ORGANIC
LETTERS

2012
Vol. 14, No. 3
855–857

Rhodium-Catalyzed Cleavage Reaction of Aryl Methyl Ethers with Thioesters

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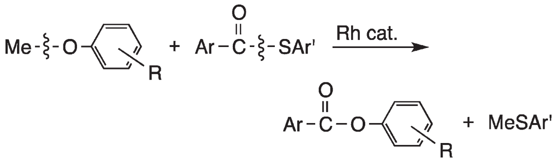
Received December 16, 2011

ABSTRACT



A rhodium complex catalyzed the reaction of aryl methyl ethers and thioesters giving the corresponding aryl esters and methyl sulfides. *S*-(*p*-Chlorophenyl) *p*-(dimethylamino)benzothioate was used for the reaction of methyl aryl ethers with electron-withdrawing groups, and an *S*-(*p*-tolyl) derivative was used for those with electron-donating groups. Polymethoxybenzenes were converted to the esters in a regioselective manner.

The cleavage of unactivated CH_3–O bonds of aryl methyl ethers catalyzed by transition-metal complexes can have significant applications in organic synthesis. For example, the method can be used for the protection/deprotection of phenols.[1] Several examples of stoichiometric ether bond cleavage reactions have been reported.[2] However, catalytic transformations remain unknown. Described in this study is the rhodium-catalyzed reaction of aryl methyl ethers and thioesters,[3] which gives aryl esters and methyl sulfides. Unlike conventional methods of aryl methyl ether cleavage, the reaction proceeds without using a stoichiometric amount of a strong acid or a base.[4–6]

When a mixture of *p*-cyanoanisole **1** (2 equiv) and *S*-(*p*-chlorophenyl) *p*-(dimethylamino)benzothioate **2** was heated without a solvent at 130 °C for 12 h in the presence of $RhH(CO)(PPh_3)_3$ (1 mol %) and 1,2-bis(diphenylphosphino)ethane (dppe, 2 mol %), *p*-cyanophenyl *p*-(dimethylamino)benzoate **3** (94%) and *p*-chlorothioanisole **4** (94%) were obtained (Table 1, entry 1).[7] The rhodium complex and dppe were both essential for the reaction; no reaction occurred in the absence of either substance. The yields of **3** and **4** decreased to 68% and 66% using equimolar amounts of **1** and **2**, respectively.

The reactivities of the thioesters were compared using the reaction of **1** (1 equiv) in chlorobenzene (2 M) in the presence of the rhodium complex (2.5 mol %) and dppe

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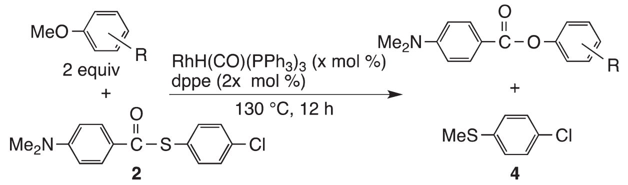
(7) In a one-neck, round-bottom flask equipped with a reflux condenser were placed $RhH(CO)(PPh_3)_3$ (1.0 mol %, 9.2 mg), 1,2-bis(diphenylphosphino)ethane (2.0 mol %, 8.0 mg), *p*-cyanoanisole **1** (2.0 mmol, 266 mg), and *S*-(4-chlorophenyl) (4-dimethylamino)benzoate **2** (1.0 mmol, 291 mg) under an argon atmosphere. Then, the mixture was heated at 150 °C for a few minutes to dissolve the rhodium complex and allowed to react at 130 °C for 12 h. After being cooled to room temperature, the mixture was purified by flash column chromatography on silica gel giving *p*-cyanophenyl (*p*-dimethylamino)benzoate **3** (250.5 mg, 94%) as a colorless solid and *p*-chlorothioanisole **4** (149.1 mg, 94%) as a colorless oil.

10.1021/ol2033724

(5 mol %). The aryl ester and **4** were obtained in comparable yields for each thioester as follows: **2**, 71% and 70%; *S*-(*p*-chlorophenyl) *p*-methylbenzothioate, 26% and 23%; *S*-(*p*-chlorophenyl) benzothioate, 19% and 17%; *S*-(*p*-chlorophenyl) *p*-chlorobenzoate, 7% and trace; *S*-(*p*-tolyl) *p*-(dimethyamino)benzothioate **5**, 44% and 42% (also see Table 1, entry 3). The results indicated the requirement of an electron-donating group at the benzoyl moiety and an electron-withdrawing group at the arylthio moiety in the thioesters.

