ORGANIC LETTERS

2004
Vol. 6, No. 13
2205−2207

ipso-Nitration of Arylboronic Acids with Chlorotrimethylsilane–Nitrate Salts

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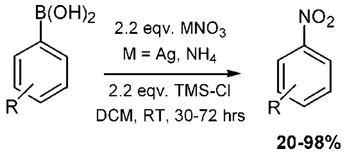
Received April 13, 2004

ABSTRACT



A mixture of nitrate salt and chlorotrimethylsilane is found to be an efficient regioselective nitrating agent for the *ipso*-nitration of arylboronic acids to produce the corresponding nitroarenes in moderate to excellent yields. High selectivity, simplicity, and convenience are the key features of the reaction.

Nitration of aromatic compounds is one of the most extensively studied reactions,[1] and nitroaryl moieties play key roles in the physical and chemical properties of many target molecules in organic synthesis. For electrophilic nitration of aromatic compounds, a wide variety of reagents[2,3] are available to date. Most of them are very strong nitrating agents and often lead to further nitration and mixture of isomers. Since most nitrating agents are oxidants, oxidation of other functional groups can also occur, giving a mixture of products. Thus, a search for milder and selective nitrating agents is a good research goal. In the last few decades, arylboronic acids[4] have been extensively used as versatile synthons in organic synthetic transformations involving various reactions such as Suzuki coupling[5] and multicomponent reactions for the synthesis of various amino acids and trifluoromethylated amines.[6,7] Fluorination of various derivatives of aryl/alkenylboronic acids has been reported.[8] In earlier studies, we have shown regeoselective halogenation[9] and nitration[10] of arylboronic acids with *N*-halosuccinimides and Crivello's reagent[11] (ammonium nitrate/trifluroacetic anhydride), respectively. However, during nitration with the relatively powerful Crivello's reagent, dinitration was also observed and the temperature had to be carefully regulated to avoid undesirable side reactions.

Herein we report a simple, convenient and mild method for the *ipso*-nitration of arylboronic acids using inorganic nitrate salt and chlorotrimethylsilane. This method provides the *ipso*-nitrated product in moderate to high yield (∼95−98% purity for the crude product itself) and is found to be more selective than our previously reported method using Crivello's reagent.[11] The reaction is easy to perform, and workup avoids further purification in many cases. Another

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(1) (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: New York, 1989. (b) Kuhn, S. J.; Olah, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4564. (c) Schofield, K. *Aromatic Nitration*; University Press: Cambridge, 1980.

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(4) Negishi, E. *Comp. Organomet. Chem.* **1983**, *7*, 323.

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(9) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141.

(10) Stefan, S.; Jurgen, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485.

(11) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.

10.1021/ol0493249 CCC: $27.50

significant feature of this method is *the complete absence of dinitro product*!

It has been reported[12] that 2-nitroketones can be synthesized from olefins using TMS-Cl/$AgNO_3$/CrO_3 as a reagent system. We have previously reported[13] that a mixture of ammonium nitrate and chlorotrimethylsilane with a catalytic amount of $AlCl_3$ can function as a good nitrating system for the electrophilic nitration of aromatics. During our search for a milder and convenient nitrating agent for *ipso*-nitration of arylboronic acids, we decided to use NH_4NO_3/TMS-Cl system without strongly Lewis acidic $AlCl_3$ present. Without $AlCl_3$ in the system, the direct nitration of aromatics is rather sluggish. However, with arylboronic acids, *ipso*-substitution was observed. We explored this reaction using different arylboronic acids and obtained *ipso*-nitro substitution in all cases with moderate to excellent yields. The behavior and activity of different nitrates and solvents have also been explored.

