# Synthesis of Heterocyclic Compounds by the Reactions of Exocyclic α,β-Unsaturated Ketones



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**Dedicated to Professor Dr. György Kalaus on the occasion of his 65th birthday.**

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## 1. Introduction.

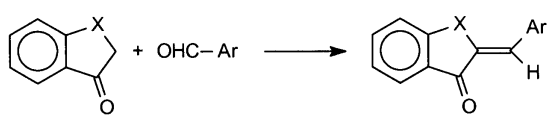
α,β-Unsaturated ketones are convenient and easily available starting materials or intermediates for the synthesis of a wide variety of heterocyclic compounds. The α,β-enone unit is favourable for dipolar cycloaddition reactions with various reagents affording heterocyclic compounds of different ring sizes with one or more hetero atoms. Their reactions with dinucleophiles provide important and useful heterocyclic ring systems as well. Among the α,β-unsaturated ketones, chalcones and their analogues have a prominent place as starting materials for the synthesis of, first of all, nitrogen-containing heterocyclic compounds. Such reactions have been reviewed in several accounts [1-5].

Utilization of the related exocyclic α,β-unsaturated ketones for such purposes made possible the synthesis of various polycyclic ring systems. Probably the most important types of these polycyclic compounds are their fused heterocyclic and spiroheterocyclic representatives. Although such compounds have been known for decades, their syntheses have hitherto been scarcely reviewed [6,7]. For this reason, the major aim of our present review article is to compile the most important types of heterocyclic compounds synthesized by the reactions of selected groups of exocyclic α,β-unsaturated ketones, represented by 2-arylidene-1-indanones (**1**), -1-tetralones (**2**), -1-benzosuberones (**3**), 3-arylidenechromanones (**4**), -1-thiochromanones (**5**), -flavanones (**6**) and -1-thioflavanones (**7**).

## 2. Synthesis of Exocyclic α,β-Unsaturated Ketones **1-7**

Several representatives of the above-mentioned exocyclic α,β-unsaturated ketones **1-7** have been well known compounds for a long time. 2-Arylidene-1-indanones (**1**), -1-tetralones (**2**) and -1-benzosuberones (**3**) were synthesized by base- [8-20] and acid-catalyzed [21-26] condensation of 1-indanone, 1-tetralone and 1-benzosuberone with aromatic aldehydes (Scheme 1). 3-Arylidenechromanones

Scheme 1

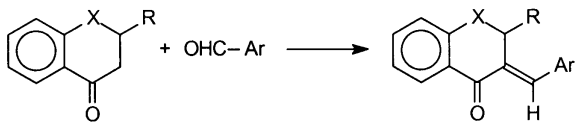



Ar = substituted phenyl
heteroaryl

**1:** X = $CH_2$
**2:** X = $(CH_2)_2$
**3:** X = $(CH_2)_3$

(**4**), -1-thiochromanones (**5**),-flavanones (**6**) and -1- thioflavanones (**7**) were prepared by the reaction of chromanone, 1-thiochromanone, flavanone and 1-thioflavanone with the appropriate aromatic aldehydes (Scheme 2). In many cases acid-catalyzed condensation of the cyclic ketone and aldehyde components have been performed [27-40]. Inorganic bases have also been used as catalysts for this purpose [47-49]. In our previous studies [50-54], piperidine proved to be a convenient catalyst for the synthesis of compounds **4-7**. All these exocyclic α,β-unsaturated ketones (**1-7**) synthesized either by acid- or base-catalyzed condensation of the appropriate cyclic ketone and aromatic aldehyde were (*E*)-diastereomers [55].

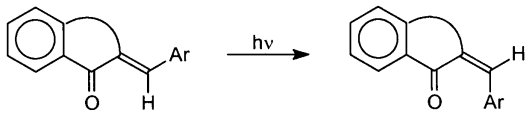
Scheme 2




**4:** X = O, R = H
**5:** X = S, R = H
**6:** X = O, R = Ph
**7:** X = S, R = Ph

The (*Z*)-diastereomers of compounds **1-7** have been prepared by the photoisomerization of their (*E*)-isomers (*E*-**1-7**) (Scheme 3) [23,44,56-63].

Scheme 3




(*E*)-**1-7** (*Z*)-**1-7**

As a result, both diastereomers of these exocyclic α,β-unsaturated ketones became easily available in stereohomogeneous form, which makes possible the study of their stereoselective chemical transformations. In this chapter the synthesis of these α,β-enones used as starting materials for the chemical transformations described in the subsequent chapters is briefly discussed, since an independent review has been devoted to this topic [64].

## 3. Epoxidation of Exocyclic α,β-Unsaturated Ketones

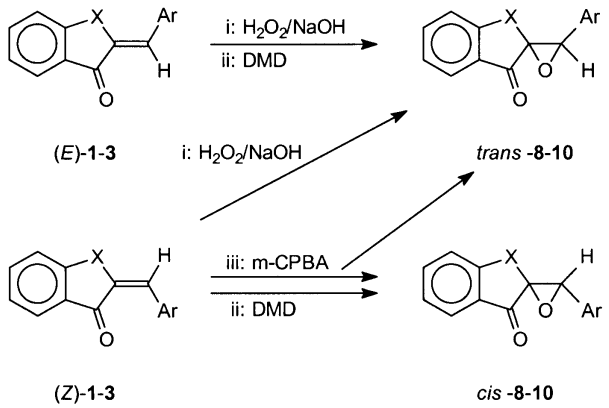
Epoxides belong to the three-membered ring oxygen-heterocyclic compounds and, therefore, the synthesis of these small ring heterocyclic compounds seems to be worthy of being included in our present review article. All these substances are spiroepoxides, the stereochemistry of which can be compared with those of the other types of spiroheterocyclic systems derived from exocyclic α,β-unsaturated ketones.

