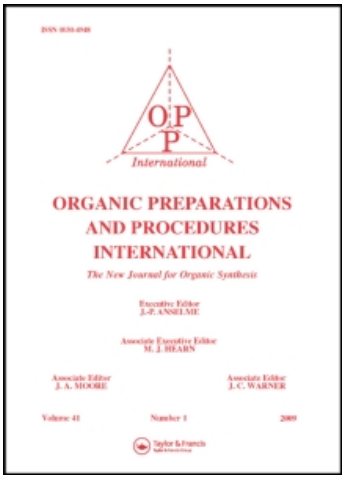

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PROGRESS IN THE FISCHER INDOLE REACTION. A REVIEW

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INTRODUCTION

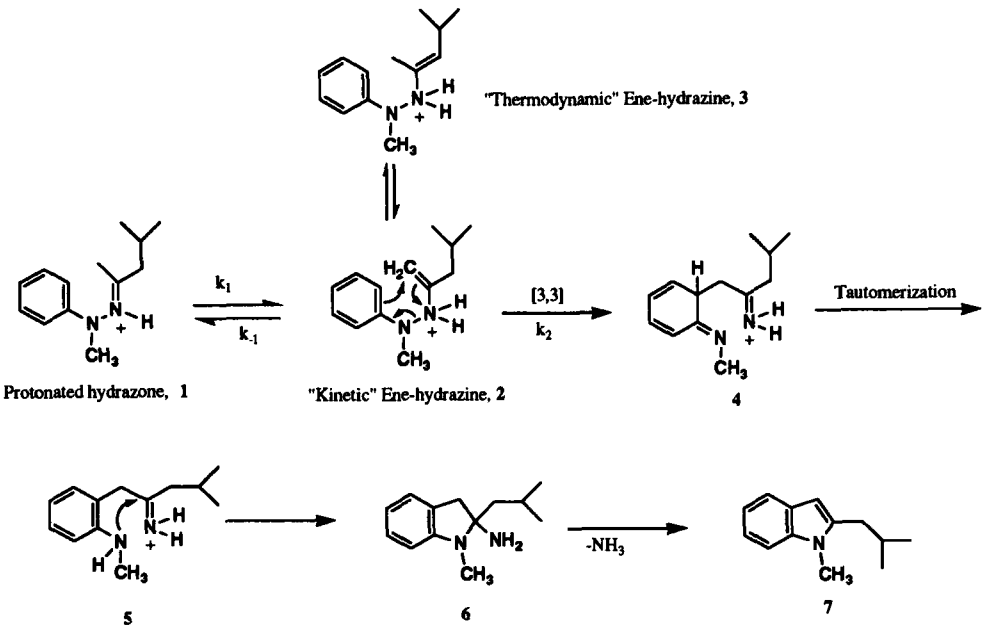
The cyclization of aryl hydrazones to form indoles, named the Fischer indole synthesis based on the discovery of the reaction a century ago by Emil Fischer, has become one of the most versatile and widely studied reactions in organic chemistry. As a testimony to the interest and usefulness of the reaction, the 1982 book on the Fischer indole synthesis by Brian Robinson covered over 900 pages and 3000 references.[1] The present review is an update on the reaction since that comprehensive review.

Two major drawbacks to the Fischer indole reaction are that yields are often low with numerous byproducts being formed, and reactions involving unsymmetrical hydrazines or ketones often give products of mixed regiochemistry. Since these are the areas of major concern, this article will focus primarily on recent studies that deal with these points.

I. MECHANISM

While a number of reaction pathways have been proposed for the indolization reaction, the one formulated by Robinson and Robinson[2] in 1924 is now generally accepted. This pathway is shown in Scheme I for the indolization of the hydrazone formed from 1-methyl-1-phenylhydrazine and methyl isobutyl ketone. Under acidic conditions, the first step involves protonation of the imine nitrogen (observed by ^{13}C and ^{15}N NMR)[3,8] followed by tautomerization to form an ene-hydrazine intermediate (**2** or **3**). The ene-hydrazine intermediate is generally not observable, being of higher energy than the hydrazone, unless it is stabilized by conjugation with an α-substituent. If the ketone is unsymmetrical as shown, the tautomerization can take place at either α-position, thus giving rise to two regioisomeric products. Following the tautomerization, a [3,3]-sigmatropic rearrangement occurs, disrupting the aromaticity of the aryl ring. Rearomatization then occurs via a proton shift to form the amine **5** which attacks the protonated imine to close the 5-membered ring **6**. Finally, loss of ammonia generates the indole nucleus **7**. Recent kinetic and spectroscopic data, plus the isolation of intermediates, have further corroborated this general mechanism.

SCHEME 1



1. Tautomerization Step

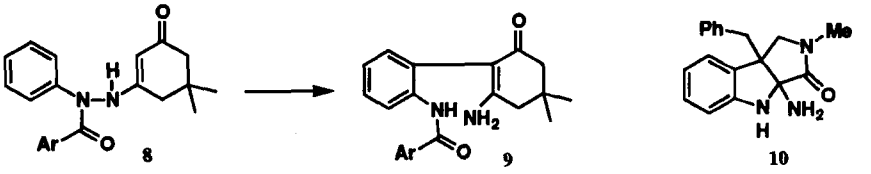
The ene-hydrazine species, **2** or **3**, can be isolated when conjugation makes them more stable than the hydrazone form, for example, in **8**.[4] For simple ketones and aldehydes, rough calculations suggest that the ene-hydrazine form is 4 Kcal less stable than the hydrazone form,[5] and thus they cannot be observed spectroscopically.

2. [3,3]-Rearrangement

Kinetic studies of thermal indolizations indicate that solvent and substituents have small effects on the rate of reaction, consistent with a concerted [3,3] rearrangement having a relatively non-polar transition state.[6] If the α-nitrogen bears an acyl group, the intermediate imine **5** can be observed by ^{13}C and ^{15}N NMR[7,8], and the enamine tautomer **9** was isolated in the reaction of ene-hydrazine **8**.[4] In these cases, the weak nucleophilicity of the amide functionality vs. the amine group makes the addition of the amide to the imine the rate-determining step so that a build-up of intermediate occurs.

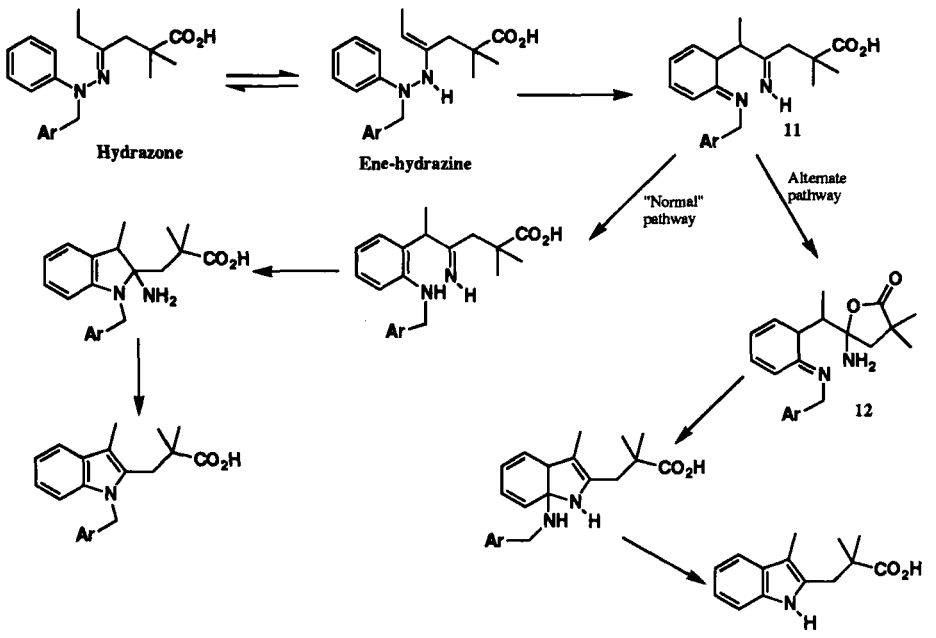
3. Cyclization to Indole Nucleus

Unfavorable ring strain, which prevents elimination of ammonia, has allowed isolation of intermediates corresponding to **6**, such as compound **10**.[9]



