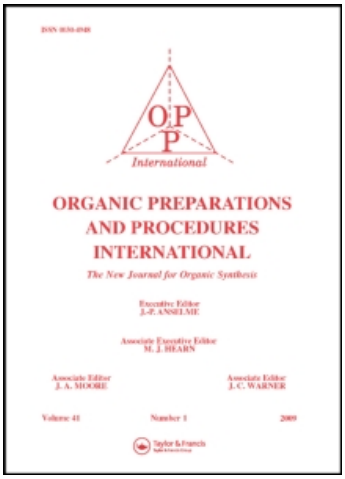

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PREPARATION AND REACTIONS OF INDOLIN-2(3*H*)-ONES. A REVIEW

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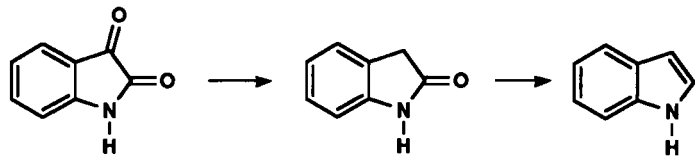
INTRODUCTION

Indolin-2(3*H*)-ones (oxindoles) represent an important class of compounds which are structurally related to the indoles. The parent member of this series, oxindole (**1**) has been known since its preparation was first reported by Baeyer in 1866 *via* the reduction of isatin (**2**).[1] Baeyer subsequently demonstrated the skeletal relationship between these ring systems upon further reduction of oxindole to indole (**3**).[2]



2 **1** **3**

In the intervening years, a plethora of synthetic methods have been developed for the preparation of the indolin-2-one ring system. A number of good reviews have been written outlining some of the classical methods of preparation as well as some of the important reactions of indolin-2-ones.[3-5] In the past twenty years a variety of newer methods have been described for the preparation of these compounds including rhodium-carbenoid insertions,[6] radical cyclizations,[7] zerovalent metal cyclizations[8] and Sommelet-Hauser type rearrangements.[9]

The burgeoning attention these compounds have received of late is due in large part to their importance in biological systems. The discovery of tetracyclic and pentacyclic oxindole alkaloids related to the secoyohimbines and heteroyohimbines in plant extracts from *Mitragyna* and related genera have fueled this interest.[10] A number of metabolites of the Indoleacetic Acid (IAA) pathway containing the indolin-2-one ring system have been isolated from plant sources as glucosyl-conjugates.[11-13] Synthetic efforts have led to compounds having potential pharmaceutical and agricultural utility. Compounds possessing the indolin-2-one moiety have shown activity as nonsteroidal cardiotonics,[14] anesthetic agents,[15] and antibacterial compounds.[16] Compounds containing the the indolin-2-one ring system have also been reported as possessing herbicidal[17,18] and insecticidal[19] activity.

The main objective of this review is to survey the synthesis and reactions of indolin-2-ones with particular emphasis on the literature coverage from 1970 to mid 1992.

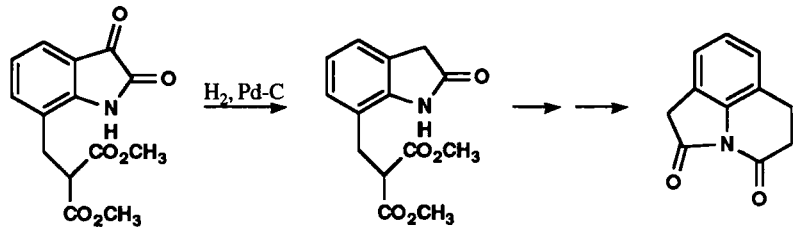
I. PREPARATION OF INDOLIN-2-ONES

1. Preparation from Isatins and Indoles

The earliest reported preparation of the indolin-2-one ring system (**1**) was *via* the reduction of isatin (**2**).[1] Because indolin-2-ones occupy a key position in the indole series between indole (**3**) and isatin (**2**), it is not surprising the number of reagents which have been employed for both the reduction of isatins and the oxidation of indoles, giving rise to a variety of substituted indolin-2-ones.[3] Some of the more recent applications are described below.

a. From Isatins

Many of the classical methods of isatin reductions to indolin-2-ones proceed stepwise



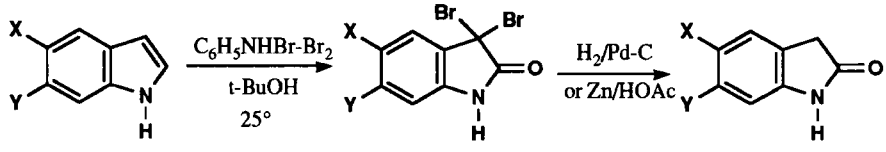
4 **5** **6**

through the the isolable dioxindole (3-hydroxyindolin-2-one). More recently, a number of substituted indolin-2-ones have been prepared directly *via* a modified Wolff-Kishner reduction.[20] In a study of benzo-fused analogs of the cognition activator rolziracetam, Pavia and co-workers[21] reduced the isatin derivative **4** directly to **5** by catalytic hydrogenation.

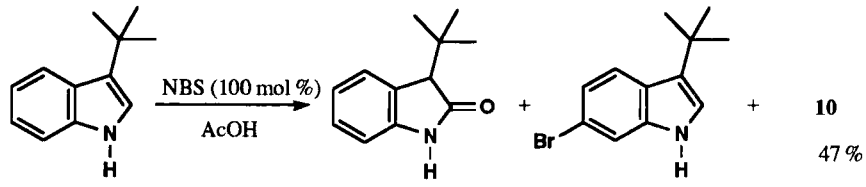
b. From Indoles

Various oxidants have been used to convert indoles to 3-halo- and 3,3-dihaloindolin-2-ones, which in turn could be reduced to 3-unsubstituted indolin-2-ones.[3,4] Recent utilization of pyridinium bromide perbromide as the oxidant has given moderate yields of 3,3-dibromo-indolin-2-ones **8**.[22,23] Reduction of **8** then gave a series of indolin-2-ones **9**. Other oxidants, including NCS[24,25] and NBS[26,27] have been used. Parrick and co-workers[26] found that mild alkaline hydrolysis of compounds like **8** gave isatins.

Oxidations of 3-alkylindoles have also been carried out. Oxidation of 3-methylindole with bromine (100 mol %)[28] gave 3-methylindolin-2-one while treatment with NBS (300 mol %)[29] has given 3,5-dibromo-3-methylindolin-2-one. Increasing the bulkiness of the 3-substituent allows competing ring bromination to take place as was demonstrated with **10**.[30]

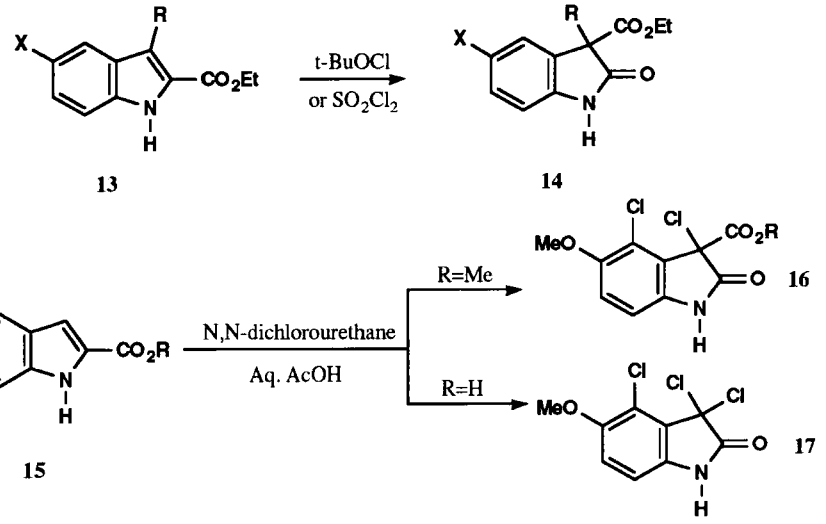


7 **8** **9**



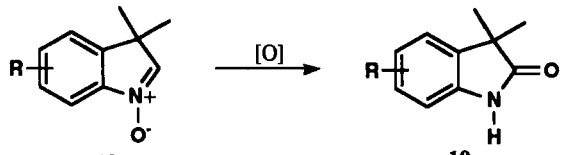
10 **11** 24 % **12** 22 %

Indoles containing a range of 3-substituents have been oxidized smoothly to indolin-2-ones using DMSO/aq. HCl.[31-34] Other reagents, although not widely used, have been reported, including MoO_5-HMPA[35] and thallium trinitrate.[36] 3-Substituted indole-2-carboxylic acid esters and amides (**13**) have undergone rearrangement to 3-carboalkoxyindolin-2-ones **14** upon treatment with *t*-butyl hypochlorite[37] and sulfuryl chloride.[38] Bass[39] reported a similar rearrangement of 3-unsubstituted analog **15** to give **16** when R=Me, but use of the indole-2-carboxylic acid **15** (R=H) has led to loss of the carboxyl group leading to **17**.[39,40] Both **16** and **17** could be converted to the 4-chloro-5-methoxyindolin-2-ones. Other 3-substituted indoles have been converted to indolin-2-ones *via* oxidative cyclization[41] and photochemical rearrangements.[42,43]



