



Thiazolinium salt: an efficient catalyst for the Mukaiyama reaction

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ABSTRACT

Mukaiyama aldol reaction between benzaldehyde and Danishefsky diene is promoted by ionic liquid-type salts. Hence, thiazolinium salts have been found to be the most efficient for this transformation. On a mechanistic point of view, only the Mukaiyama process is observed without any hetero Diels–Alder cycloaddition. In some cases, cyclisation of the Mukaiyama adduct occurred without addition of TFA. Interestingly, the thiazolinium catalyst can be recycled at least 10 times without loss of activity.

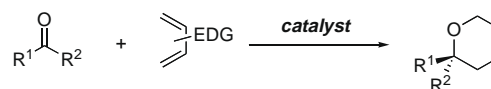
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1. Introduction

The synthesis of dihydropyranones is still an interesting question since numerous examples in this series of compounds are powerful intermediates for the construction of various natural or bioactive molecules.¹ One of the most convergent accesses to these structures relies on the [2+4] cycloaddition of an electron-rich diene to an aldehyde. To the best of our knowledge, this type of reaction generally requires the use of a catalyst (Scheme 1).²

This strategy has been extensively studied, in particular for a model reaction involving Danishefsky diene and benzaldehyde.² Two mechanisms are generally postulated, that is, Mukaiyama process leading to the silylated aldol or hetero Diels–Alder cycloaddition: however in both cases, acidic treatment converts the primary adduct into the same dihydropyranone final product (Scheme 2). The first mechanism is typically promoted by boron or titanium complexes,^{3,4} while the second one results in the use of Lewis acids derived from europium,⁵ chromium,⁶ zinc,⁷ or aluminium.⁸

Being interested in designing nonmetal, organo-catalytic processes towards biologically interesting molecules, we decided to revisit this reaction. In this Letter, we disclose the efficiency of thiazolinium salts to promote the Mukaiyama reaction smoothly under neutral conditions.



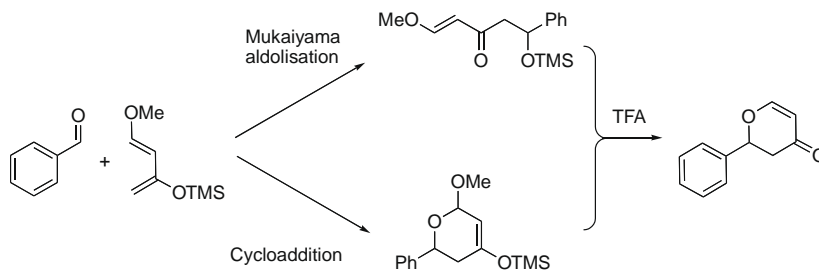
Scheme 1.

2. Results and discussion

Recently, aza-Diels–Alder cycloadditions have been studied in ionic liquids.⁹ Vo-Thanh and co-workers highlighted that the reaction of an imine with the activated diene was efficiently promoted at room temperature and without using any Lewis acid.¹⁰ Furthermore, Loh et al. have shown that an imidazolium ionic liquid was able to promote the reaction between ketene silyl acetals and aldehydes in moderate yields.¹¹ Our interest for ionic liquid chemistry^{12,13} prompted us to examine the behaviour of benzaldehyde and Danishefsky diene, as a model reaction, in either ionic solvents or using ionic materials as additives or catalysts. We expected that they could act as catalysts, avoiding the use of any added Lewis acid. We first confirmed that no reaction occurred between Danishefsky diene and benzaldehyde either in the absence of any solvent, or in molecular solvents such as methanol, chloroform and acetonitrile. Then in a first set of experiments, we performed the condensation using a series of structurally different salts used either as solvents or as additives (Table 1).

This first set of experiments allowed us to point out several interesting features, some of them being unexpected. Despite moderate yields and rather long reaction times, the transformation was

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Scheme 2.

Table 1

Entry	Ionic additive ^a	Use	Reaction time	Yield ^b (%)
1		S	6 d	27
2		A	1 d	26
3		A	6 d	30
4	[Bmim][PF ₆]	A	2.5 h	53

^a S: used as a solvent (ca. 5 equiv); A: used as an additive (1 equiv).

^b Yield in Mukaiyama product (see Scheme 2).

highly selective: the only product of the reaction is the Mukaiyama aldolisation compound, and no trace of hetero Diels–Alder adduct could be detected. The use of the ionic material as solvent (5 equiv) or additive (1 equiv) afforded similar results (Table 1, entries 1–2). The presence of an acidic cation such as [Bmim] clearly accelerated the kinetic of the reaction (Table 1, entries 4). Worthy of note is that no thermal or catalytic activation was required for this reaction to occur. In order to improve the conversion, we turned our attention to other ionic structures. Thiazolinium salts that are original ionic liquids efficiently prepared from amino-alcohols were next tested. Indeed, it has been previously shown that these salts could exert strong interactions with substrates.¹⁴ We therefore expected them to act as better catalysts than pyridinium and imidazolium salts. The reactions were performed using 1 equiv of thiazolinium salt. Various salts were tested.¹⁵ The main results are depicted in Table 2.

