Azepine Derivatives from Toadstools: The Development of New Syntheses for 3*H*- and 4*H*-Azepines

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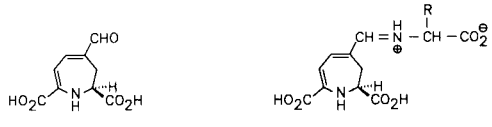
Toadstools and mushrooms produce a great variety of metabolites which often possess interesting structural and biological properties. In recent years some simple azepine derivatives have been isolated which pose specific synthetic problems.

Azepine Pigments from Toadstools.

Muscaflavin (**1**) is a minor component of the red cap skin of the fly agaric (*Amanita muscaria*) (Scheme 1) [1]. This chromoalkaloid is also responsible for the splendid yellow colors of some *Hygrocybe* species and occurs in the form of Schiff bases with amino acids in orange and red species of these toadstools [2]. The latter pigments, known as hygroaurins (**2**), are ill characterized due to their instability and the complexity of their naturally occurring mixtures. For the semisynthesis of hygroaurins a synthetic access to muscaflavin is therefore desirable. Unfortunately, Musso's biomimetic synthesis of **1** requires a large number of steps and gives the compound only in low overall yield [1,3].

Scheme 1

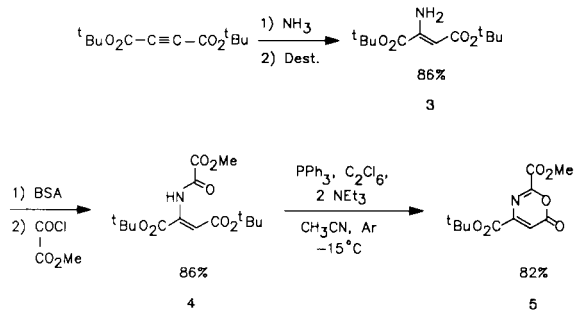


1 2

Synthesis of 4*H*-Azepines from 6*H*-1,3-Oxazin-6-ones and Cyclopropenes.

We therefore considered an alternative approach to this pigment based on the cycloaddition of a cyclopropene to a suitable 6*H*-1,3-oxazin-6-one derivative [4]. The desired oxazinone dicarboxylic ester **5** was prepared in high overall yield from di-*tert*-butyl-2-aminofumarate (**3**) (Scheme 2). N-Acylation of this compound after prior silylation of the weakly nucleophilic amino group afforded di-*tert*-butyl-2-methoxalylaminofumarate (**4**) which was then cyclized to oxazinone **5** by means of triphenylphosphine/hexachloroethane [4,5].

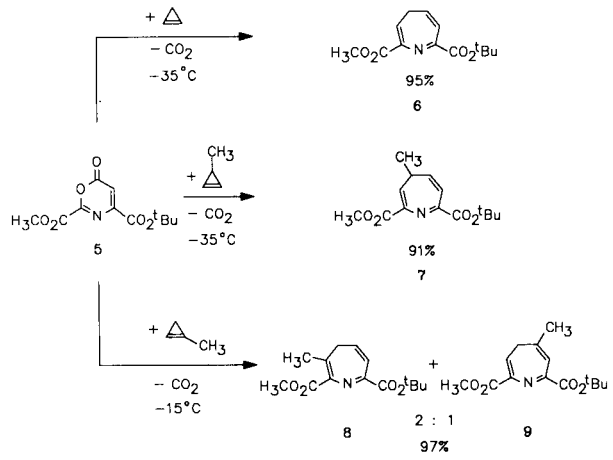
Scheme 2



3 4 5

The reaction of oxazinone **5** with cyclopropene and 3-methylcyclopropene at -35°C afforded the 4*H*-azepines **6** and **7**, respectively, whereas with 1-methylcyclopropene both regioisomers **8** and **9** were formed in nearly equal amounts (Scheme 3).

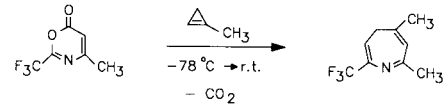
Scheme 3



6 5 7 8 9

In contrast, the reaction of 2-trifluoromethyl-4-methyl-6*H*-oxazin-6-one (**10**) with 1-methylcyclopropene proceeded regioselectively and gave only azepine **11** (Scheme 4) [4]. The lack of regioselectivity in the case of diester **5** may be explained by the counteracting electronic influence of the ester group at the 4-position of the oxazinone ring [4].

