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PRACTICAL LARGE SCALE PREPARATION OF ACTIVATED CYCLOPROPANES

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Abstract: Simple and practical experimental conditions for the large scale preparation of activated cyclopropanes by K_2CO_3 promoted cycloalkylation of malonate precursors with 1,2-dibromoethane are described.

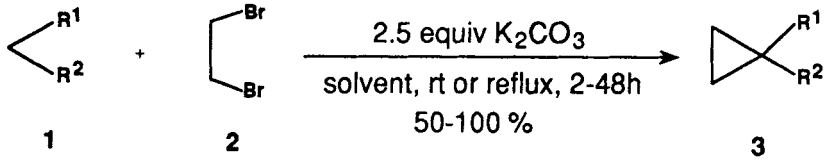
In connection with our work on the cycloalkylation of stabilized α,α'-dianions,[1] we required a rapid and practical access to large quantities of alkyl cyclopropane 1,1-cyanocarboxylates **3a,b** and methyl cyclopropane 1,1-dicarboxylate **3d**[2] by direct base induced alkylation of the corresponding malonic derivatives **1** with 1,2-dibromoethane **2**. However it appeared from the literature that the use of different basic conditions such as EtO^-Na^+/EtOH,[3] NaH/DME[4] or DBU/DMF[5] resulted in only poor yields of cyclopropane derivatives.

Moreover, the inefficiency of the cycloalkylation under these conditions implies a complicated separation of the corresponding alkyl malonates **1**.[3] An interesting two-step (cycloalkylation-esterification) alternative was provided by the utilization of phase transfer conditions,[6] which unfortunately, in our hand and for large scale application, proved to be difficult to control in the case of **3a,b** and needs a tedious aqueous extractive work-up to give the corresponding acids which have to be esterified in a second step. More recently, solid K_2CO_3 in DMSO[7] was found to be quite general for this preparation but the use of large quantities of this solvent and the isolation of products by extractive work-up make also this approach unpractical for large scale preparations.

In this paper, we describe simple and practical experimental conditions for the preparation of activated cyclopropanes **3** by direct cycloalkylation of malonates **1** with 1,2-dibromoethane promoted by K_2CO_3 in acetone, butanone, CH_2Cl_2 or THF. These simple modifications allow the rapid obtention of large quantities of pure products conveniently isolated by simple filtration (Table).

The results reported in table show that good unoptimized yields are obtained under the reported conditions after simple filtration through a short pad of celite or silica gel. Alkyl cyanoacetates **1a,b** and methyl acetoacetate **1c** react smoothly in refluxing acetone to give highly pure cyclopropanes **3a-c**.[8] In contrast, methyl malonate **1d** needs refluxing butanone and a catalytic amount of 18-C-6 in order to obtain a complete conversion. Finally in the case of malononitrile **1e**, CH_2Cl_2 in the presence of 18-C-6 (cat.) at room temperature or alternatively THF at reflux without crown ether gives the best results after many unsuccessful attempts using acetone, butanone, benzene or light petroleum ether under various experimental conditions.

Table: Cycloalkylation of malonates **1** with 1,2-dibromoethane **2**



1 **2** **3**

1,3	R^1	R^2	Condition	Yield (%)[b]
a	COOMe	CN	acetone, 20h	94
b	COOEt	CN	acetone, 5h	92
c	COOMe	COMe	acetone, 9h	75
d	COOMe	COOMe	butanone, 18-C-6 (cat.), 3h	100[c]
e	CN	CN	CH_2Cl_2, 18-C-6 (cat.), 48h[a]	52 (72)[d]
e	CN	CN	THF, 2h	50

[a] Room temp.; [b] isolated; [c] see ref. 8; [d] crude yield, >90% pure by NMR.

Experimental

Typical procedure for the cycloalkylation

1,2-Dibromoethane **2** (1.3 equiv.) was slowly added to a mixture of malonate **1** (1 equiv.) and powdered K_2CO_3 (2.5 equiv.) in anhydrous solvent and the heterogeneous mixture was stirred at room temperature or at reflux under nitrogen for the given time (see table). After completion, filtration of the reaction mixture through a short pad of celite in the cases of **3a-d** and evaporation of the volatils under reduced pressure gave the desired products pure enough for further synthetic transformations. For **3e**, filtration through a short pad of silica gel (230-400 mesh) was necessary in order to remove all yellow to orange unidentified polycondensation by-products.