Use of chlorotrimethylsilane in conjunction with inorganic salts as reagents for various organic oxidations and other reactions is well-known.[14] Lee et al. reported[15] that the reaction of chlorotrimethylsilane with sodium nitrate and nitrite gives nitryl and nitrosyl chloride, respectively. Synthetic use of the nitryl chloride generated in situ from TMS-Cl and nitrate salts has not been mentioned. A mixture of chlorotrimethylsilane and sodium nitrate was used for deoximation of aldoximes/ketoximes and for nonaqueous diazotization.[15]

Nitration of arylboronic acids with a mixture of TMS−Cl and nitrate salts takes place at the *ipso*-position of the aryl ring without ring nitration or sequential nitration. However, along with the *ipso*-nitration, 2−10% nitrochlorination was also observed in certain cases. This is not surprising since a mixture of TMS-Cl and nitrate salt can also act as a chlorinating agent. We have found that when $AgNO_3$ was used instead of NH_4NO_3 as the nitrate salt, the extent of chlorination significantly decreased. This may be due to the fact that the silver ion can remove chloride efficiently from the system by the precipitation of AgCl. The amount of chlorinated product increases, as the phenyl ring becomes more electron rich. Thus, with *p*-tolylboronic acid, a mixture of nitrated and chlorinated products was obtained. We have studied the effect of different nitrate salts on *ipso*-nitration and found $AgNO_3$ to give the best results. Table 1 shows a comparative study of the reactions using various nitrate salts. With ferric nitrate, a mixture of products was obtained, and further decomposition resulted in a low yield of the desired product.

Table 1. Effect of Different Nitrate Salts in the *ipso*-Nitration of Phenylboronic Acids[a]

nitrate salt	time (h)	yield (%)
$AgNO_3$	30	98[b]
NH_4NO_3	36	95[c]
$NaNO_3$	48	95[c]
KNO_3	100	95[c]
$Ba(NO_3)_2$	>100	0[d]
$Fe(NO_3)_3$	8	40[e]

[a] Conditions: nitrate salt (2.2 equiv), TMS-Cl (2.2 equiv), DCM (10 mL), stirred at rt for the time specified. [b] Only 2% nitrochlorobenzene was observed (GCMS). [c] Nitrochlorobenzene (5−10%) was observed. [d] No desired product was observed. [e] Some unidentified impurities, which could not be separated from the product.

The effect of different solvents on the reaction system has also been investigated (Table 2). Dichloromethane (DCM) was found to be the most suitable solvent. In other solvents such as 1,2-dichloroethane, the amount of chlorination increases. Oxygenated solvents such as ether and THF are not suitable, as TMSCl can interact with them. Alcohols are also unsuitable, as they can undergo O-silylation under the reaction conditions. No nitration was observed in acetonitrile solution. Since a relatively polar solvent is needed without any chemical interaction for the dissolution of the arylboronic acid, the solvent choice was narrowed down to haloalkanes, with DCM as the most suitable solvent.

Table 2. Effect of Solvents in the *ipso*-Nitration of Phenylboronic Acid with NH_4NO_3/TMSCl

solvent	time (h)	yield (%)[a]
CH_2Cl_2	30	95
$CHCl_3$	48	90
CCl_4	48	70[b]
$ClCH_2CH_2Cl$	20	80[c]
CH_3CN	>72	0

[a] Crude yield (without further purification) of the product. [b] Dichlorinated products (∼25%) were observed. [c] Unidentified byproducts (∼20%) were observed.

The reaction system is also good for arylboronic acids with different functionalities, though the yields vary. *m*-Chloro/bromo nitrobenzenes can be easily obtained from *m*-chloro/bromophenylboronic acids under mild conditions. Thus, the boronic acid group orients the nitro group very easily toward the ipso position to give the desired nitro aromatics in excellent yields. The method is very useful in cases where the preparation of the nitro derivatives is rather difficult or needs drastic conditions. Though a small amount of chlorinated byproduct is formed, its amount, compared to the desired nitro product, is insignificant. Nitroarylboronic acid also undergoes nitration by the same reagent system, but needs heating and purification of the final product by column chromatography. Reaction of the trifluoromethyl-substituted phenyl boronic acid has been found to be very sluggish.

There can be several possible explanations for the regioselective nitration of arylboronic acid. It is well-known that TMS-Cl reacts with nitrate salts to generate the TMS-O-

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(12) Ram Reddy, M. V.; Kumareswaran, R.; Vankar, Y. D. *Tetrahedron Lett.* **1995**, *39*, 7149.

(13) Olah, G. A.; Ramaiah, P.; Sandford, G.; Orlinkov, A.; Prakash, G. K. *Synthesis* **1994**, 468.

