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DDQ-induced and Stereoselective Functionalization at Heterosubstituted Benzylic Positions by Carbon Nucleophiles

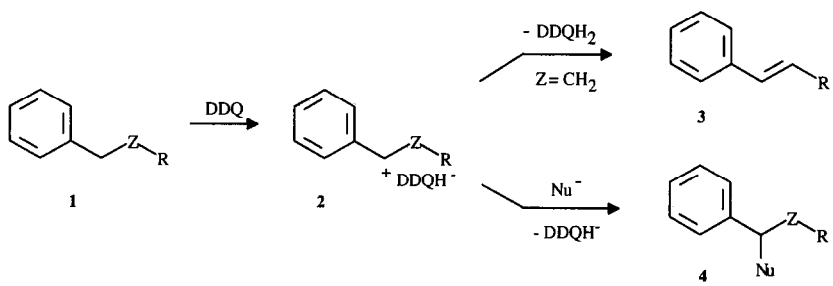
Yao-Chang Xu,* # Caroline Roy, Elaine Lebeau

BioChem Pharma Inc., 531 Blvd. des Prairies, Laval, Quebec, Canada H7V 1B7

Abstracts: 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) induced functionalization at the heterosubstituted benzylic position with a variety of carbon nucleophiles proceeds in high yield with good stereochemical control.

Oxidative transformations at the benzylic position induced by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) have received much attention as methods of organic synthesis.[1] In the presence of DDQ (Scheme 1), the benzylic substrate provides a cationic charge-transfer complex **2**, which can readily lose a proton to give an olefinic product **3**[1] or has been trapped with oxygenated nucleophiles such as alcohols[2] or acetic acid.[3] However, the oxidatively generated benzylic cationic species has been rarely employed to couple with a carbon nucleophile,[4] even though such novel oxidative carbon-carbon bond forming reaction should find a great potential in organic synthesis. We wish to disclose the first example of regio, and stereoselective addition of carbon nucleophiles to heterosubstituted benzylic positions (Z = O) assisted by DDQ.

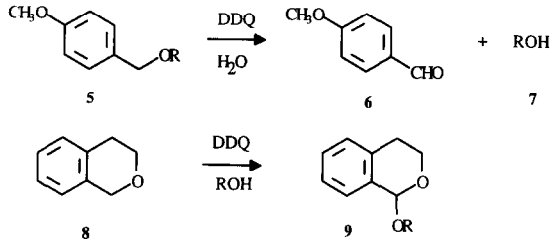
Scheme 1



Compared with the DDQ-induced dehydrogenation, the nucleophilic trapping reaction has received much less attention. The major problem hampering its synthetic utility is the competing facial dehydrogenation process. One possible solution to this problem could be envisioned by inserting a hetero atom at the α position, which will block the competing elimination process. As indicated in Scheme 2, the reaction of compound **5** with DDQ in the presence of H_2O, however, gave carbonyl compound **6** and alcohol **7**.[5] No expected trapping product was obtained. Although the α-dehydrogenation was blocked in this case, the trapped product was not stable enough to be isolated.[5a] Recently, we were able to overcome this problem by using a cyclic benzyl ether such as isochroman **8**,[6] from which the trapped products were expected to be more stable. The DDQ-induced reactions of **8** with oxygenated nucleophiles such as H_2O and alcohols indeed gave desired products **9** in excellent yields.

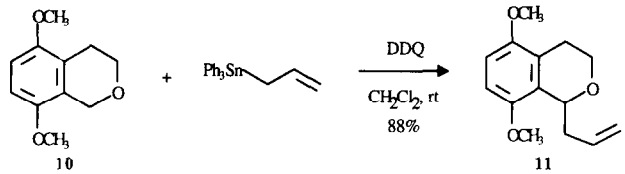
Current address: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, USA

Scheme 2



Prompted by these recent results, we began to investigate the carbon-carbon bond forming reaction on the isochroman based substrates with suitable carbon nucleophiles. When isochroman **10**[9] was treated with DDQ and allyl triphenyl stannane, the expected product **11** was obtained in 88% isolated yield. Since the allyl stannane reacts with DDQ, it was important to add it after the isochroman was treated with DDQ for about 1h. The reaction is regioselective with allyl introduced at the activated benzylic position as observed previously.[6]

Scheme 3

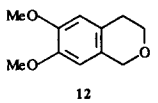
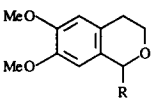
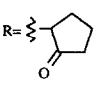
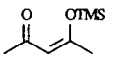
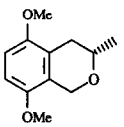
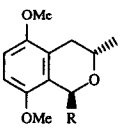
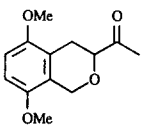
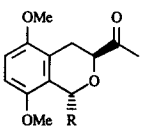
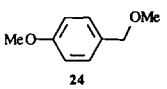
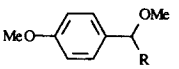


We have extended the scope of the reaction by probing different isochromans and carbon nucleophiles. The preliminary results are presented in Table 1.

