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Published on Web 03/15/2003

MgI_2-Mediated Ring Expansions of Secondary Methylenecyclopropyl Amides

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The generation of a bifunctional intermediate via ring opening of a highly strained and activated three-membered carbocycle is a synthetically useful tool for the construction of expanded ring systems.[1] Recently, we reported the MgI_2-mediated ring expansion of monoactivated methylenecyclopropanes (MCPs) whereby two different types of heterocycles, **2** and **3**, were obtained, depending on the substituent Z of the MCPs **1** (Scheme 1).[1a]

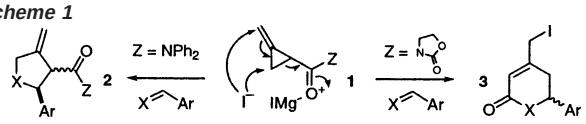
As we expanded our study to other "Z" groups, we observed a completely different process for secondary MCP amides **1** (Z = NHQ, Scheme 2). In the absence of an electrophile, the secondary MCP amides **1** (Q = aryl and heteroaryl group) underwent ring expansion to the isomeric five-membered unsaturated lactam **7**.[2] In the presence of a wide range of aryl aldimines or aldehydes, **1** afforded the γ'-amino- or -hydroxy-alkylated products **8** when the substituent Q bearing an *o*-nitrogen atom was present. The net transformation gave the difficult-to-access β-(or 4-)alkylated pyrrol-2-one skeleton via a single step under mild and neutral conditions. In addition, we showed that isomeric γ-hydroxy-alkylated products **12** could be obtained via a direct vinylogous aldol reaction of the product **7a**.

Initial experiments with amide **1a** (Q = pyrid-2-yl) and an aldimine **4** (X = NTs, Ar = aryl) using stoichiometric MgI_2 in refluxing THF (0.05 M) provided neither the five- or six-membered heterocycle **2** or **3** (Scheme 1). Instead, a mixture of five-membered unsaturated lactam **7a** and the γ'-amino-alkylated product[3] **8a** was obtained (Scheme 2). Both have a 4-methyl-1,5-dihydropyrrol-2-one as a common structural motif and may arise from a common intermediate. Either vinylogous enolate **5**[4] resulting from ring opening of **1** or cyclic enolate **6** from ring closing of **5** (dotted arrow, Scheme 2) could be intermediates which would react subsequently with a proton and/or an aldimine at the γ'-position to give a mixture of **7** and **8**.

The scope of MgI_2-mediated ring expansion for various secondary MCP amides[5] was then examined in order to determine the structural requirements of *Z*. The isomeric 2-, 3-, and 4-pyridyl and phenyl amides **1a**−**d** furnished 4-methylpyrrol-2-ones in good to excellent yields (entries 1−4, Table 1). However, the amides **1e** and **1f** having alkyl groups such as benzyl and 2-pyridylmethyl and the benzoyl imide **1g** failed to give the expected products and provided either complex mixtures (entries 5 and 7) or recovery of the starting material **1f** (entry 6). The primary amide **1h** underwent only the ring opening reaction, resulting in the iodo-substituted open chain amide **10** which was best isolated as the alkyl azide **11** (entry 8). It appears that an aryl group acidifies the N−H bond that participates in the cyclization. As a result, secondary MCP amides **1** bearing an *N*-aryl or hetero-aryl group gave rise to ring expansion, leading to the corresponding isomeric lactam **7**.

With a clearer understanding of the ring expansion process, we turned our attention to optimizing the yield of the γ-alkylative product **8**. Reaction of the pyrid-2-yl amide **1a** at 0.05 M in THF led to significant amounts of the unalkylated product **7a**. Fortunately, the desired alkylated product **8a** was obtained in better yield at 0.1 M in THF (entries 1−4, Table 2).

