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THE CHEMISTRY OF ENAMINOKETONES—V

ADDITION OF ORGANOMETALLIC REAGENTS AND THE FORMATION OF ALKYLATED PYRIDINIUM AND PYRROLINIUM SALTS

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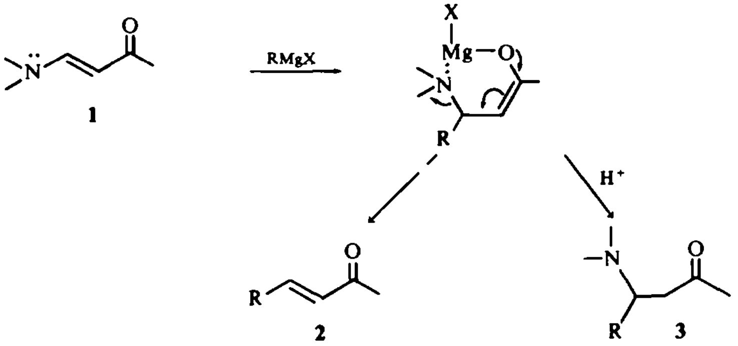
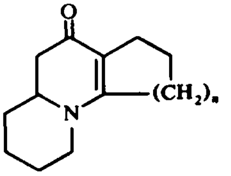
Abstract—The reaction of organolithium or the corresponding Grignard reagents with some representative enaminoketones produced 1,2-addition along with some 1,4-addition products. The former, enaminealcohols, could be converted to cyclic, conjugated, iminium salts or directly aromatized to pyridinium salts.

IN A continuing study[3–6] designed to evaluate the synthetic utility of molecules possessing the enaminoketone group (**1**) the reaction with organolithium and organomagnesium reagents were examined. Previous efforts to study and utilize this system were limited to the more accessible acyclic systems which resulted in primarily nitrogen free products (**2**)[7] along with some alkylated derivatives (**3**).[8]



The acyclic enaminoketones have also been noted for their instability toward a wide variety of nucleophiles (water,[9] amines[10]) and this behavior has deterred their development as useful synthetic intermediates. Preliminary studies[6] on the *cis*-enaminoketone **4** (n = 3), where the N—C=C—C=O moiety is part of a rigid ring system have shown that many novel and interesting derivatives can be obtained. This report will describe additional efforts utilizing organometallics on enaminoketones of the type **4**, **5** and **6**.



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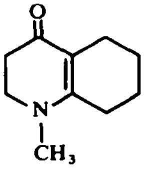

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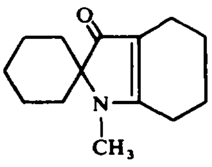

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When ether solutions of organolithium reagents (Me, t-Bu, and Ph) were added at 5° to benzene solutions of the enaminoketones **4**, **5** and **6** there were obtained, in 75–90% yield, the enamine alcohols **7–9**. These were substances which could not be adequately purified since they were unstable to heat, moisture and air; not an uncommon trait for enamines. In one instance, **7c** (n = 3) was sufficiently stable to allow complete characterization which supported the structural assignments of all the other derivatives (when comparing IR and NMR spectra). In a further attempt at purification of the enamine alcohols, the bicyclic system, **8c**, was passed through an alumina column and the diene amine, **10**, was isolated. Before it began to decompose, the spectra were examined and exhibited an IR band at 1615 cm^{-1} for the conjugated enamine, UV absorption at 312 mμ, and along with the expected NMR signals, a clear triplet at 4·90 ppm for the vinyl signal. When this substance was dissolved in cold perchloric acid solution, there was obtained the crystalline phenyl substituted dihydropyridinium salt, **11c**. Furthermore, when the enamine alcohol, **8c**, was similarly treated, the same dihydropyridinium salt was produced. Thus, it was found expedient to convert the crude enamine alcohols, **8**, to their corresponding salts immediately upon isolation. The pertinent physical data are tabulated in Table 1.

