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Tetrahedron Letters 46 (2005) 483–485

Tetrahedron Letters

New synthetic method of 1,2-diaryl-1,2-dicarba-*closo*-dodecaboranes employing aromatic nucleophilic substitution (S_NAr) reaction

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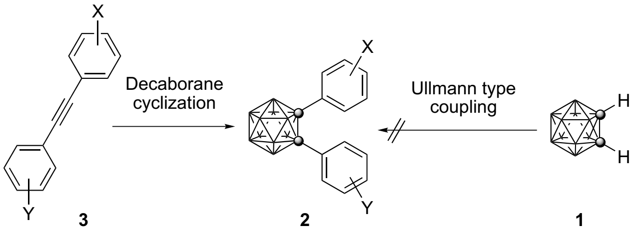
Received 4 October 2004; revised 12 November 2004; accepted 12 November 2004
Available online 7 December 2004

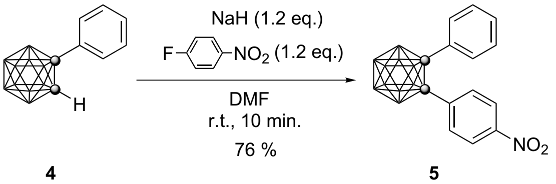
Abstract—Aromatic nucleophilic substitution (S_NAr) reaction of 1-phenyl-*o*-carborane with 4-nitrofluorobenzene in the presence of NaH or KO^{t}Bu proceeded smoothly to give 1-(4-nitrophenyl)-2-phenyl-*o*-carborane; similar reaction affords various 1,2-diaryl-*o*-carboranes, which are useful precursors for macromolecular construction and drug design.

Icosahedral carboranes (dicarba-*closo*-dodecaboranes) are a class of carbon-containing boron-cluster compounds having remarkable thermal and chemical stability and exceptional hydrophobic character, compared with other boron-containing compounds.[1] They have been also described as three-dimensional aromatic systems.[2] Diaryl-*o*-carboranes **2** with substituents at the *para*- or *meta*-position of aromatic rings are used as a backbone structure in various fields of chemistry.[3,4] In the course of application of carboranes for medicinal drug design[5] and macromolecular construction,[6] we needed to prepare 1,2-diaryl-*o*-carboranes with various substituents on both of the phenyl rings. Unfortunately, the only method available to prepare diaryl-*o*-carboranes **2** involves condensing the corresponding diaryl acetylenes **3** with decaborane(14) in the presence of Lewis bases, such as acetonitrile, amines and dialkyl sulfides.[7] However, this reaction has many limitations; the nitro group is reducible by decaborane(14), nucleophilic groups form complexes with decaborane, and acidic groups and groups susceptible to nucleophilic attack may also complicate the reaction. Wade et al. have reported on the synthesis of *C*-aryl carboranes by direct coupling reaction of the *C*-copper derivative of *o*-carborane **1** with aryl iodides.[8] This reaction can afford monoaryl-*o*-carboranes in moderate yield, but not diaryl-*o*-carboranes **2**, irrespective of the ratio of reagent to substrate (Eq. 1). This difficulty is explained by the chelating effect between the metal as a counter cation of the *o*-carboranyl anion and dimethoxyethane as the solvent.[9] Alternatively, reaction of hexafluorobenzene with lithiated carborane has been reported.[10,11] This seems to proceed via an S_NAr mechanism, but little attention has been paid to the possible use of the reaction.



(1)

Reaction of 1-phenyl-*o*-carborane (**4**) with 4-fluoronitrobenzene (1.2 equiv) in the presence of NaH (1.2 equiv) in DMF at room temperature smoothly proceeded to give 1-(4-nitrophenyl)-2-phenyl-*o*-carborane (**5**) within 10 min in 76% yield (Eq. 2).



(2)

Keywords: Carboranes; Aromatic nucleophilic substitution reaction (S_NAr).

