Synthesis of Isopropylidene Dialkylmalonates under Phase-Transfer Catalyzed Conditions

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Isopropylidene malonate (**1**; 2,2-dimethyl-4,6-dioxo-1,3-dioxane, Meldrum's acid) has high acidity ($pK_1 = 4.97$), a rigid cyclic structure, and can undergo easy hydrolysis. It has become an attractive reagent in organic syntheses[1]. For example, it can readily undergo Knoevenagel condensation[2-5], Michael addition[6,7], and acylation[8,9] reactions. However, reports on its alkylation are rare[10,11].

Recently, the phase-transfer catalyzed alkylation of active methylene compounds has been used extensively and gave excellent results[12]. Therefore, we tried to use this procedure for the alkylation of isopropylidene malonate (**1**). However, under the normal conditions [20% aqueous sodium hydroxide in presence of benzyltriethylammonium chloride (TEBA)] the ring underwent cleavage and the main product was the α,α-dimethylmalonic acid methyl ester.

0039-7881/82/0632-0452 $ 03.00

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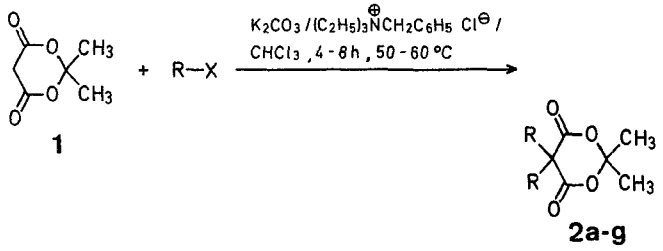
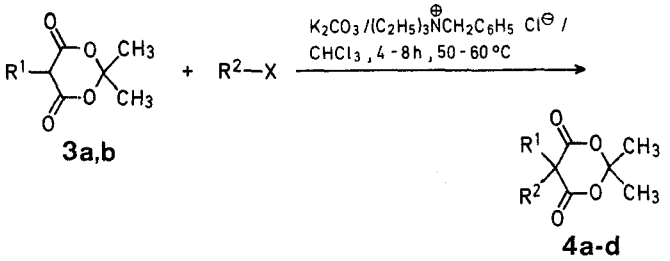
Because of the high acidity of isopropylidene malonate (**1**), we decided to use solid potassium carbonate in place of 20% aqueous sodium hydroxide to avoid hydrolysis and let the reaction to take place under solid-liquid phase-transfer conditions. This resulted in a simple and convenient method for the dialkylation of isopropylidene malonate to give products **2a-g** (Table 1).



Using isopropylidene alkylmalonates **3** as starting materials, this method is also suitable for the synthesis of the mixed dialkyl derivatives **4a-d** (Table 1).



From the experimental results, we may conclude that this procedure is a general method for the synthesis of isopropylidene dialkylmalonates **2** and **4**. The advantages of this method are the manipulative convenience and excellent yields and it appears to be superior to the previous reports[10,11]. For example, Hedge et al.[10], used sodium isopropylidenemalonate, obtained from reaction of isopropylidene malonate with sodium ethoxide, and benzyl chloride in dimethylformamide at room temperature for 6 days and obtained only a 42% yield of iso-

Table 1. Preparation of Isopropylidene Dialkylmalonates **2** and **4**

Product No.	R in **2** R¹ in **4**	R² in **4**	X	Reaction conditions time/temperature	Yield [%]	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]
2a	H_3C	—	J	4 h/50-60 °C	86 (73)[11]	60°	61°[11]
2b	C_2H_5	—	J	6 h/50-60 °C	90	40-41°	$C_{10}H_{16}O_4$ (200.2)
2c	n-C_4H_9	—	J	8 h/50-60 °C	85	86-87°	$C_{14}H_{24}O_4$ (256.3)
2d	$C_6H_5CH_2$—	—	Cl	2.5 h/50-60 °C	94 (42)[10]	232-233°	232-233°[10]
2e	O_2N-C_6H_4-CH_2—	—	Br	2.5 h/50-60 °C	96	258-259° (dec)	$C_{20}H_{18}N_2O_8$ (414.4)
2f	C_2H_5OOC-CH_2—	—	Br	3 h/50-60 °C	76	110°	108-109°[6]
2g	C_6H_5CO-CH_2—	—	Br	2.5 h/50-60 °C	86	207-208° (dec)	$C_{22}H_{20}O_6$ (380.4)
4a	$C_6H_5CH_2$—	H_3C	J	5 h/50-60 °C	97	119-120°	$C_{14}H_{16}O_4$ (248.3)
4b	$C_6H_5CH_2$—	O_2N-C_6H_4-CH_2—	Br	4 h/50-60 °C	92	187-188°	$C_{20}H_{19}NO_6$ (369.4)
4c	$C_4H_3OCH_2$—	H_3C	J	5 h/50-60 °C	90	66-67°	$C_{12}H_{14}O_5$ (238.2)
4d	$C_4H_3OCH_2$—	O_2N-C_6H_4-CH_2—	Br	4 h/50-60 °C	81	180-181°	$C_{18}H_{17}NO_7$ (359.3)

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.38.

