Preparation of 2,2-Dialkylcyclopropanes Geminally Substituted with Electron-Withdrawing Groups

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In our current studies on the chemistry and synthetic utility of allyl bromides with two activating groups in the γ-position[2], we have found a useful, general approach to 2,2-dialkylcyclopropanes geminally substituted with electron-withdrawing groups.

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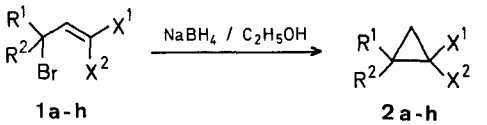
In general, the synthesis of such cyclopropanes was hitherto performed via base-induced alkylation of active methylene compounds with 1,2-dihaloalkanes[3-6], via vinylsulfonium salts and 1,4-sulfonium betaines[7,8], by pyrolysis of pyrazolines (prepared by reaction of diazomethane with activated alkenes)[9-12], by cyclopropanation of alkenes with activated diazo compounds[13,14,15], and addition of bromodicyanomethane[16,17]. However most of the preparations have been accomplished in only poor yield except in the synthesis of such cyclopropanes by phase transfer-catalysed alkylation[6].

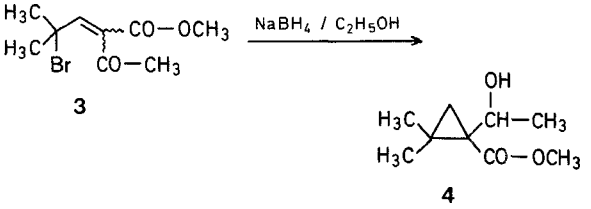
Our method consists of the following sequence of reactions. Treatment of dialkyl 2-bromoalkylidenemalonates **1**, $X^1=X^2=COOR$, prepared by Knoevenagel condensation of aliphatic aldehydes with dialkyl malonates and bromination with *N*-bromosuccinimide in carbon tetrachloride[18], with an excess of sodium borohydride (eight equivalents) in ethanol afforded 2,2-dialkylcyclopropane-1,1-dicarboxylates (**2**, $X^1=X^2=COOR$) in good yields (see Table). Reaction of alkyl (*E*)-4-bromo-2-cyano-4-methyl-2-pentenoate (**1**, $X^1=COOR$, $X^2=CN$) with sodium borohydride under the same conditions gave alkyl 1-cyano-2,2-dimethylcyclopropane-1-carboxylates (**2**, $X^1=COOR$; $X^2=CN$).



1a-h **2a-h**

1, 2	R^1	R^2	X^1	X^2
a	CH_3	CH_3	$COOCH_3$	$COOCH_3$
b	CH_3	CH_3	$COOC_2H_5$	$COOC_2H_5$
c	CH_3	C_2H_5	$COOCH_3$	$COOCH_3$
d	C_2H_5	C_2H_5	$COOCH_3$	$COOCH_3$
e	$-(CH_2)_5-$		$COOCH_3$	$COOCH_3$
f	CH_3	CH_3	$COOCH_3$	CN
g	CH_3	CH_3	$COOC_2H_5$	CN
h	CH_3	CH_3	CN	CN

However, reaction of a mixture of (*E*)- and (*Z*)-methyl 2-acetyl-4-bromo-4-methyl-2-pentenoate (**3**) with sodium boro-



3 **4**

Table. Preparation and Spectra of Cyclopropanes **2a–h**

Product	Yield [%]	b.p./torr (Lit. b.p./torr)	Molecular formula[a]	I.R. ν [cm^{-1}][b]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity)
2a	66	95°/15 (95°/16)[10]	$C_9H_{14}O_4$ (186.2)	1735	1.24 (s, 6H); 1.32 (s, 2H); 3.67 (s, 6H)	186 (M^+, 3), 155 (15), 154 (19), 122 (100), 113 (7), 94 (15), 73 (17), 67 (8), 59 (7), 55 (10), 41 (10)
2b	73	41°/0.03 (46°/0.005)[15]	$C_{11}H_{18}O_4$ (214.3)	1725	1.23 (s, 6H); 1.27 (t, J = 7 Hz, 6H); 1.30 (s, 2H); 4.14 (q, J = 7 Hz, 4H)	214 (M^+, 2), 169 (11), 168 (7), 122 (100), 94 (13), 67 (8), 59 (8), 55 (14), 41 (10)
2c	76	104°/13	$C_{10}H_{16}O_4$ (200.2)	1740	0.93 (t, J = 7 Hz, 3H); 1.17 (s, 3H); 1.20–1.65 (m, 2H); 1.30 (s, 2H); 3.68 (s, 6H)	200 (M^+, 1), 169 (7), 168 (6), 136 (100), 132 (19), 121 (8), 113 (24), 108 (15), 87 (10), 81 (11), 80 (13), 69 (20), 68 (17), 59 (17), 55 (12), 41 (26)
2d	75	114°/13	$C_{11}H_{18}O_4$ (214.3)	1740	0.88 (t, J = 7 Hz, 6H); 1.17–1.88 (m, 4H); 1.30 (s, 2H); 3.68 (s, 6H)	183 (8), 182 (7), 150 (100), 145 (13), 135 (13), 122 (18), 121 (23), 113 (18), 107 (14), 95 (12), 83 (19), 82 (29), 79 (14), 67 (12), 59 (25), 55 (43), 41 (31)
2e	70	137°/13	$C_{12}H_{18}O_4$ (226.3)	1735	1.31 (s, 2H); 1.36–1.60 (m, 10H); 3.68 (s, 6H)	226 (M^+, 1), 194 (10), 162 (100), 135 (19), 133 (12), 113 (35), 95 (12), 94 (17), 81 (12), 79 (14), 67 (18), 59 (14), 55 (12)
2f	57	87°/13	$C_8H_{11}NO_2$ (153.2)	2240, 1740	1.16 (s, 3H); 1.39 (d, J_{AB} = 5 Hz, 1H); 1.46 (s, 3H); 1.73 (d, J_{AB} = 5 Hz, 1H); 3.78 (s, 3H)	153 (M^+, 4), 138 (14), 125 (11), 124 (10), 121 (100), 120 (11), 110 (41), 106 (35), 96 (23), 95 (29), 94 (68), 93 (56), 80 (39), 67 (44), 66 (41), 65 (16), 59 (20), 57 (24), 55 (23), 42 (21), 41 (48), 39 (41)
2g	63	95–97°/13	$C_9H_{13}NO_2$ (167.2)	2250, 1740	1.27 (s, 3H); 1.33 (t, J = 7 Hz, 3H); 1.36 (d, J_{AB} = 5 Hz, 1H); 1.45 (s, 3H); 1.72 (d, J_{AB} = 5 Hz, 1H); 4.22 (q, J = 7 Hz, 2H)	167 (M^+, 5), 139 (77), 124 (12), 122 (63), 121 (100), 111 (23), 106 (17), 98 (13), 94 (58), 93 (45), 80 (12), 67 (20), 66 (24), 59 (18), 55 (11), 53 (11), 42 (11), 41 (29), 39 (24)
2h[c]	46	—	$C_7H_8N_2$ (120.2)	2260	1.49 (s, 6H); 1.60 (s, 2H)	120 (M^+, 7), 119 (26), 105 (46), 93 (91), 92 (16), 87 (16), 79 (20), 78 (26), 67 (12), 66 (23), 57 (100), 56 (12), 55 (18), 45 (47), 43 (17), 42 (64), 41 (67), 39 (20)

