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Domino Process Optimized via *ab Initio* Study for an Alternative Access to Bicyclic Lactams

Sébastien Comesse,*,† Arnaud Martel,*,‡ and Adam Daïch†

URCOM, EA 3221, CNRS FR3038-INC3M, UFR S.T. de l'Université du Havre, BP 540, 25 rue Philippe Lebon, F-76058 Le Havre cedex, France, and UCO2M, UMR 6011 & IRIM2F FR 2575 CNRS, Université du Maine, 72085, Le Mans, France

sebastien.comesse@univ-lehavre.fr; arnaud.martel@univ-lemans.fr

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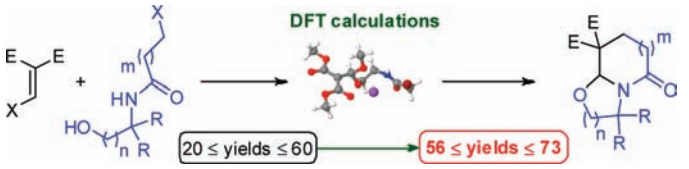
ABSTRACT



A totally new acid-free domino process to access highly functionalized bicyclic γ- and δ-lactams starting from commercially available and inexpensive ethoxymethylene derivatives is reported. Mechanisms elucidated by computational calculations led to new reaction conditions that boosted the yields up to 3.5 times higher.

Tandem and domino reactions are powerful tools forming multiple bonds in one synthetic operation.[1] In comparison to traditional stepwise approaches involving isolation of each intermediate, domino processes have gained much importance nowadays as they allow minimization of waste, energy, solvents, and time. Moreover, they are sometimes exclusive pathways to access advanced products when the intermediates are unstable and therefore difficult to isolate.[2] The efficiency of a domino process is correlated to the number of bonds formed and also to its general usefulness for the formation of molecules of interest such as heterocycles.[3]

Because of the number of steps in domino processes, we envisioned that DFT calculations could play a siginficant role in understanding the mechanistic aspects and that employing these calculations during the development of a new methodology should allow us to accelerate the optimization step by tuning the reactivity of the reaction.

Bicyclic lactams **1** first developed by A. I. Meyers have proven to be useful building blocks and have been widely used during the past decades as highly adaptable tools for the synthesis of optically pure *N*-heterocycles (Scheme 1).[4] Even if the two classical procedures employed[5] to reach such structures have proved their efficiencies, they suffer some major drawbacks. For example, there is a risk of over addition of the Grignard reagent onto cyclic imides **2** with a lack of both regio- and chemoselectivity.[6] As for the second procedure, it involves the synthesis of the γ-keto acid/ester derivatives **3**. Moreover, the acidic conditions

† Université du Havre.
‡ Université du Maine.

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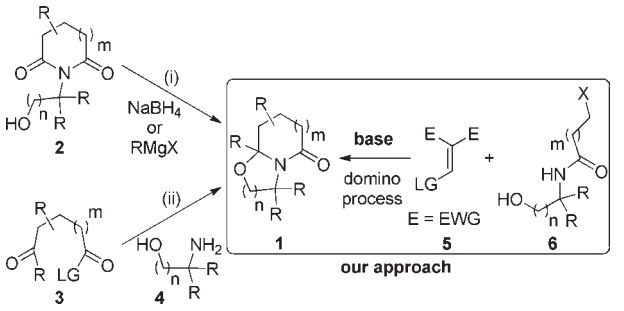
employed may prove to be incompatible with highly sensitive substrates and thus limit the scope of these methodologies.