13 **14** **15** **16** **17**

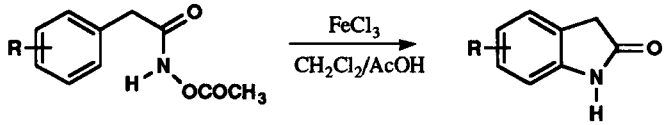
Indolenines have also been converted to indolin-2-ones. Indolenine-N-oxides of type **18** have been oxidized to **19** with tetracyanoethylene[44] and fluoranil[45] in good yields. Indolenines have also been oxidized with *m*-CPBA although in lower yields.[46] Treatment of 3-bromo-2-ethylsulfonylindolenines with ethanolic HCl has given indolin-2-ones.[47]



18 19

2. Preparation *via* (N)-(Aryl) Bond Formation

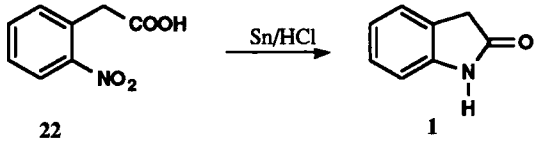
Formation of the indolin-2-one ring system *via* bond construction between the nitrogen and aryl carbon atom has recently been reported. Compounds of type **20** are converted into nitrenium ions and then trapped intramolecularly by an aromatic carbon to give the indolin-2-ones **21**.[48] Similar approaches leading to N-methoxyindolin-2-ones employing other promotors have also been reported.[49,50] Another approach which has been used is the intramolecular displacement of an *o*-bromophenylacetamide with cuprous bromide and sodium hydride *via* a modified Goldberg reaction.[51]



20 21

3. Preparation *via* (N)-(C-2) Bond Formation

This approach offers one of the more versatile and useful methods of construction of the indolin-2-one ring system from acyclic precursors. The first synthesis of oxindole from an acyclic precursor was carried out by Baeyer[52] using this method, whereby *o*-nitrophenylacetic acid (**22**) was

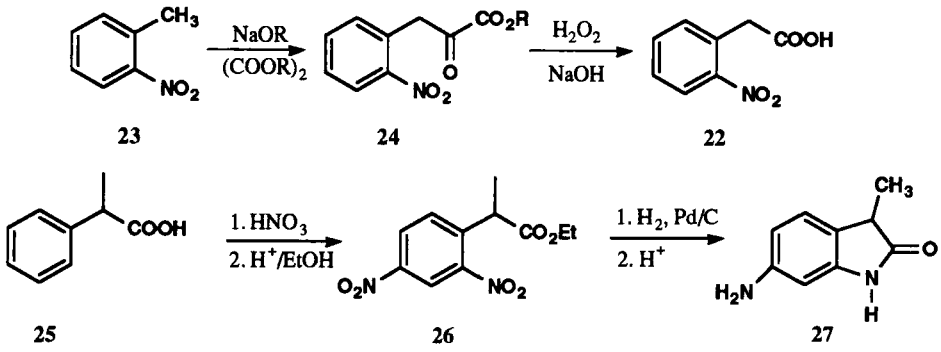


22 1

reduced to *o*-aminophenyl acetic acid and cyclized to 1. Many of the examples that have appeared in the literature prior to 1970 have been reviewed elsewhere.[3-5]

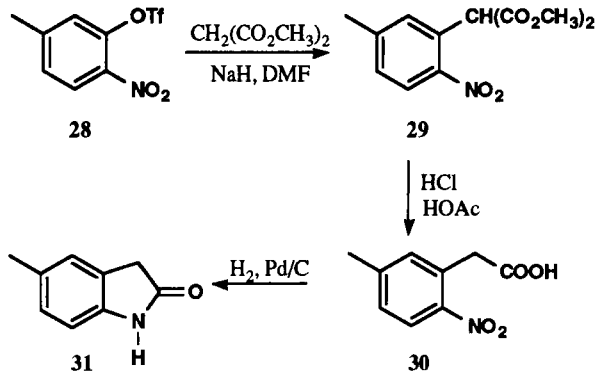
a. from o-Nitrophenylacetic Acids

One of the several approaches to *o*-nitrophenylacetic acids was first reported by Reissert[53] in which an *o*-nitrotoluene (**23**) is condensed with a dialkyl oxalate to give an *o*-nitrophenylpyruvate (**24**). Oxidative hydrolysis then furnishes the *o*-nitrophenylacetic acid (**22**). Finally, reduction of the nitro group is followed by cyclization to give the indolin-2-one. A number of substituted indolin-2-ones have been prepared by this approach.[3,4,54-60] *o*-Nitrophenylacetic acids have also been obtained by the nitration of substituted phenylacetic acids. A recent example is given in the synthesis of 3-alkyl-6-aminoindolin-2-ones **27**.[14]

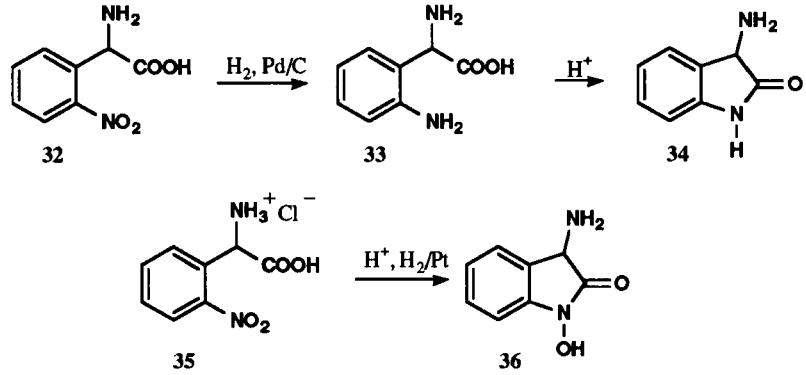


Displacement of *o*-nitroaryl triflates[61] with malonate anions also affords, after hydrolytic decarboxylation, substituted *o*-nitrophenylacetic acids. Reductive cyclization then affords the indolin-2-one, e.g., **31**. Displacement of *o*-nitroaryl halides similarly gives compounds analogous to **29**. Reductive cyclization with Pd-C[40] and tin/HCl[62] gives indolin-2-ones. A few examples of the conversion of "masked" *o*-nitrophenylacetic acids to indolin-2-ones have been reported, including *o*-nitrophenyllactols,[63] *o*-nitrophenylacetaldehydes[64] and *o*-nitroglutethimide.[65]

o-Nitrophenylacetic acids and esters have also been converted to N-hydroxyindolin-2-ones. Davis *et al.*[66] found that the presence or absence of acid during the nitro reduction determined the

