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ALKYLATION REACTION ACCOMPANIED BY DEALKOXYCARBONYLATION OF β-KETO ESTERS, GEMINAL DIESTERS AND α-CYANO ESTER IN HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA)

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In the presence of alkali halide β-keto esters, geminal diesters and ethyl cyanoacetate in HMPA reacted with alkyl halides to give α-alkylated ketones, esters and nitrile,respectively. α-Acetyl-γ-butyrolactone and its derivative afforded corresponding acylcyclopropane derivatives.

Recently Krapcho and Louey reported that geminal diesters, β-keto esters and α-cyano esters undergo dealkoxycarbonylations when heated with sodium chloride in wet dimethyl sulfoxide at temperatures of 140-186°C.[1] The dealkoxycarbonylation reaction was thought to proceed through a carbanion.

The present work was undertaken in order to utilize the intermediate carbanion for synthetic purpose[2], since the carbanion was formed under almost neutral conditions.

Diethyl malonate (1) (1.2 mmol), LiCl (1.1 mmol) and benzyl bromide (2) (1 mmol) in HMPA were heated at 160°C for 1 hr. After cooling to room temperature, the reaction mixture was poured into water and extracted with ether. From the organic layer, the mixture of ethyl hydrocinnamate (3) and ethyl α-benzylhydrocinnamate (4) were obtained by using preparative thin layer chromatography (TLC). The yields of the products were determined by GLC [(3), 51% and (4), 26%, based on benzyl bromide], and the pure products were obtained by bulb to bulb distillation.

$$\underset{(1)}{\mathrm{CH_2(COOEt)_2}} \quad + \quad \underset{(2)}{\mathrm{PhCH_2Br}} \quad \xrightarrow[\text{HMPA}]{\text{LiCl}} \quad \underset{(3)}{\mathrm{PhCH_2CH_2COOEt}} \quad + \quad \underset{(4)}{\mathrm{(PhCH_2)_2CHCOOEt}}$$

When dimethyl sulfoxide or sulfolane was used as a solvent in the above experiment, decrease of the rate of dealkoxycarbonylation was observed. Therefore HMPA was used as a solvent. As for the catalyst, LiBr, NaCl, KCl, tetraethylammonium bromide and cetyltrimethylammonium chloride were examined, but in these cases, the yields of (3) and (4) were very poor, and moreover, the products were contaminated with more than ten of unidentified by-products. Then, the effects of the reaction temperature and molar ratio of the reactants were examined and the results are shown in Table 1. The results show that the higher reaction temperature or the more excess of diethyl malonate provides the higher yield of ethyl hydrocinnamate.

Table 1. The effect of reaction temperature and the molar ratio of reactants.

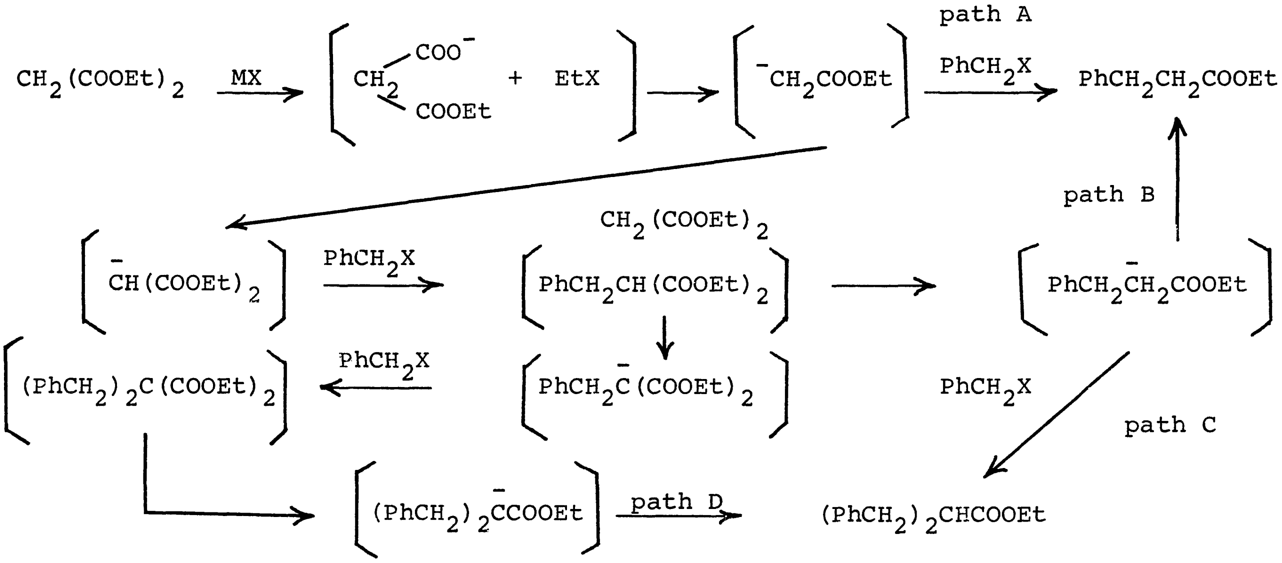
molar ratio			reaction conditions		yield(%)(a)	
$CH_2(COOEt)_2$	$PhCH_2Br$	LiCl	Temp.(°C)	Time(hr)	(3)	(4)
1.2	1	1.1	140	2	23	30
1.2	1	1.1	150	1	38	42
1.2	1	1.1	160	1	51	26
2.0	1	1.1	160	1	60	14(b)

