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Synthesis of *ortho*-Acylbenzylboronates via Cross-Coupling Reaction of (Dialkoxyboryl)methylzinc Reagents with Haloarenes. A Stable *ortho*-Quinodimethane Precursor

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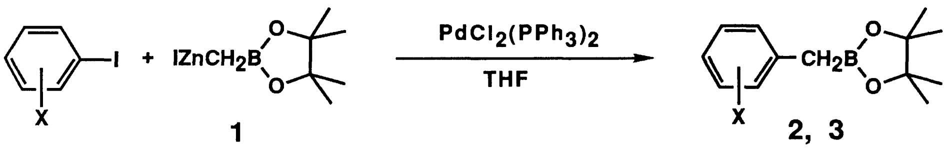
The cross-coupling reaction of $IZnCH_2B(OCMe_2)_2$ with iodoarenes in the presence of $PdCl_2(PPh_3)_2$ produces the corresponding benzylic boronates in high yields. Among them, the benzylic boronates having an acyl group at the *ortho* position readily undergo the 1,5-rearrangement to the carbonyl oxygen producing the *o*-quinodimethane derivatives under thermal or photochemical conditions. The reaction provides benzo-fused cycloalkanes by trapping with dienophiles.

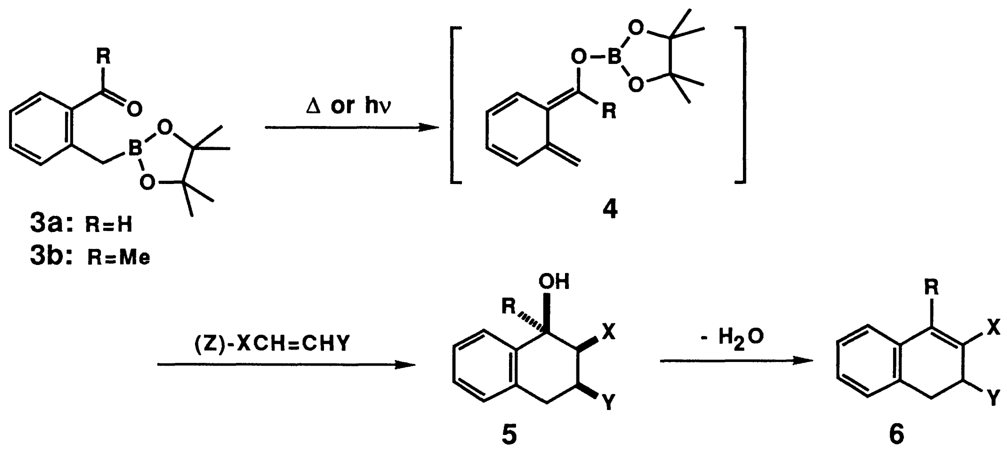
Synthetic methods for the generation of *o*-quinodimethanes have been developed by a number of research groups because of the importance of these reactive intermediates for the inter- or the intramolecular Diels-Alder reaction with dienophiles.1) We now report the synthesis of benzylic boronates having an acyl group at the *ortho*-position **3** (Eq. 1) and their facile rearrangement to the boron enolate **4** which acts as *o*-quinodimethane (Eq. 2). *o*-Quinodimethanes are excellent dienes for cycloaddition, so that the present reaction provides a method for synthesis of a variety of six-membered rings fused to benzene rings.

Benzylic boronates **2** and the starting materials **3** necessary for our investigation are readily synthesized by the cross-coupling reaction of Knochel's borylmethylzinc reagents **1**2) with haloarenes in THF at 50 °C in the presence of $PdCl_2(PPh_3)_2$ (2-4 mol%) (Eq. 1).3) Under the cross-coupling conditions, the zinc reagents are tolerant of various functional groups, so that a variety of functionalized benzylic boronates **2** and **3** having carbomethoxy, formyl, and acetyl groups are synthesized from **1** and the corresponding iodoarenes with the following yields: Ar = Ph (91%), 4-$MeOCH_2OC_6H_4$ (80%), 4-$MeO_2CC_6H_4$ (76%), 2-$MeO_2CC_6H_4$ (90%), 2-$MeSCH_2C_6H_4$ (93%), 2-NCC_6H_4 (67%), 2-BrC_6H_4 (69%), 2-$OHCC_6H_4$ (78%), and 2-$MeCOC_6H_4$ (86%).3) Under similar conditions, bromoarenes also give the corresponding benzylic boronates. (2,2-Dimethylpropanedioxyboryl)methylzinc iodide can be used in place of **1**; for example, the coupling with iodobenzene provides 2-benzyl-5,5-dimethyl-1,3,2-dioxaboronane in 90% yield.