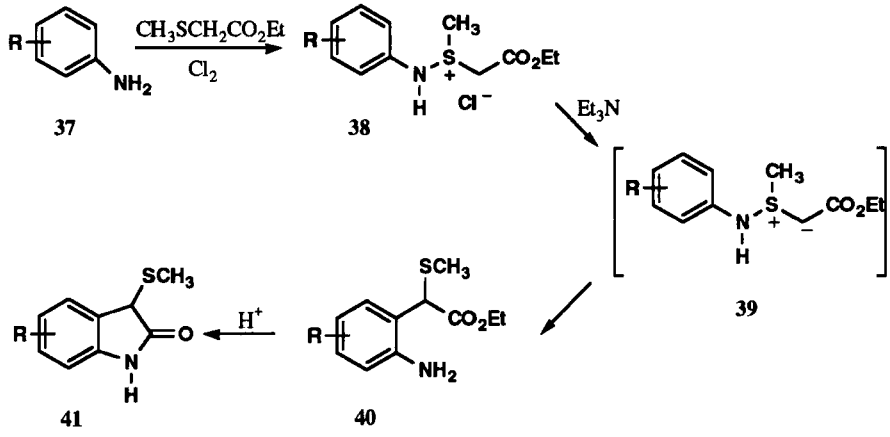


structure of the indolin-2-one. *o*-Nitrophenylglycine **32** (free base) was reduced with palladium under neutral conditions to the *o*-aminophenylacetic acid **33** which spontaneously cyclized under acid treatment to the indolin-2-one **34**. Reduction of the HCl salt of **35** with platinum under acidic conditions led to the N-hydroxyindolin-2-one **36** exclusively. Similar reductions of *o*-nitrophenylacetic acids and esters to N-hydroxyindolin-2-ones have been carried out with other reagents.[67-69]



b. Sommelet-Hauser Type Rearrangements

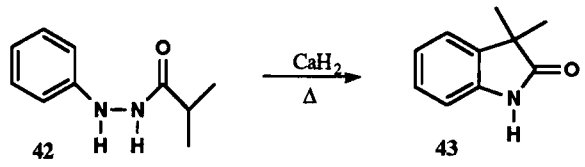
In 1973, Gassman and co-workers[9,70-74] introduced a new method of synthesis of indolin-2-ones. It involves the conversion of an aniline (**37**) into an azasulfonium salt (**38**) at low temperature followed by base-induced ylide formation to give **39**, which undergoes a Sommelet-Hauser type rearrangement to an *o*-aminophenylacetic ester. Cyclization then affords the 3-(methylthio)indolin-2-one **41**. The 3-methylthio group can then be removed by reductive desulfurization. The reaction is



mild and can tolerate a wide variety of functional groups. Symmetrical and *o*-substituted anilines give a single product upon rearrangement while unsymmetrical anilines usually give a mixture of products. Since its introduction, this method has been one of the most frequently used approaches to the synthesis of indolin-2-ones of agrochemical[17,75] and pharmaceutical[60,62,76-85] interest.

c. Cyclization of N-Acylphenylhydrazines

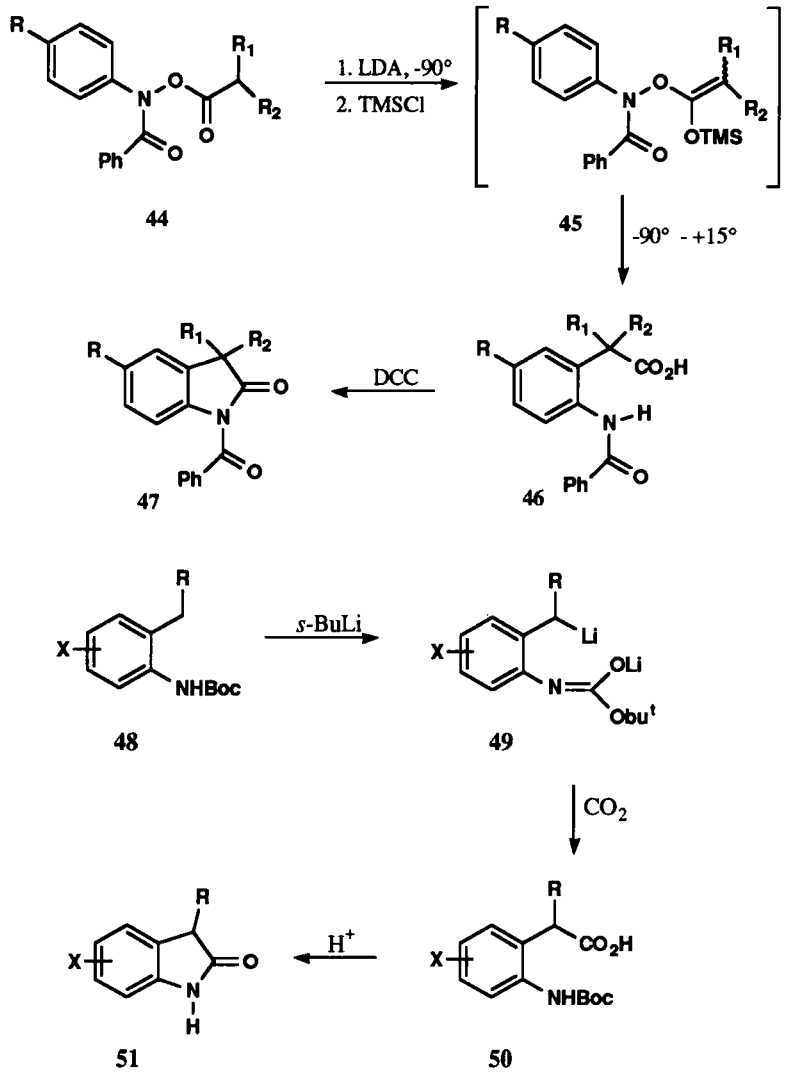
Heating N-acylphenylhydrazines (**42**) with alkali to give indolin-2-ones was first reported by Brunner[3,5,86,87] in 1896. Like Gassman's indolin-2-one synthesis above, the Brunner reaction involves a rearrangement to an ortho-substituted aniline which undergoes cyclization to an indolin-2-one (**43**). The cyclization is performed at high temperatures with a strong base and so its applicability is limited.[88-90]



42 43

d. Miscellaneous Preparations

Enol silylethers of N-acyloxybenzanilides (**44**) have been shown to undergo rearrangement

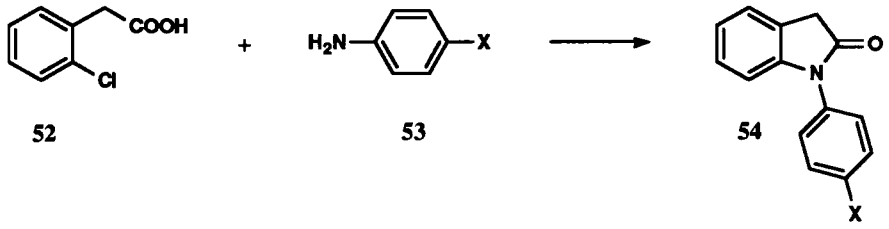


44 45 46 47 48 49 50 51

to *o*-(benzoylamino)phenylacetic acids (**46**) which can be cyclized to indolin-2-ones in moderate yields.[91] Substituted *o*-aminophenylacetic acids have also been prepared by metalation. Clark and co-workers[92] treated a series of dilithiated N-(*t*-Boc)anilines (**49**) with CO_2 to obtain N-(*t*-Boc)pheny-

lacetic acids (**50**), which were cyclized to indolin-2-ones in good yield.

N-Phenylindolin-2-ones (**54**) have been prepared by the reaction of anilines with *o*-chlorophenylacetic acids.[93,94] *o*-Nitro-*t*-butylbenzenes have been converted to N-hydroxy-3,3-dimethylindolin-2-ones.[95]



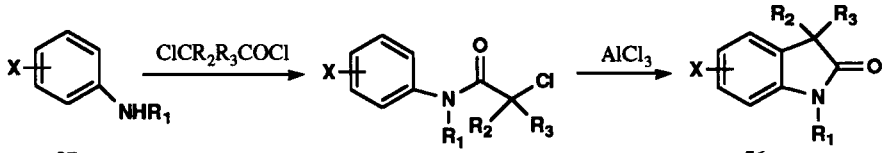
52 **53** **54**

4. Preparation *via* (C-3)-(Aryl) Bond Formation

A number of indolin-2-one preparations have been developed in which bond formation between C-3 and an aryl carbon constitute the last step. The earliest reaction of this type and one of the classical indolin-2-one syntheses was first reported by Stolle.[96] Treatment of an α-haloacetanilide (**55**) with $AlCl_3$ gives the indolin-2-one *via* a Friedel-Crafts alkylation. The syntheses of many alkyl- and aryl-substituted indolin-2-ones using this method have been reported previously.[3-5]

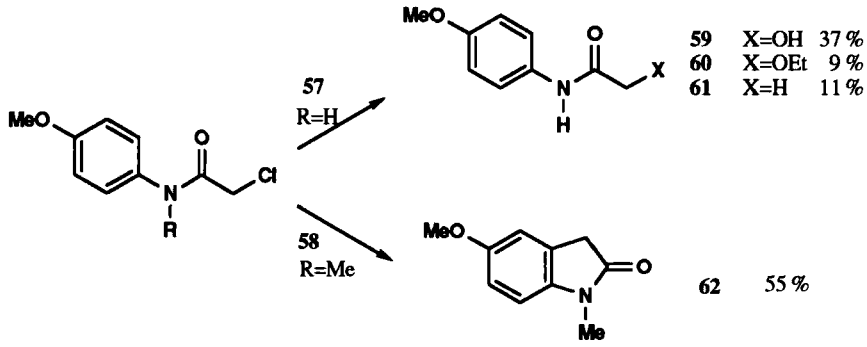
a. Friedel-Crafts Alkylation

The standard Friedel-Crafts reaction has more recently been used to prepare 5- and 6-hydroxyindolin-2-ones[55,56] and 5-haloindolin-2-ones.[97] A series of N-phenylindolin-2-ones have also recently been prepared by this method.[25,98] Due to the harsh reaction conditions, the reaction has usually been limited to compounds containing insensitive functional groups. It has been observed, however, the more highly substituted the α-haloacetanilide, the milder the conditions for the cyclization.[3]