[a] All products gave satisfactory microanalyses (C, H, N, ±0.15%).
[b] $\nu_{C=O}$ and/or $\nu_{C\equiv N}$.
[c] Pure **2h** was obtained by preparative G.L.C.

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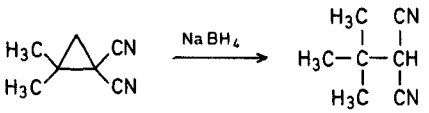
hydride produced methyl 1-(1-hydroxyethyl)-2,2-dimethylcyclopropane-1-carboxylate (**4**) by further reduction of the corresponding 1-acetylcyclopropane intermediate.



2h **5**

Treatment of methyl 2-bromo-2-methylpropylidenemalononitrile (**1h**) with sodium borohydride in dimethoxyethane gave a mixture of 46% 1,1-dicyano-2,2-dimethylcyclopropane (**2h**) and 54% *t*-butylmalononitrile (**5**), the latter product arising from ring cleavage by further attack of a hydride anion.

2,2-Dialkylcyclopropanes Geminally Substituted with Electron-Withdrawing Groups; General Procedure:

To a stirred suspension of sodium borohydride (0.2 mol) in ethanol (50 ml) is added dropwise a solution of diactivated allyl bromide **1** (0.1 mol) in absolute ethanol (10 ml) at room temperature and the reaction mixture is stirred for another 4 h. Most of the solvent is removed in vacuo and the residue is poured into water (100 ml) and extracted with dichloromethane (2 × 100 ml). After drying and evaporation of the solvent the residue is distilled under reduced pressure.

Preparation of Methyl 1-(1-Hydroxyethyl)-2,2-dimethylcyclopropane-1-carboxylate (4):

This is prepared from **3** (4.8 g, 0.02 mol) as described above: yield: 2.3 g (68%); b.p. 101–103°/13 torr.

I.R. (NaCl): $\nu = 3375$ (OH); 1730 cm^{-1} ($COOCH_3$).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.43$ (d, $J_{AB} = 4$ Hz, CH); 1.09 (s, 3H); 1.23 (d, $J_{AB} = 4$ Hz, 1H); 1.25 (d, $J = 7$ Hz, 3H); 1.32 (s, 3H); 3.07 (s broad, 1H); 3.33 (q, $J = 7$ Hz, 1H); 3.71 ppm (s, 3H).

M.S.: $m/e = 172$ (M^+, 1%), 171 (0.5), 157 (25), 154 (13), 139 (14), 125 (34), 123 (20), 122 (34), 114 (100), 97 (13), 95 (22), 82 (13), 81 (14), 79 (17), 73 (22), 59 (41), 55 (15), 45 (13), 43 (27), 41 (24).

Reaction of 2-Bromo-2-methylpropylidenemalononitrile (1h) with Sodium Borohydride:

A solution of **2h** (0.05 mol) in dimethoxyethane (20 ml) is slowly added to a suspension of sodium borohydride (0.1 mol) in dimethoxyethane (50 ml) at 0° and the reaction mixture is worked up as described above yielding 46% **2h** and 54% **5** which are separated by gas chromatography (conditions: SE 30 5%, 1.5 m, 150°).

***t*-Butylmalononitrile (5):**

I.R. (NaCl): $\nu = 2260$ cm^{-1}.

^{1}H-N.M.R.: $\delta = 1.26$ (s, 9H); 3.45 ppm (s, 1H).

M.S.: $m/e = 109$ (13), 107 (100), 106 (52), 92 (50), 87 (11), 81 (26), 80 (57), 79 (70), 68 (23), 67 (25), 65 (14), 58 (58), 57 (68), 56 (18), 55 (25), 54 (19), 53 (21), 45 (22), 43 (19), 42 (22), 41 (84), 40 (18), 39 (46).

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