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SYNTHESIS AND BENZYLATION OF (2-(1'-LITHIUM)-ETHYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-4H-1,3-OXAZINE

AN APPROACH TO THE MECHANISM OF THE REACTION

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Abstract—Metalation of 2-ethyl-4,4,6-trimethyl-5,6-dihydro-4H-1,3-oxazine with n-BuLi and subsequent preparation of its 2-aryl-methylation products are reported. The Hammett ρ-constant has been evaluated ($\rho = 2.2$) and a tentative description of the transition state for the benzylation reaction of the metalated oxazine is proposed.

A new method for C–C bond formation has been developed by Meyers *et al.*[1] These authors start with a 2 - alkyl - 4,4,6 - trimethyl - 5,6 - dihydro - 4H - 1,3 - oxazine (1), which on metalation and further alkylation yields the alkyl derivative (2). This intermediate can be easily reduced to the corresponding tetrahydro oxazine derivative (3) which, on hydrolysis affords the aldehyde (4) in good yield (Scheme 1).

This method can be used for homologation of electrophiles to aldehydes and it, therefore, represents a useful alternative to the synthesis of α-alkyl aldehides "via enamines"[2] and "via bis-thiocarbanions".[3]

Meyers *et al.*[4] have reported the reaction for several alkyl oxazines (1) such as 2-methyl-, 2-benzyl-, 2-ethoxycarbonylmethyl- and 2-vinyl oxazine.

However, when 2-ethyloxazine was used in experiments at −78° and −50°, neither methylation nor deuteration could be detected which shows that the carbanion is not formed. However, Meyers *et al.* claim that it is actually formed at higher temperatures at which it immediately gives rise to a dimer that could be detected. On heating, the dimer reverts to the starting oxazine.

RESULTS AND DISCUSSION

Since the final aim was the obtention of 2-substituted propionaldehyde derivatives, a study of the metalation of 2-ethyloxazine was carried out. The optimization of conditions for further alkylation using arylmethyl chlorides as hard electrophiles was likewise studied. The formation of the carbanion at −78° could be finally confirmed by alkylation. This was successful provided that the metalated oxazine has been completely dissolved in THF. Thus, using n-BuLi as a base 2 - (1' - lithium) - ethyl - 4,4,6 - trimethyl - 5,6 - dihydro - 4H - 1,3 - oxazine was prepared and was then used to obtain the 2 - (2' - aryl - 1' - methyl) - ethyl - 4,4,6 - trimethyl - 5,6 - dihydro-4H - 1,3 - oxazines summarized in Table 1. No N-alkylation products could be observed in any of the cases studied.

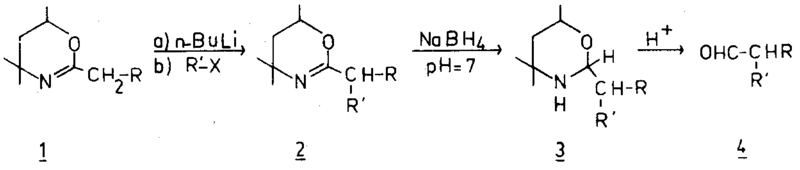
The reactivity of metalated oxazine towards arylmethyl chlorides at −78° was determined by competitive kinetics using equimolar quantities of benzyl and arylmethyl chlorides in a ratio: equimolar mixture of chlorides/oxazine = 9/1.

The mixture was analysed by mass spectrometry by interpolation in the calibration plots obtained from the analysis of model mixtures of exactly known composition. In every case, the conversion in mixture of benzyl oxazines was below 20% as could be cromatographically confirmed.