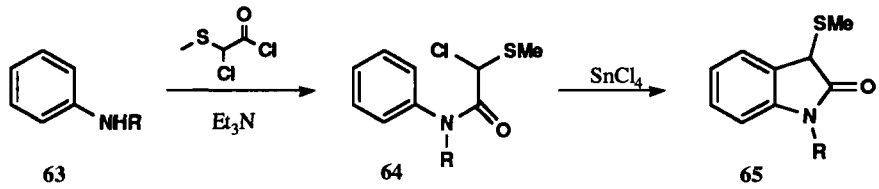


37 **55** **56**

α-Chloroacetanilides have been subjected to irradiation, with the results being highly dependent on the substitution of the acetanilide.[99] Irradiation of **57** gave only side-chain substitution products. No detectable amount of indolin-2-ones were formed. Irradiation of **58**, on the other hand, readily gave the desired indolin-2-one **62**. This observation was rationalized by the fact that N-unsubstituted acetanilides exist in the trans form while N-substituted acetanilides exist predominantly in the cis form, and it is the cis form that reacts intramolecularly to give indolin-2-ones.

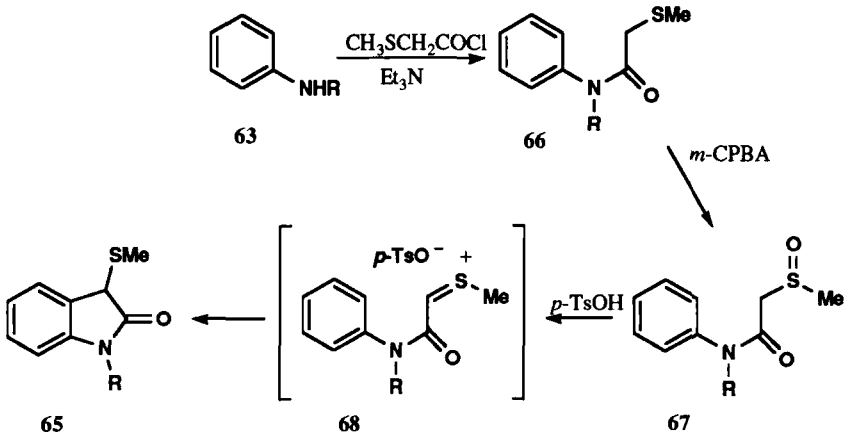


In addition to α-chloroacetanilides, α-bromo- and α-hydroxyacetanilides have been used in the past to prepare indolin-2-ones.[3] Other Lewis acids have also been used. A recent example is the Friedel-Crafts cyclization of α-chloro-α-(methylthio)acetanilide **64** with $SnCl_4$ to furnish the 3-(methylthio)indolin-2-one **65**.[100,101]



b. Pummerer Reaction

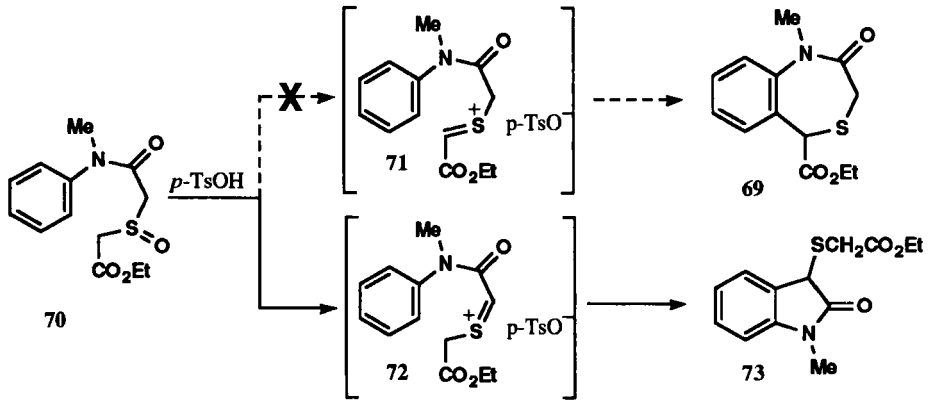
The Pummerer reaction has recently been applied to the synthesis of indolin-2-ones.[101] Sulfoxide **67**, obtained *via* the oxidation of α-(methylthio)acetanilide **66**, was converted to the intermediate **68** upon treatment with *p*-toluenesulfonic acid. Electrophilic attack on the aromatic ring gave the 3-(methylthio)indolin-2-one **65**. Tamura *et. al.*[100] found that while only poor yields (< 10 %) of **65**



were obtained when R=H, **65** was obtained in excellent yields (> 80 %) when R is methyl or phenyl. The Pummerer reaction has recently been carried out directly from the sulfide (*e.g.* **66**) by treatment

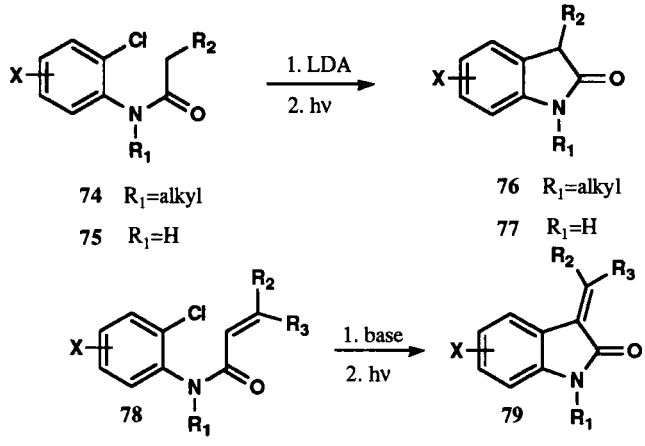
with phenyl iodosyl bis(trifluoroacetate), which generates **68** *in situ*.[102]

Attempted preparation of benzothiazepin-2-one **69** *via* the Pummerer reaction resulted in the formation of the indolin-2-one **73** instead.[103] Apparently, formation of intermediate **72** is favored over **71**, thus leading to the indolin-2-one **73** in 60 % yield.



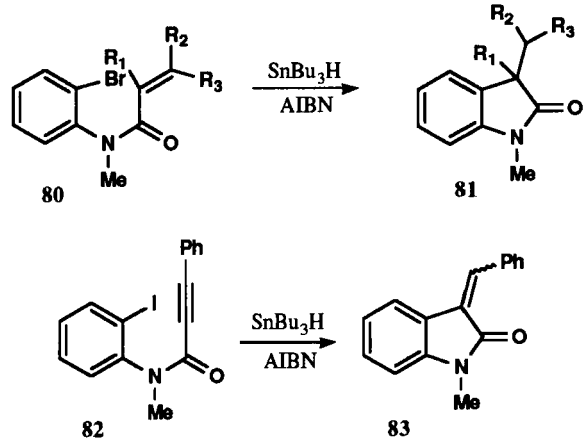
c. Radical-induced Cyclizations

Wolfe and co-workers[7,104] have recently developed a new method of preparation of indolin-2-ones. Upon treatment of *o*-chloroacetanilides with excess lithium diisopropylamide and near UV radiation, the resulting anions (monoanion of **74** and dianion of **75**) react to give indolin-2-ones **76** and **77**, respectively. 3-alkylideneindolin-2-ones have been similarly prepared by the photoinduced cyclization of α,β-unsaturated acetanilides **78**, again giving rise to both N-substituted and N-unsubstituted indolin-2-ones **79**.[104]



