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Why are benzimidazoles efficiently acylated with esters? Identification of a tetrahedral hemiacetal alkoxide intermediate

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Abstract—2-Lithio benzimidazoles were acylated with esters, lactones, and lactams. The tetrahedral hemiacetal intermediates responsible for the efficient conversion were characterized by low temperature NMR.

Substituted benzimidazoles are important intermediates for the synthesis of various drugs and natural products. Substituents at the 2-position are generally introduced by reaction of the 2-lithio derivative of N-protected benzimidazoles with electrophiles.[1] The dimethoxymethyl N-protecting group has been used because of its easy removal and ketones were obtained by acylation of the corresponding carbanion.[2] In some cases when esters were used as acylating agents the yields were low and bis addition products dominated.[3] It was reported that at low temperature, the reaction was more reproducible and higher yielding.[4] We discovered that the stability of a tetrahedral intermediate hemiacetal alkoxide plays a critical role in these reactions.

Tetrahedral intermediates have been postulated to govern the reactivity of Weinreb type *N*-methoxyamides,[5] *N*-methylamino pyridyl amides,[6] phenyl 2-pyridyl ketone *O*-acyl oximes,[7] lactones,[8] and 2-mercapto pyridine esters.[9] In the last case, experimental evidence rejected the attractive postulate.[10] Ester derived hemiacetal intermediates were trapped by silylation and characterized.[11] Furthermore, in a recent letter, a hydrogen bond stabilized hemiacetal intermediate derived from an ester was identified by NMR.[12] Hemiacetals produced by the addition of heterocyclic carbanions, including indoles and benzimidazoles to some lactones, are stable.[13]

In connection with the synthesis of an important drug candidate, we explored various routes for the efficient synthesis of benzimidazole 2-ketones. After testing various alternatives, we found that *N*-dimethoxymethyl benzimidazole can be efficiently acylated with esters when deprotonated by LDA. In this letter, we present evidence that a tetrahedral intermediate of limited stability is responsible for the selective reaction and present a general method for the preparation of 2-acyl benzimidazoles.

When the lithiated orthoamide **2a** was reacted with an equivalent amount of methyl benzoate at −78 °C, the desired ketone **4a** was produced and after acid deprotection, ketone **5a** was obtained. Only a trace of the bis addition product **7a** was detected. When the lithiate **2a** was used in excess and the reaction mixture was allowed to warm to room temperature, bis adduct **7a** became the dominant product (Scheme 1).

This prompted us to examine the temperature profile of the reaction. Two equivalents of **2a** were allowed

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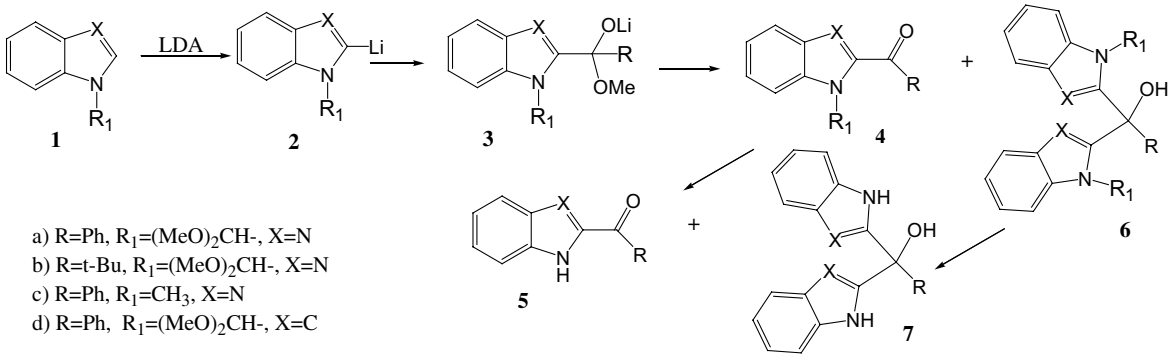


Scheme 1.

to react with methyl benzoate at −78 °C, aliquots were quenched at increasing temperatures and the product ratios were evaluated by liquid chromatography. It is clear from the results, shown in Chart 1, that at temperatures below −40 °C, addition to the ketone was minimal and only at higher temperatures did alcohol formation become dominant.

Surprisingly, *N*-methyl benzimidazole **1c** showed similar temperature profile (Chart 2). The possibility that slow reactivity of ketone **4a** at low temperature is responsible for the selectivity observed, was tested next. Ketone **4a** reacted rapidly with **2a** at −78 °C to produce the tertiary alcohol **6a**. This suggested that below −40 °C, a limited stability intermediate is protecting the ketone from further reactions.

