

The mixture was refluxed for four hours to complete the alkylation. The mixture was cooled and decomposed with acetic acid (30 ml.) and water. The organic layer was washed, dried and distilled. There were obtained 25 g. of diethyl butylethylmalonate, b. p. 124° (12 mm.),  $n_D^{20}$  1.4282 and 41 g. of a mixture of this ester and diethyl butylmalonate, b. p. 122–124° (12 mm.),  $n_D^{20}$  1.4250–1.4268. On the basis of refractive indices the yield of di-substituted ester was 34% and that of mono was 26%. Also, there was recovered 24 g. or 33% of the ethyl caproate. The diethyl butylethylmalonate was identified by hydrolyzing it to butylethylmalonic acid which melted at 116–118°.

**Dibutyl Butylcetylmalonate.**—Sodium (2.9 g.) reacted with butyl alcohol (125 ml.) and excess alcohol was vacuum distilled off until a mush containing some alcohol remained. The mixture was cooled and dibutyl carbonate (125 ml.) and dibutyl cetylmalonate (55 g.) were added. On stirring and warming to 90° the solid completely dissolved. The remaining excess alcohol and that produced by the formation of the enolate was removed by fractiona-

tion at 20 mm. The mixture was then stirred at atmospheric pressure and heated to a bath temperature of 200–210°. Within one-half hour the mixture had set to a solid mass. Heating was continued for four and one-half hours. The mixture was then cooled and acetic acid (8 ml.) and water were added. The organic layer was washed, dried and distilled. There was obtained 52 g. (83%) of dibutyl butylcetylmalonate, b. p. 265–268° (4 mm.),  $n_D^{20}$  1.4500. The ester was hydrolyzed with alcoholic sodium hydroxide and butylcetylmalonic acid, m. p. 96–98°, was obtained.

### Summary

A method is described for the successful use of alkyl carbonates as alkylating agents. It has been applied to a variety of mono-substituted malonic esters for the introduction of primary alkyl and benzyl groups. Several new malonic esters have been prepared.

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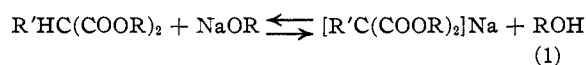
## Alkyl Carbonates in Synthetic Chemistry. V. Alkyl Carbonates as Solvents for Metalation and Alkylation Reactions<sup>1</sup>

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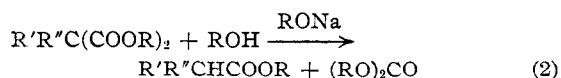
In an earlier paper<sup>2</sup> it was stated that alkyl carbonates are advantageous media for many organic reactions. The successful use of alkyl carbonates in the metalation and alkylation of a variety of malonic,  $\beta$ -keto and  $\alpha$ -cyano esters is reported in this paper. By this method, cleavage of a carbalkoxyl group by alcoholysis is avoided and the formation of the metal derivative may be forced substantially to completion.

The new procedure is particularly useful in preparing certain alkyl derivatives of malonic esters. Esters containing a highly branched substituent such as the *s*-butyl group, are very difficult to alkylate further by the ordinary procedure using sodium alcoholate in alcoholic solution. The failure of such esters to readily undergo further alkylation was first observed by Fisher and Dilthey<sup>3</sup> and later by Shonle,<sup>4</sup> and Cope<sup>5</sup> and their associates. As pointed out by previous investigators, this failure to alkylate when alcohol

is used as a reaction medium is probably due to the incomplete formation of the sodio derivative according to eq. (1).



Consequently, when such a reaction mixture is treated with an alkyl halide a large part of the reaction which takes place involves the sodium alkoxide and the alkyl halide. Furthermore, the original malonic ester or the desired alkylated product may be in part decarboxylated by alcoholysis under the conditions of the reaction as represented by eq. (2).



