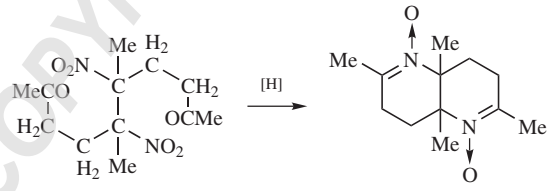
CHAPTER 1

Primary Syntheses of 1,5-Naphthyridines

The primary synthesis of 1,5-naphthyridines may be accomplished by double cyclization of appropriate aliphatic substrates; by cyclization of appropriately substituted pyridines; by cyclocondensation of pyridine substrates with one or more aliphatic synthons; or from other heterocyclic substrates by degradation, rearrangement, or the like. Partially or fully reduced 1,5-naphthyridines are often made by somewhat similar procedures; such cases are usually illustrated toward the end of each subsection. Some reviews of naphthyridine chemistry contain material on the primary synthesis of 1,5-naphthyridines.[49–52,61,231,265,670,1260,1273,1430,1432]

1.1. FROM A SINGLE ALIPHATIC SUBSTRATE

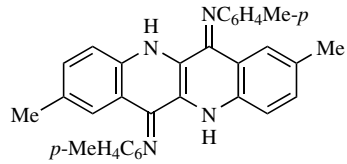
This unlikely type of synthesis is represented by the reduction of 5,6-dimethyl-5,6-dinitrodecane-2,9-dione (**1**) to give a mixture from which 2,4a,6,8a-tetramethyl-3,4,4a,7,8,8a-hexahydro-1,5-naphthyridine 1,5-dioxide (**2**) was isolated via its picrate (Zn, NH_4 Cl, H_2O, EtOH, 20°C, 6 h: ?%);[1022] the structural configuration of the foregoing compound and related products were studied later,[196]



(1) **(2)**

An essentially similar type of reaction has been used to prepare fused 1,5-naphthyridines such as 2,8-dimethyl-6,12-bis(*p*-tolylimino)-5,6,11,12-tetrahydrodibenzo[*b*, *g*][1,5]-naphthyridine (**3**).[688]

The Naphthyridines: The Chemistry of Heterocyclic Compounds, Volume 63, by D.J. Brown



(3)

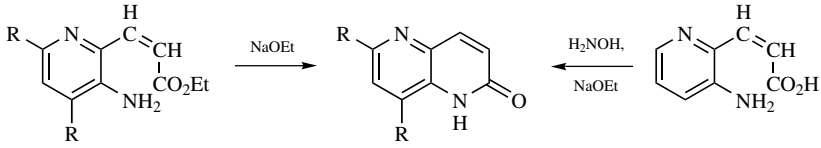
1.2. FROM A SINGLE PYRIDINE SUBSTRATE

Such syntheses may be subdivided according to which bond of the resulting 1,5-naphthyridine is formed in the process. Of the five possibilities, only three are represented in the literature.

1.2.1. By Formation of the N1,C2-Bond

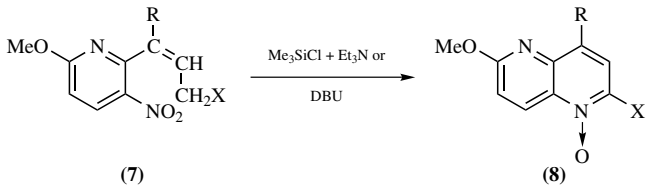
Several preparations within this category are illustrated in the following examples.

2-(2-Ethoxycarbonylvinyl)-3-pyridinamine (**4**, R = H) gave 1,5-naphthyridin-2(1*H*)-one (**5**, R = H) (EtONa, EtOH, reflux, 3 h: 72%);[1044] the homologous substrate (**4**, R = Me) likewise gave 6,8-dimethyl-l,5-naphthyridin-2(1*H*)-one (**5**, R = Me) (reflux, 2 h: 71%);[1044] and the analogous carboxy substrate, 2-(2-carboxyvinyl)-3-pyridinamine (**6**), also afforded 1,5-naphthyridine-2(1*H*)-one (**5**, R = H) using the Posner[1428] technique (H_2NOH, MeONa, MeOH, reflux, 12 h: 31%).[1000]