In the indolization of hydrazones derived from 4-ketoacids, a pathway competing with the normal cyclization from intermediate imine **11** is attack of the β-nitrogen on the imine derived from the α-nitrogen before rearomatization occurs. It is postulated that an intermediate lactone **12** is responsible for the alternate pathway, which results in elimination of the benzylamine instead of ammonia (Scheme 2).[10]

SCHEME 2

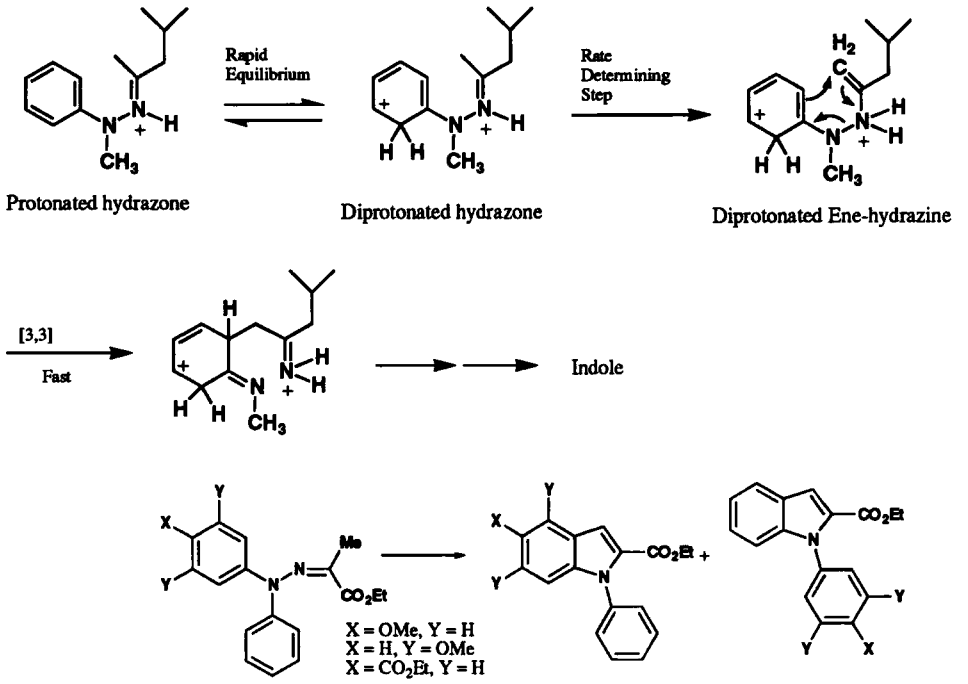


4. Rate Determining Step

Reaction conditions and the nature of the substrate dictate which step of the indolization pathway is rate determining, and can often affect the regiochemistry and the formation of side-products, as discussed further below. In general, formation of the ene-hydrazine intermediate or the [3,3] rearrangement is rate-limiting. As shown above, in special cases the later steps can be rate- determining, as in the case of α-N-acyl hydrazones, and when steric effects slow down or prevent elimination of ammonia. As shown by deuterium kinetic isotope effects, the rate determining step for a single substrate can change from the ene-hydrazine formation to the [3,3] rearrangement by changing the acidity of the medium.[3] In dilute solutions of strong acids or in weak acid solutions, the rate determining step is the [3,3] rearrangement, while in concentrated strong acid solution, the ene-hydrazine formation is rate-determining. Acceleration of the [3,3] rearrangement in strong acid solution by protonation of the aromatic nucleus, which does not occur in weak acid medium, was postulated to account for this dichotomy (Scheme 3).

This postulate is consistent with the regiochemistry observed in the indolization of unsymmetrical 1,1-diarylhydrazines under the strong acid conditions of sat. ethanolic HCl (Eq. 1).[11] In these

SCHEME 3



(1)

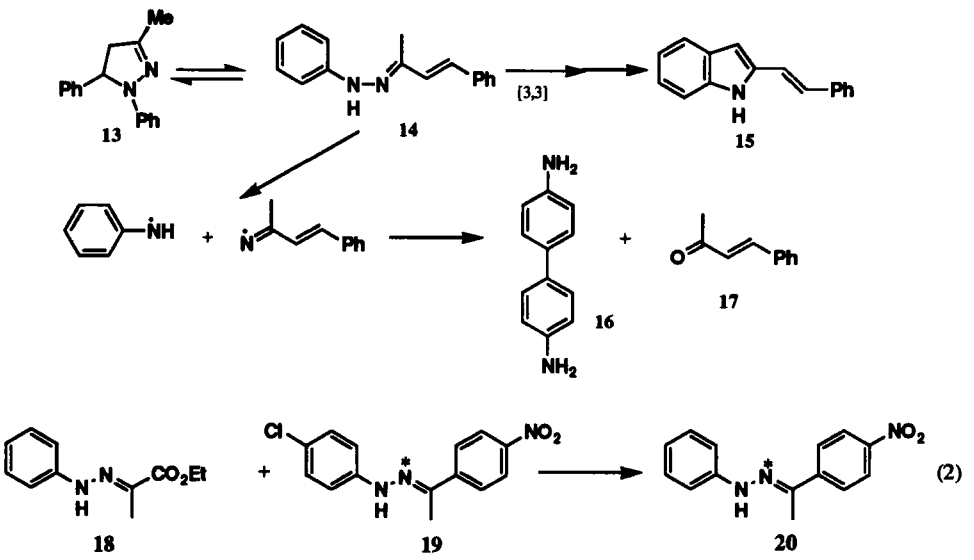
cases, one of the aromatic rings was unsubstituted while the other contained either electron-withdrawing (deactivating) or electron-donating (activating) groups. In all cases, indolization occurred preferentially on the most activated ring, which would be the ring that would be most susceptible to ring protonation. Under neutral conditions, nearly equal amounts of the two isomers were formed, although yields were low.

