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Synthesis of Cyclic Enehydrazides by Ring-Closure Metathesis. Application to the Enantioselective Synthesis of 2-Alkyl and Aryl Piperidines

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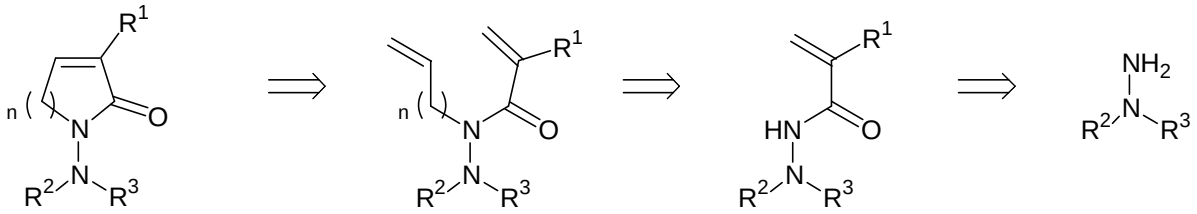
Introduction

During the past decade the ring-closing metathesis (RCM) reaction has emerged as a powerful synthetic tool for the creation of carbon-carbon bonds and this annulation technique ranks henceforth highly in the hierarchy of synthetic tactics for the elaboration of a wide array of unsaturated heterocycles [1]. Paradoxically, the synthesis of small- and medium-sized azaheterocycles such as unsaturated five- and six-membered hydrazides, **1-3** and **4** respectively, that includes this versatile technique as the synthetic key-step, has not been investigated in detail [2]. The rising interest in these classes of azacycles as putative pharmaceuticals, namely as potent potassium channel activators [3], prompted us to develop a synthetic sequence leading to this class of compounds via a RCM approach.

Retrosynthetic Approach

Our straightforward strategy towards the azacycles **1-3** (n = 1) and **4** (n = 2) hinges upon the annulation of the dienic hydrazides **5-8** which could be in turn assembled by sequential N-alkylation of enehydrazides **9-11** and N-acylation of the appropriate hydrazines **12-14**.

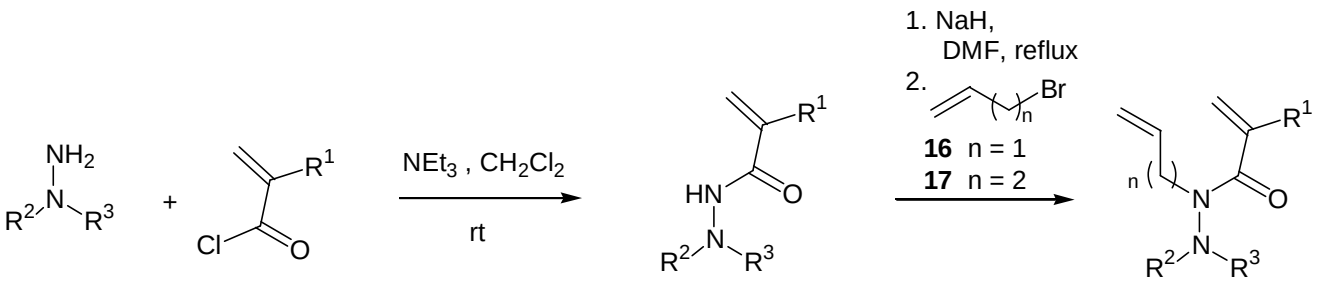


1-3, 4 **5a,b-8a,b** **9a,b-11a,b** **12-14**

Retrosynthetic Scheme.

