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The Use of 2-Vinylanilines in the Synthesis of Indole- and Quinoline-Derivatives [1])

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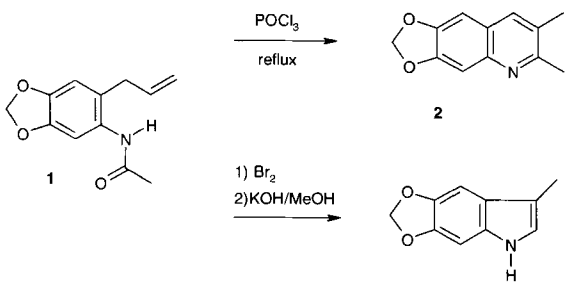
Abstract. Cyclization reactions of 2-vinylaniline derivatives, proceeding *via* anils, amides, imidic acid esters, ureas, thioureas, carbodiimides, formamidine ylids, sulfonamides or ketenes, leading to quinoline or indole derivatives, are described. In a short introduction interesting results from the literature, excluding our results, are presented. In the centre of this progress report our results on acid catalyzed reactions of 2-vinylanilines with aldehydes and ketones are discussed in a more detailed manner.

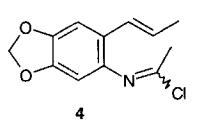
To our knowledge the first use of 2-vinylaniline derivatives in the synthesis of quinoline- and indole derivatives was described by Foulds and Robinson in 1914 [1].



1 2 3

Scheme 1

They obtained 6,7-methylendioxy-2,3-dimethylquinoline (**2**) by boiling 2-acetamidosafrole (**1**) with phosphorous oxychloride and 5,6-methylendioxy-3-methylindole (**3**) by addition of bromine to 2-acetamidosafrole (**1**) and treatment of the resulting dibromo intermediate with alcoholic potassium hydroxide solution. From the mechanistical point of view, we think, that the chloroimino-isosafrole-derivative (**4**) is a key-intermediate in the quinoline formation, which after 6π-electrocyclic rearrangement, subsequent 1,5-H-shift and loss of hydrogen chloride, gives the quinoline-derivative (**2**).



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Some years later Taylor and Hobson [2] used the methodology of Foulds and Robinson for the synthesis of C-2- alkylated quinolines. In this paper the reaction of both *cis*-and *trans*-2-acetamidostilbene with phosphorous oxychloride was also described. In both cases no quinoline derivative was obtained, but 3-benzylidene-2-methyl-3*H*-indole as the sole product. 40 years later G. Gast, J. Schmutz and D. Sorg [3] rediscovered the work of Foulds and Robinson and used the reaction of 4-methyl-*N*-[(2-(styryl)phenyl]-1-piperazincarboxamide with phosphorous oxychloride for the synthesis of 2-(4-methyl-1-piperazinyl)-4-phenylquinoline. In 1986 Kametani and coworkers [4] described the first example of a Lewis acid catalyzed cyclization of an ortho substituted vinylanile (benzylidene-(2-isopropenylphenyl) amine). However the yield of 4-methyl-2-phenylquinoline was bad (20–25%). In 1987 Hibino *et al.* [5] used the Foulds-Robinson approach for the synthesis of a series of methoxysubstituted quinolines. A modification of the phosphorous oxychloride procedure was published by Baine *et al.* [6]. They didn't use the 2-acetamido-vinylcompounds, but the *N*-(2-isopropenyl-phenyl)imidic acid ethyl esters as the precursors for the cyclization. The cyclization was carried out under thermal as well as photochemical conditions. In another approach the same authors [7] carried out cyclizations of 2-vinylanils under nonacidic conditions at reflux temperature of 1,2-dichlorobenzene.