5. Involvement of Radicals in Fischer Indole Reactions

In 1949 Pausacker and Schubert[12] suggested a radical mechanism for the indolization reaction involving initial homolytic cleavage of the N-N bond of either the hydrazone or ene-hydrazine to form two radicals. This was based on the finding that crossover products were observed when reactions were run involving two hydrazones, suggesting that the reactions were intermolecular in nature. Several later studies explained these results by showing that the hydrazones could interconvert, and that all results could still be explained based on an intramolecular [3,3]-rearrangement.[13] However, the involvement of radicals in these reactions continues to be implicated in selected reactions. In the indolization of pyrazoline **13** in polyphosphoric acid (PPA) at 170°, the expected indole **15** is formed along with products **16** and **17**, which must arise by homolytic cleavage of the hydrazone **14** (Scheme 4).[14]

When a mixture of the unlabeled hydrazone of ethyl pyruvate **18** is mixed with the ^{15}N labeled hydrazone of 4-nitroacetophenone **19**, a crossed hydrazone **20** is formed that can only originate by N-N bond cleavage, which may be occurring by a homolytic process (Eq. 2).[15]

SCHEME 4



(2)

II. CATALYSTS FOR THE FISCHER INDOLE REACTION

Given the low yields that are a persistent problem in many Fischer indole reactions, much research has been devoted to improving yields by changing the nature of the catalyst. The catalysts can be roughly grouped into 4 categories: strong acids, weak acids, solid acids, and Lewis acids. In addition, reactions employing no catalyst (thermal conditions) have gained popularity recently.

1. Strong Acids

p-Toluenesulfonic acid in benzene or toluene was found to be a superior catalyst for indolization of arylhydrazones of ethyl pyruvate, giving yields in the range of 70-90%.[16,17] Use of polyphosphoric acid (PPA) with xylene as an immiscible co-solvent gave improved yields (by 7 to 21%) for indolizations as compared to those run in neat PPA.[18]

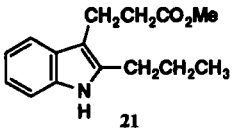
2. Weak Acids

Pyridine hydrochloride was found to be a mild and effective catalyst for Fischer indole reactions in which strong acids caused significant decomposition. The reactions are simply run by using the hydrochloride salt of the hydrazine in pyridine as solvent.[19]

3. Solid Acids

The use of heterogeneous acids is beneficial in a number of cases. Indolization of a variety of ketones and phenylhydrazine in the presence of montmorillonite KSF clay under microwave irradiation provided indoles in yields of 72-90%.[20] Similarly, acidic Zeolite catalysts such as Mordenite and Zeolite Y can be used in Fischer indolizations, generally giving higher yields than conventional acid catalysts such as acetic acid. In the cases of unsymmetrical ketones, the regioisomer distribution was different from solution acid catalysts. For example, indolization of phenylhydrazine and methyl 5-oxooctanoate, the ratio of isomers **21/22** was 65/35 for acetic acid with 60% yield, 85/15 for Mordenite with 95% yield, and 9/91 for Zeolite Y with 93% yield.[21,22] The sulfonic acid resin Amberlyst 15 in

benzene or toluene was an effective catalyst for indolization of pyruvate-derived hydrazones and had the advantage of easy isolation by simply filtering catalyst and crystallizing product.[16,17]



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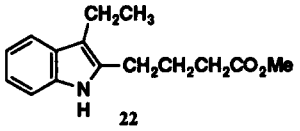


22

Indolization of acetaldehyde by typical solution phase reactions has met with failure, but vapor-phase cyclization over oxide catalysts such as alumina, MgO, and SiO_2-MgO gave yields near 60%.[23,24]

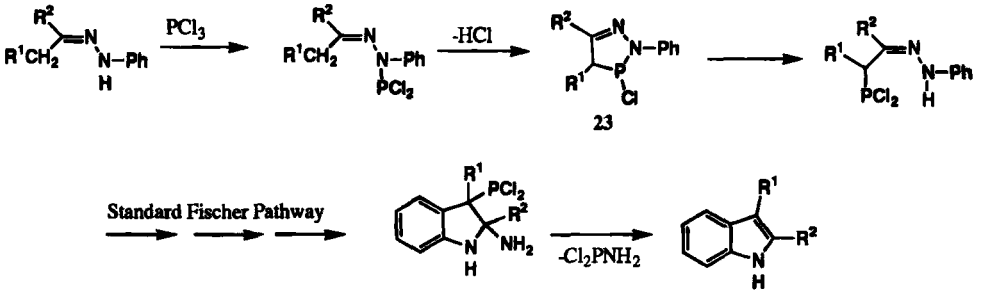
4. Lewis Acids

In a series of papers, Baccolini and co-workers[25-30] have described the use of a stoichiometric amount of PCl_3 in benzene or dichloromethane solution to effect indolizations in 70-90% yields. The reactions are run at room temperature or below and are generally complete in a few minutes, and are therefore much milder than many indolization conditions. As a result, yields are often higher using PCl_3 than with other catalysts, especially in the cases of reactions involving alkoxy-substituted hydrazines, in which yields were improved by 11-37% over conventional methods.[28] In the reactions involving 3-substituted hydrazines, the 6-substituted indole predominated over the 4-substituted indole in all cases, being 3:2 when the substituent was Cl or Me, and 3:1 to 5:1 when the substituent was alkoxy.[28] In the indolization of 3-hexanone, where two regioisomeric indoles are possible, only 3-methyl-2-*n*-propylindole was obtained.[27] However, Prochazka and Carlson could not reproduce this result, obtaining a 7:3 ratio of 3-methyl-2-*n*-propylindole to 2,3-diethylindole.[31] In the indolization of 2-methyl- and 3-methylcyclohexanone, where again two regioisomers are expected, only one isomer was isolated in each case. In the case of 2-methylcyclohexanone, indolization occurred *via* the most substituted side to give 11-methyl-1,2,3,4-tetrahydrocarbazolenine,[32] which is the same regiochemistry observed when weak acid catalysts such as HOAc are used.[33a] With 3-methylcyclohexanone the reaction toward the least substituted side occurred to give 2-methyl-1,2,3,4-tetrahydro-9*H*-carbazole,[32] which is similar to all other reports in the literature using a variety of acid catalysts.[33b] Ketones bearing amino, alkoxy, chloro, alkoxycarbonyl, phosphonic, and olefinic-funcionalities gave high yields of indoles in the PCl_3-mediated reactions.[30] A mechanism for the indolizations involving PCl_3 has been proposed which involves initial reaction of the α-nitrogen with PCl_3 followed by transposition of the phosphorus to the α-carbon *via* the diazaphospholine **23**, followed by the standard Fischer indole pathway of ene-hydrazine formation, [3,3]-rearrangement, ring closure, and elimination of Cl_2PNH_2. Support for this mechanism comes from the observation that diazaphospholes are formed from hydrazones that cannot undergo indolizations, such as alkylhydrazones (Scheme 5).[29,30]

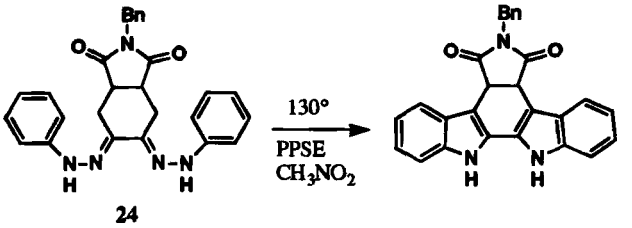
Another phosphorus-based catalyst that has been used periodically in Fischer indole reactions is polyphosphoric acid trimethylsilyl ester (PPSE). The reagent is made from P_2O_5 and hexamethyldisiloxane, and is a mixture of cyclic and linear polyphosphate esters.[34] Reaction of phenylhydrazine

and diethyl ketone with 4 equiv. of PPSE in dichloroethane for 10 min at 85° gave 2-ethyl-3-methylindole in 88% yield.[34] The same yield was obtained in this reaction using a heterogeneous analog of

