Tetrahedron Letters 51 (2010) 3095–3098

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nitrogen ylide-mediated cyclopropanation of lactams and lactones

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ARTICLE INFO

Article history:
Received 2 March 2010
Revised 6 April 2010
Accepted 7 April 2010
Available online 11 April 2010

Keywords:
Lactams
Lactones
Cyclopropanation
Nitrogen ylides
Rearrangements

ABSTRACT

Cyclopropanation of α,β-unsaturated δ-lactams and δ-lactones mediated by nitrogen ylides is described. The process tolerates different alkyl halides and gives efficiently bicyclo[4.1.0]heptanes in a totally stereoselective manner. On the other hand, ε-lactams under our experimental conditions suffer a novel process involving a skeletal reorganization to give a bicyclic[3.3.0] system.

1. Introduction

Cyclopropanes are a key structural motif in biologically active natural and non-natural compounds.[1] Among the various methods available for the cyclopropanation of unsaturated compounds, a great effort has been placed on catalytic decomposition of diazocompounds mediated by metal complexes[2] and catalytic Simmons–Smith reactions.[3] Furthermore, the ylide-mediated cyclopropanation has received high attention recently.[4] Most contributions, however, deal with sulfonium ylides whereas there are few examples that use nitrogen-derived ylides.[5] Gaunt's group was the first to report a truly catalytic cyclopropanation reaction with ammonium ylides using a tertiary amine as the catalyst.[6] Recently, this new organocatalyzed cyclopropanation approach was performed enantioselectively using chiral tertiary amines derived from alkaloids.[7]

Bicyclo[4.1.0]heptanes are interesting structures present in various biologically active compounds.[8] Our group has recently initiated the search for new azabicyclo[4.1.0]heptane compounds with potential activity against human isoform of nitric oxide synthase (*i*NOS).[9]

We were interested in the cyclopropanation of unsaturated lactams and lactones, and we envisioned the use of the nitrogen-ylide-based methodology to obtain the corresponding bicyclo[4.1.0]heptanes in an efficient and environmentally friendly way.

2. Results and discussion

We have prepared two differently protected δ-lactams, **3a–b**, and submitted them to a set of reaction conditions summarized in Table 1. The syntheses of the starting materials were accomplished from δ-valerolactam **1a** by protection and conversion of lactams **2a–b** into their α,β-unsaturated analogues via selenoxide elimination (Scheme 1). Then, a stoichiometric reaction was carried out using DABCO (1,4-diazabicyclo[2.2.2]octane) or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), as tertiary amines, exploring different solvents, bases and temperatures. The model compound **3a** was reacted with phenacyl bromide, adding this reagent slowly with a pump syringe to avoid side reactions. The reactions gave cyclopropane **4a** in different yields. Only the trans isomer of **4a** was detected in all the reactions.[10] Acetonitrile turned to be better solvent than dichloroethane (DCE) with which we only isolated a 23% yield of **4a** (entries 1 and 2). Reaction time was set to 12 h as no improvement was observed when prolonging to 24 h (entries 2 and 3). The base of choice was Cs_2CO_3. The use of harder bases (Na_2CO_3, NaOH, entries 5 and 6), led to the formation of variable amounts of another product, **5a**, as a result of a Morita–Baylis–Hillman-type reaction. Thus, the enolate resulting from the reaction of **3a** with DABCO reacts with another molecule of **3a**, with further recovery of the double bond. Michael type dimers are known to be formed in Morita–Baylis–Hillman reactions as side products because they themselves act as electrophiles.[11]

In general, the addition of NaI was favourable, increasing the conversion of the reaction (compare entries 1 with 2; 3 with 4; 7 with 8 and 9 with 10). On the other hand, DABCO was the best catalyst as the use of DBU led to significant lower yields (entries 7 and 8). Once the best stoichiometric conditions were found (entry 4), we switched to catalytic reactions using 0.2 equiv of DABCO (entry 9). Although we obtained the desired product, the yields were low. Therefore we continued the study using stoichiometric amounts of DABCO.[12]

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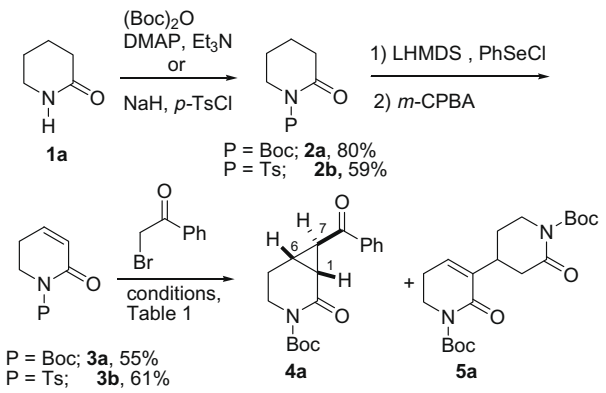
doi:10.1016/j.tetlet.2010.04.021