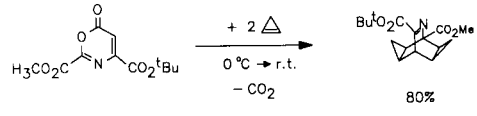
Scheme 4



10 11

Similar to the corresponding 1,2,4-triazines [6] the reaction between oxazinone **5** and cyclopropenes proceeds at 0-25°C with the formation of dimers, *e.g.* **12** (Scheme 5).

Scheme 5

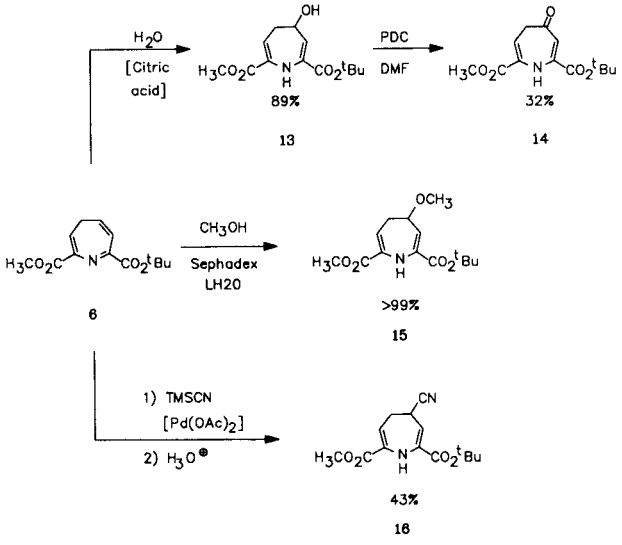


5 12

Some Reactions of 4*H*-Azepines.

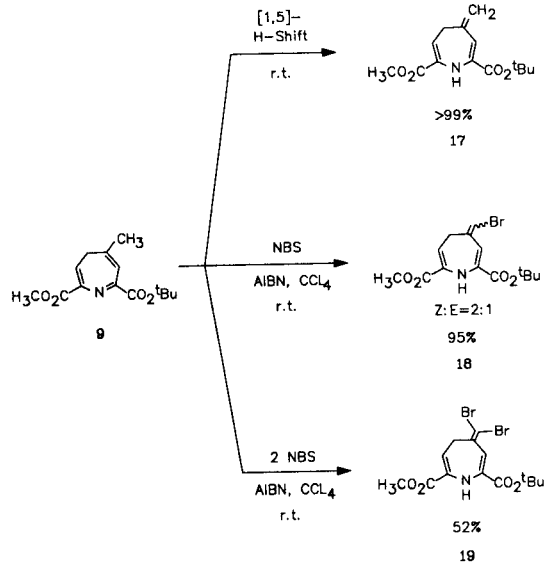
The 4*H*-azepine-2,7-dicarboxylic ester **6** undergoes smooth proton catalyzed 1,4-additions of nucleophiles (Scheme 6). Thus, on work-up with aqueous citric acid the hydroxy derivate **13** was obtained and on gel chromatography with methanol the adduct **15** was formed in quantitative yield. Addition of trimethylsilyl cyanide to **6** in the presence of palladium(II) acetate [7] afforded the nitrile **16**. Experiments to convert **16** into a cyano analogue of muscaflavin were unsuccessful as were efforts to use ketone **14** for the assembly of the muscaflavin system by attachment of a one-carbon unit.

Scheme 6



Interestingly, the 5-methyl derivative **9** underwent a smooth [1,5]H-shift on standing at room temperature under formation of the *exo*-methylene isomer **17** (Scheme 7). Similarly, treatment of **9** with *N*-bromosuccinimide yielded the mono and dibromo derivatives **18** and **19**, respectively, depending on the reaction conditions. The conversion of the new azepine derivatives into compounds with a muscaflavin chromophore is under active investigation.

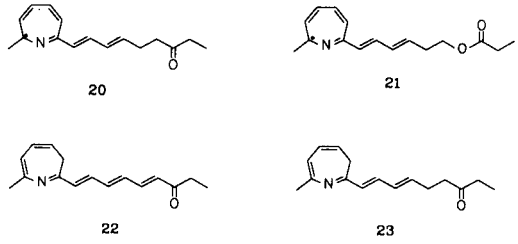
Scheme 7



Chalciporone and Related Azepine Alkaloids.

