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α-Cyclization of Tertiary Amines. Part 1.

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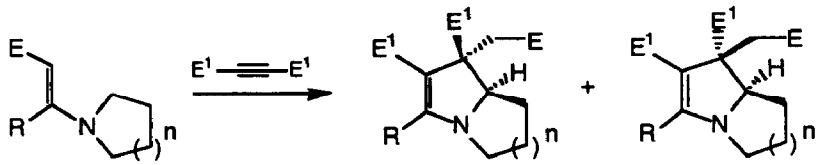
In memory of Qin Wenbi.

Abstract: A general, diastereoselective synthesis of functionalised pyrrolidine, indolizidine, pyrrolizidine and its seven-, eight-membered homologues is reported, starting from readily available enamine esters and acetylenedicarboxylate (DMAD).

This report describes a general, diastereoselective synthesis of a substituted pyrrolidine and its fused five-, six-, seven-, and eight- membered bicyclic homologues starting from enamines and acetylenedicarboxylate (DMAD) : we call this process "*α-Cyclization of Tertiary Amines*" (Scheme 1).

Scheme 1



1 **2** (44 - 72 %)

n = 1, 2, 3, 4 ; and diethylamine

E = CO_2Me, CO_2Et ; E^1 = CO_2Me

R = H, CH_3, Ph

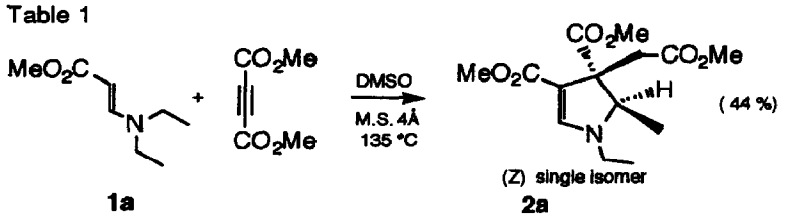
This mechanistically intriguing and synthetically useful cyclization has received little attention in the literature. It is established, though, that certain tertiary anilines or enamines having an electrophilic double bond in β-position undergo thermal ring-closure leading to annulated pyrrolidines or piperidines provided that a rigid and mostly cyclic system is present. Suschitzky and Meth-Cohn[1] have coined the term "tert-amino effect" for such processes which have been further developed by Reinhoudt and Verboom[2].

We wish to report on the extension of such cyclizations to the aliphatic tertiary enamine ester **1a** and to enamines carrying not only the common five- and six-membered rings **1b-1e** but also those with larger rings **1f** and **1g**. All enamine esters **1** may be conveniently prepared from propiolate esters and the corresponding secondary amines.

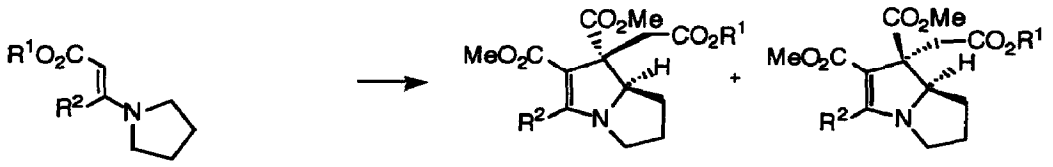
β-Aminoacrylates **1** when heated with DMAD in DMSO in the presence of molecular sieves(4Å) at 135°C for about 24hrs furnish the cyclised products **2a-2g** in mostly good yields[3] (Table 1). The intermediate dienes **3** can be isolated when the reaction is run for 1 hr. When the ester group in **1** is an

ethoxycarbonyl function it appears at the end of the aminodiene chain or at the methylene side-chain of the ring in **2**[4]. This fact indicates that the reaction proceeds first via a (2+2) cycloaddition leading to aminocyclobutenes. The latter undergo spontaneous ring-opening thereby leading to aminodienes **3** (Scheme 2).