First examples for the epoxidation of unsubstituted 2-benzylidene-1-indanone (**1**) [17] and variously substituted 2-benzylidene-1-tetralones (**2**) [17,65,66] were published by Cromwell *et al.* several decades ago. These α,β-enones were oxidized with alkaline hydrogen peroxide to afford the appropriate spiroepoxides. Prior to our own studies in this field, only these sporadic informations were available concerning the epoxidation of the 2-arylidene-1-indanones (**1**), -1-tetralones (**2**) and -1-benzosuberones (**3**) in the chemical literature. For this reason, as a part of our epoxidation program, a detailed comparative study of the epoxidation of α,β-enones **1-3** has been undertaken. As starting materials, we have synthesized both the (*E*)- and (*Z*)-diastereomers of compounds **1-3** [64].

In case 2-arylidene-1-indanones (**1**), -1-tetralones (**2**) or -1-benzosuberones (**3**) were oxidized with alkaline hydrogen peroxide (i) the thermodynamically favoured *trans*-epoxides (*trans*-**8-10**) were obtained both from their (*E*)- and (*Z*)-isomers [67-70] (Scheme 4) which is a consequence of the two-step reaction mechanism giving rise to an epimerization in the course of epoxidation. However, this method is a simple and convenient procedure for the synthesis of the *trans*-spiroepoxides of the above-mentioned α,β-enones.

If the aim is the synthesis of both *cis*- and *trans*-epoxides of these α,β-unsaturated ketones (**1-3**) such an oxidant should be used that acts under a concerted reaction mechanism resulting in the stereospecific formation of the appropriate *cis*- or *trans*-epoxides **8-10**. In this case the stereochemistry of the starting exocyclic α,β-unsaturated ketones is retained [68-70]. Electrophilic oxidants *i.e.*

Scheme 4




**1, 8:** X = $CH_2$; **2, 9:** X = $(CH_2)_2$; **3, 10:** X = $(CH_2)_3$

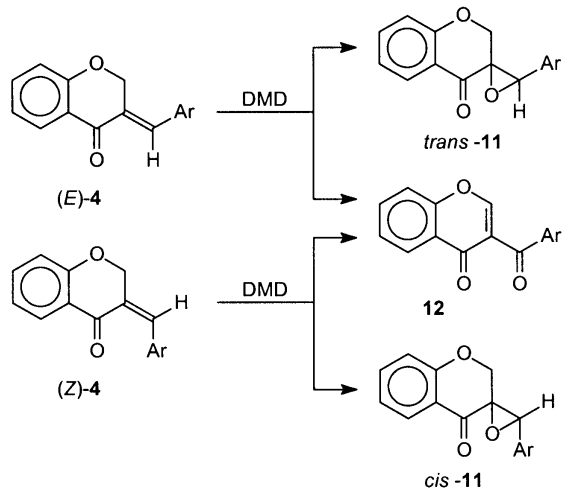
*m*-chloroperbenzoic acid (*m*-CPBA) (iii) or isolated dimethyldioxirane (DMD) (ii) were preferred for this purpose [67-69]. However, the use of *m*-chloroperbenzoic acid resulted in the partial isomerization of the (*Z*)-diastereomers into their (*E*)-isomers yielding a mixtures of *cis*- and *trans*-spiroepoxides. Therefore, the isolated dimethyldioxirane (in acetone solution) is an oxidant of choice for this stereospecific epoxidation. This reagent provides stereohomogeneous *cis*-epoxides from the (*Z*)-diastereomers and *trans*-epoxides from their (*E*)-isomers (Scheme 4) [67-70].

Recently, optically active epoxides **9** have also been prepared by the enantioselective epoxidation of 2-arylidene-1-tetralones (**2**) [71,72] by using Julia's method.

Epoxidation of 3-arylidenechromanones (**4**) and -1-thiochromanones (**5**) has been accomplished by the Weitz-Scheffer's alkaline hydrogen peroxide reagent several decades ago [33,37], but the stereochemistry of the epoxides obtained in this way was not elucidated.

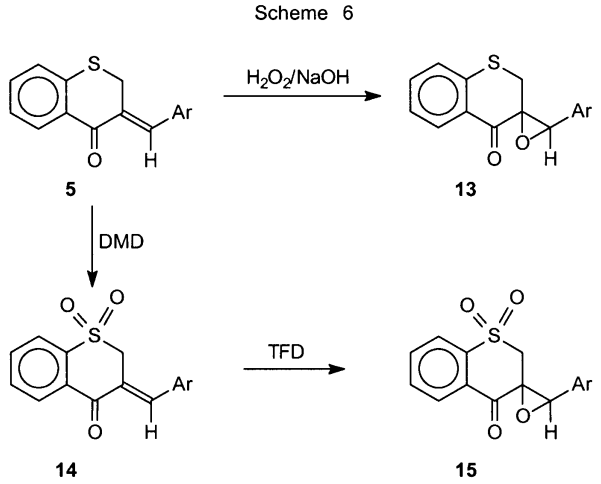
In our own experiments, both (*E*)- and (*Z*)-diastereomers of 3-arylidenechromanones (**4**) were allowed to react with isolated dimethyldioxirane (DMD) and *trans*-**11** and *cis*-**11** were prepared in a stereospecific epoxidation (Scheme 5) [73]. Under these reaction conditions considerable amount of 3-aroylchromones (**12**) are formed as well, but hitherto this is the only known procedure for the synthesis of *cis*-spiroepoxides (*cis*-**11**) of 3-arylidenechromanones.

