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Selective Synthesis of 1,4-Dialkylbenzenes from Terephthalic Acid

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Abstract: Terephthalic acid reacts with alkyl halides under Birch conditions to substituted 1,4-cyclohexadienes in high yields and good stereoselectivities. Electrophiles containing ester or nitrile groups undergo a surprising fragmentation under the reaction conditions. Subsequent treatment with chlorosulfonic acid proceeds by an interesting tandem *decarbonylation/decarboxylation*, affording 1,4-dialkylbenzenes in excellent regioselectivity. Thus our new method is superior to classical Friedel–Crafts alkylations.

Keywords: alkylations; arenes; Birch reductions; reaction mechanisms; synthetic methods

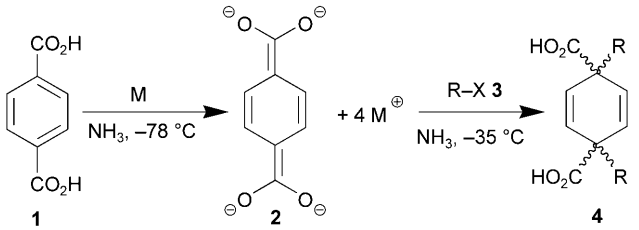
Alkylarenes represent important industrial products and are used as intermediates in organic synthesis.[1] However, the direct Friedel–Crafts bis-alkylation of benzene is difficult to control and affords regioisomeric mixtures.[2] The more selective Friedel–Crafts acylation with subsequent reduction of the ketone group requires many steps.[3] Modern methodologies start from aryl halides which are coupled with organoboron, -magnesium, -zinc or -indium compounds in the presence of various catalysts.[4] However, the synthesis of the precursors is often tedious, and many reactions are limited to sp^2 and *sp* centers due to competing β-hydride eliminations.

Aromatic carboxylic acids offer an interesting alternative, since they are commercially available, inexpensive industrial raw materials.[5] Gooßen et al. described coupling reactions and proto-*decarboxylations* of such compounds in the presence of copper or silver catalysts.[6] Our group has developed a simple two-step *ipso* substitution of benzoic acids by alkyl halides *via* Birch reduction and subsequent *decarbonylation*.[7] Very recently, we applied this methodology to naphthalenes and functionalized derivatives.[8] However, the transformations required a proton *para* to the newly introduced alkyl chain as leaving group. Herein we describe a new approach for arene alkylations starting from inexpensive terephthalic acid. The reactions proceed under double C–C bond cleavage by an interesting tandem *decarbonylation–decarboxylation*, and open a selective entry to 1,4-dialkylbenzenes from easily available precursors.

The Birch reduction of arenes is a powerful method for the synthesis of 1,4-cyclohexadienes on a large scale.[9] Especially benzoic acids react with high regioselectivity and allow subsequent alkylations in a one-pot procedure.[10] However, to the best of our knowledge, this reductive alkylation was never applied to terephthalic acid (**1**), although it is a very cheap starting material. Therefore, we investigated the Birch reduction in the presence of various alkyl halides **3** and optimized the conditions with bromoethane (**3a**) as model compound (Table 1).

First experiments were conducted with lithium as metal and a 0.05 M solution of terephthalic acid (**1**) in liquid ammonia (entry 1), suitable conditions in our previous studies on toluic acids.[11] Indeed, the 1,4-diethyl-2,5-cyclohexadiene **4a** was isolated in 73% yield, due to a moderate conversion of only 80%. Therefore, we replaced lithium by sodium and potassium, metals as often applied in Birch reductions,[9] but the conversions were even lower (entries 2 and 3). This can be rationalized by the bad solubility of the intermediately formed tetraanion **2** in liquid ammonia, resulting in its slow alkylation and reoxidation to terephthalic acid during work-up. Co-solvents like ethanol or tetrahydrofuran did not increase the solubility, but simple dilution (0.01 M) with more ammonia led to a homogenous solution, full conversion and afforded the 1,4-bis-ethyl-2,5-cyclohexadiene **4a** in 93% yield (entry 4). We applied this optimized procedure to various alkyl halides **3**, and the products **4b–d** were isolated on a 10-mmol scale in high yields in analyti-

Table 1. Birch reduction of terephthalic acid (**1**) to the substituted 2,5-cyclohexadienes **4**.