TABLE 1. 4-SUBSTITUTED-1-METHYL-2,3,5,6,7,8-HEXAHYDROQUINOLINIUM PERCHLORATE, **11**

R	m.p.	$CHCl_3$ mμ(ε)	% Yield	Anal. found[b] C	H	Cl
Me	144–145	304 (4677)	74	49·93	7·05	13·27
φ	110–111	332 (11,826)	90	58·87	6·26	11·07
t-Bu	163–164	306 (5380)[a]	65	55·20	8·34	11·89

[a] Determined in ethanol

[b] Agrees with calculated values

The tricyclic enamine alcohols, **7**, were also converted smoothly to their corresponding dihydropyridinium salts, **12**, upon addition of cold perchloric acid (Table 2). Similarly, the spiro enamine alcohols, **9**, were transformed into the 4-substituted pyrrolinium salts in good yield (Table 3). The lack of variation in the UV chromophore absorption in **13** reflects the out of plane twisting of the Ph group by the adjacent spiro-cyclohexane ring. From Tables 1 and 2, the effect of the Ph group on the conjugated iminium absorption is clearly seen when π–π overlap is allowed. It is of interest, however, to observe the decrease in π–π overlap in **12** as the size of the fused ring increases from five to eight. Molecular models support the presence of this effect.

A closer examination (TLC) of the reaction products obtained from **4** (n = 3) and methyllithium revealed that 1–5% of the 1,4-addition product, **16** (n = 2) was present. This material was isolated and the structure confirmed from its spectral characteristics (Experimental). No trace of the corresponding angularly alkylated products could be detected from the reactions involving phenyl and t-butyllithium.

TABLE 2. 6-SUBSTITUTED CYCLOALKANO[h]-1,2,3,4-TETRAHYDRO-5H-QUINOLIZINIUM PERCHLORATES, 12

R	n	mp	$CHCl_3$ λ mμ(ε)	$CHCl_3$ λ (μ)	% Yield	Anal. Found[e] C	H	Cl
Me	1	113–114[a]	306 (7552)	5·95, 6·15	80	53·62	6·87	
Me	2	149–150[a]	310 (5890)	6·06, 6·35	82	54·91	7·36	11·60
Me	3	74–80[c]	304 (6064)	6·09, 6·33	80	56·53	7·60	11·22
Me	4	56–63[c]	311 (5501)	6·09, 6·35	80	58·16	8·00	10·98
φ	1	192–193[b]	348 (16,751)	6·01, 6·26	92	61·19	6·36	10·09
φ	2	167–168[b]	338 (9309)	6·15, 6·43	95	62·41	6·71	9·75
φ	3	210–211	330 (10,000)	6·09, 6·35	92	63·06	6·79	9·61
φ	4	160–161	328 (7400)	6·11, 6·38	93	63·90	7·07	9·21
t-Bu	2	189–190	305 (4837)[d]	6·12, 6·34	65	58·50	7·89	10·26

[a] Recrystallized from CH_2Cl_2–ether.
[b] Recrystallized from abs EtOH.
[c] Hygroscopic salt.
[d] Determined in EtOH.
[e] Agrees with calculated values.