Scheme 5




3-Arylidene-1-thiochromanones (**5**) have also been epoxidized by alkaline hydrogen peroxide to afford the appropriate spiroepoxides (**13**) [37]. However, if thiochromanones **5** were oxidized with isolated dimethyldioxirane, sulfones **14** were obtained even with large excess of the oxidant [74]. Sulfones **14** can then be epoxidized only with

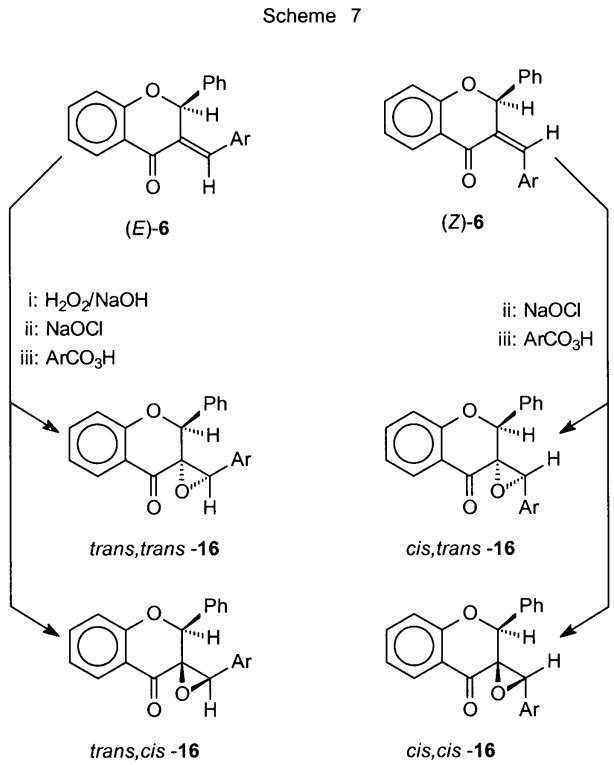
Scheme 6




the powerful methyl(trifluoromethyl)dioxirane (TFD) to provide epoxides **15** (Scheme 6).

A comparative epoxidation study of the 3-arylideneflavanones (**6**) was undertaken by Philbin *et al.* about three decades ago [75-78]. They obtained diastereomeric mixtures of epoxides **16** both from (*E*)- and (*Z*)-3-arylideneflavanones (**6**) by those oxidants (i, ii and iii) used in their experiments (*cf.* Scheme 7) [78]. The formation of diastereomeric mixtures of epoxides is a drawback of these procedures especially if the epoxides prepared should serve as starting materials for further chemical transformations.

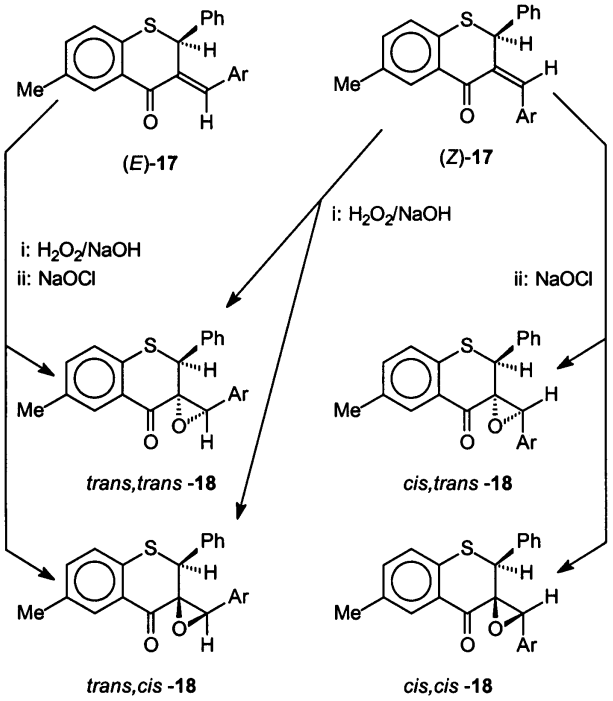
Scheme 7



Dimethyldioxirane epoxidation of a series of (*E*)-3-arylideneflavanones (*E*-**6**) provided *trans,trans*-spiroepoxides *trans,trans*-**16** in a completely diastereoselective reaction [79]. On the basis of this finding, dimethyldioxirane seems to be the oxidant of choice for the synthesis of *trans,trans*-spiroepoxides of the 3-arylideneflavanones in stereohomogeneous form. Unfortunately, the isomeric (*Z*)-3-arylideneflavanones (*Z*-**6**) could not be epoxidized by DMD [79].

In epoxidation of both (*E*)- and (*Z*)-isomers of 3-arylidene-6-methyl-1-thioflavanones (**17**) Bierne and O'Sullivan used alkaline hydrogen peroxide (i) or bleach (ii) as nucleophilic oxidants [46]. However, since these oxidants act by a two-step process, diastereomeric mixtures of epoxides **18** were obtained (Scheme 8).

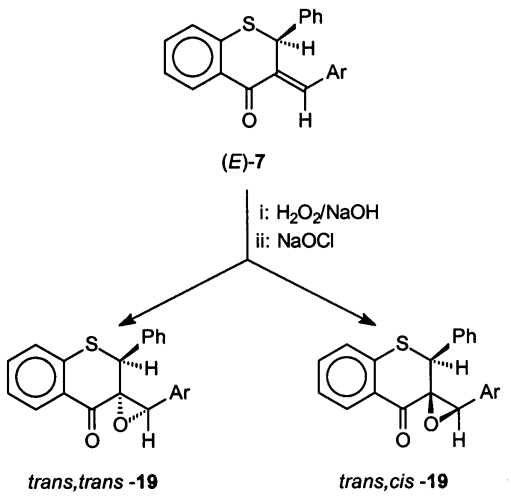
Scheme 8




In the course of our dioxirane oxidation study, (*E*)-3-arylidene-1-thioflavanones (**7**) were allowed to react with both dimethyldioxirane (DMD) and methyl(trifluoromethyl)dioxirane (TFD), but only the sulfur heteroatom was oxidized providing sulfoxides and/or sulfones depending on the amount of the oxidant. No sign of epoxide formation could be detected if these electrophilic oxidants were used.

