Rhodium-Catalyzed Addition of Arylboronic Acids to 2-Methylene-1,3-dithiane Monoxide

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Received 23 March 2007

Abstract: Treatment of 2-methylene-1,3-dithiane 1-oxide with arylboronic acid under rhodium catalysis in aqueous dioxane at 25 °C provided the corresponding adduct, which is a useful 2-arylalkanal equivalent.

Key words: rhodium, arylboronic acid, addition, methylene dithiane monoxide

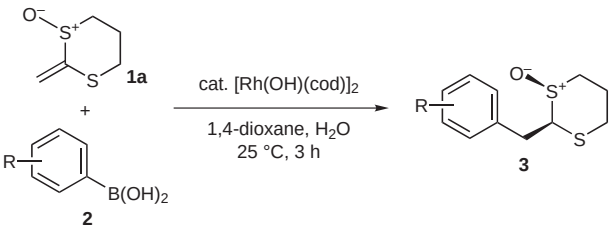
Ketene dithioacetal is useful as a ketene equivalent in organic synthesis.[1] In the course of our studies on the use of ketene dithioacetal as substrates for metal-catalyzed organic reactions,[2] we examined rhodium-catalyzed addition reactions to ketene dithioacetals. However, no reaction took place after several attempts. We turned our attention to the use of activated ketene dithioacetals. We now report that 2-methylene-1,3-dithiane 1-oxide (**1a**) undergoes rhodium-catalyzed addition of arylboronic acids.[3] Similar rhodium-catalyzed 1,4-additions to α,β-unsaturated carbonyl compounds are extensively studied.[4] On the other hand, the reactions of heteroatom-substituted electron-deficient alkenes are still unexplored.[5]

Treatment of **1a** with phenylboronic acid (**2a**, 1.2 equiv) in the presence of $[Rh(OH)(cod)]_2$ (5 mol%) in aqueous dioxane at 25 °C for 3 hours provided the corresponding adduct **3a** in 97% yield (Table 1, entry 1).[6] The reaction was completely stereoselective,[7] and none of the *trans*-isomer of **3a** was detected.[8]

A variety of arylboronic acids participated in the reaction. Electron-donating as well as electron-withdrawing substituents had little influence on the efficiency of the reactions (entries 2–5). Arylboronic acids having a substituent at the *ortho* position added to **1a** under the rhodium catalysis to yield the corresponding adducts in excellent yields (entries 6 and 7). Alkenylboronic acid **2h** was less reactive, and an excess of 1,5-cyclooctadiene and a larger amount of the rhodium complex were necessary to achieve satisfactory yield (Scheme 1).

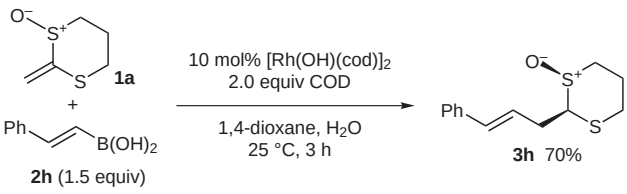
Acyclic ketene dithioacetal monoxide **4** was the less reactive Michael acceptor to furnish **5**[9] in only 41% yield and to recover 40% of **4** even at an elevated temperature and with an excess of **2a** (Scheme 2). In contrast to the reaction of **1a**, the reaction of **4** provided a mixture of stereoisomers.

Table 1 Rhodium-Catalyzed Addition of Arylboronic Acids **2** to 2-Methylene-1,3-dithiane 1-Oxide (**1a**)[a]

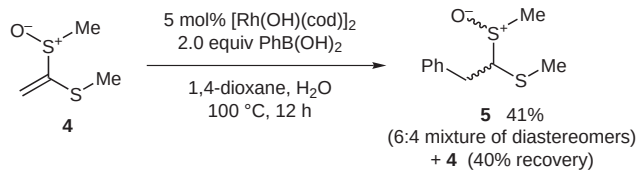


Entry	R	2	3	Yield (%)
1	H	**2a**	**3a**	97
2	*p*-MeO	**2b**	**3b**	89
3	*p*-Me	**2c**	**3c**	89
4	*p*-CF_3	**2d**	**3d**	100
5	*p*-MeOOC	**2e**	**3e**	90
6	*o*-MeO	**2f**	**3f**	96
7	*o*-BocNH[b]	**2g**	**3g**	96[c]

[a] Reaction conditions are described in ref. 6.
[b] Boc = *t*-BuOC(=O).
[c] 2 equiv of **2g**.