The bolete *Chalciporus piperatus* has a pungent taste which seems to repel insects and other animals. We have found that the main pungent principle is the 2*H*-azepine derivative chalciporone (**20**) (Scheme 8) [8]. It is accompanied by small amounts of pungent norchalciporyl propionate (**21**) and nonpungent dehydroisochalciporone (**22**). On prolonged nmr measurements in deuteriochloroform solution optically active **20** rearranges to nonpungent, achiral isochalciporone (**23**). The latter can also be isolated from the fruit bodies, however, it seems to be an artifact formed during the isolation procedure or on aging of the fruit bodies. It is interesting to note that both chalciporone and isochalciporone possess antibiotic activity against bacteria and fungi.

Scheme 8

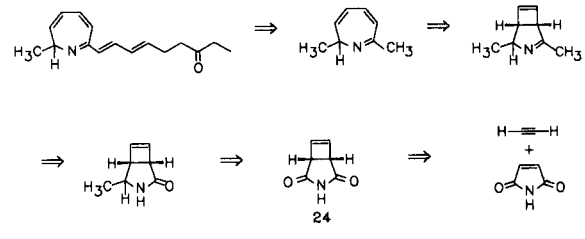


2*H*- and 3*H*-azepines have never been found in nature before. A literature research revealed that 3,5,7-triphenyl-2*H*-azepine is the only known synthetic example for a 2*H*-azepine derivative with hydrogen atoms at C-2 [9]. Whereas 3*H*-azepine itself has been synthesized by Vogel and co-workers [10], its 2-alkyl and 2,7-dialkyl derivatives are unknown. Most of the published compounds carry alkoxy or amino substituents at C-2 or owe their stability to the presence of phenyl groups or substituents which offer push-pull stabilization [11]. General syntheses of polysubstituted 3*H*-azepines based on cycloaddition reactions have been developed by Anderson and Hassner [12] and Sauer and co-workers [6].

3*H*-Azepines from 3-Azabicyclo[3.2.0]hepta-2,6-dienes.

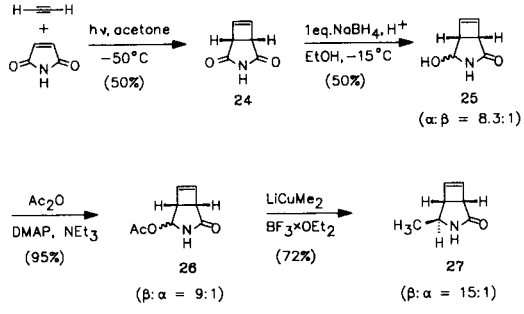
Stimulated by the interesting biological properties of chalciporone and its 3*H*-isomer we tried to develop general syntheses for simple 2*H*- and 3*H*-azepines. A retrosynthetic analysis suggested a synthetic pathway starting from the bicyclic imide **24** (Scheme 9).

Scheme 9



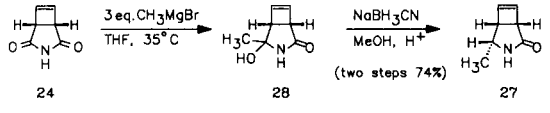
Compound **24** can be conveniently obtained in 100-200 g batches by irradiating maleimide and acetylene in acetone at –50°C in the presence of benzophenone (Scheme 10) [13,14]. Reduction of **24** to a mixture of the stereoisomeric hemiaminals **25** was achieved with one molequivalent of sodium borohydride in ethanol at -15°C [15]. On acetylation with acetic anhydride/DMAP **25** yielded a mixture of the epimeric acetates **26** in which the 2β-isomer predominated. Obviously, the 2α-acetate formed initially undergoes facile 1,2-elimination followed by addition of acetate from the less hindered β-face. Out of several methods tried for the exchange of the acetate residue against a methyl group, lithium dimethylcopper/boron trifluoride etherate [16] served best and afforded the 2β-methyl derivative of **27** in high yield. A small amount of the corresponding α-isomer can be removed by column chromatography.

Scheme 10



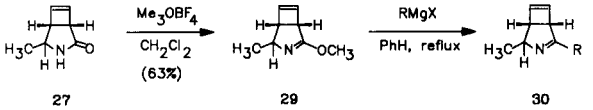
The 2α-isomer of **27** can be obtained by treatment of **24** in THF with an excess of methylmagnesium bromide (Scheme 11). Reduction of the resulting adduct **28** with sodium cyanoborohydride [17,18] afforded the pure 2α-isomer **27** in 74% overall yield.