Entry	M	R–X (**3**)	Concentration [mM]	Conversion [%][a]	*trans*:*cis* Ratio[a]	**4** (Yield [%])[b]
1	Li	EtBr (**3a**)	50	80	60:40	**4a** (73)
2	Na	EtBr (**3a**)	50	35	25:75	**4a** (29)
3	K	EtBr (**3a**)	50	15	20:80	**4a** (12)
4	Li	EtBr (**3a**)	10	>97	80:20	**4a** (93)
5	Li	MeI (**3b**)	10	>97	40:60	**4b** (83)
6	Li	*n*-HexBr (**3c**)	10	>97	>95:5	**4c** (89)
7	Li	*n*-OctBr (**3d**)	10	>97	>95:5	**4d** (84)
8	Li	*i*-PrBr (**3e**)	10	>97	90:10	**4e** (85)
9	Li	BnBr (**3f**)	10	80	>95:5	**4f** (73)
10	Li	AllylBr (**3g**)	10	85	60:40	**4g** (74)
11	Li	EtO_2CCH_2Br (**3h**)	10	<5	–	–
12	Li	$CNCH_2Br$ (**3i**)	10	<5	–	–
13	Li	$Cl(CH_2)_4Br$ (**3j**)	10	>97	85:15	**4j** (96)

[a] Determined by NMR spectra of the crude products.
[b] Yield of analytically pure product, isolated by crystallization or column chromatography.

cally pure form (entries 5–8, Experimental Section, Supporting Information).

Interestingly, all reactions afforded exclusively the bis-alkylated products **4**, mono-alkylation was not observed. Furthermore, *trans* isomers were formed with high selectivity with sterically demanding electrophiles **3c–f** (entries 6–9). This can be explained by the mono-alkylated intermediate **5**, which is attacked preferentially *anti* to the substituent R (pathway **A**, Figure 1). On the other hand, for smaller electrophiles **3a** and **3b** these interactions are less distinctive and the *cis* isomers are formed as well (pathway **B**). Further mechanistic evidence was found with sodium and potassium as counterions. Now the carboxylate group becomes sterically more demanding and the *cis*-selectivity increases (entries 2 and 3). For the same reason, more of *cis*-**4a** was formed in our first experiment (entry 1), since the higher concentration leads to more counterions at the carboxylate group. Although we describe herein the first reductive alkylation of terephthalic acid (**1**), the stereoselectivities are comparable to those of Birch reductions of anthracenes.[12]

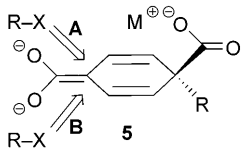
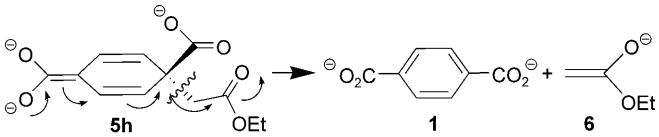


Figure 1. Preferred reactions of carboxylate **5**.

The *cis* and *trans* isomers **4** showed different characteristic NMR signals and could be directly used as mixtures for the synthesis of 1,4-dialkylbenzenes (see below). On the other hand, their separation was possible by crystallization, and the configuration was unequivocally proven by an X-ray structure of the *trans*-1,4-diethyl-2,5-cyclohexadiene **4a** (Supporting Information).

Subsequently, we investigated other functionalized alkyl halides under Birch conditions (Table 1). Benzyl (**3f**) and allyl bromides (**3g**) afforded somewhat lower conversions and yields (entries 9 and 10), which can be rationalized by the oxidation of the tetraanion **2** by electron transfer to the reactive halide. Surprisingly, only terephthalic acid (**1**) was isolated after the reaction with bromoethyl acetate (**3h**) and bromoacetonitrile (**3i**) (entries 11 and 12), although such electrophiles gave good yields with toluic and naphthoic acids.[8] Our mechanistic explanation is based on the mono-alkylated intermediate **5h** (or **5i**, respectively), which can undergo a fragmentation, due to the formation of a stabilized ester enolate **6** (Scheme 1).

