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ENE REACTION OF THE ACTIVE >C=N- AND >C=O GROUP WITH KETONES. A NOVEL SYNTHESIS OF δ-OXO-α-AMINO- AND δ-OXO-α-HYDROXY-ACIDS.

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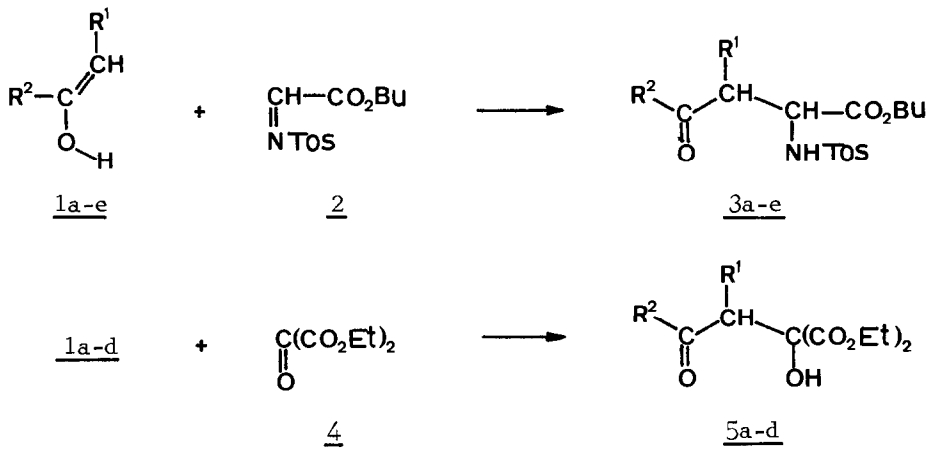
Summary: Thermal reaction of butyl N-(p-toluenesulphonyl)iminoacetate and diethyl mesoxalate with ketones leads to the derivatives of δ-oxo-α-amino-acids and δ-oxo-α-hydroxy--acids, respectively.

Recent theoretical interest[2] in the ene reaction[3], stimulated by the concept of the pericyclic reactions, was accompanied by the rapid development of its synthetic applications[4,5]. Since enophilic activity is exhibited by different types of electron-deficient multiple bonds (C=C, C≡C, C=O, N=N, C=N, etc.) the ene addition can lead to compounds with diverse structures. Moreover it can be performed often in highly stereoselective fashion, particularly for the intramolecular[4] or catalyzed[5] reactions. Usually ene reaction involves the addition of an enophile to an alkene (ene) with allylic hydrogen atom: C=C-C-H. The cases in which an enol C=C-O-H of an aldehyde or ketone undergoes intermolecular ene addition are few. Apart from the numerous examples of the intramolecular cyclization of unsaturated ketones[6] so far only four enophiles were found to react with carbonyl compounds according to the ene addition. They comprise three very active heteroenophiles: diethyl azodicarboxylate[7], carbonyl cyanide[8], N-sulphinylperfluorobutylsulphonamide[9] and dimethyl acetylenedicarboxylate[10]. The latter reacted in fact with stable enol and cis configuration of the product (substituted dimethyl malate) indicated concerted ene mechanism for this addition.

The search for other enophiles capable of addition with ketones should extend the scope of ene reaction and expand its synthetic utility. We found that butyl N-(p-toluenesulphonyl)-iminoacetate (2) and diethyl mesoxalate (4) readily undergo reaction with ketones yielding derivatives of δ-oxo-α-amino- (3) and δ-oxoalkyltartronic acid (5), respectively.

Thermal (120°C), uncatalyzed reaction of each enophile (2 and 4) with acetone, ethyl acetoacetate, cyclohexanone, acetophenone and p-nitroacetophenone gave adducts 3a-e and 5a-e, respectively, in high (69-91%) isolated yields. Adducts of iminoacetate 2 with ethyl acetoacetate (3b) and cyclohexanone (3c) each comprised two components (^{1}H NMR, TLC). In case of adduct 3c resulting diastereoisomers were separated by column chromatography and characterized individually.