Scheme 11



In order to attach the second side chain, the lactam group in **27** was converted into an imidate moiety by treatment with Meerwein's reagent (Scheme 12). The imidate **29** reacted with phenylmagnesium bromide to give the phenyl derivative **30c** in high yield. Unfortunately, the yields dropped considerably in the case of aliphatic Grignard reagents. Thus, the corresponding ethyl and propyl derivatives **30a** and **30b** were obtained in 24 and 51% yield, respectively. In the case of methylmagnesium bromide, only demethylation of **29** to the starting material **27** was observed [19]. Hopefully, the use of the corresponding thioimidate and an investigation of the full range of organometallic reagents for the coupling reaction will solve this problem.

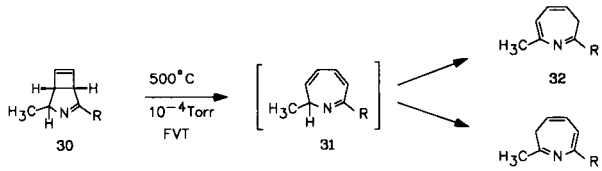
Scheme 12



30	a	b	c
R	Et	n–Pr	Ph
%	24	51	95

Conversion of the 3-azabicyclo[3.2.0]hepta-2,6-dienes **30** into azepines was achieved by flash vacuum thermolysis (FVT) at 450-500°C (Scheme 13). As anticipated, the initially formed 2*H*-azepines **31** undergo a series of [1,5]H-shifts which lead to the formation of two isomeric 2,7-disubstituted 3*H*-azepines **32** and **33** in nearly equal amounts. The isomers can be conveniently separated by column chromatography on silica gel prewashed with petrol ether/triethylamine. They exhibit a pleasant fruit-like odour. Experiments to transform the 3-azabicycloheptadienes **30** into azepines under milder conditions are in progress.

Scheme 13

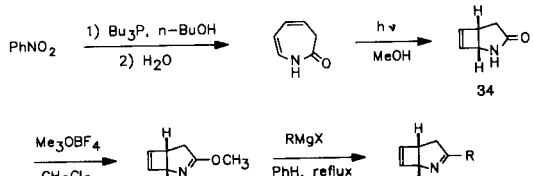


R	32	33
Pr	32%	35%
Ph	32%	39%
OMe	97%	–

3*H*-Azepines from 2-Azabicyclo[3.2.0]hepta-2,6-dienes.

The successful synthesis of 3*H*-azepines from 3-azabicycloheptadienes **30** encouraged us to investigate the synthetic potential of the corresponding 2-aza isomers **36**. Its syntheses commence from 2-azabicyclo[3.2.0]hept-6-en-3-one (**34**) [20] which can be easily prepared in three steps from nitrobenzene by known procedures (Scheme 14) [21]. Alkylation of **34** with Meerwein's reagent yielded the imidate **35** which was transformed into the alkyl and phenyl derivatives **36** by treatment with the corresponding Grignard reagents.

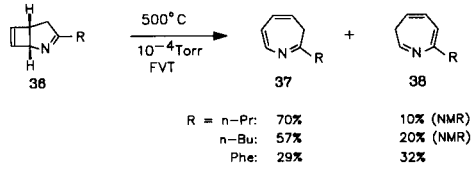
Scheme 14



36	a	b	c	d
R	Et	n–Pr	n–Bu	Ph
%	19	42	42	45

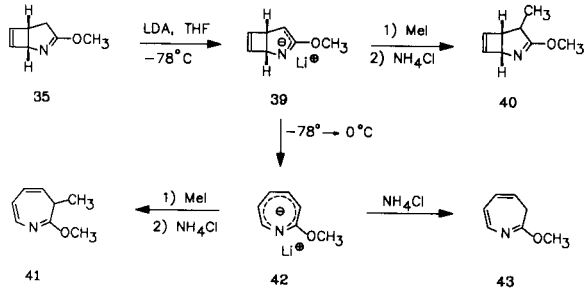
Flash vacuum thermolysis at 500°C followed by chromatographic purification afforded the 2-alkyl-3*H*-azepines **37** in high yield (Scheme 15). An analysis of the crude reaction products by ^{1}H-nmr indicated that only small amounts of the isomeric 7-alkyl-3*H*-azepines **38** were present. In the case of the phenyl derivative **36d**, however, both azepine isomers were isolated in nearly equal amounts. Experiments to achieve the transformation of **36** into azepines at lower temperatures are in progress. The thermal rearrangement of 2-azabicycloheptadienes into 3*H*-azepines has recently also been reported by Satake *et al.* [22].