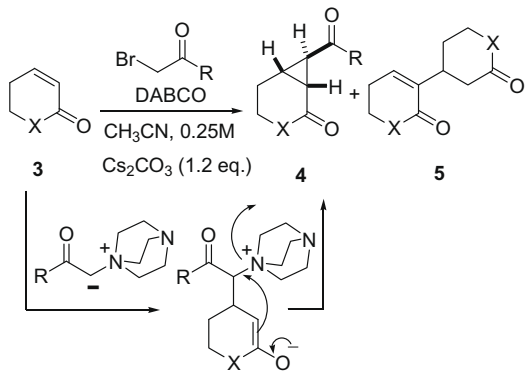
Table 1
Reaction conditions for the cyclopropanation of **3a** with phenacyl bromide

No.	Cat.[a]	Base 1.2 equiv	Solv.	Time (h)/*T* (°C)	Additive 40 mol %	Yield (%)		
						3a	**4a**	**5a**
1	DABCO	Cs_2CO_3	DCE	12/80		85	10	
2	DABCO	Cs_2CO_3	DCE	24/80	NaI	45	23	
3	DABCO	Cs_2CO_3	MeCN	24/80		30	50	
4	DABCO	Cs_2CO_3	MeCN	12/80	NaI	10	68	
5	DABCO	Na_2CO_3	MeCN	12/80		30	10	50
6	—	NaOH	MeCN	12/80		—	—	90
7	DBU	Cs_2CO_3	MeCN	12/80		90	3	
8	DBU	Cs_2CO_3	MeCN	12/80	NaI	77	15	
9	DABCO (0.2 equiv)	Cs_2CO_3	MeCN	12/80	NaI	46	23	

[a] 1 equiv except entry 9.



Scheme 1. Synthesis of starting lactams and study of cyclopropanation conditions.



Scheme 2. Synthesis of cyclopropanes **4** and reaction course.

Once the reaction conditions had been selected (Table 1, entry 4), we studied the scope of this synthesis by selecting various bromoketones (Scheme 2, Table 2).

First we carried out the reaction with compound **3b** and phenacyl chloride observing a better behaviour of this substrate, as we reached a yield of 75% for the final product (Table 2, entry 1). Substrate **3a** gave poor results with the different chlorides used. We were able to isolate a low yield of **4c** when using *tert*-butyl bromoacetate as the electrophile (30%, entry 2). On the other hand this halide gave a good yield of cyclopropane **4d** when reacting with **3b**. This result was achieved using an excess of DABCO and NaI (entries 3 and 4). We did not observe any reaction of **3a** with trifluorobromoacetone, whereas **3b** gave a 57% of the desired cyclopropane **4e** along with 25% of **5b** (entries 5 and 6).

At this point we considered extending the methodology to α,β-unsaturated lactones. Thus, we reacted 5,6-dihydro-2*H*-pyran-2-one with phenacyl bromide obtaining an excellent yield in cyclopropane **4f** (80%, entry 7). This lactone gave a good yield of product **4g** in its reaction with *tert*-butyl bromoacetate (65%, entry 8), but failed to react with the trifluoromethyl containing electrophile (entry 9). All the cyclopropanes obtained had trans stereochemistry, never detecting the cis isomers. The assignment of the relative stereochemistry was realized by NOE experiments that agreed with the values of the coupling constants.[10]

Our next aim was to apply this methodology to seven-membered lactams. Thus, we prepared substrate **3c**, following a similar procedure as for the preparation of **3a–b** (Scheme 3). The preparation of **3c** gave an excellent yield of this compound (71%, three steps from **1b**). When we submitted **3c** to our reaction conditions with phenacyl bromide (Table 1, entry 4), we did not detect any cyclopropane-containing product. However, a new product was formed in 55% yield. The structure of this compound was established by NMR methods and was further confirmed by an X-ray diffraction analysis (see Fig. 1 for an ORTEP illustration).[13] Increasing the amount of base to 2 equiv of Cs_2CO_3 allowed us to raise the

Table 2
Scope of the cyclopropanation reaction

No.	X	R	DABCO equiv	Add. 40 mol %	Time (h)/*T* (°C)	Yield (%)		
						3	4	5
1	NTs	Ph	1.3	NaI	12/80	16	**4b**: 75	—
2	NBoc	O^{t}Bu	1	NaI	12/80	25	**4c**: 30	35
3	NTs	O^{t}Bu	1.3	—	24/80	17	**4d**: 35	32
4	NTs	O^{t}Bu	1.8	NaI	48/80	17	**4d**: 65	12
5	NBoc	CF_3	1	NaI	72/80	65	—	34
6	NTs	CF_3	1.8	NaI	24/80	24	**4e**: 57	25
7	O	Ph	1.5	NaI	12/80	—	**4f**: 80	—
8	O	O^{t}Bu	1.5	NaI	12/80	—	**4g**: 65	—
9	O	CF_3	1.5	NaI	72/80	95	—	—