[1]) Presented in part at the third conference on iminium salts, Stimpfach-Rechenberg (Germany), September 17–19, 1997

2-Vinylanilines are also used in the synthesis of 3,4-dihydroquinoline-2(1*H*)-ones and quinoline-2(1*H*)-ones. The radical cyclization of 2-dichloroacetamidovinylanilines with Bu_3SnH in the presence of azobisisobutyronitril gave the 3,4-dihydroquinoline-2(1*H*)-ones [8] whereas the simple reaction of 2-(1-phenylvinyl)aniline with phosgene in refluxing toluene delivered 4-phenyl-1,2-dihydroquinolin-2-one [9]. Iminophosphoranes, which could be prepared by treatment of 2-vinylanilines with triphenylphosphine in the presence of a base, after Aza-Wittig type reactions with aromatic isocyanates, gave carbodiimides in good yields [10]. After heating these carbodiimides (160 °C, sealed tube) 6π-electrocyclization occured, and 2-arylaminoquinolines were obtained as the final products [10]. In a comparable reaction, where carbodiimides are possible intermediates, 2-isopropenylaniline, after reaction with several alkyl- and arylisothiocyanates gave thioureas, which after treatment with red mercuric oxide gave the substituted 2-aminoquinolines in good yields [11].

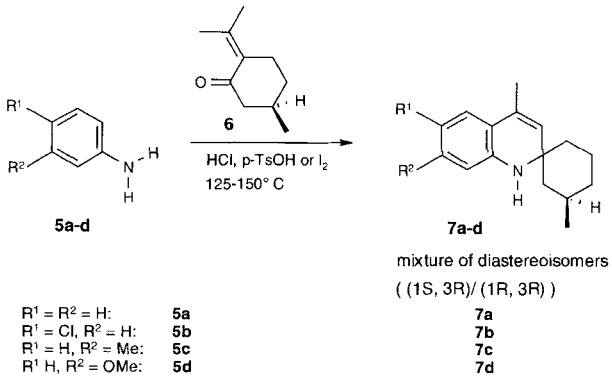
For the construction of the indole moiety, mainly five types of reactions are used, when 2-vinylanilines are the starting materials. Intramolecular nucleophilic substitutions [1], intramolecular Heck-type reactions [12–14], amidoselenation [15], intramolecular [2+2]-cycloadditions of ketene precursors [16] and intramolecular 1,3-dipolar cycloadditions [17, 18]. Especially the last two methods mentioned above, are very useful in the synthesis of alkaloids like physovenine [16] and eserethole [17, 18].

1 Historical Development of the Project

The Curious Acid or Iodine Catalyzed Reaction of Anilines with R-(+)-Pulegone

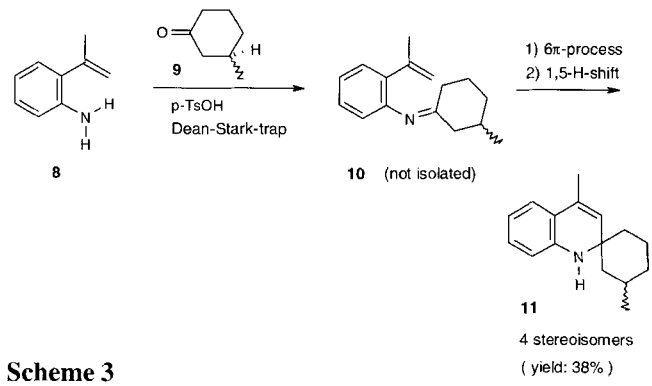
At the beginning of our investigations concerning cyclization reactions of anils, we were very interested in the synthesis of polycyclic aromatic amines, which should be used as dyestuff intermediates. Whereas the acid or iodine catalyzed reaction of cyclohexylidenecyclohexanone or cyclopentylidenecyclopentanone gave the expected hexahydrophenanthridine respectively tetrahydro-1*H*-cyclopenta[*c*]quinoline derivatives [19], the acid or iodine catalyzed reaction of monosubstituted anilines **5a–d** with *R*-(+)-pulegone (**6**), to our surprise didn't give the expected acridine- or phenanthridine derivatives, but spirocyclic 1'*H*-quinolines in moderate to good yields [20].