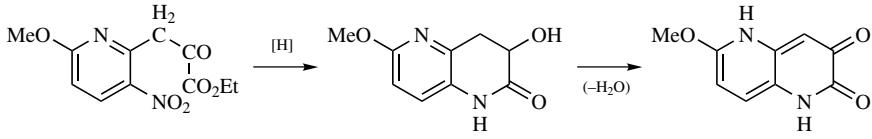
(4) (5) (6)

2-(3-Cyano-1-isopropylprop-1-enyl)-6-methoxy-3-nitropyridine (**7**, R = Pr^i, X = CN) gave 6-methoxy-4-isopropyl-1,5-naphthyridine-2-carbonitrile 1-oxide (**8**, R = Pr^i, X = CN) (Me_3SiCl, Et_3N, Me_2NCHO, 20°C, 6 h: 48%);[588] somewhat similarly, 2-(3-ethoxycarbonylprop-1-enyl)-6-methoxy-3-nitropyridine (**7**, R = H, X = CO_2Et) gave ethyl 6-methoxy-1,5-naphthyridine-2-carboxylate 1-oxide (**8**, R = H, X = CO_2Et) [Me_3SiC1, diazabicycloundecene (DBU), Me_2NCHO, 20°C, 1 h: 85%].[588]



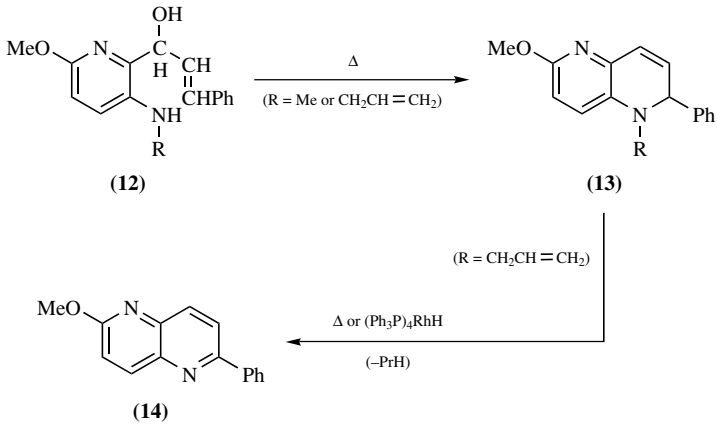
(7) (8)

2-Ethoxalylmethyl-6-methoxy-3-nitropyridine (**9**) underwent reductive cyclization to 3-hydroxy-6-methoxy-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one (**10**) (PtO_2, H_2, 3 atm, EtOH, 20°C, 2 h: 69%) that was easily aromatized to give 6-methoxy-1,5-naphthyridine-2,3(1*H*, 5*H*)-dione (**11**) [TsCl, pyridine, 150°C (?), 4 h: 83%].[234]



(**9**) (**10**) (**11**)

2-(1-Hydroxy-3-phenylallyl)-6-methoxy-3-methylaminopyridine (**12**, R = Me) underwent thermolytic cyclization to give 2-methoxy-5-methyl-6-phenyl-5, 6-dihydro-1,5-naphthyridine (**13**, R = Me) ($C_6H_4Cl_2$, 180°C, 4 h: 31%). However, when the allylamino substrate (**12**, $R = CH_2CH{:}CH_2$) was so treated, the initial product, 1-allylamino-6-methoxy-2-phenyl-1, 5-naphthyridine (**13**, $R = CH_2CH{:}CH_2$) (180°C, 20 min: 65%), underwent subsequent aromatization to 2-methoxy-6-phenyl-1,5-naphthyridine (**14**), presumably by loss of propane [180°C, 20 h: 43%; or F_3CCO_2H, $(Ph_3P)_4RhH$, EtOH, reflux, 4 h: 54%].[619]