Finally, we succeeded in the synthesis of cyclohexadiene **4j** with a halogen atom in the side chain in excellent yield (Table 1, entry 13), which is an interesting substrate for further transformations. Nucleophilic substitutions or radical reactions should allow the introduction of other functional groups. Overall, we have demonstrated the reductive alkylation of terephthalic acid (**1**) with various electrophiles **3** for the first



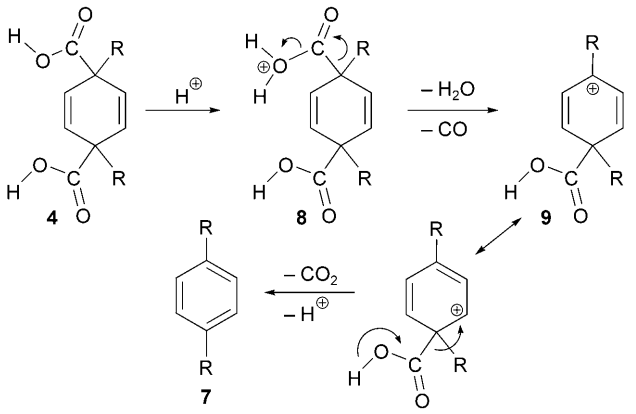
Scheme 1. Fragmentation of mono-alkylated intermediate **5h**.

time, which offered easy access to the hitherto unknown 1,4-bis-alkylated 2,5-cyclohexadienes **4** in high yields and stereoselectivities.

To obtain the desired 1,4-dialkylbenzenes, two acid groups had to be cleaved in the next step. Free radical or oxidative decarboxylations have been applied for simple cyclohexadiene-monocarboxylic acids.[13] However, a proton is required in the 4-position, and lead tetraacetate is problematic due to its high toxicity. Thus, we investigated the reactions of 2,5-cyclohexadienes **4** in the presence of chlorosulfonic acid (Table 2), a reagent that we developed for the aromatization of monocarboxylic acids.[7,8]

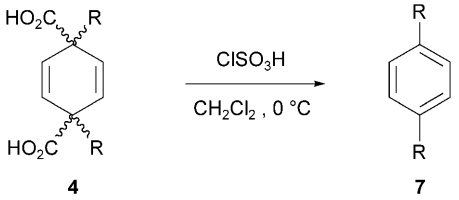
Indeed, full conversion was observed even at 0 °C, and we isolated the 1,4-dialkylbenzenes **7** in moderate to high yields in analytically pure form (Table 2, Supporting Information). Only the bisallyl derivative **4g** polymerized under the acidic reaction conditions (entry 7) and some amount of *p*-xylene (**7b**) was lost during work-up, due to its volatility (entry 2). Best results were obtained for arenes **7c** and **7d** with long alkyl chains (entries 3 and 4), which are attractive precursors for the synthesis of organic materials with interesting properties.[14] Furthermore, even halogenides are tolerated under the reaction conditions (entry 8), which afforded arene **7j** in high yield and should allow further transformations. Thus, we have realized the regioselective synthesis of various 1,4-dialkylbenzenes from easily available terephthalic acid (**1**) in only two steps.

The formation of the arenes **7** is interesting from the mechanistic point of view, since two C–C bonds have to be cleaved during the aromatization. In the first step, protonation of the carboxylic acid with the stronger Brønsted acid affords intermediate **8**, which undergoes dehydration and *decarbonylation* to the stabilized carbenium ion **9** (Scheme 2). Thus, chlorosulfonic acid has two advantages, the strong acidity and hygroscopicity, making it a superior reagent for the transformation of cyclohexadienes **4**, in accordance to our previous studies.[7,8]



Scheme 2. Proposed mechanism for the formation of arenes **7**.