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doi:10.1016/j.tetlet.2004.11.074

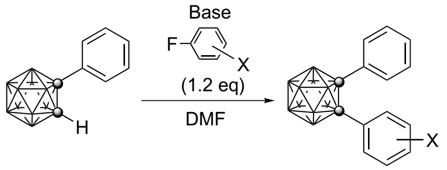
Table 1. Optimization of conditions for S_NAr reaction from **4** to **5**

Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	*n*-BuLi (1.2)	THF	0	2	6
2	(1.2)	THF–HMPA	0	2	17
3	(1.2)	Toluene	0	2	3
4	NaH (1.2)	THF	70	4	n.r.
5	(1.2)	Toluene	110	3	n.r.
6	(1.2)	DMF	0	20 min	81
7	(1.5)	DMF	0	20 min	91
8	KO^{t}Bu(1.2)	THF	rt	5.5	8
9	(1.2)	Toluene	rt	6	1.5
10	(1.2)	DMF	0	40 min	83

[a] Isolated yield.

Effects of the base and solvent are summarized in Table 1.[12] NaH, KO^{t}Bu and *n*-BuLi were selected as bases, which are often used in order to remove acidic hydrogen on carbon of *o*-carborane. In the case of the use of THF and toluene as solvents, no or only a trace quantity of the S_NAr product **5** was observed regardless of the kind of base (entries 1, 3–5, 8 and 9). The reactivity was moderately promoted by addition of HMPA (entry 2). We, therefore, suggest that the aggregation of metal carboranylate suppresses the nucleophilic attack of the anion on the aromatic carbon atom. The use of DMF as a solvent is likely to increase the interaction of counter cation and solvent, as HMPA was added in THF solvent, and it gave the best results: in the presence of NaH (method A)[13] or KO^{t}Bu (method B)[14] as a base at 0 °C, the desired compound was obtained in 91% or 83% yield, respectively (entries 7 and 10). The use of 1.5 equimolar NaH gave a better yield than 1.2 equimolar NaH (entries 6 vs 7). It is well known that deboronation of the most electron-deficient boron atom (3- or 6-position) of *o*-carborane by strong nucleophiles such as alkoxides affords nido-7,8-$C_2B_9H_{12}^-$.[15] In the present reaction, higher temperature and more prolonged reaction time reduced the yield of the S_NAr product owing to nucleophilic attack of the 1-phenyl-*o*-carboranyl anion on the starting 1-phenyl-*o*-carborane.

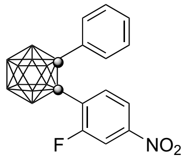
Table 2. S_NAr reaction of phenyl-*o*-carborane with fluorobenzenes having various electron-withdrawing groups



Entry	X	Method	Time (h)	Yield (%)[a]	Recovery (%)[a]
1	4-NO_2	A	20 min	91	0
2		B	40 min	83	2
3	3-NO_2	A	16	0[b,e]	0
4		B	12	0[e]	35
5	2-NO_2	A	4	0[c,e]	17
6		B	10	0[e]	43
7	2,4-$(NO_2)_2$	A	9	10[d]	84
8		B	9	28	60
9	4-CN	A	3	42[f]	0
10		B	10	20[f]	12

[a] Isolated yield.
[b] Compound **6** was obtained in 12% yield as the S_NAr product.
[c] Compound **7** was obtained in 5% yield as the S_NAr product.
[d] Compound **8** was obtained in 3% yield as the S_NAr product.
[e] Decomposition of *o*-carborane cage was observed.
[f] Decomposition of *o*-carborane cage and cyano group were observed.

To understand the differences in reactivities according to the position of the nitro group, we examined the S_NAr reaction of several fluoronitrobenzenes (Table 2). 2-Nitro- and 3-nitrofluorobenzenes failed to afford the desired products. It seems that the 2-nitro group has a steric effect and the 3-nitro group is ineffective for the activation of the S_NAr reaction (entries 3–6). However, it is surprising that other S_NAr products **6** (12%) and **7** (5%), respectively, were formed under the conditions of method A. These products indicate that the nucleophilic substitution occurs at the *para*-position of the nitro group, and suggest that the steric effect of the nucleophilic 1-phenyl-*o*-carboranyl anion alters the usual features of the S_NAr reaction, leading to the product generated by C–H activation of the 4-nitro group.[16,17] In these reactions, the steric effect of the carboranyl anion may surpass the electronic effect in the first addition step of the S_NAr mechanism. In the case of the reaction of 2-fluoronitrobenzene, the product is hydrolyzed to afford **7**. Moreover, in the reaction of 2,4-dinitrofluorobenzene, the tetra-substituted benzene (**8**) was isolated in 3% yield along with the desired product, in spite of the bulkiness of the 2-nitro group (entries 7 and 8).[18] The formation of compound **8** also suggests that the bulkiness of the carboranyl anion affects the initial formation of intermediates.