Because of the chelating ability of the dimethoxymethyl protecting group and the imidazole nitrogen, we suspected formation of a stabilized tetrahedral hemiacetal lithium alkoxide intermediate. We first detected the intermediate by a simple NMR experiment. When the lithiated benzimidazole **2a** was reacted with methyl benzoate in deuterated THF, NMR at room temperature showed only broad signals and no ketone carbonyl. This mixture was remarkably stable as it was stored in the refrigerator for several days without decomposition. Addition of water instantly generated the signals of the protected ketone **4a**. Cooling the mixture to −30 °C, sharpened the NMR signals and ^{1}H, ^{13}C, and 2D-HMBC were used to characterize the intermediate. Selected NMR data is presented with the two possible structures **3a-T1** and **3a-T2** (Scheme 2).

The significant ^{1}H chemical shift differences between the two orthoamide methoxy groups of **3a** suggested that

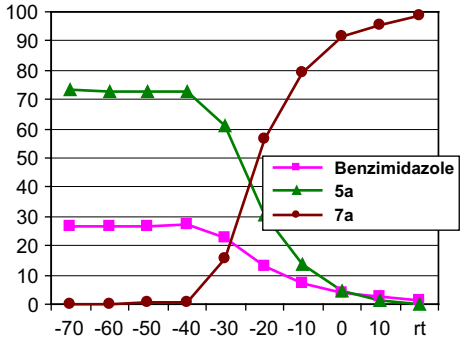


Chart 1.

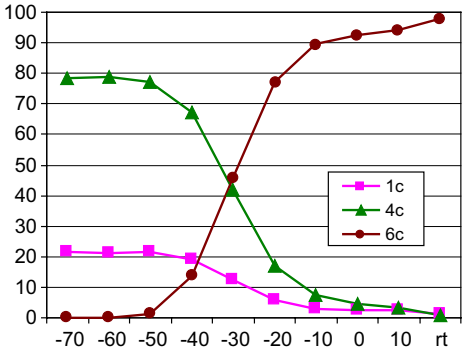
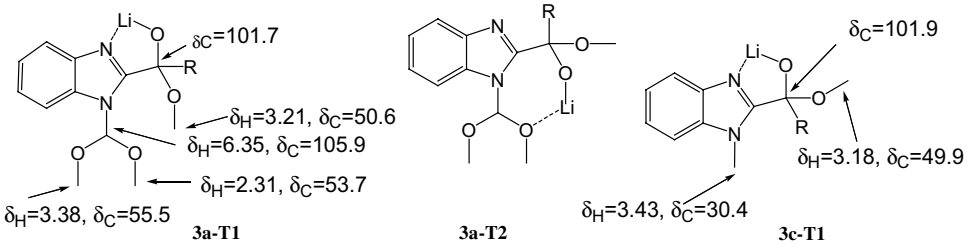


Chart 2.

one methoxy group is complexed to lithium as in **3-T2**. However, a similar experiment with *N*-methyl benzimidazole showed an analogous intermediate presumably **3c-T1**. The similarity between the NMR characteristics



Scheme 2.

of the intermediates derived from **3a** and **3c**, specifically the chemical shifts of the tetrahedral centers and the attached OMe groups advocated a **T1** type structure. A sharp, major ^{6}Li NMR signal was also observed, but this is not diagnostic since the chemical shifts of LDA, **2a**, and **3a** are very similar.

A similar experiment with ethyl pivalate also produced an analogous chelated tetrahedral intermediate but in this case, it converted to the ketone **4b** on warming to −40 °C. It is reasonable to assume that these observed dominant intermediates are responsible for the major product formation.

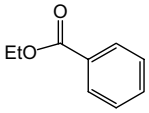
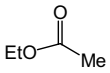
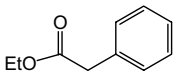
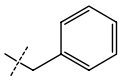
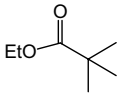
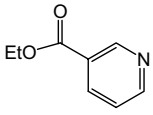
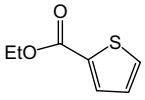
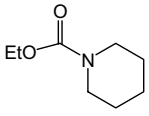
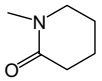
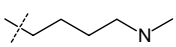
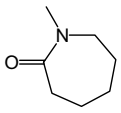
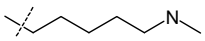
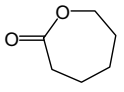
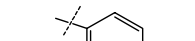
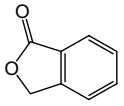
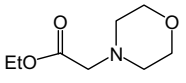
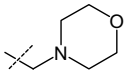
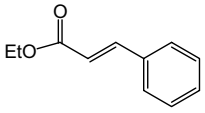
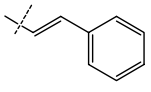
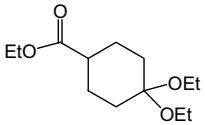
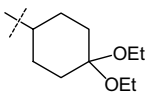
In order to clearly distinguish between the two forms of complexation, the reactivity of dimethoxymethyl indole **1d** was examined. Deprotonation with *t*-BuLi at 0 °C, and reaction with an equivalent of methyl benzoate at −78 °C only generated the bis addition product **7d**, indicating that in this case when only **T2** type chelation is possible, no stable intermediate formed and the ketone **4d** was converted rapidly to the alcohol **7d** by a rapid second addition.

