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N-ALKYLATION OF ENAMINONES

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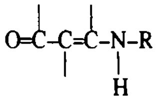
Abstract—The base catalyzed N-alkylation of a series of primary and secondary enaminones has been examined in detail. The enaminone anion was found to be a weak nucleophile. Best results were obtained in tetrahydrofuran or dioxane with sodium hydride and an alkyl iodide.

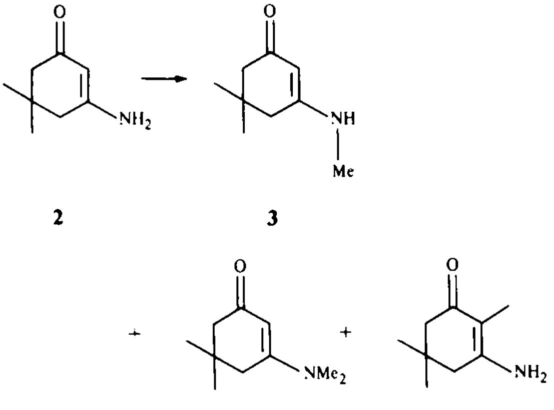
The enaminone system 1 can be N-deprotonated and the anion reacted with alkylating agents. Several groups have made use of this property,[1-3] but no systematic survey of the reaction has appeared. In principle, O-, Cα- or N-alkylation could occur. Usually only N-alkylation has been reported although some authors have observed C-alkyl derivatives as by-products.[4,5] Generally O-alkylation occurs without preliminary de-protonation, but some enaminones give C-alkyl derivatives in this reaction.[1]



$$O=\overset{|}{C}-\underset{|}{\overset{|}{C}}=\overset{|}{C}-\underset{H}{\underset{|}{N}}-R$$

1

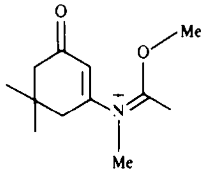
Much of the previous work has used sodium hydride in refluxing toluene to achieve deprotonation, followed by treatment with an alkyl iodide. The primary enaminone 2 with two equivalents of sodium hydride followed by two equivalents of iodomethane gave the N,N-dialkylated derivative 4, but the secondary enaminone 3 and the C-methyl derivative 5 were detected in the residues by TLC. With one equivalent each of base and reagent, compound 3 was isolated and 4 and 5 detected by TLC. Similar results were obtained with dimethyl sulphate.



2 3 4 5

Several other enaminones failed to react because of insolubility in toluene and it became evident that ethereal solvents were to be preferred. The results of a set of reactions are given in the Table. In each case the crude reaction mixture was examined by NMR, but only for the toluene reactions was a peak seen in the 1.5–2.0δ region to suggest the presence of a C-methyl derivative. TLC showed only spots corresponding with the compounds listed.

The enamidone 6 showed normal alkylation with 1 equivalent of each reagent, but with excess the de-acylated secondary enaminone 3 was obtained. Presumably the O-methyl derivative 7 formed and was hydrolysed during the work-up. The acridinedione 8 reacted normally in diglyme (it is insoluble in THF or dioxane) to give the N-methyl derivative[9] (63%).



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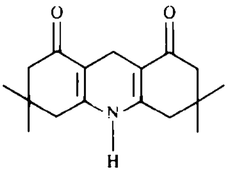

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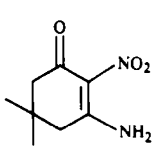
At this point attention was turned to other reactive alkyl halides: bromethane, ethyl bromoacetate, benzyl bromide and benzyl chloride. In nearly every case with enaminones 2, 3, 9 and 11, the reaction failed and starting materials were recovered. However, the anion of the primary enaminone 2 did react with benzyl bromide and the product was a mixture of the N-benzyl derivative (29%) and the C,N dibenzyl derivative (26%). This result is reminiscent of a report[5] of the reaction of 3-aminocyclohex-2-enone with a substituted benzyl chloride in the presence of sodium hydride in DMSO/toluene. The isolated products were the N,N-dibenzyl (13%), the C,N-dibenzyl (2%) and the C-benzyl (5%) derivatives. We observed no reaction between methyl iodide and compounds 2, 6 or 11 with dimsyl sodium in DMSO.

In an attempt to obtain a more reactive anion, the 2-nitroenaminone 12 was prepared.[6] This was de-protonated with sodium hydride and reacted with excess iodomethane to give the N,N-dialkyl derivative and with benzyl bromide to give the N-monoalkyl product. With bromoethane and ethyl bromoacetate, however, reaction failed both in THF and dioxane.

