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SELECTIVE ALKYLATION REACTIONS WITH VINAMIDINIUM SALTS

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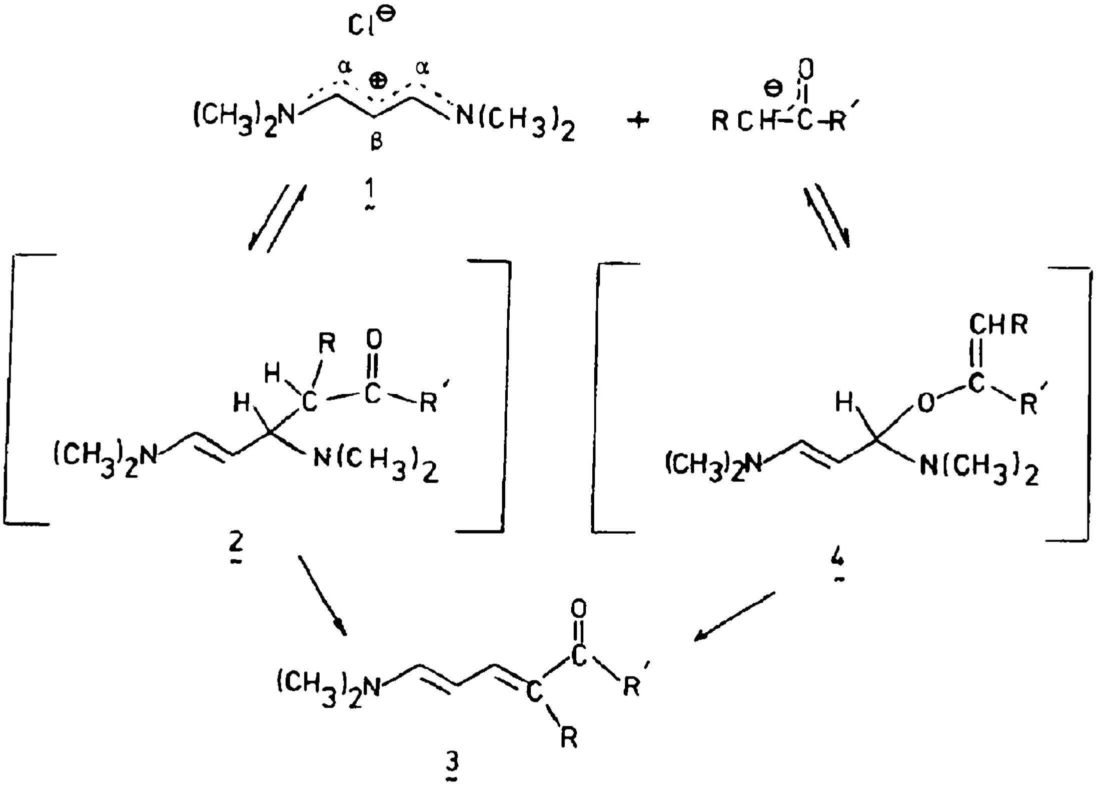
Summary: Vinamidinium salts react readily with enolates of ketones, esters, and lactones to produce multifunctional, synthetically-useful, dienaminones.

Selective alkylation of the carbon α to a carbonyl group with a variety of reagents is a major synthetic application of compounds containing activated methylene groups.[1] Vinamidinium salts,[2] vinylogs of amidinium compounds are possible alkylating agents. They normally exhibit regenerative character and are susceptible to substitution rather than addition reactions. The meneidic character of vinamidinium salts has been demonstrated in both electrophilic substitution reactions such as halogenation and nitrations, and in nucleophilic substitution reactions with amines.[3] Although reaction of vinamidinium salts with activated methylenes of nitriles has been reported,[4,5] there is only one report of the alkylation of other types of activated methylene compounds.[6] We wish to report on the utilization of vinamidinium salts in the alkylation of carbonyl enolates of cyclic and acyclic ketones, mono- and di- esters, keto esters, and lactones to produce multifunctional dienaminones **3**.

In previous work with vinamidines, perchlorate salts were used.[7] We have found a convenient method for the preparation of the tetramethylvinamidinium chloride salt **1** in good yield by reaction of β-dimethylamino acrolein[8] with dimethylamine hydrochloride. The ^{13}C NMR spectrum of **1** (in $CDCl_3$) showed the resonance for the α-carbons at 164.2 ppm and the resonance for the β-carbon at 90.3 ppm depicting the expected alternation of electron density in this push-pull system. The single resonance observed for the $C_\alpha H$ and C_α in the ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) and the vicinal proton coupling constant of 12.0 Hz are consistent with an all-*trans* or W conformation for **1**.[9,10] The UV max (ethanol) at 309 nm for **1** provided a very convenient marker for monitoring its reactions. All substrates absorbed at wavelengths shorter than that of **1**, and in the range 250-300 nm, and all the products absorbed at wavelengths longer than **1**, in the range 350-420 nm. The actual absorbance of the dienaminones could be readily predicted by using the Woodward Rules for absorption of unsaturated carbonyl compounds.[11]