3a: from methylcyanoacetate **1a** (28 g, 25 ml, 283 mmol), K_2CO_3 (98 g, 709 mmol) and 1,2-dibromoethane (68.89 g, 31.6 ml, 368 mmol) in acetone (200 ml). The general procedure gave 35 g of crude product containing some 1,2-dibromoethane. Distillation under reduced pressure (63-65°C / 2 mmHg) gave 33 g (94 %) of pure **3a**: IR (neat) 3114, 2248, 1713, 867 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.81 (s, 3H), 1,67 (m, 2H), 1,63 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 167.6, 117.9, 52.8, 29.7, 18.4 ($2CH_2$).

3b: from ethylcyanoacetate **1b** (8.5 g, 8 mol, 75.18 mmol), K_2CO_3 (31.8 g, 225.5 mmol) and 1,2-dibromoethane (28.2 g, 12.9 ml, 150.3 mmol) in acetone (60 ml). The general procedure after distillation under reduced pressure (80-82°C / 6 mmHg) gave 9.6 g (92 %) of pure **3b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.24 (q, J = 7.2 Hz, 2H), 1.65 (m, 2H), 1.61 (m, 2H), 1.32 (t, J = 7.2 Hz, 2H).

3c and **4**: from methylacetoacetate **1c** (10.8 g, 10 ml, 92.66 mmol), K_2CO_3 (32 g, 231.7 mmol) and 1,2-dibromoethane (34.7 g, 15.9 ml, 185.3 mmol) in acetone (70 ml). The general procedure after flash chromatography on silica gel using a mixture ethyl ether/pentane 1/1 gave 9.9 g (75 %) of pure **3c**, Rf = 0,54: IR (neat) 3009, 1726, 1702, 1331 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.45 (s, 3H), 1.47 (s, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 202.9, 171.5, 52.2, 34.8, 29.7, 19.1. **4**: Rf = 0,48: IR (neat) 2969, 1709, 1627, 908 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.05 (t, J = 6.1 Hz, 2H), 3.65 (s, 3H), 3.54 (t, J = 6.1 Hz, 2H), 2.30 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 171.7, 168.0, 91.8, 67.7, 50.9, 28.1, 18.9.

3d: from dimethyl malonate **1d** (11.56 g, 10 ml, 87.5 mmol), K_2CO_3 (30.2 g, 218.74 mmol) and 1,2-dibromoethane (32.8 g, 15 ml, 175 mmol). The

general procedure using butanone (80 ml) and crown ether 18-C-6 (4.6 g, 17.5 mmol) gave 14 g (100 %) of **3d** with high purety as shown by the crude NMR spectrum (200 MHz): IR (neat) 3010, 1729, 1134, 752 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.74 (s, 6H), 1.44 (s, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 169.7, 52.1, 27.6, 16.1.

3e:[9] from cyanomalonate **1e** (2 g, 30.3 mmol), K_2CO_3 (11 g, 79.6 mmol) and 1,2-dibromoethane (7.7 g, 3.54 ml, 41.2 mmol). The general procedure using CH_2Cl_2 (80 ml) and crown ether 18-C-6 (1.4 g, 5.3 mmol) gave after filtration through a short pad of silica gel (230-400 mesh) 2.2 g (72 %) of crude **3e**. Kugelrohr distillation (100°C / 10 mmHg) gave 1.57 g (52 %) of pure **3e**. Alternatively **1e** (5g, 75.7 mmol), K_2CO_3 (31g, 224 mmol) and 1,2-dibromomethane were reacted in THF (100 ml) at reflux for 2h without addition of crown ether to give after filtration through a short pad of silica gel (230-400 mesh) an orange oil, which after kugelrohr distillation (100°C / 10 mmHg) gave 3.5 g (50 %) of pure **3e:** IR (neat) 3117, 2255, 1607, 961 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.80 (s, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 115.2, 18.4, −1.7.

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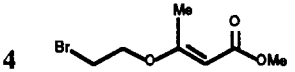
8- In the case of **1c**, compound **4** (8-12 %) arising from *o*-alkylation is also formed and eliminated by flash chromatography on SiO_2.



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