Scheme 1. General Strategies for Oxazolo-pyrrolidinone or -piperidinone Synthesis and Our Approach

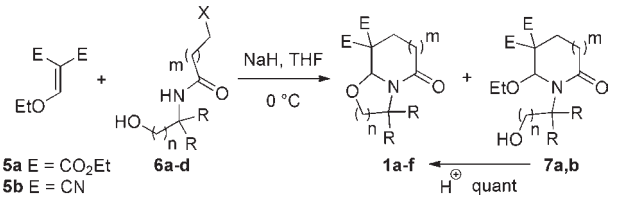


As part of an ongoing program devoted to the development of tandem reactions[7] using *N*-substituted α-bromoacetamides,[8] we recently reported a novel tandem sequence aza-Michael/intramolecular nucleophilic substitution.[9] We envisaged that the reaction between the *N*-hydroxyalkyl α-bromoacetamides **6a**−**c** or *β*-chloropropanamides **6d** and commercially available diethyl ethoxymethylene malonate (DEEM)[10] **5a** or ethoxymethylene malononitrile **5b** should furnish the corresponding bicyclic *γ*-lactams **1** (Scheme 1). A mechanistic study of this methodology, supported by DFT calculations, was performed to identify the key steps and intermediates of this domino sequence. Starting from these *ab initio* results, we were able to further optimize the reaction conditions by tuning the reactivity of both the reactants and intermediates involved and then shutting down secondary reaction pathways.

In a first set of reactions we employed DEEM **5a** with hydroxyhalogenoamides **6a,b** (Table 1). These compounds led to the formation of the corresponding mixture of **1a** and **7a** or **1b** and **7b** as a result of the competition between the 1,4-addition of the alkoxide and the amidate (Table 1, entries 1 and 2). Under acidic conditions, the *N*-acyliminium ion precursors **7a** and **7b** underwent a quantitative cationic cyclization to furnish **1a** and **1b**, respectively. The 1,4-addition competition was prevented by the use of the more sterically hindered amide **6c** (R = Me) leading to the sole bicyclic lactam **1c** in 60% yield (entry 3). In addition, δ-lactams were also obtained with an acceptable yield of 55% (entry 4).

We then extended our methodology to ethoxymethylene malononitrile **5b** leading to the desired bicycles **1e** and **1f**

Table 1. Scope of Direct Anionic Access to Bicyclic Lactams

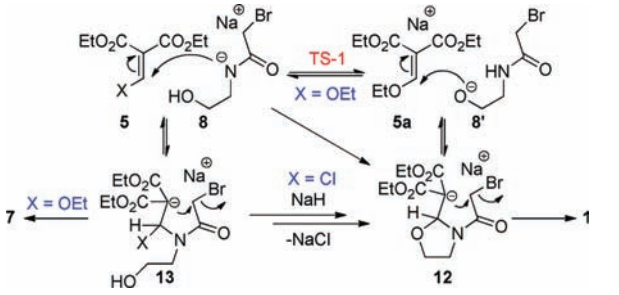


entry	*n*	*m*	**5**	R,X **6**	yield **1** [%][a]	yield **7** [%][a]
1	1	0	**5a**	H,Br **6a**	**1a** [32]	**7a** [25]
2	2	0	**5a**	H,Br **6b**	**1b** [38]	**7b** [17]
3	1	0	**5a**	Me,Br **6c**	**1c** [60]	[b]
4	1	1	**5a**	Me,Cl **6d**	**1d** [55]	[b]
5	1	0	**5b**	Me,Br **6c**	**1e** [20]	[b]
6	1	1	**5b**	Me,Cl **6d**	**1f** [30]	[b]

[a] Yield of isolated product. [b] Product **7** was not observed.

with poor yields along with undefined byproduct. The competitive formation of **1** and **7** is most probably due to the coexistence of two alternative mechanisms (Scheme 2).[11] The pathway leading to **7** can be rationalized by the initial 1,4-addition of the amidate **8** onto the double bond of the methylenemalonate **5** followed by an intramolecular nucleophilic substitution onto α-bromoacetamide **13**. In that case, the cyclization is faster than *β*-elimination of sodium ethoxide.[12]

Scheme 2. Proposed Mechanism for the Competitive Formation of **1** and **7**



Formation of **1** results from an alternative pathway assessed by DFT calculations at the B3LYP/6-31+G(d,p) level using the polarizable continuum model (PCM) for the description of THF as the solvent.[13] Reactions were modeled with methyl methoxymethylene-malonate **5a**′ and

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(8) (a) Oukli, N.; Comesse, S.; Chafi, N.; Oulyadi, H.; Daïch, A. *Tetrahedron Lett.* **2009**, *50*, 1459–1462. (b) Allous, I.; Comesse, S.; Daïch, A. *Lett. Org. Chem.* **2008**, *5*, 73–78.