Enaminones are now readily converted into enaminothiones by Lawesson's reagent.[7] Compound 13 gave the expected S-methyl derivative when treated with iodomethane. Reaction in THF with excess sodium hydride followed by iodomethane produced the N,N,S-trimethyl salt 14.

An early report[8] showed that the tertiary enaminone 15



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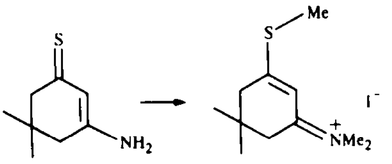
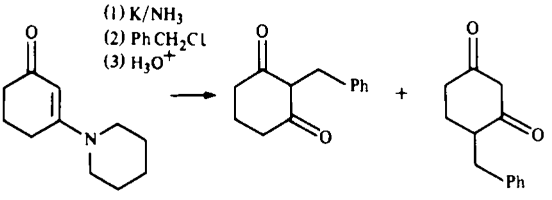


13 **14**

could be C-alkylated using potassium in liquid ammonia to give, after hydrolysis, the useful dione **16**. We repeated the reaction as described, but separated the products by column chromatography to obtain both the 2-benzyl (**16**; 22%) and the 4-benzyl (**17**; 33%) cyclohexanediones. However, the primary **2** and secondary enaminones **3** and **11** failed to react with either iodomethane or benzyl chloride under these conditions, perhaps because of insolubility in liquid ammonia.



15 **16** **17**

Clearly, enaminone anions are weak nucleophiles which react only with powerful alkylating agents. It would seem to be convenient to use iodoalkanes. It is important to use a solvent in which the enaminone is freely soluble—the choice of toluene by the early workers was unfortunate. The cyclohexanedione derivatives probably react best in suitable ethereal solvents. Other workers[1] have achieved successful alkylations in THF even at low temperature, using butyl-lithium or lithium di-isopropylamide as catalyst.

EXPERIMENTAL

Thin layer chromatograms were developed on silica plates using 20% methanol in dichloromethane.

General methods for alkylation of enaminones

(a) A soln of the enaminone (10 mmol) and sodium hydride (10 mmol) in the named solvent (100 ml) was refluxed for 1 hr and cooled. Iodomethane (10 mmol) was added and the mixture again refluxed 1-2 hr. The solvent was evaporated, the residue taken up in dichloromethane (100 ml) washed with water (2 × 10 ml), dried ($MgSO_4$) and evaporated to give the product.

(b) As for method (a) but with iodomethane (20 mmol).

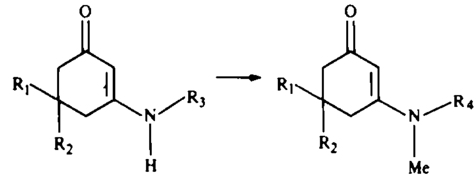
(c) As for methanol (a) but with sodium hydride (20 mmol) and iodomethane (20 mmol).

When the isolated products were known compounds, their identities were confirmed by comparison (m.p., mmp and IR) with authentic samples (refs given in the Table). The following new compounds were characterised: *5,5-dimethyl-3-methylaminocyclohex-2-enone hydrochloride* m.p. 180–182° (from ethanol-ether). Found: 56.8; H, 8.6; Cl, 18.8; N, 7.4. $C_9H_{16}ClNO$ requires: C, 57.0; H, 8.4; Cl, 18.7; N, 7.4%.

5,5-Dimethyl-3-dimethylaminocyclohex-2-enone hydrochloride m.p. 166–168° (from ethanol–ether). Found: C, 59.0; H, 8.7; Cl, 17.5; N, 6.9. $C_{10}H_{18}ClNO$ requires: C, 59.0; H, 8.9; Cl, 17.4; N, 6.9%.