Scheme 1



Scheme 2

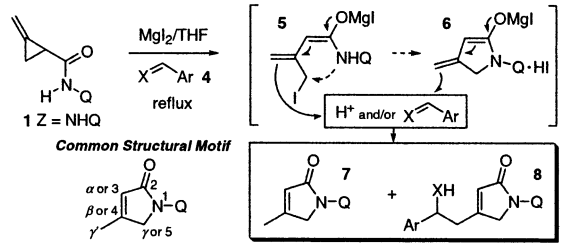
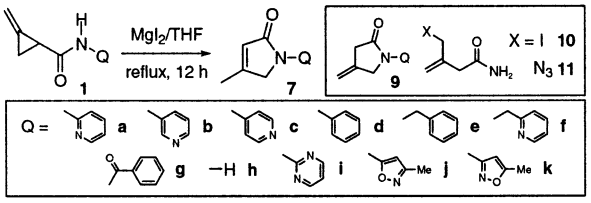


Table 1. Ring Expansion[a] of Secondary MCP Amides



entry	1	product	yield (%)	entry	1	product	yield (%)
1	**a**	**7a**	89[b]	5	**e**	**7e**	*d*
2	**b**	**7b**	95	6	**f**	**7f**	*d*
3	**c**	**7c**	87	7	**g**	**7g**	*d*
4	**d**	**7d**	80[c]	8	**h**	**11**	67

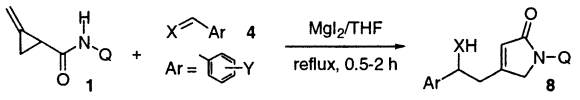
[a] All reactions were carried out using stoichiometric MgI_2. [b,c] In each case, the regioisomer **9** was obtained in 9% and 10% yields, respectively. [d] No yields; see text.

Several aryl aldimines[6] as well as aryl aldehydes furnished the amino- or hydroxy-alkylated pyrrol-2-ones in good yields (entries 5−10, Table 2). However, it was quite surprising that when the phenyl amide **1d** reacted with **4d** under the standard conditions (0.1 M THF), no desired product was obtained.[7] Even in the reactions with isomeric pyridyl amides **1b** and **1c**, only complex mixtures were produced. On the basis of these results, the *o*-nitrogen atom of the 2-pyridyl group appeared to play a crucial role in the alkylative ring expansion process.

Thus, we prepared additional hetero-aryl amides **1i**, **1j**, and **1k** (Table 1) to examine the effect of the *o*-atom for alkylative ring expansion. The pyrimid-2-yl and isoxazol-5-yl amides **1i** and **1j** did not give the desired products despite bearing two *o*-nitrogen atoms and one *o*-oxygen atom, respectively. The isoxazol-3-yl amide **1k** having one *o*-nitrogen atom reacted with aryl aldehydes, but aryl aldimines failed to react under these conditions (Table 3). Better yields were obtained at higher concentration (entries 3−4 and 6−7) or with excess MgI_2 (entries 4−5 and 9−11). The change

10.1021/ja028967l CCC: $25.00

Table 2. Alkylative Ring Expansion of MCP **1a** (Q = Pyrid-2-yl)



entry	4	X	Y	equiv of MgI_2	[1] (M)	8	yield[a] (%)
1	**a**	NTs	4-Br	1.1	0.05	**aa**	45
2	**a**	NTs	4-Br	1.1	0.1	**aa**	53
3	**b**	NTs	2,4-dimethyl	1.1	0.05	**ab**	54
4	**b**	NTs	2,4-dimethyl	1.1	0.1	**ab**	68
5	**c**	NTs	4-OMe	1.1	0.1	**ac**	71
6	**d**	NTs	H	1.1	0.1	**ad**	72
7	**e**	NTs	2-CF_3	1.1	0.1	**ae**	76
8	**f**	O	H	1.1	0.1	**af**	62
9	**g**	O	3,4-OCH_2O	1.1	0.1	**ag**	72
10	**h**	O	4-CF_3	1.1	0.1	**ah**	81

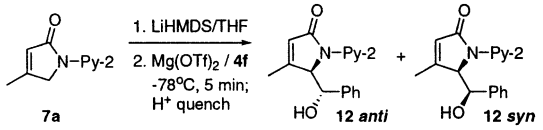
[a] In each case, the nonalkylated product **7a** was isolated in 10−30% yield.