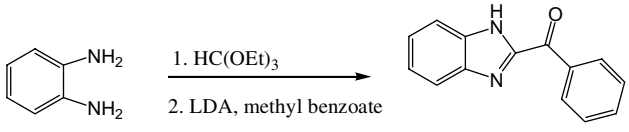
Theoretical DFT calculation at the B3LYP/6-31G(d, p) level were performed on structures **3a-T1** and **3a-T2** using the GAUSSIAN 03[16] suite of programs. The geometries of each structure were completely optimized, vibrational frequencies (all real) and enthalpies at 298 K were obtained. This indicated that five member ring **T-1** structure is calculated to be 4.8 kcal lower in enthalpy than the seven member **T-2**.

Based on the combined evidence, we propose that both *N*-methyl and dimethoxymethyl benzimidazoles form analogous chelated intermediates of the type of **T1**, which protects the ketone from further reaction at low temperature. Understanding the stability of the intermediate enabled us to develop a general method for the acylation of benzimidazoles with esters.[14] It was critical to generate the lithiate **2** in the presence of the ester or add the ester in slight excess, at low temperature and allow the reaction to proceed at that temperature. Short exposure to 2 N HCl solution removed the protecting group and generated the desired ketone. The data summarized in Table 1, illustrates the versatility of the method. Aliphatic, aromatic, heterocyclic and amino esters, urethanes, lactones, and lactams can be used to acylate **2a**, producing the corresponding carbonyl derivatives of benzimidazole in respectable yields. No attempt was made to optimize the yield of these reactions.

There are obvious cost and environmental advantages of using esters rather than acid chlorides for acylation. Also significant are the examples where the corresponding acid chlorides are not available or would require the use of protecting groups. A very practical one-pot procedure was also demonstrated for the preparation of benzimidazole ketones starting from *o*-phenylenediamine.[15] Here the protected benzimidazole was generated in one step with triethyl orthoformate and after the volatile byproducts were removed by distillation, lithiation, and acylation followed by deprotection produced the desired ketone in 76% overall isolated yield.

Table 1. Acylation of 1-dimethoxymethyl benzimidazole **1a**

Acylating agent	Product **5**, R group	Isolated yield (%)
		78
		93
		70
		60
		90
		60
		76
		70
		76
		81
		60
		81
		60
		83



We propose that the methodology presented here can be applied to the acylation of imidazoles with a variety of esters type reagents. It is critical to conduct the reaction at the correct low temperature to prevent the collapse of the tetrahedral intermediate to ketone and thereby avoid a second addition.

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14. Dimethoxymethyl benzimidazole **1a** was prepared as follows: A solution of benzimidazole (10 g), and benzenesulfonic acid (0.3 g) in trimethyl orthoformate (50 ml) was heated to reflux for 10 h followed by slow distillation for 2 h. The product was isolated by fractional distillation bp: 120–125 °C and 3 mm. *N*-Methyl benzimidazole was the major byproduct contaminating all fractions. Alternatively, **1a** can be generated in situ and acylated without isolation as follows: the solution of benzimidazole (6.6 g), trimethyl orthoformate (23 ml) and benzenesulfonic acid (0.3 g) in toluene (60 ml) was heated to reflux then slowly distilled to remove half of the solvent. Toluene (60 ml) was added again and 40 ml was removed by slow distillation. The cooled solution was neutralized with 0.8 ml of diisopropylamine, THF (60 ml), and methyl benzoate (8.4 g) were added. The mixture was cooled to −78 °C and LDA solution (34 ml, 2 M, in THF/heptane) was added dropwise. After aging for 2 h at that temperature, and warming to room temperature, 2 N HCl (57 ml) was added and the mixture was agitated for an hour. The pH was adjusted to 9 with 50% NaOH, 15 g NaCl was added and the layers were separated. The organic layer was washed with 10% sodium bicarbonate solution and concentrated to produce the ketone **5a** in 76% yield.
15. Same procedure as described above starting with *o*-phenylenediamine and triethyl orthoformate.
16. GAUSSIAN 03 Revision B03; Gaussian, Inc.: Pittsburg PA, 2003.