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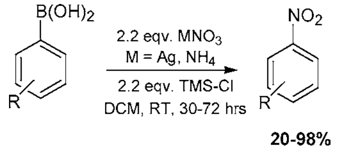
Scheme 1. *ipso*-Nitration of Arylboronic Acids



NO_2 species. Since we have not observed the dinitro product in any case, it is likely that there exists a prominent electronic interaction between the boronic acid group and the intermediate active nitrating agent TMS-O-NO_2 species through boron and the siloxy group due to the high oxophilicity of boron (Scheme 2). This helps the nitration to occur at the ipso position. TMS-O-NO_2 can undergo further reaction with excess TMS-Cl to give hexamethyldisiloxane and nitryl chloride, which can also act as the nitrating species. For the generation of the nitryl chloride, an excess of TMSCl is required, but we have found that phenylboronic acid can undergo nitration completely with 1 equiv of TMS-Cl. The reaction takes 72 h for completion. This indicates that the TMS-O-NO_2 species is the likely active nitrating intermediate. However, the reaction rate was found to increase with the increase in concentration of TMS-Cl. With more than 2 equiv of the reagents, it is possible that some nitryl chloride could be formed, which could act as a nitrating as well as a chlorinating agent. This explains the minor amount of chlorinated product formed in some cases. With aliphatic boronic acids, we were unable to obtain any nitrated product. This shows that the aromatic ring plays an important electronic role in the *ipso*-nitration.

Scheme 2. Suggested Mechanism for *ipso*-Nitration of Arylboronic Acid

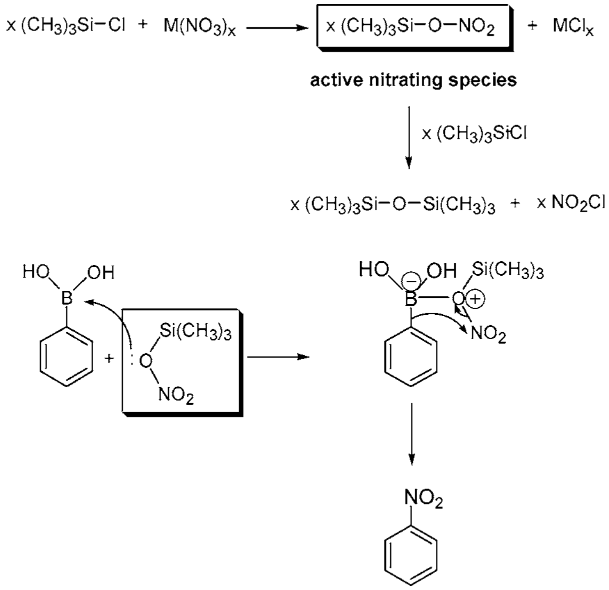
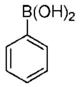
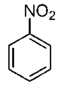
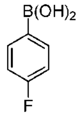
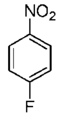
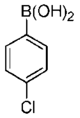
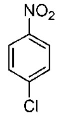
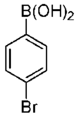
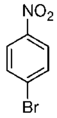
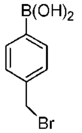
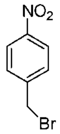
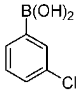
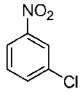
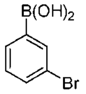
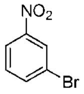
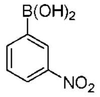
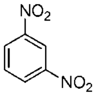
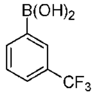
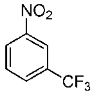


Table 3. *Ipso*-nitration of arylboronic acids using TMSCl/nitrate salts

entry	arylboronic Acid	nitrate salt	time (hr)	products	yield (%)
1		$AgNO_3$	30		98
2		NH_4NO_3	48		75
3		NH_4NO_3	48		92
4		NH_4NO_3	48		96
5		NH_4NO_3	30		75
6		$AgNO_3$	72		90
7		$AgNO_3$	72		88
8		$AgNO_3$	18		$45^{a, b}$
9		$AgNO_3$	72		20^{b}

[a] Heated in a sealed tube at 50 °C. [b] Isolated chemical yield (by column chromatography).

In conclusion, we have developed a simple and convenient method for the *ipso*-nitration of arylboronic acids. The method works well with a variety of functionalized arylboronic acids. Mild conditions and ease of workup are the salient features of this method.

Acknowledgment. Support of our work by Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: General experimental paragraph and experimental procedure for *ipso*-nitration of arylboronic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0493249