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CHARGE-DIRECTED CONJUGATE ADDITION REACTIONS OF SALTS OF UNSATURATED β-KETO-ESTERS

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Abstract -- Strong nucleophiles undergo conjugate addition reactions with enolates of Nazarov-type reagents. Yields are strongly affected by substitution patterns and the metal cation employed.

We have previously explored the charge-directed conjugate addition reactions of acceptors (1) in which proximal negative charge serves to suppress the carbonyl 1,2-addition reactions usually encountered in reactions with strong nucleophiles thereby enabling 1,4-addition reactions to predominate (eq.1).^{1,2}



Unsaturated acylphosphoranes (4) have been found to be excellent Michael acceptors in such reactions and undergo addition reactions with a variety of strong nucleophiles to give highly anionic intermediate anions (2, $X = C(=PPh_3)COOR$), which may be alkylated and subsequently transformed into a variety of esters,¹

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acids¹ and ketones¹ (3). Similarly, salts of α -silylated α , β -unsaturated carboxylic acids (5) also have been found to be excellent acceptors in such reactions.²



We have now examined the conjugate addition reactions of some salts (enolates) of Nazarov-type reagents, 6, which are analogs of 4 but whose π -systems presumably contain a greater charge burden. Results of the reactions of some highly nucleophilic reagents with this type of acceptor are shown in Table 1.

It can be seen that only alkyllithium reagents undergo satisfactory addition reactions; PhLi, 1-hexenyllithium, Grignard reagents and n-BuCu(CN)Li resulted in failures. In general, better yields were obtained with lithium salts (entries 7-9). While it is tempting to ascribe this trend to greater covalent bonding (and hence a lower system charge burden) in the case of the lithium enolates, it should be noted that a comparison of entries 1 and 5 suggests potassium salts to be better acceptors than sodium salts. It is likely that the higher yields with Li⁺ salts are at least partly due to the milder conditions of their salt formation reactions. In general, salts were formed at the lowest temperature consistent with rapid consumption of the parent ketoester (0°C with NaH, -30° to -40°C with KH and -78°C with i-Pr₂NLi). We observed that neutral precursors of **6a** and **6b** are very susceptible to condensation (polymerization) reactions under basic conditions and for a given salt-forming reaction, yields always decreased as the temperature of the salt formation reaction increased (see, for example, entry 12). Best reaction conditions were found to be Li⁺ salt formation at -78°C and alkyllithium addition

]	Reaction Temperature	<u>,,,,</u> ,_,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
	Acceptora	М	Nu⁻	(°C)	Product	Yield ^b
1.	6a OEt	Na ⁺	n-BuLi	-78 R	0 0 OEt $7a (R = n-Bu)$	52(23) ^c
2.		Na ⁺	t-BuLi	-78	7b (R = t-Bu)	49
3.		Na^+	MeLi	-78	7c(R = Me)	33
4.		Na ⁺	PhLi	-78		0
5.		K+	n-BuLi	-78	7a	73
6.		K+	PhLi	-780		0
7.		Li ⁺	n-BuLi	-78	7a	76
8.		Li+	t-BuLi	-78	7b	87
9.		Li+	MeLi	-780	7c	49 ^c
10.		Li ⁺	PhLi	-7825		0
11.	O ^M O OEt 6b	К+	n-BuLi	-30 R	O O OEt	0
12.	1	Li ⁺	n-BuLi	-78	7d (R = n-Bu)	42 ^d (6) ^e
13.		Li ⁺	t-BuLi	-7845	7e (R = t-Bu)	50 ^d
14.	Ph 6c OI	Li ⁺ St	n-BuLi	-7825		0

Table 1. Conjugate Addition Reactions of Unsaturated Enolates 6

a) From ketoester and NaH, 0° C or KH, -40° C or i-Pr₂NLi, -78° C. b) Isolated. c) HMPA (1 equiv) added. d) Glpc yield. e) Enolate prepared and addition reaction conducted at -35° C.

at -78°C with slow warming to 0°C or higher in more difficult cases (entries 9, 12 and 13).