Table 1. Physical and chromatographical characteristics of 2 - (2'-aryl - 1' - methyl) - ethyl - 4,4,6 - trimethyl - 5,6 - dihydro - 4H - 1,3 - oxazines obtained by benzylation ((X)-arylmethyl chloride) of 2 - ethyl - 4,4,6 - trimethyl - 5,6 - dihydro - 4H - 1,3 - oxazine

No.	X	b.p. (°C) (mm)	Retention time (min)†	Chromatographical yield (%)
1	H	73–74/0.01	11	64
2	*p*-OMe	120–126/0.5	17	68
3	*p*-t-Bu	90–92/0.01	19	37
4	*p*-Me	78–80/0.01	13	33
5	*m*-Me	84–85/0.01	13	31
6	*p*-F	83–87/0.01	11	47
7	*m*-OMe	105–114/0.3	16	51
8	*p*-Cl	98–101/0.2	15	58
9	*m*-F	86–89/0.2	12	50

†UCC column: 2 m × 1/4 in. Programme: 100–200° at 10°/min. Carrier gas: Nitrogen at 2 kg/cm^2. Instrument: Hewlett–Packard 5750.



Scheme 1.

On the basis of a pseudo first order approach for the rate equation, the relation of specific rate constants could be determined from the molar composition of the mixtures.

In order to elucidate the mechanism of the reaction these data were correlated with the Hammett[4] σ-values and gave a satisfactory linear correlation ($\rho = 2.2 \pm 0.2$; $r = 0.97$). However, this correlation was not so good when the Brown scale[5] was used. This allows us to suggest a S_N2 mechanism and to propose a transition state in which the functionalized C atom has a high degree of carbanionic character due to the hard nucleophilicity of the reagent (Fig. 1).

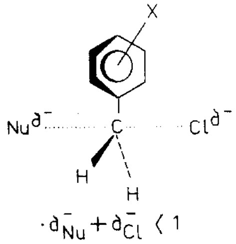


Fig. 1.

EXPERIMENTAL

2 - *Ethyl* - 4,4,6 - *trimethyl* - 5,6 - *dihydro* - 4H - 1,3 - *oxazine*. This compound was prepared according to the procedure described by Meyers[6] which is a modification of that of Ritter and Tillmans,[7] yield 52.5 g (57.4%); b.p. 86–94 (70 mm); IR (neat) 1660 cm^{-1}; NMR (Cl_4C) δ 1.00 (t, 3), 1.05 (s, 6), 1.15 (d, 3), 1.30 (m, 1), 1.65 (d, d, 1), 2.05 (q, 2), 3.90 (m, 1); MS (*m/e-%*): (245-48), (230-100), (131-43), (119-19), (91-64), (58-24).

General procedure for the preparation of arylmethyl chlorides

For the preparation of 3-methoxy, 4-methoxy and 4-t-butylphenylmethyl chlorides, the following general procedure was used.[8] The rest of the chlorides are commercially available. To a 100 ml flask equipped with an addition funnel, a refluxing system and a magnetic stirrer 18.86 g (0.072 mole) of triphenylphosphine and (0.062 mole) of arylmethyl carbinol were added. The mixture was warmed to 50° whereupon 12.32 g (0.080 mole) of CCl_4 was added. The mixture was refluxed for 30 min and distilled at reduced pressure, to give an intermediate fraction which could be identified as the corresponding aryl methyl chloride.

3-*Methoxyphenylmethyl chloride*. 7.40 g (78%); b.p. 48–50° (0.04 mm); IR (neat) 720, 1050, 1275 cm^{-1}; NMR (Cl_4C) δ 3.80 (s, 3), 4.50 (s, 2), 7.5–6.7 (m, 4).

4-*Methoxyphenylmethyl chloride*. 5.20 g (55%); b.p. 64–65° (0.01 mm); IR (neat) 735, 1035, 1250 cm^{-1}; NMR (Cl_4C) δ 3.70 (s, 3), 4.50 (s, 2), 6.7–7.2 (m, 4).

4-*t-Butylphenylmethyl chloride*. 9.81 g (90%); b.p. 60–61° (0.01 mm); IR (neat) 690, 1365, 1390 cm^{-1}; NMR (Cl_3CD) δ 1.20 (s, 9), 4.4 (s, 2), 7.1 (s, 4).