We have accomplished a comparative epoxidation study of a series of (*E*)-3-arylidene-1-thioflavanones (*E*-**7**) with alkaline hydrogen peroxide (i) and bleach (ii). By using these nucleophilic oxidants, a mixture of *trans,cis*- and

Scheme 9

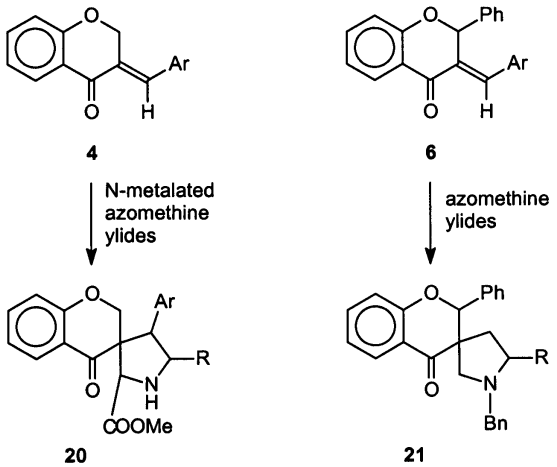



*trans,trans*-spiroepoxides **19** was obtained (Scheme 9) [80]. The diastereomeric epoxides **19** were separated by column chromatography and their stereochemistry has been elucidated by nmr techniques and quantumchemical calculations [81]. Stereohomogeneous *trans,cis*-spiroepoxides (*trans,cis*-**19**) and *trans,trans*-spiroepoxides (*trans,trans*-**19**) became easily available in this way.

4. Synthesis of Spiropyrrolidines by the Reaction of 3-Arylidenechromanones (**4**) and -flavanones (**6**) with Azomethine Ylides

Recently, spiropyrrolidine derivatives **20** and **21** have been synthesized by Subramaniyan *et al.* [82,83]. 3-Arylidenechromanones (**4**) and -flavanones (**6**) were

Scheme 10

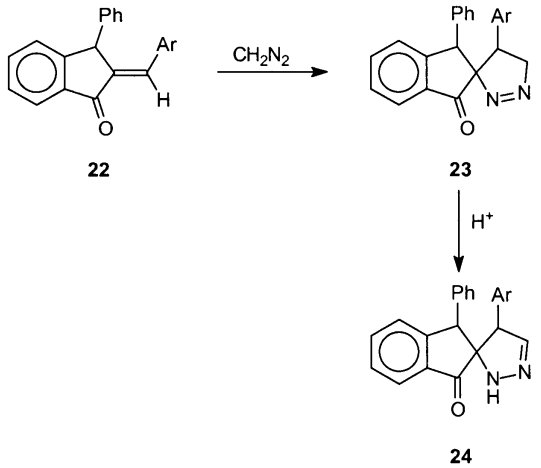


allowed to react with N-metalated azomethine ylides giving spiropyrrolidines **20** and **21** in good yields (Scheme 10). This spiroheterocyclic ring system with one nitrogen heteroatom is a new group of heterocyclic compounds derived from exocyclic α,β-unsaturated ketones. 1,3-Dipolar cycloaddition of azomethine ylides to these α,β-enones offers a versatile procedure for the synthesis of nitrogen-containing heterocyclic compounds with spirocyclic skeleton.

5. Synthesis of Spiro-1-pyrazolines by the 1,3-Dipolar Cycloaddition of Exocyclic α,β-Unsaturated Ketones with Diazoalkanes

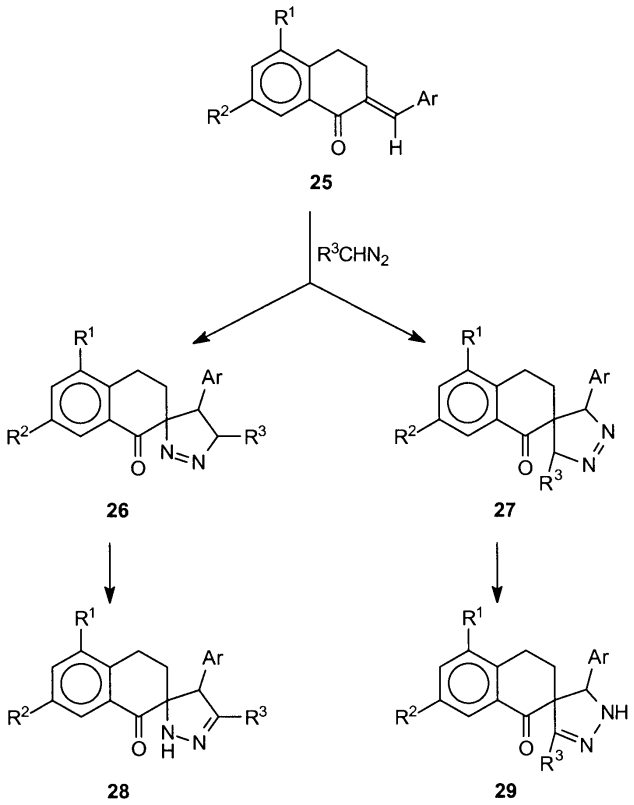
Synthesis of spiro-1-pyrazolines by the reaction of exocyclic α,β-unsaturated ketones and diazoalkanes has been investigated for several decades. Cycloaddition of 2-arylidene-3-phenyl-1-indanones **22** and diazomethane accomplished by Mustafa and Hilmi in 1951 [8] is probably the first example for the synthesis of spiro-1-pyrazoline type compounds by this method. These spiro-1-pyrazolines (**23**) can be rearranged into the appropriate spiro-2-pyrazolines (**24**) (Scheme 11). It is worth mentioning that the above authors were unable to establish whether the compounds synthesized by them were spiro-1-pyrazolines (**23**) or spiro-2-pyrazolines (**24**) (Scheme 11) [8]. Spiro-1-pyrazolines were then synthesized by Neudeck by similar 1,3-dipolar cycloaddition of 2-arylidene-1-indanones (**1**) with diazomethane [84].

Scheme 11




Reaction of 2-arylidene-1-tetralones (**25**) with diazoalkanes has been published by Fateen *et al.* [85,86]. Formation of various pyrazoline isomers (**26-29**) has been supposed (Scheme 12). Since no spectroscopic data are included in their papers, the structure elucidation of the products remained questionable.

