



Installation of carbon chain onto 2-cyclohexene-1,4-diol monoacetate

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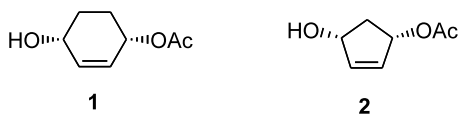
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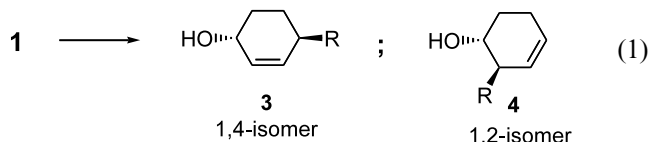
Abstract—Alkylation of cyclohexenyl monoacetate **1** with $R_2Cu(CN)(MgCl)_2$ or $RMgBr/CuCN$ (cat.) in Et_2O produced *trans* 1,2-isomers **4**, while arylation and alkenylation of **1** was accomplished with lithium borates **5** and a nickel cat. to afford *trans* 1,4-isomers **3** selectively. Furthermore, several transformations of the products were carried out to demonstrate synthetic advantages of the present reactions. © 2002 Elsevier Science Ltd. All rights reserved.

Monoacetate (**1**) of 2-cyclohexene-1,4-diol is an attractive starting compound for synthesis of biologically interesting cyclohexenes and cyclohexanes possessing carbon chain(s) on the ring, because monoacetate **1** is readily available in optically active¹ and racemic² forms. So far, among the possible carbon–carbon bond forming reactions, allylic substitution with soft nucleophiles is only investigated by Minami.³ On the other hand, allylic reaction with hard nucleophiles is not reported, though the reaction has the potential to cover a variety of carbon nucleophiles. Recently, we have reported reactions to install carbon nucleophiles onto 4-cyclopenten-1,3-diol monoacetate (**2**).⁴

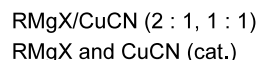


Alkylation by using reagents derived from $RMgX$ and $CuCN$ affords *trans* 1,2-isomer or 1,4-isomer among the four possible isomers.⁵ The striking feature of this reaction is that the regioselectivity is controlled by the ratio of $RMgX/CuCN$ (10~20:1, 2:1, 1:1)⁶ and the solvent (THF, Et_2O). On the other hand, arylation and alkenylation, realized with lithium borates and a nickel catalyst in THF, produces *trans* 1,4-isomer, where the

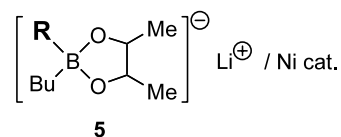
high 1,4-regioselectivity is attained with combination of additives such as *t*-BuCN and NaI.⁷ Consequently, we felt it important to clarify efficiency (yield and regioselectivity) of these reagents and solvents when applied to **1** (Eq. (1), Chart 1). Herein, we report preliminary results investigated with racemic **1**.



For alkylation:



For arylation and alkenylation



a, R = *n*-Bu; **b**, *c*-C₆H₁₁;
c, Ph; **d**, *p*-MeC₆H₄; **e**, *p*-MeOC₆H₄;
f, (E)-CH=CHC₅H₁₁

Keywords: coupling reaction; cyclohexene-1,4-diol monoacetate; Grignard reagent; copper catalyst; lithium borates; nickel catalyst.
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Chart 1. Reagents examined for alkylation, arylation, and alkenylation of **1**.