Results and Discussion

1. Synthesis of the parent N-alkenyl-N-acylhydrazines 5-8

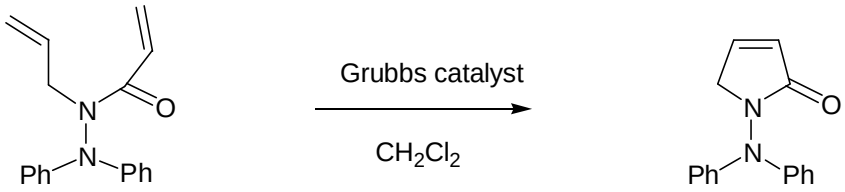


12-14 **15a** **15b** **9a-11a** **9b-11b** **5ab-7a,b** n = 1 **8a,b** n = 2

	R^1	R^2	R^3	n	Yield (%)
12	-	Ph	Ph	-	-
13	-	$(CH_2)_5$		-	-
14	-	$(CH_2)_3$-CH(CH_2OMe)		-	-
9a	H	Ph	Ph	-	91
9b	Me	Ph	Ph	-	93
10a	H	$(CH_2)_5$		-	87
10b	Me	$(CH_2)_5$		-	90
11a	H	$(CH_2)_3$-CH(CH_2OMe)		-	85
11b	Me	$(CH_2)_3$-CH(CH_2OMe)		-	81
5a	H	Ph	Ph	1	80
5b	Me	Ph	Ph	1	81
6a	H	$(CH_2)_5$		1	78
6b	Me	$(CH_2)_5$		1	75
7a	H	$(CH_2)_3$-CH(CH_2OMe)		1	79
7b	Me	$(CH_2)_3$-CH(CH_2OMe)		1	72
8a	H	Ph	Ph	2	57
8b	Me	Ph	Ph	2	55

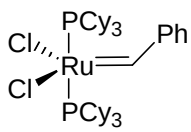
2. Determination of experimental conditions for the optimal formation of the annulated compounds

In order to ensure the optimal formation of the target cyclic enehydrazides **1-4**, variation of the nature of the catalyst, the amount of ruthenium catalyst, temperature profile and time were screened. The diolefinic hydrazide **5a** was chosen as the starting material and only the commercially available Grubbs catalysts **18** and **19** were employed.

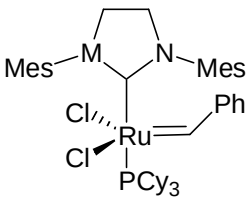


5a **1a**

Catalyst	Reaction Time (h)	T (℃)	Yield (%)
Grubbs 1st generation 5 mol %	36	20℃	0
Grubbs 1st generation 5 mol %	36	reflux	0
Grubbs 1st generation 15 mol %	36	reflux	20
Grubbs 2nd generation 5 mol %	**24**	**reflux**	**82**
Grubbs 2nd generation 3 mol %	24	reflux	55



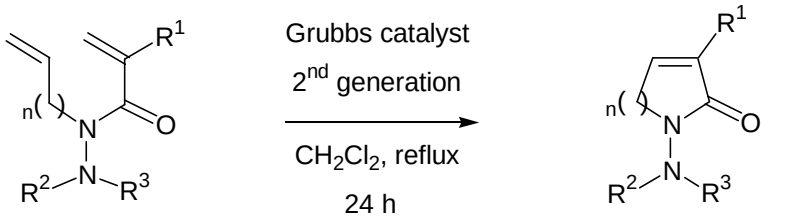
18
Grubbs catalyst
1st generation



19
Grubbs catalyst
2nd generation

The optimal conditions were subsequently used to perform the planned RCM of the acyclic enehydrazides **5a,b-8a,b**.