As shown in Table 1, this trapping reaction was found to be quite general. A variety of carbon nucleophiles such as silyl enol ether, allyl stannane, allyl silane, TMSCN, and even Grignard reagents and alkyl lithium can all be employed in the carbon-carbon bond forming reaction with different isochromans. For example, the reaction of isochroman **12**[9] with 1-(trimethylsilyloxy)cyclopentene gave a 1 : 1 diastereomeric mixture of **13** (78%). Similarly, the presumed carbon cation could be trapped by acyclic silyl enol ethers to give coupled products **14-16** (49-73%). The reaction of 3-substituted, optically pure isochroman **18**[9] with allyl stannane gave a mixture of optically pure *trans* and *cis* products in excellent yields (77-97%) with *trans* favored (10-13 : 1). The *trans* stereoselectivity increased significantly (>20 : 1) with more nucleophilic reagents such as n-butyl magnesium chloride and n-butyllithium. The stereochemistry was determined by comparing the long-range coupling constant of the benzylic proton with those of the eleutherin and isoeleutherin epimeric pair.[7]

It was found that the nucleophilic trapping reactions with isochroman **21**[6] was much slower than those with either **18** or **12**. For example, treatment of **21** with allyl silane at room temperature for 3 days gave only 34% yield of coupled product **22** along with the unreacted starting materials. The reaction of **18** with the same nucleophile, however, finished in 2h and afforded product **19** in 45% yield. The lowered reactivity associated with isochroman **21** was attributed to the 3-substituted electron-withdrawing acetyl group, which can increase the activation energy by destabilizing the cationic transition state through inductive effects. Addition of $LiClO_4$,[8] which can stabilize the cationic intermediate, has indeed resulted in the higher yield of coupled product **22** (78%). The cationic intermediate can also couple with TMSCN to afford 1-

Table 1[a]

Substrates	Nucleophiles[b]	Products[c]		Yields (%)	*trans/cis*
 12			13 	78	-
			14 $R = CH_2COCH_3$	49	-
			15 $R = CH_2COPh$	50	-
			16 $R = CH(COCH_3)_2$	73	-
	$CH_2 = CHMgBr$		17 $R = CH = CH_2$	25	-
 18	$Bu_3SnCH_2CH = CH_2$		19 $R = CH_2CH = CH_2$	77	10:1
	$Ph_3SnCH_2CH = CH_2$		19	97	13:1
	$TMSCH_2CH = CH_2$		19	45	d
	nBuMgCl		20 R = nBu	54	d
	BuLi		20	48	d
 21	$TMSCH_2CH = CH_2$[e]		22 $R = CH_2CH = CH_2$	34	d
	$TMSCH_2CH = CH_2$[e,f]		22	78	d
	TMSCN[e]		23 R = CN	52	12:1
 24	$Ph_3SnCH_2CH = CH_2$		25 $R = CH_2CH = CH_2$	71	-

a) Unless specified, all the reactions were carried out by adding 1.0-1.5 eq. of DDQ to a mixture of heterosubstituted benzylic substrate and molecular sieves in dry CH_2Cl_2. After stirring at room temperature for 5-60 minutes, the nucleophiles were added.

b) All the nucleophiles were purchased from Aldrich and used without further purification.

c) All the products were characterized by ^1H NMR, ^{13}C NMR, IR spectra, and by HRMS or elemental analysis.

d) No *cis* isomer could be detected by ^1H and ^{13}C NMR.

e) The nucleophile was added at the beginning of the reaction.

f) Catalytic amount of $LiClO_4$ was added.

cyanoisochroman **23** (52%).The last example in the Table 1 indicated that an acyclic benzyl ether can also be functionalized by carbon nucleophile.

A typical procedure is as follows: To a stirred solution of compound **10** (124.5 mg, 0.64 mmol) in 4 ml of dichloromethane was added molecular sieves (4A,100 mg) under argon. After stirring for 10 to 15 min, DDQ (218 mg, 0.96 mmol) was introduced and the mixture was stirred at room temperature for about 1h. Allyltriphenyl stannane (577 mg, 1.47 mmol) in dry dichloromethane (1 ml) was added dropwise to the above mixture. After stirring for 5h, 10 ml of aqueous $NaHCO_3$ (5%) was added. The mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography using toluene and ethyl acetate (95 : 5, v/v) as eluent to give a colorless oil **11** (132.3 mg, 0.57 mmol, 88%). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.68 (d, 1H, J = 9.0 Hz), 6.64 (d, 1H, J = 9.1 Hz), 5.94 (m, 1H), 5.09 (m, 2H), 4.94 (dd, 1H, J = 8.9, 3.0 Hz), 4.02 (m, 1H), 3.74-3.83 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.50-2.75 (m,. 4H); ^{13}C NMR (60 MHz, $CDCl_3$) δ: 150.90, 149.66, 136.15, 127.75, 124.33, 116.16, 107.67, 107.39, 71.74, 59.38, 55.60, 55.37, 37.52, 23.09; IR (neat): 3076m, 2942s, 1644m, 1598m, 1477s, 1437s, 1333s, 1253s, 1098s, 1052s, 799s, 704s cm^{-1}; HRMS for $C_{14}H_{17}O_3$ calcd 233.1178, found 233.1149. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.39; H, 7.80.

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