A reaction mechanism proceeding via several 6π-electrocyclic rearrangements and H-shifts is proposed for the formation of 1'*H*-quinolines **7a–d**. We think, that cyclohexanone-anils, are key intermediates in the reaction sequence, which after 6π-electrocyclic rearrangement and 1,5-H-shift gave the final spiro[cyclohexane-1,2'(1'*H*)quinolines]. For the corroboration of the specific 6π-electrocyclic rearrangement of cyclohexanone-anils, we investigated the *p*-TsOH-catalyzed reaction of 2-isopropenylaniline (**8**) with racemic 3-methylcyclohexanone (**9**). The resulting stereoisomeric mixture of 3,4'-dimethylspiro[cyclohexane-1,2'(1'*H*)quinoline] (**11**) in this reaction gave clear evidence for the proposed mechanism.



Scheme 2

This result was our starting point for a more profound investigation of cyclization reactions of 2-vinylsubstituted anils.

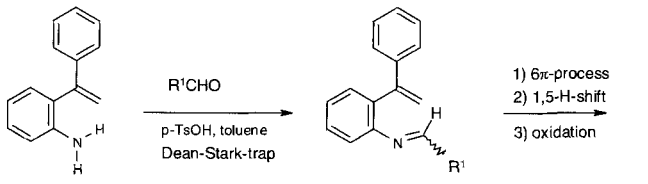


Scheme 3

2 Acid Catalyzed Reactions of 2-Vinylanilines with Aromatic and Heteroaromatic Aldehydes

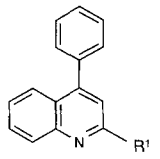
In the search for an efficient synthesis of 2,4-disubstituted quinolines, we carefully studied the TsOH-catalyzed reaction of 2-(1-phenylvinyl)anilines with several aromatic and heteroaromatic aldehydes [21]. Our results showed, that the 6π-electrocyclic-rearrangement-approach works in these cases, but the yields are not spectacular (36–60%). The yields of the 'aldehyde-approach' are limited by the fact, that the intermediary anils **13** are used to oxidize the 1,2-dihydroquinolines **15**. To supress the formation of the benzylic amines **16**, additional oxidants like nitrobenzene were added in

some cases, but no drastic improvement of the yields could be detected.



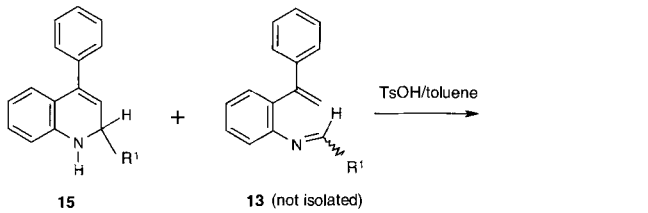
12 13 (not isolated)

	R^1	t (h)	yield (%)
14a	phenyl	15	50
14b	4-(4-chlorophenoxy)phenyl	15	48
14c	2,4-diethylphenyl	15	57
14d	pyridin-2-yl	15	43
14e	pyridin-3-yl	15	42
14f	pyridin-4-yl	15	60
14g	quinolin-2-yl	15	58
14h	3-phenoxythien-2-yl	15	47
14i	2,3-dihydro-benzo[*b*]furan-5-yl	15	36
14k	3,4-methylendioxyphenyl	15	40

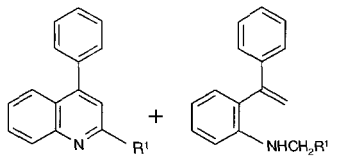


14a-k

Scheme 4



15 13 (not isolated)



14a-k 16

Scheme 5

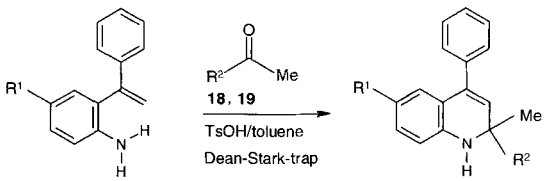
3 TsOH-Catalyzed Reactions of 2-(1-vinyl)anilines with Acetophenone Derivatives, 1-(Naphthalene-1-yl)ethanone and some Heterocyclic Ketones

We first studied the TsOH-catalyzed reaction of 2-(1-phenylvinyl)aniline (**12**) with acetophenone (**17**). The high selectivity and yield (90%) in this reaction encouraged us to use mono- and disubstituted acetophenenes as well as 1-(naphthalen-1-yl)ethanone (**18**) and 1-(furan-2-yl)ethanone (**19**) as keto compounds in this new reaction [22] .

