CHAPTER 1

Primary Syntheses of Cinnolines

The primary synthesis of cinnolines or hydrocinnolines may be done by cyclization of carbocyclic substrates already bearing appropriate substituents; by cyclocondensation of carbocyclic substrates with acyclic synthons that provide one or more of the ring atoms needed to complete the cinnoline system; by similar processing of pyridazine substrates; or by rearrangement, ring expansion, ring contraction, degradation, or modification of suitable derivatives of other heterocyclic systems. Typical pre-1972 examples in each category may be found from the cross-references to Simpson's volume[906] (e.g., *H* 16) or to Singerman's volume[907] (e.g., *E* 62) that appear at some section headings. Some pre- and post-1972 primary syntheses have also been reviewed elsewhere.[903–905,908–916]

1.1. FROM A SINGLE CARBOCYCLIC SUBSTRATE
(*H* 3, 6, 16, 46; *E* 18, 22, 62, 70, 190, 255)

Such syntheses are subdivided according to whether the N1–C8a, N1–N2, N2–C3, C3–C4, or C4–C4a bond is formed during the procedure to afford a cinnoline.

1.1.1. By Formation of the N1–C8a Bond

This process usually involves cyclization of *o*-halogeno-α-hydrazonoacetophenones or related substrates, as illustrated in the following examples.

Using *o*-Halogeno-α-hydrazonoacetophenones as Substrates

α-Ethoxycarbonyl-2,4,5-trifluoro-α-hydrazonoacetophenone (**1**) gave ethyl 6,7-difluoro-4-oxo-1,4-dihydro-3-cinnolinecarboxylate (**2**) (dioxane, reflux,

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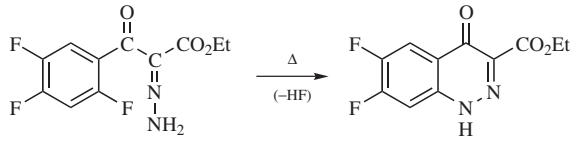
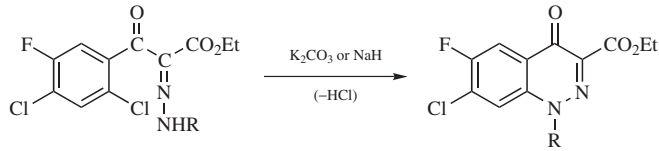
16 h: 70%).[414]



(**1**) (**2**)

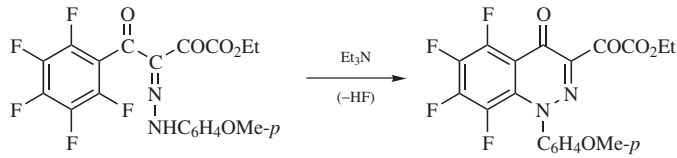
2,4-Dichloro-α-ethoxycarbonyl-5-fluoro-α-(*p*-fluorophenylhydrazono)acetophenone (**3**, R = C_6H_4F-*p*) gave ethyl 7-chloro-6-fluoro-1-*p*-fluorophenyl-4-oxo-1,4-dihydro-3-cinnolinecarboxylate (**4**, R = C_6H_4F-*p*) (K_2CO_3, 18-crown-6, Me_2NCHO, 100°C, 1 h: 94%); analogs likewise.[617]



(**3**) (**4**)

2,4-Dichloro-α-ethoxycarbonyl-5-fluoro-α-(methylhydrazono)acetophenone (**3**, R = Me) gave ethyl 7-chloro-6-fluoro-1-methyl-4-oxo-1,4-dihydro-3-cinnolinecarboxylate (**4**, R = Me) (NaH, dioxane, 10°C→90°C, 15 min: 93%).[414]

α-Ethoxalyl-2,3,4,5,6-pentafluoro-α-(*p*-methoxyphenylhydrazono)acetophenone (**5**) gave 3-ethoxalyl-5,6,7,8-tetrafluoro-1-*p*-methoxyphenyl-4(1 *H*)-cinnolinone (**6**) (Et_3N, $CHCl_3$, reflux, 4 h: 89%).[781]

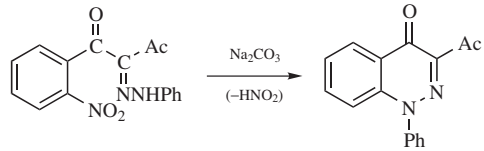


(**5**) (**6**)

Also other examples.[333,359,765]

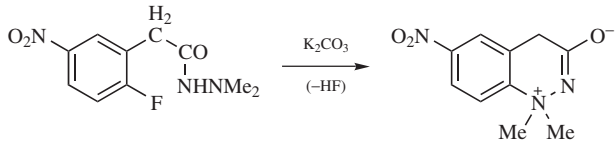
Using Related Substrates

1-Nitro-2-[2-(phenylhydrazono)acetoacetyl]benzene (**7**) gave 3-acetyl-1-phenyl-4(1*H*)-cinnolinone (**8**) (Na_2CO_3, EtOH, H_2O, reflux, 1 h: 92%); several analogs likewise.[140]



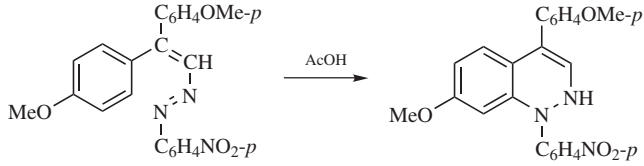
(**7**) (**8**)

2-(2-Fluoro-5-nitrophenyl)-*N*′,*N*′-dimethylacetohydrazide (**9**) gave 1,1-dimethyl-6-nitro-1,4-dihydrocinnolin-1-ium-3-olate (**10**) (K_2CO_3, H_2O, reflux, 3 h: 82%); analogs likewise.[717]



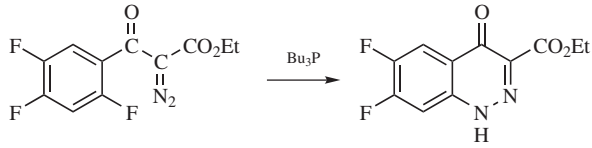
(**9**) (**10**)

6-Methoxy-α-*p*-methoxyphenyl-β-(*p*-nitrophenylazo)styrene (**11**) gave 6-methoxy-4-*p*-methoxyphenyl-1-*p*-nitrophenyl-1,2-dihydrocinnoline (**12**) (AcOH, reflux, 3 h: 90%);[639] the identities of this product and analogs made similarly are not fully established; they could be isomeric indole derivatives.[639]



(**11**) (**12**)

α-Diazo-α-ethoxycarbonyl-2,4,5-trifluoroacetophenone (**13**) gave ethyl 6,7-difluoro- 4-oxo-1,4-dihydro-3-cinnolinecarboxylate (**14**) (Bu_3P, dioxane, 20°C → reflux, 5 h: 60%); analogs likewise.[414]



(**13**) (**14**)

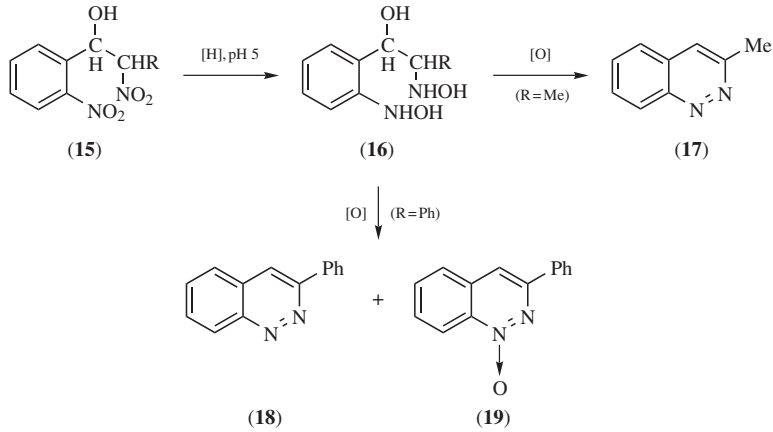
Also other examples.[324,325]

1.1.2. By Formation of the N1–N2 Bond

This unusual procedure is represented by the controlled electroreduction of appropriate dinitro alcohols followed by aerial oxidative cyclization under basic conditions; these processes are illustrated in the following examples.

1-(1-Hydroxy-2-nitropropyl)-2-nitrobenzene (**15**, R = Me) gave 3-methylcinnoline (**17**), via the unisolated intermediate (**16**, R = Me) ([H], pH 5, 0°C; then K_2CO_3↓, open to air, 12 h: 59%; for details, see original).[747]

In contrast, 1-(α-hydroxy-β-nitrophenethyl)-2-nitrobenzene (**15**, R = Ph) likewise gave a separable mixture of 3-phenylcinnoline (**18**) and its 1-oxide (**19**) (47% and 22%, respectively).[747]



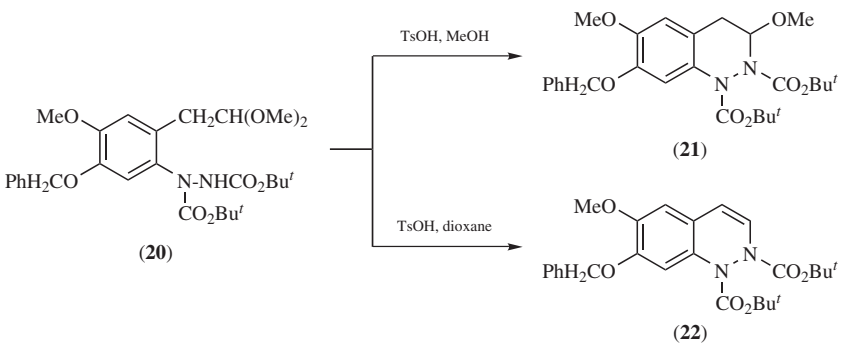
1,4-Dihydrocinnoline (45%), cinnoline (65%), and 3,3-dimethyl-3,4-dihydrocinnoline (12%) have been made somewhat analogously;[64,341,983] also benzo[*c*]cinnoline and its 5-oxide.[1035]

1.1.3. By Formation of the N2–C3 Bond

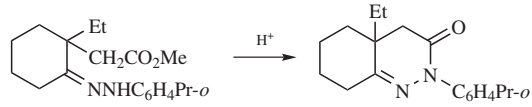
Several types of substrate may be used for this cyclization, as illustrated by the following broadly classified examples.