SCHEME 5



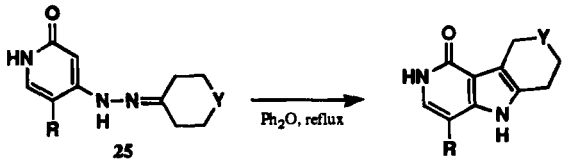
PPSE made from P_2O_5 and silica gel.[34] Bis-indolization of dihydrazone **24** was accomplished in 74% yield using PPSE in nitromethane, whereas conventional Bronsted and Lewis acids gave poor yields and complex mixtures.[35]



5. "Non-catalytic" Thermal Fischer Indole Reactions

In 1957 Fitzpatrick and Hiser reported that Fischer indole reactions could be run in the absence of acid by heating to 180° to 250° in solvents such as ethylene glycol, diethylene glycol, and tetralin.[36] The "non-catalytic" thermal reactions have gained popularity recently, and are particularly effective in indolizations involving heteroaromatic hydrazines, such as pyridines, that are difficult to cyclize under acid conditions due to protonation of the heteroatom.

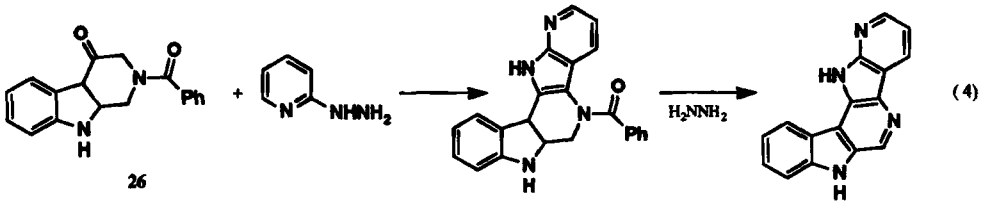
In a series of papers Bisagni and coworkers have described the indolization of a series of pyridone-based hydrazones **25** in 70-95% yield by refluxing for 30 min in diphenyl ether (Eq. 3).[37-41] The



(3)

resulting indoles were aromatized *via* dehydrogenation using Pd/C to give compounds useful in the treatment of cancer.

Cook and coworkers have used the thermal indolization to react ketone **26** with a variety of arylhydrazines, including 2- and 3-hydrazinopyridine, phenylhydrazine, 1- and 2-hydrazinonaphthalene, 2- and 3-hydrazinoquinoline, 1-hydrazinoisoquinoline, and 1-hydrazinophthalazine, giving yields generally around 70%.[42-46] The resulting indoles were deamidated and air oxidized to give the fully aromatized products, as shown in Eq. 4 for the reaction with 2-hydrazinopyridine, which are

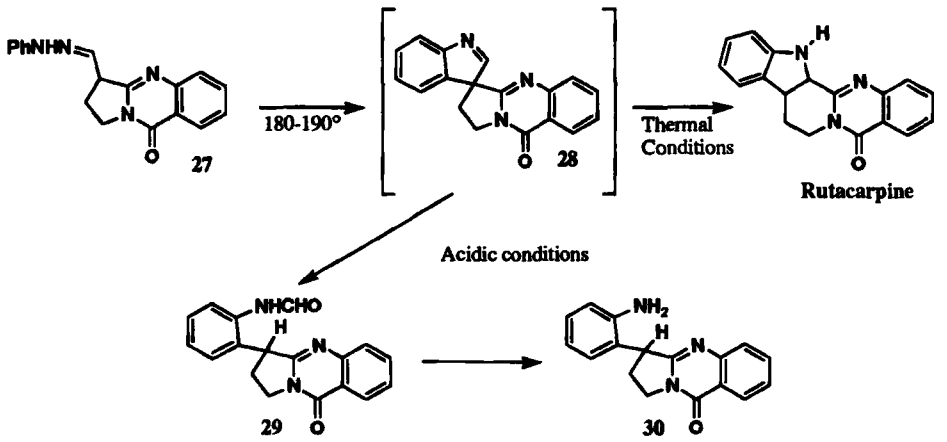


(4)

useful as benzodiazepine receptor agonists. The thermal reactions were run either neat at 160° or in refluxing ethylene glycol.

Thermal indolization of hydrazone **27** in Dowtherm A at 180-190° for 0.5 hr provided the spiroindole **28** which then rearranged to the alkaloid rutaecarpine. Using acid catalysis (10% aq. HCl in *n*-BuOH) instead of the thermal conditions, the spiroindole undergoes a retroaldol reaction to form **29** which then loses formaldehyde to give **30** (Scheme 6).[47] Although most thermal indolizations

SCHEME 6



reported in the literature have been performed with hydrazones derived from ketones, the reaction with hydrazone **27** is an example of a reaction with an aldehyde-derived hydrazone. Likewise, 3,5-dimethylindole was prepared from propionaldehyde *p*-tolylhydrazone under thermal conditions.[48]

A comparison of the thermal reaction vs. the reaction catalyzed with 2 moles of H_2SO_4 for a series of cyclohexanone arylhydrazones in ethylene glycol solution indicated that the acid-catalyzed indolizations were 7- to 30-fold faster, depending on the substituent in the aryl ring and the temperature at which the comparison was made. For the thermal reaction, there was no difference in rate

between glycol and *n*-decane as solvents, indicating that the hydroxylic solvent was not serving as an acid catalyst.[49-50]

A few reports in the literature indicate that the Fischer indole reaction can be run in the presence of base, suggesting that base catalysis is also possible. However, a study of the indolization of cyclohexanone 4-pyridylhydrazone and acetophenone N-butylphenylhydrazone in the presence of NaOEt, KOH, or $LiNEt_2$ demonstrated that the rate of reaction in sulfolane solution was unaffected by the presence of base.[51,52] In other words, the reactions were simply thermal, uncatalyzed reactions. The study also indicates that the high temperature thermal reactions are not being catalyzed by acidic sites on the glass surface, since the presence of the base would definitely eliminate that possibility. Hence, the thermal reactions appear to be truly noncatalytic in nature.

III. THE KETONE/ALDEHYDE COMPONENT

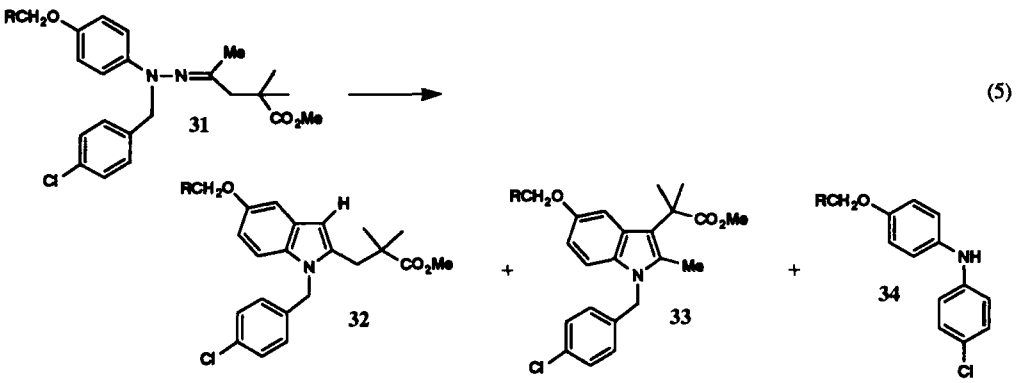
1. Regiochemistry in Unsymmetrical Monoketones

As discussed above in Section I on mechanism, unsymmetrical ketones can tautomerize in either direction, resulting in formation of two regioisomers (Scheme 1). Three factors that control the regiochemistry are the acidity of the medium, electronic effects in the hydrazine, and steric effects in the ketone. The outcome of many indolizations is often affected by a combination of these factors.