Preparation of 2 - (1′ - *lithium*) - *ethyl* - 4,4,6 - *trimethyl* - 5,6 - *dihydro* - 4H - 1,3 - *oxazine*. A 100 ml 3-necked flask equipped with a magnetic stirrer, a 30 ml addition funnel and a N_2 inlet tube was successively evacuated and flushed with N_2. Anhyd THF (26 ml) and 4 g (0.026 mole) of 2 - ethyl - 4,4,6 - trimethyl - 5,6 - dihydro - 4H - 1,3 - oxazine were added. The stirred soln was cooled to −78° (dry ice–acetone bath) and 17.44 ml (0.029 mole) of n-BuLi soln 1.6 M in hexane were added dropwise over a period of 15 min. Then the mixture was kept stirring at −78° for 30 min. In these conditions, the metalated oxazine did not precipitate, and the dark orange soln was used for a subsequent benzylation.

General procedure for the benzylation of metalated oxazine

The electrophile (0.029 mole of arylmethyl chloride), dissolved in 10 ml of THF, was slowly added to the anion soln keeping the temp. below −78°. Once the addition was complete, the mixture was stirred for 3 hr, until the soln was almost colourless. Then the mixture was allowed to slowly warm to room temp. The mixture was then poured into ice-water and acidified (pH 2–3) with 9N HCl. The acidic soln was extracted with three 25 ml portions of ligroine (discarded) and brought to pH ≈ 9–10 by careful addition of 40% NaOHaq. Ice was added to keep the mixture cool during the neutralization. The resulting oil was extracted with three 25 ml portions of ether and the ether extracts were dried over K_2CO_3. The ether was removed by rotatory evaporation to give the crude benzylated dihydro - 1,3 - oxazine (DHO-X) (31-68%):

(DHO-4-OMe). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.65–1.37 (m, 13), 1.53 (d.d, 1), 2.50 (m, 3), 3.57 (s, 3), 3.75 (m, 1), 6.65 (m, 4); MS (*m/e-%*): (275-34), (260-100), (161-80), (121-56.5), (58-9.5).

(DHO-4-t-Bu). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.85–1.30 (m, 13), 1.25 (s, 9), 1.55 (d.d, 1), 2.50 (m, 3), 3.80 (m, 1), 6.90 (m, 4); MS (*m/e-%*): (301-30), (286-100), (187-40), (147-21), (58-29).

(DHO-4-Me). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.80–1.45 (m, 13), 1.60 (d.d, 1), 2.20 (s, 3), 2.50 (m, 3), 3.95 (m, 1), 6.80 (s, 4); MS (*m/e-%*): (259-36.4), (244-100), (145-78), (133-12), (105-63), (58-20.5).

(DHO-3-Me). IR (neat) 1670 cm^{-1}; RMN (Cl_4C) δ 0.90–1.40 (m, 13), 1.60 (d.d, 1), 2.30 (s, 3), 2.60 (m, 3), 3.90 (m, 1), 6.90 (q, 4); MS (*m/e-%*): (259-40), (244-100), (145-68), (133-13), (105-60), (58-21).

(DHO-4-F). IR (neat 1660 cm^{-1}; RMN (Cl_4C) δ 0.80–1.42 (m, 13), 1.57 (d.d, 1), 2.57 (m, 3), 3.90 (m, 1), 6.80 (m, 4); MS (*m/e-%*): (263-40), (248-100), (149-56), (137-23), (109-85), (58-97).

(DHO-3-OMe). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.70–1.40 (m, 13), 1.57 (d.d, 1), 2.57 (m, 3), 3.63 (s, 3), 3.77 (m, 1), 6.70 (m, 4); MS (*m/e-%*): (275-33), (260-96), (161-100), (121-56), (58-33).

(DHO-4-Cl). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.73–1.42 (m, 13), 1.58 (d.d, 1), 2.57 (m, 3), 3.85 (m, 1), 6.92 (s, 4); MS (*m/e-%*): (279-32), (264-100), (165-51), (125-78), (58-78).