(a) Yields were based on benzyl bromide.

(b) Ethyl α-benzylbutyrate was also isolated in 13% yield by TLC.

The formation of ethyl hydrocinnamate (3) and α-benzylhydrocinnamate (4) may be accounted for in terms of alternative pathways for each of the products (path A and path B for (3) and path C and path D for (4)), but it is not clear which path is predominant.

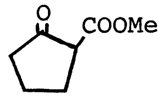
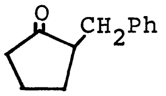
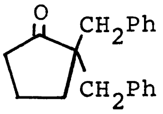
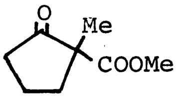
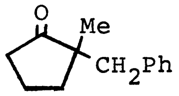
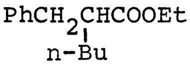
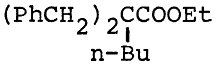
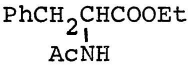
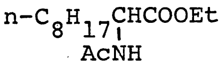
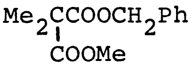
Scheme (I).



When n-octyl bromide reacted with diethyl malonate under the same reaction conditions, GLC of the products indicated that two by-products were produced along with the mono- and di-alkylated products. From the NMR data of the mixture of the products, the by-products seem to be n-octyl acetate and n-octyl decanoate. These ester exchanged products may be formed by the reaction of intermediate carboxylate anion with n-octyl bromide. When dimethyl malonate reacted with benzyl bromide, the expected products were contaminated with at least three by-products, two of which were confirmed to be benzyl acetate and benzyl hydrocinnamate.

Next, alkylation of ethyl cyanoacetate, β-keto esters and substituted malonic diesters were tried and the results were listed in Table 2. It is notable that when α-mono substituted malonate was used, mono-alkylated products were successfully obtained even in the cases of α-amino acid derivatives. According to this procedure, above products were obtained in one operation under almost neutral conditions, but known procedure requires three operations, namely, alkylation under basic conditions, acid or base catalyzed hydrolysis and decarboxylation.

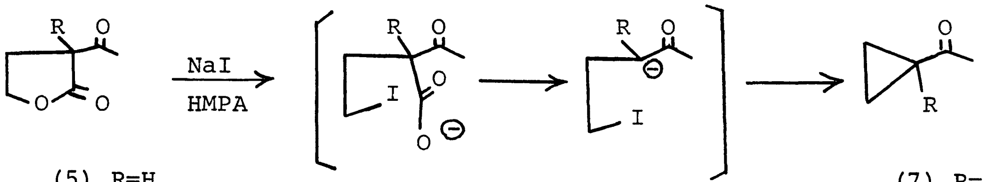
Table 2. Alkylations of geminal diesters, β-keto esters and ethyl cyanoacetate.

