

Reduction of 3-Substituted 1-Arylcyclobutanols

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Abstract. A useful and specific method for the the title reaction (**1** → **2**) involves treatment with NaBH₄ in CF₃COOH whereas other procedures from the literature yield hard-to-separate mixtures. 1-Arylcyclohexanols **3** give mainly cyc-

lohexenes with borohydride/trifluoroacetic acid. Their reduction to compounds **4**, however, is possible with MeSO₃H/NaBH₄.

In the context of our work on novel model compounds for liquid crystals which contain cyclobutyl groups, [1–4] we were interested in an effective benzylic alcohol → hydrocarbon conversion of 1-arylcyclobutanols **1** to give compounds **2**. Ideally this should be a one-pot process.

Hydrogenolysis as well as elimination/catalytic hydrogenation led to unpleasant product mixtures frequently. Likewise, Olah's method (Pd/cyclohexene/AlCl₃) [4] or our own previous procedure (Me₂NBH₂/TiCl₄) [5] gave unsatisfactory yields oftentimes. When, however, compound **1a** was treated with lithium aluminumhydride/aluminum trichloride in *tert*-butyl methyl ether according to Brewster *et al.* [6], **2a** was obtained in 51% as a 58:42 mixture of *trans* and *cis* isomers. Both chemical yield (93%) and stereoselectivity (7:3) were improved when applying a modification of the method of Gribble *et al.* (NaBH₄ in CF₃COOH) [7, 8].

Consequently, this last mentioned procedure was applied to an entire series of 3-substituted 1-arylcyclobutanols **1a–1o**. A preponderance of the desired *trans* isomers (52–76%) was observed in all cases, and most chemical yields were satisfactory (Table 1). It is remarkable that the *cis/trans* ratios vary widely with the type of aryl substituent. Whereas the

fluorine carrying aryls led to high proportions of the *trans* isomers, the 4-methoxy and 4-alkyl phenyl gave poor selectivities.

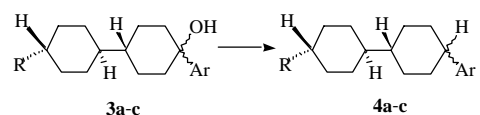
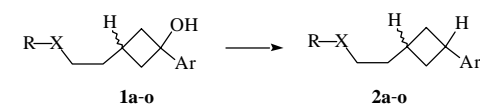
It is assumed that a benzylic cation is formed initially under the Gribble conditions and that this is quenched by NaBH₄·x(O₂CCF₃)_x [8]. This mechanistic proposal is supported by the occurrence of an intensive red coloration early on in the course of the reaction. The coloration fades away as the conversion proceeds.

Investigating the scope of the present method, 1-arylcyclohexanols **3a–c** were reacted likewise. Quite in contrast to the cyclobutanol case, here elimination of water was the main reaction path unfortunately, and only little **4** was formed.

As trifluoroacetic acid is not a cheap reagent for industrial purposes, we made a few cursory experiments to replace it by methanesulfonic acid. It turned out that MeSO₃H/NaBH₄/CH₂Cl₂ could be adapted to the **3** → **4** reduction. Isomer mixtures **4** obtained in this way with methanesulfonic acid were remarkably rich in the *cis* epimers (70–85%; *cf.*, Table 1). Although this is less desirable for liquid crystal purposes, this finding might be useful in other cases. On the other hand, MeSO₃H/NaBH₄/CH₂Cl₂ reduction was not suitable at all for the **1** → **2** conversion.

These results show that the deoxygenation of substituted benzylic alcohols is very sensitive to their detailed structure. A specific method useful (at least) for the 1-arylcyclobutanols of this study involves modified conditions proposed first by Gribble [7], and 1-arylcyclohexanes can be reduced best with methanesulfonic acid and sodium borohydride in dichloromethane.

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	R	Ar
a	C ₃ H ₇	4-F-C ₆ H ₄
b	C ₅ H ₁₁	4-F-C ₆ H ₄
c	C ₅ H ₁₁	4-F ₃ C-OC ₆ H ₄

Scheme 1 Synthesis of 3-Substituted 1-Arylcyclobutanes and of 4-Substituted 1-Arylcyclohexanes

Experimental

Isomer ratios were determined by ¹H NMR spectroscopy. The signals for the tertiary benzylic protons on the four-membered rings resonate around δ/ppm = 3–4 as multiplets which are well separated. The lower field group can be assigned to the *trans* isomer. Starting compounds **1a–o** and **3a–c** were obtained by Grignard reactions of the corresponding cyclobutanones [10] or cyclohexanones.

Table 1 Reduction of substituted 1-arylcyclobutanols **1** to give compounds **2** (using NaBH₄ in CF₃COOH) and of substituted 1-arylcyclohexanols **3** to give Compounds **4** (using NaBH₄/MeSO₃H in CH₂Cl₂)