Scheme 12



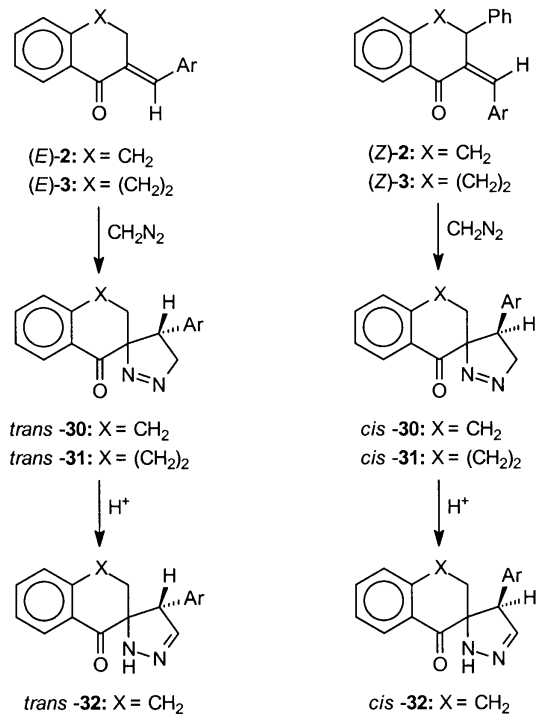

$R^1$ = H, Me; $R^2$ = Me, OMe, Et; $R^3$ = H, OMe, $NO_2$

We have demonstrated that the 1,3-dipolar cycloaddition of the 2-arylidene-1-tetralones (**2**) and -1-benzosuberones (**3**) and diazomethane is stereospecific and the (*E*)-diastereomers provide *trans*-spiro-1-pyrazolines *trans*-**30** and *trans*-**31**, while their (*Z*)-isomers afford the diastereomeric *cis*-**30** and *cis*-**31** (Scheme 13) [87-90] in stereohomogeneous form. Spiro-1-pyrazolines *trans*-**30** and *cis*-**30** were then converted into the corresponding spiro-2-pyrazolines *trans*-**32** and *cis*-**32** (Scheme 13) [88,90] on an acid-catalyzed rearrangement.

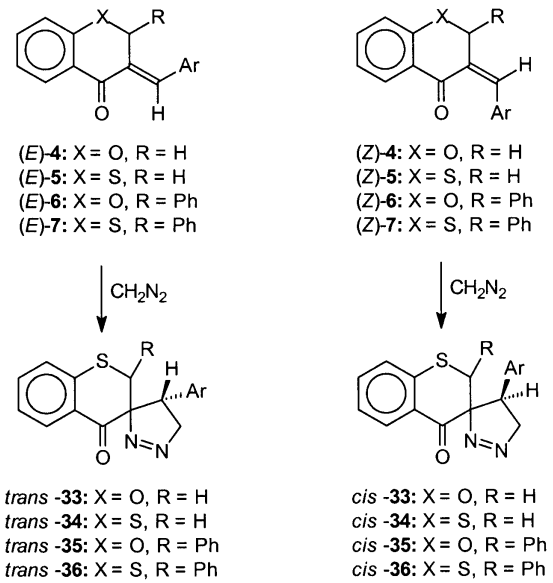
1,3-Dipolar cycloaddition of both diastereomers of 3-arylidenechromanones (**4**), -1-thiochromanones (**5**), -flavanones (**6**) and -1-thioflavanones (**7**) with diazomethane provided *trans*- and *cis*-spiro-1-pyrazolines *trans*-**33-36** and *cis*-**33-36** in stereohomogeneous form (Scheme 14) [87,89-91]. Kamecki *et al.* [92,93] investigated a similar reaction of 3-arylideneflavanones (**6**), but they failed to determine the correct structures of the pyrazolines synthesized.

Reaction of (*E*)-2-arylidene-1-indanones (*E*-**1**), (*E*)-aurones (*E*-**37**), (*E*)-1-thioaurones (*E*-**38**) and (*E*)-2-arylidene-2,3-dihydro-1*H*-indol-3-ones (*E*-**39**) and diazo-

Scheme 13

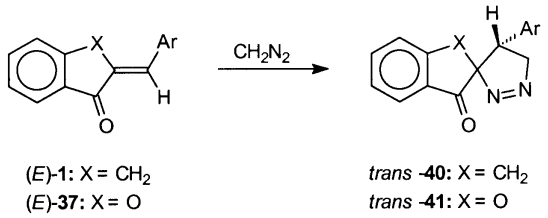



Scheme 14



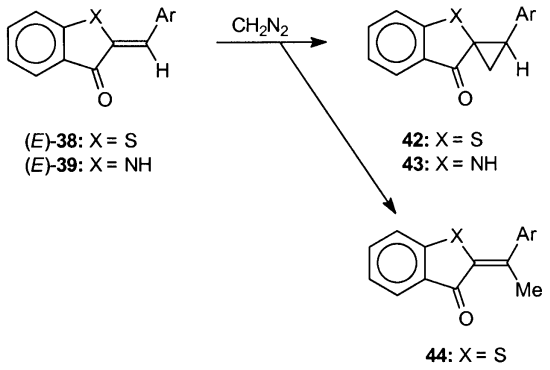

methane has been investigated by us [94]. Compounds (*E*)-**1** and (*E*)-**37** yielded *trans*-spiro-1-pyrazolines *trans*-**40** and *trans*-**41** as stable compounds (Scheme 15). The reaction proved to be stereospecific as in the case of the related exocyclic α,β-unsaturated ketones.

Scheme 15




If (*E*)-1-thioaurones (*E*-**38**) and (*E*)-2-arylidene-2,3-dihydro-1*H*-indol-3-ones (*E*-**39**) were allowed to react with diazomethane, no pyrazoline type compound could be detected in the crude reaction mixtures [94]. A spontaneous denitrogenation of the pyrazolines formed has taken place to afford mixtures of spirocyclopropanes **42** and **43** and β-methyl-α,β-enones **44** (Scheme 16) [94].