3. Synthesis of cyclic enehydrazides by ring-closure metathesis reaction



5a,b-7a,b n = 1
8a,b n = 2

1a,b-3a,b n = 1
4a,b n = 2

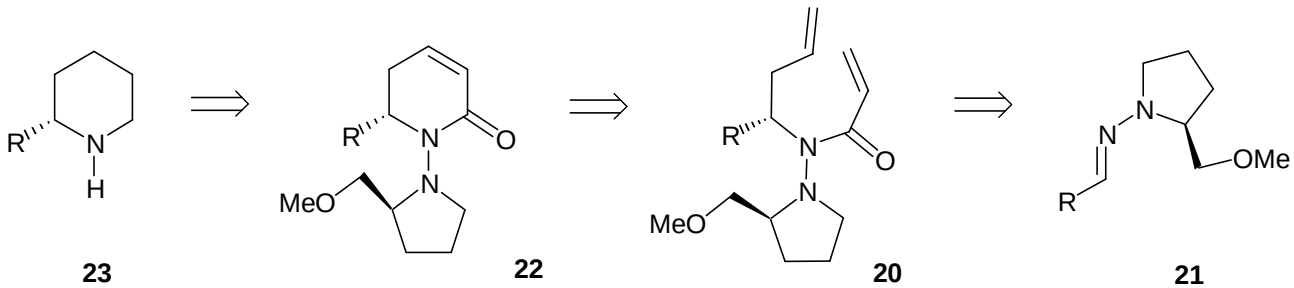
Starting Material	R^1	R^2	R^3	n	Product	Yield (%)
5a	H	Ph	Ph	1	**1a**	82
5b	Me	Ph	Ph	1	**1b**	76
6a	H	$(CH_2)_5$		1	**2a**	73
6b	Me	$(CH_2)_5$		1	**2b**	78
7a	H	$(CH_2)_3$-CH(CH_2OMe)		1	**3a**	84
7b	Me	$(CH_2)_3$-CH(CH_2OMe)		1	**3b**	80
8a	H	Ph	Ph	2	**4a**	72
8b	Me	Ph	Ph	2	**4b**	78

From the Table it can be seen that the method tolerates the presence of diversely substituted hydrazido groups. The synthetic sequence gives rise to a number of α,β-unsaturated lactam-type compounds which can be regarded as versatile building blocks for further synthetic planning toward a variety of 2-alkyl and 2-arylpiperidines.

Developments – Application to the Enantioselective Synthesis of 2-Alkyl and Aryl Piperidines

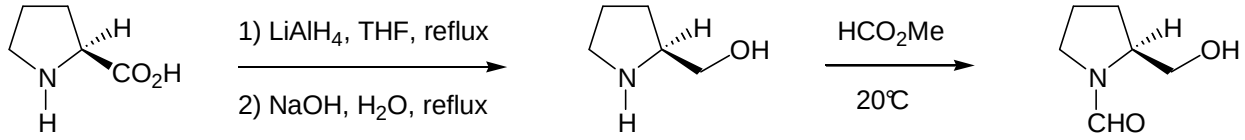
1. Retrosynthetic analysis

The key step of our conceptually new synthetic approach to the targeted compounds relies on the RCM reaction of diastereochemically pure olefinic hydrazides **20** deriving from the hydrazones **21** equipped with a chiral auxiliary.