3-(N-Cyclohexyl-N-methyl)aminocyclohex-2-enone hydrochloride. mp. 160–162° (from ethanol–ether). Found: C, 64.1, H, 9.0; Cl, 14.6; N, 5.7. $C_{13}H_{22}ClNO$ requires: C, 64.1; H, 9.0; Cl,

Table 1. Reaction of enaminone anions with iodomethane



						Isolated Products			By-Products	
Enaminone	R_1	R_2	R_3	Solvent	Conditions	R_4	%Yield	ref	R_4	Footnote
2[9]	Me	Me	H	Toluene	a	H	39	9	H,(C-Me)	1,2
					a	H	30	9	H,(C-Me)	2
					b	H,Me	26,24	9		2
					c	Me	49	9	H,(C-Me)	2
				THF	a	H	40	9	Me	
					b	H,Me	35,33	9		
				Dioxane	a	H	35	9	Me	
					c	Me	75	9	H	
				Diglyme	b	H	35	9	Me	
					c	Me	35	9	H	
3[9]	Me	Me	Me	Dioxane	c	Me	60	9		
6[11]	Me	Me	Ac	THF	a	Ac	63		H	
					c	H	54		Ac	
				Dioxane	c	H	40		Ac	
9[4]	H	H	C_6H_{11}	Dioxane	c	C_6H_{11}	52			
				Diglyme	c	C_6H_{11}	37			
10[10]	Ph	H	H	THF	c	Me	46		H	
11[12]	Me	Me	$(CH_2)_2Ph$	THF	c	$(CH_2)_2Ph$	78			
				Dioxane	c	$(CH_2)_2Ph$	78			
				Diglyme	c	$(CH_2)_2Ph$	55			

1) Dimethylsulphate used instead of iodomethane
2) Each reflux period 3 hr

14.6; N, 5.8%; NMR δ (CD_3OD) 3.25 (3H, s, NCH_3), 2.88 (1H, m, N–CH), 2.58–1.90 (16H, m, 8 × CH_2).

3-*Dimethylamino-5-phenylcyclohex-2-enone* m.p. 71–73° (from petroleum ether b.p. 80–100°). Found: C, 77.9; H, 7.8; N, 6.4. $C_{14}H_{17}NO$ requires: C, 78.1; H, 7.9; N, 6.5%; NMR δ ($CDCl_3$) 7.30 (5H, s, Ph-), 5.20 (1H, s, =CH), 2.97 (6H, s, $N(CH_3)_2$), 2.62–244 (5H, m, 2 × $CH_2 \div CH$).

5,5-*Dimethyl-3-(N-methylacetamido)cyclohex-2-enone* m.p. 73–75° (from toluene–petroleum ether). Found: C, 68.0; H, 8.8; N, 7.2. $C_{11}H_{17}NO_2$ requires: C, 67.7; H, 8.7; N, 7.2%; IR ν (KBr) 1675, 1640, 1605 cm^{-1}; NMR δ ($CDCl_3$) 5.81 (1H, s, =CH), 3.18 (3H, s, NCH_3), 2.55 (2H, s, CH_2), 2.30 (2H, s, CH_2), 2.19 (3H, s, $COCH_3$), 1.10 (6H, s, 2 × CH_3).

5, 5-*Dimethyl-3-(N-methyl-2-phenethylamino) cyclohex-2-enone* m.p. 61–62° (from petroleum ether b.p. 80–100°). Found: C, 79.7; H, 8.8, N, 5.5. $C_{17}H_{23}NO$ requires: C, 79.4; H, 9.0; N, 5.5%; IR ν (KBr) 1605, 1570 cm^{-1}; NMR δ ($CDCl_3$) 7.24 (5H, s, Ph), 5.17 (1H, s, =CH), 3.50 (2H, t, NCH_2), 2.92–2.70 (5H, m, NCH_3 + $PhCH_2$), 2.08 (4H, s, 2 × CH_2), 0.99 (6H, s, 2 × CH_3). *Hydrochloride* m.p. 149–150° (from ethanol–ether). Found: C, 69.5; H, 7.9; Cl, 12.0, N, 4.8. $C_{17}H_{24}ClNO$ requires: C, 69.5; H, 8.2; Cl, 12.1, N, 4.8%.

Reaction of enaminone **2** *anion with benzyl bromide.* 3-Amino-5, 5-dimethylcyclohex-2-enone **2** and benzyl bromide in THF by general method (C) gave a crude product which was dissolved in toluene and chromatographed on a silica gel column. Elution with toluene gave 2-benzyl-3-benzylamino-5, 5-dimethylcyclohex-2-enone. m.p. 120–122° (from petroleum ether b.p. 80–100°). Found: C, 82.8; H, 7.9; N, 4.6. $C_{22}H_{25}NO$ requires: C, 82.8; H, 7.8; N, 4.4%; IR ν (KBr) 1580, 1530 cm^{-1}; NMR δ ($CDCl_3$) 7.20(10H, s, 2 × Ph). 6.85 (1H, br., NH), 4.30 (2H, d, NCH_2), 3.25 (2H, s, CH_2Ph), 2.27 (4H, s, 2 × CH_2), 1.0 (6H, s, 2 × CH_3). Further elution with ethyl acetate gave 3-benzylamino-5, 5-dimethylcyclohex-2-enone m.p. 129–130° (from toluene), lit.[14] m.p. 129–130°.