The yields are generally high and independant of the chosen starting aniline derivative. Furthermore, it can be seen that the reaction process tolerates a lot of functional groups. Only the reduced yield in the case of 1-(furan-2-yl)ethanone (**19**) seemed to be curious. But we think, that the reduced yield in the furane case is probably due to the instability of the furane ring under the acidic reaction conditions. Upon investigation of the TsOH-catalyzed reaction of the 2-isopropenylanilines **8** and **22** with acylated aromatic or heteroaromatic compounds a first limitation of the used methodology was discovered. These reactions generally took an unselective course and either gave mixtures of 1,2-dihydroquinolines **23** and 2,2a,3,7b-tetrahydro-1*H*-cyclobut[*b*]indoles **24** (R^1= H, R^2 = 3-methoxyphenyl, 4-nitrophenyl and 2,4-dimethylphenyl),which could hardly be separated, or only compounds of the general formula **24** (R^1 = H, R^2 = phenyl, furan-2-yl, pyridin-2-yl).

For the formation of the interesting 1*H*-cyclobut[*b*]indoles of the general formula **24** at the moment we favour a mechanism, which is shown below [23].

Step 1 (anil-formation) is common for all the ketones. In all cases this step required the presence of acid. The acid catalyzed tautomerization (step 2) to the enamines **26**, cyclization to the azomethine ylid-intermediate **27** (step 3) and subsequent intramolecular [1,5] dipolar cyclization (step 4) leads to the 1*H*-cyclobut[*b*]indoles of the general formula **24**. The reaction pathway leading to cyclobut[*b*]indoles, we call the '1,5-dipole-route', whereas the pathway leading to 1,2-dihydroquinolines, we designate the '6π-route'. As approaches to cyclobut[*b*]indoles are rare, or depending on the structure, unknown, a new and general approach to these types of compounds may be of considerable interest.Our next goal therefore, was to find out, which changes in the structure of 2-vinylaniline derivatives respectively ketones must be made for strongly favouring the '1,5-dipole route'.