The structure of compounds 3a-e and 5a-e followed from their analytical and spectral



1a-e 2 3a-e

1a-d 4 5a-d

a: R^1=H, R^2=CH_3 b: R^1=CO_2Et, R^2=CH_3 c: $R^1 + R^2$= $(-CH_2-)_4$

d: R^1=H, R^2=C_6H_5 e: R^1=H, R^2=p-$C_6H_4NO_2$

SCHEME

data. In their IR spectra (Table 1) appeared bands of an ester and a ketone carbonyl group as well as bands of sulphonylamide (3a-e) and hydroxyl group (5a-d). In the ^{1}H NMR spectra the signals corresponding to all the protons of the substituted starting ketone and diethyl tartronate or butyl N-(p-toluenesulphonyl)glycinate moieties could be unequivocally assigned (Table 2).

Obtention of adducts 3a-e and 5a-d could be interpreted as an ene reaction of enols 1a-e with iminoacetate 2 and diethyl mesoxalate 4, respectively, as shown on Scheme. Formation of approximately equal amounts of diastereoisomers of 3b and 3c (^{1}H NMR) reflects the lack of decided preference for exo or endo addition in the reaction of cyclohexanone or ethyl acetoacetate with iminoacetate 2. This observation is in accord with stereochemical results of other uncatalyzed ene reactions[11]. The foregoing ene addition in case of butyl N-(p-toluenesulphonyl)iminoacetate 2 opens a convenient route to δ-oxo-α-amino-acids, a type of compounds occuring among natural products[12], whereas adducts of diethyl mesoxalate with ketones: δ-oxoalkyltartronates, could be readily transformed by hydrolysis and subsequent decarboxylation[13] into corresponding δ-oxo-α-hydroxyacids.

General procedure.

Butyl N-(p-toluenesulphonyl)iminoacetate[14] (2) or diethyl mesoxalate[15] (4) and 1.5 molar equivalent of a ketone were heated in a sealed tube for 5 hours at 120°C. Then excess of a ketone (except for p-nitroacetophenone which was removed by column chromatography) was evaporated and the residue filtered in benzene solution through short silica gel (Merck 60, 230-400 mesh) column and evaporated again. Adducts 3a,c,d and e were purified by crystallization (from benzene-hexane 1:5 mixture) and 5a-d by distillation. Their yields,

b.p's or m.p's and IR spectra are collected in Table 1 and ^{1}H NMR data in Table 2. All new compounds gave correct C,H,N elemental analyses.

TABLE 1

Compound	Yield (%)	M.p.(°C) (B.p. [°C/Torr])	IR[a]: ν_{max} (cm^{-1}) NH(OH)	C=O(ester)	C=O(ketone)	SO_2
3a	81	86	3320	1735	1710	1345, 1165
3b	89	thick oil[b]	3320	1740	1720sh	1340, 1160
3c[c]	78	87 84	3300 3300	1740 1730sh	1700 1705	1335, 1160 1335, 1160
3d	91	87	3300	1740	1680	1345, 1160
3e	71	106	3350	1730	1685	1330, 1160
5a	91	(120/0.4)	(3500)	1740	d	-
5b	87	(135/0.4)	(3500)	1740	d	-
5c	88	(145/0.4)	(3500)	1730	1710sh	-
5d	69	(140/10^{-3})	(3500)	1740	1690	-

a. The IR spectra were obtained on Unicam SP-200 using KBr discs for solids and films for liquids. b. Analytical sample was obtained by column chromatography on silica gel and evaporation in high vacuum. c. Separate data for each diastereoisomer. d. Covered by strong band of an ester carbonyl group.

TABLE 2

Chemical shifts[a] and coupling constants for adducts[b] 3a-e and 5a-d

3a: δ 5.69 (d, 1H, $J_{NH,2}$=8 Hz, NH); 4.06 (dt, 1H, $J_{NH,2}$=8, $J_{2,3}$=4.8 Hz, -N-CH-); 3.06 (AB part of ABX system, 2H, -COCH$_2$-); 2.18 (s, 3H, -COCH$_3$).