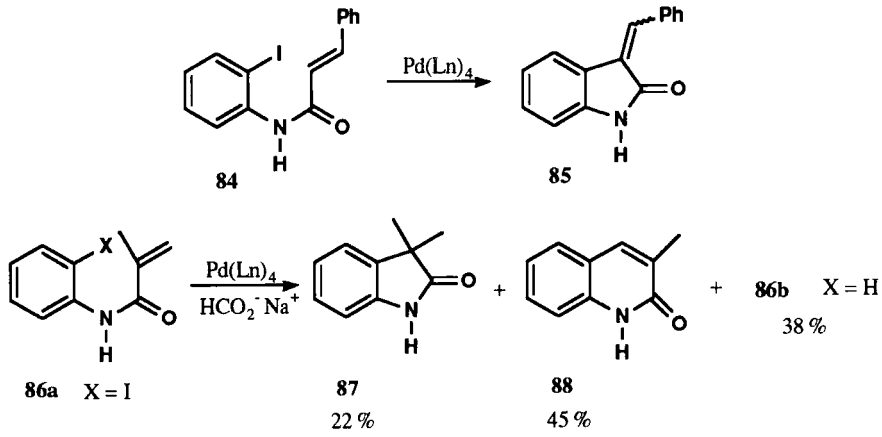
Jones and co-workers[105-107] have obtained 3-substituted and 3,3-disubstituted indolin-2-ones by treatment of N-acryloyl-*o*-bromoanilines **80** under radical conditions. Similar cyclizations were carried out with the nitrogen atom containing a chiral auxiliary, but only low optical yields (< 39 %) were obtained.[108] Radical-induced cyclization of the *o*-iodopropynamide **82** under similar conditions

has given 3-alkylideneindolin-2-ones **83** (mixture of E and Z isomers).[109]

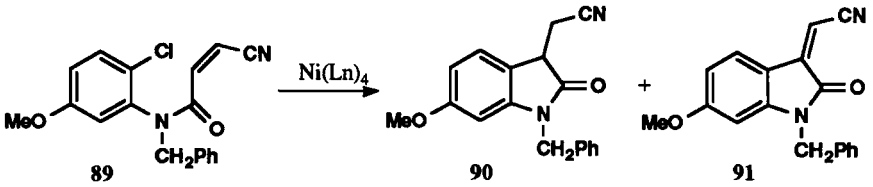


d. Zerovalent Metal-mediated Cyclizations

N-acryloyl-*o*-haloanilines also undergo cyclization to indolin-2-ones when heated with transition metal catalysts.[8,110,111] Treatment of **84** with a zerovalent palladium complex[110] forms an organopalladium species which cyclizes to give the indolin-2-one **85** in high yield, arising from a 5-exo-trig cyclization pathway. Depending upon the substituents on the double bond, the 6-endo-trig pathway can compete to form quinolones. In some instances quinolones are formed as the major product as in the case of reaction of **86a**.[111] Palladium-mediated cyclization has recently been exploited using a chiral diphosphine ligand to give spirocyclic indolin-2-ones with moderate asymmetric induction.[112]



Zerovalent nickel complexes have also been used to cyclize N-acryloyl-*o*-haloanilines.[113-118] Nickel-mediated cyclizations often result in the formation of mixtures of saturated and unsaturated indolin-2-ones. A typical example is the cyclization of **89** to give **90** and **91**.[115] In some cases,[113,118] dihydroquinolones are formed as byproducts.

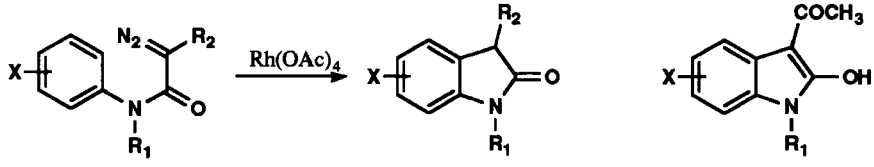


89 90 91

40 % 23 %

e. Rhodium-carbenoid Insertion

The rhodium-carbenoid insertion reaction has recently been extended to the synthesis of indolin-2-ones. N-aryldiazoamides undergo facile intramolecular aromatic substitution *via* the decomposition of the diazoamides in the presence of rhodium (II) acetate. Doyle and co-workers[6] have shown that the decomposition of N-aryldiazoacetoacetamides (**92**) and N-aryldiazoacetamides (**93**) leads smoothly to indolin-2-ones **94** and **95**, respectively. Similar results were obtained by Durst and co-workers[119] for the formation of indolin-2-ones possessing N-substitution, but the only example given of an N-H indolin-2-one was obtained in poor yield (7 %). Spectroscopic evidence demonstrates that the 3-acylindolin-2-ones **94** generally exist as the tautomeric 2-hydroxyindole form **96**.



92 $R_2 = COCH_3$
93 $R_2 = H$

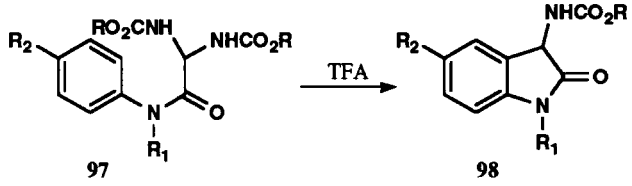
94 $R_2 = COCH_3$
95 $R_2 = H$

96

f. Miscellaneous Preparations

Some of the less common indolin-2-one preparations obtained by construction of the (C-3)-(aryl) bond have not been previously discussed. This section includes a brief survey of some of these methods.

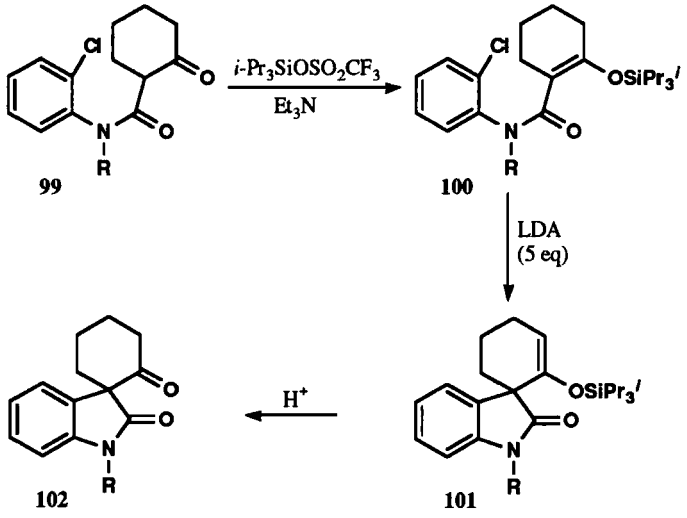
The acid-promoted intramolecular amidoalkylation of **97** has led to modest yields of 3-(alkoxycarbonylamino)indolin-2-ones (**98**).[120,121] Similarly, acidic treatment of N-methylpyruvanilides[122,123] affords indolin-2-ones. A spirocyclohexane-substituted indolin-2-one was obtained by the acid promoted cyclization of N-phenyl-1-hydroxycyclohexanecarboxamide.[124]



97 **98**

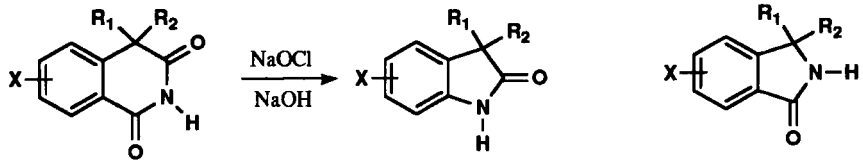
Irradiation of a series of N-(methylanilino)acetoacetates gave 2-carboethoxy-3-hydroxyindolines which rearrange to 3-carboethoxyindolin-2-ones in the presence of lead tetraacetate.[125]

A recent procedure has been developed whereby 3-(silyloxy)acryloyl-2'-haloanilides, e.g., **100**, upon treatment with a large excess of lithium diisopropylamide, are converted to 3,3-spiroindolin-2-one ketones (**102**) in moderate yields.[126] The reaction is believed to go through a benzyne intermediate. In a similar vein, treatment of fumarate amides of *o*-iodoanilines with *n*-butyllithium gives 3-substituted indolin-2-ones.[127]



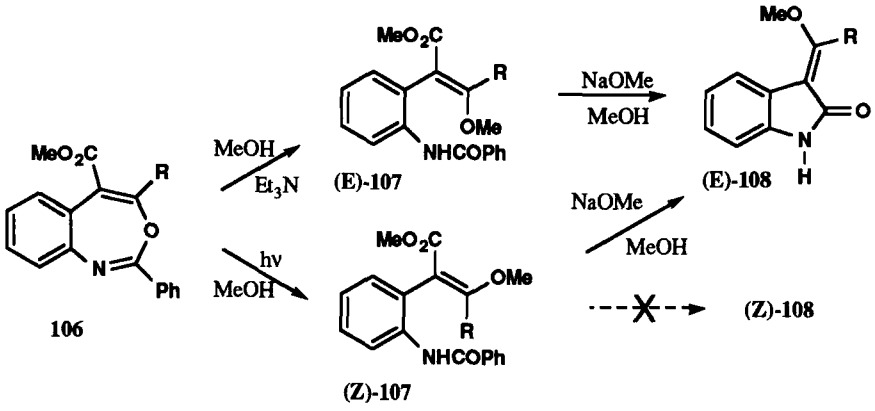
5. Preparation from Other Ring Systems.