By substituting an alkyl carbonate for alcohol as a reaction medium, it is possible to complete the formation of the metal derivative (eq. 1) by distilling all alcohol from the reaction mixture. The metal derivative can then be treated with the alkylating agent with no fear of alcoholysis according to eq. 2.

We have used alkyl carbonates as media for the alkylation of representative members of the ma-

(1) Presented before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, September 9, 1941.

(2) Wallingford, Homeyer and Jones, *THIS JOURNAL*, **63**, 2056 (1941).

(3) Fisher and Dilthey, *Ann.*, **335**, 337 (1904).

(4) Shonle, Keltch and Swanson, *THIS JOURNAL*, **52**, 2440 (1930).

(5) Cope, Hartung, Hancock and Crossley, *ibid.*, **62**, 314 (1940).

TABLE I  
 ALKYLATION OF MALONIC ESTERS IN DIETHYL CARBONATE SOLUTION

RHC-(CO <sub>2</sub> Et) <sub>2</sub> R <sup>-</sup>	Alkyl halide	Metal deriv.	Hours heated	RR'C(CO <sub>2</sub> Et) <sub>2</sub> R <sup>-</sup>	Yield, %	B. p., °C. (mm.) (uncor.)	n <sub>D</sub> (t°)	Formula	Carbon, %		Hydrogen, %	
									Calcd.	Found	Calcd.	Found
Ethyl	EtI	Mg	25	Ethyl Ethyl	83	113-114 (18)	1.4240 (19.5)					
Ethyl	<i>i</i> -AmBr	Na	30	Ethyl <i>i</i> -Amyl	75	140-142 (20)	1.4290 (23.4)					
<i>n</i> -Butyl	<i>i</i> -AmBr	Na	14	<i>n</i> -Butyl <i>i</i> -Amyl <sup>a</sup>	78	91-93 (1.5)	1.4316 (23)	C <sub>16</sub> H <sub>30</sub> O <sub>4</sub>	67.15	66.69	10.47	10.38
<i>n</i> -Butyl	<i>s</i> -BuBr	Na	100	<i>n</i> -Butyl <i>s</i> -Butyl <sup>a</sup>	70	114-116 (4.5)	1.4339 (24.5)	C <sub>15</sub> H <sub>28</sub> O <sub>4</sub>	66.2	66.67	10.3	10.39
<i>s</i> -Butyl	<i>i</i> -AmBr	Na	135	<i>s</i> -Butyl <i>i</i> -Amyl <sup>a</sup>	75	95-99 (2-2.5)	1.4370 (20)	C <sub>15</sub> H <sub>28</sub> O <sub>4</sub>	67.15	67.17	10.47	10.29
<i>s</i> -Butyl	Allyl Br	Na	7	<i>s</i> -Butyl Allyl <sup>a</sup>	86	109-111 (5)	1.4430 (21)	C <sub>14</sub> H <sub>24</sub> O <sub>4</sub>	65.65	66.12	9.37	9.82
