General Synthesis of Methyl- and Dimethyl-cyclobutanes from Simple 1,3-Diols by Phase Transfer Catalysis

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A general method is described for the preparation of methyl- and dimethyl-cyclobutanes from simple 1,3-diols. The key steps of the procedure are a phase transfer catalysed ring closure and the transformation of a carboxyl group to a methyl group. Phase transfer catalysis provides good yields in the synthesis of the cyclobutane skeleton.

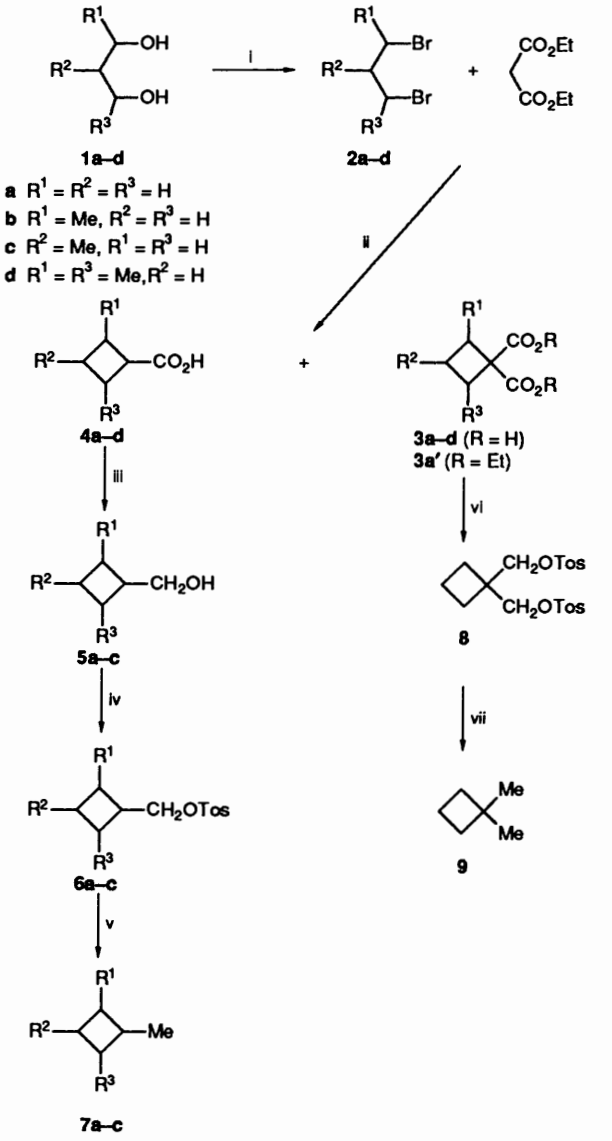
For use in further studies, the synthesis of different methyl- and dimethyl-cyclobutanes was recently required. A literature search revealed that there are two basic routes available for the preparation of alkylcyclobutanes. One is pericyclic reactions, *i.e.* the cycloaddition of allene[1] or the electrocyclic reaction of substituted butadienes,[2] followed by hydrogenation. This method permits the synthesis of symmetric molecules only and requires the use of a suitable UV source. Another, more general synthetic route to alkylcyclobutanes was reported by Kazanskii and Lukina.[3] Their tedious procedure has the disadvantage of too many steps. For example, the synthesis of 1,3-dimethylcyclobutane was carried out in ten reaction steps.

In light of this information, a more effective and shorter synthesis of the title compounds was decided on. Since simple 1,3-diols in suitable variations are readily available, our method is based on these diols as starting materials. The procedure consists of two essential parts. First, the cyclobutane ring is constructed through the ring-closure reaction of diethyl malonate and 1,3-dibromo compounds derived from 1,3-diols. The novelty of the present method is provided by the use of phase transfer catalysis (PTC) and the thorough studies conducted to optimize the reaction conditions of this step. Although PTC is scarcely used in cyclobutane chemistry, careful application of this method to construction of the cyclobutane ring permitted very good yields in the ring-closure reaction. In the second part of the synthesis, hydroxy groups formed by the reduction of the ethoxycarbonyl groups are transformed into methyl substituents *via* tosylation and subsequent reduction (Scheme 1). The procedures applied are facile and all the products can be purified without difficulty.