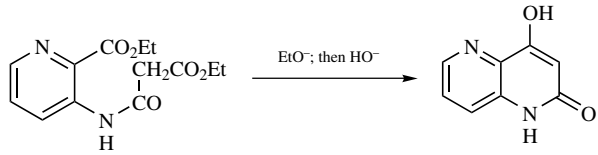


(**12**) (**13**) (**14**)

1.2.2. By Formation of the C3,C4-Bond

Such a synthesis is evident in the Dieckmann cyclization[981] of ethyl 3-[2-(ethoxycarbonyl)acetamido]-2-pyridinecarboxylate (**15**) (prepared *in situ*) to give

4-hydroxy-1, 8-naphthyridin-2(1*H*)-one (**16**) (EtONa, EtOH, reflux, 5 h; resulting solid, NaOH, H_2O, reflux until gas-ceased: 69%).[1023]

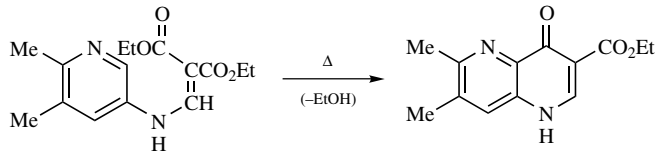


(**15**) (**16**)

1.2.3. By Formation of the C4,C4a-Bond

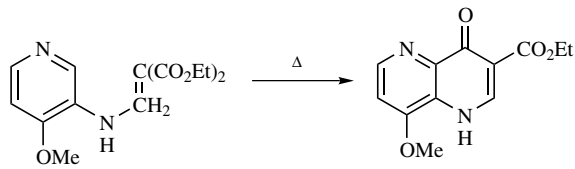
Although it involves the formation of a C,C-bond, this synthesis has been widely used, as illustrated in the following typical examples.

3-[(2,2-Diethoxycarbonylvinyl)amino]-5,6-dimethylpyridine (**17**) underwent regioselective thermal cyclization to give ethyl 6,7-dimethyl-4-oxo-1,4-dihydro-1,5-naphthyridine-3-carboxylate (**18**) (Dowtherm A, reflux, 15 min: 89%; analogs likewise).[1398]



(**17**) (**18**)

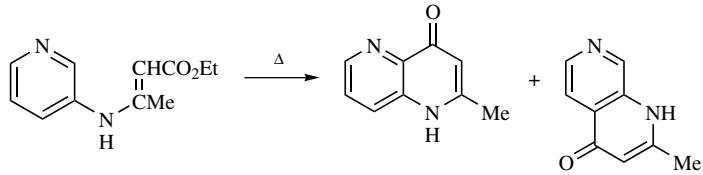
3-[(2,2-Diethoxycarbonylvinyl)amino]-4-methoxypyridine (**19**) gave ethyl 8-methoxy-4-oxo-1,4-dihydro-1,5-naphthyridine-3-carboxylate (**20**) (Ph_2O, reflux, 25 min: 72%);[301] a similar substrate likewise gave ethyl 6-butoxy-4-oxo-1,4-dihydro-1,5-naphthyridine-3-carboxylate (Ph_2O, reflux, 15 min: ~75%).[1036]



(**19**) (**20**)

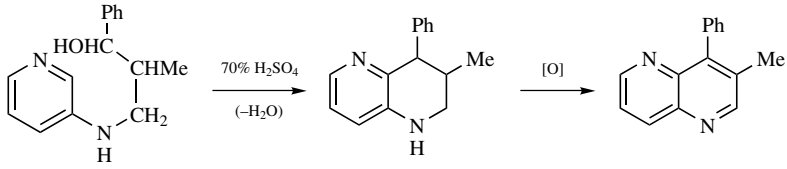
In contrast, regioselectively was less marked in the thermal cyclization of 3-[(2-ethoxycarbonyl)amino]pyridine (**21**), which gave a 4:1 mixture of

2-methyl-1,5-naphthyridin-4(1*H*)-one (**22**) and 2-methyl-1,7-naphthyridin-4(1*H*)-one (**23**) (Ph_2O, reflux, 1 h: 75% of mixture).[828]



