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TANDEM MICHAEL REACTIONS FOR THE CONSTRUCTION OF PYRROLIDINE AND PIPERIDINE RING SYSTEMS

Achille Barco[a], Simonetta Benetti[a], Alberto Casolari[b], Gian Piero Pollini[b] and Giampiero Spalluto[a]
[a]Dipartimento di Chimica- Via L. Borsari 46, 44100, Ferrara
[b]Dipartimento di Scienze Farmaceutiche- Via Scandiana 21, 44100 Ferrara

Summary: A convergent one-pot construction of disubstituted pyrrolidine and piperidine frameworks has been accomplished through a simple protocol involving intermolecular conjugate addition of a nitrogen nucleophile to an electrophilic olefin followed by intramolecular trapping of the generated enolate by a built-in α,β-unsaturated acceptor.

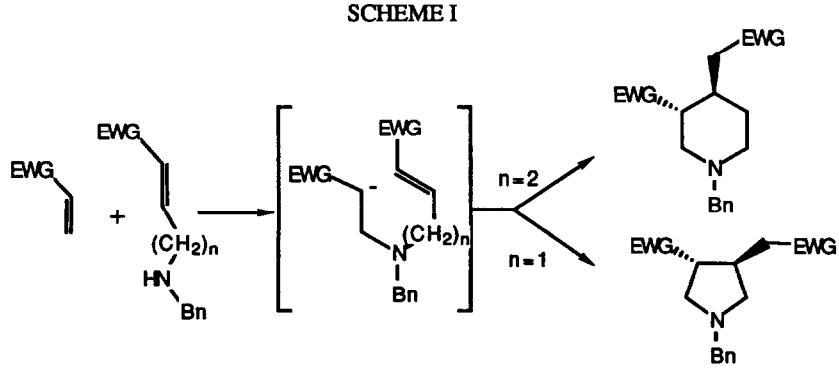
Many natural products contain pyrrolidine and piperidine substructures and so the development of methods for preparing five- and six-membered nitrogen heterocycles has received much attention.

The most common methodologies utilized to gain access to these materials entail pericyclic reactions such as the ene reaction[1], 1,3-dipolar cycloadditions[2] and sigmatropic rearrangements[3] as well as intramolecular cationic[4], anionic[5] or radical[6] promoted heterocyclizations.

Recently, several groups have reported efficient variants of Michael-Michael ring closure procedures for the preparation of functionalized cyclic rings[7]. However, most of this work is confined to the cyclization by carbon nucleophiles, less attention being directed towards nitrogen nucleophiles.

As a part of our ongoing interest in the area of neuroexcitory amino acids we were intrigued to evaluate the feasibility of a conceptually simple approach to five- and six-membered nitrogen heterocycles involving intermolecular conjugate addition of a nitrogen nucleophile to an acceptor molecule to generate an enolate intermediate, which is subsequently captured intramolecularly by the built-in α,β-unsaturated acceptor leading to cyclization as indicated in the Scheme I.

SCHEME I

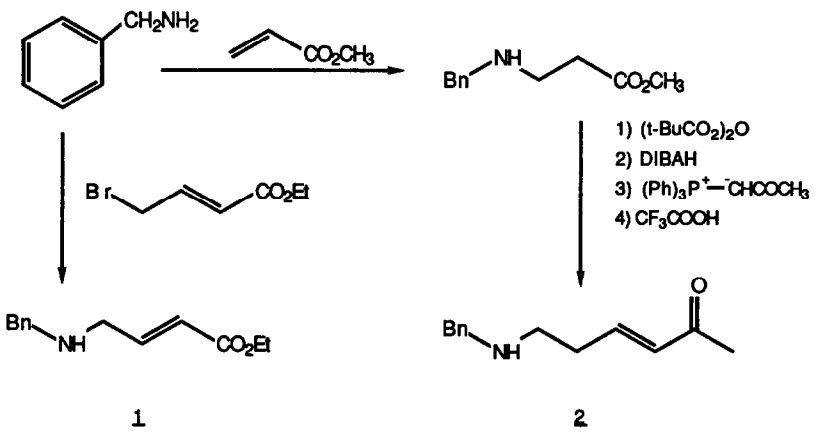


In this letter we report the successful execution of this strategy which allows a convergent construction of substituted pyrrolidine and piperidine frameworks in a very convenient one-pot procedure.

