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Tetrahedron Letters 45 (2004) 1567–1570

Tetrahedron Letters

An expedient synthesis of diversified pyrrolizines and indolizines

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Received 14 October 2003; revised 7 November 2003; accepted 18 November 2003

Abstract—A general and rapid synthesis of new families of pyrrolizines and indolizines in good overall yields via an intramolecular [3+2] cycloaddition reaction is described. Diversity of substitutions can be achieved by the appropriate choice of readily available starting materials. The experimental procedures are straightforward and are performed under neutral conditions. New syntheses are also described for the preparation of *N*-propargylic 2-amino-benzaldehydes and *S*-propargylic 2-thiobenzaldehydes.

Indolizines and pyrrolizines are compounds generally associated with pharmaceutical activities[1] such as anti-inflammatory (oxygenase inhibitors), anti-tumour (alkylating) agents or even CNS activity (Fig. 1). Amongst these important properties, however, selectivity in biological activity cannot be modulated in order to allow improvement in their activity or toxicity. Access to structural analogues and new classes of compounds by methods allowing the synthesis of diversely substituted derivatives would be an important target for research in medicinal chemistry. Although some methods[2] have been reported describing the preparation of such compounds, often they are limited to the synthesis of specific examples. We report here the synthesis of variously substituted tetracyclic (hydro)-pyrrolizines and indolizines (Fig. 1) by choice, using a general method. The process makes use of commercial or readily available starting materials, which allow the introduction of diversity and the parallel preparation of numerous derivatives. The capacity for diversity by this method is illustrated by the synthesis of compounds belonging to new structural families. The added functionalities and rigidification of the structure could modulate bioavailability or activity.

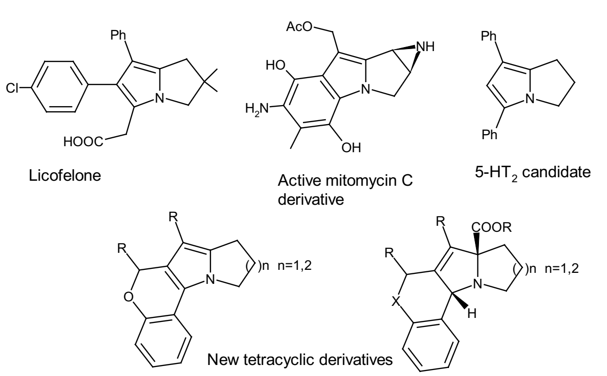

Figure 1. Pyrrolizines and indolizines with potential biological activity.

The [3+2] dipolar cycloaddition reaction involving azomethine ylides is a useful tool for the synthesis of aza heterocycles. These ylides are 1,3-dipolar species, which can be either stabilized or non-stabilized and can undergo cycloadditions with a variety of alkynes, including non-activated examples to provide pyrrolines and pyrroles efficiently[3] (Scheme 1).

We applied an intramolecular [3+2] cycloaddition wherein the azomethine ylides were generated in the presence of the required alkyne moiety. In this manner, contrary to intermolecular cycloadditions, the regiochemistry and substitution pattern is totally controlled. Both types of ylides were prepared in situ, the non-stabilized examples being derived from the condensation of α-amino acids with aldehydes, while the stabilized examples are obtained by condensation with α-amino esters.

The *O*-propargylic salicylaldehydes **1a–d** were prepared by conventional methods, usually in quantitative yields, from salicylaldehyde and a propargylic halide in dimethylformamide (DMF) in the presence of potassium carbonate. The condensation and intramolecular

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Keywords: Pyrrolizines indolizines diversity.

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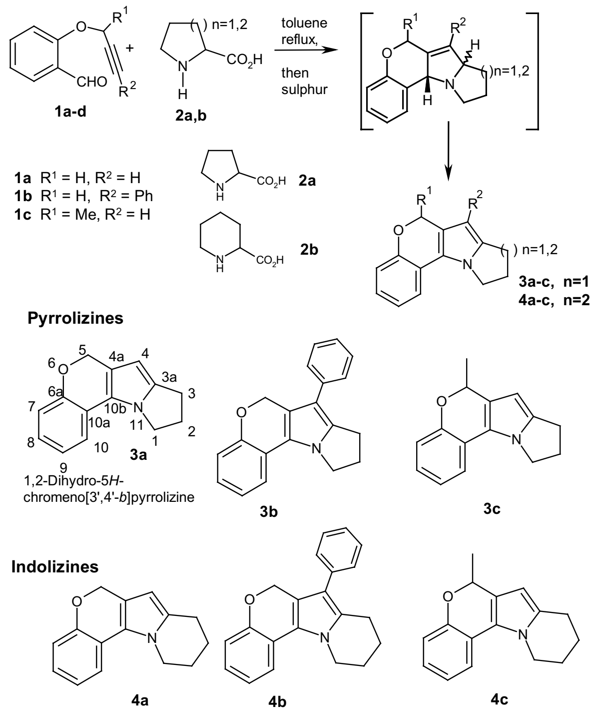
doi:10.1016/j.tetlet.2003.11.146