Table 1. Reaction of cyclohexene monoacetate **1** and reagents derived from RMgX and CuCN

Entry	Reagent ^a	Solvent	Temp. (°C)	Yield, % (calcd, %) ^c		
				1,4-Isomer	1,2-Isomer	1
1	BuMgCl/CuCN (cat.) ^b	THF	rt	3a 26 (25)	4a 49 (48)	–
2	Bu ₂ Cu(CN)(MgCl) ₂	THF	–18	3a 23	4a 58	–
3	BuCu(CN)(MgCl)	THF	–18	3a <2	4a 41	27
4	Bu ₂ Cu(CN)(MgCl) ₂	Et ₂ O	–18	3a 4	4a 79	–
5	BuCu(CN)(MgCl)	Et ₂ O	–18	3a (<2)	4a (12)	88
6	Bu ₂ Cu(CN)(MgCl) ₂	DME	–18	3a 39	4a 47	–
7	BuCu(CN)(MgCl)	DME	–18	3a 0	4a 0	100
8	Bu ₂ Cu(CN)(MgBr) ₂	THF	–18	3a 28 (29)	4a 47 (51)	–
9	BuCu(CN)(MgBr)	THF	–18	3a (<2)	4a (60)	40
10	BuMgBr/CuCN (cat.) ^b	Et ₂ O	rt	3a 2	4a 83	–
11	BuCu(CN)(MgBr)	Et ₂ O	–18	3a (<2)	4a (50)	50
12	(<i>c</i> -C ₆ H ₁₁) ₂ Cu(CN)(MgCl) ₂	Et ₂ O	–18	3b (<2)	4b 66 (74)	–
13	(<i>c</i> -C ₆ H ₁₁)Cu(CN)(MgCl)	Et ₂ O	–18~0	3b (<2)	4b (77)	18

^a 3 equiv.^b 20 mol%.^c Yield: isolated yield; calcd: calculated yield by ¹H NMR spectroscopy with pyridine added as an internal standard.

First, we examined the reagents which afford the 1,4-isomer **3** from cyclopentenyl acetate **2**. However, reaction with *n*-BuMgCl (3 equiv.) and CuCN (20 mol%) in THF afforded a mixture of 1,4-isomer **3a** (R=*n*-Bu) and 1,2-isomer **4a** (R=*n*-Bu) with a low regioselectivity favoring the opposite isomer **4a** (Table 1, entry 1). The other reagent, Bu₂Cu(CN)(MgCl)₂ in THF, also furnished a 2:5 mixture of **3a** and **4a** (entry 2). These results suggest the inherent preference of **1** producing the 1,2-isomer. Next, the reagents which afford the 1,2-isomer from cyclopentene **2** were investigated. Among the reagents shown in entries 3–5, Bu₂Cu(CN)(MgCl)₂ in Et₂O afforded the 1,2-isomer **4a** efficiently (entry 4). Again, the high propensity for favoring 1,2-isomer is observed.

Since the selection of the solvent among THF and Et₂O is critical in controlling the regioselectivity of cyclopentene **2**, bidentate solvents such as dioxane and DME were also examined in the reaction of **1**. Reaction in dioxane was less effective, resulting in co-production of the corresponding diol (data not shown), while the reaction with Bu₂Cu(CN)(MgCl)₂ in DME furnished a mixture of **3a** and **4a** (entry 6).

The reagents derived from BuMgBr and CuCN were also studied for the reaction. Among the reagents shown in entries 8–11, BuMgBr/CuCN (cat.) in Et₂O produced 1,2-isomer **4a** efficiently (entry 10).

Next, the above results were applied to *c*-C₆H₁₁MgCl as a representative of *sec*-alkyl reagents. The reagent, (*c*-C₆H₁₁)₂Cu(CN)(MgCl)₂, in Et₂O afforded the 1,2-isomer **4b** (R=*c*-C₆H₁₁) efficiently (entry 12), while (*c*-C₆H₁₁)Cu(CN)(MgCl) in Et₂O (entry 13) or (*c*-C₆H₁₁)_nCu(CN)(MgCl)_n in THF (*n*=1, 2; data not shown) recorded poor results.

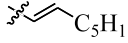
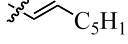
Installation of aryl groups such as Ph, *p*-MeC₆H₄, *p*-MeOC₆H₄ onto the ring of **1** was examined with aryl borates **5c–e** and NiCl₂(PPh₃)₂ (10 mol%) in THF at

room temperature (Table 2, entries 1–6). As is observed with cyclopentene **2**, addition of NaI (1 equiv.) and *t*-BuCN (5 equiv.) raised the regioselectivity and yield of 1,4-isomers **3c–e** (entries 2, 4, 6; cf. entries 1, 3, 5).