Scheme 16

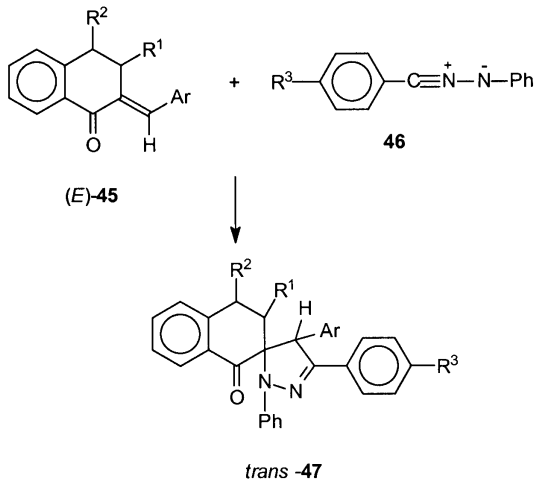



## 6. Synthesis of Spiro-2-pyrazolines by the Cycloaddition of Nitrile Imines with Exocyclic α,β-Unsaturated Ketones

Laude *et al.* prepared *trans*-spiro-2-pyrazolines *trans*-**47** by the 1,3-dipolar cycloaddition of (*E*)-2-arylidene-1-tetralones (*E*-**45**) with diarylnitrile imines **46** (Scheme 17) [95]. Structure elucidation of compounds **47** performed by nmr spectroscopic measurements unequivocally proved a regioselective and diastereoselective ring formation.

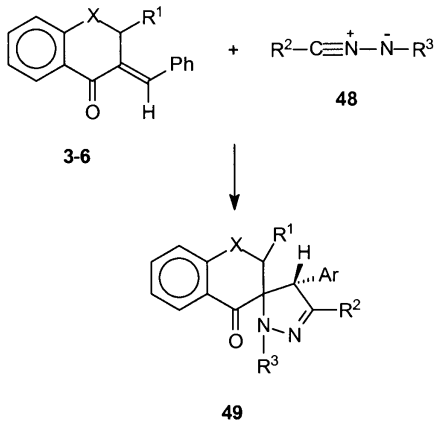
Spiro-2-pyrazolines **49** have been synthesized by Fisera and Lévai [96-98] by the reaction of (*E*)-2-benzylidene-1-tetralone (*E*-**2**), (*E*)-3-benzylidenechromanone (*E*-**4**), -1-thiochromanone (*E*-**5**) and -flavanone (*E*-**6**) with *in situ* generated nitrile imines **48** (Scheme 18). The stereochemistry of spiro-2-pyrazolines **49**, determined by nmr spectroscopic measurements, refers to a completely regioselective and diastereoselective cycloaddition in these cases, too.

Scheme 17



$R^1$ = H, Me; $R^2$ = H, Me, Et, iPr, tBu; $R^3$ = H, Me, OMe

Scheme 18

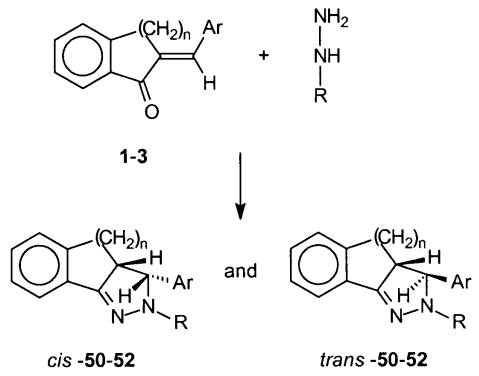


X = $CH_2$, O, S; $R^1$ = H, Ph;
$R^2$ = 4-nitrophenyl, 5-nitro-2-furyl; $R^3$ = Me, Ph

## 7. Synthesis of Tricyclic Fused 2-Pyrazolines by the Reaction of Exocyclic α,β-Unsaturated Ketones with Hydrazines

Synthesis of tricyclic fused 2-pyrazolines (**50-52**) by the reaction of 2-arylidene-1-indanones (**1**), -1-tetralones (**2**) and -1-benzosuberones (**3**) with hydrazines has been accomplished in several research laboratories [100-112]. Compounds **1-3** and hydrazines were allowed to react under various reaction conditions and tricyclic 2-pyrazolines **50-52** were prepared (Scheme 19). Since two new centres of chirality are introduced into the products in the course of the pyrazoline ring formation, diastereomeric mixtures of compounds **50-52** are obtained in some cases. However, the *cis*/*trans* diastereomers can be easily separated by chromatography. In special cases these diastereomers can be isomerized into each other [110].

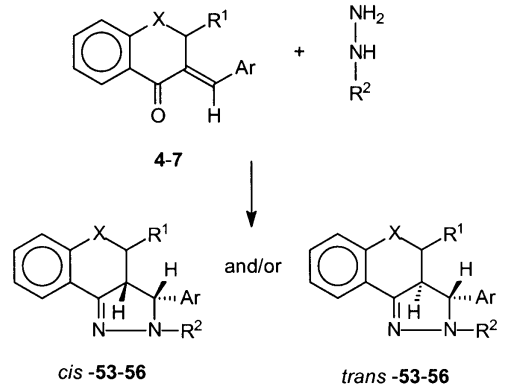
Scheme 19



**1, 50:** n = 1; **2, 51:** n = 2; **3, 52:** n = 3
R = H, alkyl, Ph

Tricyclic fused 2-pyrazolines **53-56** have also been synthesized by the reaction of 3-arylidenechromanones (**4**), -1-thiochromanones (**5**), -flavanones (**6**) and -1-thioflavanones (**7**) and hydrazines (Scheme 20) [92,103,104,107,113-116]. If the reaction of compounds **4** and **6** and hydrazines was accomplished in alcoholic solution or in acetic acid, a *cis*/*trans*-mixture of tricyclic 2-pyrazolines were obtained [92,103,107]. However, if pyridine was used as solvent, *trans*-**53-56** were obtained in each case (Scheme 19) [104,113-116]. If the same reaction was performed in the presence of hydrochloric acid, *cis*/*trans*-diastereomeric mixtures of compounds **53-56** were obtained [117,118]. The *cis*-diastereomer was the major product in each case.