Using Derivatives of *o*-Ethylphenylhydrazine as Substrates

3-Benzyloxy-*N*′,*N*′-di-*tert*-butoxycarbonyl-6-(2,2-dimethoxyethyl)-4-methoxyphenylhydrazine (**20**) gave either di-*tert*-butyl 7-benzyloxy-3,6-dimethoxy-1,2,3,4-tetrahydro-1,2-cinnolinedicarboxylate (**21**) (TsOH, MeOH, 20°C, 16 h: 72%) or di-*tert*-butyl 7-benzyloxy-6-methoxy-1,2-dihydro-1,2-cinnolinedicarboxylate (**22**) (TsOH, dioxane, 20°C, 16 h: 80%).[494]

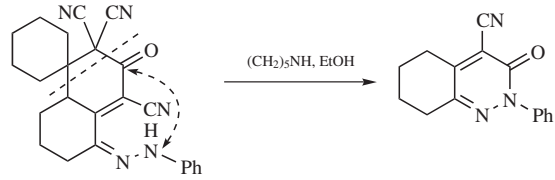


1-Ethyl-1-methoxycarbonylmethyl-2-(*o*-propylphenylhydrazono)cyclohexane (**23**) (prepared in situ) gave 4a-ethyl-2-(*o*-propylphenylhydrazono)-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (**24**) (20% H_2SO_4, reflux, 30 min: 26% after separation from another product); analogs likewise.[212]



(**23**) (**24**)

3′-Oxo-5-phenylhydrazono-3′,5′,7′,8′,8a′-hexahydrospiro[cyclohexane-1,1′(2′*H*)-naphthalene]-2′,2′,4′-tricarbonitrile (**25**) gave 3-oxo-2-phenyl-2,3,5,6,7,8-hexahydro-4-cinnolinecarbonitrile (**26**), a reaction said to involve attack by NH at the carbonyl group and loss of cycloalkylidenemalononitrile as shown [$HN(CH_2)_5$, EtOH, 35°C, 1 h: 18%]; analogs likewise.[954]

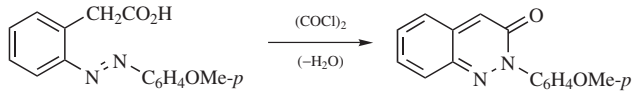


(**25**) (**26**)

Also other examples.[233,383]

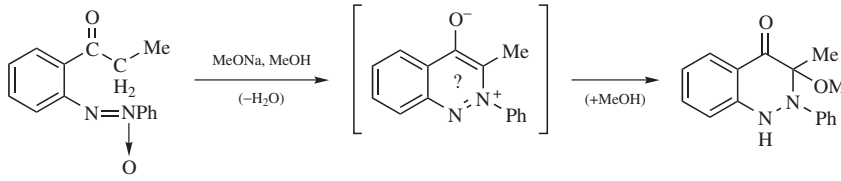
Using Derivatives of 2-Ethylazo- or 2-Ethylazoxybenzene

2-Carboxymethyl-4′-methoxyazobenzene (**27**) gave 2-*p*-methoxyphenyl-3(2*H*)-cinnolinone (**28**) (ClOCCOCl, CH_2Cl_2, 20°C, 15 min: 95%).[83]



(**27**) (**28**)

2-Propionyl-*NNO*-azoxybenzene (**29**) gave 3-methoxy-3-methyl-2-phenyl-2,3-dihydro-4(1*H*)-cinnolinone (**31**), possibly via the intermediate (**30**) (MeONa, MeOH, 20°C, 4 h: 22% after separation from another product).[741]

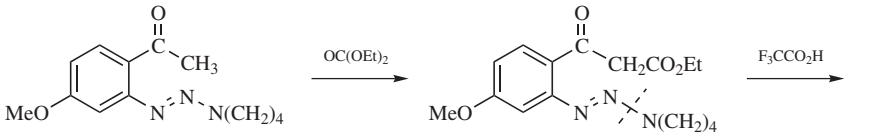


(**29**) (**30**) (**31**)

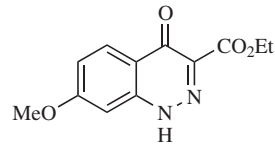
Also other examples.[83,722]

Using Derivatives of *o*-Ethylphenyltriazene as Substrates

4-Methoxy-2-(3,3-tetramethylenetriazeno)acetophenone (**32**) was converted into the sodium salt of ethyl 2-[4-methoxy-2-(3,3-tetramethylenetriaz-1-eno)benzoyl]acetate (**33**) [NaH, $OC(OEt)_2$, THF, reflux; substrate↓ during 8 h: crude] and thence into ethyl 7-methoxy-4-oxo-1,4-dihydro-3-cinnoline-carboxylate (**34**) with loss of pyrrolidine (neat F_3CCO_2H, 0°C, 12 h: 83% overall).[387]

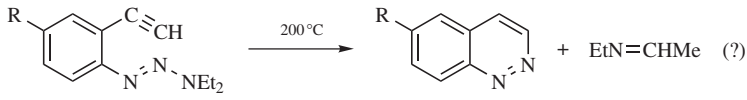


(**32**) (**33**)



(**34**)

o-(3,3-Diethyltriaz-1-eno)phenylacetylene (**35**, R = H) gave cinnoline (**36**, R = H) ($C_6H_4Cl_2$-*o*, 200°C, sealed, 12 h: 99%; the stoichiometry is unclear).[817,819]



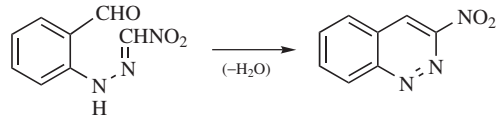
(**35**) (**36**)

3-Chloro-6-(3,3-diethyltriaz-1-eno)phenylacetylene (**35**, R = Cl) likewise gave 6-chlorocinnoline (**36**, R = Cl) (96%)[816,817,819] and other 6-substituted analogs were made similarly.[817,819]

1.1.4. By Formation of the C3–C4 Bond

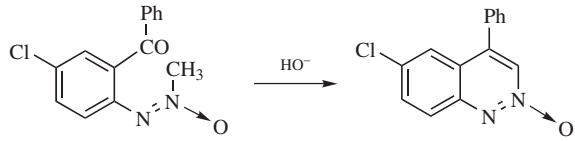
Although several procedures within this category have been reported, none has been developed to any extent. However, the following examples may point toward useful general syntheses.

o-(Nitromethylenehydrazino)benzaldehyde (**37**) gave 3-nitrocinnoline (**38**) (1,4-diazabicyclo[2.2.2]octane, H_2O, 60°C, 3 h: 86%).[370]



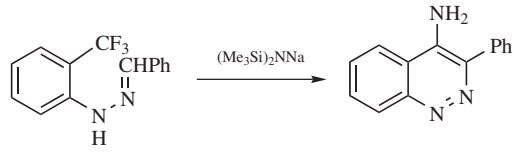
(**37**) (**38**)

3-Chloro-6-(methyl-*ONN*-azoxy)benzophenone (**39**) gave 6-chloro-4-phenylcinnoline 2-oxide (**40**) (KOH, H_2O, EtOH, reflux, 10 min: 72%).[11]



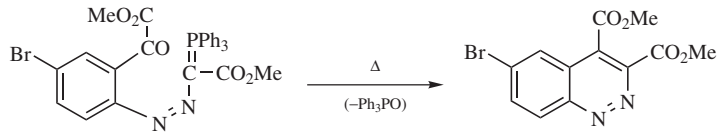
(**39**) (**40**)

N′-Benzylidene-*o*-trifluoromethylphenylhydrazine (**41**) gave 3-phenyl-4-cinnolinamine (**42**) [$NaN(SiMe_3)_2$ (4 equiv), THF (tetrahydrofuran), $-78° \rightarrow$ 20°C, 4 h: 68%); several substituted-phenyl analogs were made similarly, and a mechanism was proposed.[93]



(**41**) (**42**)

1-Bromo-3-methoxalyl-4-(α-methoxycarbonyl-α-triphenylphosphoranylidenemethylazo)benzene (**43**) gave dimethyl 6-bromo-3,4-cinnolinedicarboxylate (**44**) (PhMe, reflux, 48 h: 46%);[43] several related processes have been reported, but all gave unsatisfactory yields.[26,43,515]



(**43**) (**44**)

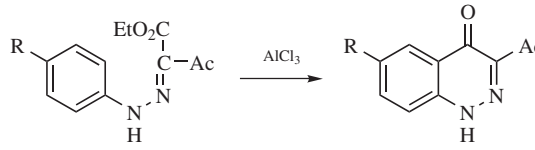
1.1.5. By Formation of the C4–C4a Bond

This is a frequently used synthesis with wide applicability. The required substrates, such as diethyl α-phenylhydrazonomalonate, are easily made by

coupling a benzenediazonium salt with an activated methylene synthon, and subsequent cyclization can be done in several ways. An interesting study on the regioselectivity of such cyclizations has been presented.[739] The following examples are classified according to the terminal groups that actually take part in the ring closure.

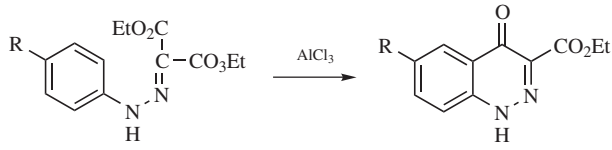
Using (Alkoxycarbonylmethylene)hydrazinobenzenes as Substrates

N′-(1-Ethoxycarbonylacetonylidene)hydrazinobenzene (**45**, R = H) gave 3-acetyl-4(1*H*)-cinnolinone (**46**, R = H) ($AlCl_3$, PhCl, 100°C, 1 h: 65%); several *p*-substituted analogs were made similarly.[619,620]



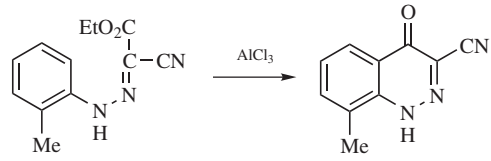
(**45**) (**46**)

1-[*N′*-(Diethoxtcarbonylmethylene)hydrazino]-4-(*p*-nitrophenylthio)benzene(**47**, R = $SC_6H_4NO_2$-*p*) gave ethyl 4-oxo-1,4-dihydro-3-cinnolinecarboxylate (**48**, R = $SC_6H_4NO_2$-*p*) ($AlCl_3$, PhCl, reflux, 1 h: 69%);[795] several 6-substituted analogs were made similarly.[663,795]



(**47**) (**48**)

o-(α-Cyano-α-ethoxycarbonylmethylene)toluene (**49**) gave 8-methyl-4-oxo-1,4-dihydro-3-cinnolinecarbonitrile (**50**) ($AlCl_3$, PhCl, reflux, 1 h: 71%); analogs likewise.[505]

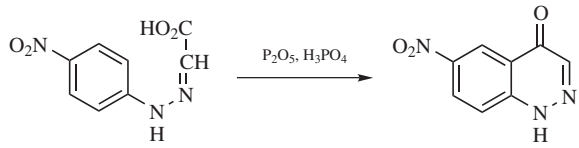


(**49**) (**50**)

Note: The evident preference in the foregoing examples for ring closure to involve an ester rather than an acyl or cyano group is important.