Table 1

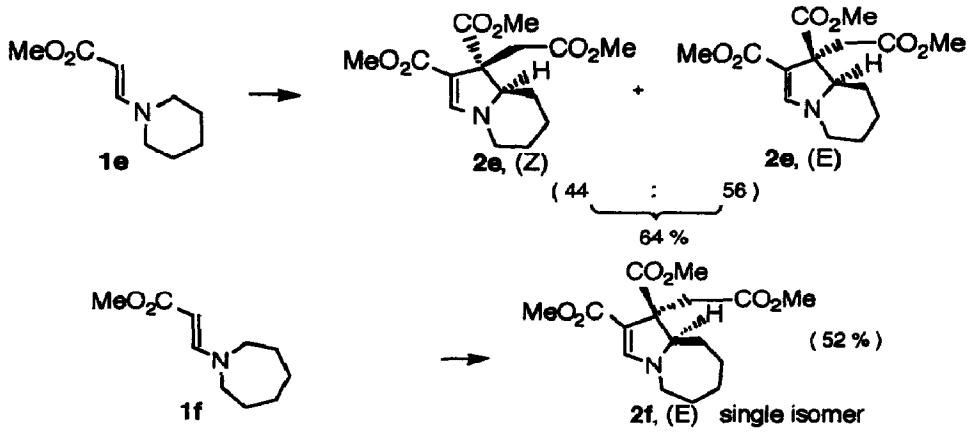


1a **2a**



1b - 1d **2b - 2d**

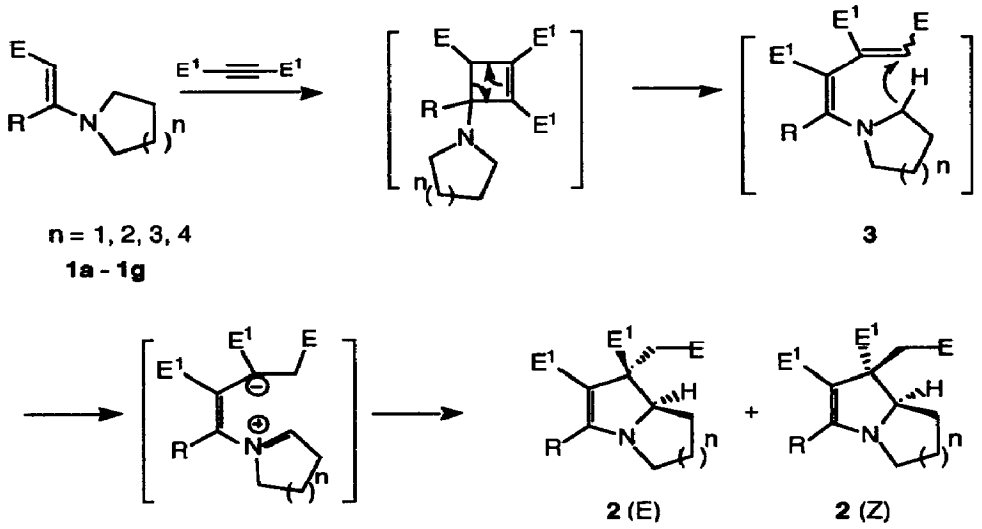
Entry	Substrate	R^1	R^2	Products (ratio)	Yield
1	**1b**	Me	H	**2b**, (Z) **2b**, E (6 : 94)	70%
2	**1c**	Et	Me	**2c**, (Z) **2c**, (E) (36 : 64)	72 %
3	**1d**	Et	Ph	**2d**, (Z) single isomer	67 %



1e **2e**, (Z) **2e**, (E)