Table 3. Alkylative Ring Expansion of MCP **1k** (Q = Isoxazol-3-yl)

entry	4	X	Y	equiv of MgI_2	[1] (M)	8	yield[a] (%)
1	**c**	NTs	4-OMe	1.1	0.1	**kc**	38
2	**i**	NTs	3,4-OCH_2O	1.1	0.1	**ki**	53
3	**b**	O	H	1.1	0.05	**kb**	55
4	**b**	O	H	1.1	0.1	**kb**	65
5	**b**	O	H	3.0	0.1	**kb**	74
6	**j**	O	2-CF_3	1.1	0.1	**kj**	48
7	**j**	O	2-CF_3	1.1	0.2	**kj**	61
8	**h**	O	4-CF_3	1.1	0.2	**kh**	68
9	**g**	O	3,4-OCH_2O	1.1	0.2	**kg**	73
10	**g**	O	3,4-OCH_2O	0.3	0.2	**kg**	29[b]
11	**g**	O	3,4-OCH_2O	3.0	0.1	**kg**	82
12	**k**	O	4-OMe	1.1	0.2	**kk**	67

[a] In most cases, the nonalkylated product **7k** was isolated in 10−30% yield. [b] The major product was **7k** which was isolated in 65% yield.

Scheme 3



in reactivity in the presence of a Q with one *o*-nitrogen atom may be due to coordination effects.[8]

Using this method, highly functionalized γ'-amino- or -hydroxy-alkylated five-membered lactams **8** can be produced in a single step under mild and neutral conditions. Regioselective alkylation took place at the γ-position of either a vinylogous intermediate **5** or **6** (Scheme 2). The resulting β-(or 4-)alkylated pyrrol-2-one scaffolds[9] are not easily prepared by other methods. In fact, aldol or alkylation of a pyrrol-2-one always yields isomeric products.[10] For example, a modified direct vinylogous aldol process[10a] for the 4-methylpyrrol-2-one **7a** yielded a mixture of the γ-substituted pyrrol-2-ones **12**[11] in 77% yield (*anti*:*syn* = 2.3:1) (Scheme 3).

Finally, we compared the analogous cyclopropane (CP) compounds of **1a** and **1k**. Under the same conditions the CP amides were found to be completely inert leading to recovery of the starting materials. It appears that the driving force for preferential reaction of the MCP is the release of strain energy (a MCP is 13.6 kcal/mol[12] more strained than the CP ring).

In summary, we have observed a novel ring expansion of the secondary MCP amide **1** in the presence of MgI_2. A key feature in this rearrangement was the dual effect of the activating group Q. The amide nitrogen atom, which is generally considered nonnucleophilic, was incorporated into the newly formed ring under neutral conditions. Through hetero-aryl MCP amides bearing one *o*-nitrogen atom, the alkylative ring expansion with aryl aldimines and aldehydes was achieved, resulting in the exclusive formation of γ'-amino- or -hydroxy-alkylated pyrrol-2-ones. Currently, we are studying further applications of a variety of MCP substrates with Lewis acids including chiral variants.

Acknowledgment. We thank NSERC (Canada) and the University of Toronto for funding this research. W.H. thanks the University of Toronto for financial support.

Supporting Information Available: Details of all experimental procedures and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) It is unusual that the amide nitrogen was incorporated instead of the carbonyl oxygen of the activating group (CONHQ) in these types of rearrangements. For a comparison see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 248 and ref 1l.

(3) The structure of **8ad** was identified by X-ray crystallography.

(4) The *E*-enolate should be a prerequisite for the product formation. Otherwise isomerization of double bond would be necessary.

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JA028967L