Alkaline sodium hypochlorite treatment of 4,4-disubstituted isoquinoline-1,3-diones (**103**) causes rearrangement to 3,3-disubstituted indolin-2-ones *via* Hofmann hypohalite degradation.[128,129] If



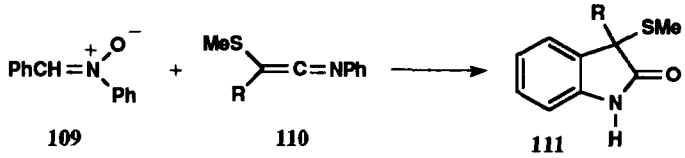
the isoquinoline-1,3-diones are subjected to alkaline hydrolysis prior to treatment with hypohalite, a mixture of indolin-2-ones and isoindolin-1-ones (**105**) is obtained. The rearrangement has also been effected in good yield with bromine.[14,130]

Benzoxazepine **106** has been converted to the (E)-indolin-2-one (**108**) *via* the intermediate (E)- and (Z)-2-(amidophenyl)acrylates (**107**) upon methanolysis.[131] Studies of the ring opening of benzoxazepines with other nucleophiles leading to substituted indolin-2-ones have also been reported.[132,133] Indolin-2-ones have also been prepared by the ozonolysis of 3-cyano-1,4-dihydroquinolines.[134]

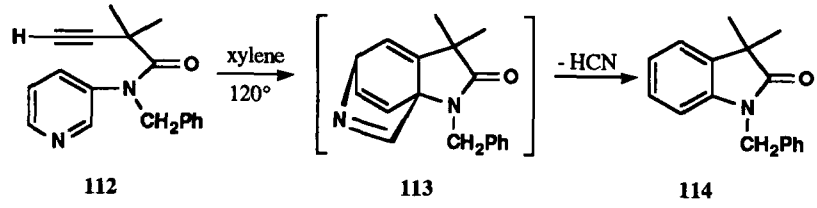


6. Miscellaneous Preparations of Indolin-2-ones

Reaction between C,N-diphenylnitrones (**109**) and C-sulfenylketenimines (**110**) give 3-(methylthio)indolin-2-ones.[135] It has also been demonstrated that reaction with N-phenyldialkylketenimines also leads to indolin-2-ones.[136] N-benzoyldiphenylamine diesters, upon treatment with excess



sodium methoxide, rearrange to indolin-2-ones.[137,138] The intramolecular Diels-Alder reaction of N-arylamide **112** results in the formation of indolin-2-one **114** in excellent yield. The expected product, azabarrelene **113**, could not be isolated presumably from loss of HCN *via* the retro-Diels-Alder reaction of adduct **113**.[139]

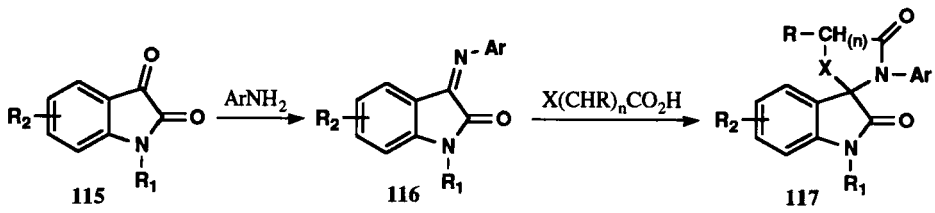


7. Spirocyclic Indolin-2-ones derived from Isatin.

Recently, there has been a heightened interest in the preparation of spirocyclic-containing indolin-2-ones for pharmacological evaluation.[140] The overwhelming majority of these spirocyclic ring systems are comprised of heterocyclic moieties. These heterospirocyclic indolin-2-ones are generally prepared from derivatives of isatin. One method of preparation is the conversion of an appropriately substituted isatin (**115**) into an isatin imine (**116**) followed by condensation with a nucleophile.

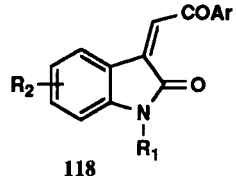
In the past few years a number of spirocyclic-containing indolin-2-ones have been prepared in this manner, including azetidin-2-ones,[141-143] thiazolidine-4-ones,[143-147] thiazin-4-ones,[148] 1,2,4-tria-

zoloquinazolin-9-ones,[149] and pyrazolothiadiazepin-5-ones.[150]



115 116 117

The other main route to the preparation of these compounds consists of the Aldol condensation of isatin derivatives with carbonyl compounds, to give, after dehydration, 3-alkylideneindolin-2-ones (**118**). Michael-addition of **118** with the appropriate nucleophile leads to a wide variety of spirocyclic-containing indolin-2-ones. In the past few years, dihydropyrazole,[16,151] tetrahydropyrazolopyridin-3-one,[152,153] dihydropyrimidin-2-one,[154] isoxazoline,[155] pyranobenzopyran,[156] pyranopyrazole[157] and other[19,158,159] moieties have been prepared by this sequence. The preparation of alkylideneindolin-2-ones from indolin-2-ones will be discussed further in section II.2.



118

II. ALKYLATION OF INDOLIN-2-ONES

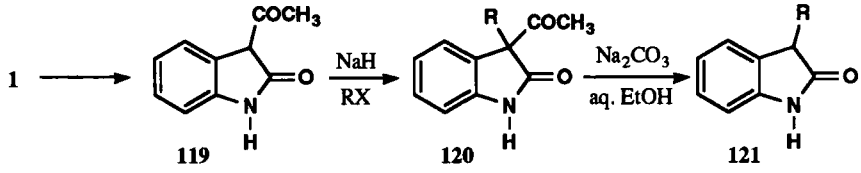
1. Reaction of Indolin-2-ones with Alkylating Agents

Oxindole (1) has been the object of numerous alkylation studies. Deprotonation leads to a monoanion which, in theory, is capable of reaction at three sites; nitrogen, carbon, and oxygen. In practice, competition for alkylating agents exists primarily between the nitrogen and carbon anions. The oxygen atom is normally alkylated under special conditions.[5]

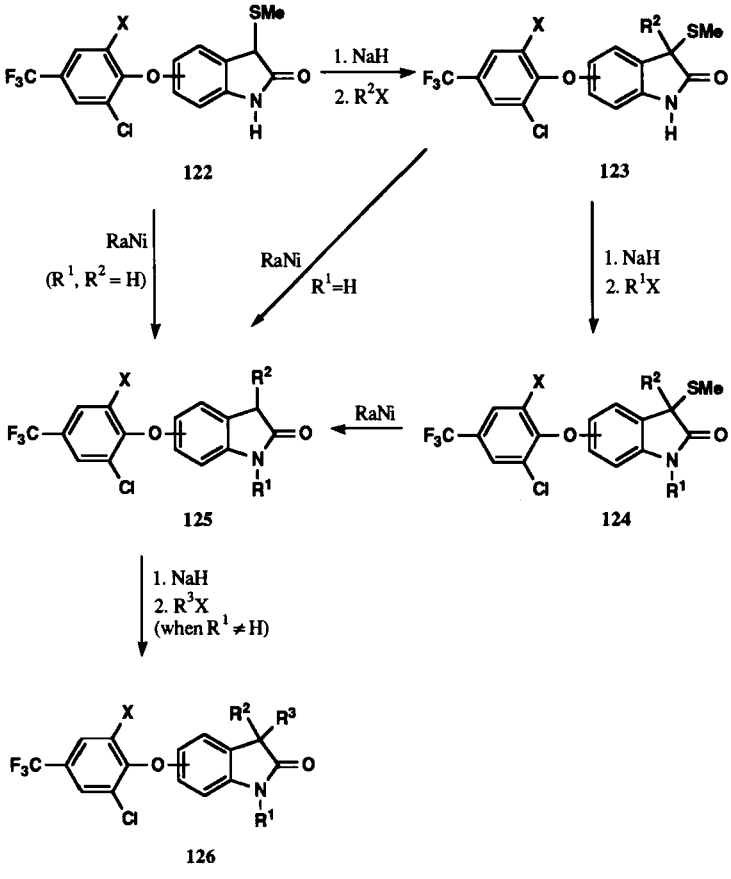
The alkylation of oxindole and other 1,3,3-unsubstituted indolin-2-ones has generally proceeded with poor selectivity, resulting in varying amounts of C- and N-substituted indolin-2-ones.[15,160-162] The C-alkylation of N-alkylindolin-2-ones has often led to mixtures of 3-alkyl- and 3,3-dialkylated products as well.[163-165] Alkylation of 1,3-disubstituted indolin-2-ones[166] and intramolecular C-3 alkylations of 3-alkylated indolin-2-ones[167,168] occur readily, the latter due to the kinetic preference for intramolecular cyclization. Gruda[169] studied the kinetics of the alkylation of oxindole and determined that C-3 is twice as reactive as N-1. Once alkylated, the reactivity of C-3 of the 3-monosubstituted compound is 30 times greater than N-1.