Scheme 1. Cycloaddition with α-amino acids—one-pot synthesis of dihydropyrrolizines and tetrahydroindolizines.

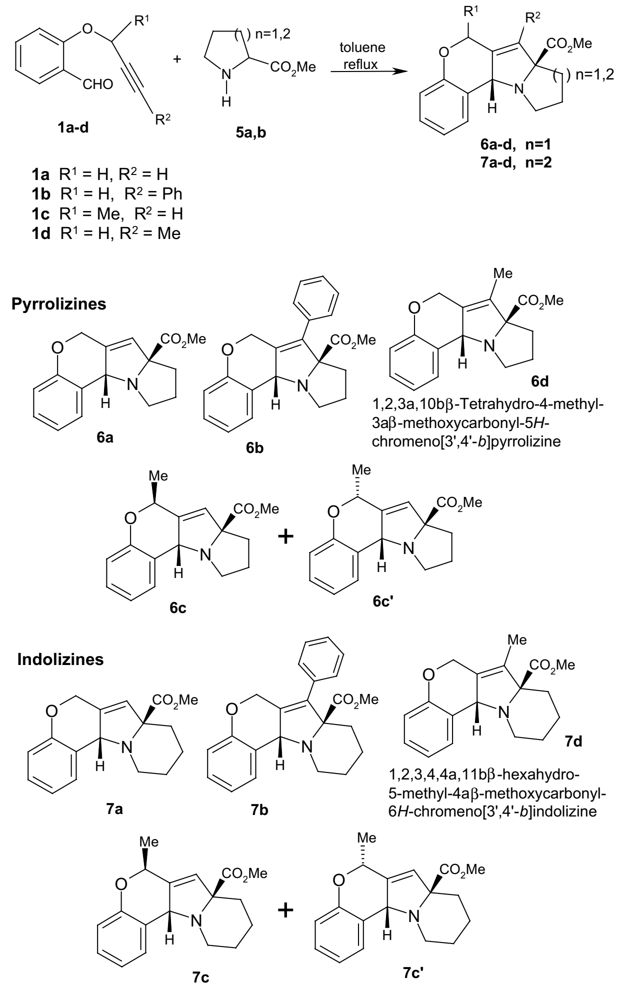
cycloaddition of these salicylaldehyde derivatives with α-amino acids **2a**,**b** gave the expected pyrroline intermediates (Scheme 1). The diastereoisomers (ratio 1/1) were not systematically isolated, although it is indeed possible to do so for structural characterization, and the crude reaction mixture was treated with sulfur[4] in toluene at reflux to give new tetracyclic pyrroles **3a**–**c** and **4a**–**c**. This one-pot procedure provided the required dihydropyrrolizines and tetrahydroindolizines in good overall yields (Table 1).

The cycloaddition of stabilized azomethine ylides generated from aldehydes **1a**–**d** and methyl prolinate **5a** or methyl pipecolinate **5b** (Scheme 2, Table 2) on heating in refluxing toluene provided cycloadducts derived from the anti-dipole[6] in good yields. These new tetrahydropyrrolizines **6a**–**d** and hexahydroindolizines **7a**–**d** possessing a quaternary carboxylic group all had the same stereochemistry in which the angular (**10b** or **11b**) proton and the quaternary carboxylic group are *cis* to one another. In the case of the secondary *O*-(1-methylpropargyl)salicylaldehyde **1c** (entries 3 and 7), cycloaddition with the two amino esters led to two diastereoisomeric adducts **6c**/**6c**′ and **7c**/**7c**′, each in a 1:1 ratio in which only the methyl substituents (C-5 or C-6) are of opposite configuration.