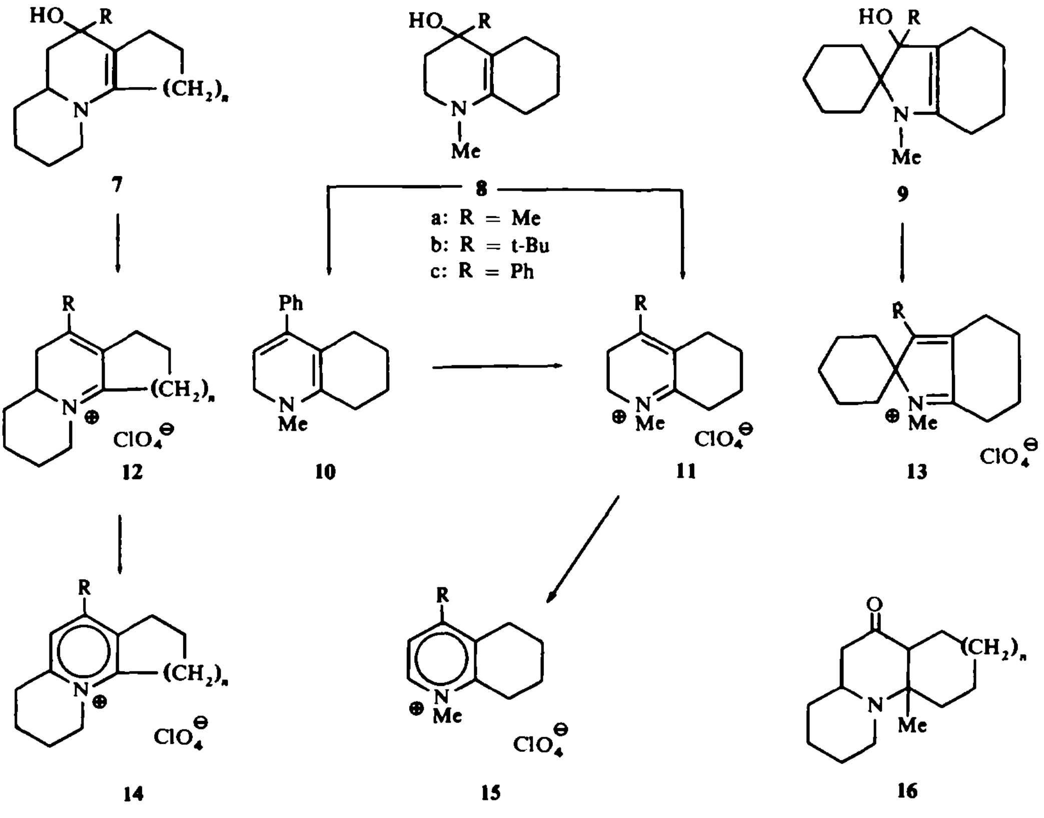

TABLE 3. 1-METHYL-4-SUBSTITUTED-5,6,7,8-TETRAHYDRO-2,2-PENTAMETHYLENE-2H-INDOLIUM PERCHLORATES, **13**

R	m.p.[a]	$\lambda^{EtOH}_{m\mu(\epsilon)}$	$\lambda^{CHCl_3}_{m\mu(\epsilon)}$	% Yield	Anal. found[b] C	H	Cl
Me	170–171	282 (7015)	6·07, 6·36	80	56·60	7·79	11·40
ϕ	239–240	285 (6500)	6·07, 6·24, 6·36	75	63·15	7·00	9·4
t-Bu	181–182	284 (6736)	6·14, 6·45	70	59·90	8·75	

[a] From abs EtOH–ether.
[b] Agrees with calculated values.

TABLE 4. 1-METHYL-4-SUBSTITUTED-5,6,7,8-TETRAHYDROQUINOLINIUM PERCHLORATES, **15**

R	m.p.[a]	λ^{EtOH}	% Yield	Anal. found[b] C	H	Cl
Me	120–121	271 (6700)	55	50·31	4·27	
ϕ	133–134	284 (15,684)	65	59·13	5·68	
t-Bu	207–208	276 (6973)	55	55·21	7·70	11·87

[a] From EtOH–EtOAc or CH_2Cl_2–ether.
[b] Agrees with calculated values.

TABLE 5. 6-SUBSTITUTED-CYCLOALKANO[h]-1,2,3,4-TETRAHYDROQUINOLIZINIUM PERCHLORATES, **14**

R	n	m.p.	$\lambda^{CHCl_3}_{m\mu(\epsilon)}$	$\lambda^{CHCl_3}_{(\mu)}$	% Yield	Anal. found[b] C	H	Cl
Me	2	136–136[a]	280 (7226)	6·12, 6·38	70	55·43	7·13	11·52
Me	3	129[a]	282 (8770)	6·15, 6·40	75	57·01	6·83	11·19
Me	4	118–119[a]	281 (9050)	6·11, 6·35	72	58·66	7·43	10·88
ϕ	3	220	288 (12,873)	6·16, 6·45	70	63·35	6·21	9·53
t-Bu	2	182–183	284 (6145)[c]	6·20, 6·44	50	59·42	7·72	4·39[b]

[a] Recrystallized from EtOAc–EtOH.
[b] Analyses for N.
[c] Determined in EtOH.
[d] Agrees with calculated values.

