

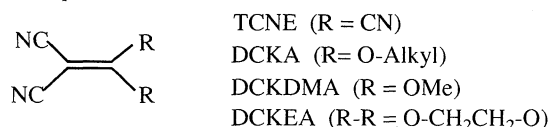
Mild Esterification and Transesterification of Carboxylic Acids Catalyzed by Tetracyanoethylene and Dicyanoketene Dimethyl Acetal

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A π -acid tetracyanoethylene (TCNE) and its derivative dicyanoketene dimethyl acetal (DCKDMA) were found to catalyze esterification of lauric acid with various types of alcohols. This method was successfully applied to methyl esterification of a variety of carboxylic acids including aromatic, α,β -unsaturated, α -hydroxy, and *N*-Cbz and *N*-Boc-protected α -amino acids without racemization at the range from room temperature to 60 °C. TCNE was also found to operate as a catalyst in transesterification reaction of methyl laurate.

Esterification of carboxylic acids is one of the most fundamental and important reactions in organic synthesis and a great number of methods have been explored and developed.¹ Among the direct methods using carboxylic acids and alcohols, catalytic use of inorganic and organic protic acids is the most popular tool in view of simplicity and applicability to large-scale operations. A great need, however, still exists for a versatile and simple process whereby esters may be formed from carboxylic acids with various functional groups including acid-labile ones. A progress has been made in the development of mild catalysts in the sense, e.g., polymer-supported AlCl_3 ,^{2a} $\text{BF}_3\cdot\text{Et}_2\text{O}$,^{2b} Me_3SiCl ,^{2c} organotin related compounds $[\text{R}_2\text{SnO}]$ and $(\text{R}_2\text{Sn})_2\text{O}$,^{2d} R_2SnCl_2 ,^{2e} $[(\text{R}_2\text{Sn})_2\text{O}]_2$,^{2f} and triarylbismuthane (Ar_3Bi) .^{2g} We have studied on the development of new functions of a representative π -acid tetracyanoethylene (TCNE) as well as capto-dative olefin dicyanoketene acetals (DCKA) in organic synthesis and found that TCNE and DCKA, particularly dicyanoketene ethylene acetal (DCKEA),³ catalyze interesting substitution reactions of epoxides and acetals with *O*-, *S*-, and *C*-nucleophiles.⁴

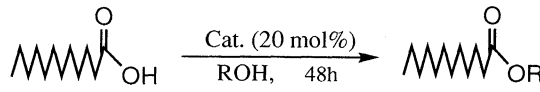






We report here on a novel and mild esterification reaction of carboxylic acids with alcohols catalyzed by TCNE and a representative DCKA, dicyanoketene dimethyl acetal (DCKDMA),³ and also note catalytic activities of TCNE in transesterification.⁵ One of the notable features of the present method is the first catalytic esterification of carboxylic acids using π -acid which allows the acid-labile functional groups such as *N*-Cbz and *N*-Boc groups intact under the essentially neutral and mild conditions.

First, lauric acid was stirred in MeOH with 20 mol% of TCNE at room temperature for 48 h to give in a nearly quantitative yield the methyl ester. It is known that TCNE is converted slowly into DCKDMA on exposure to MeOH.^{4a} The same treatment of lauric acid in MeOH with 20 mol% of DCKDMA produced methyl laurate also in excellent yield.

Results of the esterification reaction of lauric acid in the presence of catalytic amounts of TCNE and DCKDMA using the representative primary, secondary, tertiary, allylic, benzylic, and functionalized alcohols such as 2-trimethylsilylethanol and 2,2,2-trichloroethanol are summarized in Table 1.

Table 1. Esterification of lauric acid catalyzed by TCNE and DCKDMA

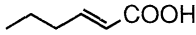
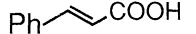
		Catalyst, Yield/%	
ROH	Temp.	TCNE	DCKDMA
MeOH	r.t.	99	96
EtOH	r.t.	93	93
ⁿ PrOH	r.t.	83	84
	r.t.	quant.	quant.
ⁱ PrOH	r.t.	7	19
	60°C	97	65
	60°C	54	31
^t BuOH	60°C	no reaction	no reaction
BnOH	r.t.	37	57
	60°C	quant.	—
	r.t.	73	7
	r.t.	6	no reaction
	60°C	93	3
TMS-CH ₂ -CH ₂ -OH	r.t.	93	96
Cl ₃ C-CH ₂ -OH	60°C	4	trace

