Tosyl chloride (3.66 g, 19.2 mmol) was added, and the solution stirred at room temperature under nitrogen for 12 h. After removal of insoluble material by filtration, the solvent was removed from the filtrate under reduced pressure. The residue was taken up in acetone (100 ml) and filtered, yielding (**4a**) as a white, crystalline solid (3.82 g, 60%), m.p. 220—224 °C (decomp.); ^1H n.m.r. (D_2O): δ 8.45 (br.s, 1H), 7.7—7.5 (m, 7H), 7.35 (d, *J* 8 Hz, 2H), 4.67 (s, 2H), 3.64 (s, 6H), and 2.39 (s, 3H); ^{13}C n.m.r. (CD_3SOCD_3): δ 195.0, 157.5, 145.3, 137.8, 134.3, 130.6, 128.8, 128.1, 127.7, 125.6, 125.4, 68.7, 54.8, and 20.7; $\nu_{max.}$ (KBr): 3045, 1728, 1204, 1185, 1119, 1030, 1009, and 680 cm^{-1}. Salts substituted at C–4 (**4**, $R^1 \neq H$) were consistently isolated as white solids, occasionally crystalline, whereas unsubstituted examples tended to exist as brown oils.

‡ Or the corresponding mesyloxy or diethylphosphato enone in the case of formation of (**5a**) and (**6a**).

§ A possible rationalization for this behaviour is that the cyclization occurs *via* the resonance contributor ii (rather than i), thus being a favoured 5-*exo-trig* process.



formate (undetectable by n.m.r.) are catalysing this exchange, and account for the variations between samples of the same compound.

Cyclic salts (**4**) exhibit a second mode of reactivity in aqueous solution, namely hydrolysis of the vinyl-ammonium moiety, presumably *via* an addition–elimination sequence, as shown in Scheme 2. The reaction is slow [the half-life of (**4a**) in water is ~10 days at room temperature] and is believed to proceed *via* the β-formyl compound (**9a**) although this has never been isolated. Instead, it is readily decarbonylated to give the α-aminoketone (**2**), existing in solution as its tosylate salt. Neutralization and extraction with dichloromethane allow isolation of (**2**). When ethanol is used as the solvent however, we are able to isolate the intermediate β-ethoxy enone (**9b**), the structure of which has been determined by spectroscopic means (high field n.m.r., i.r., mass). As would be expected, these reactions are accelerated upon heating. Although not extensively studied, such room temperature hydrolysis has not been observed in aqueous solutions of acyclic alkenylammonium salts.

In conclusion then, cyclic alkenylammonium salts (**4**) can be readily prepared by a short, general synthetic route, and exhibit several interesting characteristics not shared by acyclic alkenylammonium salts. Use of cyclic salts (**4**) as dienophiles in Diels–Alder reactions is currently being investigated.

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