In the first part of the method (construction of the cyclobutane ring *via* ring closure) the 1,3-diols **1a–d** were transformed into the corresponding 1,3-dibromo compounds **2a–d**. For these reactions phosphorus tribromide was used.[4]

The key step in the proposed synthesis is the ring closure reaction between 1,3-dibromo compounds and diethyl malonate. The conventional method[5] led to the required cyclobutane derivatives (diethyl cyclobutanedicarboxylates) in relatively low yields (35–50% in the transformations of **2a–d**). In most cases, further transformations were carried out with the corresponding monocarboxylic acids. This requires subsequent hydrolysis and decarboxylation, with a resulting additional decrease in overall yield. After these disappointing results, our attention turned to PTC, despite the fact that previous applications of this method in small-ring cycloalkane chemistry did not appear very promising.[6–8]

In the work of Diez-Barra *et al.* the dependence of the selectivity of the ring formation on ring size was investigated.[8] The interpretation of the results was based on Baldwin's rules.[9] These rules state that alkylation is usually kinetically controlled and cyclization is a favoured *exo-tet* process. In competitive



Scheme 1 *Reagents:* i, PBr_3; ii, phase transfer catalyst, 50% NaOH; iii, (a) conc. HCl–EtOH, (b) $LiAlH_4$; iv, TosCl, pyridine; v, $LiAlH_4$; vi, (a) $LiAlH_4$, (b) TosCl, pyridine; vii, $LiAlH_4$

reactions, the selectivity depends on the probability of the intermediate adopting an appropriate conformation for the cyclization and on the distance between the reacting centres in this conformation. The results observed point to the kinetically favourable formation of three- and six-membered rings (3-*exo*-

Table 1 Reactions of 1,3-dibromo compounds **2a–d** with diethyl malonate and phase transfer catalysts[a]

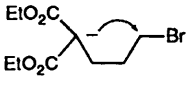
Catalyst	Compound	Substituents R[1]	R[2]	R[3]	Product	Yield (%)	Isomeric ratio[b]
TEBA	**2a**	H	H	H	**4a**	41	—
	2b	Me	H	H	**4b**	61	2:1
	2c	H	Me	H	**4c**	42	3:1
	2d	Me	H	Me	**4d**	63	4:1
DDABr	**2a**	H	H	H	**4a**	27	—
	2b	Me	H	H	**4b**	61	1.8:1
	2c	H	Me	H	**4c**	45	2:1
	2d	Me	H	Me	**4d**	57	5:1
TBACl	**2a**	H	H	H	**4a**	56	—
	2b	Me	H	H	**4b**	37	1.7:1
	2c	H	Me	H	**4c**	50	2.8:1

[a] All reactions were carried out at room temperature in 50% aqueous NaOH for 1 h. TEBA: triethylbenzylammonium chloride; DDABr: didecyldimethylammonium bromide; TBACl: tetrabutylammonium chloride. [b] **4b**—*trans*/*cis*, **4c**—*trans*/*cis*, **4d**—2,4-*trans*,*trans*/2,4-*cis*,*cis*.

Table 2 Transformations of 1,3-dibromo compounds **2a–d** to substituted cyclobutanes

Starting compound	Yield of **4** and **3a'** from **2** (%)	Yield of cyclobutane from **4** and **3a'** (%)	*trans*/*cis* ratio
2a	**4a** (56)[a]	**7a** (18)	—
2b	**4b** (61)[b]	**7b** (15)	2:1
2c	**4c** (50)[a]	**7c** (14)	2.8:1
2d	**4d** (63)[b]	—	—
2a	**3a'** (50)[c]	**9** (26)	—

[a] The reaction was catalysed by TBACl. [b] The reaction was catalysed by TEBA. [c] The reaction was carried out by the conventional method (see Scheme 1).



4-*exo*-*tet*

tet and 6-*exo*-*tet* processes, respectively), while formation of the four-membered ring (4-*exo*-*tet* process) is kinetically unfavourable.