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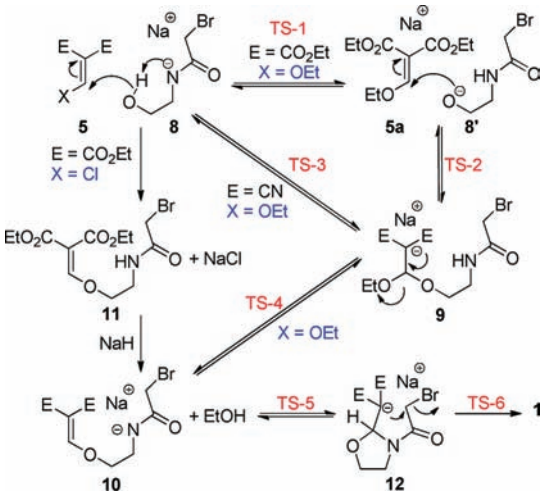
(11) As expected and confirmed by DFT calculation, the amidate **8** is more stable than the alcoholate **8**′ (ΔE = 7.7 kCal/mol, ΔH = 7.3 kCal/mol, ΔG = 7.6 kCal/mol; Scheme 3, **8** and **8**′) and consequently should add preferentially. However, as proved by **TS-1** and revealed by entries 1 and 2 in Table 1, the amidate plays the role of an internal base promoting the addition of the alcohol.

(12) Unlike acidic media allowing the total conversion of **7** into **1**, the basic conditions involved in the reaction do not allow such transformation.

(13) See Supporting Informations for details.

methoxymethylene-malononitrile **5b′** as Michael acceptors (chosen as models for the calculations) in reaction with **6a**.[14] The proposed mechanism for this domino reaction is a four- or five-step event starting from **5** and **8** (Scheme 3).

Scheme 3. Proposed Mechanism for the Domino Process



Surprisingly, depending on the Michael acceptor, the formation of **9** can involve a one- or two-step process. Indeed, in the case of **5a′**, the reaction proceeds by first the deprotonation of the alcohol by the amidate **8** (**TS-1**, Scheme 3 and Figure 1) and then addition of the corresponding alkoxide **8′** onto the double bond (**TS-2**).

Interestingly, contrary to **5a′**, the use of a stronger electrophile such as **5b′** allows the direct 1,4-addition of the alcohol assisted by concomitant deprotonation by the amidate **8** (**TS-3**, Scheme 3 and Figure 1).[15] The following step is the β-elimination of the methoxide, which simultaneously deprotonates the amide in **9** leading directly to the amidate **10**. The last two steps of the sequence involve two intramolecular cyclizations: an aza-Michael addition of the amidate **10** onto the double bond and then a nucleophilic substitution onto intermediate **12** to provide the bicyclic system **1**. Unexpectedly, the key steps of the mechanisms differ completely depending on the electrophile involved. In the case of methoxymethylene-malonate **5a′**, the rate-limiting step is clearly the addition of the alkoxide **8′** onto the double bond, whereas for the highly reactive methoxymethylene-malononitrile **5b′**, the two limiting steps of the sequence (**TS-4** and **TS-6**) involve energy barriers below 18 kcal/mol, noticeably lower than the highest energy barrier of 22.1 kcal/mol for **5a′**.

(14) A prime will be added at the end of the number and be used to describe the replacement of ethyl groups by methyl groups.

(15) Intrinsic reaction coordinate (IRC) calculation was performed and confirmed that no additional transition state from the alcoholate to the addition product **9** is involved in the process.

(16) Considering the formation of methanol during the reaction, the second part of the calculations (Figure 2) was performed without formal representation of MeOH in order to avoid useless calculation time consumption. Consequently, energies for the second part are given relatively to **10** in absence of methanol.

