



## Reactions of Ethylidene Diacetate: Formation of N-Vinylamide Precursors Ethylidene Bisacetamide and Ethylidene Bisformamide

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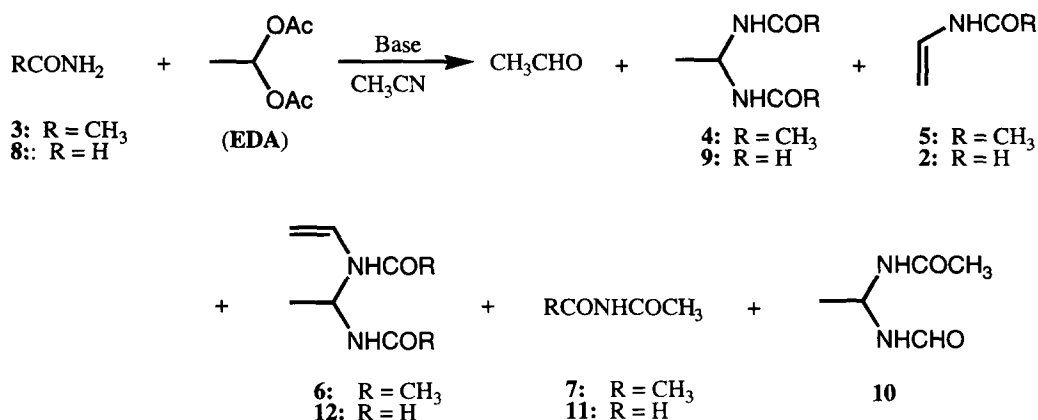
**Abstract:** Ethylidene diacetate (**EDA**) reacts with formamide or acetamide under stoichiometric base or catalytic Lewis acid conditions to afford the corresponding ethylidene bisamides and N-vinylamides.  $\text{Sn}(\text{OAc})_2$  afforded an overall 82.6% selectivity to the desired acetamide derivatives.  $\text{Sn}(\text{OAc})_2$  and  $\text{Zn}(\text{OAc})_2$  facilitate amide attack at the tertiary carbon of **EDA**. © 1997 Elsevier Science Ltd.

**Background.** The chemistry of ethylidene diacetate (**EDA**) has not been extensively studied. Bronsted acids such as benzenesulfonic or p-toluenesulfonic acid at 140°C, catalytically crack ethylidene diacetate to vinyl acetate and acetic acid.<sup>1</sup> Aniline has been shown to react with **EDA** to give acetanilide, acetaldehyde, and acetic acid.<sup>2</sup> N-butanol also reacts in the presence of an acid catalyst to give n-butyl acetate.<sup>3</sup> In both cited examples nucleophilic attack occurs at the carbonyl carbon of the acetate group. Substitution at the tertiary carbon is less well documented in the literature, although  $\text{NaOH}/\text{CHX}_3$ , where X = Br or Cl, was shown to react with **EDA** via acetate displacement to give  $\text{CH}_3\text{CH}(\text{CX}_3)\text{OAc}$ .<sup>4</sup>

Compounds of the type  $\text{CH}_3\text{CH}(\text{X})\text{NHCHO}$  (**1**), where X = CN, OMe, or NHCHO, are prepared from acetaldehyde. Subsequent cracking leads to N-vinylformamide (**NVF**, **2**), a precursor to polyvinylamine.<sup>5</sup> The acetamide based derivatives of **1** lead to another polyvinylamine precursor, N-vinylacetamide (**NVA**, **5**). In this regard, we began to explore alternate routes to **NVF** and **NVA**, and their precursors (**9** and **4**, respectively). We chose to work with **EDA** since its carbon skeleton is identical to **1**. Although **EDA** has not been employed as a precursor to mono- and bisamide ethanes or to N-vinylamides, we surmised that appropriate catalysts could exploit the leaving group ability of the acetate groups, but realized the desired chemistry could compete with other available pathways.