For primary alcohols, reactions generally proceeded successfully to give the corresponding esters in high to excellent yield with TCNE as well as DCKDMA. Unfortunately, *tert*-butyl esters could not be obtained even at 60 °C, although secondary alcohols such as 2-propanol and cyclohexanol afforded the esters in moderate to good yield. Difference of catalytic activity between TCNE and DCKDMA was shown in the reaction using allyl, benzyl, and propargyl alcohols, where TCNE appeared superior to DCKDMA. It should be worth noting that 2-TMS-ethyl ester, an useful carboxy protecting group,⁶ was obtained in an excellent yield either with TCNE or DCKDMA at room temperature, although trichloroethanol reacted sluggishly even at 60 °C and failed to give the corresponding ester in a practical yield.

Next, efficiency of the catalysts TCNE and DCKDMA was investigated in methyl esterification of a variety of carboxylic acids including aromatic, α,β -unsaturated, α -hydroxy, and α -amino acids. Results are summarized in Table

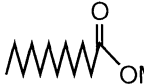
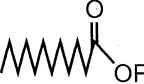

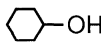


2. Dramatic acceleration was observed in esterification of *o*-methoxybenzoic acid, whereas aromatic and α,β -unsaturated carboxylic acids generally gave moderate to low yields of the methyl esters. Esterification of α -hydroxy acids proceeded smoothly without protection of hydroxyl group. With α -amino acids, *N*-Cbz and *N*-Boc protected ones afforded the methyl esters in good to quantitative yields at the range of room temperature to 60 °C, although non-protected alanine never reacted even at 60 °C. No racemization of the starting carboxylic acids and product esters was observed in esterification of (*S*)-(+)-mandelic acid and (*S*)-(-)-*N*-Boc-alanine. Catalytic activity of TCNE in esterification was found to be superior to DCKDMA throughout the present experiments.

Table 2. Methyl esterification of carboxylic acids catalyzed by TCNE (and DCKDMA)

RCOOH	TCNE (20 mol%) MeOH, 48 h		RCOOMe
RCOOH	Temp, Yield/%		
	r.t.	60 °C	
C ₆ H ₅ -COOH	trace	trace	
<i>p</i> -MeO-C ₆ H ₄ -COOH	12	43	
	13 (DCKDMA)	41 (DCKDMA)	
<i>m</i> -MeO-C ₆ H ₄ -COOH	23	55	
	—	58 (DCKDMA)	
<i>o</i> -MeO-C ₆ H ₄ -COOH	70	—	
	50 (DCKDMA)	95 (DCKDMA)	
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	18	43	
	30	50	
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CH ₃ CH(OH)CO ₂ H	88	87	
PhCH(OH)CO ₂ H	96	—	
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CH ₃ CH(NH ₂)CO ₂ H	no reaction	no reaction	
CH ₃ CH(NH-Z)CO ₂ H	quant.	—	
(CH ₃) ₂ CHCH(NH-Z)CO ₂ H	19	64	
PhCH(NH-Z)CO ₂ H	87	—	
	73 (DCKDMA)	—	
CH ₃ CH(NH-Boc)CO ₂ H	78	—	
	69 (DCKDMA)	—	

TCNE was also found to operate as a catalyst in transesterification of methyl laurate, although DCKDMA appeared not so potent in the reaction. Thus, methyl laurate was treated in various alcohols in the presence of 20 mol% of TCNE or DCKDMA at the range from room temperature to 60 °C for 48 h. Results are summarized in Table 3. Transesterification of methyl laurate occurred with TCNE in alcohols at rather elevated temperature (60 °C) to give moderate to high yields of the corresponding esters, whereas DCKDMA revealed little activity except in ethanol.

Table 3. Transesterification of methyl laurate catalyzed by TCNE and DCKDMA

 $\xrightarrow[\text{ROH, 60 } ^\circ\text{C, 48 h}]{\text{Cat. (20 mol\%)}}$ 		
ROH	Catalyst, Yield/%	
	TCNE	DCKDMA
EtOH	24 ^a quant.	20 ^a 70
ⁿ PrOH	92	26
	56	21
ⁱ PrOH	63	trace
	58	no reaction
BnOH	79	27
	57	trace
	40	no reaction

^a Yield for the reaction at room temperature.

In conclusion, we found the first catalysts of a π -acid TCNE and a capto-dative olefin DCKDMA, which promote mild esterification reaction of functionalized carboxylic acids.

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