Comp.	R	X	Ar	Yield (%)	<i>cis</i> : <i>trans</i>	
2a	H ₃ C-O	C ₆ H ₅	4-F-C ₆ H ₄	93	30	70
2b	F	C ₆ H ₅	3,4,5-tri-F-C ₆ H ₂	93	28	72
2c	F	C ₆ H ₅	4-F ₃ C-O-C ₆ H ₄	67	31	69
2d	C ₂ H ₅	cyclohexyl	4-F-C ₆ H ₄	89	29	71
2e	C ₂ H ₅	cyclohexyl	3,4,5-tri-F-C ₆ H ₂	89	26	74
2f	C ₂ H ₅	cyclohexyl	4-H ₃ C-O-C ₆ H ₄	50	42	58
2g	C ₂ H ₅	cyclohexyl	4-(C ₃ H ₇)-C ₆ H ₄	76	51	49
2h	C ₃ H ₇	cyclohexyl	4-F-C ₆ H ₄	61	26	74
2i	C ₃ H ₇	cyclohexyl	3,4,5-tri-F-C ₆ H ₂	66	24	76
2j	C ₃ H ₇	cyclohexyl	4-H ₃ C-O-C ₆ H ₄	49	33	67
2k	C ₃ H ₇	cyclohexyl	4-(C ₃ H ₇)-C ₆ H ₄	42	32	68
2l	C ₃ H ₁₁	cyclohexyl	4-F-C ₆ H ₄	80	31	69
2m	C ₃ H ₁₁	cyclohexyl	3,4,5-tri-F-C ₆ H ₂	88	25	75
2n	C ₃ H ₁₁	cyclohexyl	4-H ₃ C-O-C ₆ H ₄	68	48	52
2o	C ₃ H ₁₁	cyclohexyl	4-(C ₃ H ₇)-C ₆ H ₄	65	44	56
4a	C ₃ H ₇	–	4-F-C ₆ H ₄	81	80	20
4b	C ₃ H ₁₁	–	4-F-C ₆ H ₄	83	75	25
4c	C ₃ H ₁₁	–	4-F ₃ C-O-C ₆ H ₄	81	70	30

Reduction of 1-Arylcyclobutanols 1 (General Method)*Synthesis of 3-Substituted 1-Arylcyclobutanes*

2 g (53 mmol) of sodium borohydride was added gradually to 50 ml of dry trifluoroacetic acid at 0–5 °C under argon. The mixture was warmed to 15 °C, and a solution of 10 mmol of **1** in 25 ml of dry dichloromethane was dropped in within 15 min. The solution turned dark red, the colour fading later slowly. After 19 h at room temperature, water was added carefully for workup. The mixture was made alkaline with NaOH pellets and extracted repeatedly with ether. The combined ethereal extracts were washed with 15 ml of concentrated brine,

dried with sodium sulfate, and concentrated *in vacuo* leaving compounds **2**.

Reduction of 1-Arylcyclohexanols 3 (General Method)*Synthesis of 4-Substituted 1-Arylcyclohexanes*

4.73 g (125 mmol) of sodium borohydride and 12.5 mmol of compound **3** were suspended in 30 ml of dry dichloromethane at –10 to 0 °C under nitrogen. A solution of 78.49 g (817 mmol) of methanesulfonic acid in 50 ml of dry dichloromethane was slowly dropped in within 1 h. The mixture was allowed to warm to room temperature and stirred for

Table 2 Analytical data of compounds **2a–o** and **4a–c** (Boiling points refer to air bath temperatures of a Kugelrohr distillation)

Comp.	<i>m.p.</i> (°C) or <i>b.p.</i> (°C/Torr)	formula	molec. weight	MS (mol peak, base peak)	calcd./found C		calcd./found H	
2a	141/0.4	C ₁₉ H ₂₁ FO	284.37	284, 121	80.25	80.05	7.44	7.21
2b	120/0.2	C ₁₈ H ₁₆ F ₄	308.31		69.67	69.70	5.85	5.82
2c	120/0.2	C ₁₉ H ₁₈ F ₄ O	338.34		67.45	67.19	5.36	5.50
2d	160/0.1	C ₂₀ H ₂₉ F	288.44	288, 122	83.28	83.03	10.13	10.18
2e	130–40/0.1	C ₂₀ H ₂₇ F ₃	324.42	324, 158	74.04	73.88	8.39	8.42
2f	165/0.1	C ₂₁ H ₃₂ O	300.48	300, 134	83.94	83.89	10.73	10.86
2g	130–40/0.2	C ₂₃ H ₃₆	312.53	312, 146	88.39	88.27	11.61	11.49
2h	175/0.2	C ₂₁ H ₃₁ F	302.47	302, 122	83.39	83.34	10.33	10.57
2i	160/0.2	C ₂₁ H ₂₉ F ₃	338.45	338, 158	74.52	74.40	8.64	8.32
2j	190/0.2	C ₂₂ H ₃₄ O	314.51	314, 134	84.02	83.93	10.90	11.37
2k	175/0.2	C ₂₄ H ₃₈	326.56	326, 146	88.27	88.24	11.73	11.42
2l	160–80/0.1	C ₂₃ H ₃₅ F	330.53	330, 122	83.58	83.80	10.67	10.72
2m	160/0.1	C ₂₃ H ₃₃ F ₃	366.51	366, 158	75.37	75.31	9.08	9.20
2n	180/0.1	C ₂₄ H ₃₈ O	342.56	342, 134	84.15	84.20	11.18	11.31
2o	170–90/0.1	C ₂₆ H ₄₂	354.61	354, 146	88.06	88.06	11.94	12.05
4a	73	C ₂₁ H ₃₁ F	302.48	302 (100%)				
4b	40	C ₂₃ H ₃₅ F	330.53	330, 122				
4c	165/0.1	C ₂₄ H ₃₅ F ₃ O	396.54	396 (100%)				

1 h. It was worked up then by addition of 120 ml of 25% NaOH under cooling and vigorous stirring. 50 ml of ether were added, and stirring was continued for 15 min. Thereafter the phases were separated, and the aqueous layer was extracted again twice with 50 ml of ether. The combined organic phases were washed 25 ml of concentrated brine, dried over sodium sulfate, and concentrated *in vacuo* leaving compounds **4**.

Data for compounds **2a–o** and **4a–c** are recorded in Table 2.

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