Scheme 20



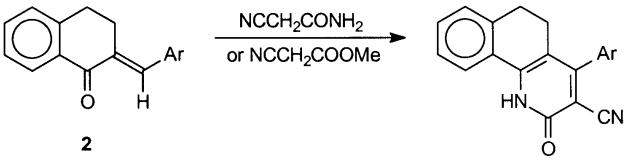
**4, 53:** X = O, $R^1$ = H; **5, 54:** X = S, $R^1$ = H;
**6, 55:** X = H, $R^1$ = Ph; **7, 56:** X = S, $R^1$ = Ph
$R^2$ = H, Me, Ph, $CONH_2$, $CSNH_2$

8. Reaction of Exocyclic α,β-Unsaturated Ketones with Cyanoacetic Acid Derivatives

Cyanoacetic acid derivatives are convenient and versatile reagents for the synthesis of a wide variety of heterocyclic ring systems by their reactions with α,β-enones [119,120]. Numerous pyridine type compounds were obtained starting from chalcones and related α,β-unsaturated ketones by their base-catalyzed reactions with these reagents. Reaction of several representatives of exocyclic α,β-unsaturated ketones and cyanoacetic acid derivatives has also been studied and tricyclic fused heterocycles were synthesized in this way. Selected examples are included in our present review article to illustrate the utility of such reactions for the preparation of nitrogen-containing heterocyclic compounds.

2-Arylidene-1-tetralones (**2**) were allowed to react with methyl cyanoacetate or cyanoacetamide to afford the 4-aryl-3-cyano-1,2,5,6-tetrahydrobenzo[*h*]quinolin-4-ones (**57**) under alkaline reaction conditions (Scheme 21) [121,122].

Scheme 21



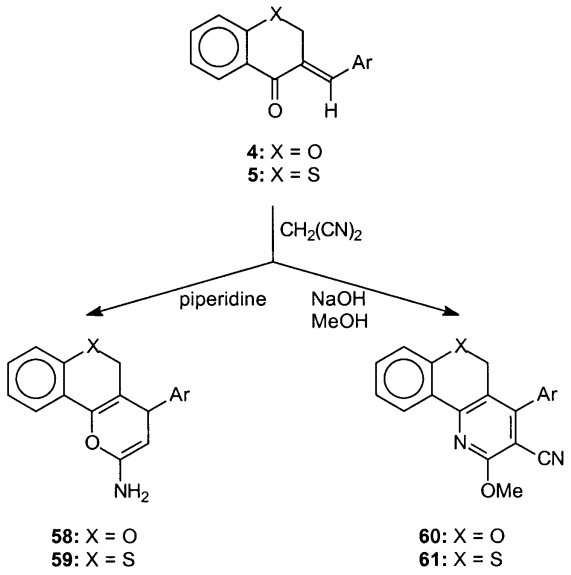

**2** **57**

Reaction of 3-arylidenechromanones (**4**) or -1-thiochromanones (**5**) and malonitrile provided 2-amino-4-arylpyrano[3,2-*c*]benzopyran-3-carbonitriles (**58**) or 2-amino-4-arylpyrano[3,2-*c*]benzothiopyran-3-carbonitriles (**59**) in the presence of a weak base, *víz.* piperidine. However, the use of a strong inorganic base like sodium hydroxide resulted in the formation of 4-aryl-3-cyano-2-methoxy[1]benzopyrano[4,3-*b*]pyridines (**60**) or 4-aryl-3-cyano-2-methoxy[1]benzothiopyrano[4,3-*b*]pyridines (**61**) (Scheme 22) [123-125].

9. Synthesis of Pyrimidines and Thiazines by the Reaction of Exocyclic α,β-Unsaturated Ketones with Thiourea

Thiourea may react with α,β-unsaturated ketones **62** in two different ways depending on the reaction conditions. The base-catalyzed reaction provides pyrimidines **63**, whereas the use of an acid catalyst results in the formation of 1,3-thiazines **64** (Scheme 23) [126-130].

Scheme 22

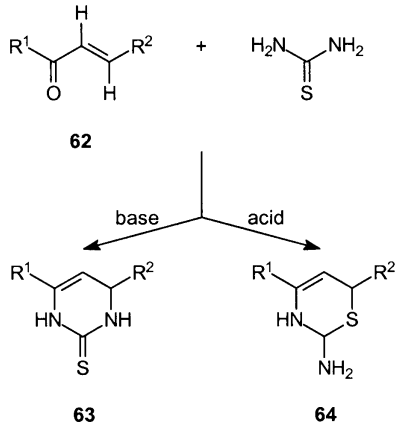



**4:** X = O
**5:** X = S

**58:** X = O
**59:** X = S

**60:** X = O
**61:** X = S

Scheme 23

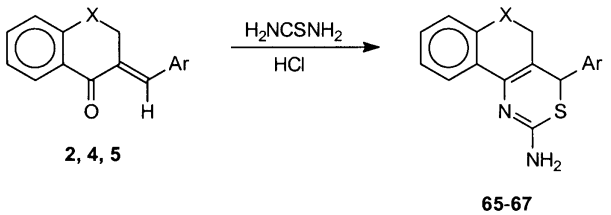



**62**

**63** **64**

If 2-arylidene-1-tetralones (**2**), 3-arylidenechromanones (**4**) or -1-thiochromanones (**5**) were reacted with thiourea by using hydrochloric acid catalyst, fused tricyclic 3,1-thiazines **65-67** were prepared (Scheme 24) [131].

Scheme 24



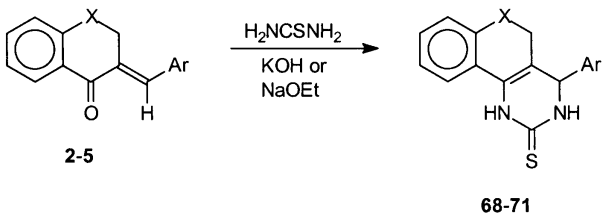

**2, 4, 5**

**65-67**

**2, 65:** X = $CH_2$; **4, 66:** X = O; **5, 67:** X = S

In the case where 2-arylidene-1-tetralones (**2**), -1-benzosuberones (**3**), 3-arylidenechromanones (**4**) or -1-thiochromanones (**5**) and thiourea were refluxed in ethanolic solution in the presence of potassium hydroxide or sodium ethoxide, tricyclic pyrimidines **68-71** were obtained (Scheme 25) [131-135].