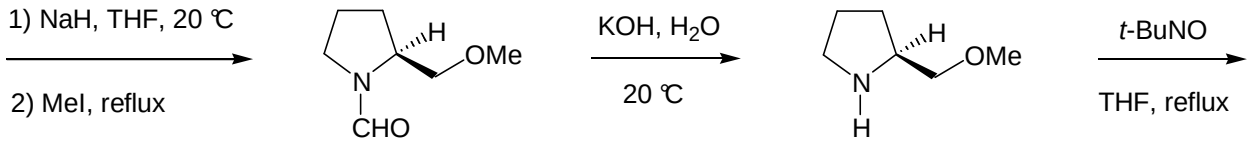


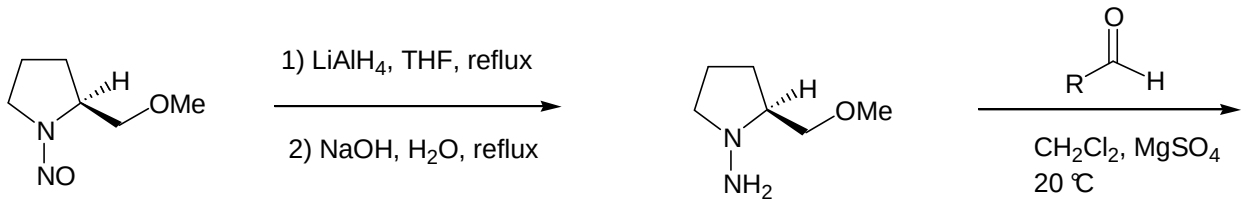
23 **22** **20** **21**

2. Synthesis of the N-acylhydrazines precursors **20**



(*S*)-proline

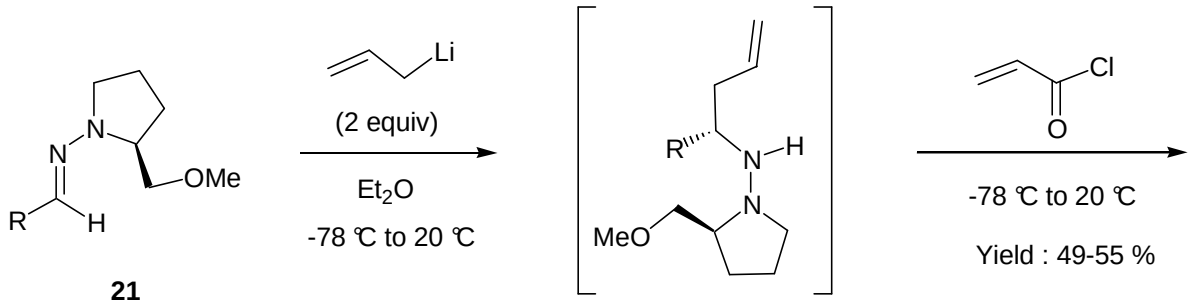




SAMP

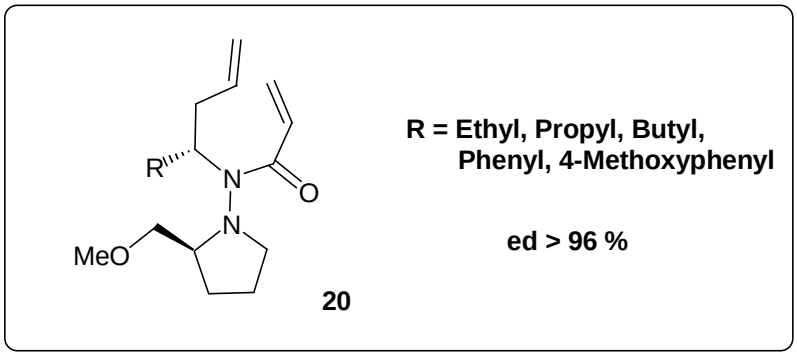
Yield : 88-95 %

(Yield from (*S*)-proline = 60 %)