Table 1. One-pot synthesis of pyrrolizines and indolizines

Entry	Aldehyde/ amino acid	Time[a]	Product[5]	Yield (%)
1	**1a/2a**	2 h+4 h	**3a**	71
2	**1b/2a**	2 h+3 h	**3b**	69
3	**1c/2a**	3 h+4 h	**3c**	66
4	**1a/2b**	4 h+4 h	**4a**	75
5	**1b/2b**	4 h+4 h	**4b**	73
6	**1c/2b**	4 h+4 h	**4c**	64

[a] Heat **1** and **2** in toluene, then add sulfur and heat.

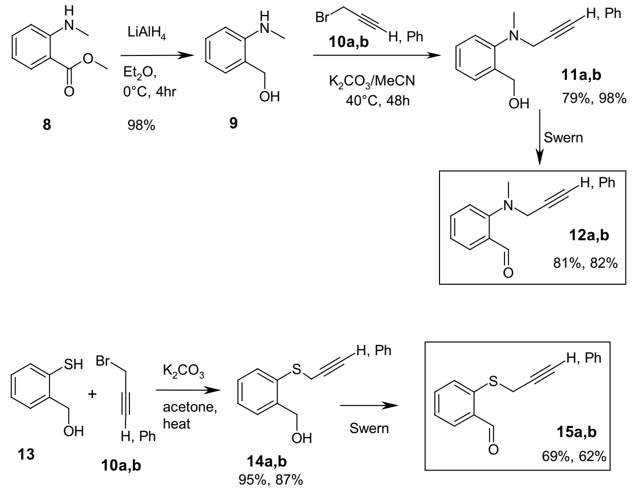


Scheme 2. Cycloaddition with α-amino esters—carbomethoxy pyrrolizines and indolizines. (For reasons of clarity, only one of the *cis* enantiomers is depicted.)

Table 2. Oxa-pyrrolizines and -indolizines

Entry	Aldehyde/ amino ester	Time (h)	Product	Yield (%)
1	**1a/5a**	2	**6a**	77
2	**1b/5a**	2	**6b**	91
3	**1c/5a**	3.5	**6c**/**6c**′	82
4	**1d/5a**	4	**6d**	74
5	**1a/5b**	3	**7a**[2d]	76
6	**1b/5b**	3	**7b**	94
7	**1c/5b**	4	**7c**/**7c**′	70
8	**1d/5b**	6	**7d**	80

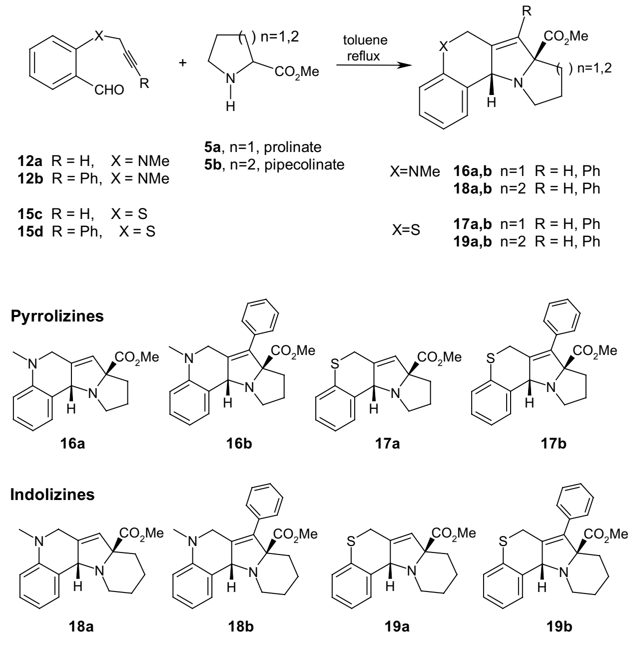
As an extension to this work, we wished to study the condensations using other heteroatom-containing propargylic derivatives for which we describe new syntheses (Scheme 3). We thus prepared *N*-propargylic 2-aminobenzaldehydes **12a**,**b** and *S*-propargylic thio-



Scheme 3. Preparation of propargylic benzaldehydes.

salicylaldehydes **15a**,**b**, which then underwent the same condensations as described above with α-amino esters **5a** and **5b**. These examples led to the stereoselective synthesis of a new series of aza- and thia-tetrahydropyrrolizines **16a**,**b** and -hexahydroindolizines **18a**,**b** possessing a chiral quaternary carboxylic moiety. (Scheme 4).