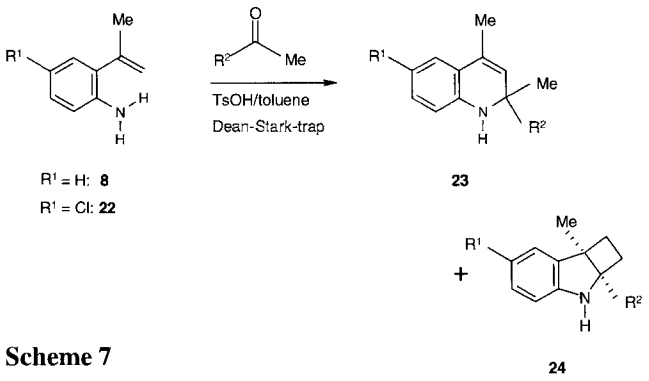


R^1 = H: **12**
R^1 = Cl: **20**

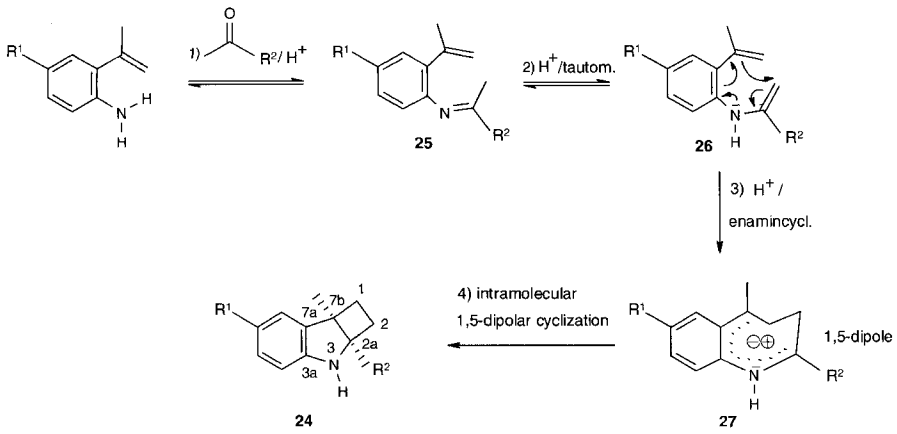
21a-r

	R^1	R^2	t (h)	yield (%)
21a	H	phenyl	8	90
21b	H	2-fluorophenyl	6	92
21c	H	2-methoxyphenyl	15	67
21d	H	3-(trifluoromethyl) phenyl	6	86
21e	H	4-fluorophenyl	12	92
21f	H	4-chlorophenyl	15	81
21g	H	4-hydroxyphenyl	8	89
21h	H	4-methoxyphenyl	8	81
21i	H	2,4-dimethylphenyl	16	80
21j	H	3,4-dimethoxy phenyl	6	96
21k	H	3,5-difluorophenyl	7	72
21l	H	naphth-1-yl	12	75
21m	H	furan-2-yl	12	40
21n	Cl	phenyl	15	89
21o	Cl	4-chlorophenyl	15	87
21p	Cl	4-hydroxyphenyl	8	88
21q	Cl	4-nitrophenyl	15	86
21r	Cl	4-methoxyphenyl	15	91

Scheme 6



Scheme 7



Scheme 8

4 The TsOH-Catalyzed Reaction of 2-Vinylaniline Derivatives with N-Substituted Piperidin-4-ones

In the next phase of our project, we chose cyclohexanones containing additional heteroatoms in the ring. To our opinion, *N*-methyl- and *N*-benzyl piperidin-4-ones seemed to be the first ideal candidates, due to their commercial availability. To our surprise, the TsOH-catalyzed reaction of 2-vinylaniline derivatives with these cyclic ketones gave new polycyclic cyclobut[1,2-*b*]indoles as sole products in diastereoisomeric pure form [24].

As we have seen earlier, the same reaction carried out with cyclohexanones instead of N-substituted piperidin-4-ones, led to 1,2-dihydroquinolines as sole products. This means that the substituted nitrogen atom is responsible for the change of the selectivity in these reactions.

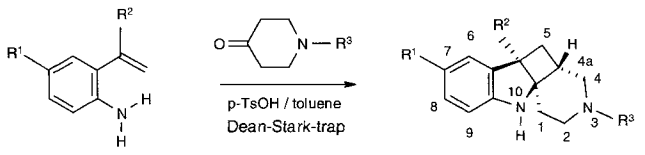
The unoptimized yields are often better than 50% and therefore interesting from the preparative point of view. These results showed for the first time the usefulness of our new methodology for the synthesis of new and complex heterocycles.

5 The TsOH-Catalyzed Reaction of 2-Vinylaniline Derivatives with Cyclic Ketones of the Tetralone-, Chroman-4-one and 2,3-Dihydro-1*H*-quinoline-4-one Series

To get a more complete picture of the selectivity of acid catalyzed reactions of 2-vinylaniline derivatives with ketones, we studied the reactions with bicyclic ketones with and without additional heteroatoms in the cyclohexanone ring. In a first exploratory phase, α-tetralone, chroman-4-one and 2,3-dihydro-1-methyl-1*H*-quinoline-4-one were choosen as model ketones. In this chapter, we discuss the results of the TsOH-catalyzed reaction of several 2-vinylaniline derivatives with these ketones [25].

For the TsOH catalyzed reaction of the 2-(1-phenylvinyl)anilines **12** and **20** with α-tetralone, we expected spirocyclic 1'*H*-quinolines in good yields in analogy to the reactions with acetophenone derivatives. This was indeed the case. In the reactions of the 2-isopropenylanilines **8** and **22** with α-tetralone, we expected mixtures of 1'*H*-quinolines and polycyclic cyclobut[*b*]indoles. This was the case in the reaction of the chloro-substituted aniline **22** but in the reaction with 2-isopropenylaniline (**8**), a polycyclic indole derivative was obtained as sole product in a very good yield.