(21) **(22)** **(23)**

3-[(3-Hydroxy-2-methyl-3-phenylpropyl)amino]pyridine (**24**) underwent dehydrative cyclization to give 3-methyl-4-phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine (**25**) (70% H_2SO_4, 0°C →25°C, ~15 h: 65%) that was easily dehydrogenated to give 3-methyl-4-phenyl-1,5-naphthyridine (**26**) (neat substrate, Pd/C, 200°C, 3 h: 56%).[879] Also other examples.[48,485,865,967,1232,1245]



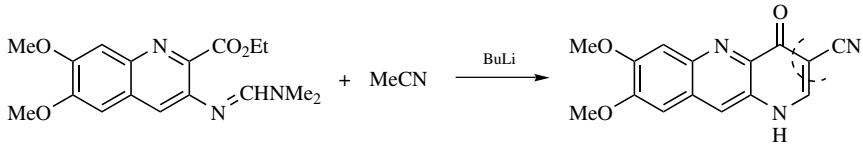
(24) **(25)** **(26)**

1.3. FROM A PYRIDINE SUBSTRATE WITH ONE SYNTHON

Most primary syntheses of 1,5-naphthyridines fall into this basket. Procedures are divided initially into categories in which the synthon provides one, two, or three atoms to the final 1,5-naphthyridine; when necessary, such categories are further subdivided according to which specific atoms are provided by the synthon.

1.3.1. Where the Synthon Supplies One Atom

There appears to be no example of such a synthesis in the parent 1,5-naphthyridine series, but benzo-1,5-naphthyridines have been so made. Thus ethyl 3-dimethylaminomethyleneamino-6,7-dimethoxyquinoline (**27**) gave 7,8-dimethoxy-4-oxo-1,4-dihydrobenzo[*b*]-1,5-naphthyridine-3-carbonitrile (**28**)[$NaCH_2CN$ (made *in situ*), THF, −78°C; substrates dropwise, −78°C, 3 h; then 20°C, 12 h: 58%].[208]

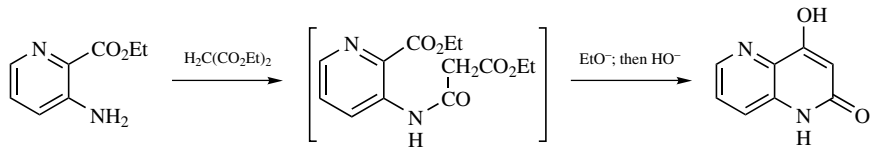


(27) **(28)**

1.3.2. Where the Synthon Supplies Two Atoms

Nearly all the reported syntheses in this category have used the synthon to supply C2 + C3 of the resulting 1,5-naphthyridine, but C3 + C4 may be so supplied, as illustrated at the end of the following list of typical examples.

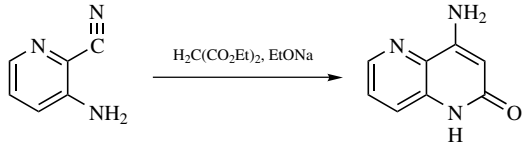
Ethyl 3-aminopicolinate (**29**) with diethyl malonate gave 4-hydroxy-1,5-naphthyridin-2(1*H*)-one (**30**) [neat reactants, 120°C, 5 h; solid, EtONa, EtOH, reflux, 5 h; solid, 2.5M NaOH, reflux until gas ceased: 96%].[1151]



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

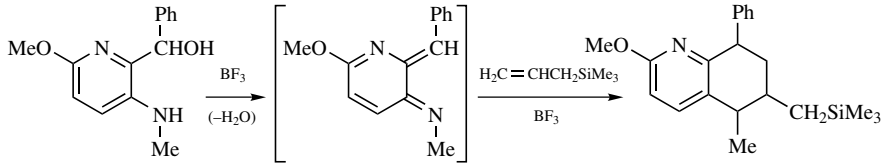
Somewhat similarly, 3-aminopicolinic acid with ethyl acetoacetate gave 2-methyl-1,5-naphthyridin-4(1*H*)-one (neat reactants, reflux, 4 h: 13%).[1000]