Using (Carboxymethylene)hydrazinobenzenes as Substrates

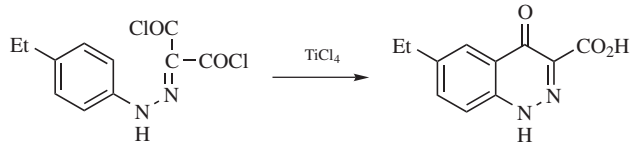
1-[(Carboxymethylene)hydrazino]-4-nitrobenzene (**51**) gave 6-nitro-4(1*H*)-cinnolinone (**52**) (P_2O_5, H_3PO_4, 65° → 135°C, 90 min: 56%); the 8-nitro isomer (47%) was made similarly.[497]



(**51**) (**52**)

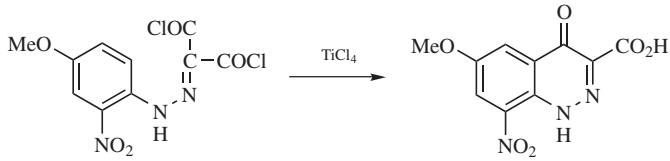
Using (Chloroformylmethylene)hydrazinobenzenes as Substrates

1-[Di(chloroformyl)methylene]hydrazino-4-ethylbenzene (**53**) gave 6-ethyl-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (**54**) ($TiCl_4$, PhCl, 100°C, 6 h; then 20°C, 10 h: 81%; note hydrolysis of the chloroformyl group during workup).[782]



(**53**) (**54**)

4-[Di(chloroformyl)methylene]hydrazino-3-nitroanisole (**55**) gave 6-methoxy-8-nitro-4-oxo-1,4-dihydro-3-cinnolinecarboxylic acid (**56**) ($TiCl_4$, $PhNO_2$, 100°C, 24 h: 51%).[27]



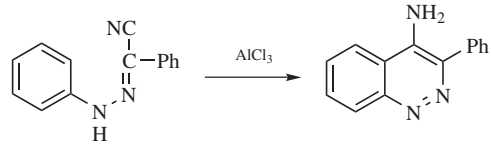
(**55**) (**56**)

Also other examples.[1034]

Using (Cyanomethylene)hydrazinobenzenes as Substrates

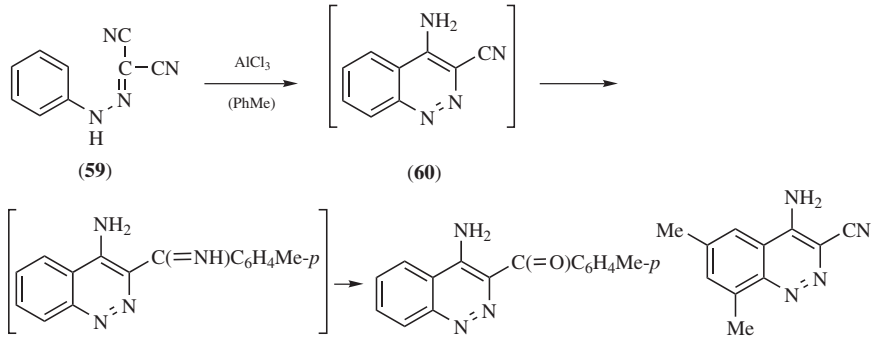
(α-Cyanobenzylidene)hydrazinobenzene (**57**) gave 3-phenyl-4-cinnolinamine (**58**) ($AlCl_3$, PhMe, reflux, 1 h: 95%); several analogs bearing substituents

on the carbocyclic ring were made similarly.[940]



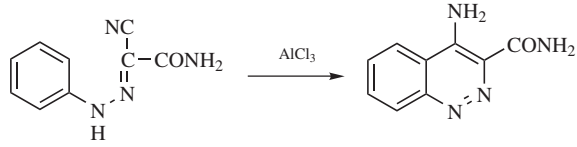
(**57**) (**58**)

(Dicyanomethylene)hydrazinobenzene (**59**) gave 3-(*p*-methylbenzoyl)-4-cinnolinamine (**62**), arising from a Friedel–Crafts reaction of the expected product (**60**) with solvent via intermediate (**61**) ($AlCl_3$, PhMe, reflux, 3 h: 32%);[487] many substituted-phenyl analogs of the substrate (**59**) likewise gave only appropriate derivatives of the product (**62**).[815,830] However, similar treatment of 1-[(dicyanomethylene)hydrazino]-2,4-dimethylbenzene did give a separable mixture of 4-amino-6,8-dimethyl-3-cinnolinecarbonitrile (**63**) and 6,8-dimethyl-3-(*p*-methylbenzoyl)-4-cinnolinamine (33% and 47%, respectively).[830,cf. 677,1011]



(**59**) (**60**) (**61**) (**62**) (**63**)

N′-(α-Carbamoyl-α-cyanomethylene)hydrazinobenzene (**64**) gave only 4-amino-3-cinnolinecarboxamide (**65**) ($AlCl_3$, PhCl, reflux, 1 h: 50%);[487] many analogs were made similarly.[487,502,503,556,667,670]

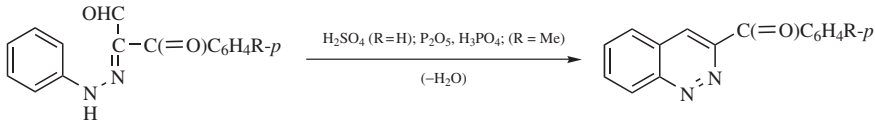


(**64**) (**65**)

Using (Acylmethylene)hydrazinobenzenes as Substrates

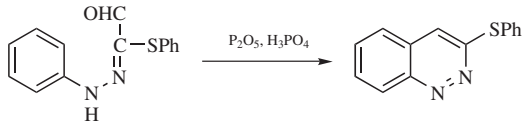
Note: As might be expected, such substrates with a terminal aldehydo group (formyl) appear to undergo cyclization more readily than do those with a terminal ketonic group (e.g., acetyl or benzoyl).

N′-(α-Benzoyl-α-formylmethylene)hydrazinobenzene (**66**, R = H) gave 3-benzoylcinnoline (**67**, R = H) (96% H_2SO_4, 100°C, 4 min: 60%); *N*′-[α-formyl-α-(*p*-methoxybenzoylmethylene]hydrazinobenzene (**66**, R = OMe) gave 3-*p*-methoxybenzoylcinnoline (**67**, R = OMe) (P_2O_5, H_3PO_4, 110°C, 9 min: 55%); several analogous products were made by each procedure.[824] The kinetics of such cyclizations have been studied.[818]



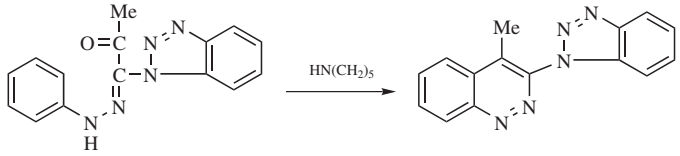
(**66**) (**67**)

N′-(α-Formyl-α-phenylthiomethylene)hydrazinobenzene (**68**) gave 3-phenylthiocinnoline (**69**) [P_2O_5, H_3PO_4, 80°C (exothermic), 10 min: 18%]; analogs likewise.[518]



(**68**) (**69**)

1-[α-Acetyl-α-(phenylhydrazono)methyl]benzotriazole (**70**) gave 3-(benzotriazol-1-yl)-4-methylcinnoline (**71**) [$HN(CH_2)_5$, xylene, reflux, 1 h: 80%].[835]

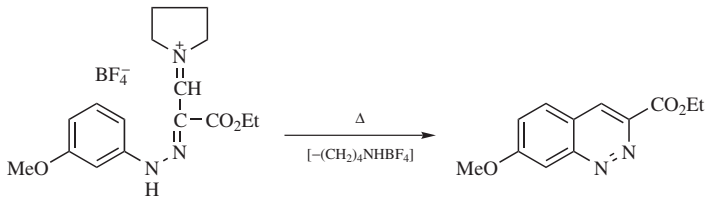


(**70**) (**71**)

Also other examples.[637]

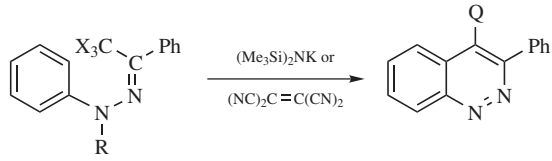
Using Miscellaneous Substrates

N-[2-Ethoxycarbonyl-2-(*m*-methoxyphenylhydrazono)ethylidene]pyrrolidinium tetrafluoroborate (**72**) gave ethyl 7-methoxy-3-cinnolinecarboxylate (**73**) (MeCN, reflux, 60 h: 63%).[292,cf. 570]



(**72**) (**73**)

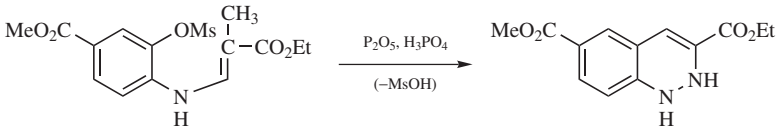
N′-(α-Trifluoromethylbenzylidene)hydrazinobenzene (**74**, R = H, X = F) and potassium bis(trimethylsilyl)amide gave 3-phenyl-4-cinnolinamine (**75**, Q = NH_2) (THF, −78°C, 4 h: ~70%); analogs likewise using the same or different amides.[85]



(**74**) (**75**)

The related substrate, [1-(*N*′-methyl-*N*′-phenylhydrazono)ethyl]benzene (**74**, R = Me, X = H), with tetracyanoethylene, gave 3-phenyl-4-cinnolinecarbonitrile (**75**, Q = CN) (MeCN, reflux, A, 8 h: 60%); analogus were made similarly, but the mechanism and categorization remain uncertain).[91]

Methyl 4-[(2-ethoxycarbonylethylidene) hydrazino]-3-(methanesulfonyloxy)-benzoate (**76**) gave methyl 3-ethoxycarbonyl-1,2-dihydro-6-cinnolinecarboxylate (**77**) (P_2O_5, H_3PO_4, 80°C, 75 min: 22% after separation from another product).[827]



(**76**) (**77**)

1.2. FROM A CARBOCYLIC SUBSTRATE AND ONE SYNTHON (*H* 6, 17, 47; *E* 20, 63)

Of the 10 possible subcategories within this major category, no less than 5 (in which the synthon would supply N1, C3, C4, N1 + N2 + C3, or N2 + C3 + C4) appear to be unrepresented in the 1972–2004 literature. However, the remaining subcategories are of considerable importance, as indicated in the following subsections.