In contrast with these conclusions, we found that the reaction of diethyl malonate with different 1,3-dibromo compounds catalysed by various phase transfer catalysts provides a 1:1 mixture of crystalline diacids **3a–d** and the corresponding monocarboxylic acids **4a–d**, in good yields in most cases (Table 1). It appears that this favourable change is due to the different reaction conditions. In ref. 8, K_2CO_3, KOH or KOBu^t was used without solvent, while all the phase transfer catalysts in our case were generated *in situ* from quaternary ammonium halides in 50% aqueous sodium hydroxide. The altered reaction conditions may contribute to an increased rate of ring closure and make competitive reactions less significant.

It is important to note that the overall yield of the substituted cyclobutanecarboxylic acids under appropriate experimental conditions is much better than that in the traditional process. A unique feature of this step is that both ester hydrolysis and partial decarboxylation take place under the reaction conditions and during work-up of the reaction mixture. A subsequent simple distillation of the reaction product (a mixture of **3** and **4**) at 150 °C *in vacuo* permits the isolation of pure cyclobutanemonocarboxylic acids **4a–d** in good yield. The short reaction time and the application of room temperature and aqueous reaction conditions as additional noteworthy characteristics make this procedure much simpler than the conventional synthesis. This procedure produced a mixture of *cis* and *trans* isomers in every possible case **4b–d** as revealed by GC–MS. The structure of isomers was identified by ^1H and ^{13}C NMR spectroscopy. Assignment of *cis* and *trans* stereochemistry to the series of **4b–d** is based on chemical shifts and coupling constants which are in agreement with spectral data described previously.[11] In the ^1H NMR spectra the methyl protons of *cis* isomers all appear at slightly higher field than those of the corresponding *trans* isomers. Another consistent trend noted was the variation in the apparent coupling constants of the methyl protons. It was consistently smaller for the *trans* isomers (6.0–6.4 Hz) than for the *cis* isomers (6.6–6.8 Hz) which coincides with earlier results.[11,15] This was proven by studying the ^1H NMR spectra of the methyl ester of **4b** synthetized by two independent routes.[11]

In general the preferential formation of the *trans* isomer was observed. The *trans*/*cis* ratio varies between 3:1 and 1.5:1 depending on the conditions. In the case of **4d** only two isomers were found, the third isomer only was present in traces (Table 1). The formation of isomeric mixture is in contrast with earlier studies in which the derivative of a single isomer[5,10] was reported, but coincide with more recent results.[11,12] The mixture of isomers was carried further in the synthesis.

In further steps towards substituted cyclobutanes, well-known and simple experimental procedures were used: esterification of **4a–c** with ethanolic hydrogen chloride, then reduction with lithium aluminium hydride giving the hydroxymethylcyclobutanes **5a–c**. A simple modification of the process reported by Caserio and coworkers[13] *i.e.* tosylation[14] and final reduction resulted in a significant improvement in the yield of the cyclobutanes.

It is clear from the above discussion that *in situ* monodecarboxylation is characteristic of this phase transfer catalysed ring closure. As a result, it was not feasible to carry out the synthesis of 1,1-dimethylcyclobutane **9** in this way. Instead, the traditional synthetic process was applied. Fortunately, as concerns the four 1,3-dibromo compounds studied, this method gives the best yield for the ring closure of 1,3-dibromopropane (Table 2). In the further transformation of the diester **3a'**, the same steps were employed as in the synthesis of the other compounds, ensuring the highest yield for this reaction sequence in the formation of **9**.

In conclusion, PTC was successfully applied in the synthesis of substituted cyclobutanes. The notable advantages of the procedure described are the ready availability and inexpensive nature of the starting materials and reagents, the relative

simplicity and speed of the process, and the better overall yields of the substituted cyclobutanes.

Experimental

Three diols used in this study (propane-1,3-diol, butane-1,3-diol and, pentane-2,4-diol) were Fluka products. 2-Methylpropane-1,3-diol was prepared from diethyl methylmalonate by reduction with lithium aluminium hydride.

Gas chromatographic analyses were performed on a 50 m HP-1 capillary column with an HP 5890 GC coupled with an HP 5970 MSD system, and He as the carrier gas. The calculations were carried out with an HP 59970 Chemstation.

