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Unusual *N*-acylation of sterically congested *trans*-4,5-disubstituted 2-imidazolidinones: remarkably facile C–C bond formation

Alaa A.-M. Abdel-Aziz, Hirofumi Matsunaga and Takehisa Kunieda*

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862-0973, Japan

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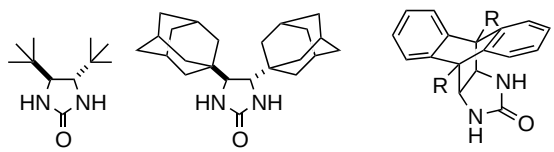
Abstract—Sterically congested *trans*-4,5-di-*tert*-butyl-2-imidazolidinone (DTBIm) and *trans*-4,5-di-(1-adamantyl)-2-imidazolidinone (DAIm), which are prepared from the parent 1,3-dihydro-2-imidazolone, undergo an unusual *N*-acylation reaction with acyl chlorides in the presence of organic amines to give the 3-oxoacyl derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

Steric requirements of molecules, as well as electrostatic effects are major determinants of the rates and equilibria of many organic reactions and can strongly modify the course of a reaction, thus affecting the distribution of products.[1]

Steric bulkiness, which is inherent in heterocyclic auxiliaries such as chiral 2-oxazolidinones[2] and 2-imidazolidinones[3] plays an effective role in greatly enhancing stereoselectivity and, because of this, highly sterically congested chiral 2-oxazolidinones[4] and 2-imidazolidinones[5] represent promising auxiliaries for providing excellent diastereocontrol.

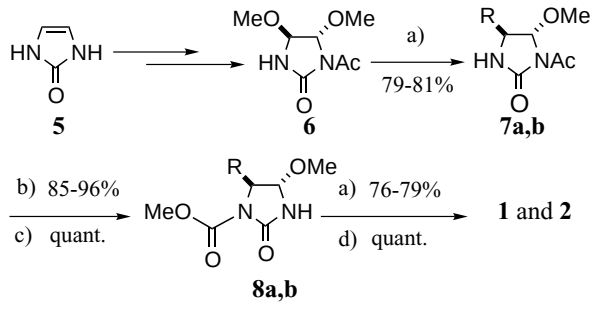


1: (DTBIm) **2: (DAIm)** **3:** R= H **4:** R= Me

During the course of studies on the synthesis of sterically congested heterocyclic auxiliaries, we found that highly hindered *trans*-4,5-di-*tert*-butyl-2-imidazolidinone **1** (DTBIm) underwent an unexpected acylation with acetyl chloride in the presence of triethylamine to give the doubly acylated *N*-(3-oxobutyryl)-2-imidazolidinone **9a**. This unusual acylation leading to remarkably facile C–C bond formation, which proceeded under quite mild conditions, at temperatures below 0°C, prompted us to examine the reaction of sterically congested 2-imidazolidinones including 4,5-di-(1-adamantyl) **2** (DAIm) and the cycloadducts with anthracenes, **3**[6] and **4**[6] with acylating agents such as propionyl, butyryl and phenylacetyl chlorides. Highly bulky groups, when located at the *trans*-4,5 position, were shown to play a crucial role in accelerating this type of unusual acylation reaction.

Synthesis of sterically congested 2-imidazolidinones, DTBIm and DAIm (Scheme 1)

The synthetic route for novel **1** (DTBIm) and **2** (DAIm) is illustrated in Scheme 1. The *trans*-4,5-dimethoxy-1-acetyl-2-imidazolidinone **6**,[7] which was prepared from the parent heterocycle 1,3-dihydro-2-imidazolone **5**, via



a: R = *t*-Bu, **b:** R = 1-Adamantyl

Scheme 1. (a) *t*-BuCuCNLi or (1-adamantyl)CuCNMgBr, LiCl, $BF_3{\cdot}OEt_2$, THF, −30°C, 24 h; (b) ClCOOMe, BuLi, THF, −78°C to rt, 1 h; (c) Cs_2CO_3, MeOH, rt, 10 min; (d) LiOH, dioxane, H_2O, 50°C, 1 h.