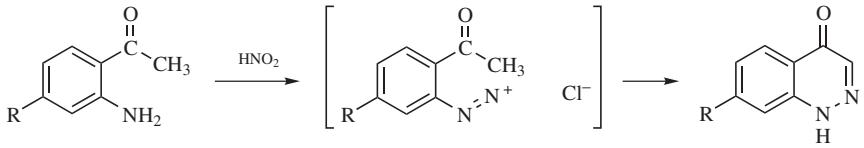
1.2.1. When the Synthon Supplies N2 of the Cinnoline

This synthesis always involves diazotization of an *o*-ethylaniline derivative followed by spontaneous cyclization.[265] The following examples, classified according to the type of substrate, illustrate the procedures employed. Fused cinnolines have been made likewise.[831,832,834]

Using *o*-Aminoacetophenones as Substrates

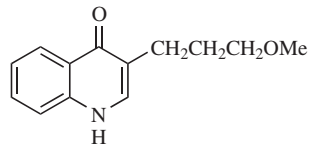
Note: Such substrates naturally produce 4(1*H*)-cinnolinone or its derivatives.

o-Aminoacetophenone (**78**, R = H) gave 4(1*H*)-cinnolinone (**80**, R = H) by spontaneous cyclization of the intermediate diazonium salt (**79**, R = H) (HCl, H_2O, $NaNO_2\downarrow$ slowly, $< 5°C$, 45 min; then 0°C, 1 h; then 80°C, 48 h: 35%);[509] 2-amino-4-(pyridin-4-yl)acetophenone (**78**, R = pyridin-4-yl) gave 7-(pyridin-4-yl)-4(1*H*)-cinnolinone (**80**, R = pyridin-4-yl) (HCl, $NaNO_2\downarrow$ slowly, $< 2°C$, 45 min; then 0°C, 2 h; then 20°C, 12 h: 77%);[45] analogs likewise.[828]



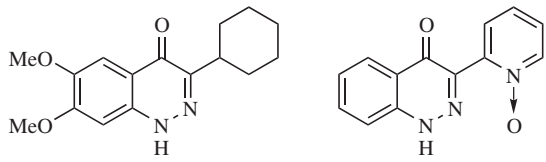
(**78**) (**79**) (**80**)

o-(5-Methoxyvaleryl)aniline gave 3-(2-methoxypropyl)-4(1*H*)-cinnolinone (**81**) (HCl, H_2O, $NaNO_2\downarrow$ slowly, $< 5°C$, 40 min; then 20°C, 3 days: ~40%).[693]



(**81**)

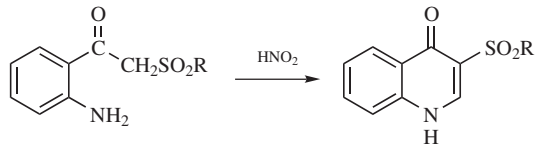
2-(Cyclohexylacetyl)-4,5-dimethoxyaniline gave 3-cyclohexyl-6,7-dimethoxy-4(1*H*)-cinnolinone (**82**) (HCl, H_2O, $NaNO_2\downarrow$ slowly, −5°C, 30 min; then 0°C, 1 h; then 70°C, 4 h; ~30%);[20] *o*-(pyridin-2-ylacetyl)aniline *N*-oxide gave 3-(*N*-oxidopyridin-2-yl)-4(1*H*)-cinnolinone (**83**) (HCl, H_2O, $NaNO_2\downarrow$ slowly, 5°C; then 20°C, 20 min: 63%).[13]



(**82**) (**83**)

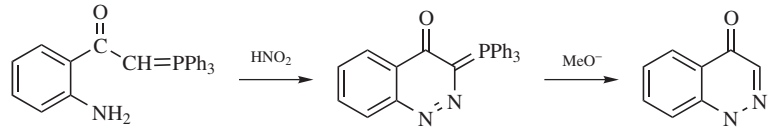
o-Sulfoacetyl)aniline, as the crude sodium salt (**84**, R = ONa), gave 4-oxo-1,4-dihydro-3-cinnolinesulfonic acid as its sodium salt (**85**, R = ONa) (HCl, H_2O, $NaNO_2\downarrow$ slowly, −5°C; then 20°C, 12 h: 64%); 4-oxo-1,4-dihydro-3-cinnolinesulfonanilide (**85**, R = NHPh) (19%), 3-phenylsulfonyl-4(1*H*)-cinnoli-

none (**85**, R = Ph) (62%), and other such analogs were made essentially by the same process.[485]



(**84**) (**85**)

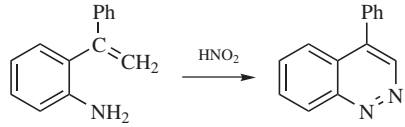
o-[(Triphenylphosphoranylidene)acetyl]aniline (**86**) gave 3-triphenylphosphoranylidene-3,4-dihydro-4-cinnolinone (**87**) ($C_5H_{11}ONO$, HCl, EtOH, 0°C → 20°C, ~1 h: 91%) and thence 4(1*H*)-cinnolinone (**88**) (NaOH, MeOH, reflux, 2 h: 97%); several analogs likewise.[335]



(**86**) (**87**) (**88**)

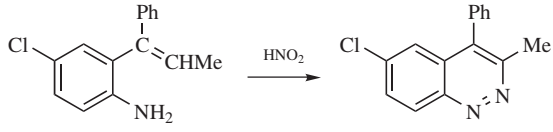
Using *o*-Aminostyrenes as Substrates

o-Amino-α-phenylstyrene (**89**) gave 4-phenylcinnoline (**90**) (MePrCHONO, Ac_2O, PhH, 80°C, 20 h: 53%).[486]



(**89**) (**90**)

2-Amino-5-chloro-β-methyl-α-phenylstyrene (**91**) gave 6-chloro-3-methyl-4-phenylcinnoline (**92**) (HCl, H_2O, $NaNO_2\downarrow$ slowly, 0°C; then 4°C, 64 h: > 47%).[290]

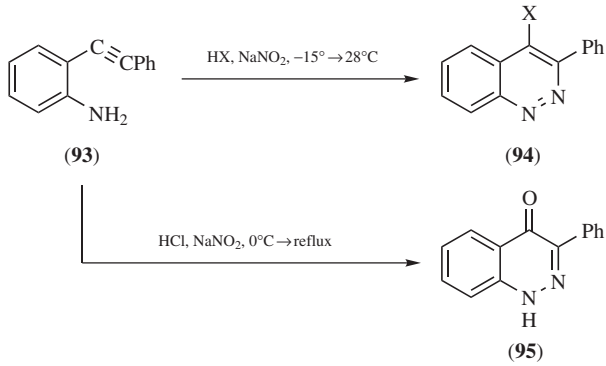


(**91**) (**92**)

Also other examples.[272,637,711]

Using *o*-Aminophenylacetylenes as Substrates

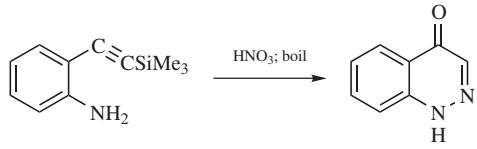
1-(*o*-Aminophenyl)-2-phenylacetylene (**93**) gave 4-bromo-3-phenylcinnoline (**94**, X = Br) (47% HBr, $NaNO_2\downarrow$ slowly, −15°C, 10 min; then 28°C, ∼15 min: 86%; note the addition of HBr to the triple bond prior to cyclization); the same reaction using 36% HCl afforded 4-chloro-3-phenylcinnoline (**94**, X = Cl) (41%); and several bromo and chloro analogs were made similarly.[388,492]



(**93**) (**94**) (**95**)

In contrast, the same substrate (**93**) under less gentle conditions gave only 3-phenyl-4(1*H*)-cinnolinone (**95**), presumably via the initial product (**94**, X = Cl) (36% HCl, $NaNO_2\downarrow$ slowly, 0°C, 2 h; then reflux, 1 h: 82%).[585]

1-(*o*-Aminophenyl)-2-trimethylsilylacatylene (**96**) gave 4(1*H*)-cinnolinone (**97**) (6M HCl, $NaNO_2\downarrow$ slowly, < 0°C, 30 min; then reflux, 3 h: 73%).[822]



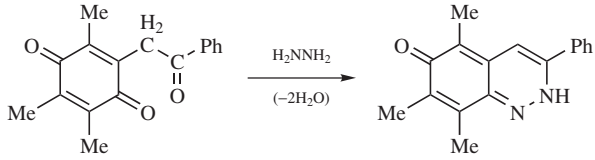
(**96**) (**97**)

1.2.2. When the Synthon Supplies N1 + N2 of the Cinnoline

This type of synthesis has proved particularly useful for the preparation of partially nucleus-reduced cinnolines, although regular aromatic cinnolines have also been so made. The N–N fragment is easily supplied by a hydrazino, diazo, or azo synthon. The use of such synthons with convenient substrates is illustrated in the following examples. Fused cinnolines have been made similarly.[833]

2,3,5-Trimethyl-6-phenacyl-1,4-benzoquinone (**98**) gave 5,7,8-trimethyl-3-phenyl-6(2*H*)-cinnolinone (**99**) ($H_2NNH_2 \cdot H_2O$, trace AcOH, PhMe, 20°C,

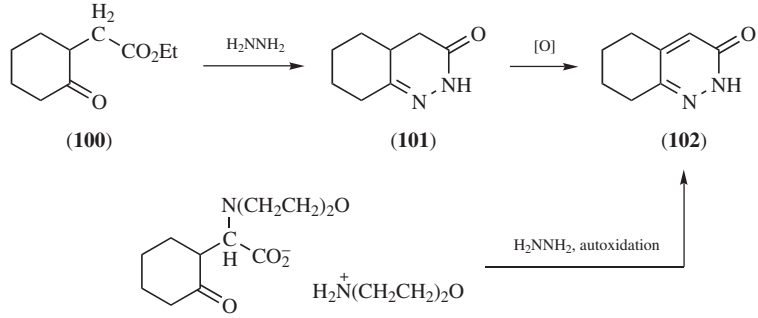
18 h: ~25%).[706]



(**98**) (**99**)

2-(Ethoxycarbonylmethyl)cyclohexane (**100**) gave 4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (**101**) ($H_2NNH_2 \cdot H_2O$, EtOH, reflux, 1 h: 72%) and thence 5,6,7,8-tetrahydro-3(2*H*)-cinnolinone (**102**) ($CuCl_2$, MeCN, reflux, 1 h: 87%);[600] minor variations in the foregoing reaction produced lower yields.[925]

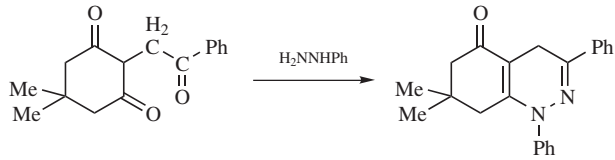
In contrast, 2-(α-carboxy-α-morpholinomethyl)cyclohexanone, as its morpholinium salt (**103**), gave 5,6,7,8-tetrahydro-3(2*H*)-cinnolinone (**102**) directly; oxidation was provided by spontaneous loss of morpholine ($H_2NNH_2 \cdot H_2O$, EtOH, reflux, 4 h: 75%).[952]



(**100**) (**101**) (**102**)

(**103**)