A. Acidity of Medium.

As discussed in the section on mechanism, the acid strength of the solution in many cases determines the regiochemical outcome of the Fischer indole reaction. Strong acid conditions favor formation of the least substituted ene-hydrazine, while weak acid conditions favor the more substituted ene-hydrazine. Eaton's acid (10% P_2O_5 in $MeSO_3H$) has been shown to be an effective strong acid for preparation of 3-unsubstituted indoles from methyl ketones. For example, reaction of the hydrazone **31** in strong acids such as PPA and H_2SO_4 led to low yields and large amounts of aniline **34**. Use of a 1:1 mixture of Eaton's acid in sulfolane gave a 40:1 ratio of indole **32** to **33** in 85% yield.[53]

Hydrazone **35** cyclized through the most substituted ene-hydrazine to give indolenine **36** in an HCl/CH_2Cl_2 solution, but to the angular indole **37** when treated with 85% H_2SO_4.[54] Indolization of



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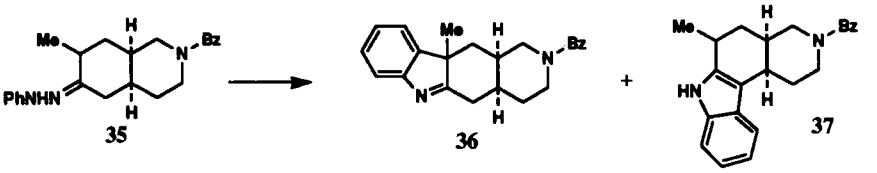
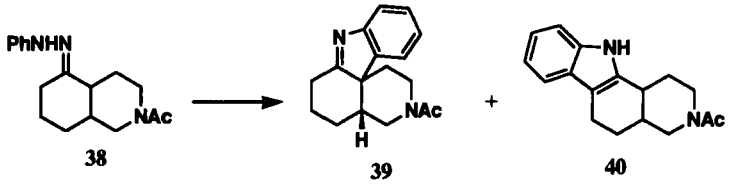


(6)

hydrazone **38** gives cyclization through the least substituted ene-hydrazine to make indole **40** exclusively in HOAc or HOAc saturated with HCl or with $ZnCl_2$ in HOAc. However, attenuating the acidity by adding NaOAc to the medium resulted in formation of a 3 : 2 ratio of **39** : **40**.[55]

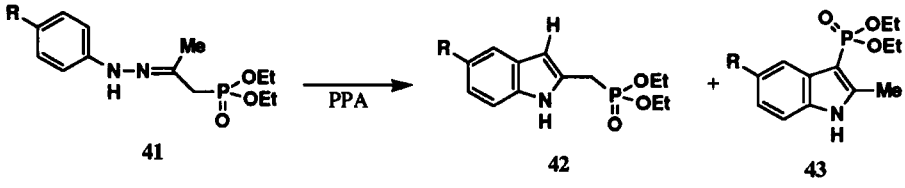


(7)

A survey of 11 Lewis acids in 8 solvents at varying temperatures for the indolization of the phenylhydrazones of 3-hexanone, 2-hexanone, 3-undecanone, 1-phenyl-2-butanone, and 5-methyl-3-heptanone indicated that the Lewis acid, solvent, and temperature played little role in determining regioselectivity.[31]

B. Electronic Effects in the Hydrazine

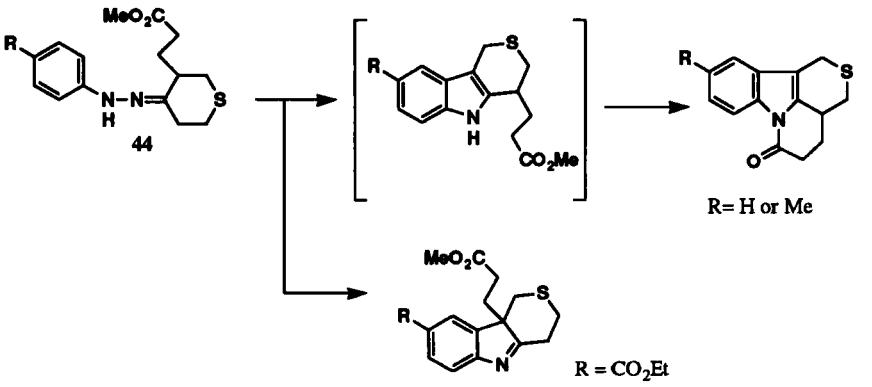
Another factor controlling regiochemistry is the substituent in the aryl hydrazine. In the indolization of the hydrazone **41**, cyclization occurs mainly through the most substituted ene-hydrazine with electron-donating substituents while with the unsubstituted hydrazine the indole arising from cyclization through the methyl group predominates (Eq. 8).[56]



R = 4-MeO	0%	63%
4-Me	23%	48%
H	45%	25%
4-Cl	25%	25%

(8)

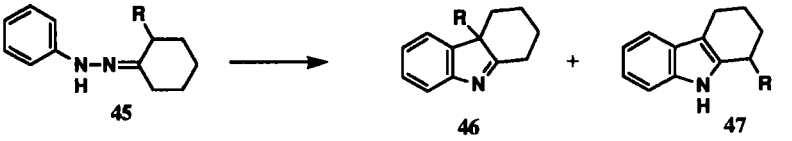
However, opposed to this, indolization of hydrazones **44** gave only cyclization to the more branched side with an electron-withdrawing substituent (R = CO_2Et) and only to the least branched side with R = H or Me (Eq. 9).[57]



(9)

C. Steric Effects in the Ketone

Reaction of the phenylhydrazones of 2-alkylcyclohexanones **45** demonstrated that steric effects can also control the regiochemistry of indolization (Eq. 10).[58] With increasing bulk at the tertiary carbon, more indolization occurs at the secondary carbon.