Ester	Alkyl halide	Reaction conditions$^{a)}$		Products$^{b)}$			
		Temp.(°C)	Time(hr)				
$NCCH_2COOEt$	$PhCH_2Br$	140	2.0	$PhCH_2CH_2CN$	15%	$(PhCH_2)_2CHCN$	52%
$NCCH_2COOEt$	$PhCH_2Br$	160	1.0	$PhCH_2CH_2CN$	30%	$(PhCH_2)_2CHCN$	64%
$NCCH_2COOEt$	$n\text{-}C_8H_{17}Br$	160	1.0	$n\text{-}C_8H_{17}CN$	16%	$(n\text{-}C_8H_{17})_2CHCN$	4%
CH_3COCH_2COOEt	$PhCH_2Br$	160	1.5	$PhCH_2CH_2COCH_3$	24%		
	$PhCH_2Br$	160	0.33		47%		10%
	$PhCH_2Br$	160	0.25		35%		
$n\text{-}BuCH(COOEt)_2$	$PhCH_2Br$	155	1.5	 $PhCH_2\underset{n\text{-}Bu}{CH}COOEt$	71%	 $(PhCH_2)_2\underset{n\text{-}Bu}{C}COOEt$	10%$^{c)}$
$AcNHCH(COOEt)_2$	$PhCH_2Br$	150	1.0	 $PhCH_2\underset{AcNH}{CH}COOEt$	52%		
$AcNHCH(COOEt)_2$	$n\text{-}C_8H_{17}Br$	160	1.0	 $n\text{-}C_8H_{17}\underset{AcNH}{CH}COOEt$	22%		
$Me_2C(COOMe)_2$	$PhCH_2Br$	155	1.0	 $Me_2\underset{COOMe}{C}COOCH_2Ph$	30%	$Me_2C(COOCH_2Ph)_2$	18%$^{c)}$

a) LiCl was used as a catalyst. Molar ratio of [ester : alkyl halide : LiCl] is [1.2 : 1 : 1.1]. b) Products were isolated by using TLC and yields were based on alkyl halide. c) Products were isolated by bulb to bulb distillation.
The structures of products were confirmed by comparison with authentic samples, or by elemental analyses and spectral data.

As an example of the intramolecular alkylation reactions, α-acetyl-γ-butyrolactone (5) (50 mmol) and NaI (10 mmol) in HMPA (5 ml) were heated at 170°C for 1.5 hr. During the reaction the product, cyclopropyl methyl ketone (7) (86% b.p. 114°C), had been removed by distillation. When LiCl (10 mmol) was used as a catalyst and the reaction was carried out at 160-170°C for 2.5 hr, 42% of (7) was obtained. In a similar manner, when α-acetyl-α-methyl-γ-butyrolactone (6) (50 mmol) and NaI (20 mmol) were treated at temperature of 180°C for 1.5 hr, methyl 1-methylcyclopropyl ketone (8) (81%, b.p. 128-129°C) was obtained.

The reaction can be explained by considering an initial formation of γ-halo carboxylate (9) from α-acetyl-γ-butyrolactone by a nucleophilic attack of halide anion. The carboxylate (9) was then converted with a loss of carbon dioxide to a carbanion intermediate (10), which in turn underwent intramolecular cyclization.



(5) R=H
(6) R=Me

(9)

(10)

(7) R=H
(8) R=Me

It should be noted that, this procedure for the synthesis of acylcyclopropanes provides more convenient method than the reported one$^{3)}$ and affords higher yield of the product.

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REFERENCES

1) A. P. Krapcho and A. J. Louey, Tetrahedron Lett., 1973, 957.
2) While these dealkoxycarbonylations are now well known, at the best of our knowledge, only a few examples using the carbanion for synthetic purpose are reported.
a) G. A. Smith and D. H. Silliams, J. Chem. Soc. Perkin I, 1972, 2811.
b) E. S. Behare and R. B. Miller, Chem. Commun., 1970, 402.
3) a) G. N. Cannon, R. C. Ellis, and J. R. Leal, "Organic Syntheses", Coll. Vol, IV p. 597 (1967).
b) M. Julia, S. Julia, and Y. Noël, Bull. Soc. Chim. France, 1708 (1960).
4) S. Takei and Y. Kawano, Tetrahedron Lett., in press.

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