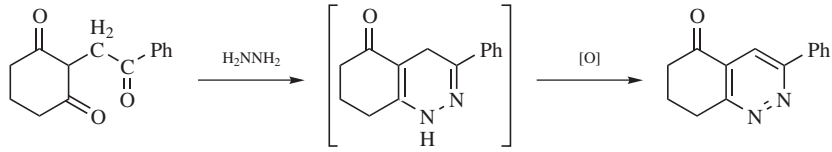
5,5-Dimethyl-2-phenacyl-1,3-cyclohexanedione (**104**) (formulated as the corresponding enol) gave 7,7-dimethyl-1,3-diphenyl-4,6,7,8-tetrahydro-5(1*H*)-cinnolinone (**105**) (H_2NNHPh, EtOH, reflux, 20 h: ~60%);[656] analogs likewise.[139,186,656]



(**104**) (**105**)

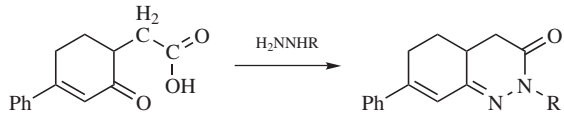
2-Phenacyl-1,3-cyclohexanedione (**106**) gave 3-phenyl-4,6,7,8-tetrahydro-5(1*H*)-cinnolinone (**107**; unisolated) and thence 3-phenyl-5,6,7,8-tetrahydro-5-cinnolinone (**108**) by oxidation (H_2NNH_2, EtOH, 20°C, 30 min; then dichloro-

dicyanobenzoquinone↓, reflux, 30 min: 78%).[284]



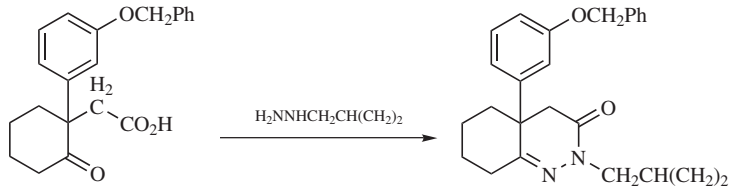
(**106**) (**107**) (**108**)

2-Carboxymethyl-5-phenylcyclohex-5-enone (**109**) gave 7-phenyl-4,4a,5,6-tetrahydro-3(2*H*)-cinnolinone (**110**, R = H) (neat $H_2NNH_2 \cdot H_2O$, reflux, 4 h: 92%) or 2-methyl-7-phenyl-4,4a,5,6-tetrahydro-3(2*H*)-cinnolinone (**110**, R = Me) (H_2NNHMe, EtOH, reflux, 16 h: 65%); analogs likewise.[517]



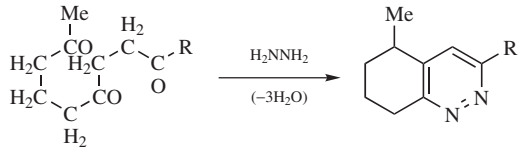
(**109**) (**110**)

2-(*m*-Benzyloxyphenyl)-2-(carboxymethyl)cyclohexanone (**111**) gave 4a-(*m*-benzyloxyphenyl)-2-cyclopropylmethyl-4,4a,5,6,7,8-hexahydro-3(2*H*)-cinnolinone (**112**) [$H_2NNHCH_2(CH_2)_2$, PhH, reflux, 6 h: 70%]; analogs likewise.[185,572,962]



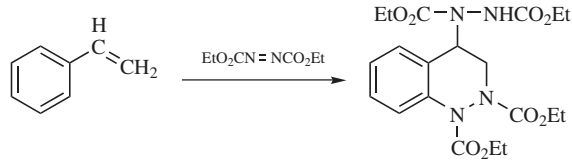
(**111**) (**112**)

2,5,9-Decanetrione (**113**, R = Me) gave 3,5-dimethyl-5,6,7,8-tetrahydrocinnoline (**114**, R = Me) ($H_2NNH_2 \cdot H_2O$, AcOH, 60°C, 1 h: 89%); the 3-ethyl, 3-propyl, and other such homologs (**114**, R = Et, Pr, etc.) were made similarly.[129]



(**113**) (**114**)

A kinetic study of the reaction of styrene (**115**) with diethyl azodicarboxylate (2 mol) to give diethyl 4-(*N*,*N*′-diethoxycarbonylhydrazino)-1,2,3,4-tetrahydro-1,2-cinnolinedicarboxylate (**116**) showed the reaction to be first-order with respect to each reactant and to be suppressed strongly in the presence of a radical inhibitor.[746]



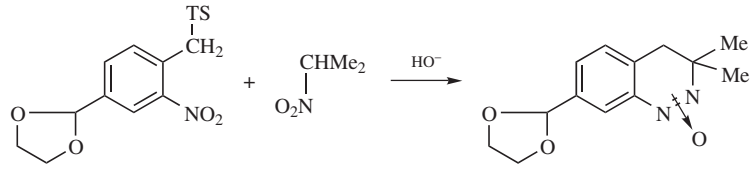
(**115**) (**116**)

Also other examples.[40,65,361,973,978]

1.2.3. When the Synthon Supplies N2 + C3 of the Cinnoline

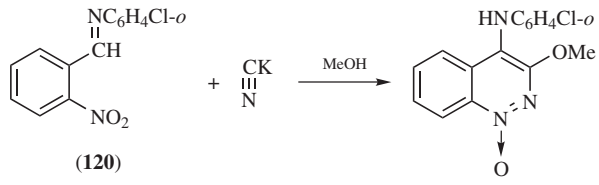
This type of synthesis is rarely used but is illustrated in the following examples.

4-(1,3-Dioxan-2-yl)-2-nitro-α-(*p*-tolylsulfonyl)toluene (**117**) and 2-nitropropane (**118**) gave 2,3-dimethyl-7-(1,3-dioxan-2-yl)-3,4-dihydrocinnoline 1/3-oxide (**119**) [NaOH, H_2O, reflux, >2 days [until substrate invisible on thin-layer chromatography (tlc)]: 40%; mechanism obscure].[529]



(**117**) (**118**) (**119**)

o-Chloro-*N*-(*o*-nitrobenzylidene)aniline (**120**) gave 4-(*o*-chloroanilino)-3-methoxycinnoline 1-oxide (**121**) (KCN, MeOH, reflux, 3 h: 55%).[709] Different substitution patterns in the substrate (**120**) led to many analogous products but all in lower yields;[72,194,709] a detailed mechanism has been proposed.[709]



(**120**) (**121**)

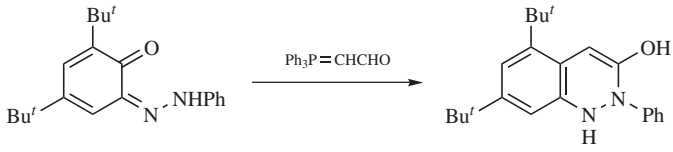
1.2.4. When the Synthon Supplies C3 + C4 of the Cinnoline

A variety of substrate and synthon types may be used for this synthesis, resulting in its widespread use. The oxidation levels of the products depend on those of both reactants. For pragmatic reasons, the examples that follow are classified broadly according to the degree of unsaturation in the synthon that supplies C3 + C4 of the cinnoline produced.

Using Ethane Derivatives as Synthons

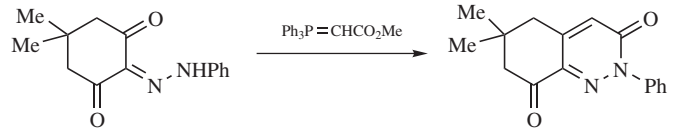
Note: Not surprisingly, simple ethane derivatives are inactive as synthons, but activated derivatives of acetaldehyde, acetic acid, or acetonitrile are ideal for this purpose.

3,5-Di-*tert*-butyl-1,2-benzoquinone mono(phenylhydrazone) (**122**) and 2-(triphenylphosphoranylidene)acetaldehyde gave a dihydrocinnoline formulated as 5,7-di-*tert*-butyl-2-phenyl-1,2-dihydro-3-cinnolinol (**123**) (EtOH, Et_3N, reflux, 2 days: 48%).[390]



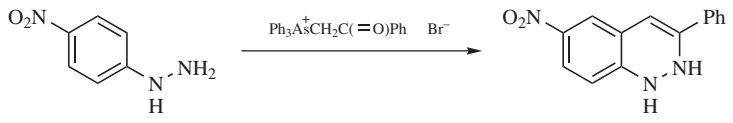
(**122**) (**123**)

5,5-Dimethyl-2-phenylhydrazono-1,3-cyclohexanedione (**124**) and methyl 2-(triphenylphosphoranylidene)acetate gave a product formulated as 6,6-dimethyl-2-phenyl-5,6,7,8-tetrahydro-3,8(2*H*)-cinnolinedione (**125**) (PhMe, reflux, 15 h: 70%); analogs likewise.[383]



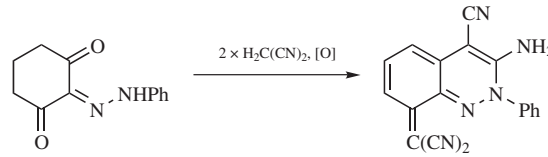
(**124**) (**125**)

p-Nitrophenylhydrazine (**126**) and phenacyltriphenylarsonium bromide gave 6-nitro-3-phenyl-1,2-dihydrocinnoline (**127**) (neat $PhNMe_2$, reflux, 4 h: 56%); several analogs were made similarly.[651]



(**126**) (**127**)

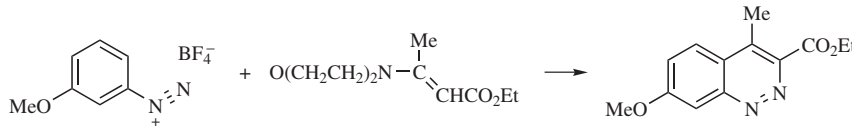
2-Phenylhydrazino-1,3-cyclohexanedione (**128**) and malononitrile (2 mol) gave 3-amino-8-dicyanomethylene-2,8-dihydro-4-cinnolinecarbonitrile (**129**) [HN $(CH_2)_5$, EtOH, 100°C, 40 min: 51%: aerial (?) oxidation]; analogs likewise.[533]



(**128**) (**129**)

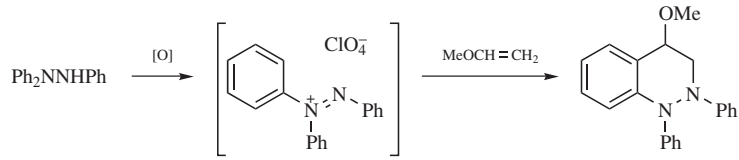
Using Ethylene Derivatives as Synthons

m-Methoxybenzenediazonium tetrafluoroborate (**130**) and ethyl 3-morpholinoisocrotonate (**131**) gave ethyl 7-methoxy-4-methyl-3-cinnolinecarboxylate (**132**) (MeCN, 20°C, 1 h; then reflux 24 h: 57%).[292]

