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Unsaturated Lactams: New Inputs for Povarov-Type Multicomponent Reactions

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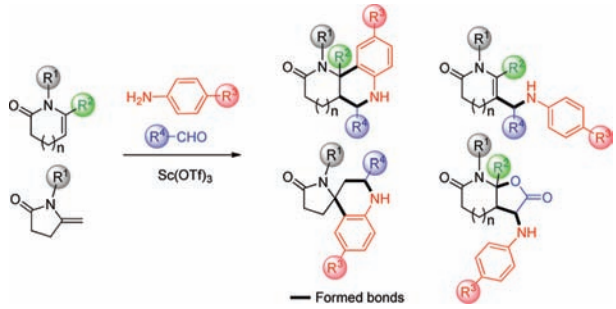
ABSTRACT



Unsaturated lactams with endo- or exocyclic C−C double bonds constitute a set of reactive inputs that serve as the electron-rich olefin component in Povarov reactions. These substrates afford the multicomponent adducts in convenient yields and offer a wide range of structural diversity. Postcondensation transformations allow direct access to a variety of lactam-fused and amide-substituted quinoline derivatives.

Multicomponent reactions (MCRs) constitute a large group of transformations of growing relevance in organic chemistry as they display many features of the ideal synthesis.[1] Among these domino processes, the Povarov MCR, which involves the interaction of a carbonyl compound (normally an aldehyde), an aniline, and an activated alkene to yield a tetrahydroquinoline adduct, is currently the focus of intense research.[2] This transformation links the following three main steps: the generation of an imine, followed by a Mannich-type reaction with the activated olefin, and ending with the intramolecular aromatic electrophilic substitution upon the aniline ring. The presence of tetrahydroquinolines (or oxidized derivatives) in natural products, bioactive compounds, and drugs has recently elicited much interest in this process.

The original protocol has been considerably improved, and recent findings include the possibility to perform catalytic enantioselective versions of this MCR,[3] the introduction of a fourth component to trap the final iminium ion intermediate,[4] and the spatial-temporal control of this MCR to functionalize microelectrodes.[5] With respect to the reactivity range, the process is useful with a broad set of anilines, carbonyl derivatives, and much effort has been devoted to expand the range of activated olefin input. Apart from alkenes

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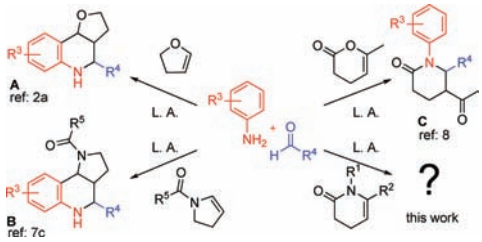
and cyclic enol ethers which have been used widely in this MCR (**A**, Scheme 1), the introduction of enamine-type

Scheme 1. Enol Ethers and Enamides in Povarov MCRs



functional groups has been successfully exploited.[2,6] In this context, cyclic enamides are specially appealing since they allow access to a new set of functionalized tetrahydroquinolines **B**.[7] Importantly, the development of this chemistry by Batey has allowed a straightforward synthesis of the alkaloids Martinelline and Martinellic acid.[7a−c] The MCR adducts in these processes show a normal connectivity pattern, thereby leading to the expected tetrahydroquinolines. In sharp contrast, when cyclic enol esters were tested in Povarov-type conditions, the *N*-aryl lactams **C** were obtained.[8] The origin of these compounds may lie in the intramolecular interception of the activated cationic intermediate by the nucleophilic aniline nitrogen, which overrides the usual aromatic electrophilic substitution. Here we studied the chemistry of unsaturated lactams in Povarov processes to determine their synthetic usefulness and to establish the mechanistic trends of these substrates in the MCR (Scheme 1).

Several unsaturated lactams were prepared by known methods (or modifications thereof), usually from the corresponding N-substituted imides by a reduction−elimination sequence.[9] The set included six- and seven-membered rings, displaying distinct substituents at the nitrogen atom and also at the neighboring position (**1a**−**f**, Figure 1). The pyrrolidone derivative **1g** with an exo double bond was also considered.[10]

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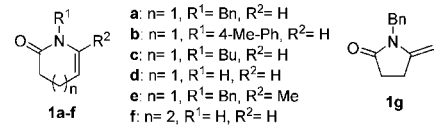
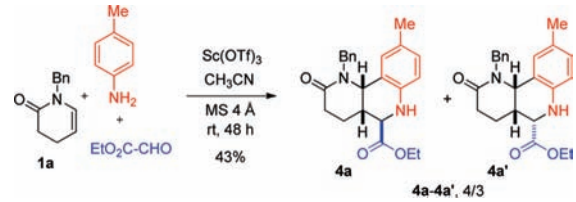


Figure 1. Unsaturated lactams used in this study.