3-Amino-2-pyridinecarbonitrile (**31**) with diethyl malonate gave 4-amino-1,5-naphthyridin-2(1*H*)-one (**32**) (neat reactants, EtONa, reflux, 7.5 h: 36%).[725]



(**31**) (**32**)

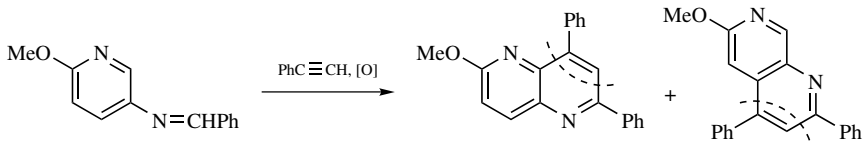
2-(α-Hydroxybenzyl)-6-methoxy-3-methylaminopyridine (**33**) with allyltrimethylsilane gave 2-methoxy-5-methyl-8-phenyl-6-(trimethylsilylmethyl)-5,6,7,8-tetrahydro-1,5-naphthyridine (**34**) (reactants, BF_3,Et_2O. 60–80°C, 4.5 h: 50%); analogs likewise.[619]



(**33**) (**34**)

3-Benzylideneamino-6-methoxypyridine (**35**) underwent partially regioselective cyclocondensation with phenylacetylene in the presence of oxidizing agents to afford a separable mixture of 2-methoxy-6,8-diphenyl-1,5-naphthyridine (**36**) and 6-methoxy-2,4-diphenyl-1,7-naphthyridine (**37**) (reactants, $FeCl_3$,

tetrachlorobenzoquinone, MeCN, reflux, ~45 min; 50% and 7%, respectively, after separation).[455] Also other examples.[312,1302]

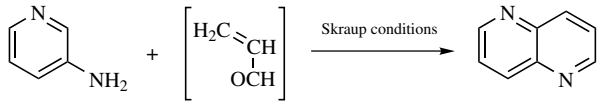


(35) **(36)** **(37)**

1.3.3. Where the Synthon Supplies Three Atoms

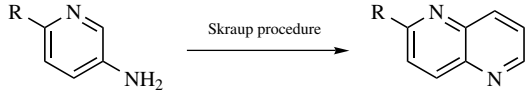
Of the two possibilities in this category (to supply N1 + C2 + C3 or C2 + C3 + C4), only the latter has been employed, often by submission of a 3-pyridinamine to a Skraup-like synthesis. Typical examples follows.

3-Pyridinamine (**38**) and acrolein (**39**) (formed from glycerol under Skraup-like conditions) gave 1,5-naphthyridine (**40**) [$O_2NC_6H_4SO_3Na$-*m*, H_2SO_4, H_3BO_3, $FeSO_4$, 0°C; $HOHC(CH_2OH)_2\downarrow$, substrate $\downarrow$, H_2O $\downarrow$; 135°C, 4 h: 90%;[873] $HOCH(CH_2OH)_2$, $O_2NC_6H_4SO_3Na$-*m*, ~70% H_2SO_4, 135°C, 4 h: 50%;[45] earlier versions, using As_2O_5 as the oxidizing agent, gave <30% yields.[14,32,113,155,104,]



(38) **(39)** **(40)**

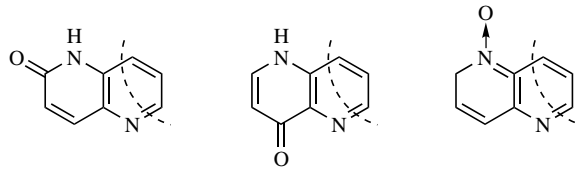
6-Methyl-3-pyridinamine (**41**, R = Me) gave 2-methyl-1,5-naphthyridine (**42**, R = Me) [96% H_2SO_4,$O_2NC_6H_4SO_3Na$-*m*, H_3BO_3, $FeSO_4$, $7H_2O$, $HOHC(CH_2OH)_2\downarrow$, substrate$\downarrow$, $H_2O\downarrow$, then 135°C, 18 h: 55%];[268] 2,5-pyridinediamine (**41**; R = NH_2) gave 1,5-naphthyridine-2-amine (**42**, R = NH_2) [70% H_2SO_4, $O_2NC_6H_4SO_3Na$-*m*, $HOCH(CH_2OH)_2$, 135°C, 5 h: 88%].[811,1371]