* Corresponding author. Tel.: +81-96-371-4680; fax: +81-96-362-7692; e-mail: tkuni@kumamoto-u.ac.jp

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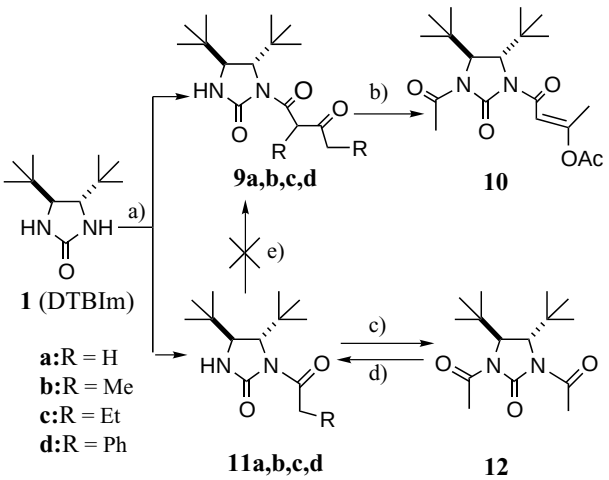
the 4-bromo-5-methoxy derivative, was treated with *tert*-butyl and 1-adamantyl cuprates (*t*-BuCuCNLi or (1-adamantyl) CuCNMgBr/LiCl) in the presence of $BF_3{\cdot}OEt_2$ at −30°C, resulting in the *regio*- and *trans*-stereoselective replacement of the methoxy group with *tert*-butyl and 1-adamantyl groups, respectively. The *trans*-attack of cuprate toward the acyliminium ion intermediate, which is generated in situ, might be effectively controlled by the *vicinal* methoxy group. The subsequent *N*-protection of **7a** and **b** with methyl chloroformate, followed by deacetylation with Cs_2CO_3, yielded compounds **8a** and **b**, respectively. Each product was treated with organocuprates, as described above, and subsequent hydrolysis with LiOH gave the *trans*-4,5-disubstituted 2-imidazolidinones **1** (DTBIm) and **2** (DAIm), which are highly sterically congested.

Acylation of DTBIm with acyl chlorides (Scheme 2, Table 1)



Scheme 2. (a) AcCl, THF. *Conditions*; Table 1; (b) BuLi, AcCl, 0°C, 15 min; (c) BuLi, AcCl, rt, 2 h; (d) Cs_2CO_3, MeOH, rt, 30 min; (e) Et_3N, AcCl, rt, 6 h.

When the sterically hindered **1** (DTBIm) was reacted with acetyl chloride in the presence of triethylamine at temperatures below 0°C, the unexpected *N*-(3-oxobutyryl)-2-imidazolidinone **9a** was obtained as a major product, in addition to *N*-acetyl-2-imidazolidinone **11a**, as seen in Table 1. The former was formed exclusively when the reaction was carried out at −78°C for 5 h or at −10°C for 15 min, although in low yield. The formation of the 3-oxobutyryl product **9a** was optimized to give a 69% yield by performing the reaction at 0°C for 5 h. The unexpected structure of compound **9a** was unequivocally determined by X-ray analysis.[8] When the reactions were performed above room temperature increasing yields of *N*-monoacetyl- and *N*,*N*′-diacetyl products **11a** and **12** resulted. The conversion of **11a** to **9a** was not observed on reaction with acetyl chloride in the presence of organic amines including triethylamine under identical conditions. Treatment of **11a** with BuLi and acetyl chloride resulted in the exclusive formation of *N*,*N*′-diacetyl product **12**. The *N*-monoacetyl-2-imidazolidinone **11a** was found to exclusively exist in the *s-transoid* form by X-ray crystal analysis,[8] while the *s-cisoid* *N*-acetyl rotamer was not isolated from the reaction performed at −78°C. Organic bases such as pyridine, diisopropylethylamine (DIPEA) and 1,8-diazabicycloundecene (DBU) were equally effective in the formation of the 3-oxobutyryl compound **9a**. Moreover, the reaction of **9a** with acetyl chloride and BuLi afforded the *N*,*O*-diacetylated product **10**.[8] When acylating agents such as propionyl chloride, butyryl chloride and phenylacetyl chloride were used in place of acetyl chloride in the reaction with **1** (DTBIm), the corresponding *N*-(α-monosubstituted β-oxoacyl)-2-imidazolidinones **9b–d** were smoothly formed in good yields, while the branched chain α-methylbutyryl chloride gave only the expected *N*-butyryl derivative, with no detectable *N*-β-oxobutyryl type of product.

Table 1. Acylation of DTBIm with acyl chlorides[a]

Entry	R	Base (equiv.)	Time/temp.	Yield (%)	
				9	**11**
1	H	Et_3N (2)	5 h/−78°C	11	0
2	H	Et_3N (2)	15 min/−10°C	21	0
3	H	Et_3N (2)	24 h/−78°C	58	16
4	H	Et_3N (2)	5 h/0°C	69	30
5	H	Et_3N (2)	15 min/rt	39	57
6	H	Et_3N (6)	5 h/reflux[b]	30	43
7	H	Pyridine (3)	5 h/reflux	32	38
8	H	DIPEA[c] (2)	15 min/rt	38	43
9	H	DBU[d] (6)	24 h/rt	28	30
10	Me	Et_3N (2)	5 h/0°C	71	27
11	Et	Et_3N (2)	5 h/0°C	64	33
12	Ph	Et_3N (2)	5 h/0°C	35	23

[a] The reaction was carried out with an acyl chloride (3 equiv.) in the presence of organic amines in THF.
[b] In addition to **9** and **11**, 1-acetyl-3(α-acetoxyvinyl)-2-imidazolidinone was isolated in 8% yield.
[c] Diisopropylethylamine.
[d] 1,8-Diazabicycloundecene.