The first experiment involved the interaction of the unsaturated lactam **1a**, with *p*-toluidine and ethyl glyoxalate under $Sc(OTf)_3$ catalysis[11,6b] in the presence of 4 Å molecular sieves in acetonitrile at room temperature. After chromatographic purification, the tetrahydroquinolines **4a** and **4a′** were isolated (isomer ratio 4/3) in 43% overall yield (Scheme 2).

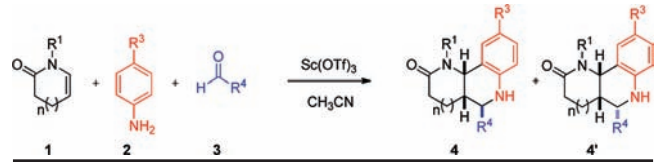
Scheme 2. Povarov MCR with Unsaturated Lactam **1a**



The stereochemical assignment of compounds **4a**−**4a′** was performed by spectroscopical means. The low stereoselectivity observed is the usual outcome in these processes.[2]

Next we examined the scope of the reaction, regarding all the components (Table 1). The aniline input showed

Table 1. Scope of the Povarov MCR with Unsaturated Lactams



entry	n	R^1	R^3	R^4	compound	overall yield (%)	isomer ratio (**4**/**4′**)
1	1	Bn	Me	CO_2Et	**4a**−**4a′**	43	4/3
2	1	Bn	CO_2Et	2-furyl	**4b**	38	1/-
3	1	H	OMe	3-pyridyl	**4c**−**4c′**	42	3/2
4	1	H	F	2-furyl	**4d**	33	1/-
5	1	Bu	OMe	4-CF_3-Ph	**4e**−**4e′**	42	1/1
6	1	Bn	Me	4-Cl-Ph	**4f**−**4f′**	64	1/1
7	1	4-Me-Ph	Me	CO_2Et	**4g**−**4g′**	61	8/5
8	1	H	Me	4-Cl-Ph	**4h**−**4h′**	56	5/8
9	2	H	Me	CO_2Et	**4i**−**4i′**	35	3/2

appropriate reactivity, ranging from deactivated to activated derivatives (entries 1−4). Also, the carbonyl range included

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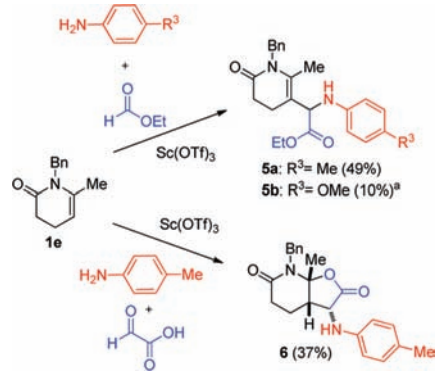
the usual set of aromatic and highly electrophilic aldehydes.[12] Thus, ethyl glyoxalate (entries 1 and 7) and diversely substituted aromatic and heteroaromatic aldehydes (entries 2−6 and 8) afforded the expected adducts. Interestingly, when using 2-furaldehyde in combination with ethyl *p*-aminobenzoate and *p*-fluoroaniline (Table 1, entries 2 and 4), we detected the formation of only the isomers **4b** and **4d**, respectively. Finally, we screened the unsaturated lactams, first studying the substitution pattern at the nitrogen atom (entries 1−8) and looking at the ring size (six- and seven-membered rings, entries 1−8 and 9, respectively). We obtained acceptable yields in all cases.

We explored further variations in the structure of the unsaturated lactams, and alkyl substitution at the α-position was also examined. When derivative **1e** (Scheme 3) was

Scheme 3. α-Substituted Unsaturated Lactam **1e**



[a] Unoptimized reaction.

reacted with *p*-toluidine or 4-methoxyaniline and ethyl glyoxalate, under the usual conditions, we obtained the Mannich-type products **5a** and **5b**, respectively, in moderate yields. In these cases, the final electrophilic substitution did not take place, probably due to steric reasons. In these reactions, the cationic intermediate evolved via a proton loss at the α-position of the acyliminium moiety to regenerate the unsaturated lactam system. This outcome also differed from the described reactivity of cyclic enol esters, where the aniline nitrogen attacks the carbonyl group of the intermediate.[8] Furthermore, when using glyoxylic acid as the carbonyl component, the carboxylate moiety acts as a nucleophile and captures the final iminium ion intermediate.[4a,13] Thus, adduct **6** (37%) was stereoselectively obtained in this way.

