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Knoevenagel condensation of aromatic bisulfite adducts with 2,4-thiazolidinedione in the presence of Lewis acid catalysts

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ABSTRACT

Several commercial Lewis acids, specifically $TiCl_4$, were able to promote the condensation reaction between aromatic bisulfite adducts and 2,4-thiazolidinedione to produce 5-arylidene derivatives. The product distribution was not affected by the equivalents of $TiCl_4$ used, but was dependent on temperature and the nature of the solvent medium. In all cases, the reaction required activation of the aromatic bisulfite adducts by Lewis acids, followed by the loss of SO_2 and subsequent regeneration of the parent aldehyde. The in situ formed aldehyde ultimately underwent acid-catalyzed carbon–carbon bond formation to give 5-arylidene derivatives. The reaction with $TiCl_4$ afforded the products from aromatic and aliphatic bisulfite adducts in moderate to good yields. When hydrated Lewis acids were used, in addition to 5-arylidenes, the in situ formed aldehyde underwent a disproportionation reaction to give a carboxylic acid as a by-product.

Introduction

The synthesis of 5-arylidene-2,4-thiazolidinediones is of great interest because of their important applications in the pharmaceutical industry.[1] These molecules are particularly fascinating because of the diversity of synthetic procedures that can be used for their synthesis.[2] Given their medicinal as well as synthetic interest, 5-arylidenes are of significant importance in the area of heterocyclic chemistry. Extensive effort has been expended in the search for efficient processes to synthesize these compounds.

The most common methodology adopted for the synthesis of 5-arylidene-2,4-thiazolidinediones is the condensation of aromatic aldehydes with active methylene groups such as 2,4-thiazolidinedione in a single step. Above base-promoted condensation, leading to carbon-carbon bond formation is the key step in this reaction. In general, these reactions are catalyzed by bases, but there are reports of Knoevenagel condensations promoted by Lewis acids.[3] In most of these cases, the Lewis acid was used in a quantity greater than the stoichiometric amount and aldehydes were used as the starting material. The use of aldehydes on a commercial scale has several disadvantages owing to their inherent instability. Therefore, bisulfite adducts can be the preferred intermediates for many commercially manufactured aldehydes as these adducts are usually crystalline and stable, thus making their handling and storage more suitable. Unlike other reactions between aldehydes and active methylene groups, the bisulfite adduct has rarely been used for direct carbon–carbon bond formation. Therefore, our main effort was directed toward exploring the possibility of using bisulfite adducts for condensation reactions in the presence of various catalysts, without the need for deprotection of the bisulfite adducts to its parent aldehyde. Herein, we report our preliminary results on this subject.

In our attempt to use bisulfite adduct in condensation reactions, we have shown previously that the condensation of bisulfite adducts with 2,4-thiazolidinedione was feasible in the presence of acetic anhydride[4] and $POCl_3$[5] resulting in 5-arylidene-2,4-thiazolidinediones in good yields along with unprecedented high level of (*Z*)-isomer selectivity. We speculated that in addition to acetic anhydride and $POCl_3$, various other catalysts could not only help the formation of the corresponding aldehyde but also promote Knoevenagel-type reactions between 2,4-thiazolidinedione and an in situ formed aldehyde.

A model condensation reaction between a bisulfite adduct (**1a**) and 2,4-thiazolidinedione (**2**) was selected for this investigation

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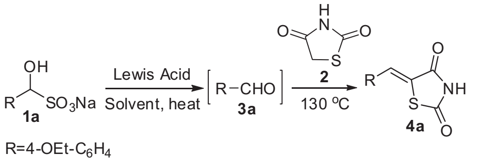


Scheme 1. Synthesis of thiazolidinedione **4a** using Lewis acids.

(Scheme 1). As a first step, various Lewis acids were screened (Table 1) to find a suitable catalyst.[6] Based on prior experience,[5] all screening experiments were performed using toluene as the solvent at 110 °C with 2.0 equiv of Lewis acids as reported (Table 1). Product conversion in the reaction mass was determined by HPLC (area%). As evident from Table 1, all Lewis acids that were screened, afforded a mixture of unreacted **2**, in situ released parent aldehyde **3a**, and the desired product **4a** in different ratios.

It is evident from Table 1 that the conversion of product **4a** varied significantly among the Lewis acids and their hydrated salts ($ML_n \cdot XH_2O$). Lewis acids such as $TiCl_4$, $AlCl_3$, and $SnCl_4$ were the most effective, displaying 58–69% conversion of bisulfite adduct **1a**. On the other hand, all the hydrated Lewis acids ($ML_n \cdot XH_2O$; X = 1–7) resulted in poor yields and an unknown impurity (0.5–37% in HPLC) at RRT 0.86 (Table 1; entries 3–7); this is discussed later. No product formation was observed with $BaCl_2 \cdot 2H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, and $PdCl_2 \cdot 2H_2O$ (not shown in Table 1).

The most promising results were obtained with $TiCl_4$ and $SnCl_4$; in particular, the reaction with $TiCl_4$ was completed within 30 min of heating, that is, the reaction was found to be complete before the reaction temperature reached 110 °C. The course of the reaction was monitored using HPLC and LC–MS; the reaction was found to proceed via the in situ generation of aldehyde **3a** (Scheme 1). Inspired by this success, we then focused on solvent screening. The preferred choice of Lewis acid for our subsequent study was $TiCl_4$. For comparison, the reaction (Scheme 1) was performed with solvents (bp ranging from 39 °C to 130 °C) at reflux temperature (Table 2).