The products were identified and their stereochemistry was studied *via* their ^1H and ^{13}C NMR (400 MHz Bruker AM 400 instrument), MS (Hewlett–Packard 5970 MSD, 70 eV) and IR (Unicam SP 2000 spectrophotometer) spectra. All J values are given in Hz.

The synthetic procedure described below for the preparation of methylcyclobutane is representative of the synthesis of all substituted cyclobutanes.

Cyclobutanecarboxylic Acid **4a**.—Triethyl(benzyl)ammonium chloride (TEBA) (3.54 g, 15 mmol), diethyl malonate (4.5 cm^3, 45 mmol), and 1,3-dibromopropane (4.6 cm^3, 45 mmol) were combined in 50% aqeuous sodium hydroxide (60 cm^3) and the mixture was then stirred mechanically for 1 h, then diluted with water (140 cm^3) and extracted with diethyl ether (2 × 50 cm^3). The aqueous phase was cooled in ice and acidified with concentrated hydrochloric acid to pH 1. After extraction with diethyl ether (3 × 50 cm^3) and evaporation, the crude product (1.3 g of a 1 : 1 mixture of **3a** and **4a**) was distilled at 150 °C under reduced pressure to yield 1.0 g (41%) of cyclobutanecarboxylic acid **4a**, b.p. 200–201 °C; m/z (%) 100 (7.5, M^+), 99 (10, M − 1), 55 (100, $C_4H_7^+$); δ_H 1.98 (m, 2 H, CH_2), 2.28 (m, 4 H) and 3.17 (m, 1 H, C*H*-CO_2H).

Ethyl Cyclobutanecarboxylate.—To a solution containing **4a** (18 g, 0.18 mol) in absolute ethanol (150 cm^3), was added concentrated hydrochloric acid (0.5 cm^3) and the mixture was allowed to stand overnight at room temp. The ethanol was distilled off through a 30 cm Vigreaux column. The acid was neutralized with trimethylamine (1 cm^3), and the salt was removed by filtration and washed with benzene (20 cm^3). After the evaporation of benzene, ethyl cyclobutanecarboxylate (17.6 g, 76%) was isolated, b.p. 158–159 °C; m/z (%) 128 (3, M^+), 113 (5, M − CH_3), 55 (100, $C_4H_7^+$) and 41 (9, $C_3H_5^+$); δ_H 1.25 (t, J 7.2, 3 H, CH_2CH_3), 1.95 (m, 2 H, CH_2), 2.26 (m, 4 H), 3.12 (m, 1 H, C*H*CO_2Et) and 4.12 (q, J 7.1, CH_2CH_3).

Cyclobutylmethanol **5a**.—A solution of ethyl cyclobutanecarboxylate (17.2 g, 0.135 mol) in diethyl ether (100 cm^3) was added dropwise in 20 min to lithium aluminium hydride (5.0 g, 0.137 mol) suspended diethyl ether (200 cm^3). The mixture was allowed to stand at room temp. for 24 h, and then heated under reflux for 1.5 h. After cooling, it was carefully hydrolysed by the slow addition of water (20 cm^3). The ether layer was separated and the aqueous phase was extracted with diethyl ether (5 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled through a 30 cm Holzman column to give **5a** (11.5 g, 53%), b.p. 143–144 °C; m/z (%) 85 (2, M^+ − 1), 57 (100, $C_4H_9^+$) and 55 (22, $C_4H_7^+$); δ_H 1.72 (m, 2 H, CH_2), 2.01 (m, 4 H), 2.49 (m, 1 H, *CH*-CH_2OH), 2.92 (s, 1 H, OH) and 3.55 (m, 2 H, CH_2OH).

Cyclobutylmethyl Toluene-p-*sulfonate* **6a**.—To a stirred solution of **5a** (8.6 g, 0.1 mol) in absolute pyridine (80 cm^3) maintained at 0 °C under nitrogen atmosphere, of toluene-*p*-sulfonyl chloride (17 g, 0.13 mol) was added in small portions during 30 min. The resulting yellow solution was kept at 0 °C for 3 h, and then poured into an ice-cooled solution of hydrochloric acid (6 mol dm^{-3}, 500 cm^3). Extraction of the product with chloroform (4 × 50 cm^3) after drying ($MgSO_4$–Norite) and evaporation under reduced pressure gave a yellow viscous oil (18.1 g, 65%). It was used without further purification in the preparation of **7a**; m/z (%) 240 (3, M^+), 173 (58) and 91 (100, $C_7H_7^+$).

