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Substitution effect on the regioselective halogen/metal exchange of 3-substituted 1,2,5-tribromobenzenes

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Abstract

Regioselective halogen/metal exchange reactions using isopropylmagnesium chloride were studied on 3-substituted 1,2,5-tribromoarenes. Seven examples are given.

Keywords: 1,2-Dibromobenzene; Grignard reactions; Halogen/metal exchange; Regioselectivity; Carboxylic acids

1. Introduction

Due to the ever increasing need for accessing highly functionalized benzene rings, the regioselective functionalization of di- and tribromoarenes has drawn increased attention from organic chemists. Regioselective cross coupling[1–4] and halogen/metal exchange reactions[5,6] of 1,4- and 1,3-dibromobenzenes are well documented in the literature. Conversely, only few examples of 1,2-dibromobenzene and 1,2,4-tribromobenzene derivatives have been studied in these same regioselective reactions.[7,8] Herein, we report the results of a site selective halogen/metal exchange reaction using isopropylmagnesium chloride with 3-substituted 1,2,5-tribromobenzenes.

2. Results and discussion

In general, the functionalization of the *ortho*-positions to the bromide in 3,5-substituted bromobenzene derivatives affords complex regioisomeric mixtures. Based on a recent report from Krasovskiy and Knochel[8a] on the regioselective halogen/metal exchange of 1,2,4-tribromobenzene, we envisioned that 3,5-substituted 1,2-dibromobenzene derivatives could be regioselective functionalized in a halogen/metal exchange reaction (Scheme 1). Regioselective halogen/metal exchange on 1,4- and 1,3-dibromoarenes using butyllithium has demonstrated low functional group compatibility even at −78 °C.[5,6] In contrast, Knochel and co-workers showed that isopropylmagnesium chloride undergoes smooth halogen/ magnesium exchange in the presence of a variety of functional groups including cyanides and esters.[9] More importantly, these exchange reactions occur typically between 0 and −40 °C without significant degradation of the arylmagnesium intermediates,[10] which prompted us to study the effects of substitution at the 3-position of 1,2,5-tribromobenzenes on the corresponding halogen/metal exchange reaction with isopropylmagnesium chloride.

A series of 3-substituted 1,2,5-tribromobenzene derivatives (**1a**–**g**, Table 1) were prepared following a standard bromination protocol[11,12] and were utilized as starting

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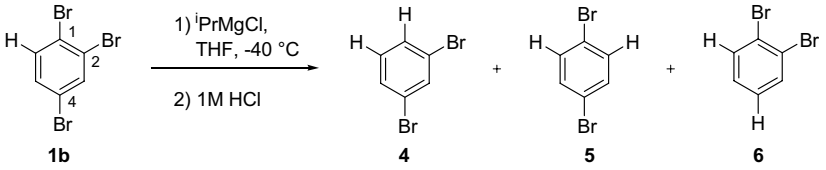


Scheme 1. Halogen/metal exchange on 1,2,4-tribromobenzene and its possible regioisomers studied by Knochel.

Table 1
Regioisomeric ratio and isolated yield of carboxylic acids **2** and **3**

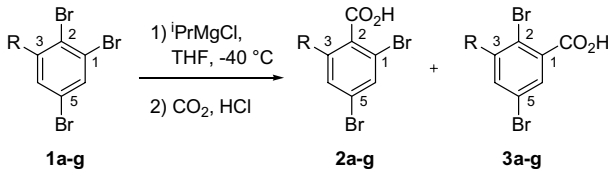
Entry	Compound	R	Ratio **2**:**3**	Yield[a] [%]
1	**1a**	Me	1:32	85
2	**1b**	H	1:5	78
3	**1c**	OMe	1:1	80
4	**1d**	CN	2.3:1[b]	N.D.[c]
5	**1e**	Cl	3:1	82
6	**1f**	CF_3	6:1	50
7	**1g**	F	11:1	90

[a] Isolated yield of mixture **2**:**3** (average of two runs).
[b] Ratio was determined after quench of the arylmagnesium intermediate with aqueous HCl.
[c] **2d** could not be isolated due to the formation of 4,6-dibromo-isobenzofuran-1,3-dione; the major signal by HPLC related to the formation of isobenzofuran while the minor signal remained unchanged during the work up conditions.

materials in a halogen/metal exchange using isopropylmagnesium chloride at −40 °C in THF.