The reactions of the 2-vinylaniline derivatives **8**, **12**, **20** and **22** with chroman-4-one were comparable to the α-tetralone case, with the exception, that the yields obtained in these reactions generally were much lower. In the reaction of chroman-4-one with the isopropenylanilines **8** and **22** mixtures of spiro[chroman-4,2'(1'*H*)quinolines] and cyclobut[1,2-*c*]chromans were obtained in moderate yields, showing, that in these cases the '6π-route' competed with the '1,5-dipole-route'. The 2-(1-

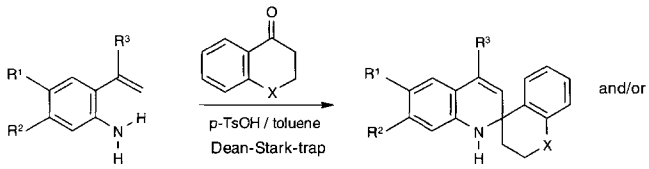


R^1 = H, R^2 = Me: **8**
R^1 = H, R^2 = Ph: **12**
R^1 = Cl, R^2 = Ph: **20**

28a-e (racemic)

	R^1	R^2	R^3	yield (%)
28a	H	methyl	methyl	67
28b	H	methyl	benzyl	32
28c	H	phenyl	methyl	43
28d	Cl	phenyl	methyl	81
28e	Cl	phenyl	benzyl	76

Scheme 9



R^1 = R^2 = H, R^3 = Me. **8**
R^1 = Cl, R^2 = H, R^3 = Me: **22**
R^1 = R^2 = H, R^3 = Ph: **12**
R^1 = Cl, R^2 = H, R^3 = PH: **20**

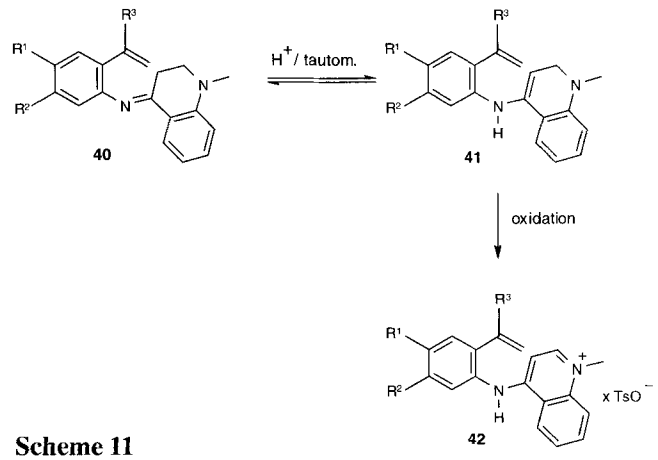
29a-39a (racemic)

29b-39b (racemic)

X = CH_2, O, NMe

	R^1	R^2	R^3	X	yield (%)
29b	H	H	methyl	CH_2	88
30b	H	Cl	methyl	CH_2	50
31a	H	H	phenyl	CH_2	86
32a	Cl	H	phenyl	CH_2	60
33b	H	H	methyl	O	20
34b	H	Cl	methyl	O	27
35a	H	H	phenyl	O	22
36a	Cl	H	phenyl	O	74
37b	H	H	methyl	NMe	54
38b	H	Cl	methyl	NMe	43
39b	H	H	phenyl	NMe	23

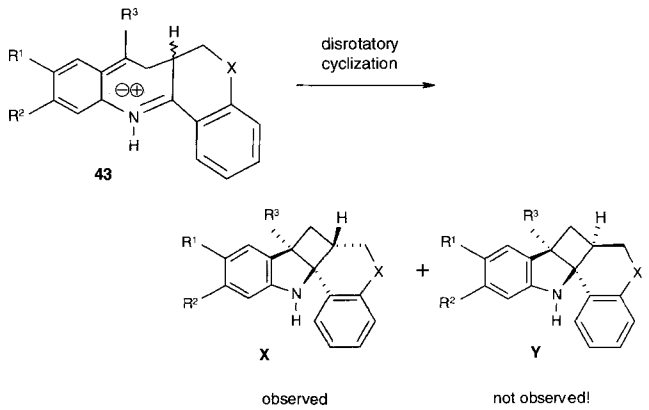
Scheme 10



40 **41** **42**

Scheme 11

eoisomeric polycyclic systems **X** and **Y** are the possible reaction products.