**Base-Induced EDA Chemistry.** When ethylidene diacetate and acetamide (**3**) are exposed to a base, such as cesium carbonate or sodium hydroxide, in acetonitrile, five major products are produced (Scheme I).<sup>6</sup> Substitution of both acetoxy groups with **3** leads to ethylidene bisacetamide (**EBA**, **4**). N-Vinylacetamide (**NVA**, **5**) is also formed and probably arises from the base-induced elimination of **3** from compound **4** under the reaction conditions. GC/MS was used to analyze the reaction mixture composition and **EBA** does crack to **NVA** in the GC injection port. Although the presence of **NVA** (trace quantities) in the reaction mixture was confirmed by HPLC analysis, the majority of **NVA** (and **NVF**, see below) reported here is formed during the GC/MS analysis. The dimer of **5** (compound **6**) is found in small amounts, and its presence provides further evidence that **NVA** is a real component of the reaction mixture. The other two products produced are acetaldehyde and diacetamide (**7**). Diacetamide is presumably derived from the addition of acetamide to the carbonyl carbon of the acetoxy group. Acetaldehyde can be derived from this same pathway by decomposition of the resulting acetoxy alcohol to acetaldehyde and acetic acid. However, acetaldehyde can also be derived from the retro-reaction of ethylidene diacetate.

Table I lists the selectivity to the products shown in Scheme I with several different bases. Cesium carbonate appears to be the best base to effect the desired substitution chemistry. **EDA** is not entirely accounted for here since some products were not identified. Cesium hydrogen carbonate and Proton Sponge®



**Scheme I.** Products from the base-induced EDA/amide reaction.

**Table I.** Selectivity for EDA reacting with Acetamide (3) and Various Bases

Ex.	Base	Temp. (°C)	Time (h)	Selectivity <sup>a</sup>				
				4	5	6	7	AcH
1	CsHCO <sub>3</sub>	50	3	0	0.2	0	2.0	3.8
2	Cs <sub>2</sub> CO <sub>3</sub>	50	3	12.1	23.8	1.6	17.2	19.6
3	NaOH	50	3	5.1	6.5	0.4	13.8	16.8
4	NaH/THF <sup>b</sup>	25	1	7.8	3.4	0.8	1.3	5.5
5	Proton Sponge <sup>c,d</sup>	50	7.5	0	0	0	0.3	0.4

<sup>a</sup>Selectivity defined as (mmol product)/(mmol EDA charged) x 100. <sup>b</sup>Reaction carried out with 2:1:2.1 molar ratio of acetamide:EDA:NaH. <sup>c</sup>Reaction carried out with 4:1:2.4 molar ratio of acetamide:EDA:Proton Sponge<sup>®</sup>. <sup>d</sup>Proton Sponge<sup>®</sup> is 1,8-bis(dimethylamino)naphthalene.

are virtually inactive. The lack of activity for cesium hydrogen carbonate suggests that the substitution reaction with cesium carbonate may stop at the bicarbonate stage, although it is probably consumed via acetic acid neutralization. Of course, Cs<sub>2</sub>CO<sub>3</sub> can also react with acetic acid which lowers EDA conversions.

When ethylidene diacetate and formamide (8) are exposed to stoichiometric base in acetonitrile, six products are produced along with an undetermined amount of acetamide (Scheme I). Like the acetamide reaction, substitution of the acetoxy groups for formamide leads to ethylidene bisformamide (9) and N-vinylformamide (2). Compounds 4, 5, and 10 contain the acetamide moiety which arise from the substitution of the acetoxy group for acetamide instead of formamide. Acetamide is likely to derive from the reaction of formamide with base to produce formate anion and ammonia (or amide). Ammonia (amide) can then react with ethylidene diacetate via carbonyl addition to afford acetamide. Several control reactions were performed to address this issue. The reaction of EDA with only cesium carbonate in acetonitrile afforded no products, EDA was recovered unchanged. Furthermore, replacing acetonitrile with propionitrile in the reaction of EDA with formamide and cesium carbonate afforded similar product distributions, indicating acetamide is not arising from acetonitrile hydrolysis. Lastly, a control reaction in which ammonia was bubbled through a solution of ethylidene diacetate, cesium carbonate, and acetonitrile did produce acetamide. Acetaldehyde is also produced in this reaction, but no significant amount of the acylated formamide (11) is found which would come from addition of formamide to the carbonyl carbon of ethylidene diacetate. This supports the notion that acetaldehyde may predominantly be derived from the direct decomposition of ethylidene diacetate.