The reaction was applicable to aryl methyl ethers with electron-withdrawing groups such as formyl, benzoyl, acetyl, chloride, and ethoxycarbonyl groups at the *o*-, *m*-, and *p*-positions in the presence of the rhodium complex (1−5 mol %) (entries 1−14). The reaction proceeded efficiently without affecting the functional groups. 1- and 2-Methoxynaphthalenes showed similar reactions (entries 15−17). The reaction mechanism cannot be a nucleophilic substitution reaction at the methyl group, which should require better leaving phenoxy groups with strong electron-withdrawing groups at the *o*- or *p*-position.

Table 1. Reactions of Various Aryl Methyl Ethers with Electron-Withdrawing Groups

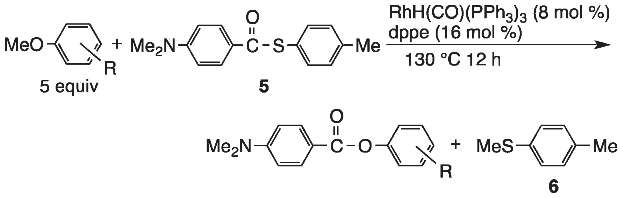


entry	R	*x* (mol %)	yield (%) aryl esters	yield (%) **4**
1	*p*-CN (**1**)	1	94	94
2[a]	*p*-CN (**1**)	1	68	66
3[b]	*p*-CN (**1**)	1	64	60
4	*p*-CHO	1	92	94
5	*p*-COPh	1	99	98
6	*p*-COMe	2.5	91	86
7	*p*-Cl	2.5	87	88
8	*p*-CO_2Et	2.5	78	73
9	*o*-CN	1	90	87
10	*o*-COMe	2.5	90	88
11	*o*-Cl	2.5	82	75
12	*o*-Cl	5	95	94
13	*m*-CN	2.5	90	90
14	*m*-COPh	5	87	85
15	1-MeO-naphthalene	2.5	81	79
16	4-NC-1-MeO-naphthalene	1	92	90
17	2-MeO-naphthalene	2.5	63	60

[a] Thioester (1 equiv) was used. [b] *S*-(*p*-Tolyl) *p*-(dimethyamino)-benzothioate **5** was used.

The reaction of aryl methyl ethers with electron-donating groups also proceeded under slightly forced conditions when another thioester was employed. When *o*-dimethoxybenzene (5 equiv) and *S*-(*p*-tolyl) *p*-(dimethylamino)benzothioate **5** were heated at 130 °C for 12 h in the presence of $RhH(CO)(PPh_3)_3$ (8 mol %) and dppe (16 mol %), *o*-methoxyphenyl *p*-(dimethylamino)-benzoate (92%) and *p*-tolyl methyl sulfide (86%) were obtained (Scheme 1). The use of **2**, *S*-(*p*-trifluoromethyl-phenyl) *p*-(dimethylamino)benzothioate, or *S*-(*p*-cyano-phenyl) *p*-(dimethylamino)benzothioate in place of **5** resulted in lower yields (71%, 50%, 24%) of the corresponding esters. *m*-Dimethoxybenzene and **5** showed similar reaction properties (91%). Anisole and *m*- and *p*-(*tert*-butyl)anisoles also gave the corresponding aryl esters. Notably, *p*-dimethoxybenzene gave a mixture of mono- and didemethylated products in 42% and 30% yields [based on the (*p*-dimethylamino)benzoyloxy group], respectively. The result indicated that the second demethylation was much faster than the first one.