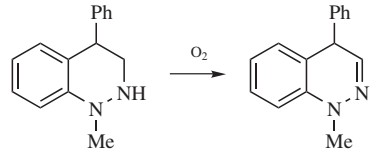


(**130**) (**131**) (**132**)

A solution of the substrate, triphenyldiazenium perchlorate (**134**), was prepared by electrochemical oxidation of triphenylhydrazine (**133**) in acetonitrile containing lithium perchlorate;[60,736] this solution and an excess of methoxyethylene (methyl vinyl ether) gave 4-methoxy-1,2-diphenyl-1,2,3,4-tetrahydrocinnoline (**135**) (MeCN, 20°C, 8 h: 96%).[736] Analogous products were made similarly,[60,61,69,71,442,443,730,736,786] and some were oxidized to the dihydro analogs; for example, 1-methyl-4-phenyl-1,2,3,4-tetrahydrocinnoline (**136**) gave 1-methyl-4-phenyl-1,4-dihydrocinnoline (**137**) (Et_2O, $O_2\downarrow$, 24 h: 90%).[730]



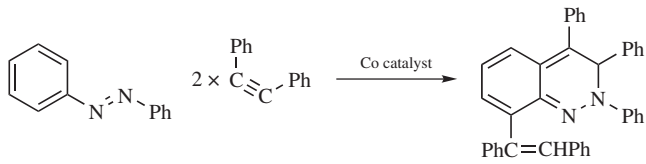
(**133**) (**134**) (**135**)



(**136**) (**137**)

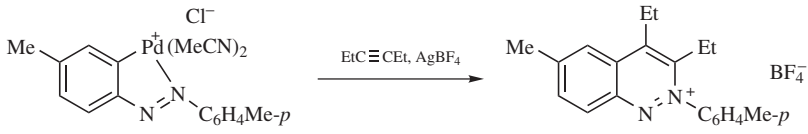
Using Acetylene Derivatives as Synthons

Azobenzene (**138**) and diphenylacetylene (**139**) (2 mol) gave 8-(1,2-diphenylvinyl)-2,3,4-triphenyl-2,3-dihydrocinnoline (**140**) [reactants mixed together at 85°C; $Co(N_2)(PPh_3)_3\downarrow$ portionwise (gas↑); then 85°C, 2 h: 70%].[722,749] Such reactions have been explored in some detail.[722,749–751]



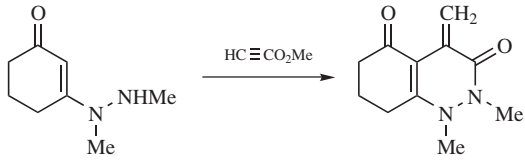
(**138**) (**139**) (**140**)

4,4′-Dimethylazobenzene, as its Pd complex (**141**), and diethylacetylene gave 3,4-diethyl-6-methyl-2-*p*-tolylcinnolin-2-ium tetrafluoroborate (**142**) ($AgBF_4$, $MeNO_2$, N_2, 20°C, 4 h: 81%); analogs, such as 3,4-dimethoxycarbonyl-2-phenylcinnolin-2-ium tetrafluoroborate, were made in a broadly similar way.[768,769]



(**141**) (**142**)

3-(*N*,*N*′-Dimethylhydrazino)cyclohex-2-en-1-one (**143**) and methyl propiolate gave 1,2-dimethyl-4-methylene-1,4,5,6,7,8-hexahydro-3,5(2*H*)-cinnolinedione (**144**) (PhMe, reflux, 6 h: 8% after chromatographic separation from two other products).[127]

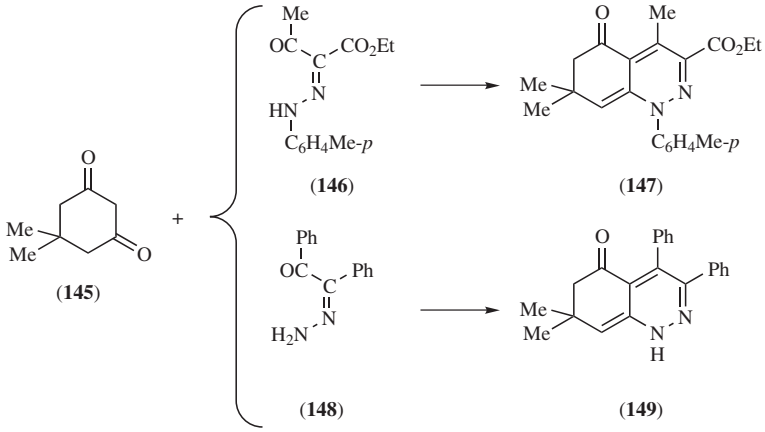


(**143**) (**144**)

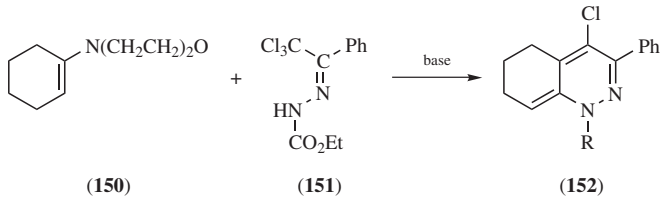
1.2.5. When the Synthon Supplies N1 + N2 + C3 + C4 of the Cinnoline

Nearly all examples in this category employ cyclohexane rather than benzene derivatives as substrates and accordingly afford partially reduced cinnolines, as illustrated here.

5,5-Dimethyl-1,3-cyclohexanedione (dimidone, **145**) and ethyl 2-(*p*-tolylhydrazono)acetoacetate (**146**) gave ethyl 4,7,7-trimethyl-5-oxo-1-*p*-tolyl-1,5,6,7-tetrahydro-3-cinnolinecarboxylate (**147**) (neat $AcONH_4$, 170°C, 30 min: 80%);[534] the same substrate (**145**) and benzil monohydrazone (**148**) gave 7,7-dimethyl-3,4-diphenyl-6,7-dihydro-5(1*H*)-cinnolinone (**149**) (or tautomer) (Et_3N, EtOH, reflux, 2 h: 80%).[673]



1-Morpholinocyclohex-1-ene (**150**) and ethyl (2,2,2-trichloro-1-phenylethylidene)hydrazinecarboxylate (**151**) gave a separable mixture of ethyl 4-chloro-3-phenyl-1,5,6,7-tetrahydro-1-cinnolinecarboxylate (**152**, R = CO_2Et) and 4-chloro-3-phenyl-1,5,6,7-tetrahydrocinnoline (**152**, R = H) (or tautomer) ($EtPr^i_2N$, CH_2Cl_2, N_2, reflux, 5 h: 44% and 9%, respectively).[86,123,cf. 287]



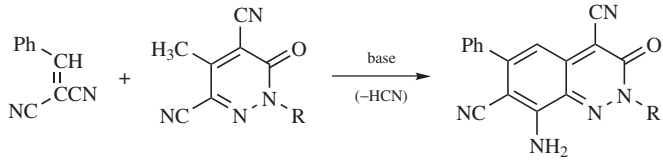
Also other examples.[516,548,602,618]

1.3. FROM A PYRIDAZINE SUBSTRATE

This potentially wide area of primary synthesis appears to be represented by only two types in which appropriate pyridazine substrates undergo cyclocondensation with synthones that supply either C6 + C7 or C6 + C7 + C8 of the resulting cinnolines. Examples follow.

1-*m*-Chlorophenyl-4-methyl-6-oxo-1,6-dihydro-3,5-pyridazinedicarbonitrile (**154**, R = C_6H_4Cl-*m*) and α-benzylidenemalononitrile (**153**) gave 8-amino-2-

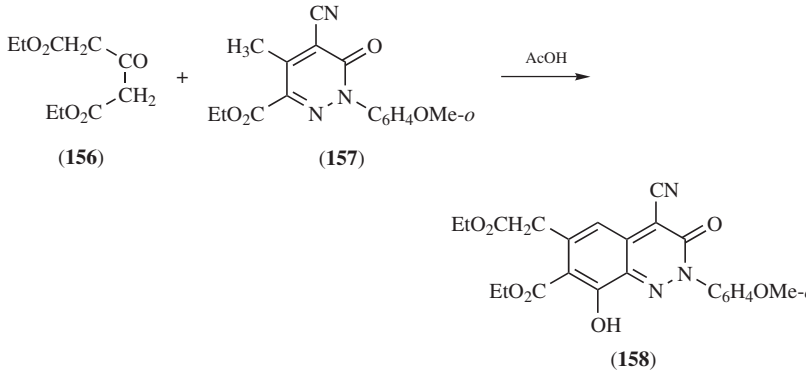
m-chlorophenyl-3-oxo-6-phenyl-2,3-dihydro-4,7-cinnolinedicarbonitrile (**155**, R = C_6H_4Cl-*m*) [trace $HN(CH_2)_5$, EtOH, reflux, 1 h: 38%]; two analogs likewise.[297]



(**153**) (**154**) (**155**)

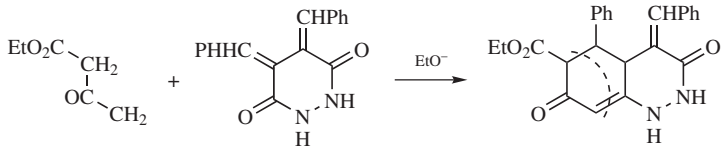
The related substrate, 4-methyl-6-oxo-1-phenyl-1,6-dihydro-3,5-pyridazinedicarbonitrile (**154**, R = Ph), and α-benzylidenemalononitrile (**153**) gave 8-amino-3-oxo-2,6-diphenyl-2,3-dihydro-4,7-cinnolinedicarbonitrile (**155**, R = Ph) [$HN(CH_2)_5$, pyridine, reflux, 4 h: 75%];[535] analogs likewise.[67,535]

Ethyl 5-cyano-1-*o*-methoxyphenyl-4-methyl-6-oxo-1,6-dihydro-3-pyridazinecarboxylate (**157**) and diethyl 3-oxoglutarate (**156**) gave ethyl 4-cyano-6-ethoxycarbonylmethyl-8-hydroxy-2-*o*-methoxyphenyl-2,3-dihydro-7-cinnolinecarboxylate (**158**) (AcOH, dioxane, reflux, 8 h: 79%); one analog likewise.[618]



(**156**) (**157**) (**158**)

4,5-Dibenzylidene-4,5-dihydro-3,6(1*H*,2*H*)-pyridazinedione (**160**) and ethyl acetoacetate (**159**) gave ethyl 4-benzylidene-3,7-dioxo-5-phenyl-1,2,3,4,4a,5,6,7-octahydro-6-cinnolinecarboxylate (**161**) [synthon (**159**), EtONa, EtOH, 20°C, 1 h; then substrate (**160**)↓, reflux, 3 h: 60%].[969]



(**159**) (**160**) (**161**)

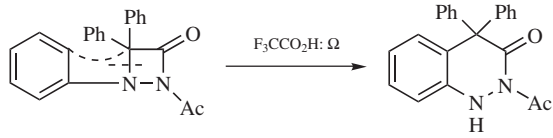
Note: Fused cinnolines may also be made from pyridazine substrates.[977]

1.4. FROM OTHER HETEROMONOCYCLIC SUBSTRATES

The formation of cinnolines from heteromonocyclic systems other than pyridazine is rare. However, at least three such systems have been so used, as illustrated in the following examples.