Table II demonstrates the performance of cesium carbonate for converting formamide and ethylidene

**Table II.** Conversions and Selectivity for Formamide/EDA/Cs<sub>2</sub>CO<sub>3</sub> Reaction at 25 °C.<sup>a</sup>

Ex.	Time	Conversion (%)		Mass Balance (%)		Selectivity (%) <sup>b</sup>					
		8	EDA	8	EDA	2	4	5	9	10	AcH
6	1h	47.8	13.8	60	97	12.3	6.5	5.1	0	10.1	44.2
7	24h	83.3	54.6	80	94	22.7	23.6	9.9	2.2	15.6	14.5

<sup>a</sup>Reaction carried out with a 1:1:1.2 ratio of formamide:ethylidene diacetate:cesium carbonate in acetonitrile at 25°C.

Conversion, mass balance, and selectivity determined via gas chromatography using toluene as an internal standard. <sup>b</sup>Based on EDA conversion.

diacetate to the listed products in Scheme I, including mass balance data and product selectivity based on EDA conversion (as opposed to EDA charged). The use of formamide itself as the solvent in this case actually diminished the yield of the desired products. Several other bases were examined for activity in this regard (Table III). Carbonates of lithium, strontium, and ammonium were inactive, and potassium carbonate was only active in the presence of 18-crown-6. DBU, NaOH, KO<sup>t</sup>Bu, and NaH/THF all showed some activity.

**Table III.** Effect of Base on Formamide Conversion and Product Selectivity for Scheme I at 25 °C.<sup>a</sup>

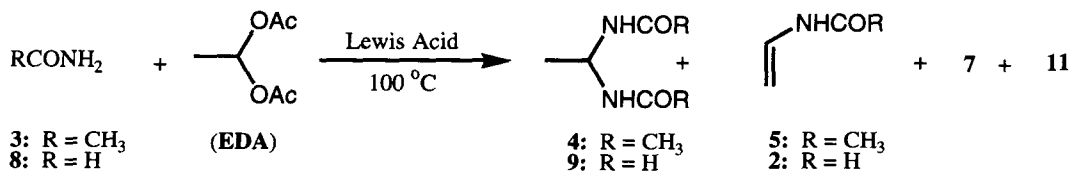
Ex.	Base	Time (h)	Conversion				Selectivity (%) <sup>b</sup>			
			8 (%)	2	4	5	9	10	AcH	
8	K <sub>2</sub> CO <sub>3</sub>	7	21	0	0	0	0	0	0	
9	K <sub>2</sub> CO <sub>3</sub> /18-c-6 <sup>c</sup>	22	44	8.9	1.8	7.6	0	1.3	7.6	
10	Cs <sub>2</sub> CO <sub>3</sub>	1.5	51	2.3	1.7	1.0	0.8	5.6	5.6	
11	Cs <sub>2</sub> CO <sub>3</sub>	23	85	10.5	9.4	3.5	5.4	21.2	5.9	
12	DBU <sup>d</sup>	3	37	7.8	N.D. <sup>e</sup>	2.2	4.9	16.9 <sup>e</sup>	8.5	
13	NaOH	5	72	2.1	4.3	1.2	0	3.1	8.4	
14	KO <sup>t</sup> Bu	1	59	1.9	1.5	0.8	0.7	3.4	10.5	
15	NaH/THF	1	83	3.5	1.6	1.1	1.7	6.4	5.9	

<sup>a</sup>Reaction carried out with a 1:1:1.2 ratio of formamide:ethylidene diacetate:cesium carbonate in acetonitrile at 25°C.

<sup>b</sup>Selectivity defined as (mmol product)/(mmol EDA charged) x 100. <sup>c</sup>18-c-6 is 18-crown-6, 0.2 equivalents used. <sup>d</sup>DBU is 1,8-Diazabicyclo[5.4.0]undec-7-ene. <sup>e</sup>Selectivity unreliable due to co-elution of DBU.