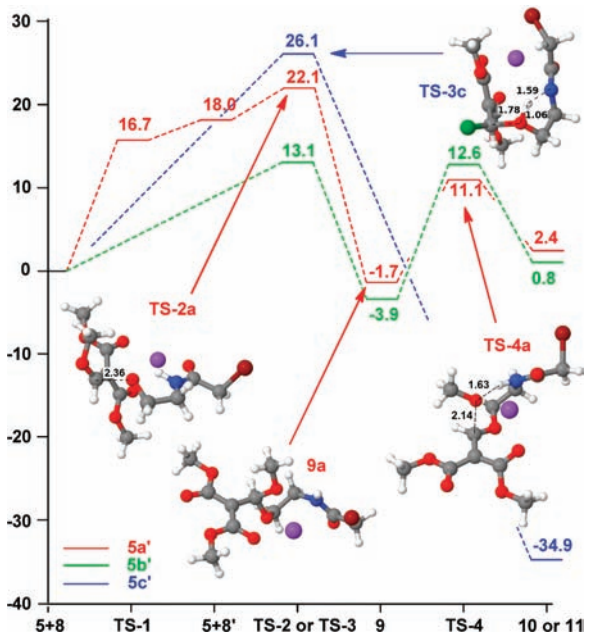


Figure 1. Reaction pathway from **5** and **8** to **10** or **11** calculated at PCM(THF)-B3LYP/6-31+G(d,p) level. Distances given in angstroms.

In fact, **9** and **12** are the most stable intermediates involved (respectively, $\Delta G = -3.9$ and -3.0 kcal/mol; Figures 1 and 2), and the following energy barriers to get over (**TS-4**, $\Delta G = 16.5$ kcal/mol and **TS-6**, $\Delta G = 17.4$ kcal/mol) are also the highest in the sequence. As shown by Figures 1 and 2,[16] the stability of the carbanions **9** and **12** are increased by an intramolecular complexation of the sodium cation. The lifetime of these basic and nucleophilic intermediates in the solution are most likely long enough to initiate the polymerization of the Michael acceptors **5a′**,**b′**. This side reaction is almost certainly responsible of the moderate to low yields observed, particularly in the case of the highly reactive acceptor **5b′** (entries 5 and 6, Table 1). In view of the elements listed above resulting from DFT calculations, we anticipated that it should be possible to increase both the selectivity and efficiency of our domino process. One of the main drawback in the case of DEEM **5a′** is the competitive formation of **7**, which could be overcome by the use of a better leaving group such as a chlorine atom (Scheme 2). This transformation in the acceptor **5c** will render the sequence irreversible toward the formation of **12** whichever the pathways, i.e., addition of the alkoxide **8′** or addition of the amidate **8** followed by the elimination of NaCl (Scheme 2). Indeed, due to the presence of the chlorine atom, the primary 1,4-addition of the amidate **8** instead of the alkoxide did not lead to the subsequent S_N2 cyclization but to an enamide by a β-elimination process. The competitive formation of **7** was totally overcome by using the Michael acceptor **5c**. Thus, only the bicyclic lactams **1a** and **1b** were isolated in higher yields of 56% and 58%, respectively, corresponding to

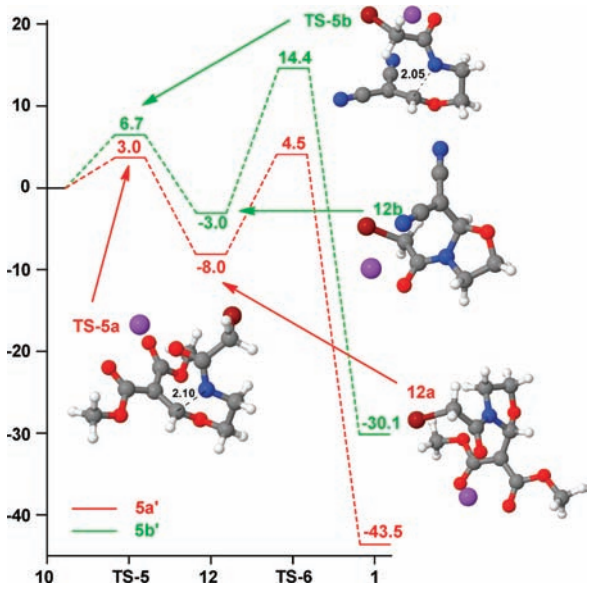


Figure 2. Reaction pathway from **11** to **1** calculated at the PCM-(THF)-B3LYP/6-31+G(d,p) level. Distances given in angstroms.