1,2-Diazete Derivatives as Substrates

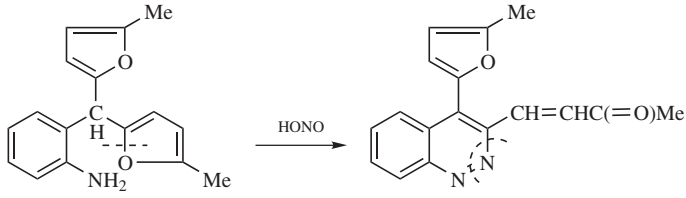
2-Acetyl-1,4,4-triphenyl-1,2-diazetidin-3-one (**162**) rearranged into 2-acetyl-4,4-diphenyl-1,4-dihydro-3(2*H*)-cinnolinone (**163**) (neat F_3CCO_2H: $> 95\%$; no further details).[720]



(**162**) (**163**)

Furan Derivatives as Substrates

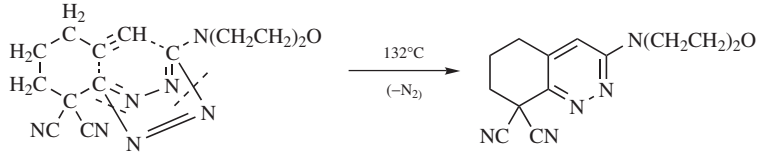
o-[Bis(5-methylfuran-2-yl)methyl]aniline (**164**) gave 3-acetonylidenemethyl-4-(5-methylfuran-2-yl)cinnoline (**165**) (Me_3SiCl, $Me_2CHCH_2CH_2ONO$, MeCN, 20°C, 15 min: 79%; a logical mechanism via a diazonium intermediate was suggested); several analogs were made similarly.[823]



(**164**) (**165**)

1,2,4,5-Tetrazine Derivatives as Substrates

3-(1,1-Dicyanohex-5-ynyl)-6-morpholino-1,2,4,5-tetrazine (**166**) underwent loss of nitrogen and recyclization to give 3-morpholino-5,6,7,8-tetrahydro-8,8-cinnolinedicarbonitrile (**167**) (xylene, 132°C, 8 h: 58%); its 4-phenyl derivative was made similarly.[953]



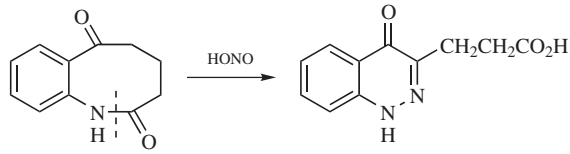
(**166**) (**167**)

1.5. FROM HETEROBICYCLIC SUBSTRATES

Several heterobicyclic systems have been used to make cinnolines, but only one has been so employed to any extent. The following examples illustrate the variety of reactions involved.

1-Benzazocine Derivatives as Substrates

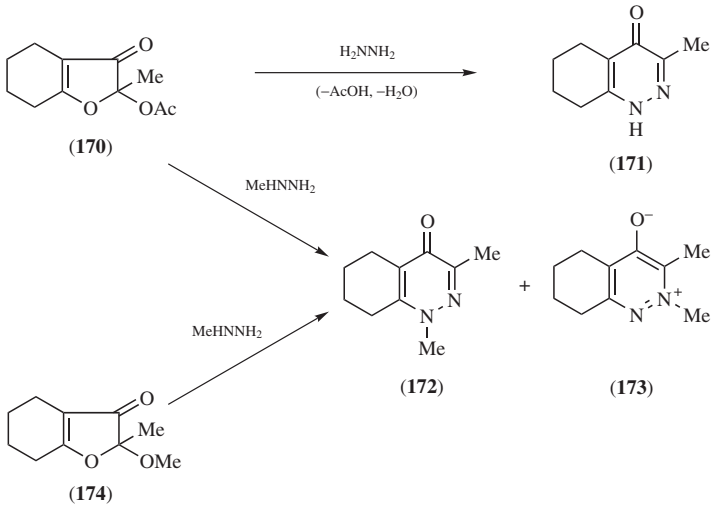
3,4,5,6-Tetrahydro-1-benzazocine-2,6(1*H*)-dione (**168**) gave 3-(2-carboxyethyl)-4(1*H*)-cinnolinone (**169**) ($MeOCH_2CH_2OMe$, trace H_2O, BuONO, HCl gas↓, 25°C, 5 min; then stirred, 25°C, 12 h; then suspension of crude diazonium intermediate, 100°C, 5 min: 61%); a dozen analogs, substituted in the phenyl ring, were made similarly.[213]



(**168**) (**169**)

Benzofuran Derivatives as Substrates

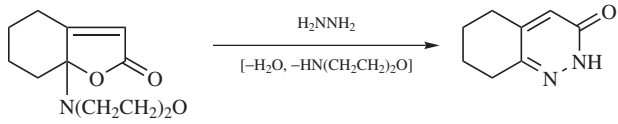
2-Acetoxy-2-methyl-2,3,4,5,6,7-hexahydrobenzofuran-3-one (**170**) with hydrazine gave 3-methyl-5,6,7,8-tetrahydro-4(1*H*)-cinnolinone (**171**) (EtOH, 20°C, 12 h: 85%) or with methylhydrazine gave a separable mixture of 1,3-dimethyl-5,6,7,8-tetrahydro-4(1*H*)-cinnolinone (**172**) and 2,3-dimethyl-5,6,7,8-tetrahydrocinnolin-2-ium-4-olate (**173**) (EtOH, 0°C → 20°C, 12 h: 67% and 15%, respectively); the related substrate, 2-methoxy-2-methyl-



(**170**) (**171**) (**172**) (**173**) (**174**)

2,3,4,5,6,7-hexahydrobenzofuran-3-one (**174**), with methylhydrazine, also gave a separable mixture of the products **172** and **173** but in approximately reverse proportion (6% and 58%, respectively).[577]

7a-Morpholino-2,4,5,6,7,7a-hexahydrofuran-2-one (**175**) gave 5,6,7,8-tetrahydro-3(2*H*)-cinnolinone (**176**) ($H_2NNH_2 \cdot H_2O$, EtOH, 20°C → reflux, 4 h: 80%).[55]

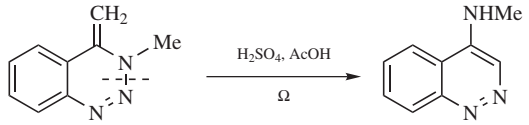


(**175**) (**176**)

Also other examples.[30]

1,2,3-Benzotriazine Derivatives as Substrates

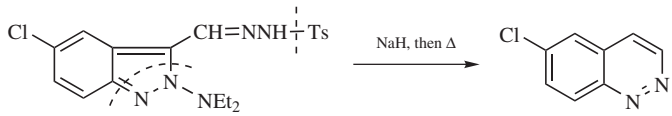
4-Methylene-3,4-dihydro-1,2,3-benzotriazine (**177**) rearranged into 4-methylaminocinnoline (**178**) (98% H_2SO_4, AcOH, 37°C → 55°C, 5 min: 12–30%).[627]



(**177**) (**178**)

Indazole Derivatives as Substrates

6-Chloro-2-diethylamino-3-(tosylhydrazonomethyl)-2*H*-indazole (**179**) was converted into its crude sodio derivative and thence into 6-chlorocinnoline (**180**) (NaH, THF, 20°C, 15 min, evaporation; then $C_6H_4Cl_2$-*o*↓, 200°C, 12 h: 51%).[816]

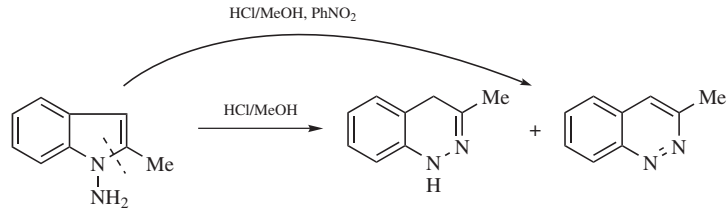


(**179**) (**180**)

Indole Derivatives as Substrates

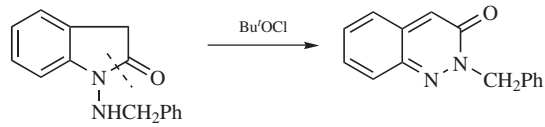
2-Methyl-1-indolamine (**181**) in methanolic hydrogen chloride gave a separable mixture of 3-methyl-1,4-dihydrocinnoline (**182**) and 3-methylcinnoline (**183**) (3%HCl/MeOH, reflux, 14 h: 56% and 24%, respectively; presumably some of the dihydro product suffered aerial oxidation during workup);[604] the same substrate (**183**) in methanolic hydrogen chloride containing nitrobenzene

gave only the aromatic product (**183**) (3% HCl/MeOH, $PhNO_2$, reflux, 42 h; 92%);[605] analogous products of both types were made similarly.[604,605]



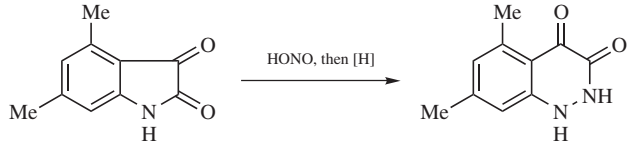
(**181**) (**182**) (**183**)

1-Benzylamino-2-indolinone (**184**) underwent oxidative rearrangement into 2-benzyl-3(2*H*)-cinnolinone (**185**) (Bu^tOCl, PhH, 20°C until substrate gone: 76%);[42] analogs likewise.[38,42] Lead tetracetate has also been used for such reactions, but it appears to be less effective.[38,187,373]



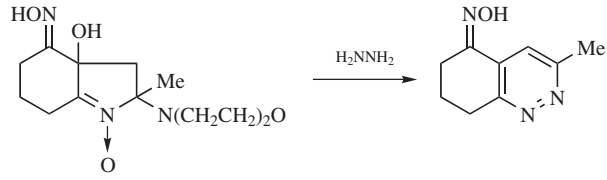
(**184**) (**185**)

4,6-Dimethyl-2,3-indolinedione (4,6-dimethylisatin, **186**) gave 5,7-dimethyl-3,4(1*H*,2*H*)-cinnolinedione (**187**) ($NaNO_2$, HCl, 15°C, 5 min; then $SnCl_2\downarrow$, 0°C, 1 h: 80%); several analogs likewise.[809]



(**186**) (**187**)

4-Hydroxyimino-2-methyl-2-morpholino-2,3,4,5,6,7-tetrahydro-3a*H*-indole 1-oxide (**188**) gave 5-hydroxyimino-3-methyl-5,6,7,8-tetrahydrocinnoline (**189**) ($H_2NNH_2 \cdot H_2O$, AcOH, H_2O, reflux, 15 min: 85%).[744]



(**188**) (**189**)

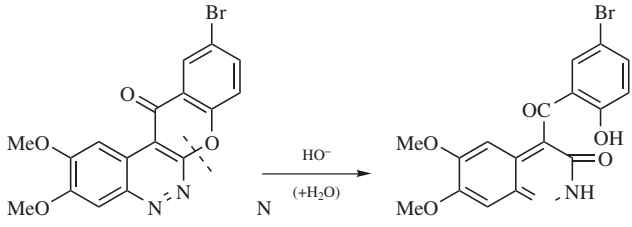
Also other examples.[2,cf. 812,325]

1.6. FROM HETEROPOLYCYCLIC SUBSTRATES

A few heterotri- to heteropentacyclic substrates have been used to prepare cinnolines, but, to date, such procedures are more of interest than utility. The following examples illustrate the processes involved.

