UNIVERSITY OF SALERNO

DEPARTMENT OF CHEMISTRY AND BIOLOGY

Ph.D. Course in "Chemistry" - XXXIII Cycle

Abstract

NEW APPLICATIONS OF ESTER/AMIDE SURROGATES IN ORGANIC SYNTHESIS

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ABSTRACT

Masked esters/amides are scaffolds endowed with a great potential in the field of organic synthesis. This PhD project has been conceived, in the context of non-covalent organocatalysis, with the aim to exploit unsaturated (**a**) and saturated (**b**) masked esters/amides (Figure A) as starting materials to accomplish the synthesis of different classes of organic compounds in a one-pot fashion.

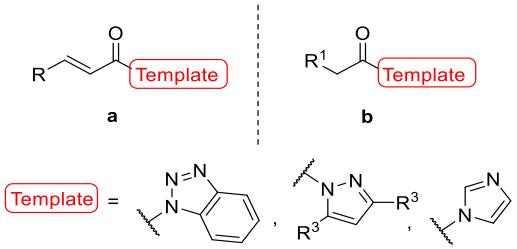


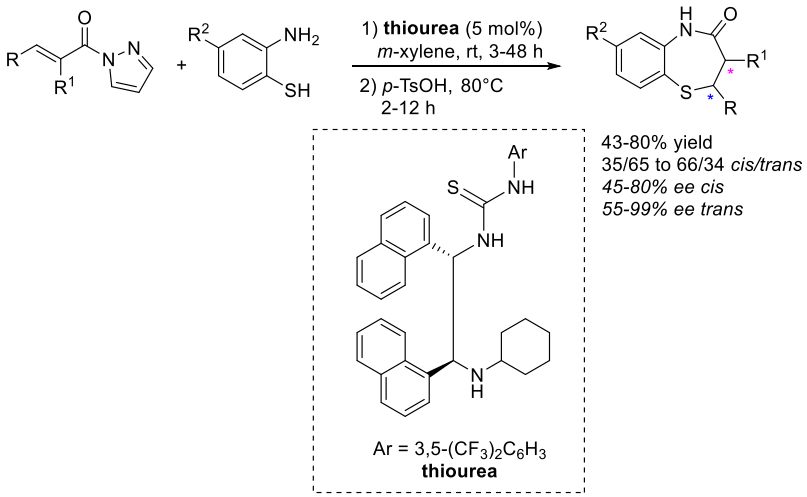
Figure A. General structure of an *α*,*β*-unsaturated (a) and a saturated (b) masked ester/amide.

Masked esters/amides (Figure A) exhibit some important features which make them valid substrates for organocatalytic one-pot sequences. Firstly, the presence of a nitrogen-based heterocycle renders them more reactive if compared with esters or amides: the heterocycle "steals" electron density from the molecule, resulting in an enhanced electrophilicity at the *β* position of reagent **a** or an enhanced acidity of *α*-proton in type **b** substrates. Secondly, nitrogen atoms of the heterocycle offer to these substrates more possibilities of interaction with an organocatalyst through further H-bonds formation. This provides a major rigidity in the transition state and a subsequent increase in the stereochemical outcome of the reaction. Finally, another important property of these compounds, due to the ability of the aza-heterocycle as leaving group, is the possibility to obtain ester or amide functionality through simple treatment with alcohols or amines via typical addition/elimination mechanism (hence the name "ester/amide surrogates").

We tried to achieve the stereocontrolled formation of carbon-carbon and carbon-heteroatom bonds to obtain cyclic compounds of different nature and size (such as benzothiazepines and bicyclic pyrazolidinones) and non-cyclic compounds, such as imines, *β*-aminoalcohols and nitrones.

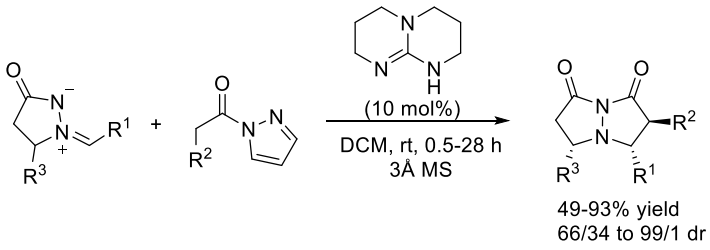
In this doctoral thesis, the first stereoselective cascade sulfa-Michael/lactamization sequence for the synthesis of *cis*- and *trans*-2,3-diaryl substituted 1,5-benzothiazepines has been developed, starting from *α*,*β*-unsaturated *N*-acylpyrazoles and 2-aminothiophenols. The two steps are promoted by catalytic amounts of a readily available bifunctional thiourea and *p*-toluenesulfonic acid, respectively. Our work provides access to both *N*-unprotected diastereoisomers of the product with satisfactory results (Scheme A).