**Lewis Acid Assisted EDA Chemistry.** Lewis acids were found to catalyze the substitution reaction of amides with EDA. If similar reactions conditions are used as stated above, but using a Lewis acid in place of the base, little to no reaction takes place. However, when the reaction temperature is raised to 100 °C and replacing acetonitrile with excess amide, both Zn(OAc)<sub>2</sub> and Sn(OAc)<sub>2</sub> catalyze the substitution. Scheme II shows the products detected when acetamide reacts with EDA in the presence of a Lewis acid. Table IV shows that tin (II) acetate (Example 17) is slightly more selective than zinc (II) acetate (Example 16) for attack at the tertiary carbon by forming more ethylidene bisacetamide and less diacetamide.

Like the base induced reactions, the Lewis acid catalyzed reaction between EDA and formamide is more complex compared to the acetamide chemistry. A mixture of products derived from both formamide and

**Scheme II.** Products from the Lewis acid catalyzed EDA/amide reaction.

**Table IV.** Selectivity for Lewis Acid Catalyzed EDA/Acetamide Substitution<sup>a</sup>

Ex.	Catalyst	Time (h)	Selectivity <sup>b</sup>			AcOH <sup>d</sup>
			4	5	7	
16	Zn(OAc) <sub>2</sub>	5	28.0	1.8	9.2	26.0
17	Sn(OAc) <sub>2</sub>	5	31.3	0.4	7.8	29.1
18	Sn(OAc) <sub>2</sub>	15	81.8	0.8	12.9	80.8
19	Sn(OAc) <sub>4</sub>	5	5.5	0.3	4.5	11.1
20	Sn(OAc) <sub>2</sub> <sup>c</sup>	5	39.0	0.2	9.5	31.1
21	SnCl <sub>2</sub>	5	8.5	0.2	4.4	1.8
22	SnCl <sub>4</sub>	5	19.5	1.4	6.0	28.5

<sup>a</sup>Reactions carried out with a 5:1:0.052 molar ratio of acetamide:EDA:catalyst at 100 °C. <sup>b</sup>Selectivity defined as (mmol product)/(mmol EDA charged) x 100. <sup>c</sup>3:1:0.052 acetamide:EDA:catalyst molar ratio. <sup>d</sup>Acetic acid.

acetamide reactions are formed (**2**, **3**, **5**, **9**, **10**, **11**, and acetic acid). For example, ethylidene bisformamide (**9**) is the predominant product (41%) in this mixture when tin (II) acetate is used. Other products include NVF (10%) and compound **10** (14%). Tin (II) acetate is again more selective compared to zinc (II) acetate.

In conclusion, we have found that ethylidene diacetate is an attractive starting material for the production of bisamide ethanes and N-vinylamides. Both stoichiometric base and catalytic Lewis acids promote two competing reaction pathways: attack by amide at the carbonyl carbon and attack at the tertiary carbon. The reaction of EDA with acetamide is less complex than the corresponding reaction with formamide due to products derived from the decomposition of formamide. Tin (II) acetate catalyzes the attack at the tertiary carbon of EDA leading to the formation of ethylidene bisacetamide in high selectivity.

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- General synthetic procedure: To a round bottom flask equipped with a magnetic stirrer and nitrogen inlet is placed ethylidene diacetate (10 mmol), acetamide (40 mmol), acetonitrile (40 mL), and toluene (~0.010 g) as an internal standard. The mixture is heated to 50 °C followed by the addition of base (20 mmol). The resulting slurry is stirred at the specified temperature and time. Aliquots are removed periodically and analyzed via gas chromatography with the following conditions: Hewlett-Packard HP-5890 equipped with FID detector and OV-1701 capillary column (25m x 0.53mm ID, 1.0 µm film thickness) and an oven program of 40 °C for 3 minutes, 15 °C/minute ramp to 200 °C, and 10.0 minutes at 200 °C. All compounds were identified either by retention times, co-injection, IR, and/or GC/MS.

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