(1)

Generation of *o*-quinodimethane and its trapping *in situ* with dienophiles under thermal or photochemical conditions are summarized in Eq. 2 and Table 1.



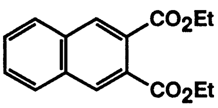
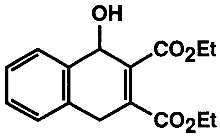
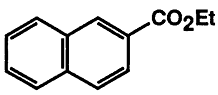
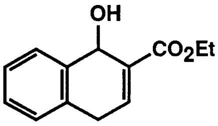
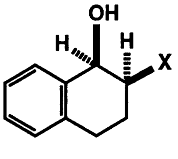
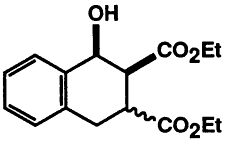
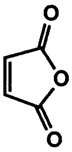
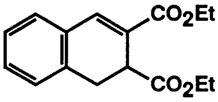
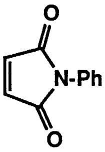
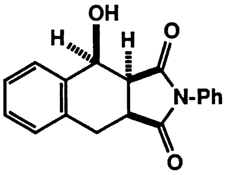
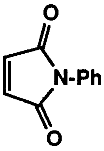
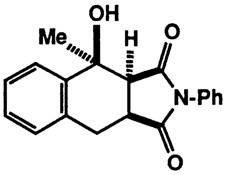
(2)

Heating a mixture of 2-acetyl or 2-formyl derivatives of benzylic boronate **3** and an alkyne or alkene dienophile (3 equiv.) in toluene for 24 h at 110-180 °C produces the naphthalene derivative by dehydration (entries 1, 3, and 8).[4] In contrast, the adducts with N-phenylmaleimide are sufficiently stable to permit isolation of the alcohol products **5** (entries 9 and 10). The formation of the *cis* isomer predominates as is established by the presence of NOE and the coupling constant (3.4 Hz) between two hydrogens at the benzylic and the α to the carbonyl carbons (entry 9).[5] Although the adduct obtained from **3b** and N-phenylmaleimide exhibits only a very weak NOE (0.9%) between a bridged hydrogen and methyl hydrogens, its stereochemistry is tentatively assigned to the structure shown in entry 10.[6] No other epimeric adducts are detected in these reactions.

The generation of *o*-quinodimethane can be carried out under milder conditions by irradiation of a benzene solution of **3a** in a pyrex flask with a 500W-high pressure mercury lamp for 5 h at 15 °C.[7] Although the adducts with alkyne dienophiles still have a tendency to cause aromatization (entry 2), the cycloaddition products with alkene dienophiles are less labile to dehydration. Thus, the synthesis of primary adducts **5** which are not available by the thermal reaction is readily achieved (entries 5-7). The photochemical reaction again provides the cycloaddition products of all *cis*-configurations, as shown in Table 1.

When the 1,5-rearrangement proceeds through coordination of boron to the carbonyl oxygen, the (*Z*)-boron enolate can be produced. However, the stereochemistry and regiochemistry of products both in the thermal and the photochemical reactions suggest the formation of (*E*)-quinodimethane intermediates **4** which give the *cis*-adducts **5** through the *endo*-addition[1] of dienophiles. Although the mechanism of rearrangement is not clear at present, the photochemical rearrangement can be initiated by the intramolecular attack of an excited triplet carbonyl (n-π^*) on boron, in analogy with the related photochemical S_H2 reaction of organoboranes with ketones reported by Davies.[8] We reported previously the oxygen- or peroxide-induced radical reaction of organoboranes.[9] The present reaction is not thermally accelerated by radical initiators such as benzoylperoxide or is not inhibited by scavengers such as galvinoxyl, copper(II)