3b: δ 5.77 (bd, 1H, $J_{NH,2}\approx$8.8 Hz, NH); 4.54 (dd, 1H[c], $J_{NH,2}$=9.1, $J_{2,3}$=4.3 Hz, -N-CH-) and 4.48 (dd, 1H[c], $J_{NH,2}$=8.3, $J_{2,3}$=4.2 Hz, -N-CH-); 4.20 (m, 2H, -OCH$_2$-); 2.28 (s, 3H[c], -COCH$_3$) and 2.27 (s, 3H[c], -COCH$_3$); 1.25 (t, 3H, -CH$_2$-CH$_3$).

3c[d]: δ 5.49 (d, 1H, $J_{NH,2}\approx$9.6 Hz, NH); 3.73 (dd, 1H, $J_{NH,2}$=9.6, $J_{2,3}$=4.3 Hz, -N-CH-); 3.15 (m, 1H) and 2.5-1.55 (m, 8H, cyclohexyl);
5.58 (d, 1H, $J_{NH,2}$= 8.5 Hz, NH); 3.88-3.76 (m, 1H, -N-CH-); 2.80 (m, 1H) and 2.46-1.50 (m, 8H, cyclohexyl).

3d: δ 7.90-7.20 (m, 5H, phenyl); 5.84 (d, 1H, $J_{NH,2}$=8.0 Hz, NH); 4.29 (dt, 1H, $J_{NH,2}$= 8.0, $J_{2,3}$=4.6 Hz. -N-CH-); 3.61 (d, 2H, $J_{2,3}$=4.5 Hz, -COCH$_2$-).

3e: δ 8.40-7.95 (m, 4H, p-NO$_2$-phenyl); 5.81 (d, 1H, $J_{NH,2}$=7.5 Hz, NH); 4.39 (dt, 1H,

$J_{NH,2}$=7.5, $J_{2,3}$=4.3 Hz, -N-C<u>H</u>-); 3.67 (d, 2H, $J_{2,3}$=4.3 Hz, -COC<u>H</u>$_2$-).

5a: δ 3.29 (s, 2H, -COC<u>H</u>$_2$-); 2.19 (s, 3H, -COC<u>H</u>$_3$).

5b: δ 4.58 (s, 1H, -COC<u>H</u>-); 3.26 (q, 2H, J=7.1 Hz, -OC<u>H</u>$_2$-); 2.32 (s, 3H, -COC<u>H</u>$_3$); 1.32 (t, 3H, J=7.1 Hz, -CH$_2$-C<u>H</u>$_3$).

5c: δ 3.65-3.35 (m, 1H, -COC<u>H</u>-); 2.55-2.25 (m, 2H, -COC<u>H</u>$_2$-); 2.20-1.50 (m, 6H, cyclohexyl).

5d: δ 8.05-7.34 (m, 5H, phenyl); 3.84 (s, 2H, -COC<u>H</u>$_2$-).

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a. The ^{1}H NMR spectra were measured on Jeol JNM-4H-100 spectrometer at 100 MHz in $CDCl_3$ solutions and chemical shifts are reported in δ scale (ppm downfield from internal TMS. b. Signals corresponding to the protons of -SO_2-C_6H_4-CH_3-p, -$CO_2C_4H_9$ and $(CO_2CH_2CH_3)_2$ groups in all adducts were analogous and appeared in the similar range; e.g. for adduct 3a: 7.9 and 7.2 (m, 4H, C_6<u>H</u>$_4$); 3.96 (t, 2H, J=6.75 Hz, -OC<u>H</u>$_2$-); 2.48 (s, 3H, C<u>H</u>$_3$-Ar); 1.62-1.03 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$-); 0.86 (t, 3H, J=6.75 Hz, -[CH$_2$]$_3$-C<u>H</u>$_3$); for adduct 5a: 4.26 (q, 4H, J=7.0 Hz, 2^x-OC<u>H</u>$_2$-); 4.10 (s, 1H, O<u>H</u>); 1.27 (t, 6H, 2^xC<u>H</u>$_3$). c. Separate signals for each diastereoisomer. d. Pair of diastereoisomers for which the relative configuration of chiral centers was not assigned.

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