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DECARBALKOXYLATIONS OF GEMINAL DIESTERS AND β-KETO ESTERS IN WET DIMETHYL SULFOXIDE. EFFECT OF ADDED SODIUM CHLORIDE ON THE DECARBALKOXYLATION RATES OF MONO- AND DI-SUBSTITUTED MALONATE ESTERS

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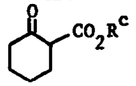
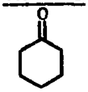
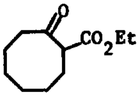
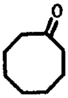
Recently Krapcho and Lovey have reported that geminal diesters, β-keto esters and α-cyano esters undergo decarbalkoxylations when heated with sodium chloride in wet dimethyl sulfoxide at temperatures of 140-185° (1). We now wish to report further experiments addressed to the question of whether added NaCl is necessary in this reaction or whether water alone is sufficient to effect the decarbalkoxylation process. The substrates investigated along with the experimental conditions and results are tabulated in Table I.

Let us examine some of the pertinent results which can be found in the Table. The decarbalkoxylations of 2-carbalkoxycyclohexanone (entry 1, mixed methyl and ethyl esters) and 2-carbethoxycyclooctanone (entry 2) proceed readily in DMSO-H_2O. After 3 hrs of heating good yields of cyclohexanone and cyclooctanone can be isolated. The decarbalkoxylation of 2-carbalkoxycyclohexanone also occurs in DMF-H_2O although at a slower rate than in DMSO-H_2O. This presumably merely reflects the lower reaction temperature attainable in the DMF-H_2O medium.

Diethyl phenylmalonate (entry 3) on heating in DMSO-H_2O undergoes a facile decarbethoxylation to produce ethyl phenylacetate in an excellent yield. In order to assess the effect of added NaCl on the decarbethoxylation of this diester duplicate runs were performed simultaneously in the presence and absence of NaCl. The progress of the reaction was monitored by nmr analysis and the reaction proceeds at nearly the same rate in the two runs. In this case the presence of NaCl has practically no effect on the decarbethoxylation rate.

TABLE I

DECARBALKOXYLATIONS OF β-KETO ESTERS AND MALONATE ESTERS

REACTANT	PRODUCT	REACTION MEDIA[a]	TEMP (HRS)[b]	% YIELD
		$DMF-H_2O^{d, e}$	134-135 (3)	$64^{f, g}$
		$DMSO-H_2O^{d, e}$	155-156 (3)	87^{f}
		$DMSO-H_2O^{d, h}$	162-162 (3.2)	70^{f}
$PhCH(CO_2Et)_2$	$PhCH_2CO_2Et$	$DMSO-H_2O^{d, e, i}$	163-160 (3)	90^{f}
		$DMSO-H_2O-NaCl^{e, i, j}$	163-160 (3)	90^{f}
$MeCH(CO_2Et)_2$	$MeCH_2CO_2Et$	$DMSO-H_2O^{h, k}$	167-? (3)	32^{l}
		$DMSO-H_2O-NaCl^{h, m}$	165-? (2)	56^{l}
$EtCH(CO_2Et)_2$	$EtCH_2CO_2Et$	$DMSO^{h, n}$	183-185 (11)	$5^{l, o}$
		$DMSO-H_2O^{d, h}$	163-150 (15)	80^{l}
		$N,NDMA-H_2O^{d, h}$	140-137 (17)	$30^{l, p}$
		$DMSO-H_2O^{d, e}$	164-162 (3)	19^{l}
		$DMSO-H_2O-NaCl^{e, j}$	161-155 (3)	74^{l}
$(Me)_2C(CO_2Et)_2$	$(Me)_2CHCO_2Et$	$DMSO-H_2O^{h, q}$	176-176 (5.2)	$-^{r}$
		$DMSO-H_2O-NaCl^{h, s}$	176-164 (5.2)	$65^{l, t}$

[a] All runs were performed in flasks fitted with a reflux condenser and a gas bubbler. In most runs the flask was also equipped with an internal thermometer.

[b] The first temperature is the maximum internal temperature at refluxing at the beginning of the reaction while the second temperature is the temperature at the end of the run. The total reaction time is the time in hrs commencing when heating was begun.

[c] Arapahoe Chemicals sample which by nmr analysis contains 35% methyl and 65% ethyl ester.

[d] 0.03 moles of substrate and 0.06 moles of water in 25 mls of dry solvent.

[e] Done simultaneously in a common oil bath maintained at 190-205°.

[f] The product was isolated by addition of cold water, extraction with pentane and concentration of the pentane. Product identification was done by nmr and/or ir comparisons and in some cases by vpc comparisons. Yields are based on isolated product.