Table 1. Thermal and Photochemical Cycloadditions (Eq. 1)

Entry	**3**	Dienophile	Procedure a)	Product and Yield/% b)	
					
1	**3a**	$EtO_2C-C\equiv C-CO_2Et$	150 °C / 24 h	75	0
2	**3a**		hν	46	46
					
3	**3a**	$H-C\equiv C-CO_2Et$	180 °C / 24 h	52	0
4	**3a**		hν	trace	64
5	**3a**	$CH_2=CHCO_2Me$	hν	 X=CO_2Et	60
6	**3a**	$CH_2=CHCOMe$	hν	X=COMe	65
7	**3a**	(Z)-$EtO_2CCH=CHCO_2Et$	hν		66 c)
8	**3a**		110 °C / 12 h		63 d)
9	**3a**		110 °C / 12 h		87
10	**3b**		110 °C / 12 h		92

a) See the procedures in the Text. b) Isolated yields by chromatography. c) A 1:1 stereoisomeric mixure. d) The product was isolated after the esterification by ethanol / TsOH at reflux temperature.

diethyldithiocarbamate, and DPPH. Thus, the thermal reaction may take place in another process, presumably the intramolecular migration through the coordination of boron with the carbonyl oxygen, followed by the isomerization to (*E*)-*o*-quinodimethane.

References

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2) P. Knochel, *J. Am. Chem. Soc.*, **112**, 7431 (1990).

3) A mixture of iodoarene (5 mmol), **1** (7.5 mmol), $PdCl_2(PPh_3)_2$ (0.2 mmol) in THF (ca. 20 ml) was stirred for 3-5 h at 50 °C under nitrogen. After cooling to room temperature, the mixture was diluted with benzene (30 ml), washed with water and brine, and finally dried over $MgSO_4$. The product was isolated by Kugelrohr distillation, **3a**: Bp 70-80 °C/0.1 mmHg (oven temperature of Kugelrohr); Mp 39-41 °C. Under the above conditions, the yield of **3b** was only 62%; thus this synthesis was carried out only in dioxane at 75 °C for 1.5 h using 2 equiv. of **1** in THF. **3b**: Bp 90 °C/0.1 mmHg; Mp 51-51 °C. Distillation at lower temperature in high vacuo is essential because of the thermal instability of the compounds.

4) A mixture of **3** (1 mmol) and dienophile (3 mmol) in toluene (2 ml) was sealed in an ampule and heated at the temperature indicated in Table. After the reaction was completed, the mixture was washed with brine and dried over $MgSO_4$. The products were isolated by chromatography over silica gel.

5) ^{1}H HMR (400 MHz, DMSO) δ 3.01 (dd, 1H, J = 2.44 and 14.16 Hz), 3.36 (dd, 1H, J = 6.34 and 14.16 Hz), 3.40 (ddd, 1H, J = 2.44, 6.34, and 8.79 Hz), 3.57 (dd, 1H, J = 3.42 and 8.79 Hz), 5.01 (dd, 1H, J = 3.42 and 3.42 Hz), 5.68 (d, 1H, J = 3.42 Hz), 6.77 (d, 2H, J = 6.84 Hz), 7.19-7.28 (m, 3H), 7.32-7.39 (m, 4H).

6) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 3H), 2.76 (s, 1H), 3.09 (dd, 1H, J = 10.26 and 19.04 Hz), 3.37 (d, 1H, J = 9.27 Hz), 3.48-3.56 (m, 2H), 7.13 (d, 2H), 7.22-7.46 (m, 6H), 7.61 (d, 1H, J = 7.32 Hz).

7) A mixture of **3** (1 mmol) and dienophile (3 mmol) in benzene (2 ml) was charged in a pyrex tube under nitrogen, and it was placed before a 500 W-Hg lamp immersed in cold water (15 °C). After irradiation for 5 h, the product was isolated by the same procedure as the thermal reaction.

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9) G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, and M. Itoh, *J. Am. Chem. Soc.*, **92**, 710 (1970) and Ref. 6b, p. 558.

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