combined yields of **1** and **7** obtained with **5a** (comparison of Table 1 with Table 2, entries 1 and 2).

This significant change in reactivity of **5c** is the result of an entirely different mechanism involving only one transition state from **8** to **11** as shown in Scheme 3 (Figure 1). As expected, prevention of the formation of intermediate **9** results in a slight increase in the yield of **1c** with even higher yield with LiHMDS employed as a more selective base (comparison of Table 1, entry 3 with Table 2, entries 3 and 4). Moreover, the existence of surviving intermediates such as **9** and **12** in the reaction mixture, together with the presence of unreacted Michael acceptor **5b** (Table 1, entries 5 and 6), are responsible of the low yields observed in these cases. We found that by decreasing the lifetime of the carbanion species **9** and **12** it should be possible to increase the efficiency of the domino reaction. Assuming that intramolecular processes such as β-elimination or cyclization should be entropically favored at higher temperature, we decided to perform the reaction in refluxing acetonitrile.[17] In addition, considering the high reactivity of **5b**, the use of a softer base such as potassium carbonate should also contribute to reduce the lifetime of the carbanion species, thanks to the equilibrium with the corresponding protonated species. In these conditions, a dramatic change was observed yielding the desired products **1e** and **1f** in 70% and 73%, respectively, i.e., up to 3.5 times higher than previously obtained (comparison of Tables 1 and 2, entries 5 and 6).

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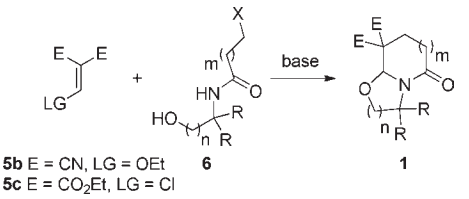
Table 2. Optimized Conditions for the Domino Process



5b E = CN, LG = OEt **6** **1**
5c E = CO_2Et, LG = Cl

entry	5	6	base	yield **1** [%][a]
1	**5c**	**6a**	NaH	**1a** [56][d]
2	**5c**	**6b**	NaH	**1b** [58][d]
3	**5c**	**6c**	NaH[b]	**1c** [67][d]
4	**5c**	**6c**	LiHMDS	**1c** [73][d]
5	**5b**	**6c**	K_2CO_3[c]	**1e** [70][d]
6	**5b**	**6d**	K_2CO_3[c]	**1f** [73][d]

[a] Yield of isolated product. [b] In THF at 0 °C, 3 h. [c] In CH_3CN at reflux, 2 h. [d] Product **7** was not observed.

In conclusion, we have developed a new approach for the synthesis of Meyers bicyclic lactams by a one-pot process using an unprecedented domino reaction. In order to overcome some limitations of this methodology, better understanding of the insights of the mechanism were investigated by DFT calculations. Thus, bearing in mind the key intermediates, modifications of the reaction conditions were considered and successfully applied to our domino process. Indeed, the formation of a side product could be avoided, enhancing the yields significantly. The DFT study gives various information on the relative reactivity of methylenemalonate and methylenemalonitirile in addition or elimination reactions. The data gained (key steps, position of the cation, geometry and relative energy of the intermediates, etc.) will be applied to the optimization of the stereoselective approaches and to the total synthesis of heterocyclic alkaloids using this methodology.

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Supporting Information Available. Experimental details, analytical data, and DFT calculations details. This material is available free of charge via the Internet at http://pubs.acs.org.