(41) **(42)**

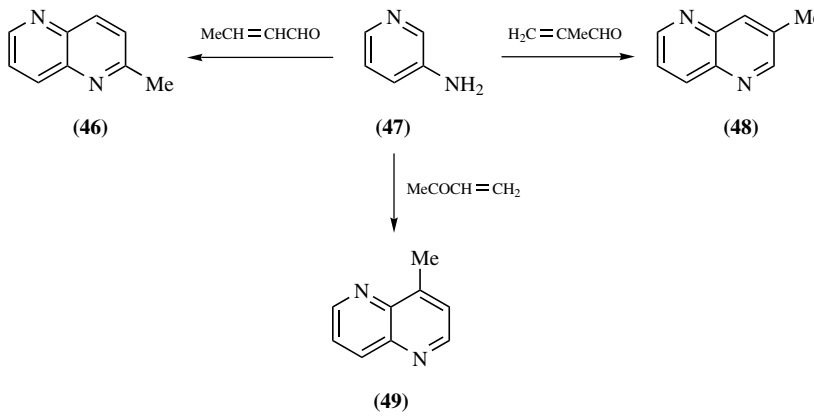
Appropriate pyridine substrates similarly gave 1,5-naphthyridine-2(1*H*)-one (**43**) [$HOHC(CH_2OH)_2$, As_2O_5, 165°C, ~90 min: 57%;[1037] likewise but 160°C, 45 min: 15%];[1051] 1,5-naphthyridin-4(1*H*)-one (**44**)(likewise, 160°C, ~2.5 h:

37%);[1047] and 1,5-naphthyridine 1-oxide (**45**) [$O_2NC_6H_4SO_3H$, H_2SO_4, $FeSO_4$, $7H_2O$, H_3BO_3, 0°C; $HOCH(CH_2OH)_2\downarrow$, substrate $\downarrow$, H_2O $\downarrow$; then 130°C, 5 h: 19%].[1033]



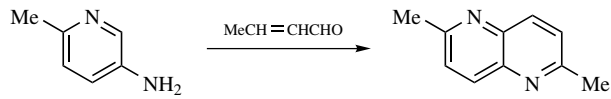
(43) **(44)** **(45)**

3-Pyridinamine (**47**) with crotonaldehyde gave 2-methyl-1,5-naphthyridine (**46**)(substrate, $O_2NC_6H_4SO_3H$, H_2SO_4, H_2O, 125°C; MeCH=CHCHO in dropwise, 1 h: then 150°C, 12 h: ~10%), with methacrylaldehyde gave 3-methyl-1,5-naphthyridine (**48**) (substrate, $FeSO_4.7H_2O$, As_2O_5, 96% H_2SO_4, 120°C; $H_2CCMeCHO$ in dropwise during 7 h; the 170°C, 15 h: 30%); or with methyl vinyl ketone gave 4-methyl-1,5-naphthyridine (**49**)[as for isomer (**46**) but $MeCOCH{=}CH_2$; 11%].[155]



(46) **(47)** **(48)** **(49)**

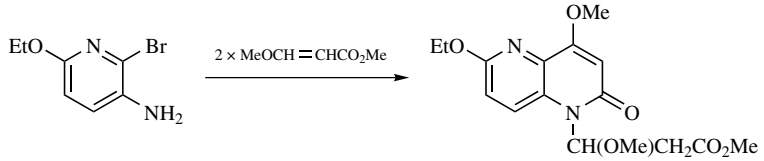
6-Methyl-3-pyridinamine (**50**) with crotonaldehyde gave 2,6-dimethyl-1,5-naphthyridine (**51**) [substrate, $O_2NC_6H_4SO_3H$, H_2SO_4 (?), H_2O, 125°C; MeCH=CHCHO in slowly; then 150°C, 8 h: ~10%];[1169] analogs somewhat similarly.[269]



