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

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Abstract—Alkylation of cyclohexenyl monoacetate 1 with R₂Cu(CN)(MgCl)₂ or RMgBr/CuCN (cat.) in Et₂O 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 $(10 \sim 20:1, 2:1, 1:1)^6$ and the solvent (THF, Et₂O). On the other hand, arylation and alkenylation, realized with lithium borates and a nickel catalyst in THF, produces *trans* 1,4-isomer, where the

Keywords: coupling reaction; cyclohexene-1,4-diol monoacetate; Grignard reagent; copper catalyst; lithium borates; nickel catalyst. * Corresponding author. Tel.: +81-45-924-5789; fax: +81-45-924-5789; e-mail: ykobayas@bio.titech.ac.jp

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.

1
$$\longrightarrow$$
 HOIIII ; HOIIII (1)

3 R 4

1,4-isomer 1,2-isomer

For alkylation:

RMgX/CuCN (2:1, 1:1) RMgX and CuCN (cat.)

For arylation and alkenylation

a, R = n-Bu; **b**, c-C₆H₁₁;

 \mathbf{c} , Ph; \mathbf{d} , p-MeC₆H₄; \mathbf{e} , p-MeOC₆H₄;

f, (E)-CH=CHC₅H₁₁

Chart 1. Reagents examined for alkylation, arylation, and alkenylation of 1.

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	$Bu_2Cu(CN)(MgBr)_2$	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	$(c-C_6H_{11})_2Cu(CN)(MgCl)_2$	Et ₂ O	-18	3b (<2)	4b 66 (74)	_
13	$(c-C_6H_{11})Cu(CN)(MgCl)$	Et ₂ O	$-18 \sim 0$	3b (<2)	4b (77)	18

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

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, $p\text{-MeC}_6H_4$, $p\text{-MeOC}_6H_4$ onto the ring of 1 was examined with aryl borates $\mathbf{5c}$ - \mathbf{e} and $\text{NiCl}_2(\text{PPh}_3)_2$ (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), R₂Te/(2-Th)Cu(Bu)(CN)Li₂ (R=alkenyl), and PhSnMe₃/Pd (cat.). 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			Yield, % (calcd, %)c		
	R for 5, 3,	Additives ^b	1,4-Isomer	1,2-Isomer	
1	Ph	Not added	3c (48)	4c (44)	
2	Ph	Added	3c 63 (73)	4c 13 (15)	
3	p-MeC ₆ H ₄	Not added	3d 42	4d 33	
4	p-MeC ₆ H ₄	Added	3d 55 (66)	4d 20 (24)	
5	p-MeOC ₆ H ₄	Not added	3e (39)	4e (31)	
6	p-MeOC ₆ H ₄	Added	3e 43 (43)	4e 19 (20)	
7		Not added	3f 40	4f 32	
	38 C5H1	1			
8		Added	3f 53 (55)	4f 18 (20)	
	c_5H_1	1			

^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.

^a 3 equiv.

^b 20 mol%.

^c Yield: isolated yield; calcd: calculated yield by ¹H NMR spectroscopy with pyridine added as an internal standard.

^b NaI (1 equiv.) and t-BuCN (5 equiv.).

^c Yield: isolated yield; calculated yield by ¹H NMR spectroscopy with pyridine added as an internal standard.

of optically active **6** suffers from the low efficiency.¹² Regarding 1,2-isomers **4**, only **4a** (as the acetate) is synthesized as a major product by reaction of 1-acetoxy-4-chloro-2-cyclohexene (7) with BuMgBr/Li₂CuCl₄.¹³ However, substrate **7** is available only in racemic form.¹⁴

In order to demonstrate usefulness of the 1,4- and 1,2-products **3** and **4** in organic synthesis, several transformations were studied. Oxidation of **3c** furnished ketone **8** in 88% yield (Eq. (2)). In principle, 4-substituted ketones such as **8** would be synthesized by the Stork method using 3-ethoxy-2-cyclohexenone, but in racemic forms. Similarly, alcohol **4a** was transformed cleanly to ketone **9** in 71% yield without migration of the double bond to the more stable α,β -position (Eq. (3)). Ketones such as **9** are probably produced by the classical alkylation of cyclohexenone under the conditions of the thermodynamic control. However, the classical method is limited to production of racemic ketones. In addition, the β,γ -double bond of the product would be migrated to the α,β -position under the thermodynamic conditions.

HOIII Jones oxidn
88%

So
$$=$$
 Ph (2)

HOIII $=$ Jones oxidn
71%

O= Ph (2)

Βú

9

As shown in Eq. (4), the Mitsunobu inversion of 1,4-isomer **3c** took place stereo- and regioselectively to afford the corresponding alcohol **10** in 90% yield.

Bu

3c
$$\xrightarrow{1) \text{ AcOH, DIAD, PPh}_3}$$
 $\xrightarrow{\text{toluene, } -78 \text{ °C}}$ $\xrightarrow{\text{Ph}}$ (4) $\xrightarrow{\text{2) K}_2\text{CO}_3}$ $\xrightarrow{\text{MeOH/H}_2\text{O} (4:1)}$ $\xrightarrow{\text{10, 90}\%}$

In summary, we have found conditions to obtain the *trans* 1,4- and 1,2-products from cyclohexene 1 regioand stereoselectively. In addition, the products were successfully converted into compounds, which had been hardly accessible in optically active forms. We believe that the present reactions will provide a new way for synthesis of cyclohexene (or cyclohexane) derivatives such as yohimbine, reserpine, Δ^9 -THC, In etc.

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- 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.
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