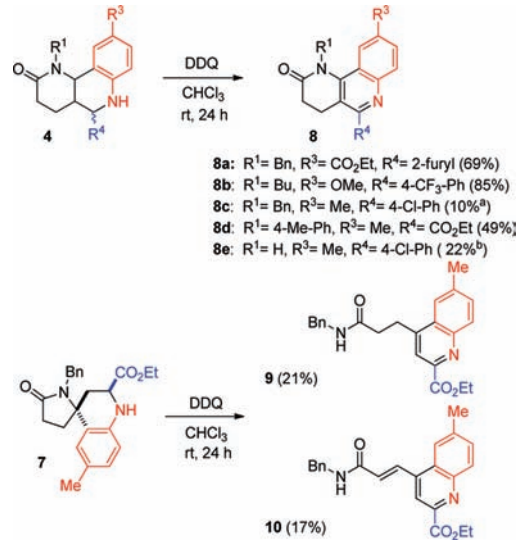
Finally, the pyrrolidone derivative displaying an exo double bond (**1g**) was reacted to afford the spiro-Povarov adduct (Scheme 4). First, the standard conditions were tested affording the MCR adduct in low yield (20%). Performing the reaction under microwave irradiation (MW) resulted in a substantial optimization (**7**−**7′**, 60% overall yield). Barluenga and co-workers recently reported an elegant domino process for the synthesis of related systems by a sequence involving the in situ formation of an exocyclic enol ether,

Scheme 4. Spiro-Adduct from Substrate **1g**

via a metal-catalyzed alkoxylation of an ω-hydroxyalkyne, followed by a Povarov reaction.[14]

Next, we explored some postcondensation reactions upon the previously prepared Povarov adducts. Thus, the DDQ-oxidation of the tetrahydroquinolines **4** yielded the corresponding lactam-fused quinolines **8** (Scheme 5).[15,16] The

Scheme 5. DDQ oxidation of Povarov adducts **4** and **7**



[a] Unoptimized result. [b] The overoxidation product **8f** (R^1 = H, R^3 = CHO, R^4 = 4-Cl-Ph) was also isolated in 40% yield.

process was satisfactory and afforded the products in reasonable yields. Adduct **4h** suffered overoxidation, thereby

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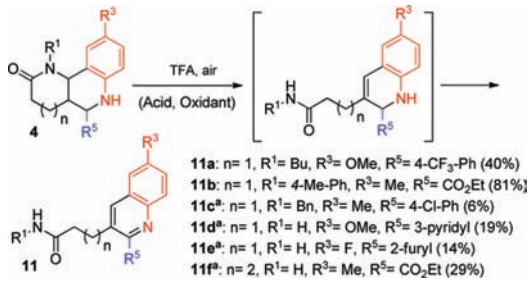
resulting in a mixture of the expected quinoline **8e** (22%), together with the aldehyde derivative **8f** (40%).[16] The treatment of spiro-adduct **7** (Scheme 5) with DDQ gave two compounds arising from an oxidative fragmentation: quinoline **9** (21%) and its dehydrogenated derivative **10** (17%).

In search for variants of this transformation, we tested a TFA treatment to promote an acid-catalyzed elimination[17] of the amide moiety of the Povarov adducts, which would lead to a 1,2-dihydroquinoline prone to spontaneus oxidation to give the 2,3-disubstituted quinoline derivatives (**11a**,**b**). In this way, quinolines **11a** and **11b** were directly prepared from compounds **4e** and **4g**, respectively (Scheme 6). This type of oxidative fragmentation was also observed at a reduced extent in the DDQ-oxidation of adduct **4f**, which allowed the isolation of **11c**. Also in the $Sc(OTf)_3$-catalyzed Povarov reactions, the quinolines **11d**, **11e**, and **11f** were isolated as byproduct (entries 3, 4, and 9, Table 1). These products may have arisen from the full domino sequence.

In conclusion, unsaturated lactams are synthetically useful substrates for Povarov MCRs and allow direct and convenient access to tetrahydroquinoline scaffolds with novel connectivity and functionalization patterns. These adducts are readily converted to a variety of quinoline derivatives in a straightforward manner.

Scheme 6. Acid-Catalyzed Fragmentation−Oxidation Process



[a] Isolated as byproduct in Povarov MCRs or in DDQ oxidations of the Povarov adducts **4**.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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