Table 2. Effect of 4,5-disubstituents on *N*-acetylation[a]

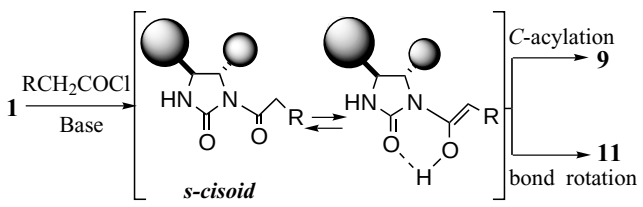
Entry	Compound	Yield (%)	
		N-3-Oxobutyryls	*N*-Acetyls
1	**1**	39 (69)[b]	57 (30)[b]
2	**2**	45 (67)[b]	53 (32)[b]
3	DPIm[c]	0	89
4	**3**	0	84
5	**4**	0	79

[a] The reaction was performed with acetyl chloride in the presence of triethylamine (2 equiv.) at rt for 15 min.
[b] Performed at 0°C for 5 h.
[c] *trans*-4,5-Diphenyl-2-imidazolidinone.

As was the case with DTBIm (**1**), DAIm (**2**), with a similar steric requirement, gave the β-oxobutyryl type of product in reasonable yield, as summarized in Table 2. In strong contrast, *trans*-4,5-diphenyl-2-imidazolidinone (DPIm), that was less sterically congested than DTBIm and DAIm,[5b] gave only the *N*-monoacetyl product under identical conditions. Even the sterically congested, *cis*-4,5-disubstituted 2-imidazolidinones,[6] **3** and **4** failed to give the unusual β-oxoacylation products.

Rationalization of the unusual acylation

On the basis of the above facts, we propose a possible mechanism for the double acylation, including *N*-acylation followed by prompt *C*-acylation, as illustrated in Scheme 3. The initial step is the formation of kinetically controlled *s-cisoid* *N*-acetyl derivatives which are stabilized by intramolecular hydrogen bonding to form the enol derivatives. These highly reactive rotamers may be the key intermediates reinforced by bulky *tert*-butyl and 1-adamantyl groups, which can either react with the acylating agents through *C*-attack to give compounds **9** or can afford the thermodynamically stable *s-transoid* rotamers **11** by internal bond rotation. On the other hand, *s-transoid* rotamers **11** are very stable and not reactive enough to be converted to



Scheme 3. Plausible key intermediates.

9. Dipole–dipole repulsions might be the driving forces for tautomerization and internal bond rotation.

In conclusion, the highly congested *trans*-4,5-di-*tert*-butyl and *trans*-4,5-di-(1-adamantyl)-2-imidazolidinones (**1** and **2**) smoothly undergo an unusual acylation with acyl chlorides in the presence of organic amines to give good yields of 3-oxoacyl derivatives, such as **9**, which represent potential precursors for a variety of five- and six-membered heterocycles.[9] This unusual acylation can be rationalized through key intermediates, *s-cisoid* *N*-acyl rotamers, which are initially formed on the basis of both steric and electrostatic control.

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8. X-Ray crystal data for **9a** [mp 118–119°C (from hexane/CH_2Cl_2)]: triclinic, $P\bar{1}$ (# 2), $a=13.034(1)$ Å, $b=14.289(1)$ Å, $c=9.2032(7)$ Å, $\alpha=93.134(6)°$, $\beta=90.291(6)°$, $\gamma=102.806(6)°$, $V=1668.7(2)$ Å^3, $Z=4$, $\mu=6.30$ cm^{-1}, $R=0.044$. **11a** [mp 141–142°C (from hexane/CH_2Cl_2)]: monoclinic, $P2_1/c$ (# 14), $a=12.313(4)$ Å, $b=15.090(2)$ Å, $c=16.246(2)$ Å, $\beta=98.33(1)°$, $V=2986.8(9)$ Å^3, $Z=8$, $\mu=5.74$ cm^{-1}, $R=0.040$. **10** [mp 104–105°C (from hexane)]: monoclinic, $P2_1/n$ (# 14), $a=8.128(3)$ Å, $b=29.245(3)$ Å, $c=8.860(3)$ Å, $\beta=98.42(3)°$, $V=2083.4(10)$ Å^3, $Z=4$, $\mu=6.92$ cm^{-1}, $R=0.045$. We are much indebted to the Research Laboratories, Welfide corporation (Fukuoka, Japan) for the X-ray crystallographic analysis.
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