Scheme 1



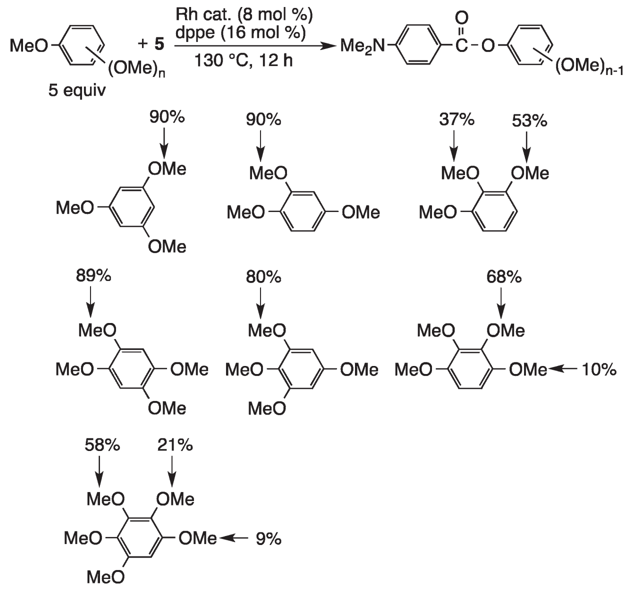
R		**6**
R = *o*-MeO	92%	86%
= *m*-MeO	91%	90%
= *p*-MeO	42%[a)]	84%
= H[b)]	68%	63%
= *m*-(*t*-Bu)[b)]	56%	62%
= *p*-(*t*-Bu)[b)]	33%	32%

[a)] The didemethylated product was obtained in 30% yield.
[b)] Rh complex (10 mol %) and dppe (20 mol %) were used.

It is shown that aryl methyl ethers with electron-withdrawing groups reacted efficiently with **2** and those with electron-donating groups with **5**. This may be due to the polarity of thioesters and anisoles: Polar aryl methyl ethers with electron-withdrawing groups reacted with polar thioesters **2** having electron-withdrawing groups at the arylthio moiety; less polar aryl methyl ethers with electron-donating groups reacted with less polar thioester **5** having electron-donating groups at the arylthio moiety. This is probably related to the metal-catalyzed nature of this reaction.

The reaction was applied to polymethoxybenzenes to examine regioselectivity in demethylation (Scheme 2). The reaction of 1,3,5-trimethoxybenzene and 1,2,4,5-tetramethoxybenzene with **5** in the presence of a rhodium catalyst gave monoesters in 90% and 89% yields, respectively. The reactions of polymethoxybenzenes with methoxy groups in different environments are also summarized. The reactions occurred in one methyl group, and no didemethoxylated products were obtained. In general, demethylation occurred at methoxy groups with one or two adjacent methoxy groups. However, the steric effect appeared to be nonessential, as observed in the reaction of 1,2,3,4-tetramethoxybenzene and pentamethoxybenzene.

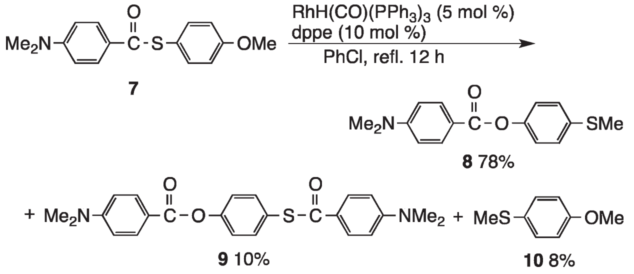
Scheme 2



These results showed a tendency to provide 1,4-dimethoxy derivatives as products, which might minimize the polarity of the product. This notable selectivity may also reflect the transition-metal-catalyzed nature. Regioselectivity in the demethylation of polymethoxybenzenes could not be clearly examined using conventional acid- or base-promoted methods, with some exceptions, e.g., *o*-methoxyacetophenone derivatives.[4b,8]

A formal intramolecular reaction was conducted using *S*-(*p*-methoxyphenyl) *p*-(dimethylamino)benzothioate **7**. The rhodium-catalyzed reaction gave *p*-methylthiophenyl *p*-(dimethylamino)benzoate **8** (78%) along with small amounts of intermolecular reaction products, i.e., *S*-(*p*-dimethylaminophenylcarbonyl)-*p*-dimethylaminobenzothioate **9** (10%) and *p*-methoxythioanisole **10** (8%) (Scheme 3).

Scheme 3



In summary, a rhodium complex catalyzed the reaction of aryl methyl ethers and thioesters, giving the corresponding aryl esters and methyl sulfides. The use of appropriate thioesters was critical for efficient reaction, and notable regioselectivity was observed in the reaction of polymethoxybenzenes. It should be emphasized that rhodium catalysis could be used for transformation involving the cleavage of the unactivated sp^3-C$-$O bond of aryl methyl ethers: demethylation of aryl methyl ethers and methylation of thioesters.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 21229001), the GCOE program, and the WPI Initiative from JSPS. M.A. expresses her appreciation for financial support from a Grant-in-Aid for Scientific Research (No. 22689001), the Japan Science Technology Agency, and the Asahi Glass Foundation.

Supporting Information Available. General experimental procedures and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.