(50) **(51)**

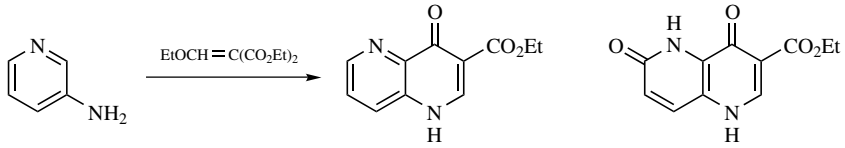
2-Bromo-6-ethoxy-3-pyridinamine (**52**) reacted with methyl 3-methoxyacrylate (2 equiv) to give 6-ethoxy-4-methoxy-1-(1-methoxy-2-methoxycarbony-

lethyl)-1,5-naphthyridin-2(1*H*)-one (**53**) [$Pd(OAc)_2$, $P(C_6H_4Me\text{-}p)_3$, Et_3N, N_2, 100°C bath, 5 days: 28%].[1015]



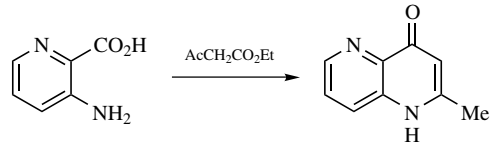
(52) **(53)**

3-Pyridinamine (**54**) with diethyl ethoxymethylenemalonate gave ethyl 4-oxo-1,4-dihydro-1,5-naphthyridine-3-carboxylate (**55**) (reactants, Dowtherm A, 150°C, reflux, 1 h: 80%);[101] somewhat similarly, 5-amino-2(1*H*)-pyridinone gave ethyl 4,6-dioxo-1,4,5,6-tetrahydro-1,5-naphthyridine-3-carboxylate (**56**) [$EtOCH{=}C(CO_2Et)_2$, Ph_2O, reflux, 1 h: 20%].[233]



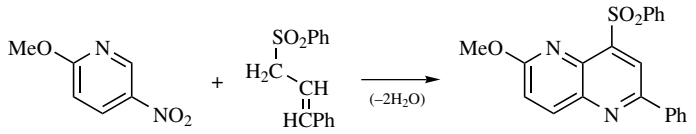
(54) **(55)** **(56)**

3-Aminopicolinic acid (**57**) with ethyl acetoacetate gave 2-methyl-1,5-naphthyridin-4(1*H*)-one (**58**) (neat reactants, reflux, 4 h: 13%).[828,1000]



(57) **(58)**

2-Methoxy-5-nitropyridine (**59**) with 1-phenyl-3-phenylsulfonylpropane (**60**) gave 2-methyl-6-phenyl-8-phenylsulfonyl-1,5-naphthyridine (**61**) (reactants, MeCN, Bu^tMe_3 SiCl, DBU, 20°C, 3 days: 54%),[521,554] Also other examples,[181,273,316,760,827,1272,1377]

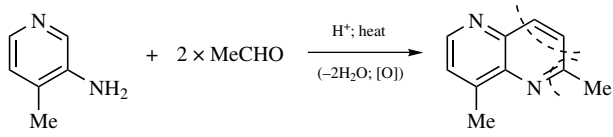


(59) **(60)** **(61)**

1.4. FROM A PYRIDINE SUBSTRATE AND TWO SYNTHONS

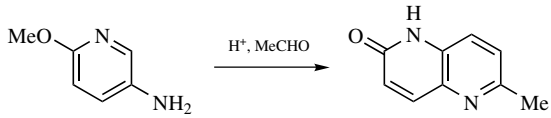
This type of synthesis is represented only by several procedures akin to the Doebner–Miller quinoline synthesis, in which both synthons are the same.