It can also be seen that carbanion substitution in **6b** results in diminished yields (compare entries 12 and 13 with entries 7 and 8). This may be due to a charge-density-increasing inductive effect of the methyl group. Substitution at the β -carbon renders **6c** unreactive in these reactions; β -substitution is often observed to hinder Michael-type processes.³

In conclusion, while it appears that the concept of charge-directed conjugate addition can be extended to simple salts of unsaturated β -ketoesters when alkyllithium reagents are employed, this class of acceptor is less versatile than the more stable ylide acceptors (4) previously studied.

Experimental Section⁴

Typical Procedure for the Addition of RLi to Li⁺ Enolates: Ethyl 6.6-Dimethyl-3-oxo-heptanoate (7b) (entry 8): A solution containing 390 μ L (2.7 mmol) of i-Pr2NH in 10 mL of dry THF was treated with 2.0 mL (2.7 mmol) of 1.35 N n-BuLi (hexane) at -78°C. After 10 min., 355 mg (2.5 mmol) of ethyl 3-oxo-4-pentenoate⁵ in 5 mL of THF was added dropwise and the mixture was stirred for 3 min. whereupon 2.9 mL (5.5 mmol) of 2.9 N t-BuLi (pentane) was added dropwise. The mixture was stirred at -78°C for 15 min. and then quenched with 1 N HCL. The mixture was extracted three times with Et₂O (25 mL) and the extracts were washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. Bulb-to-bulb distillation gave 436 mg (87%) of 7b as an oil: ¹H NMR (90 MHz, CDCl₃) δ 0.89 (s, 9H), 1.28 (t, 3 H, J = 7.1), 1.52 (t, 2 H), 2.52 (t, 3 H, J = 8.2), 3.45 (s, 2 H), 4.20 (q, 2 H, J = 7.1); ¹³C NMR (22.5 MHz, CDCl₃) δ 14.1, 29.1, 29.9, 37.0, 38.8 49.3, 61.3, 167.2, 203.2.

Similarly prepared (see Table 1 for variations):

<u>Ethyl 3-oxo-nonanoate (7a)</u> (entry 7): 76% after bulb-to-bulb distillation (150°C, 0.3 mm); ¹H NMR (90 MHz, CDCl₃) δ 0.88 (s, 3 H), 1.28 (t, 3 H, J = 7.1), 1.1 - 1.7 (m, 8 H), 2.53 (t, 2 H, J = 7.1), 3.42 (s, 2 H), 4.18 (q, 2 H, J = 7.1) (enol form: 1.95, 4.98). This material was identical to an authentic sample.⁶

<u>Ethyl 3-oxo-hexanoate</u> (7c) (entry 9): 49% after bulb-to-bulb distillation (120°C, 0.3 mm) (lit.⁶ bp 97-102°C, 20 mm); ¹H NMR (90 MHz, CDCl₃) δ 0.93

(t, 3 H, J = 6.8), 1.28 (t, 3 H, J = 7.1), 1.63 (m, 2 H, J = 7.1, 6.8), 2.53 (t, 2 H), 3.43 (s, 2H), 4.19 (q, 2 H); ¹³C NMR (22.5 MHz, CDCl₃) δ 13.4, 13.9, 16.8, 44.7, 49.1, 61.0, 167.0, 202.4.

Addition to K⁺ Enolates: Typical Procedure (entry 5): A solution containing 0.54 g (3.8 mmol) of ethyl 3-oxo-4-pentenoate⁶ in 10 mL of THF was cooled to -40°C and transferred by cannula to a suspension of 167 mg (4.2 mmol) of KH in 25 mL of THF (-40°C). The mixture was stirred for 5 min, cooled to -78°C and treated with 3.0 mL (4.0 mmol) of 1.35 N n-BuLi. After 10 min, the mixture was slowly warmed to 0°C and quenched with 1 N HCl. Workup as above gave 555 mg (73%) of 7a.