Table 2. Spectral Data for Products **2** and **4**

Product	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
2a	1773, 1732, 1380, 1370	1.55 (s, 6H); 1.65 (s, 6H)
2b	1760, 1730, 1387, 1372	0.90 (t, 6H); 1.68 (s, 6H); 2.01 (q, 4H)
2c	1765, 1725, 1385, 1375	0.80 (t, 6H); 1.24 (m, 8H); 1.67 (s, 6H); 1.92 (t, 4H)
2d	1760, 1727, 1380, 1370, 760, 700	0.58 (s, 6H); 3.39 (s, 4H); 7.06 (s, 10H)
2e	1763, 1732, 1519, 1377, 1342, 854	0.68 (s, 6H); 3.56 (s, 4H); 7.4 (m, 4H); 8.2 (m, 4H)
2f	1780, 1731, 1712, 1383, 1374	1.23 (t, 6H); 1.92 (s, 6H); 3.08 (s, 4H); 4.13 (q, 4H)
2g	1750, 1715, 1682, 1390, 1375, 748, 685	2.12 (s, 6H); 3.82 (s, 4H); 7.5-7.8 (m, 10H)
4a	1773, 1732, 1380, 1330, 775, 708	0.84 (s, 3H); 1.56 (s, 3H); 1.70 (s, 3H); 3.26 (s, 2H); 7.17 (s, 5H)
4b	1770, 1730, 1515, 1392, 1378, 855, 755, 700	0.53 (s, 3H); 0.72 (s, 3H); 3.40 (s, 2H); 3.50 (s, 2H); 7.2 (m, 7H); 8.16 (d, 2H)
4c	1765, 1734, 1392, 1373, 1280, 1014	1.25 (s, 3H); 1.64 (s, 3H); 1.67 (s, 3H); 3.36 (s, 2H); 6.2 (m, 2H); 7.27 (d, 1H)
4d	1765, 1732, 1526, 1390, 1379, 1271, 1009, 856	0.78 (s, 3H); 0.96 (s, 3H); 3.39 (s, 2H); 3.44 (s, 2H); 6.2 (m, 2H); 7.3 (m, 3H); 8.1 (m, 2H)

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propylide e dibenzylmalonate. Because the substituted isopropylide e malonates are easily hydrolyzed to carboxylic acids[13] or converted to carboxylic esters[14], the method described he e may also be considered as a new method for the synthesis f α,α-dialkylacetic acids or their esters.

The struct res of all products were confirmed by their microanalyses a id I.R. and N.M.R. spectra (Table 2).

Isopropylid ie Dialkylmalonates 2 and 4; General Procedure:
To a stirred solution of isopropylidene malonate (**1**; 1.44 g, 10 mmol) in chlorofo n (15 ml) is added finely powdered potassium carbonate (4.15 g, 30 mmol) and benzyltriethylammonium chloride (6.83 g, 30 mmol). The , a solution of the alkyl halide (30 mmol) in chloroform (15 ml) is a ded dropwise. [For monoalkylation reactions of **3**, the molar ratio of **3**:alkyl halide:potassium carbonate:benzyltriethylammonium ch oride used is 1:1.2:1:1.] The resultant mixture is stirred for 4–8 h at 0–60 °C, until T.L.C. analysis (silica gel G, benzene/chloroform) ind cates complete disappearence of the starting material **1** or **3**. Water (2(ml) is then added, the organic layer is separated, and the aqueous lay r is extracted with chloroform (2 × 20 ml). The combined organic laye s are evaporated. To the residue water (20 ml) and ether (20 ml) are a ded. [For **2d, 2e, 2g, 4b, 4d** the crude product can be obtained dire ly after addition of water]. The ethereal solution is washed wit water (10 ml) and dried with anhydrous sodium sulfate. After r moval of the solvent, the product is purified by crystallization or by chromatography over silica gel eluting with benzene.