Generally, the halogen/metal exchange on 3-substituted 1,2,5-tribromobenzenes **1a**–**g** formed exclusively two regioisomers as confirmed by LC/MS. The unambiguous assignments of the regioisomers formed in the halogen/metal exchange and the regioisomeric ratio were achieved by converting the arylmagnesium intermediates generated from **1a**–**g** into the corresponding benzoic acids by the addition of CO_2 as depicted in Scheme 2. The advantage of the benzoic acid was the simplified purification and the opportunity to analyze the products by a variety of NMR experiments.[13,14] The NMR experiments confirmed that under the reaction conditions, two regioisomers were formed (**2** and **3**) in various ratios depending upon the electronics of the substituent in the 3-position.[15,16] The regioisomeric ratios and isolated yields obtained in the halogen/metal exchange reaction are summarized in Table 1.

The bromide at C-1 was preferentially exchanged when electron neutral or donating groups were studied. 3-Methyl-1,2,5-tribromobenzene (**1a**) resulted in the formation of the carboxylic acids **2a**:**3a** as a 1:32 mixture. In



Scheme 2. Site selective halogen/metal exchange on 3-substituted 1,2,5-tribromobenzenes.

agreement with Knochel's observation,[8a] the bromide in 2-position of 1,2,4-tribromobenzene (**1b**) was predominantly exchanged using isopropylmagnesium chloride, although we obtained the carboxylic acids **2b**:**3b** as a 1:5 mixture.[17] Also the methoxy group with its positive mesomeric effect was expected to activate the bromide at C-1; however, treatment of **1c** with isopropylmagnesium chloride furnished a 1:1 mixture of regioisomers. This non-selective exchange could be rationalized by a competitive halogen/metal exchange of the bromides at C-2 and C-1 through the mesomeric effect and additional *ortho*-directing ability of the methoxy group.

Compounds, bearing electron withdrawing groups at C-3, preferentially exchanged the bromide at C-2 in the presence of isopropylmagnesium chloride as would be predicted from the inductive effect. Interestingly, the reactivity and extent of exchange of the bromide at C-2 varied and appears to depend on the extent of electronegativity of the substituent at C-3 ($F > CF_3 > Cl > CN$).[18] High regioselectivity ratios of the carboxylic acids **2**:**3** were observed for fluorobenzene (**1g**) (11:1) and trifluoromethylbenzene (**1f**) (6:1), respectively. Substituents at C-3 with a comparably lower electronegativity, like chlorobenzene (**1e**) and cyanobenzene (**1d**) led to decreased regioselective ratios for **2**:**3** of 3:1 and 2:1, respectively.

Although there was no spectroscopic evidence that the bromide at C-5 was exchanged,[19] the electron withdrawing ability of this bromide affected the reaction rate and site selectivity of the compounds in Table 1. For example, all of the C-3 substituted 1,2,5-tribromobenzenes studied (Table 1) underwent smooth exchange at −40 °C in 2 h and reactions went to completion in the presence of 1.1 equiv isopropylmagnesium chloride. In comparison to **1a**, for example, 2,3-dibromotoluene exchanged the bromide at C-2 at −20 °C in 18 h in the presence of 7 equiv of isopropylmagnesium chloride.[8c,20] Additionally, the presence of a bromide at C-5 led to decreased regioselective ratios compared to compounds without substitution at that position.

3. Conclusion and summary

We have demonstrated the regioselective halogen/metal exchange reaction between ^{i}PrMgCl and various 3-substituted 1,2,5-tribromobenzenes. As anticipated, we have found that the electronic nature of the substituent at C-3 greatly influences the regioselectivity in these reactions and in some cases provides exclusive access to a single

regioisomer. In general, electron withdrawing groups tend to activate the bromide at C-2 for exchange, while electron neutral and donating groups direct the Grignard reagent predominantly to the bromide at C-1. Additionally, a bromide at C-5 affected the overall reactivity of the compound and the regioselective ratios compared to compounds without substitution at C-5.

4. Experimental

4.1. General information

All starting materials were prepared according to Doyle et al.[11] and gave satisfactory ^{1}H and ^{13}C NMR spectra. All reactions were carried out under an inert gas atmosphere, using Schlenk techniques.

5. Typical procedures

5.1. General procedure for the halogen/metal exchange reaction: 2-bromo-6-fluorobenzoic acid (2g)

In a Schlenk flask 782 mg (2.35 mmol) of 3-fluoro-1,2,5-tribromobenzene was dissolved in 5 mL of THF under nitrogen. The reaction mixture was cooled to −40 °C and charged slowly with 1.30 mL (2.58 mmol, 1.98 M) of ^{i}PrMgCl in THF. The reaction mixture was aged for 2 h at −40 °C before a slow stream of CO_2 was passed through the reaction mixture for 1 h at −40 °C. The reaction mixture was added to 10 mL of 1 M NaOH and the organic layer was extracted two times with a total of 20 mL of 1 M NaOH. The combined aqueous layer was acidified using 3 M HCl and extracted three times with a total amount of 30 mL EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum. The white residue was purified by flash column chromatography (EtOAc/hexane 10:1). Compound **2g**: ^{1}H NMR ($CDCl_3$, 300 MHz): 10.29 (br s, 1H), 7.74–7.73 (m, 1H), 7.50 (dd, $J = 1.65$ Hz, 8.82 Hz, 1H); **3g**: ^{1}H NMR ($CDCl_3$, 300 MHz): 10.29 (br s, 1H), 7.78–7.77 (m, 1H), 7.61 (dd, $J = 2.31$ Hz, 8.13 Hz, 1H).