<i>s</i> -Butyl	<i>n</i> -AmBr	Na	8	<i>s</i> -Butyl <i>n</i> -Amyl <sup>a</sup>	84	89.5-92.5 (1-1.5)	1.4380 (20)	C <sub>15</sub> H <sub>28</sub> O <sub>4</sub>	67.15	67.19	10.47	10.39
<i>s</i> -Butyl	EtBr	Na	54	<i>s</i> -Butyl Ethyl	95	69-72 (1)	1.4331 (21)					
<i>s</i> -Butyl	<i>s</i> -BuBr	Na	130	<i>s</i> -Butyl <i>s</i> -Butyl <sup>a</sup>	15 <sup>b</sup>	94-98 (2)	1.4366-					
							1.4443 (21)					
<i>s</i> -Butyl <sup>c</sup>	<i>s</i> -BuBr	K <sup>d</sup>	52	<i>s</i> -Butyl <i>s</i> -Butyl <sup>a</sup>	25 <sup>e</sup>	112-114 (1.5)	1.4433 (26)	C <sub>15</sub> H <sub>28</sub> O <sub>4</sub>	69.5	69.25	10.98	10.84
<i>i</i> -Butyl	<i>i</i> -BuBr	Na	17	<i>i</i> -Butyl <i>i</i> -Butyl	76	138-142 (17)	1.4333 (22.5)					
<i>i</i> -Butyl	Allyl Br	Na	9	<i>i</i> -Butyl Allyl <sup>a</sup>	36 <sup>f</sup>	94-95.5 (3.5)						
<i>i</i> -Propyl	Allyl Br	Na	9	<i>i</i> -Propyl Allyl	84	126-127 (16)	1.4393 (23)					
<i>i</i> -Propyl	<i>i</i> -BuBr	Na	68	<i>i</i> -Propyl <i>i</i> -Butyl <sup>a</sup>	67	119-121 (10)	1.4352 (18)	C <sub>14</sub> H <sub>26</sub> O <sub>4</sub>	65.15	65.32	10.08	10.14
<i>i</i> -Propyl	<i>s</i> -BuBr	Na	39	<i>i</i> -Propyl <i>s</i> -Butyl <sup>a</sup>	26 <sup>b</sup>	120-123 (10)	1.4363-					
							1.4389 (21)					
<i>n</i> -Propyl	<i>n</i> -AmBr	Na	42	<i>n</i> -Propyl <i>n</i> -Amyl <sup>a</sup>	73	99-101 (2.6)	1.4323 (19)	C <sub>14</sub> H <sub>26</sub> O <sub>4</sub>	66.2	65.78	10.3	10.27
Phenyl	EtBr	Na	5	Phenyl Ethyl	79	135-145 (4-6)						
Phenyl	EtI	Mg	48	Phenyl Ethyl	65	126-130 (2-3)						
<i>p</i> -Tolyl	EtBr	Na	36	<i>p</i> -Tolyl Ethyl	80	116-117 (0.5)	1.4912 (25.6)	C <sub>16</sub> H <sub>20</sub> O <sub>4</sub>	69.1	68.63	7.92	7.97
Cetyl	C <sub>18</sub> H <sub>37</sub> Cl	K <sup>g</sup>	4	Cetyl Benzyl <sup>a,h</sup>	67	238-240 (1)	1.4712 (27)					
Allyl	<i>n</i> -BuBr	Na	2	Allyl <i>n</i> -Butyl	87	129-134 (11)	1.4378 (20)					