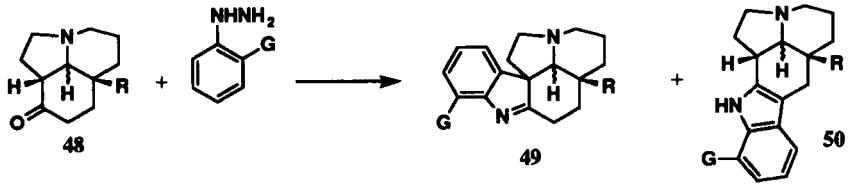


(10)

Acid Catalyst	Product Ratios **46** / **47**			
	2-Me	2-Et	2-*i*-Pr	2-*t*-Bu
HOAc	40	12	6.5	0
H_2SO_4	1.8	4.1	0.8	0
BF_3	0.9	2.7	0.1	0
$ZnCl_2$	0.3	3.0	0.5	0
PPA	0.2	4.4	0.6	0

D. Regiochemistry in the Synthesis of Indole Alkaloids

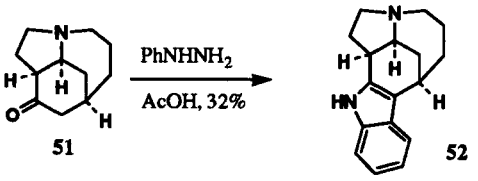
Cyclizations to form the indole nucleus of several naturally occurring indole alkaloids have been the subject of numerous studies over the past 30 years, with the control of regiochemistry being a primary problem. In the synthesis of *Aspidosperma* alkaloids, the cyclization of the tricyclic ketone **48** with 2-methoxyhydrazine in refluxing acetic acid affords the indole **49** arising from cyclization from the tertiary carbon when G = MeO and when R is allyl,[59-60] ethyl,[61-62] and 2-methoxyethyl[63] (Eq. 11).



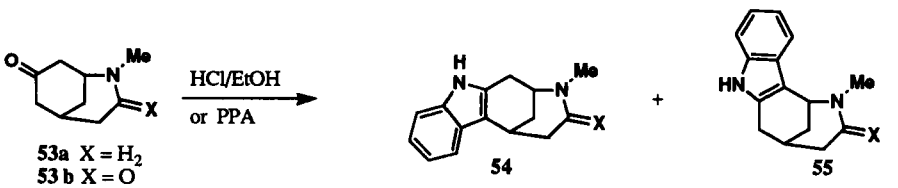
(11)

However, with G = H and R = H, cyclization through the secondary carbon occurs to give **50**, apparently due to the reduced steric effects when R is H.[64] Even with R = Et and G = MeO, Ban and coworkers report a mixture of **49** and **50** when the reaction is run in formic acid at reflux, suggesting that both isomers may have been formed but only one isolated in the other reports.[65]

In the attempt to prepare *Strychnos* alkaloids, indolization of the ketone **51** in acetic acid gave only the undesired linear regioisomer **52** (Eq. 12).[66] In related work, indolization of the amino-ketone **53a** in HCl/EtOH gave only a single regioisomer **54a** in 62% yield, while the amide-ketone **53b** gave a 3:1 mixture of indole isomers **54b** and **55** in PPA (Eq. 13).[67,68]



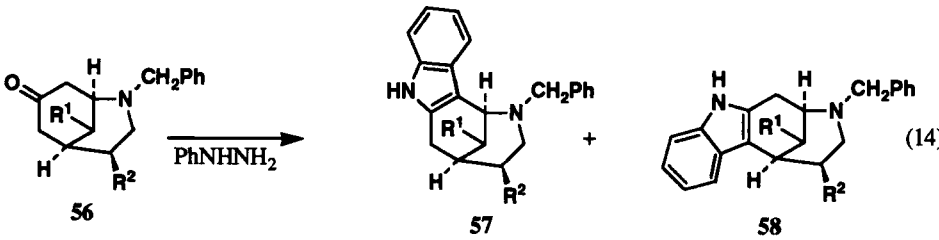
51 **52** (12)



53a X = H_2
53b X = O

54 + **55** (13)

Both medium and steric effects were observed in the related indolizations of ketone **56**. With R^1 and R^2 = H, isomer **58** is formed exclusively in HCl/EtOH, while mixtures are formed in acetic acid and PPA. With R^1 = H and R^2 = Et, isomer **58** predominates under all conditions. As opposed to this, when R^1 = Et and R^2 = H, **57** is the major isomer formed (Eq. 14).[69]

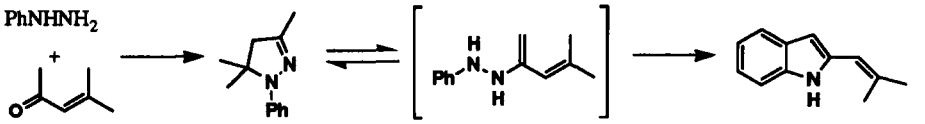


56 **57** + **58** (14)

R^1	R^2	Conditions	%57	%58
H	H	HOAc	13	9
		HCl/EtOH	--	40
		PPA	12	18
H	Et	HOAc	--	20
		HCl/EtOH	--	57
		PPA	14	20
Et	H	HOAc	26	--
		HCl/EtOH	30	15
		PPA	17	10

2. Indolization of α,β-Unsaturated Ketones

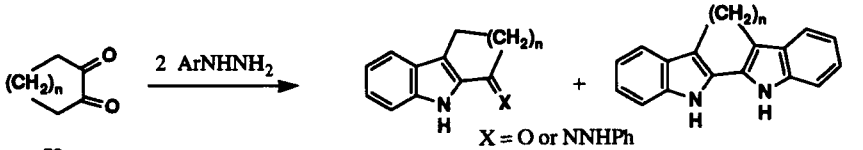
Indolizations of α,β-unsaturated ketones have generally been unsuccessful since the ketones form unreactive 2-pyrazolines. However, Bergman and Pelcman found that mesityl oxide could be cyclized in 26% yield using either HOAc or PPA as catalysts to form the vinyl indoles (Eq. 15), which had been previously prepared in a multi-step synthesis.[70]



(15)

3. Indolizations of 1,2-Diketones

Cyclic 1,2-diketones can form either the mono- or bis-indole depending on conditions (Eq. 16). In general, the mono-indole is formed when strong acids are used in alcoholic solvents, while the best method for preparing the bis-indole is refluxing acetic acid.



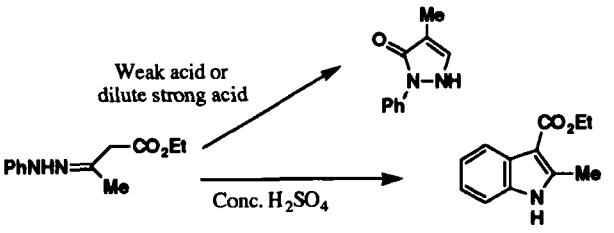
59 60 61

(16)

n	Ar	Conditions	% Yield **60**	% Yield **61**	Ref.
2	Ph	HCl/EtOH	50-89	–	71
2	Ph	HOAc/MeOH,reflux	70	60-73	72
2	Ph	HOAc,reflux	–		71,72
3	Ph	HOAc, reflux	60	23	73
4	Ph	HOAc, reflux	60	21	73
2	4-ClC_6H_5	H_2SO_4, EtOH, 65°	72	–	74
2	4-ClC_6H_5	HOAc, reflux, 12 hrs	–	75	74
4	8-Hydrazino-quinoline	PPA	–	68	75

4. Indolizations of 1,3-Diketones

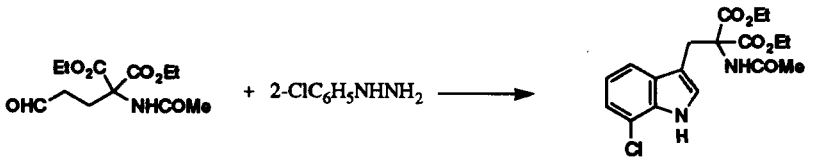
Fischer indole reactions of acyclic 1,3-diketones or 1,3-ketoesters are problematic as the phenylhydrazones form pyrazoles or pyrazol-3-ones. However, a 60% yield of indole was obtained from reaction of the phenylhydrazone of ethyl acetoacetate when the reaction was carried out at -10° in conc. sulfuric acid (Eq. 17).[4] N-protonation in the concentrated acid prevents pyrazol-3-one formation.