[1]Benzopyrano[2,3-*c*]cinnoline Derivatives as Substrates

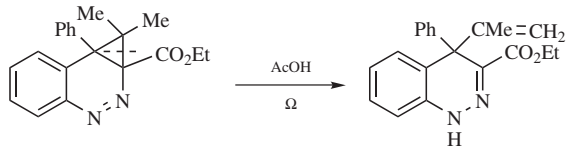
10-Bromo-2,3-dimethoxy-12*H*-[1]benzopyrano[2,3-*c*]cinnolin-12-one (**190**) underwent hydrolytic ring fission to 4-(3-bromo-6-hydroxybenzoyl)-6,7-dimethoxy-3(2*H*)-cinnolinone (**191**) (NaOH, H_2O, no further details: $> 60\%$).[227]



(**190**) (**191**)

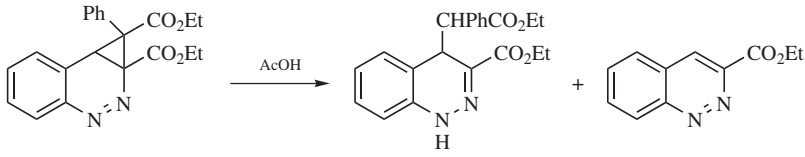
Cyclopropa[*c*]cinnoline Derivatives as Substrates

Ethyl 1,1-dimethyl-7b-phenyl-1a,7b-dihydro-[1*H*]-cyclopropa[*c*]cinnoline-1c-carboxylate (**192**) underwent rearrangement into ethyl 4-isopropenyl-4-phenyl-1,4-dihydro-3-cinnolinecarboxylate (**193**) (AcOH, reflux, 30 min: 55% after separation from another product).[702]



(**192**) (**193**)

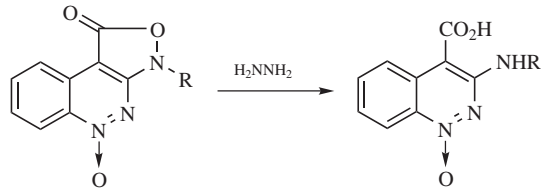
Diethyl 1-phenyl-1a,7b-dihydro-[1*H*]-cyclopropa[*c*]cinnoline-1,1a-dicarboxylate (**194**) gave a separable mixture of ethyl 4-(α-ethoxycarbonylbenzyl)-1,4-dihydro-3-cinnolinecarboxylate (**195**) and ethyl 3-cinnolinecarboxylate (**196**) (AcOH, reflux, 30 min: ~40% and ~5%, respectively, after separation from another product).[702]



(**194**) (**195**) (**196**)

Isoxazolo[3,4-*c*]cinnoline Derivatives as Substrates

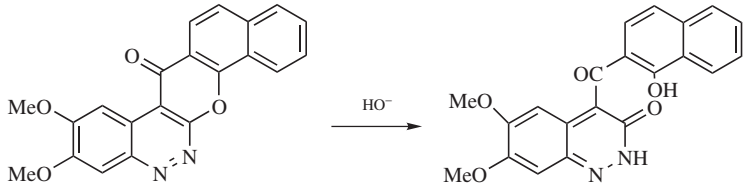
Isoxazolo[3,4-*c*]cinnolin-1(3*H*)-one 5-oxide (**197**, R = H) or its 3-methyl derivative (**197**, R = Me) underwent reductive cleavage to give 3-amino- (**198**, R = H) or 3-methylamino-4-cinnolinecarboxylic acid 1-oxide (**198**, R = Me), respectively ($H_2NNH_2 \cdot H_2O$, EtOH, reflux, ? h: 98% or 83%, respectively); analogs likewise.[147]



(**197**) (**198**)

Naphtho[2′,1′:5,6]pyrano[2,3-*c*]cinnoline Derivatives as Substrates

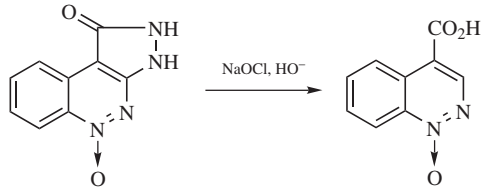
2,3-Dimethoxy-14*H*-naphtho[2′,1′:5,6]pyrano[2,3-*c*]cinnolin-14-one (**199**) gave 4-(1-hydroxy-2-naphthoyl)-6,7-dimethoxy-3(2*H*)-cinnolinone (**200**) (NaOH, H_2O, no details: > 60%).[227]



(**199**) (**200**)

Pyrazolo[3,4-*c*]cinnoline Derivatives as Substrates

3*H*-Pyrazolo[3,4-*c*]cinnolin-1(2*H*)-one 5-oxide (**201**) underwent ring fission with loss of N_2 to give 4-cinnolinecarboxylic acid 1-oxide (**202**) (NaOCl, NaOH, H_2O, 20°C, 30 min: > 95%); analogs likewise.[146]

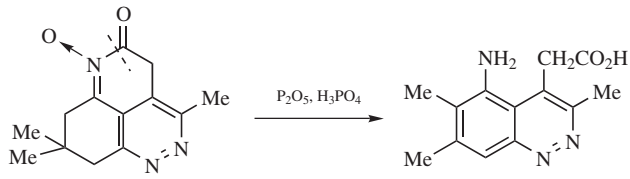


(**201**) (**202**)

Pyrido[4,3,2-*de*]cinnoline Derivatives as Substrates

3,8,8-Trimethyl-4,7,8,9-tetrahydro-5*H*-pyrido[4,3,2-*de*]cinnolin-5-one 6-oxide (**203**) isomerized into 4-carboxymethyl-3,6,7-trimethyl-5-cinnolinamine (**204**)

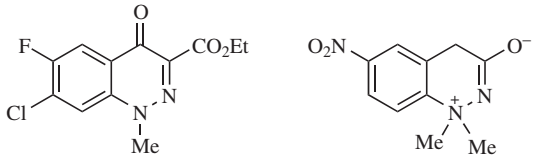
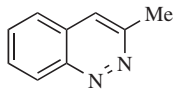
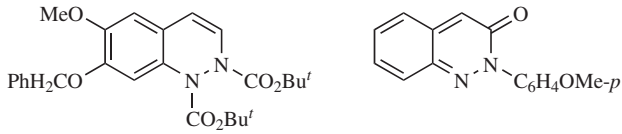
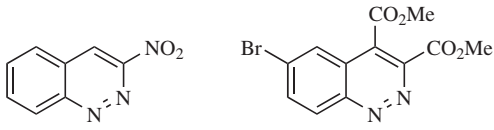
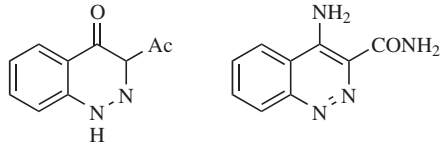
(P_2O_5, H_2PO_4, 135°C, 7 h: 85%; structure consistent with spectra).[656]



(**203**) (**204**)

1.7. GLANCE INDEX TO TYPICAL CINNOLINE DERIVATIVES AVAILABLE BY PRIMARY SYNTHESES

This glance index may assist in the choice of a primary synthesis for a required cinnoline derivative; such syntheses are based on aliphatic, carbocyclic, or heterocyclic substrates with or without ancillary synthons. In using the index, it should be borne in mind that products broadly analogous to those formulated may often be obtained by minor changes to the substrates and/or synthons involved.

Section	Typical Products
1.1.1	
1.1.2	
1.1.3	
1.1.4	
1.1.5	

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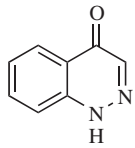
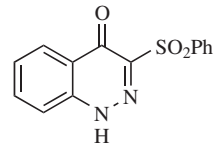
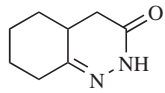
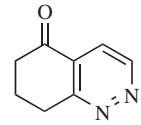
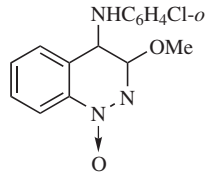
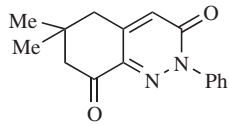
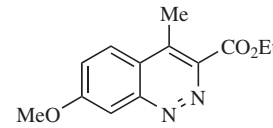
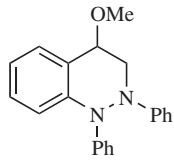
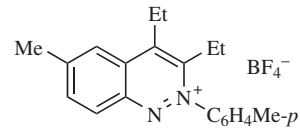
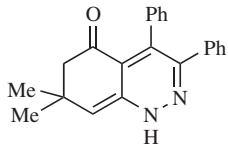
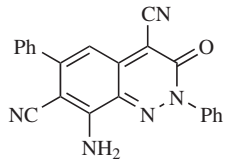
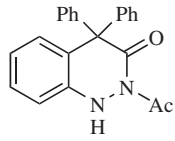
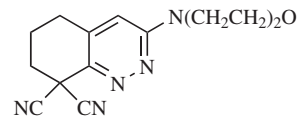
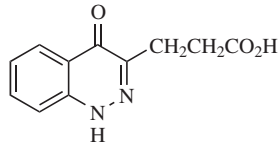
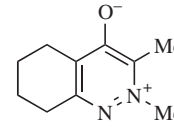
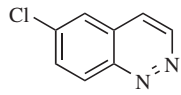
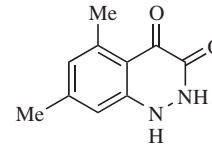
1.2.1	 
1.2.2	 
1.2.3	
1.2.4	 
	 
1.2.5	
1.3	
1.4	 

(*Continued*)

Section	Typical Products	
1.5		
		
1.6