Alkenylation was also successful with alkenyl borate **5f** under the above conditions to produce **3f** selectively (entry 8; cf. entry 7).

Previously, 1,4-isomers **3** have been synthesized from cyclohexadiene monoepoxide (**6**)⁸ by reactions with [RCu(L)]Li (R = alkyl, aryl, alkenyl; L = ligand),⁹ R₂Te/(2-Th)Cu(Bu)(CN)Li₂ (R = alkenyl),¹⁰ and PhSnMe₃/Pd (cat.).¹¹ However, the regioselectivity is varied. In addition, epoxide **6** is unstable for handling, and synthesis

Table 2. Nickel-catalyzed reaction of **1** with borates **5c–f**^a

Entry	R for 5 , 3 , 4	Additives ^b	Yield, % (calcd, %) ^c	
			1,4-Isomer	1,2-Isomer
1	Ph	Not added	3c (48)	4c (44)
2	Ph	Added	3c 63 (73)	4c 13 (15)
3	<i>p</i> -MeC ₆ H ₄	Not added	3d 42	4d 33
4	<i>p</i> -MeC ₆ H ₄	Added	3d 55 (66)	4d 20 (24)
5	<i>p</i> -MeOC ₆ H ₄	Not added	3e (39)	4e (31)
6	<i>p</i> -MeOC ₆ H ₄	Added	3e 43 (43)	4e 19 (20)
7		Not added	3f 40	4f 32
8		Added	3f 53 (55)	4f 18 (20)

^a Borates **5c–f** (1.5–1.8 equiv.) and NiCl₂(PPh₃)₂ (10–20 mol%) were used with or without the additives at rt for 6–10 h.^b NaI (1 equiv.) and *t*-BuCN (5 equiv.).^c Yield: isolated yield; calcd: calculated yield by ¹H NMR spectroscopy with pyridine added as an internal standard.

17. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: California, 1972; Chapter 9.
18. **General procedure using RMgCl and CuCN:** To a suspension of CuCN in Et₂O was added a solution of RMg in Et₂O and the mixture was stirred for 20 min at the specified temperature (–18°C, 0°C, or rt). A solution of **1** (50 mg, 0.32 mmol) in Et₂O (1–1.5 mL) was added to the mixture. The reaction was carried out for 3–6 h and quenched by addition of saturated NH₄Cl and 28% NH₃. The mixture was extracted and the crude product was purified by chromatography on silica gel to afford the products shown in Table 1. The stoichiometries of RMgX and CuCN were 3 and 0.2–0.3 equiv. for RMgX/CuCN (cat.), 6.5 and 3 equiv. for R₂Cu(CN)(MgX)₂, and 3 and 3.5 equiv. for RCu(CN)(MgX), respectively.
- General procedure using borate 5 and Ni cat.:** To an ice-cold mixture of borate **5** (1.5–1.8 equiv.), NiCl₂(PPh₃)₂ (10–20 mol%), and NaI (10 mg, 1 equiv.) in THF (2.5 mL) was added a solution of *n*-BuLi (1.5–1.8 equiv.) in hexane dropwise. After 15–20 min of stirring at rt, *t*-BuCN (0.35 mL, 5 equiv.) and a solution of **1** (100 mg, 0.64 mmol) in THF (2.5 mL) were added to the mixture. The reaction was carried out at rt for 6–10 h, and quenched by addition of saturated NH₄Cl. The mixture was extracted with EtOAc and the crude product was purified by chromatography on silica gel to afford the products shown in Table 2.
19. (a) William, A. D.; Kobayashi, Y. *Org. Lett.* **2001**, *3*, 2017–2020; (b) Rickards, R. W.; Rönneberg, H. *J. Org. Chem.* **1984**, *49*, 572–573.