4-Methyl-3-pyridinamine (**62**) and an excess of acetaldehyde gave 2,8-dimethyl-1,5-naphthyridine (**63**) (substrate, 10M HCl, 5°C; MeCHO in dropwise; 0°C, 1 h; then reflux, 1 h; 16%; note the necessity for oxidation, either aerial or by the excess of MeCHO?),[268]



(**62**) (**63**)

Similar treatment of 6-methoxy-3-pyridinamine (**64**) involved an additional hydrolysis of the methoxy group to afford 6-methyl-1,5-naphthyridin-2(1*H*)-one (**65**)(36%).[268]



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

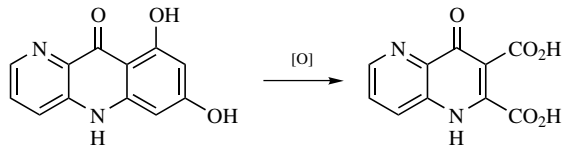
Also other examples.[94]

1.5. FROM OTHER HETEROCYCLIC SUBSTRATES

This general approach to 1,5-naphthyridines has seldom been used, but classified examples follow.

From Benzo[*b*]-1,5-naphthyridines

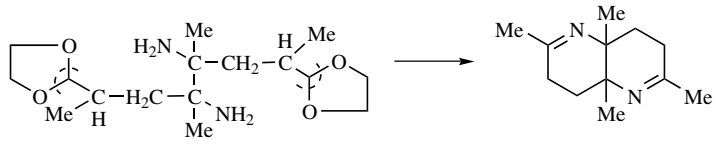
7,9-Dihydroxybenzo[*b*]-1,5-naphthyridin-10(5*H*)-one (**66**), easily made by fusion of 3-aminopicolinic acid with phloroglucinol, underwent oxidation to 4-oxo-1,4-dihydro-1,5-naphthyridine-2,3-dicarboxylic acid (**67**) [HNO_3 (d. 1.5), 20°C, then 95°C, 40 min: ?%, after separation from a byproduct].[17]



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

From 1,3-Dioxolanes

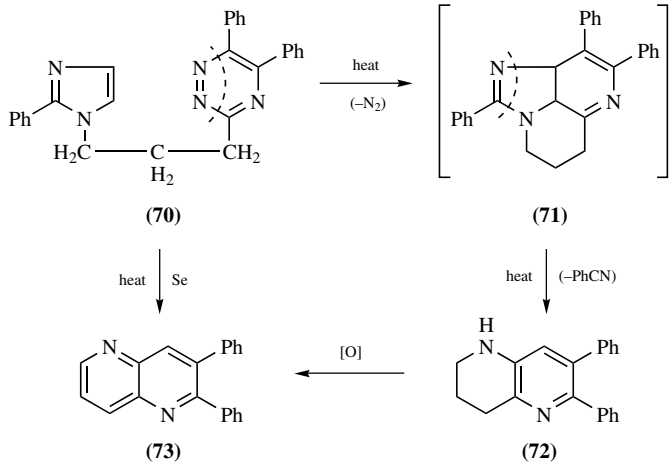
4,5-Diamino-2,7-bis(1,3-dioxolan-2-yl)-4,5-dimethyloctane (**68**) [a bis(cycloacetal) of the corresponding dialdehyde] gave 2,4a,6,8a-tetramethyl-3,4,4a,7,8,8a-hexahydro-1,5-naphthyridine (**69**) (1M H_2SO_4: no details).[196]



(68) **(69)**

From 1,2,4-Triazines

5,6-Diphenyl-3-[3-(2-phenylimidazol-1-yl)propyl]-1,2,4-triazine (**70**) underwent thermal intramolecular addition (with loss of nitrogen) to give the tricyclic intermediate (**71**) and thence (by loss of benzonitrile) 2,3-diphenyl-5,6,7,8-tetrahydro-1,5-naphthyridine (**72**) [substrate, antioxidant (2,6-di-*tert*-butyl-4-methylphenol), 1,3,5-$Pr^i_3C_6H_3$, reflux, 3 h: 92%] that could be aromatized to 2,3-diphenyl-1,5-naphthyridine (**73**) (1,3,5-$Pr^i_3C_6H_3$, reflux, air, 24 h: 91%); the latter product (**73**) was also made directly from the triazine (**70**) (neat substrate, Se, 330°C, 10 h: 85%); analogs likewise.[137,522]



(70) **(71)** **(72)** **(73)**