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13. Compound **3a** was identified by derivatization to the methyl ester. The methyl ester was subjected to NOE experiment and a strong NOE was observed with the ortho proton signal. 2,5-Dibromo-3-methylbenzoic acid methyl ester ^{1}H NMR ($CDCl_3$, 300 MHz): 7.74 (d, $J = 2.14$ Hz, 1H), 7.64 (d, $J = 2.15$ Hz, 1H), 3.83 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 166.2, 142.1, 136.4, 136.0, 130.2, 121.4, 120.7, 53.3, 23.2.; **2/3b** was confirmed by hydrolyzing the arylmagnesium intermediate with 1 M hydrochloric acid and comparing the product mixture with the commercial products: 1,4- and 1,3-dibromobenzene.; **2/3c**, **e**–**g** were identified by a proton coupled ^{13}C NMR experiment, where the carbonyl carbon was observed as a singlet for carboxylic acid **2** and a doublet (∼J = 7.5 Hz) for **3**.
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derivative (isobenzofurandione): melting point: 121 °C (121.5 °C, Ullmann, K. *Chem. Ber.* **1911**, *44*, 427); ^{1}H NMR (MeOH-d_4, 300 MHz): 9.05 (br s, acidic proton), 8.13 (d, $J = 1.53$ Hz, 1H), 7.95 (d, $J = 1.34$ Hz, 1H); ^{13}C NMR (MeOH-d_4, 75 MHz): 166.6, 166.3, 140.1, 136.3, 129.1, 128.1, 125.3, 118.1; **2e** (Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *38*, 1559: ^{1}H NMR (MeOH-d_4, 300 MHz): 7.81 (d, $J = 1.65$ Hz, 1H), 7.70 (d, $J = 1.66$ Hz, 1H); **2f**: ^{1}H NMR (MeOH-d_4, 300 MHz): 8.16 (d, $J = 1.23$ Hz, 1H), 8.01 (d, $J = 1.43$ Hz, 1H), acidic proton was not observed; ^{13}C NMR (MeOH-d_4, 75 MHz): 166.5, 138.8 (two signals), 134.3, 129.4 (q, $J = 30$ Hz)), 128.3 (q, $J = 7.5$ Hz), 123.1, 120.7; **2g** (Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 6551): ^{1}H NMR ($CDCl_3$, 300 MHz): 10.29 (br s, 1H), 7.74–7.73 (m, 1H), 7.50 (dd, $J = 1.65$ Hz, 8.82 Hz, 1H); **3a**: ^{1}H NMR (MeOH-d_4, 300 MHz): 7.57 (d, $J = 2.16$ Hz, 1H), 7.54 (d, $J = 2.14$ Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (MeOH-d_4, 75 MHz): 169.1, 143.3, 138.1, 136.5, 131.4 122.5, 121.7, 23.8; **3b**: ^{1}H NMR (MeOH-d_4, 300 MHz): 7.89 (d, $J = 2.36$ Hz, 1H), 7.56 (s, 1H), 7.52 (d, $J = 2.39$ Hz, 1H); ^{13}C NMR (MeOH-d_4, 75 MHz): 167.8, 136.9, 136.4, 135.9, 134.9, 122.0, 121.1; **3c**: ^{1}H NMR (MeOH-d_4, 300 MHz): 7.36 (d, $J = 2.23$ Hz, 1H), 7.24 (d, $J = 2.13$ Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (MeOH-d_4, 75 MHz): 167.3, 157.3, 137.0, 124.1, 121.1, 116.9, 109.1, 56.2; **3d**: ^{1}H NMR (MeOH-d_4, 300 MHz); **3e**: ^{1}H NMR (MeOH-d_4, 300 MHz): 7.84 (d, $J = 2.34$ Hz, 1H), 7.74 (d, $J = 2.35$ Hz, 1H); **3f**: ^{1}H NMR ($CDCl_3$, 300 MHz); **3g**: ^{1}H NMR ($CDCl_3$, 300 MHz): 10.29 (br s, 1H), 7.78–7.77 (m, 1H), 7.61(dd, $J = 2.31$ Hz, 8.13 Hz, 1H).

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