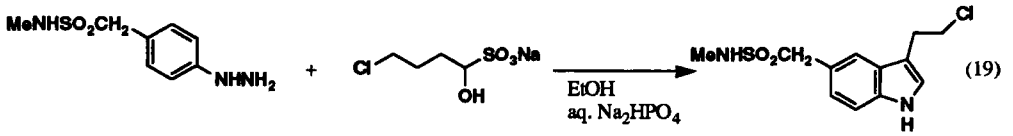
(17)

5. Aldehydes and Acetals

Fischer indole reactions with aldehydes give 2-unsubstituted indoles.[76-82] An example using sulfuric acid as catalyst is shown in Eq. 18 in which a 99% yield of indole was obtained.[76] Since aldehydes are labile to oxidation and aldol reactions, the aldehyde is often protected as the acetal, which is hydrolyzed *in situ* during hydrazone formation.[83-84] An attractive alternative is protection of the aldehyde as the bisulfite addition product, as used in the synthesis of the anti-migraine drug Sumatriptan (Eq. 19).[85]

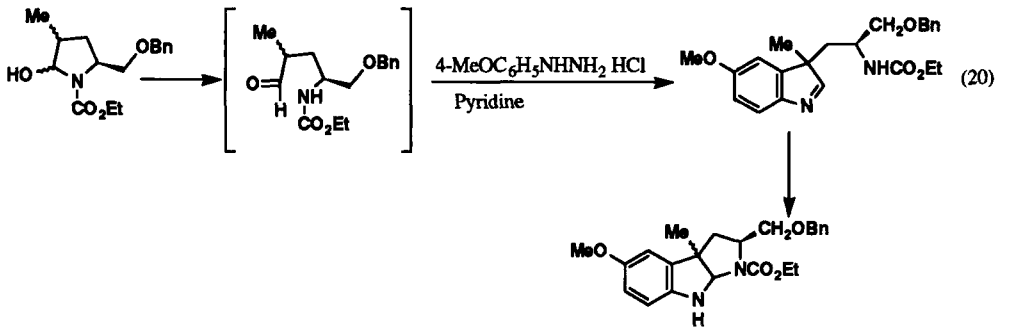


(18)



(19)

The aldehyde can also be protected intramolecularly as an aminal, as shown in Eq. 20 in the synthesis of the alkaloid physostigmine.[86]



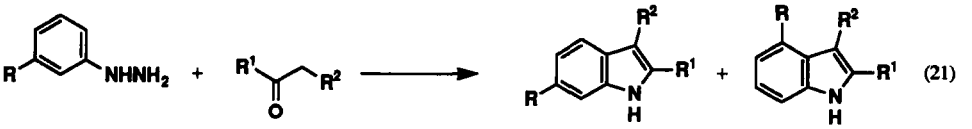
(20)

IV. THE HYDRAZINE COMPONENT

The hydrazine component of the Fischer indole synthesis is usually generated from the corresponding aniline by formation of the diazonium salt with $HCl/NaNO_2$ and subsequent reduction by a variety of agents. Since the hydrazines are often unstable as their free bases, they are generally stored as HCl salts, and can often be used directly as the HCl salt in the indolizations. Stoddart and co-workers have found that the hydrazine could be protected with the Boc group, which has the advantage of allowing further chemical transformations of the hydrazine, and that the Boc-protected hydrazine could be used directly in the Fischer indole reaction, since it was removed in the aq. acidic conditions.[87]

1. Regiochemistry in 3-Substituted Hydrazines

3-Substituted hydrazines react in the Fischer indole reaction to give mixtures of 4- and 6-substituted indoles (Eq. 21).[88] The electronic nature of the substituent affects the regiochemical



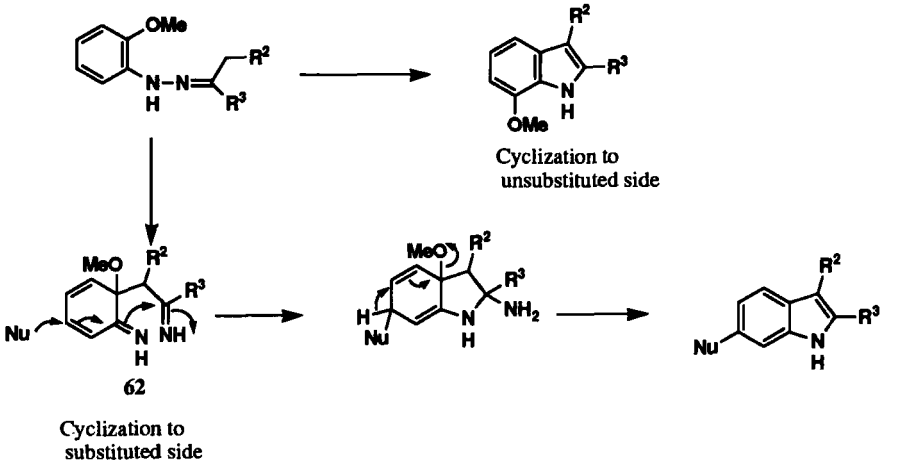
(21)

outcome to only a slight extent, with electron-donating substituents generally producing slightly more of the 6-substituted indole (up to a 5:1 ratio for 3-MeO or 3-EtO[28,89]) and electron-withdrawing substituents producing somewhat more of the 4-substituted indole (up to 3:1 ratio for 3-NO_2[90]). Since the regiochemistry is established during the [3,3]-rearrangement, the substituents are expected to have only a minimal effect, as observed.

2. Indolizations of 2-Substituted Hydrazines

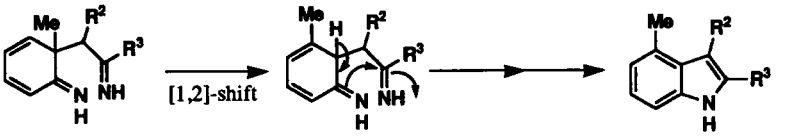
Ortho-substituted hydrazines often react more sluggishly than the 3- or 4-substituted analogs, and in several cases give low yields of desired indole products along with numerous side-products.[91] A number of papers have been devoted to identifying these byproducts and in understanding the reasons for the unusual behavior of 2-substituted hydrazines under Fischer indole conditions. In general, cyclization of the 2-substituted arylhydrazone can occur either to the unsubstituted side to give the "normal" indole product, or to the substituted side, which leads to an intermediate **62** that cannot easily rearomatize (Scheme 7). Therefore, other reactions take place. As shown in Scheme 7, where

SCHEME 7



the *ortho*-substituent is OMe, nucleophilic attack occurs on the ring (by Cl^- if HCl is used as the acid catalyst) with subsequent loss of MeOH to reform the aromatic nucleus.[92] When R^2 is H, this route is particularly favored, since there is little steric hindrance in the intermediate **62** between OMe and R^2 = H. When the *ortho* substituent is not a leaving group such as OMe, then the substitution route

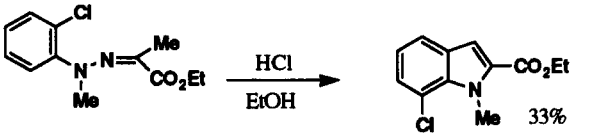
shown in Scheme 7 is not viable because there is no way to rearomatize. In these cases, rearrangement often occurs, as shown in Eq. 22 for the o-Me compound.[93] After the methyl shift, the usual



(22)

indolization mechanism applies, with proton transfer now being available to initiate rearomatization. Since the reactions are run in strong acid, it is likely that protonation to form cations occurs, which aids in the methyl shifts.

