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DICYANOKETENE ETHYLENE ACETAL AS A MILD AND EFFICIENT CATALYST FOR TETRAHYDROPYRANYLATION OF ALCOHOLS

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Abstract. Alcohols can react with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of dicyanoketene ethylene acetal under neutral conditions to afford the corresponding tetrahydropyranyl ethers in good yields.

Tetrahydropyranyl (THP) ether is a versatile protecting group for hydroxyl groups in organic synthesis. Due to its stability in a variety of reactions under neutral and basic conditions,¹ THP ether is often the protective group of choice in the synthesis of peptides, nucleotides, carbohydrates, and steroids.²

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The common method for preparation of THP ethers is the reaction of hydroxyl group with 3,4-dihydro-2*H*-pyran (DHP) in the presence of appropriate catalysts such as hydrochloric acid,³ *p*-toluenesulfonic acid,⁴ BF₃-Et₂O,⁵ pyridinium *p*-toluenesulfonate (PPTS),⁶ electrogenerated acid (EG acid),⁷ Amberlyst H-15,⁸ Nafion-H,⁹ montmorillonite clay K-10,² H-Y Zeolite,¹⁰ spanish sepiolite clay,¹¹ and poly(4-vinylpyridine) as the *p*-toluenesulfonate¹² and hydrochloride.¹³ Contrary to the acidic catalysts mentioned above, few are known about the neutral catalysts.¹⁴⁻¹⁶ Therefore, it is still of considerable interest to develop new efficient catalysts which can be easily prepared, handled, and used under neutral conditions.

Recently, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) which is one of the representative one electron oxidants was reported to catalyze alcoholysis of epoxides,^{17a} tetrahydropyranylation of alcohols,^{17b} C-glycosidation of glycals,^{17c} and deprotection of acetals^{17d} and orthoesters.^{17e} In the context, we have reported that tetracyanoethylene (TCNE), a typical π -acid and one-electron acceptor,¹⁸ accelerates catalytically substrate-specific rearrangement, acetonidation,^{19a} and alcoholysis of epoxides,^{19b} and Mukaiyama Aldol reaction of acetals.^{19c} Recently, we have found that dicyanoketene acetals, a new type of π -acid which has a capto-dative ethylene structure, catalyzed monothioacetalization of acetals.²⁰ Now we report that dicyanoketene ethylene acetal (DCKEA) prepared easily²¹ serves as an excellent catalyst for tetrahydropyranylation of alcohols.

First, the reaction of benzyl alcohol (1a) with DHP was investigated in the presence of a catalytic amount of DCKEA in several solvents, and the corresponding THP ether (2a) was found to be produced in DMSO and DMF at room temperature in 19 % and 34 % yields, respectively. Raising the reaction temperature to 60 °C in DMF increased the yield (88 %) of 2a. (Table 1)

$\begin{array}{c} NC \\ NC \\ O \end{array} \qquad (DCKEA) \\ (0.2 equiv.) \end{array}$						
BnOH —— 1a	DMF	Bn-O O 2a				
Solvent	Temp.	Time	Yield			
CH ₂ Cl ₂	R.T.	23 h	0 %			
benzene	R.T.	24 h	0 %			
THF	R.T.	24 h	0 %			
CH ₃ CN	R.T.	23 h	0 %			
CH ₃ NO ₂	R. T.	24 h	0 %			
DMSO	R.T.	24 h	19 %			
DMF	R .T.	18 h	34 %			
DMF	60 °C	7 h	88 %			

Table 1. Tetrahydropyranylation of Benzyl Alcohol

 Catalyzed by Dicyanoketene Ethylene Acetal (DCKEA).

As summarized in Table 2, several alcohols reacted smoothly with DHP in the presence of a catalytic amount of DCKEA to afford the corresponding THP ether in excellent yields. Both primary and secondary alcohols are converted smoothly into the corresponding THP ethers, except for menthol (1i), a hindered secondary alcohol. Because DCKEA is an extremely mild and neutral catalyst, no serious problems occurred for the tetrahydropyranylation of alchols (1k, 1l, 1m) possessing acid-labile functional groups such as 1,5-diene, allylic alcohol, and acetal. DCKEA was a poor catalyst for the reaction with tertiary alcohols and phenol (1j) to give the significant recovery of the starting materials. In the reaction with 4-hydroxybenzyl alcohol (1n), the primary hydroxyl group reacted

DCKEA (0.2 equiv.)						
R-OH	(3 equiv.)		R-	R-OO		
(Alcohol)) DMF , 60 °C		(1	(THP Ether) 2		
Alcohol (1)			Time	Yield of 2		
1-octanol		1b	6 h	83 %		
2-octanol		1c	12 h	77 %		
cyclohexanol		1d	12 h	82 %		
4-chrolo-1-butanol		1e	3.5 h	90 %		
5-hydroxy pentan-2-one		lf	8 h	82 %		
Cholesterol		1g	12 h	92 %		
furfuryl alcohol		1h	6 h	93 %		
menthol		1i	12 h	45 %		
phenol		1j	13 h	16 %		
geraniol		1k	5 h	82 %		
cinnamyl alcohol		11	11 h	84 %		
solketal		1m	12 h	95 %		
4-hydroxybenzyl alcohol		1n	11 h	76 % ^{a)}		

 Table 2.
 Tetrahydropyranylation of Alcohols Catalyzed by Dicyanoketene Ethylene Acetal (DCKEA).

a) The benzylic alcohol was selectively protected as a THP ether.

with DHP faster than the phenolic hydroxyl group to afford mono-THP ether (2n) in 76 % yield.

In conclusion, we have shown that DCKEA is an efficient and mild catalyst for tetrahydropyranylation of alcohols under neutral condition.

Experimental

General Procedure for Tetrahydropyranylation of Alcohols Catalyzed by DCKEA: 3,4-Dihydro-2*H*-pyrane (146 mg, 1.740 mmol) was added to a solution of DCKEA (15.8 mg, 0.116 mmol) and benzyl alcohol (**1a**, 62.7 mg, 0.580 mmol) in dry DMF (1.5 ml). The reaction mixture was stirred at 60 °C for 7 h, then crude product was extracted AcOEt. The organic extract was wasded with brine, and dried over anhydrous Na₂SO₄, then solvent was removed in vacuo. The crude product thus obtained was purified by silica gel column chromatography to give the corresponding THP ether **2a** (98.5mg, 88 %) as a colorless oil. (Table 1)

THP ethers (2c, 2g, 2i, and 2m) were obtained as an inseparable mixture of diastereomers.

Compounds (2a-m) were identified by comparision of their spectroscopic behaviors with those described in the references.^{10, 17b, 22}

Analytical data of compound **2n** is as follow. **2n**: IR (neat) 3320 (OH), 1520, 1120 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.50-1.90 (6H, m), 3.57 (1H, m), 3.94 (1H, m), 4.43 (1H, d, *J* = 11.7 Hz), 4.71 (2H, m), 5.64 (1H, s), 6.79 (2H, m), 7.23 (2H, m). HRMS (EI) Calcd for C₁₂H₁₆O₃ (M⁺): 208.1099. Found: 208.1088.

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