5,5-*Dimethyl-3-dimethylamino-2-nitrocyclohex-2-enone.* 3-Amino-5, 5-dimethyl-2-nitrocyclohex-2-enone[6] and iodomethane in THF by general method (c) gave the tertiary enaminone (43%) m.p. 171–173° (from ethyl acetate). Found: C, 56.5; H, 7.7; N, 13.3. $C_{10}H_{16}N_2O_3$ requires: C, 56.6; H, 7.6; N, 13.2%; IR ν (KBr) 1640, 1560, 1475, 1292 cm^{-1}; UV $\lambda_{max.}$ (H_2O) 355 nm (ϵ 4100), 284 nm (ϵ 14000); (0.1M HCl) 355 nm (ϵ 4300), 285 nm (ϵ 14000); (0.1M NaOH) 337 nm (ϵ 2600), 262 nm (ϵ 14300); NMR δ (DMSO-d_6) 3.03 (6H, s, $N(CH_3)_2$), 3.87 (2H, s, CH_2), 3.17 (2H, s, CH_2), 1.00 (6H, s, 2 × CH_3).

3-*Benzylamino-5,5-dimethyl-2-nitrocyclohex-2-enone* (57%) m.p. 167–168° (from ethyl acetate) was prepared similarly. Found: C, 65.6; H, 6.8; N, 10.3. $C_{15}H_{18}N_2O_3$ requires: C, 65.7; H, 6.6; N, 10.2%; IR ν (KBr) 1660, 1580 cm^{-1}; UV λ_{max} (H_2O) 335 nm (ϵ 8300), 268 nm (ϵ 19400); (0.1M HCl) 335 nm (ϵ 8300), 268 nm (ϵ 20800); (0.1M NaOH) 340 nm (ϵ 7100), 269 nm (ϵ 18400); NMR δ (DMSO-d_6) 7.38 (5H, s, Ph), 4.75 (2H, d, NCH_2), 2.70 (2H, s, CH_2), 2.25 (2H, s, CH_2), 0.90 (6H, s, 2 × CH_3).

3-*Amino-5,5-dimethylcyclohex-2-enethione* (**13**) 2, 4-Bis (4-methoxyphenyl)-1, 3-dithia-2, 4-diphosphetane-2, 4-disulphide (Lawesson reagent, 10.8 g, 26.5 mmol) was added to a stirred solution of 3-amino-5, 5-dimethylcyclohex-2-enone (7.0 g, 50 mmol) in dry THF (500 ml). Within 10 min the solution cleared and the colour changed to deep orange. It was poured into water and extracted with dichloromethane (3 × 200 ml). The extract was dried ($MgSO_4$) and concentrated to 80 ml. The solution was filtered through a column containing silica gel and basic alumina (1 : 1). The column was washed with ethanol (500 ml) and the solvent evaporated to give the enaminothione (7.0 g; 90%) m.p. 152–153° (from ethyl acetate-light petroleum b.p. 40–60°). Found: C, 62.1; H, 8.7; N, 9.2; S, 20.4. $C_8H_{13}NS$ requires: C, 61.9; H, 8.4; N, 9.0; S, 20.6%; IR ν (KBr) 1650, 1510, 1040 cm^{-1}; UV λ_{max} (H_2O) 352 nm (ϵ 37100), (0.1MHCl) 350 nm (ϵ 6600), 310 nm (ϵ 17700); (0.1MNaOH) 352 nm (ϵ 16600), 316 nm (sh) (ϵ 9700); (MNaOH) 313 nm (ϵ 17000) NMR δ (CD_3OD) 6.47 (1H, s, =CH), 2.59 (2H, s, CH_2), 2.28 (2H, s, CH_2), 1.00 (6H, s, 2 × CH_3).