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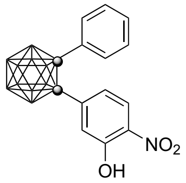

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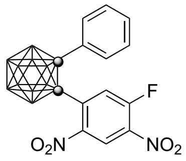

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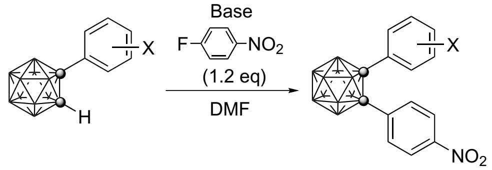
We also investigated the S_NAr reaction of fluorobenzenes with several electron-withdrawing groups, which could be readily transformed into various substituents, at the *para*-position (entries 9–14). Reactions of 4-cyanofluorobenzene proceeded in moderate yields (42% in method A and 20% in method B) to afford the desired compound, as was observed for 4-nitrobenzene (entries 9 and 10). However, 4-ethoxycarbonyl and formyl groups are ineffective activators of S_NAr reaction, and the reaction afforded a complex mixture owing to nucleophilic attack of the carboranyl anion on the *o*-carboranes and carbonyl group, as well as activated aromatic carbon.

We also investigated functional group tolerance on the aryl *o*-carboranes (Table 3). A wide range of functional groups was tolerated by this S_NAr reaction, which proceeded efficiently (51–91%, within 15–40 min) by method A or method B for phenyl-*o*-carboranes incorporating electron-donating (entries 3 and 4) and electron-

Table 3. $\mathrm{S_NAr}$ reaction of 4-fluoronitrobenzene with a variety of aryl-*o*-carboranes



Entry	X	Method	Time (min)	Yield (%)[a]
1	H	A	20	91
2		B	40	83
3	4-OCH_3	A	20	88
4		B	15	91
5	4-Cl	A	30	90
6		B	20	87
7	4-Br	A	30	82
8		B	15	86
9	4-Ph	A	25	85
10		B	40	83
11	4-CO_2Et	A	20	66
12		B	40	75
13	3-NO_2	A	40	63
14		B	40	51
15	4-NO_2	A	30	80
16		B	20	78

[a] Isolated yield.

withdrawing groups (entries 5–16). Moreover, the desired $\mathrm{S_NAr}$ products were obtained with little influence of the position of the substituents (entries 13 and 14 vs 15 and 16).

In conclusion, we have developed a synthetic method for 1,2-diaryl-*o*-carboranes with various substituents on both of the phenyl rings. The present procedure should overcome the limitations of known synthetic methods for 1,2-diaryl-*o*-carboranes, and make it easier to utilize aromatic molecules with carborane cages in the fields of medicinal chemistry, macromolecular chemistry and materials science.

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12. It was also found that the corresponding $\mathrm{S_NAr}$ product was not obtained under these conditions when *o*-carborane was used as starting material.
13. Experimental procedure for aromatic nucleophilic substitution with NaH (method A): To a suspension of NaH (washed with *n*-hexane; 36 mg, 1.5 mmol) in dry DMF was added aryl-*o*-carborane (1.0 mmol), then 4-fluoronitrobenzene (0.13 mL, 1.2 mmol) was added and the mixture was stirred at 0 °C. The reaction mixture was poured into aqueous 10% HCl solution and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$ and then concentrated. The residue was purified by column chromatography on silica gel to give diaryl-*o*-carborane.
14. Experimental procedure for aromatic nucleophilic substitution with KO^tBu (method B): To a suspension of KO^tBu (135 mg, 1.2 mmol) in dry DMF was added aryl-*o*-carborane (1.0 mmol), then 4-fluoronitrobenzene (0.13 mL, 1.2 mmol) was added and the mixture was stirred at 0 °C. The reaction mixture was poured into aqueous 10% HCl solution and extracted with AcOEt. The organic layer was washed with water and brine, dried over $MgSO_4$ and then concentrated. The residue was purified by column chromatography on silica gel to give diaryl-*o*-carborane.
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18. We have tried to search for the corresponding phenol compounds to **6** and **8** or fluoro-compound to **7**. However, these compounds were not found in the crude mixture. It is not understood why the phenol product **7** was obtained just in case of the use of 2-fluoronitrobenzene as an electrophile.