Methylcyclobutane **7a**.—A solution of **6a** (18 g, 0.075 mol) in dry diglyme (40 cm^3) was added dropwise to a stirred, ice-cooled mixture of lithium aluminium hydride (5.0 g, 0.13 mol) and diglyme (40 cm^3). After 1 h at room temp., another portion of the hydride (4.5 g, 0.12 mol) was added. The mixture was heated at 50 °C under stirring and the product was distilled into a solid CO_2-cooled flask. The crude product, containing about 5% pent-1-ene as by-product, was purified by preparative gas chromatography (Carlo Erba Fractovap Mod P, 4 m 15% squalane/kieselguhr column) to yield methylcyclobutane (2.9 g, 56%), b.p. 36 °C; m/z (%) 70 (11, M^+), 55 (23, $C_4H_7^+$), 42 (100) and 41 (35, $C_3H_5^+$); δ_H 1.03 (d, J 6.7, 3 H, CH_3), 1.54 (m, 2α H), 1.80 (m, 2β H), 2.05 (m, 2 H, CH_2) and 2.37 (m, 1 H, C*H*-CH_3).

2-*Methylcyclobutanecarboxylic Acid* **4b**.—TEBA (3.54 g, 15 mmol), diethyl malonate (1.5 cm^3, 15 mmol), and 1,3-dibromobutane (1.3 cm^3, 15 mmol) were combined in 50% aqueous sodium hydroxide (60 cm^3) and the mixture was then stirred mechanically for 1 h, then diluted with water (70 cm^3) and extracted with diethyl ether (2 × 50 cm^3). The aqueous phase was cooled in ice and acidified with concentrated hydrochloric acid to pH 1. After extraction with diethyl ether (3 × 50 cm^3) and evaporation, the crude product (2.0 g of a 1 : 1 mixture of **3b** and **4b**) was distilled at 150 °C under reduced pressure to yield 61% of 2-methylcyclobutanecarboxylic acid **4b**, mixture of *cis*- and *trans*-isomers and 15% of 3-methylpent-4-enecarboxylic acid as byproduct after distillation through a 15 cm Vigreaux column. The isomeric distribution was determined by GC–MS on HP-1 capillary column (Table 1).

cis-**4b**, m/z (%) 114 (34, M^+), 99 (9, $M^+ - CH_3$), 96 (8, $M^+ - H_2O$), 69 (26, $M^+ - CO_2H$), 55 (100, $C_4H_7^+$) and 45 (22, $^+CO_2H$); δ_H 1.08 (d, J 6.8, 3 H, CH_3), 1.64 (m, 1 H, C*H*-CH_3), 2.34 (m, 2 H, CH_2), 2.42 (m, 2 H, CH_2) and 5.8 (m, 1 H, C*H*-CO_2H); δ_C 18.8, 25.5, 33.3, 40.3, 44.7 and 178.2; ν_{max}(film)/cm^{-1} 1695.

trans-**4b**, m/z (%) (near) identical with *cis*-**4b**; δ_H 1.14 (d, J 6.4, 3 H, CH_3), 1.56 (m, 1 H, C*H*-CH_3), 2.04 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2) and 5.48 (m, 1 H, C*H*-CO_2H); δ_C 16.0, 26.7, 31.9, 34.4, 40.9 and 179.0; ν_{max}(film)/cm^{-1} 1710.