21

Yield : 49-55 %

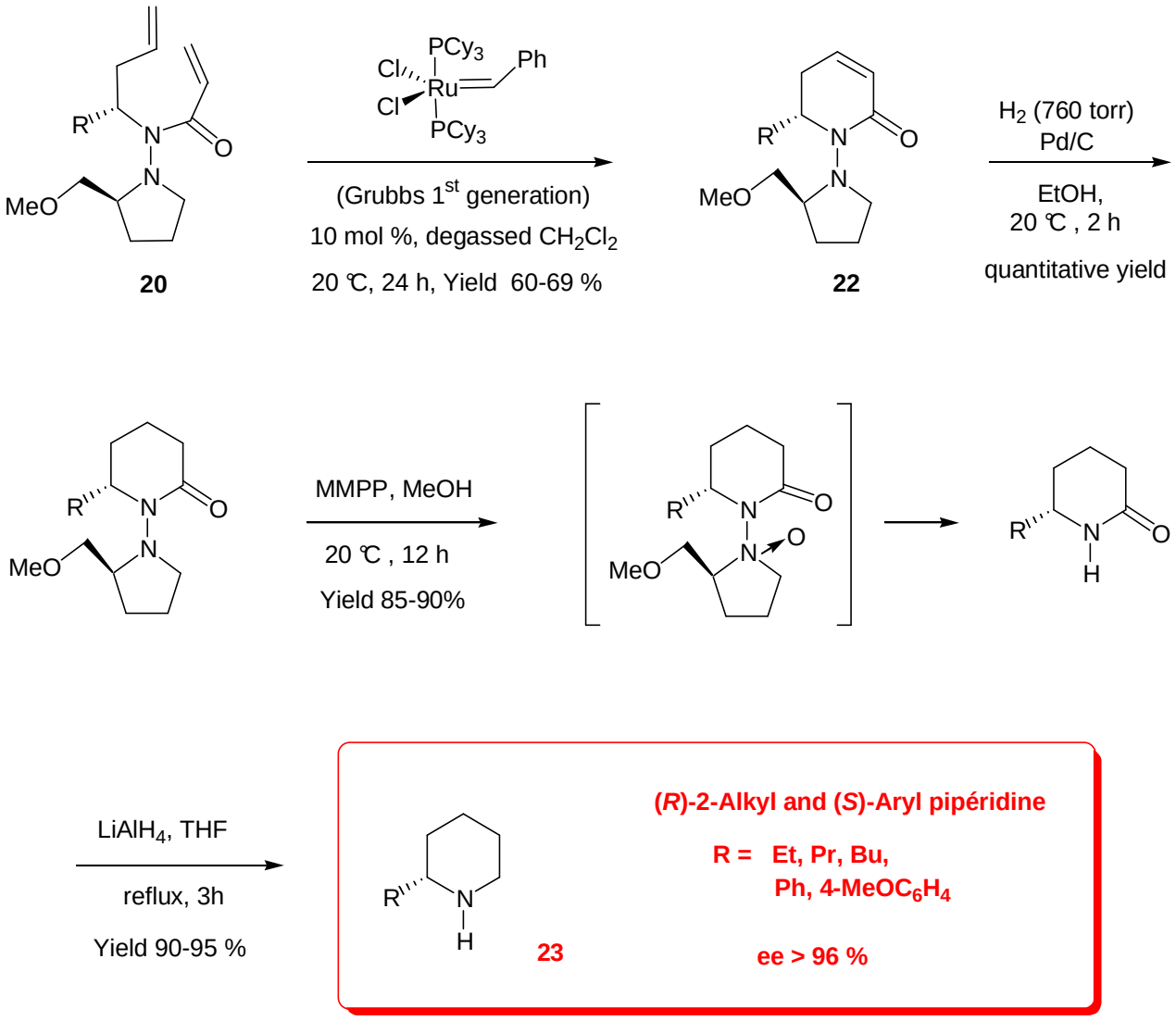


20

R = Ethyl, Propyl, Butyl, Phenyl, 4-Methoxyphenyl

ed > 96 %

3. Enantioselective synthesis of (R)-2-alkyl and (S)-2-arylpiperidines



Conclusion

In summary we have identified a novel and flexible synthetic approach to a variety of α,β-unsaturated *N*-(dialkyl and diarylamino)lactames (cyclic enehydrazides). The simplicity and the versatility of this new RCM process have been emphasized by the asymmetric synthesis of an array of 2-alkyl and arylpiperidines which were easily accessible through simple chemical transformation from the preliminary annulated compounds.

References

[1] For reviews, see: (a) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (b) Schultz-Fademrecht, C.; Deshmukh, P. H.; Malagu, K.; Procopiou, P. A.; Barrett, A. G. M. *Tetrahedron* **2004**, *60*, 7515. (c) Dieters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199.

[2] For reviews, see: (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (b) Campagne, J.-M.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 6175. (c) Nadin, A. *J. Chem. Soc., Perkin Trans 1* **1998**, 3493. (d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans 1* **1999**, 2553. (e) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans 1* **2000**, 2862. (f) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (g) Gonzáles-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002,** *43*, 4765. (h) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693. (i) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932. (j) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem*. **2004**, *69*, 8372.

[3] Matsumoto, Y.; Tsuzuki, R.; Matsuhisa, A.; Takayama, K.; Yoden, T.; Uchida, W.; Asano, M.; Fujita, S.; Yanagisawa, I.; Fujikura, T. *Chem. Pharm. Bull*. **1996**, *44*, 103.