Ethyl 3-(Bicyclo[2.2.1]hept-5-en-2-yl)-3-oxo-2-methyl-propanoate (8): To a mixture containing 58 mmol of NaH (2.47 g of 57% NaH in oil, washed with pentane) and 50 mL of THF was added at 0°C 9.0 g (49 mmol) of ethyl 3-(bicyclo[2.2.1]hept-5-en-2-yl)-3-oxo-propanoate⁵ in 15 mL of THF over several min. After 15 min, 6.1 mL (98 mmol) of MeI was added and the mixture was stirred at 20°C for 1 h, poured into water and extracted with EtOAc (2 x 25 mL). The extracts were washed with brine, dried (MgSO₄) and concentrated. Distillation gave 8.8 g (91%) of 8 : bp 95-96°C (0.4 mm); ¹H NMR (90 MHz, CDCl₃) δ 1.26 (t, 3 H, J = 7.1), 1.35 (d, 3 H, J - 7.3), 1.6 - 1.9 (m), 2.30 - 2.65 (m), 2. 9 (b), 3.15 - 3.35 (m), 3.65 (q, 1 H), 4.19 (q, 2 H, J = 7.1), 6.13 (b, 2 H). M/E 222 (m⁺), 177, 149.

Ethyl 3-oxo-2-methyl-4-pentenoate (6, $R_1 = H$, $R_2 = Me$): Using the method of Caselli and co-workers,⁵ 12.6 g (56.7 mmol) of **8** was added over 25 min. to a 600°C pyrolysis tube (2 mm). Product was collected in a -30°C trap. Redistillation gave 5.7 g (65%) of **6** : bp 68-70°C (2.3 mm); ¹H NMR (90 MHz, CDCl₃) keto form δ 1.25 (t, 3 H, J = 7.1), 1.37 (d, 3 H, J = 7.1 Hz), 3.80 (q, 1 H, J = 7.1 Hz), 4.18 (q, 2 H, J = 7.1), 5.5 - 6.8 (m, 2 H); ¹³C NMR (22.5 MHz, CDCl₃) (keto and enol forms) δ 12.6, 13.8, 14.1, 21.5, 60.5, 61.1, 122.1, 128.0, 128.8, 129.2, 131.2, 134.3, 170.2, 173.4, 195.0, 196.2. M/e 156 (m⁺).

Ethyl 2-Methyl-3-oxo-nonanoate (7d) (entry 12): ¹H NMR (90 MHz, CDCl₃) δ 0.88 (b), 1.20 - 2.75 (b), 1.31 (d, 3 H, J = 7.1), 2.54 (t, 2 H, J = 7.3), 3.52 (q, 1 H, J = 7.1), 4.18 (q, 2 H, J = 7.1); ¹³C NMR (22.5 MHz, CDCl₃) δ 12.5, 13.7, 13.8, 22.2, 23.3, 28.6, 31.4, 41.1, 52.6, 60.9, 170.3, 205.5. Anal. Calcd for C₁₂H₂₂O₃: C, 67.25; H, 10.35. Found: C, 67.30; H, 10.19.

Ethyl 2.6.6-Trimethyl-3-oxo-heptanoate (7e) (entry 13): 1H NMR (90 MHz, CDCl₃) δ 0.89 (s, 9 H), 1.27 (t, 3 H, J = 7.1), 1.33 (d, 3 H, J = 7.1), 1.50 (t, 2 H, J = 8.0), 2.53 (dt, 2 H, J = 2.4, 8.0), 3.54 (q, 2 H, J = 7.1), 4.18 (q, 2 H, J = 7.1); ¹³C NMR (22.5 MHz, CDCl₃) δ 12.8, 14.0, 29.0, 29.9, 37.1 (2c) 52.9 61.2, 170.6, 206.1. Anal. Calcd for C₁₂H₂₂O₃: C, 67.25; H, 10.35. Found: C, 67.45; H, 10.34.

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