The *N*-propargylic 2-aminobenzaldehydes **12a**,**b** were prepared from methyl anthranilate[7] in a three-step sequence, starting with lithium aluminium hydride ($LiAlH_4$) reduction to the benzylic alcohol **9** followed by *N*-alkylation with the appropriate propargylic halide **10a**,**b**, then Swern oxidation to the required benzaldehyde. The two compounds **12a** and **12b** were obtained in overall yields of 63% and 79%, respectively.



Scheme 4. Aza- and thia-pyrrolizines and indolizines.

Table 3. Aza- and thia-pyrrolizines and -indolizines

Entry	Aldehyde/ amino ester	X	Time (h)	Product	Yield (%)
1	**12a/5a**	NMe	2	**16a**	68
2	**12b/5a**	NMe	2	**16b**	76
3	**15a/5a**	S	2	**17a**	68
4	**15b/5a**	S	2	**17b**	75
5	**12a/5b**	NMe	4	**18a**	81
6	**12b/5b**	NMe	4	**18b**	83
7	**15a/5b**	S	4.5	**19a**	65
8	**15b/5b**	S	4	**19b**	74

The *S*-propargylic 2-thiobenzaldehydes **15a**,**b** were prepared in a similar manner from 2-mercaptobenzyl alcohol **13** by *S*-alkylation then Swern oxidation. The overall yields of **15a** and **15b** were 67% and 54%, respectively.

The 2-*N*- and 2-*S*-propargylic benzaldehydes **12** and **15** thus obtained were treated with methyl prolinate or methyl pipecolinate in toluene at reflux for 2–4 h. With no other workup other than cooling and evaporation of the solvent, the crude mixtures were purified by column chromatography to provide single diastereomeric aza- and thia-compounds in good yields ranging from 65% to 83% (Table 3).

The added physical and electronic effects of the different heteroatoms in the compounds described in this work can have varying effects on possible biological activities in these series. Most importantly, though, we are currently taking advantage of the chemical properties of these compounds.

In conclusion, we report a rapid synthesis of new families of pyrrolizines and indolizines in good overall yields via an intramolecular [3+2] cycloaddition reaction. The method is general and diversity of substitutions can be achieved by the appropriate choice of readily available starting materials. The experimental procedures are straightforward and are performed under neutral conditions. New syntheses are also described for the preparation of *N*-propargylic 2-amino-benzaldehydes and *S*-propargylic 2-thiobenzaldehydes.

Acknowledgements

G.B. wishes to thank the Centre National pour la Recherche Scientifique (CNRS) for a grant (“Aide Jeune Equipe”).

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5. Typical experimental procedure: Secondary-amino acid (5 mmol) and *O*-propargylic salicylaldehyde (2.5 mmol) were stirred and heated in toluene (15 mL) at reflux. When carbon dioxide gas evolution had ceased and starting aldehyde had been consumed (TLC), sulfur powder (12.5 mmol) was added and heating was continued for approximately 1 h or until completion (TLC). After cooling, the crude mixture was filtered and the solvent removed under reduced pressure. The expected pyrrolizine or indolizine was purified by column chromatography on silica gel (dichloromethane/pentane 1:1): Example compound **3a** (1,2-dihydro-5*H*-chromeno[3′,4′-*b*]pyrrolizine): ^{1}H NMR (300 MHz, CDCl$_3$): 7.21 (dd, 1H, H-10, *J* 7.4 and 1.6 Hz); 6.98 (dd, 1H, H-8, *J* 7.1 and 1.7 Hz); 6.92–6.84 (m, 2H, H-7 and H-9); 5.63 (s, 1H, H-4); 5.25 (s, 2H, 2H-5); 4.13 (m, 2H); 2.82 (m, 2H); 2.54 (quint, 2H, 2H-2, *J* 7.2 Hz); ^{13}C NMR 75 MHz (CDCl$_3$): 152.0 (C$_{6a}$); 139.5 (C$_{3a}$); 125.8 (C$_8$); 121.2 (C$_9$); 119.5, 118.9 and 118.8 (C$_{10a}$, C$_{4a}$ and C$_{10b}$); 118.8 (C$_{10}$); 116.6 (C$_7$); 95.4 (C$_4$); 66.4 (C$_5$); 46.3 (C$_1$); 28.0 (C$_2$); 23.7 (C$_3$).
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