(DHO-3-F). IR (neat) 1665 cm^{-1}; RMN (Cl_4C) δ 0.70–1.35 (m, 13), 1.53 (d.d, 1), 2.55 (m, 3), 3.80 (m, 1), 6.70 (m, 4); MS (*m/e-%*): (263-45.5), (248-100), (149-38), (137-31), (109-100), (58-88).

Determination of relative specific rate constants

Preparation of metalated oxazine. In a flask equipped with a magnetic stirrer, 1.55 g (0.010 mole) of freshly distilled oxazine and 0.155 g of biphenyl (internal standard) were introduced. Over this mixture, THF was distilled under N_2 to a total volume of 13.76 ml. This mixture was cooled to −78° by means of a dry ice–acetone bath, and it was kept stirring at this temp., under N_2, for 30 min. Then, 6.24 ml (0.010 mole) of a 1.6 M n-BuLi soln in n-hexane were added dropwise. Once the addition was complete, the mixture was kept stirring at −78° for 30 min to complete the formation of the carbanion.

Competitive benzylation. A 3-necked flask equipped with a magnetic stirrer and a N_2 inlet tube was charged with 5.69 g (0.045 mole) of benzyl chloride and (0.045 mole) of arylmethyl chloride. Over this mixture of halogenated derivatives, THF was distilled under N_2 up to a total volume of 90 ml. The mixture was stirred at −78°, under N_2 for 30 min. Whereupon, the soln mentioned above was poured. The mixture was stirred for 5 min and then 10 ml water were added in order to quench the reaction. The crude product was dissolved in 500 ml ether, dried over K_2CO_3, and evaporated to dryness *in vacuo*. The samples thus obtained were analyzed by glc (trimethylolpropanotripelargonate column: 3 m × 1/4 in. Col. temp. = 190°). In all the cases, the conversion in benzylation products was below 20% evaluated over biphenyl.

Analysis method of the reaction mixtures. The mixtures were analyzed by mass spectrometry† by means of an interpolation in the calibration plots obtained from the analysis of sinthetic samples prepared from mixtures of pure oxazines. To make sure that the results are not dependent on the different volatility of the components of the reaction mixtures, these, as well as the model substances, were injected in the spectrometer through a gas chromatograph.‡ A hollow stainless steel column (30 cm long ϕ

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†Mass Spectrometer 5930A—Hewlett Packard. Emission 70 eV. T^{a}I.F.: 180°.

‡Gas Chromatograph 5710A—Hewlett Packard.

1/8 in.) was used at a temp. of 290° and helium as carrier gas at 100 ml/min. To minimize the errors, six to eight spectra of each sample were recorded (six for each calibration). The least squares method provided, in every case, excellent correlation coefficients ($r = 0.99$–1.00), when % DHO(X)/% DHO(H) was represented vs the intensity ratio of the corresponding molecular peaks. The percentages of each of the oxazines are summarized in Table 2.

Table 2. Intensity ratio of the molecular peaks: $M^{+\cdot}_{DHO(X)}/M^{+\cdot}_{DHO(H)}$† and composition of the mixtures of the competitive benzylation of metalated oxazines

No.	X	$M^{+\cdot}_{DHO(X)}/M^{+\cdot}_{DHO(H)}$	% DHO(X)
1	*p*-OMe	0.53 ± 0.09	19 ± 3
2	*p*-t-Bu	0.58 ± 0.13	35 ± 5
3	*p*-Me	1.36 ± 0.10	34 ± 3
4	*m*-Me	1.46 ± 0.06	36 ± 2
5	*p*-F	0.61 ± 0.09	68 ± 2
6	*m*-OMe	0.17 ± 0.02	62 ± 2
7‡	*p*-Cl	0.19 ± 0.03	82 ± 6
8	*m*-F	0.38 ± 0.02	82 ± 2

†DHO(X) is *m*- or *p*-substituted benzyl oxazine and DHO(H) is benzyl oxazine.

‡It was confirmed that the same results were obtained by using the intensity ratio of the molecular peaks corresponding to ^{35}Cl than by the ratio corresponding to the addition of intensities of the molecular peaks of the ^{35}Cl and ^{37}Cl isotopes.

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