Recently, Kende[170] reported conditions for the controlled C-3-alkylation of oxindole, giving mono- and dialkylated products selectively. The alkylation was performed *via* the dianion, generated from *n*-butyllithium. This method has been more recently applied by DeMarinis and co-workers.[171] While the selectivity obtained by this method is notable, the strongly basic conditions might be

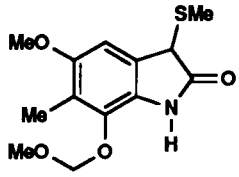
incompatible with sensitive functionality. Asymmetric alkylations of indolin-2-ones have recently been reported. Lee and Wong[172] have carried out the chiral phase transfer alkylation of 1,3,5-trisubstituted indolin-2-ones in their study of the synthesis of physostigmine, obtaining moderate yields of asymmetric induction. Blocking groups have often been used to direct the alkylation of indolin-2-ones. Conversion of oxindole to 3-acetylindolin-2-one (**119**) allows for the selective C-3 alkylation to give **120**. Deacetylation then affords the monoalkylated product **121**.[173,174] N-acetylation has similarly allowed for the symmetrical[175] and unsymmetrical[176] C-3 alkylation of indolin-2-ones.



A study of the selective C- and N-alkylations of 3-(methylthio)indolin-2-ones has recently been carried out as part of an herbicide analog synthesis program.[17,75] Alkylation of 3-(methylthio)-indolin-2-ones, obtained from the Sommelet-Hauser rearrangement reported by Gassman,[9,70-74] offers



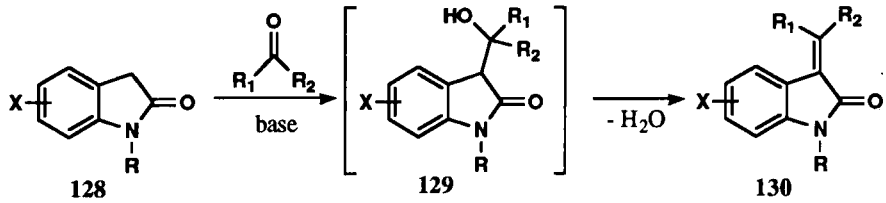
a mild and regiospecific method for the alkylation of indolin-2-ones. Primary alkyl halides react at C-3 without any competitive N- or O-alkylation (**123**). A second alkylation occurs at N-1 (**124**). Reductive desulfurization coupled with this stepwise alkylation gives 3-, 1,3- and 1,3,3-substituted indolin-2-ones. Lower yields with competitive O-alkylation are obtained from reaction with hindered alkyl halides.[75] Kukla and co-workers[177] successfully alkylated 4-cyano-3-(methylthio)indolin-2-one to give an intermediate in the preparation of the azepino[5,4,3-*cd*]indolin-2-one ring system. Interestingly, Raphael and Ravenscroft[84] were unable to selectively C-alkylate **127** under a variety of conditions.



127

2. Preparation of Alkylidene-substituted Indolin-2-ones

Alkylidene-substituted indolin-2-ones can be prepared by the condensation of a carbonyl compound with a 3-unsubstituted indolin-2-one. Aldehydes[165,178-180] and ketones[75,165,181] have been used as substrates with both N-substituted and unsubstituted indolin-2-ones. The intermediate alcohol (**129**) is not normally isolated as it is dehydrated under the reaction conditions, although exceptions are known.[178,182] Michael addition of acetylenedicarboxylic esters has also afforded 3-alkylideneindolin-2-ones.[183]



128 **129** **130**

3-Alkylidene-substituted indolin-2-ones can be converted to 3-alkylindolin-2-ones by reduction of the double bond. This offers an alternate method of preparation of 3-monoalkylated indolin-2-ones. Reduction of 3-alkylidineindolin-2-ones **130** derived from ketones allows for the introduction of branched substituents into the 3-position in high yield.[75,165,181,183]

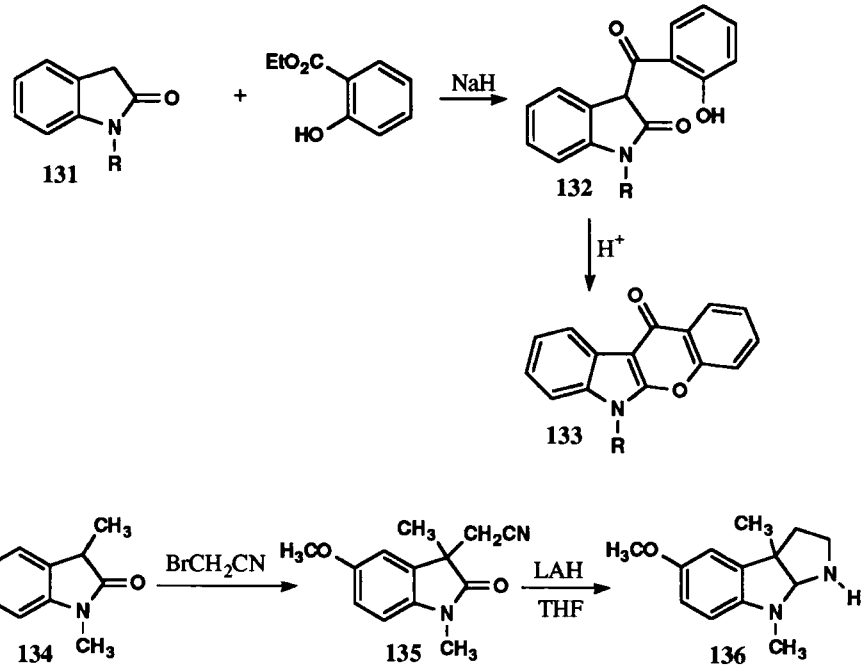
III. CONVERSION OF INDOLIN-2-ONES TO ISATINS AND INDOLINES

Indolin-2-ones have been used as substrates in the preparation of isatins and indolines. Isatins have been prepared by the oxidation of indolin-2-ones with N-chlorosuccinimide and mercuric oxide[85,184] and by air oxidation.[185] Substituted indolin-2-ones have been reduced to the corresponding indolines using borane,[186] lithium borohydride[187] lithium aluminum hydride[188] and diisobutylaluminum hydride.[188] Use of the latter two reagents resulted in mixtures of indoles and indolines depending upon the substituents at N-1 and C-3 of the starting indolin-2-one.

IV. ANNULATIONS OF INDOLIN-2-ONES

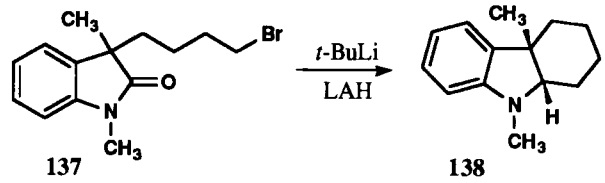
Owing to the importance of the indolin-2-one ring system, both as a component of natural products and as a frequent target of synthetic chemists, it is not surprising that a number of other heterocyclic ring systems have been synthesized from substituted indolin-2-ones. This section contains a brief overview of some of transformations that have recently been reported.