As expected, the yields obtained with this series of thiazolinium salts are much higher than with imidazolium or pyridinium salts, especially when R³ is a benzyl group (entries 1, 2 and 5). Moreover, the reaction times are considerably shortened, in the 0.5–3 h range when the 2-position of the thiazolinium ring is either unsubstituted (Table 2, entries 1 and 2) or substituted by a methyl group (Table 2, entries 6–8) indicating that the reaction rate is quite sensitive to the steric hindrance on this position (compare with entries 4 and 5, Table 2). One can easily imagine that hydrogen bonding is one of the factors determining the strong acceleration observed with 2*H*-thiazoliniums (Fig. 1, left), as already suggested by Welton for Diels–Alder reactions in imidazolium ionic liquids.¹⁶ For 2-alkyl thiazoliniums, Lewis acidity is believed to be the factor controlling the transformation (Fig. 1, right). To give some credit to this hypothesis, we performed a series of test reactions. The results are reported hereafter:

Table 2

Entry	R ¹	R ²	R ³	Melting point (°C)	Reaction time (h)	Isolated yield ^a (%)
1	H	<i>n</i> -Bu	Bn	132 ^d	1.5	90 ^b
2	H	Bn	Bn	136 ^d	3.5	88 ^b
3	H	<i>n</i> -Bu	Bn	132 ^d	16 ^c	90 ^b
4	<i>i</i> -Pr	C ₁₂ H ₂₅	Et	63	48	35
5	<i>i</i> -Pr	<i>n</i> -Bu	Bn	172	48	96
6	Me	Me	H	235	0.5	57
7	Me	<i>n</i> -Bu	H	– ^e	1	60
8	Me	Me	CH ₂ OH	– ^e	0.5	64

^a For an experimental protocol, see note 15.

^b In these experiments, the dihydropyranone was spontaneously obtained from the aldol intermediate without any addition of TFA.

^c A catalytic amount (0.05 equiv) of thiazolinium salt was used instead of 1 equiv.

^d The value given corresponds to the glass transition temperature (*T_g*).

^e The compound was obtained as an oily salt.

- (i) No reaction occurred without thiazolinium salt as already mentioned.
- (ii) No reaction occurred when adding the parent thiazoline instead of the corresponding thiazolinium salt.
- (iii) Using a Brønsted acid (HCl) yielded only hydrolysed products.

These preliminary results are in agreement with a Lewis acid-type activation, however, a nucleophilic catalysis involving the anion of the salt cannot be ruled out.

We next focused on the efficiency of the thiazolinium salt. We were pleased to see that a catalytic amount (0.05 equiv) of this salt (entry 3) was sufficient to promote the reaction. Under this condition, the aldolisation reaction is completed in 16 h and the cyclisation in 66 h in the absence of TFA.

Since the thiazolinium salt depicted in entry 6 of Table 2 is one of the cheaper and more easily available compounds of the series, we used it in order to gain further information on the course of the reaction:

- First, an equal yield with constant reaction rate was observed when using only 1 equiv of benzaldehyde.
- Second, after extraction and purification of the dihydropyranone, the thiazolinium salt was washed, recycled and re-engaged in the reaction for at least 10 times, giving in all cases full conversion with yields ranging from 51% to 62%, very

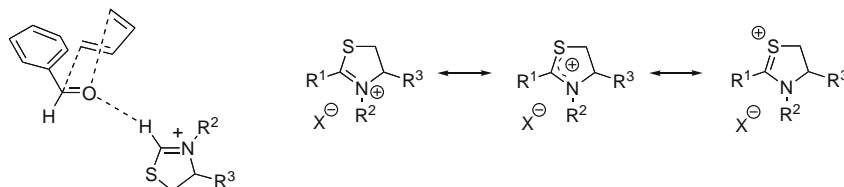


Figure 1.

similar to that obtained in the first run. This demonstrates the possibility of recycling the ionic additive used in the Mukaiyama process.

3. Conclusion

In conclusion, this study demonstrates the powerful catalytic activity of thiazolinium salts in the reaction between benzaldehyde and Danishefsky diene to afford the corresponding aldolisation product. The resulting dihydropyranone is obtained in high yields without the need of thermal activation, high pressure or any other catalyst than the ionic additive, especially when thiazolinium salts are used. These results highlight the peculiarity of these salts. An interesting mechanistic feature is that no direct cycloaddition is observed, and that the unique pathway is the Mukaiyama-type aldolisation. Interestingly, the ionic catalyst could be recycled at least 10 times without any loss in activity.

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- Thiazolinium salt (1 equiv) was placed in a flame-dried Schlenk tube and dried overnight under vacuum. The Schlenk tube was then flushed under nitrogen and benzaldehyde (1.9 equiv) and Danishefsky diene (1 equiv) were added. The mixture was stirred at room temperature, and reaction was monitored by GC. Samples of the mixture were diluted in diethyl ether and filtered before being injected in GC (GC method: injector temperature: 280 °C; oven temperature: 50 °C (2 min), 50–250 °C (20 °C/min), 250 °C (8 min), detector (FID) temperature: 300 °C). When the reaction was completed, TFA (1 equiv) was added and the reaction was stirred for 1.5 h at rt. After neutralisation, classical work-up afforded the expected dihydropyranone. The NMR of the dihydropyranone is consistent with the literature data.⁶
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