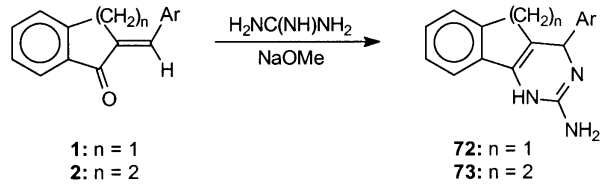
Scheme 25




**2, 68:** X = $CH_2$; **3, 69:** X = $(CH_2)_2$; **4, 70:** X = O; **5, 71:** X = S

Tricyclic 2-aminopyrimidine derivatives **72** and 2-aminoquinazolines **73** have been synthesized by the base-catalyzed reaction of 2-arylidene-1-indanones (**1**) and -1-tetralones (**2**) and guanidine (Scheme 26) [136,137].

Scheme 26




**1:** n = 1
**2:** n = 2

**72:** n = 1
**73:** n = 2

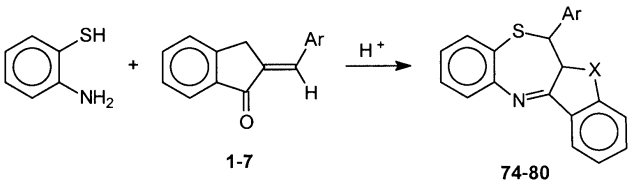
All these results described in this chapter prove that several carbonic acid derivatives are convenient and useful reagents for the synthesis of polycyclic ring systems by their reactions with exocyclic α,β-unsaturated ketones.

10. Synthesis of Tetracyclic Benzothiazepines by the Reaction of Exocyclic α,β-Unsaturated Ketones with 2-Aminothiophenol

Numerous 2,4-disubstituted 2,3-dihydro-1,5-bezothiazepines have been synthesized by the reaction of α,β-enones and 2-aminothiophenol [2,5,138-145]. Prior to our own studies, synthesis of tetracyclic benzothiazepines obtained by the same reaction of the related exocyclic α,β-unsaturated ketones was mentioned in the literature only in one case [140]. For this reason, our aim was to work out convenient procedures for the preparation of such tetracyclic benzothiazepines.

Compounds **1-7** were allowed to react with 2-aminothiophenol under acid-catalyzed reaction conditions, affording benzothiazepines **74-80** in good yields (Scheme 27) [146-151]. Similar tetracyclic benzothiazepines were synthesized by Pant *et al.* [152] by reacting substituted 2-aminothiophenols and 3-arylideneflavanones (**6**) under acid-catalyzed reaction conditions invented by us [146,147].

Scheme 27




**1-7**

**74-80**

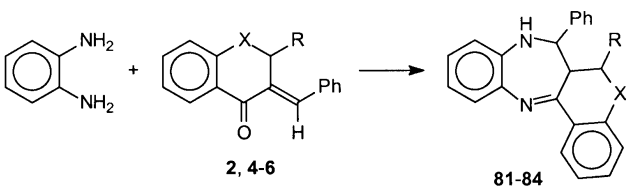
**1, 74:** X = $CH_2$; **2, 75:** X = $(CH_2)_2$; **3, 76:** X = $(CH_2)_3$;
**4, 77:** X = $CH_2O$; **5, 78:** X = $CH_2S$; **6, 79:** X = PhCHO; **7, 80:** X = PhCHS

Stereochemical studies based on nmr spectroscopic measurements unequivocally proved that all these tetracyclic benzothiazepines were obtained in stereohomogeneous form. No diastereomeric mixtures were detected although two new centres of chirality were introduced in the molecules in the course of the ring formation.

11. Synthesis of Tetracyclic Benzodiazepines by the Reaction of Exocyclic α,β-Unsaturated Ketones with 1,2-Phenylenediamine

Prior to our own work, benzodiazepines with fused ring system were hardly mentioned in the literature [153,154]. For this reason, in the course of a comprehensive study on the synthesis of nitrogen-containing heterocyclic compounds by the reaction of exocyclic α,β-unsaturated ketones with dinucleophiles, 1,2-phenylenediamine has also been used as reagent to obtain tetracyclic bezodiazepines. 2-Benzylidene-1-tetralone (**2**), 3-benzylidenechromanone (**4**), -1-thiochromanone (**5**) and -flavanone (**6**), respectively, were allowed to react with 1,2-phenylenediamine in hot ethanol and tetracyclic benzodiazepines **81-84** were obtained in medium yields (Scheme

Scheme 28




**2, 4-6**

**81-84**

**2, 81:** X = $CH_2$, R = H; **4, 82:** X = O, R = H;
**5, 83:** X = S, R = H; **6, 84:** X = O, R = Ph

28) [155]. Structure elucidation performed by various nmr techniques proved that all the benzodiazepines synthesized were stereohomogeneous products.

## 12. Closing Remarks

In our present review, the most important heterocyclic compounds obtained by various reactions of exocyclic α,β-unsaturated ketones have been compiled. These substances comprise either a spirocyclic or a fused ring system. Examples included in this article reveal the versatility of these α,β-enones for the synthesis of a wide variety of polycyclic nitrogen-containing organic compounds. In this respect, especially the synthesis of 1-pyrazolines, 2-pyrazolines, tetracyclic benzothiazepines and benzodiazepines should be emphasized. Owing to their bioactivities, these compounds are important in drug research. Therefore, the exocyclic α,β-unsaturated ketones are easily available and useful intermediates for drug research.

To our knowledge, only one independent review [3] has hitherto been devoted to deal with the synthesis of heterocyclic compounds by the reactions of these α,β-enones. This is why we decided to compile the above-discussed results in an independent review article. Literature data published to November 2003 have been included as references to provide original information for the synthesis of a particular substance.

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