Received: December 22, 1981

1 H. McN ab, *Chem. Soc. Rev.* **7**, 345 (1978).
2 G. J. Ba ter, R. F. C. Brown, *Aust. J. Chem.* **28**, 1551 (1975).
3 P. Marg retha, O. E. Polansky, *Tetrahedron Lett.* **1969**, 4983.
4 G. A. B lmayer, F. J. Kunz, O. E. Polansky, *Monatsh. Chem.* **97**, 1293 (19 6).
5 G. J. Ba ter, R. F. C. Brown, G. L. McMullen, *Aust. J. Chem.* **27**, 2605 (19 4).
6 R. B. M ne, G. S. K. Rao, *Chem. Ind. (London)* **1976**, 786.
7 L. G. Si erko, F. X. Smith, *Synth. Commun.* **9**, 383 (1979).
8 Y. Oika va, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **43**, 2087 (1978).
9 T. A. H se, K. Salonen, *Synth. Commun.* **10**, 221 (1980).
10 J. A. H dge, C. W. Kruse, H. R. Snyder, *J. Org. Chem.* **26**, 992 (1961).
11 D. Davi lson, S. A. Bernhard, *J. Am. Chem. Soc.* **70**, 3426 (1948).
12 J. Dock . *Synthesis* **1973**, 441.
C. M. S arks, C. Liotta, *Phase-Transfer Catalysis: Principles and Techniq es*, Academic Press, New York, 1978.
W. P. V eber, G. W. Gokel, *Phase Transfer Catalysis in Organic Synthes* . Springer Verlag, Berlin, Heidelberg, New York, 1977.
E. V. D hmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, Verlag Chemie Weinheim, 1980.
13 G. Swo oda, J. Swodoba, F. Wessely, *Monatsh. Chem.* **95**, 1283 (1964).
14 Y. Oika a, H. Hirasawa, O. Yonemitsu, *Tetrahedron Lett.* **1978**, 1759.

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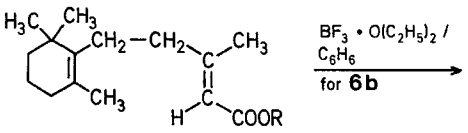
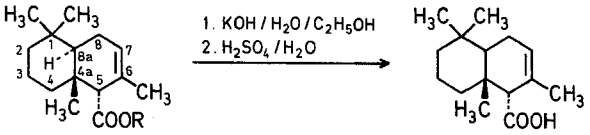
C. Schmidt, N. H. Chishti, T. Breining, *Synthesis* **1982** (5), 391-393:
The formula scheme for the reaction **6**→**7** (p. 391) should be:



6a R = H
6b R = CH_3
6c R = C_2H_5



7b R = CH_3 **7a** R = H

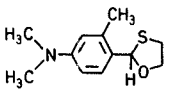
B. A. Arbuzov, N. N. Zobova, *Synthesis* **1982** (6), 433-450:
The correct name for compound **15** (p. 436) is *N'*-benzoyl-*N,N*-dimethyl-2-phenyl-2-butenamidine and for compound **30b** (p. 439) is 4-trifluoroacetylimino-2-trifluoromethyl-4*H*, 9a*H*-pyrido[2,1-*b*]-1,3,5-oxadiazine.

Chen-Chu Chan, Xian Huang, *Synthesis* **1982** (6), 452-454:
The last sentence on page 452 should read: However, under the normal conditions [20% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride (TEBA)] the ring underwent cleavage and the main product was dimethylmalonic acid in the case of methylation.

P. Molina, A. Arques, A. Ferao, *Synthesis* **1982** (8), 645-647:
Compounds **3,4,** and **6** are substituted pyrido[2,1-*b*][1,3,4]thiadiazinium salts.

Abstract 6431, *Synthesis* **1982** (9), 801
The correct name for the title compounds **3** is 2-oxoalkanehydroximic chlorides.

B. Burczyk, Z. Kortylewicz, *Synthesis* **1982** (10), 831-832:
In Table 1 (p. 832) the b.p. of product **6a** should be 113-114°C/0.3 torr; the structure and molecular formula of product **7d** should be



and $C_{12}H_{17}NOS$ (223.2); the b.p. and n_D^{20} of product **8a** should be 114-116°C/60 torr and 1.5346, respectively. In Table 2 (p. 832) the second term in the ^{1}H-N.M.R. spectrum of product **7b** should be 1.90 (s, 3H, CH_3).

K. D. Deodhar, A. D. D'Sa, S. R. Pednekar, D. S. Kanekar, *Synthesis* **1982** (10), 853-854:
The correct name for compounds **4a,b** (p. 854) is (*E*)- and (*Z*)-6-benzylidene-3-oxo-2,3,4,6-tetrahydro[1,2,4]triazino[3,4-*a*]isoindoles.

L. Lepage, Y. Lepage, *Synthesis* **1982** (10), 882-884:
The correct name for compound **10** (p. 884) is 2-acetyl-1,4-diphenyl-1,2,3,4-tetrahydro-1,4-epithiopentacene-7,12-quinone.

R. R. Schmidt, A. Wagner, *Synthesis* **1982** (11), 958-962:
It should be noted that the numbers in the products **5**-**16c** in Table 1 refer only to the ^{1}H-N.M.R. data in Table 2 and are not identical with the numbering used for the systematic nomenclature of the products.

T. Takajo, S. Kambe, W. Ando, *Synthesis* **1982** (12), 1080-1081:
The compounds **7** should be named 2,4,6,12-tetraaryl-2,5,6,7-tetrahydro-4*H*-3,6a-methanoindeno[1,2-*f*][1,3,5]triazocines.

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