According to the Scheme I, the opening step called for the preparation of two subunits, such as 1 and 2, containing both the Michael donor nitrogen nucleophile and a suitably located acceptor moiety.

This task has been accomplished in a straightforward manner for 1 through the reaction of benzylamine with ethyl 4-bromo-2-butenoate, while the preparation of 2 has been realized, again starting from benzylamine, by standard steps as illustrated in the Scheme II.

SCHEME II

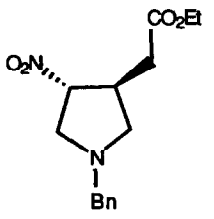


1 2

We chose secondary benzylated amines as partners for cyclization since preliminary experiments indicated that primary amines afford mixture of mono- and bis-adducts in the intermolecular step. Moreover, chiral building-blocks could be derived by alkylation of readily available optically active phenethylamines.

The second donor-acceptor subunit should be characterized by a carbon-carbon double bond conjugated with an electron-withdrawing group, which could be transformed or removed at a later stage after heterocyclic ring formation.

The well known versatility of the nitro group suggested the choice of nitroethylene for a model study, its propensity to anionic polymerization in the presence of aliphatic amines being overcome by its generation *in situ* from 1-benzoyloxy-2-nitroethane[8]. Thus, treatment of equimolecular amounts of the latter with both 1 and 2 at room temperature led to the direct formation of the corresponding cyclization products 3 and 4 in good yield after flash chromatography[9].



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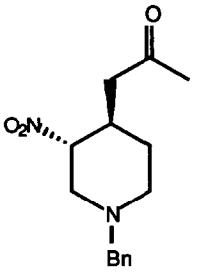

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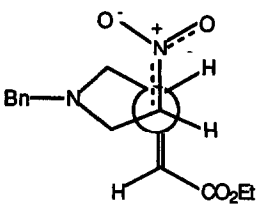
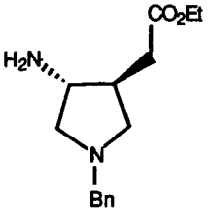
The stereospecific course[10] of the sequence leading to a trans-arrangement of the two substituents in the heterocycle can be explained by the intramolecular Michael addition taking place through the transition state A, depicted for the formation of 3 , with an antiperiplanar orientation between the nitro group and the acceptor chain[11]. The same stereochemical outcome has been observed by Bunce et al[7b] in related carbocyclizations.



A



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Moreover, chemical proof of the trans-relationship of the nitro group and the acetic chain rests on the reluctance of the derived amino-ester 5 to undergo intramolecular lactamization, in sharp contrast with the facile aminolysis of γ-aminoesters to form γ-butyrolactams.

In summary, the present methodology provides a new and promising access to functionalized pyrrolidines and piperidines, which could be extended to the synthesis of biologically active compounds.

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8. The utility of β-acetoxynitro precursors for the *in situ* generation of nitroalkenes has been previously experienced: D.H.R. Barton, S.Z. Zard, J. Chem. Soc. Commun., 1985, 1098.
9. Satisfactory analytical and spectroscopic data have been obtained for all new compounds.
10. The ^{1}HNMR integration of both crude reaction mixtures reveals the presence of a minor product (20:1) identified as the cis-isomer.
11. The same ratio of cyclized products has been obtained by reaction of 1-phenyl-1-nitroethylene, generated *in situ* from 2-benzoyloxy-1-phenyl-1-nitroethane, and 1. Therefore the possibility of stereochemical equilibration via a reverse Michael reaction in the cyclization step or through basic epimerization appears unlikely.

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