[g] Nmr analysis indicated the presence of about 20% starting material.

[h] Heated to refluxing with a heating mantle.

[i] The course of the reaction was monitored by nmr. The aromatic protons of the diester and the product mono ester exhibited singlets at different field positions in the DMSO. In both runs 80%, 92%, and nearly quantitative product formation was found after 1, 2, and 3 hrs, respectively.

[j] 0.03 moles of substrate, 0.06 moles of water, and 0.03 moles of NaCl in 25 mls of solvent. The reaction mixture remained heterogeneous since not all the salt dissolved.

[k] 0.05 moles of substrate and 0.10 moles of water in 50 mls of DMSO (Fisher, undistilled).

[l] Low boiling material was distilled from the reaction pot, washed with water and isolated.

[m] As in k except 0.005 moles of NaCl added. Insoluble salt remains during the course of the reaction.

[n] 0.03 moles of diester in 25 mls of dry DMSO.

[o] Over 80% starting diester could be isolated by adding cold water to the pot residue.

[p] As in o to yield 50% starting diester.

[q] 0.015 moles of diester and 0.03 moles of water in 25 mls of dry DMSO.

[r] The low boiling material which steam distilled from the reaction mixtures was identified as starting material by nmr analysis. Quenching the reaction pot with water followed by pentane extration led to recovered starting material (90% recovery). No mono ester could be detected. A separate run done over a 12 hr period yielded only starting material.

[s] As in q except 0.015 moles of NaCl was added. The reaction mixture was heterogeneous.

[t] About 30% starting diester could be recovered from the pot residue by quenching with water and extracting with pentane.

The decarbethoxylation of diethyl methylmalonate (entry 4) was found to proceed about 3 times faster in DMSO-H_2O-NaCl than in DMSO-H_2O. In the former case a 10 to 1 molar ratio of diester to NaCl was utilized in the reaction.

Diethyl ethylmalonate (entry 5) was studied under a variety of conditions. Refluxing this diester in dry DMSO led to about 5% ethyl butyrate (from traces of water present in the DMSO or from water formed in the decomposition of DMSO). An 80% yield of ethyl butyrate could be isolated when this diester was heated in DMSO-H_2O (15 hrs, 160°). Decarbethoxylation of this diester also occurred on refluxing in N,N-dimethylacetamide-H_2O. Duplicate runs done in DMSO-H_2O and in DMSO-H_2O-NaCl (equal molar amounts of diester and NaCl) gave 19 and 74% yields of ethyl butyrate, respectively. In this diester the NaCl accelerates the rate of ester formation by about a factor of 4.

The decarbethoxylation of diethyl dimethylmalonate (entry 6) does not occur in DMSO-H_2O to any detectable extent (nmr). However, in refluxing DMSO-H_2O-NaCl a 65% yield of ethyl isobutyrate can be isolated after 5.2 hrs. The effect of added NaCl on the decarbethoxylation of this substrate is quite dramatic. It might also be noted that in order to reach higher internal temperatures in DMSO-H_2O-NaCl the reaction mixture was 0.6M in diester (1.2M in water) in this case while in the other monosubstituted malonate esters the reactions were about 1.2-2M in diester (2.4-4M in water).

Certain reactive substrates undergo facile decarbethoxylations when heated in DMSO-H_2O (and other dipolar aprotic solvents) while in other less reactive substrates the presence of NaCl in the DMSO-H_2O accelerates product formation. One might be tempted to speculate that H_2O attacks the carbonyl group of the diester and this is followed by elimination to form ethyl carbonate (decomposition to CO_2 and EtOH) and a carbanion (see reference 1). In the runs containing H_2O and NaCl perhaps we are dealing with competing reactions, the relative importance of which depends on 1) substrate reactivity and 2) reactivity of the attacking nucleophile ($Cl^- > H_2O$). With a relatively reactive substrate such as diethyl phenylmalonate the rate of reaction with H_2O is fast enough so that addition of Cl^- has little effect on the reaction rate at the temperatures used. Less reactive substrates (mono- and dialkyl substituted malonate esters) are able to discriminate between H_2O and Cl^- and the presence of this anion has a progressively more marked accelerating effect. Note that diethyl dimethylmalonate leads to practically no reaction in DMSO-H_2O. We also wish to emphasize that all the runs done with NaCl were heterogeneous. Clearly further studies to examine possible surface catalysis effects must be performed. Additional experiments must surely be performed to probe more deeply into the actual mechanism of this "hydrolysis-decarboxylation" process.

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REFERENCE

1. A. P. Krapcho and A. J. Lovey, *Tetrahedron Letters*, 957 (1973).