<sup>a</sup> New compound. <sup>b</sup> Alkylated product contaminated with by-products due to alkylating action of diethyl carbonate. <sup>c</sup> Di-*s*-butyl ester used instead of diethyl ester. <sup>d</sup> *s*-Butyl alcoholate and di-*s*-butyl carbonate used. <sup>e</sup> Making correction for recovered unalkylated ester, yield was 59%. <sup>f</sup> Making correction for recovered unalkylated ester, yield was 53%. <sup>g</sup> *n*-Butyl alcoholate and di-*n*-butyl carbonate used. <sup>h</sup> Identified by hydrolyzing to the malonic acid, decarboxylating to cetylbenzylacetic acid, m. p. 46-47° (uncor.), and converting latter to the 2,4,6-tribromoanilide, m. p. 85-87° (uncor.). *Anal.* Calcd. for C<sub>31</sub>H<sub>44</sub>ONBr<sub>3</sub>: Br, 35.0. Found: Br, 35.1.

 TABLE II  
 ALKYLATION OF ACETOACETIC ESTERS IN DIETHYL CARBONATE SOLUTION

CH <sub>3</sub> COCHRCO <sub>2</sub> Et R <sup>-</sup>	Alkyl halide	Metal deriv.	Hours heated	CH <sub>3</sub> COCRR'/CO <sub>2</sub> Et R <sup>-</sup>	Yield, %	B. p., °C. (mm.) (uncor.)	n <sub>D</sub> (t°)
H	<i>n</i> -BuBr	Na	29	H <i>n</i> -Butyl	58	108-109 (16)	1.4283 (20)
H	<i>i</i> -AmBr	Na	54	H <i>i</i> -Amyl	58	84- 86 (5)	1.4289 (21)
H	<i>s</i> -BuBr	Na	58	H <i>s</i> -Butyl	11	87- 89 (6)	1.4248 (28)
H	<i>n</i> -Hexyl Br	Na	49	H <i>n</i> -Hexyl	62	127-129 (10)	1.4317 (26)
<i>n</i> -Butyl	<i>n</i> -BuBr	Na	92	<i>n</i> -Butyl <i>n</i> -Butyl	49	78- 83 (0.5-1.0)	1.4368 (28)

 TABLE III  
 ETHYLATION OF β-KETO AND α-CYANO ESTERS IN DIALKYL CARBONATE SOLUTION

Ester	(RO) <sub>2</sub> CO R <sup>-</sup>	Alkyl halide	Metal deriv. <sup>a</sup>	Hours heated	α-Alkyl ester	Yield, %	B. p., °C. (mm.) (uncor.)	n <sub>D</sub> (t°)
<i>n</i> -Butyl benzoylacetate	<i>n</i> -Butyl	EtBr	K	49	<i>n</i> -Butyl α-ethyl-benzoyl-acetate <sup>b,e</sup>	80	116-117 (1)	1.5003 (26)
<i>n</i> -Propyl α-cyano-isocaproate	<i>n</i> -Propyl	EtBr	Na	5	<i>n</i> -Propyl α-ethyl-α-cyano-isocaproate <sup>b,d</sup>	78	64- 67 (1)	1.4298 (26)
Ethyl α-cyano- <i>p</i> -Me-phenylacetate	Ethyl	EtBr	Na	45	Ethyl α-ethyl-α-cyano- <i>p</i> -Me-phenylacetate <sup>b,e</sup>	60	105-110 (2.5-3)	1.4982 (27)
<i>n</i> -Propyl β-keto-pelargonate	<i>n</i> -Propyl	EtBr	K	18	<i>n</i> -Propyl α-ethyl-β-keto-pelargonate <sup>b,f</sup>	81	103-105 (3.5)	1.4355 (25)

<sup>a</sup> Prepared from alcoholate MOR in which R corresponded to that of the dialkyl carbonate used. <sup>b</sup> New compound. <sup>c</sup> Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>: C, 72.6. H, 8.06. Found: C, 72.0; H, 7.9. <sup>d</sup> Calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>2</sub>N: N, 6.64. Found: N, 6.54. <sup>e</sup> Calcd. for C<sub>14</sub>H<sub>17</sub>O<sub>2</sub>N: N, 6.06. Found: N, 6.28. <sup>f</sup> Calcd. for C<sub>14</sub>H<sub>23</sub>O<sub>3</sub>: C, 69.4. H, 10.7. Found: C, 69.8; H, 11.0.

ionic, β-keto and α-cyano ester series with the results summarized in the tables. Although many of these alkylations can be successfully accomplished in alcoholic solution, the advantages of alkyl carbonates as reaction media are evident in

a number of cases. Shonle, Keltch and Swanson were able to obtain only insignificant yields in attempting to introduce either the ethyl or allyl group into diethyl *s*-butylmalonate. Using diethyl carbonate as a reaction medium with ethyl

bromide and allyl bromide as the alkylating agents, we were able to obtain yields of 95 and 86%, respectively. The method has enabled us to obtain malonic esters containing two *s*-alkyl groups as substituents, a type hitherto impossible to prepare.