The results of the $TiCl_4$-mediated (2.0 equiv) reaction carried out with different solvents are summarized in Table 2. It appears that any solvent with a bp greater than 60 °C is sufficient for conversion to product **4a**; however, with CH_2Cl_2, there was no product formation (40 °C). In the case of cyclohexane, the conversion to the product was low (13.2%) because of the poor solubility of **1a** and **2**. The best conversions were obtained in high boiling non-polar solvents, such as *o*-xylene and chlorobenzene (Table 2; entries 6 and 7). *o*-Xylene was selected for further optimization, as it is a common industrial solvent that can be recovered and recycled easily.

Last phase of the optimization was to study the effect of different equivalents of $TiCl_4$ on the conversion. Literature search showed that Titanium chloride ((Ti(IV)-base)) has been well documented to facilitate carbon-carbon bond formation reactions.[7] There are instances where Ti(IV)-derivatives, in combination with organic bases ($TiCl_4/Et_3N$,[8] Ti(O-*i*-Pr)$_4$,[9] $TiCl_4$/pyridine,[10] $TiCl_4$/N-methyl morphorine,[11] and $TiCl_4$–Et_3N,[12]), have been used to promote Knoevenagel condensations; but, in such cases, they have been used in stoichiometric amounts and the ratio of $TiCl_4$ to base used was 1:1. In order to find the optimized equivalent of $TiCl_4$ required for maximizing the conversion, reactions were conducted with different equivalents of $TiCl_4$ and the conversion to product **4a** with respect to yield and purity was monitored (Table 3).[13]

Table 1
Lewis acid screening for the condensation of **1a** and **2**

Entry	Lewis acid	$TiCl_4$ (equiv)	Time (h)	*T* (°C)	Product	% area
1	$TiCl_4$	2.0	0.5	110	**4a**	69.7
2	$AlCl_3$	2.0	6.0	110	**4a**	58.3
3	$SnCl_4$	2.0	2.0	110	**4a**	68.0
4	$LiCl.H_2O$	2.0	8.0	110	**4a**	12.6
5	$ZnBr_2.2H_2O$	2.0	8.0	110	**4a**	28.1
6	$CrCl_3.6H_2O$	2.0	8.0	110	**4a**	8.7
7	$MgCl_2.6H_2O$	2.0	6.0	110	**4a**	3.0
8	$CeCl_3.7H_2O$	2.0	6.0	110	**4a**	2.9

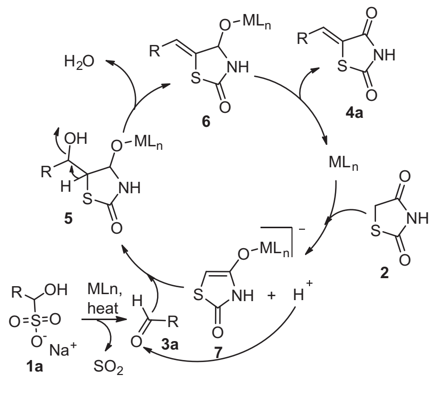
Table 2
Screening of solvents for the $TiCl_4$-mediated condensation of **1a** and **2**

Entry	Solvent	*T* (°C)	Time (h)	$TiCl_4$ (equiv)	Product	% area
1	CH_2Cl_2	40	8.0	2.0	**4a**	–
2	$CHCl_3$	60	6.0	2.0	**4a**	72.8
3	Cy(C_6H_5)	80	4.0	2.0	**4a**	13.2
4	Benzene	80	1.5	2.0	**4a**	58.0
5	Toluene	105	1.5	2.0	**4a**	69.7
6	*o*-Xylene	130	1	2.0	**4a**	83.5
7	Cl-C_6H_5	130	0.5	2.0	**4a**	86.6

It is apparent that the reaction involves two chemical step (Scheme 1), first step involves insitu deprotection of bisulfite adduct **1a** to parent aldehyde **3a** and this deprotection was found to be instantaneous in the presence of a Lewis acid and heat. The second step is the condensation of insitu generated aldehyde with thiazolidine-2,4-dione **2** in the presence of Lewis acid catalyst. Moreover, Knoevenagel condensation is a net dehydration reaction and water is a by-product. Therefore, we envisioned that a minimum of 1 equiv or more of $TiCl_4$ would be required for the transformation of **1a** to **4a**; surprisingly, however, only 0.5 to 1.0 equiv of $TiCl_4$ led to the product **4a** with good yield (Table 3; entries 4 and 5). The reaction proceeded with even 0.1 equiv of $TiCl_4$; however, an optimal yield was obtained with 0.5–1.0 equiv of $TiCl_4$. To our delight, the reaction proceeded directly from bisulfite adduct **1a** with only a less than stoichiometric amount of $TiCl_4$.

Table 3
Study of different equivalents of $TiCl_4$ on conversion of **1a** to **4a**

Entry	$TiCl_4$ (equiv)	Adduct **1a** (g)	*T* (°C)	Product **4a** (g)	Yield (%)	Purity
1	0.1	5.0	110	1.1	24.3	68.1
2	0.2	5.0	110	2.7	56.8	97.9
3	0.3	5.0	110	3.6	75.0	84.7
4	0.5	5.0	110	4.4	91.1	91.8
5	1.0	5.0	110	4.0	83.0	96.4
6	1.5	5.0	110	3.5	71.9	96.4
7	2.0	5.0	110	2.5	52.6	97.9



Scheme 2. ML_n-mediated condensation of **2** with bisulfite adduct **1a**.

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