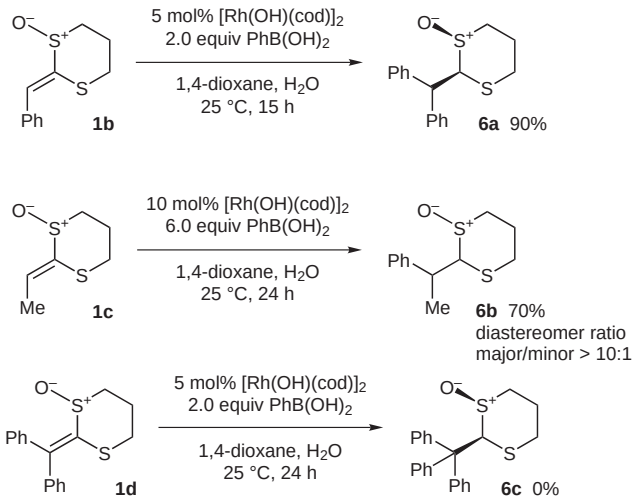
Scheme 1



Scheme 2

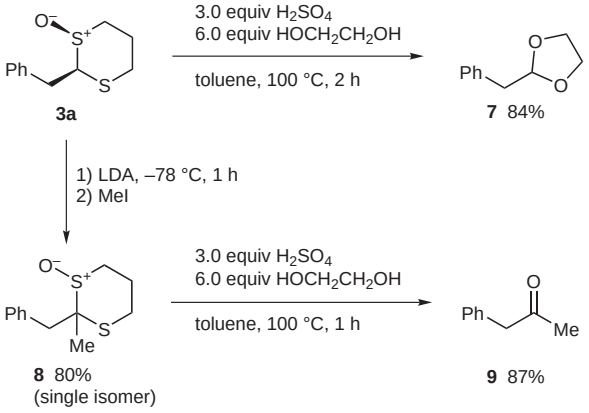
SYNLETT 2007, No. 10, pp 1622–1624
Advanced online publication: 07.06.2007
DOI: 10.1055/s-2007-980373; Art ID: U02507ST

The phenylation reaction of **1b** required a longer reaction time and two equivalents of phenylboronic acid, yet affording an excellent yield of the corresponding product **6a** (Scheme 3). The reaction of **1c** with a large excess of phenylboronic acid proceeded to completion within 24 hours with the aid of 10 mol% of $[Rh(OH)(cod)]_2$. In this case, a small amount of a stereoisomer was detected, the configuration of which has not been assigned yet.[10] Unfortunately, *gem*-diphenyl-substituted **1d** resisted the reaction.