Reactions of the vinamidinium salt **1** were carried out with the enolates generated *in situ* by reaction of sodium hydride with the carbonyl compound in triethylamine or pyridine (Scheme 1 The results with several different classes of activated methylene containing compounds were a variety of dienaminone products (Table 1). Close inspection of the spectral data of the



SCHEME 1

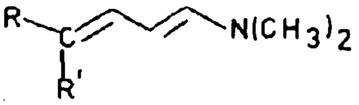
dienaminones revealed a number of common features which could also be used to identify new dienaminones. The ^{1}H NMR data (in CDCl$_3$) indicate that all of the dienaminones exist in the all-trans or W conformation ($J \sim 12$ Hz). The chemical shifts for the proton on the carbon β to the amino group were all similar with the resonance observed as a triplet at 4.87-6.41 ppm. The C$_\alpha$ proton characteristically appeared as a doublet at 6.32-7.33 ppm. Similar trends were found in the ^{13}C NMR data. Further, in the case of cyclopentanone (and other cyclic ketones), the structure was shown to be 9a and not its stereoisomer 9b by observation of a trans allylic coupling constant of 2.0 Hz between the C-3 protons and the exocyclic methylene proton.[12] The chemical shift of the exocyclic methylene proton at 7.08 ppm (in CDCl$_3$) is also consistent with 9a.[13,14]

When an unsymmetrical ketone such as 2-butanone was treated with 1, two products 8a and 8b were isolated by preparative gas chromatography in a 70:30 ratio, respectively. The predominance of 8a is consistent with the expected greater stability of primary versus secondary anions. This type of regioselectivity could be exploited in a synthetic scheme involving unsymmetrical compounds.

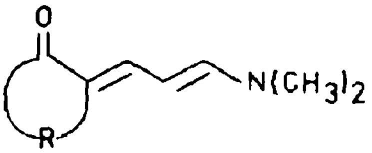
A plausible mechanism for formation of the dienaminones involves initial nucleophilic attack of the enolate on 1 to generate the σ-complex 2 which subsequently eliminates a molecule of dimethylamine with the assistance of a tertiary amine, such as triethylamine (Scheme 1). Elimination of amine from the σ-complex displaces the equilibrium and produces a new push-pull

Table 1: Method and Yield for the Preparation of the Dienaminones

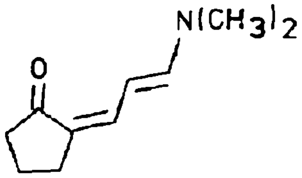
Reaction of 1 With:	Method[18]	Reaction Conditions		Product	Yield (%)	MP (^{o}C)
		Temp ^{o}C	(Time)			
Diethyl Malonate	A	Reflux	(10 hrs)	5	73	51-3
Ethyl Acetoacetate	B	25	(25 hrs)	7a,7b	57	88-90
Cyclopentanone	B	25	(26 hrs)	9a	88	88-91
Cyclohexanone	B	25	(30 hrs)	10	73	86-9
γ-Butyrolactone	B	25	(48 hrs)	11	91	99-102
dℓ-Camphor	C	Reflux	(40 hrs)	12	33	oil
3-Pentanone	C	25	(33 hrs)	6	66	oil
2-Butanone	B	25	(46 hrs)	8a,8b	78	oil
Estrone-3-Methyl Ether	B	25	(5 days)	13	56	209-11



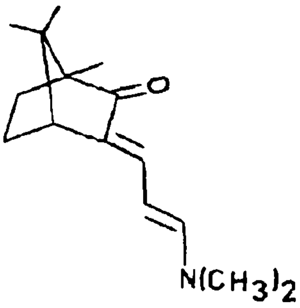
5	R=R'=$CO_2CH_2CH_3$	
6	R=$COCH_2CH_3$	R'=CH_3
7a	R=$COCH_3$	R'=$CO_2CH_2CH_3$
7b	R=$CO_2CH_2CH_3$	R'=$COCH_3$
8a	R=$COCH_2CH_3$	R'=H
8b	R=$COCH_3$	R'=CH_3



9a R=$(CH_2)_3$
10 R=$(CH_2)_4$
11 R=$O(CH_2)_2$



9b



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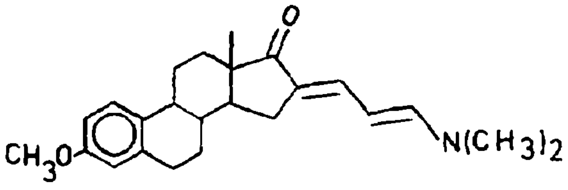

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system. O-Alkylation, a troublesome side reaction in many direct alkylations of activated methylenes,[15-17] is not important in these reactions because the σ-complex **4** if formed can undergo a Claisen rearrangement and $(CH_3)_2NH$ elimination to give **3**.

The dienaminones (**5**-**13**) produced in these interesting transformations are of interest in themselves but also provide functionally substituted carbonyl compounds which are potentially useful intermediates in natural products synthesis. We are presently extending the scope of this work by examining the latter.

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18. The carbonyl compound in THF was added to a stirred suspension of the salt **1** and NaH in the specified solvent. Method A, Pyridine; Method B, Triethylamine; Method C, Triethylamine and 4 Å molecular sieves.

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