43 **X** **Y**

Scheme 12

phenylvinyl)anilines **12** and **20** showed selective reactions and gave spirocyclic 1'*H*-quinolines in moderate to good yields.

The TsOH-catalyzed reaction of the 2-vinylanilines **8**, **12**, **20** and **22** with 2,3-dihydro-1-methyl-quinoline-4-one gave cyclobut[1,2-*c*]quinolines as major products in yields of 40–50%. No products arising from the '6π-route' could be observed. This again demonstrates, the substituted nitrogen atom in the cyclohexanone ring, as in the case of the reactions with N-substituted piperidin-4-ones, to be responsible for the observed selectivity. The yields were generally lower than those obtained in the reactions with *N*-methyl- and *N*-benzylpiperidin-4-one, due to the formation of quinolinium-*p*-toluenesulfonates of the general formula **42** as by-products.

Concerning the diastereoselectivity of the '1,5-dipole-route', we think, that the [1,5]-dipolar cyclization step mainly determines the stereochemical outcome. When applying the Woodward-Hoffmann rules [26, 27] to the cyclization of dipole **43**, it turned out, that two diastereoisomeric polycyclic systems **X** and **Y** are the possible reaction products.

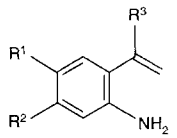
In all the reactions carried out by us, we only found one diastereoisomer, namely **X**. The study of molecular models clearly showed the isomer **Y** to be a very strained molecule with a twisted C-6a-C-12a-bond in the cyclobutane ring. We assume, that this steric strain in the transition state avoids the formation of the diastereoisomer **Y**, and therefore **Y** could not be observed as a reaction product.

6 Conclusions

Our current knowledge on acid catalyzed reactions of 2-vinyl aniline derivatives is summarized in Table 1. In summary, three major observations were made during our investigations:

1) The strong '[1,5]-dipole-route'-directing effect of a N–Me respectively N–Bzl-group in para position to the carbonyl group bearing C-atom in cyclic ketones such

Table 1 Expected Products in Acid Catalyzed Reactions of 2-Vinylaniline Derivatives with Several Ketones



R^1	R^2	R^3	ketone	expected product(s)
H	H	Me	acetylated aromatic or heteroaromatic compound	1*H*-quinoline and /or cyclobut[*b*]indole
H	H	Me, Ph	cyclohexanone and subst. cyclohexanones	1*H*-quinoline
H, Cl	H	Me, Ph	*N*-substituted piperidine-4-ones	cyclobut[*b*]indole
H	H	Me	α-tetralone	cyclobut[*b*]indole
H	Cl	Me	α-tetralone	1*H*-quinoline and cyclobut[*b*]indole
H, Cl	H	Ph	α-tetralone	1*H*-quinoline
H	H, Cl	Me	chroman-4-one	1'*H*-quinoline and cyclobut[*b*]indole
H, Cl	H	Ph	chroman-4-one	1'*H*-quinoline
H	H, Cl	Me, Ph	1-methyl-2,3-dihydro-quinolin-4-one	cyclobut[*b*]indole and 1-methylquinolinium-*p*-toluenesulfonate

as piperidin-4-ones and 2,3-dihydroquinoline-4-ones. In these reactions, the substitution pattern of the used 2-vinylanilines is not important for the selectivity.

2) The '6π-route'-directing effect of the 2-(1-phenylvinyl)-group observed in the reactions with acetophenone derivatives and α-tetralone.

3) The poor selectivity in the reactions of 2-isopropenylanilines **8** and **22** with acetophenone derivatives, α-tetralone and chroman-4-one (in the most cases mixtures of products arising from the '6π-route' as well as the '[1,5]-dipole-route' were obtained).

Our results from the last few years, impressively demonstrate, that if suitable ketones and 2-vinylaniline derivatives are used in the TsOH-catalyzed reactions, new and complex heterocycles are available in good to excellent yields.

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