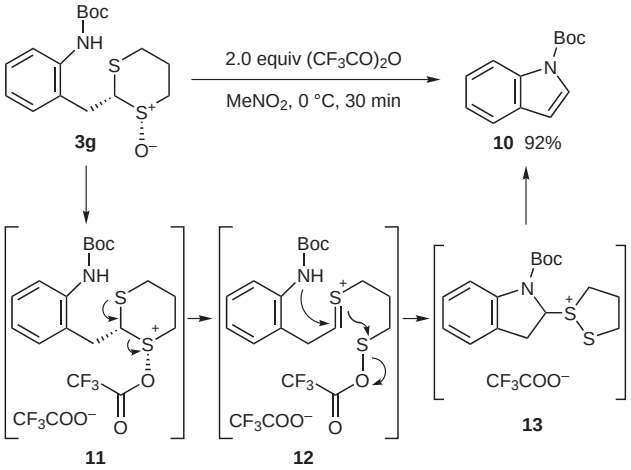
Scheme 3

The products **3** and **6** are 2-arylalkanal equivalents. We examined the utility of the products (Scheme 4). All the attempts to convert **3a** into phenylacetaldehyde resulted in the formation of complex mixtures or no conversion. Instead, treatment of **3a** with ethylene glycol in the presence of sulfuric acid in hot toluene afforded 2-benzyl-1,3-dioxolane (**7**) in 84% yield.[11] Deprotonation of **3a** with lithium diisopropylamide followed by addition of iodomethane provided a benzyl methyl ketone equivalent **8** in good yield.[12] Interestingly, under conditions similar to those in the transformation of **3a** to **7**, the attempted acetalization of **8** unexpectedly produced benzyl methyl ketone (**9**) in high yield.



Scheme 4

Treatment of **3g** with trifluoroacetic anhydride in nitromethane provided *N*-Boc-protected indole **10** in excellent yield (Scheme 5). The trifluoroacetylation of the sulfoxide oxygen followed by the cleavage of the carbon–sulfur bond[13] would yield the cationic intermediate **12**. Intramolecular attack of the Boc-protected amino group led to the formation of the dihydroindole **13** with concomitant liberation of trifluoroacetate. Elimination of dithiacyclopentane yielded **10**.



Scheme 5

In summary, we have found rhodium-catalyzed addition of arylboronic acids to ketene equivalents **1**. The products are 2-arylalkanal equivalents, which can be subjected to a variety of organic transformations.

Acknowledgment

This work was supported by Grants-in-Aid for Scientific Research and COE Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and Notes

(1) (a) Kolb, M. *Synthesis* **1990**, 171. (b) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.
(2) Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Organomet. Chem.* **2007**, *692*, in press; doi: 10.1016/j.jorganchem.2006.12.029.
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(5) Addition to alkenylphosphonates: (a) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (b) Addition to nitroalkenes: Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

(6) **Experimental Procedure**
The $[Rh(OH)(cod)]_2$ (7.3 mg, 0.016 mmol) was placed in a flask under an atmosphere of argon. A dioxane (3.0 mL) solution of 2-methylene-1,3-dithiane 1-oxide (**1a**, 44.1 mg, 0.30 mmol) and H_2O (0.3 mL) were added. Then, phenylboronic acid (**2a**, 43.8 mg, 0.36 mmol) was added, and the mixture was stirred at 25 °C for 3 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated in vacuo. Purification by chromatography on a silica gel column provided 2-benzyl-1,3-dithiane 1-oxide (**3a**, 65.6 mg, 0.29 mmol, 97%).

(7) The product **3a** is a known compound. The ^1H NMR and ^{13}C NMR spectra of **3a** were identical to the reported data: Page, P. C. B.; Wilkes, R. D.; Namwindwa, E. S.; Witty, M. J. *Tetrahedron* **1996**, *52*, 2125.

(8) The mechanism for the stereoselective formation of the *cis*-product **3a** is not clear at this stage. Protonation of the intermediate shown in Figure 1 would be the key step.

(9) The relative stereochemistry of **5** is not clear.

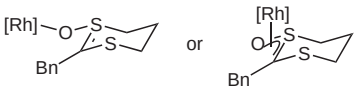
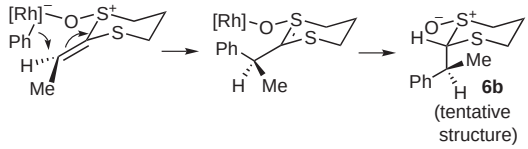


Figure 1

(10) We are tempted to assume the stereochemistry of **6b** based on the plausible reaction mechanism shown here (Scheme 6). Attempts to prepare X-ray-quality crystals of **6b** or related compounds are in progress.



Scheme 6

(11) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1971**, *34*, 3151.

(12) The relative stereochemistry of **8** has not been determined.

(13) Page, P. C. B.; Shuttleworth, S. J.; McKenzie, M. J.; Schilling, M. B.; Tapolczay, D. J. *Synthesis* **1995**, 73.