Scheme 15



An unexpected base induced ring opening of imidate **35** was observed during methylation studies. On addition of lithium diisopropylamide at -78°C, the solution of **35** in THF turned dark brown and after addition of methyl iodide and usual work-up the 4-methyl derivative **40** was obtained (Scheme 16). When the brown solution was allowed to warm up to 0°C an irreversible color change to dark violet took place and after addition of methyl iodide at -78°C and quenching with ammonium chloride 2-methoxy-3-methyl-3*H*-azepine (**41**) was isolated as single product. Similarly, quenching of the dark violet solution with ammonium chloride yielded 2-methoxy-3*H*-azepine (**43**). These results indicate that the bicyclic anionic species **39** formed initially rearranges to a lithiated 2-methoxyazepine species **42** under very mild conditions. The latter is then regioselectively trapped in 3-position by electrophiles. The formation of a black violet anion by treatment of 2-diethylamino-5-phenyl-3*H*-azepine with bases has already been reported by Streef and van der Plas [23].

Scheme 16



These results show that the chemistry of azepines is still in a rather premature state and that further efforts will be necessary to devise methods for the synthesis of optically active 2*H*-azepines like chalciporone.

REFERENCES AND NOTES

[1] H. Barth, G. Burger, H. Döpp, M. Kobayashi, and H. Musso, *Liebig's Ann. Chem.*, 2164 (1981).

[2] R. von Ardenne, H. Döpp, H. Musso, and W. Steglich, *Z. Naturforsch.*, **29c**, 637 (1974).

[3] H. Barth, M. Kobayashi, and H. Musso, *Helv. Chim. Acta*, **62**, 1231 (1979).

[4] W. Steglich, R. Jeschke, and E. Buschmann, *Gazz. Chim. Ital.*, **116**, 361 (1986).

[5] R. Appel and H. Schöler, *Chem. Ber.*, **110**, 2382 (1977).

[6] U. Göckel, U. Hartmannsgruber, A. Steigel, and J. Sauer, *Tetrahedron Letters*, 595 (1980)

[7] Y. Yamasaki, T. Maekawa, T. Ishihara, and T. Ando, *Chem. Letters*, 1387 (1985).

[8] O. Sterner, B. Steffan, and W. Steglich, *Tetrahedron*, 43, 1075 (1987).

[9] K. Narasimhan, P. R. Kumar, and T. Selvi, *Heterocycles*, **22**, 2751 (1984).

[10] E. Vogel, H.-J. Altenbach, J.-M. Drossard, H. Schmickler, H. Stegelmeier, *Angew. Chem.*, **92**, 1053 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 1016 (1980).

[11] R. K. Smalley in "Comprehensive Heterocyclic Chemistry", Vol 7, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, Oxford, 1984, p 491.

[12] D. J. Anderson and A. Hassner, J. *Am. Chem. Soc.*, **93**, 4339 (1971).

[13] P. G. Fuß, Dissertation, University of Bonn, 1967.

[14] W. Hartmann, *Chem. Ber.*, **102**, 3974 (1969).

[15] T. Nagasaka, S. Esumi, N. Ozawa, Y. Kosugi, and F. Hamaguchi, *Heterocycles*, **16**, 1987 (1981).

[16] Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 2318 ((1980); see also J. F. Normant, A. Alexakis, A. Ghribi, and P. Mangeney, *Tetrahedron*, **45**, 507 (1989).

[17] D. J. Hart and Y.-M. Tsai, *Tetrahedron Letters*, **22**, 1567 (1981).

[18] P. M. Esch, H. Hiemstra, W. J. Klaver, and W. N. Speckamp, *Heterocycles*, **26**, 75 (1987).

[19] A. Ohta, S. Masano, E. Maeda, T. Ohwada, Y. Akita, and T. Watanabe, *Chem. Pharm. Bull.*, **25**, 817 (1977).

[20] E. Vogel, R. Erb, G. Lenz, A. A. Bothner-By, *Liebig's Ann. Chem.*, **682**, 1 (1965).

[21] E.g. M. Masaki, K. Fukui, and J. Kita, *Bull. Chem. Soc. Japan*, **50**, 2013 (1977).

[22] K. Satake, H. Saitoh, M. Kimura, and S. Morosowa, *J. Chem. Soc., Chem. Commun.*, 1121 (1988).

[23] J. W. Streef and H. C. van der Plas, *Tetrahedron Letters*, 2287 (1979).