Although the amount of 1,4-addition product was low, further efforts at varying conditions to increase the yield were fruitless.*

The use of phenylmagnesium bromide upon **4**, **5** and **6** produced the enamine alcohols **7c–9c** in yields comparable to those obtained using phenyllithium. However,

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* Conditions for exclusive angular methylation have been obtained and were described in preliminary form.[6] Further studies in this area are still under investigation.

M.ps are corrected. Spectral data were recorded using a Perkin–Elmer 257 Grating Infrared Instrument, Beckman DB, and a Varian A-60 instrument. The organometallic reagents were all commercial products obtained from Lithium Corporation of America and Foote Chemical Company.

methylmagnesium bromide on **4** (n = 2) resulted in 30–40% recovered starting material, considerable tarry material and 5–10% of the angularly methylated derivative, **16** (n = 1). The latter could be clearly discerned by IR (normal CO, 1710–1720 cm^{-1} and NMR (Me singlet 0·9–1·1 ppm). Due to the apparent inefficiency of this process, no attempts were made to further utilize this technique.

The dihydropyridinium salts **11** and **12** were found to undergo facile air oxidation to the pyridinium salts **14** and **15** by merely refluxing in ethanol. Alternatively, the enamine alcohols, **7** and **8**, could be directly converted to pyridinium salts by the addition of perchloric acid (or hydrochloric, hydrobromic, and hydroiodic acids) and refluxing in ethanol. In the case of **7a** (n = 1), repeated attempts to aromatize this substance failed, even under forcing conditions. When the Ph substituted derivative **7c** (n = 1) was investigated, it too was recovered unchanged. The use of 2,3-dichloro-5,6-dicyanoquinone as an aromatization agent also failed to produce the corresponding pyridinium salts. Why the fused 5-membered ring in **7a** and **7b** would not allow transformation to **14a** and **14b** is not obvious at this time.

The 1,2-addition of organometallics, particularly organolithium reagents, to the *cis*-enaminoketone group appears to be a rather general and useful technique which leads to alkyl and aryl substituted heterocycles, otherwise inaccessible. Studies to obtain other enaminoketone systems which would provide additional scope to this method are in progress.

EXPERIMENTAL

Enaminoketones **4–6**. The bicyclic **5** and tricyclic **6** systems have already been described.[4] The spiro system, **6**, was prepared from 1-cyano-1-(N-methylamino)cyclohexane[11] and cyclohexanone utilizing a recently reported procedure;[12] b.p. 145–150° (0·25 mm); λ_{max}^{EtOH} 320 (12,916); λ_{film} 6·16, 6·35 μ; *m/e* (Calc. 219; Found 219).*

Addition of organolithium reagents to enaminoketones **4–6**

General procedure. A soln of 6·0 mmole enaminoketone in 10 ml dry benzene was cooled to 0–5° and treated with commercially prepared PhLi (ether, 3M, 10 ml), MeLi (ether, 1·6M, 15 ml), or t-BuLi (pentane, 2M, 10,ml). The soln was stirred under N_2 for 2 hr at 0–5°, allowed to warm to room temp, and stirred continuously overnight. The contents of the flask were cooled and carefully decomposed with ice-water (20–30 ml). The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4) and concentrated. The residue was triturated with n-hexane and the enamine alcohols **7–9** precipitated or oiled out and were washed rapidly with cold hexane. In the case of **7c** (n = 3), the product was sufficiently stable to purify and characterize, m.p. 147–148° (hexane), IR ($CHCl_3$) 2·73, 2·90, 6·10 μ; NMR ($CDCl_3$),δ 7·21–7·68 (aromatic), 1·89 (OH, exchangeable with D_2O), yield 81%. (Found: C, 80·73; H, 9·21; N, 4·57. Calc. for $C_{20}H_{27}NO$: C, 80·80, H, 9·09; N, 4·71%).