Table 2. Synthesis of 1,4-dialkylbenzenes **7**.



Entry	Cyclohexadiene **4**	R	Conv. [%][a]	Arene **7** [%][b]
1	**4a**	Et	>97	**7a** (85)
2	**4b**	Me	>97	**7b** (64)
3	**4c**	*n*-Hex	>97	**7c** (91)
4	**4d**	*n*-Oct	>97	**7d** (95)
5	**4e**	*i*-Pr	>97	**10** (84)[c]
6	**4f**	Bn	>97	**7f** (78)
7	**4g**	Allyl	>97	–
8	**4j**	$Cl(CH_2)_4$	>97	**7j** (92)

[a] Determined by TLC.
[b] Yield of analytically pure product, isolated by column chromatography.
[c] Formation of 4-isopropylbenzoic acid (**10**).

Since direct deprotonation of carbenium ion **9** is not possible due to the quaternary carbon atom, the only pathway to arenes **7** is an additional C–C bond cleavage under *decarboxylation* (Scheme 2). The formation of CO *and* CO_2 was unequivocally proven by chemical trapping and IR spectroscopy (Supporting Information).

Further evidence for such a mechanism was found with cyclohexadiene **4e** (R = *i*-Pr). Now the fragmentation of the alkyl group is faster, since a stabilized secondary isopropyl cation is formed, which affords 2-chloropropane as side-product under the reaction conditions (Supporting Information). Thus, 4-isopropylbenzoic acid (**10**) was isolated in 84% yield (Table 2, entry 5). Overall, the reaction proceeds by an interesting tandem *decarbonylation–decarboxylation*, which was hitherto unknown and offers easy access to arenes **7** by a double C–C bond cleavage.

In conclusion, we have developed a convenient and selective synthesis of 1,4-dialkylbenzenes. The hitherto unknown Birch reduction of terephthalic acid af-

forded bisalkylated products in high yields and stereoselectivities. A surprising fragmentation was observed with electrophiles containing ester or nitrile groups. The rearomatization proceeded smoothly with chlorosulfonic acid by an interesting tandem *dehydration–decarbonylation–decarboxylation*. Finally, 1,4-dialkylbenzenes were isolated in high yields and exclusive regioselectivity, which is superior to classical Friedel–Crafts alkylations. Future studies will focus on the synthesis of functionalized arenes and applications in natural product chemistry.

Experimental Section

General Procedure for the Birch Reductions

Lithium (0.555 g, 80 mmol) was added in small portions at −78 °C to a suspension of terephthalic acid (**1**) (1.66 g, 10.0 mmol) in liquid ammonia (500 mL) until the blue color persisted. After five hours at this temperature, the alkyl halide **3** (100 mmol) was added slowly. The reaction mixture was allowed to warm up to −35 °C before adding 1-bromooctane (**3d**) and benzyl bromide (**3f**). Ammonia was evaporated over night, and the solid residue was dissolved in water (100 mL). After cooling to 0 °C, concentrated HCl was added to reach pH 1, and the resulting precipitate was filtered off and dried in a desiccator. The products were purified by recrystallization (**4a**, **4b**, **4e**, **4g** from water; **4c**, **4d**, **4f**, **4j** from water/ethanol 1/1) and gave correct analytical data, including elemental analysis (Supporting Information).

General Procedure for the Synthesis of 1,4-Dialkylbenzenes 7

The cyclohexadienes **4** (2.0 mmol) were suspended in dry dichloromethane (10 mL) and cooled to 0 °C. A solution of chlorosulfonic acid (2.0 to 4.0 mmol, 1 M in dichloromethane) was added dropwise under evolution of CO and CO_2 until TLC showed full conversion. The solution was neutralized with saturated sodium carbonate (20 mL) and the aqueous phase was extracted with dichloromethane (4 × 10 mL). The combined organic phases were dried over magnesium sulfate. After removal of the solvent, the arenes **7** were purified by column chromatography on silica gel (dichloromethane) and gave correct analytical data, including elemental analysis (Supporting Information).

Acknowledgements

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