Condensation of indolin-2-one **131** with ethyl *o*-hydroxybenzoate gives **132** which, upon treatment with acid, cyclizes to the benzopyrano[2,3-*b*]indole **133**.[189] Substituted pyrano[2,3-*b*]indoles have been prepared in a similar fashion.[190] Using the same protocol, Eiden and Dobinsky[191] converted substituted indolin-2-ones into indolo[2,3-*b*]quinolines and benzothiopyrano[2,3-*b*]indoles as well as benzopyrano[2,3-*b*]indoles. Benzopyrano[2,3-*b*]indoles have also been prepared by treating indolin-2-ones with phosgene and reacting the resultant mixture with β-dicarbonyl compounds.[192] Alkylation of indolin-2-one **134** with bromoacetonitrile followed by reductive cyclization affords the tetrahydropyrrolo[2,3-*b*]indole precursor to physostigmine (**136**).[193] Similarly, alkylation of **134** with methyl bromoacetate and subsequent reductive cyclization gives the tetrahydrofuro[2,3-*b*]indole ring system.[194] A longer approach was used to obtain the 1,2-oxazino[6,5-*b*]indole ring system of the alkaloid geneserine.[195]



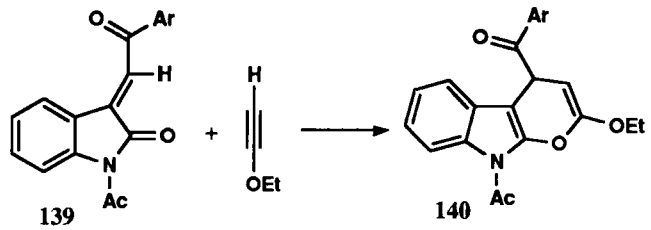
Intramolecular cyclizations have been used in the preparation of other ring systems. Indolin-2-one **137**, obtained by the alkylation of 1,3-dimethylindolin-2-one with 1,3-dibromobutane, when subjected to metal-halogen exchange and subsequent reductive cyclization, gave the hexahydrocarbazole **138**.[196] Intramolecular lithiation has also been employed to construct the tetrahydropyrrolo[1,2-

a]indole ring system.[197] A series of substituted pyrano[2,3-*b*]indoles are obtained as the major



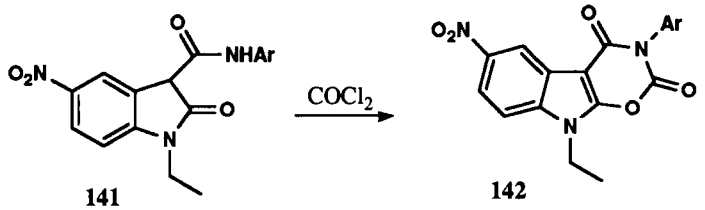
137 138

products by the Diels-Alder reaction between alkylideneindolin-2-one (**139**) and ethyl propargyl ether.[198] Similar studies were carried out using analogs of **139** with ethyl vinyl ether.[199,200] Indolin-2-

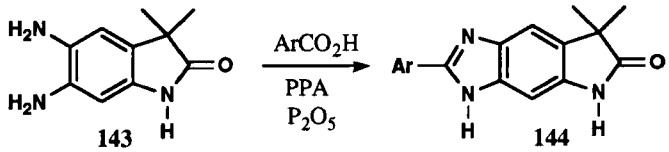


139 140

one-3-carboxamide **141**, upon treatment with phosgene, cyclizes to the novel oxazino[6,5-*b*]indolin-2,4-dione ring system (**142**).[201] Similar treatment of indolin-2-one-1-carboxamides led to the 1,3,5-oxadiazino[3,2-*a*]indolin-2,4-dione ring system. A number of heterocyclic ring systems were prepared

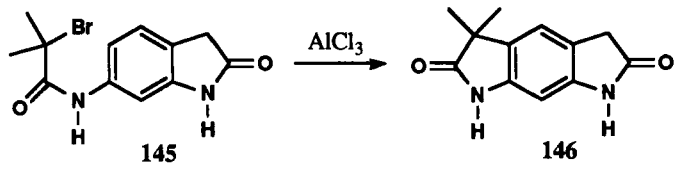


141 142



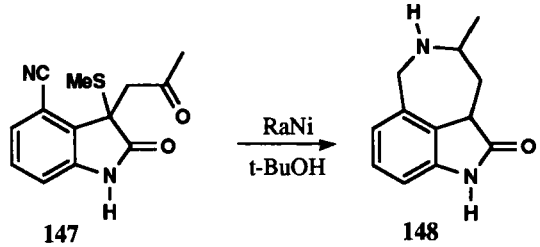
143 144

for study as potential cardiotonic agents. Acylation of 5,6-diaminoindolin-2-ones with carboxylic acids leads to a variety of substituted pyrrolo[2,3-*f*]benzimidazoles **144**.[14,202] Diazotization of 5,6-diaminoindolin-2-ones have given pyrrolo[2,3-*f*]benzotriazoles upon intramolecular cyclization. Acylation of 6-aminoindolin-2-ones followed by Friedel-Crafts intramolecular alkylation has given benzo[1,2-*d*:4,5-*d'*]dipyrroles **146**.[202]



145 146

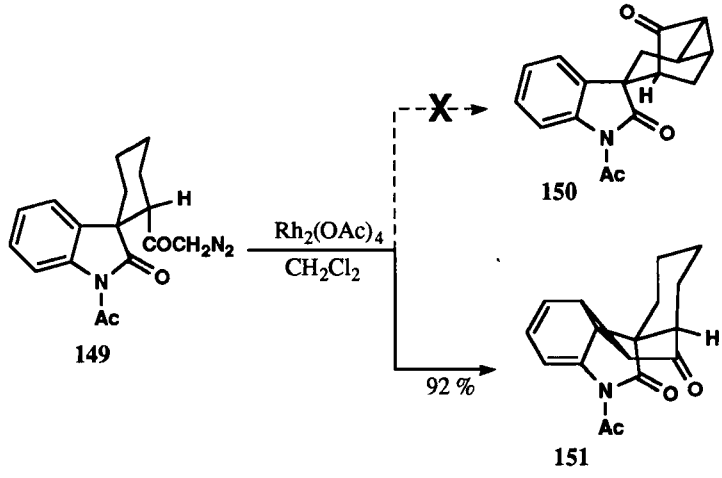
Desulfurization and subsequent reductive amination of **147**, obtained from the alkylation of 4-cyano-3-(methylthio)indolin-2-one with chloroacetone, gave the azepino[5,4,3-*cd*]indolin-2-one **148**.[177] A series of interesting pentacyclic ring systems have been prepared from the decomposition of



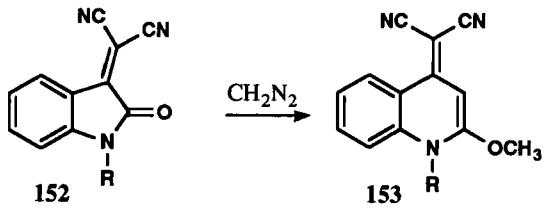
147 148

diazo ketones. It was expected that rhodium carbenoid insertion would take place at an aliphatic C-H in the cyclohexane moiety of **149** leading to **150**.[203] Insertion took place, however, into an aromatic C-H, leading to **151**. Additional reactions were carried out with structurally related ring systems to give similar results.

3,3-Disubstituted indolin-2-ones undergo rearrangement to quinolin-2-ones at high temperatures.[204] Flash-vacuum-pyrolysis of 3,3-dibenzylindolin-2-one leads to a mixture of 3-phenyl- and 4-phenylquinolin-2-ones in a ratio of 3:1. The mixture obtained was rationalized on the basis of the results of ^{13}C labelling experiments. Upon treatment of 3-(dicyanomethylene)indolin-2-ones (**152**) with diazomethane, rearrangement to the 1,4-dihydroquinoline system (**153**) is observed.[205] Reisch

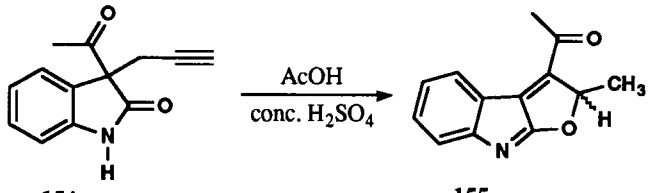


149 150 151



152 153

and co-workers[206] reported that treatment of 3-acetyl-3-propargylindolin-2-one (**154**) with acid gave 3-acetyl-2-methyl-2*H*-furo[2,3-*b*]indole **155** *via* an acyl shift rather than the expected 2-methyl-furo[2,3-*b*]indole. 3-*o*-Nitrobenzylideneindolin-2-one has been reported to undergo rearrangement to



154 155

a substituted 2-hydroxyquinoline N-oxide.[207] A number of reports of the conversion of 3-(2-aminoethyl)indolin-2-one (oxytryptamine) to alkaloids have also appeared.[208-211] Recently, Kende and co-workers[212] described the preparation of an analog of the pentacyclic oxindole alkaloid gelsedine from 1-methoxyindolin-2-one.

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