The reaction of **4–6** with PhMgBr was performed under identical conditions except that the enaminoketone was dissolved in equal volumes of ether and benzene.

Isolation of 1,4*-addition product*, **16** (*n* = 2) *from* **4** (*n* = 3) *and methyllithium.* After the separation of **7a** (above) the supernatant hexane soln was passed through an alumina column (pH 7·8) hexane to wash the column. The crude angularly methylated product was purified by preparative layer chromatography (Brinkman, PF_{254}, 2 mm) exhibiting a band (R_f = 0·6, ether-pet. ether, 4 : 6) which was cut from the plate and extracted with ether. Recrystallization of the residue (pet. ether) afforded **16** (n = 2), m.p. 56°, IR ($CHCL_3$) 5·81 μ; NMR ($CDCL_3$),δ 0·87 (s, CH_3). (Found: C, 76·80; H, 10·86; N, 6·20. Calc. for $C_{15}H_{25}NO$: C, 76·55; H, 10·71; N, 5·90%).

Reaction of **4** (*n* = 2) *with methylmagnesium bromide.* A soln of 1·2 g (5·6 mmole) in 10 ml benzene was treated at 0–5° with 5 ml MeMgBr soln (ether, 3 M). The soln was allowed to warm to room temp

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* A detailed description of this and related systems will be reported in a future publication.

and stirred overnight, after which it was poured into ice water. The organic layer was removed and the aqueous layer extracted with CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$) and concentrated. The deep red residue was triturated with hexane and the hexane decanted. Concentration of the hexane washings provided a mixture of starting material and **16** (n = 1). The mixture was chromatographed on alumina (pH 7·8) using hexane as the eluent. The eluate contained the ketone **16** (n = 1) which was purified by preparative layer chromatography (R_f = 0·6, ether–pet. ether, 4:6). Removal from the plate and ether extraction gave an oil, b.p. 128–134° (0·7 mm) IR (film) 3·36, 5·81 μ, NMR ($CDCl_3$), δ 0·84 (s, CH_3); picrate m.p. 226–228°. (Found: C, 54·00; H, 5·99; N, 12·27. Calc. for $C_{20}H_{26}N_4O_8$: C, 53·33; H, 5·82; N, 12·44%).

The alumina column was eluted with benzene and produced 400–450 mg (30–35%) of **4** (n = 2). The remainder of the dark colored hexane insoluble material could not be identified.

Formation of conjugated iminium perchlorates, **11–13**. The enamine alcohols, prepared above, were used in the crude form. A soln containing 3–5 mmole of enamine alcohol in 10 ml cold 70% perchloric acid was allowed to stand at room temp for 14–16 hr. The soln was diluted with an equal volume of water and extracted with CH_2Cl_2 repeatedly. The extracts were dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from CH_2Cl_2–ether or abs EtOH. The physical data are reported in the accompanying Tables.

Pyridinium salts, **14** *and* **15**

(*a*) *From direct aromatization of enamine alcohols* **7** and **8**. A soln of the enamine alcohol (3–5 mmoles) in 10 ml 70% perchloric acid and 20 ml abs EtOH was refluxed for 24–36 hr. The EtOH was removed under vacuum and 20 ml water was added to dilute the aqueous soln. The latter was extracted twice with CH_2Cl_2 and the extracts dried (Na_2SO_4) and concentrated. The residue was crystallized from EtOH–EtOAc or CH_2Cl_2–ether. The physical data are given in the accompanying Tables.

(*b*) *From aromatization of the dihydropyridinium salts*, **11** *and* **12**. This procedure was not as satisfactory as the preceding one due to extensive decomposition that ensued during the heating. A soln of **11** or **12** (3–5 mmoles) in 5 ml 70% perchloric acid and 20 ml abs EtOH was refluxed for 48–72 hr before reaction was complete. The EtOH was removed *in vacuo* and the products isolated as described above. The yields *via* this procedure were lower and the products more difficult to purify. The data in Tables 4 and 5 were composed from the procedure involving direct oxidation form the enamine alcohols.

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