Moreover, we demonstrated that these products can be easily elaborated to prepare libraries of compounds for biological tests.



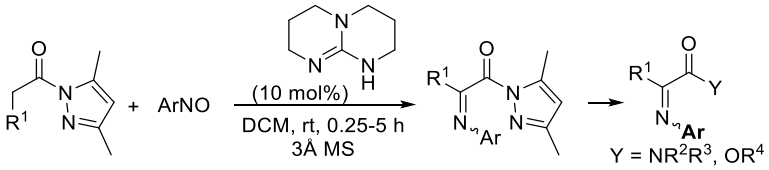
Scheme A. Our approach for the synthesis of *cis*- and *trans*-2,3-diaryl substituted 1,5-benzothiazepines from *α,β*-unsaturated *N*-acylpyrazoles.

Regarding the use of reagent **b**, the greatest acidity of alpha protons easily allows the formation of an enolate which can react with an opportune electrophile, thus creating a first addition product. The presence of a nucleophilic site on this product, results in an intramolecular cyclization with the formation of an heterocyclic compound. In this case, we developed a diastereoselective one-pot [3+2] cycloaddition of *N,N'*-cyclic azomethine imines and *N*-acylpyrazoles to access bicyclic pyrazolidinones (Scheme B). Despite literature precedents, our protocol contemplates the use of readily available starting materials and a catalytic amount of a commercial base under mild reaction conditions.



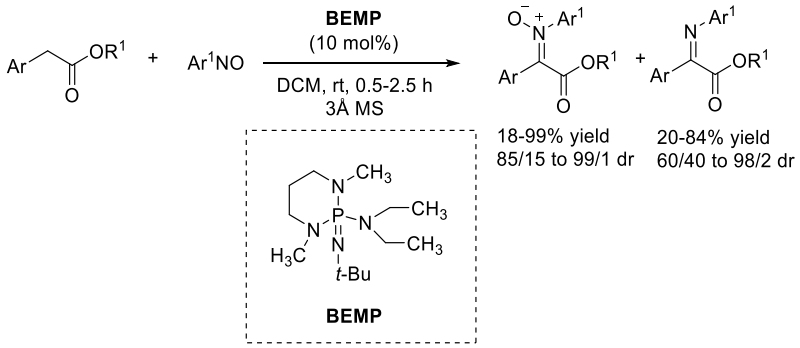
Scheme B. Stereoselective synthesis of tetrahydropyrazolo[1,2-a]-pyrazole-1,7-diones.

If the first adduct cannot give following reactions, the presence of heterocyclic ring enables a subsequent simple elaboration with synthesis of esters and amides for example. About this, we worked out a facile synthesis of *α*-iminoesters derivatives by reacting nitrosobenzenes with acylpyrazoleamides: the nucleophilic addition of the enolate to nitrosoarene, followed by dehydration, leads to the formation of these compounds. Moreover, the *α*-imino *N*-acyl pyrazoles, a new class of compounds never reported before, represent new versatile intermediates to easily access a range of synthetically useful derivatives in convenient one-pot transformations (Scheme C).



Scheme C. Direct *α*-Imination of *N*-acylpyrazoles with nitrosoarenes and one-pot functionalization.

Finally we discovered that the use of esters, instead of acylpyrazoles, for reaction with nitrosoarenes leads to interesting results: depending on the substituents in the aromatic ring of the esters, and therefore on the acidity of the α-proton, our catalytic system afforded nitrones and imines with good selectivity in most cases (Scheme D). Our protocol enables a facile access to nitrones and imines working under mild reaction conditions and with readily available reagents. Nitrones are useful starting materials in cycloaddition reactions for the formation of nitrogen-based heterocycles.



Scheme D. Synthesis of nitrones and imines through the reaction of arylacetic esters and nitrosoarenes.