The above examples indicate that electron-donating groups such as Me and OMe in the 2-position tend to direct cyclization to that position instead of the unsubstituted position, especially when there is no steric hindrance to cyclization arising from the ketone portion of the hydrazone. When an electron-withdrawing group such as CF_3 or Cl is present in the 2-position, indolization is then favored at the unsubstituted side (Eq. 23).[92,94] The 2-tosylate and 2-triflate groups also direct the

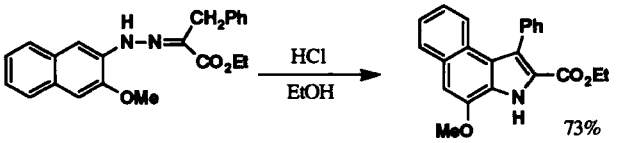


+ 12% of 4 products arising from cyclization to the substituted side

(23)

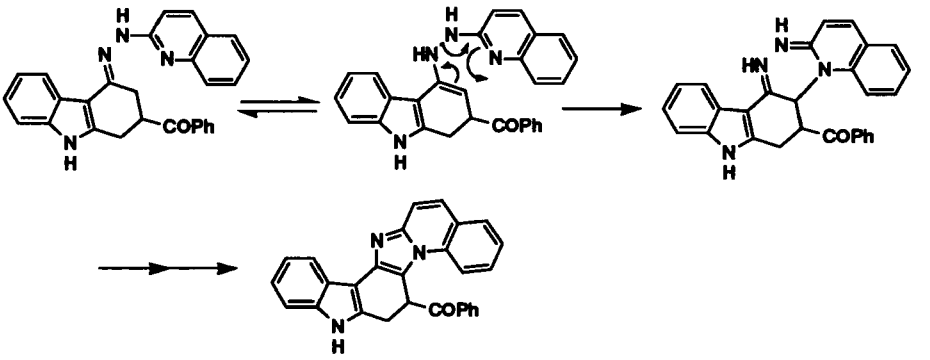
indolization to the unsubstituted side, indicating the increased electron-withdrawing nature of these groups compared to alkoxy.[95]

With hydrazones derived from 2-hydrazinonaphthalene, indolization always occurs to the 1-position instead of the 3-position of the naphthalene because there is less disruption of the aromaticity during the [3,3]-rearrangement. In an attempt to induce cyclization to the 3-position, a 3-OMe group was introduced, but cyclization still occurred at the 1-position (Eq. 24).[96] Even by



(24)

introducing electron-withdrawing groups at the 1-position, which should direct cyclization to the unsubstituted side, no cyclization occurred at the 3-position.[97] The tendency of naphthalenes to cyclize to the 1-position is also manifested in the quinolines. Indolization of the hydrazone of 2-hydrazinoquinoline results in cyclization with the quinoline nitrogen to form a new N-C bond, rather than cyclization at the 3-position (Eq. 25).[46]



(25)

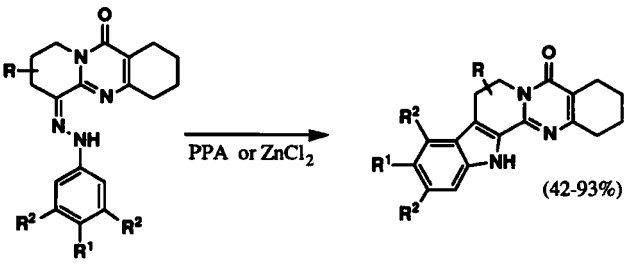
3. Fischer Indole Reactions with Deactivated Hydrazines

Indolizations involving hydrazines having electron-withdrawing substituents such as nitro groups are often sluggish and low yielding reactions. A few examples are given below that involve nitro-substituted hydrazines wherein experimental conditions have been optimized, giving good yields of the desired indoles. Reaction of the 4-nitrophenylhydrazone of 2-pentanone and other simple ketones was carried out in concentrated HCl at reflux for overnight to give the 5-substituted indoles in 69-76% yield.[98] Likewise, indolization of naltrexone with 2-, 3-, and 4-nitrophenylhydrazone was carried out in concentrated HCl or a 1:1 mixture of conc. HCl and HOAc to give the corresponding nitroindoles in yields ranging from 50-100%.[99] In the indolization of 2-methoxy-5-nitro-4-[N-(2-propenyl)methanesulfonamido]phenylhydrazone of ethyl 2-oxobutanoate, a yield of 66% was obtained by running the reaction in 5 % trifluoroacetic acid in toluene at reflux for 8 hrs.[100] The indolization of propionaldehyde 3-nitrophenylhydrazone was carried out in a 2-phase mixture of toluene and 85% phosphoric acid at 100° for 3 hrs to give a nearly equal mixture of the 4- and 6-nitroindoles in overall 90% yield.[101]

4. Heterocyclic Hydrazines

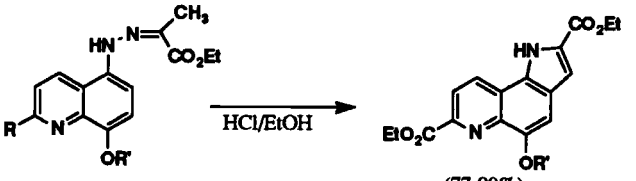
Several natural products and synthetic drugs which contain the indole moiety also have other heterocyclic rings, and therefore the indolization of heterocyclic hydrazines has been important in the synthesis of these complex compounds. As discussed in the section on Catalysts, often the best way of cyclizing these hydrazines is *via* the "non-catalytic" thermal indole reactions. Several examples were given in that section; this section deals with more examples, several of which are acid catalyzed.

Rutaecarpine and its derivatives can be derived by a Fischer indole reaction as the final step, using either zinc chloride at 200° or polyphosphoric acid at 180° (Eq. 26).[102-104]



(26)

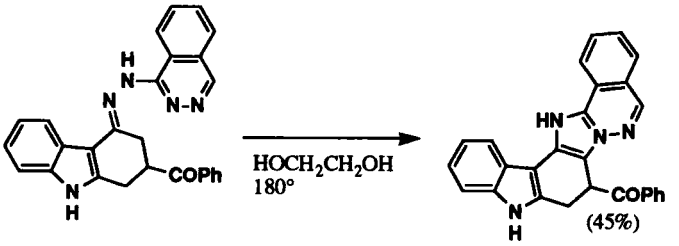
Methoxatin analogs were prepared by a Fischer indole reaction in saturated ethanolic HCl (Eq. 27).[105-106]



R = CN or EtO_2C
R' = H or Me

(27)

The aza-Fischer indole reaction of 1-hydrazinophthalazine afforded cyclization *via* the nitrogen atom as shown in Eq. 28.[46]



(28)

Other examples of the use of heterocyclic hydrazines include the synthesis of quinoline-based indoles for anti-neoplastic drugs[107] and tricyclic quinoline-indoles for anticonvulsant drugs.[108]

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