3-*Methylcyclobutanecarboxylic Acid* **4c**.—TBACl (2.0 g, 10 mmol), diethyl malonate (1.05 cm^3, 11 mmol), and 2-methyl-1,3-dibromopropane (1.0 cm^3, 10 mmol) were combined in 50% aqueous sodium hydroxide (30 cm^3) and the mixture was then stirred mechanically for 1 h, then diluted with 70 cm^3 water and extracted with diethyl ether (2 × 25 cm^3). The aqueous phase was cooled in ice and acidified with concentrated hydrochloric acid to pH 1. After extraction with diethyl ether (3 × 25 cm^3) and evaporation, the crude product (0.7 g of a 1 : 1 mixture of **3c** and **4c**) was distilled at 150 °C under reduced pressure to yield 50% of 2-methylcyclobutanecarboxylic acid **4c**, mixture of *cis*- and *trans*-isomers and 12% of 4-methylpent-4-enecarboxylic acid as byproduct after distillation through a 15 cm Vigreaux column. The isomeric distribution was determined by GC–MS on HP-1 capillary column (Table 1).

cis-**4c**, m/z (%) 114 (32, M^+), 99 (10, $M^+ - CH_3$), 96 (8, $M^+ - H_2O$), 69 (24, $M^+ - CO_2H$), 55 (100, $C_4H_7^+$) and 45 (24, $^+CO_2H$); δ_H 1.08 (d, J 6.7, 3 H, CH_3), 1.61 (m, 1 H, C*H*-

CH_3), 2.06 (m, 2 H, CH_2), 2.47 (m, 2 H, CH_2) and 4.12 (m, 1 H, C*H*-CO_2H).

trans-**4c**, *m*/*z* (%) (near) identical with *cis*-**4c**; δ_H 1.12 (d, *J* 6.5, 3 H, CH_3), 1.72 (m, 1 H, C*H*-CH_3), 2.04 (m, 2 H, CH_2), 2.30 (m, 2 H, CH_2) and 4.21 (m, 1 H, C*H*-CO_2H).

2,4-*Dimethylcyclobutanecarboxylic Acid* **4d**.—TEBA (3.54 g, 15 mmol), diethyl malonate (1.5 cm^3, 15 mmol), and 2,4-dimethyl-1,3-dibromopropane (1.4 cm^3, 15 mmol) were combined in 50% aqueous sodium hydroxide (30 cm^3) and the mixture was then stirred mechanically for 1 h, then diluted with water (70 cm^3) and extracted with diethyl ether (2 × 50 cm^3). The aqueous phase was cooled in ice and acidified with concentrated hydrochloric acid to pH 1. After extraction with diethyl ether (3 × 50 cm^3) and evaporation, the crude product (2.1 g of a 1 : 1 mixture of **3d** and **4d**) was distilled at 150 °C under reduced pressure to yield 2,4-dimethylcyclobutanecarboxylic acid **4d** (63%), mixture of three isomers and 3,4-dimethylpent-4-enecarboxylic acid (14%) as byproduct after distillation through a 15 cm Vigreaux column. The isomeric distribution was determined by GC–MS on HP-1 capillary column (Table 1).

2,4-*trans*,*trans*-Dimethylcyclobutanecarboxylic acid *m*/*z* (%) 128 (14, M^+), 113 (6, $M^+ - CH_3$), 110 (5, $M^+ - H_2O$), 83 (17, $M^+ - CO_2H$), 55 (25, $C_4H_7^+$), 45 (18, $^+CO_2H$) and 41 (100, $C_3H_5^+$); δ_H 1.64 (d, *J* 6.0, 6 H, 2 CH_3), 2.30 (m, 2 H, C*H*-CH_3), 2.62 (m, 2 H, CH_2) and 5.37 (q, *J* 1.4 and 5.7, 1 H, C*H*-CO_2H).

2,4-*cis*,*cis*-Dimethylcyclobutanecarboxylic acid *m*/*z* (%) (near) identical with 2,4-*trans*,*trans*-**4d**; δ_H 1.05 (d, *J* 6.6, 6 H, 2 CH_3), 2.28 (m, 2 H, 2 C*H*-CH_3), 2.58 (m, 2 H, CH_2) and 5.49 (q, *J* 0.8 and 6.0, 1 H, C*H*-CO_2H).

The third isomer was found in traces.

Acknowledgements

We acknowledge the support provided for this research by the Hungarian National Science Foundation through grant OTKA 1885/1991.

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Paper 2/06421I
Received 1*st December* 1992
Accepted 7*th January* 1993