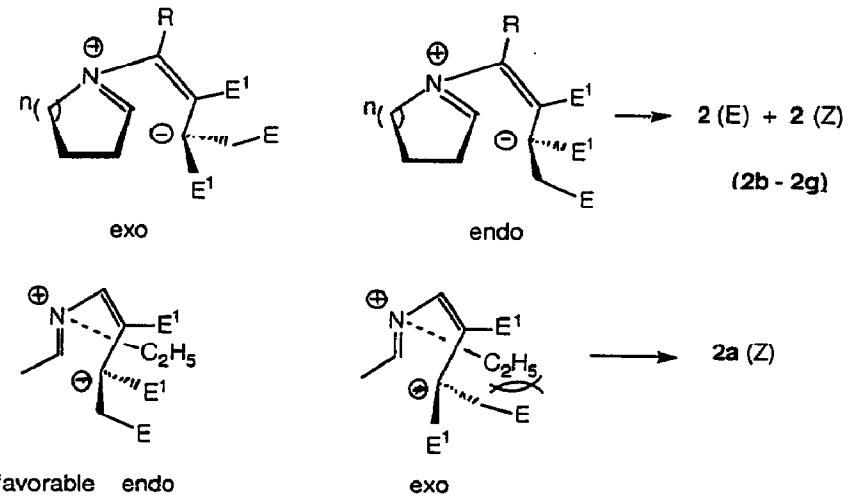
1f **2f**, (E) single isomer

Scheme 2



Subsequently, on heating apparently an internal redox process takes place to generate a 1,5-dipole through a hydrogen shift[5], followed by ring-closure to the observed products **2** (Scheme 2). Interestingly, this cyclization proceeds in a diastereoselective fashion (**2a,2d,2f,2g**) where single diastereomers are detected and **2bE** largely predominates[6]. This shows that sterically well-defined transition states or intermediates are involved. In the cases of **1f** and **1g**, ring- closure takes place in the exo sense to avoid the steric interations between CH_2E group and the seven- and eight-membered rings giving rise to **2f**(E) and **2g**(E) exclusively (Scheme 3). The entries 1,2,3 illustrate also the favorable exo ring-closure, and the influence of the group R on the double bond, the bulk of which competes with that of the CH_2E moiety. Thus with R = phenyl **2d**(Z) is formed as a single isomer. In contrast to substrates with cyclic amines **1a** shows preference for the endo ring-closure to give **2a**(Z). Product **2a**(E) is absent because of the unfavourable steric interaction between the CH_2E group and the ethyl group in the exo fashion (Scheme 3). In brief, the carbocyclization of the 1,5-dipole proceeds in a favourable exo fashion when cyclic amines are employed, but when the R group is bulky endo cyclization predominates. Ring-closure in an endo sense takes place when open-chain amines are used.

Scheme 3



In summary, we have demonstrated that a simple procedure using readily available β-tertiary enaminoesters and DMAD affords functionalised pyrrolidine, pyrrolizidine, indolizidine and its seven-, eight-membered homologues with high stereoselectivity. The key-step in this protocol is the thermal "*α-Cyclization of Tertiary Amines*" by internal redox process via electron-poor dienes.

References and notes

1. Suschitzky, H; Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1972**, *14*, 211.
2. Verboom, W; Reinhoudt, D.N. *Recl. Trav. Chim. Pay-Bas.* **1990**, *109*, 311 and references cited therein.
3. Typical procedure is following: A solution of DMAD (1.2 mmol) in 3 ml of DMSO is added dropwise to a solution of β-tert-amino acrylates (1 mmol) in 4 ml of DMSO in the presence of 4 g of molecular sieves (4Å) at room temperature. The mixture is stirred for 22 hrs at 135°C, and then 20 ml of ethyl acetate are added and the mixture is filtered through celite and washed with water. The organic phase is dried over $MgSO_4$. After removal of the solvent, flash chromatography of the residue (silicagel, hexane/ethyl acetate 5:4) afforded pure products. Satisfactory MS, IR, ^1H NMR, ^{13}C NMR are obtained for all products.
4. The structure of **2d** and its stereochemistry are determined by X-ray diffraction, and will be published later.
5. A simple intramolecular hydrogen transfer between tertiary amines and non-conjugated electron-deficient olefins was reported : ten Broeke, J.; Douglas, A.W; Grabowski, E.J.T. *J. Org. Chem.* **1976**, *41*, 3159.
6. The diastereoisomers were assigned on the basis of ^1H NMR with agreement of X-ray structure analysis, as in the case of **2d**.

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