5, 5 - *Dimethyl - 3 - imino - 1 - methylmercaptocyclohex - 1 - ene hydriodide.* A solution of 3-amino-5, 5-dimethylcyclohex-2-enethione (1g) in iodomethane (20 ml) was stirred at room temperature (9 hr) and the precipitate collected to give the hydriodide (1.6 g, 84%) m.p. 196–198° (from ethanol–ether). Found: C, 36.3; H, 5.5; I, 42.6; N, 4.7; S, 11.2. $C_6H_{16}INS$ requires: C, 36.4; H, 5.4; I, 42.3; N, 4.7; S, 10.8%; IR ν (KBr) 1675, 1550 cm^{-1}; NMR δ (DMSO-d_6) 10.7 (2H, Br., NH_2), 6.50 (1H, s, =CH), 2.72 (2H, s, CH_2), 2.54 (5H, s, CH_2 + SCH_3), 1.00 (6H, s, 2 × CH_3).

5,5-*Dimethyl-3-dimethylimino-1-methylmercaptocyclohex-1-ene hydriodide* (**14**). 3-Amino-5, 5-dimethylcyclohex-2-enethione and iodomethane in THF by general method (c) gave the hydriodide (51%) m.p. 178–180° (from ethanol–ether). Found: C, 40.5; H, 6.2; I, 39.3; N, 4.4; S, 10.0 $C_{11}H_{20}INS$ requires: C, 40.6; H, 6.2; I, 39.1; N, 4.3; S, 9.9%; IR ν (KBr) 1595, 1540 cm^{-1}, $UV_{\lambda max.}$ (H_2O) 330 nm (ϵ 28400), 225 nm (ϵ 16900); (0.1MHCl) 330 nm (ϵ 28400), 265 nm (17500) 225 nm (17500) NMR δ (CD_3OD) 6.40 (1H, s, =CH) 3.58 (3H, s, NCH_3), 3.52 (3H, s, NCH_3), 2.80 (2H, s, CH_2), 2.63 (3H, s, SCH_3), 2.52 (2H, s, CH_2), 1.10 (6H, s, 2 × CH_3).

Reaction of 3-*piperidinocyclohex-2-enone with benzyl chloride.* A solution of the enaminone[8] (1.8g, 10 mmol) was added to a solution of potassium (0.8 g, 20 mmol) in liquid ammonia (300 ml) and stirred ($\frac{1}{2}$ hr). Benzyl chloride (2.4 ml, 20 mmol) was added, the mixture again stirred ($\frac{1}{2}$ hr) and then treated with ammonium chloride (2g). The ammonia was allowed to evaporate and the residue shaken with water (25 ml) and ether (100 ml). The ether layer was evaporated and the residue refluxed with dilute hydrochloric acid (20 ml) for 2 hr. The cooled soln was basified (NaOH) washed (ether) reacidified (HCl) and extracted with dichloromethane (2 × 100 ml). The extract was dried ($MgSO_4$), evaporated, dissolved in toluene and chromatographed on a silica column. Elution with toluene gave 2-benzylcyclohexane-1, 3-dione (0.4 g, 22%) m.p. 184–185° (from toluene) (lit.[8] m.p. 183–184°); NMR δ (CD_3OD) 7.20 (5H, s, Ph), 3.63 (2H, s, CH_2Ph), 2.60–1.70 (6H, m, 3 × CH_2). Elution with ethyl acetate gave 4-benzylcyclohexane-1, 3-dione (0.65 g, 33%) m.p. 109–110° (from petroleum ether b.p. 80–100°) (lit.[8] m.p. 109–110°); NMR (δ $CDCl_3$) 7.18 (5H, s, Ph). 3.30 (2H, s, CH_2 position 2), 2.90 (2H, d, CH_2Ph) 1.90–1.40 (5H, m, 2 × CH_2 + CH).

3-*Amino*-2,5,5-*trimethylcyclohex-2-enone* **5**. Ammonia was passed through a soln of 2,5,5-trimethylcyclohexane-1, 3-dione[13] (7g) in ethanol (100 ml) during $1\frac{1}{2}$ hr reflux. The solvent was evaporated to give the *enaminone* (2g, 29%) m.p. 194–195° (from benzene). Found: C, 70.3; H, 9.4; N, 9.3. $C_9H_{15}NO$ requires: C, 70.6; H, 9.8; N, 9.2%. *Hydrochloride* m.p. 273°(d) (from ethanol-ether). Found: C, 57.2; H, 8.3; Cl, 18.7; N, 7.4. $C_9H_{16}ClNO$ requires: C, 57.0, H. 8.5; Cl, 18.7; N, 7.4%.

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