With complete formation of the metal derivative accomplished and the danger of alcoholysis eliminated, we were interested to discover what other factors might limit the alkylation. In our first attempts to introduce the *s*-butyl group into a malonic ester already containing one such group, a mixture of products was obtained which indicated that during the prolonged heating the diethyl carbonate used as a medium had exerted a slight but noticeable alkylating action.<sup>6</sup> This difficulty was overcome by using as a medium di-*s*-butyl carbonate, in which case any slight alkylation by the carbonate would also produce the desired product. Even under these conditions it will be noted from Table I that the yield of malonic ester containing two *s*-butyl groups was somewhat low. We believe that the limiting factor in this case is the tendency for the secondary bromide to split out hydrogen bromide. This conclusion is substantiated by experiments designed to introduce the *t*-butyl group into malonic ester. Negligible yields with either *t*-butyl chloride or bromide were obtained and isobutylene was collected and identified as the principal by-product.

### Experimental

**General Procedure.**—Sodium (or potassium) alcoholate was prepared by dissolving the clean metal in an excess of anhydrous alcohol in a 3-necked flask and distilling to dryness at reduced pressure. An equimolar quantity of the ester and an excess of alkyl carbonate (4–6 mols) were then added to the cooled solid and the mixture stirred at room temperature until the alcoholate was completely in solution. The reaction flask was then connected to a small electrically heated column of the total condensation, controllable take-off type, having a 13 mm. inside diameter and packed throughout a length of 44 cm. with glass helices. All alcohol present and that which was formed by heating the mixture, was fractionated off under reduced pressure. The flask was then disconnected and set up with reflux condenser, stirrer and dropping funnel. An excess (10–15%) of the desired halide was added over a fifteen to

twenty minute period. The temperature of the well stirred reaction mixture was then cautiously raised to 95–105° and held in this range until no longer alkaline to phenolphthalein. After cooling, the mixture was poured into about an equal volume of cold water, neutralized with acetic acid and extracted with isopropyl ether. The ether extract was dried and then fractionated.

In many cases, conditions for obtaining maximum yields were not worked out. Unless otherwise noted, the yields are based on ester introduced as starting material, without allowance being made for that which might be unreacted and recoverable. A typical example is described below.

**Diethyl Allyl-*s*-butylmalonate.**—Sodium ethylate was made by dissolving clean sodium metal (6 g.) in anhydrous ethyl alcohol (100 ml.) and distilling to dryness at reduced pressure. After cooling, dry diethyl carbonate (110 ml.) and diethyl *s*-butylmalonate (54 g.) were added to the broken up cake of sodium ethylate. The reactants were stirred at room temperature until all solid dissolved. The flask was then connected to the column and alcohol removed under reduced pressure (about 150 mm.). When no more alcohol was obtainable as distillate, the reaction to form the metal derivative was considered complete. The mixture was cooled and the flask fitted with a reflux condenser, mercury-sealed stirrer and dropping funnel. Allyl bromide (35 g.) was added to the well-stirred mixture. A temperature rise on addition of the first few milliliters of bromide was observed, and therefore that remaining in the funnel was added cautiously over a forty-five minute period. Sodium bromide began to separate almost immediately. The well-stirred mixture was slowly heated to 100–105° and held at this temperature for seven hours. The cooled reaction mixture, no longer alkaline to phenolphthalein, was poured into cold water (200 ml.), acidified with glacial acetic acid (1 ml.) and the diethyl carbonate-ester layer separated. To this was added an isopropyl ether extract (120 ml.) of the aqueous solution. After drying, the ether and diethyl carbonate were distilled off and the residual ester fractionated through the column. The ester distilled at 109–110.5° (uncor.) (5–5.5 mm.),  $n_D^{20}$  1.4427. The yield was 54.7 g. (85.5%). The ester condensed with urea to give a 65% yield of 5,5-allyl-*s*-butyl barbituric acid, m. p. 108–109.5° (uncor.).

### Summary

Alkyl carbonates have been used as reaction media for the metalation and alkylation of malonic esters,  $\beta$ -keto esters and  $\alpha$ -cyano esters. By this procedure the formation of the metal derivative may be forced to completion and cleavage by alcoholysis avoided.

Several new malonic esters unobtainable by usual methods have been prepared.

(6) Wallingford and Jones, *THIS JOURNAL*, **63**, 578 (1941).