# THE PYRAZINES

## Supplement I

**D. J. Brown**

Research School of Chemistry
Australian National University
Canberra

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## Supplement I

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**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

A SERIES OF MONOGRAPHS

**EDWARD C. TAYLOR and PETER WIPF,** *Editors*

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*To*
*Professor Emeritus Felix Bergmann*[†]
*(heterocyclic chemist and pharmacologist)*
*now in his ninety-fifth year*

[†]Felix Bergmann was born in Frankfurt an der Oder in 1908 and graduated with doctorates in chemistry and medicine from Berlin in 1933. He then joined his brother Ernst at the Weizmann Institute, Rehovot, until he was elected in 1950 to the chair of Pharmacology within the Hebrew University of Jerusalem. During retirement, he has remained active in research until quite recently.

# The Chemistry of Heterocyclic Compounds
# Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

*The Chemistry of Heterocyclic Compounds*, has been published since 1950 under the initial editorship of Arnold Weissberger, and later, until his death in 1984, under the joint editorship of Arnold Weissberger and Edward C. Taylor. In 1997, Peter Wipf joined Prof. Taylor as editor. This series attempts to make the extraordinarily complex and diverse filed of heterocylic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled General Heterocyclic Chemistry, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

It is a major challenge to keep our coverage of this immense field up to date. One strategy is to publish Supplements or new Parts when merited by the amount of new material, as has been done, *Inter alia*, with pyridines, purines, pyrimidines, quinazolines and isoxazoles. This strategy was also the case recently with *Pyrazines*, (published in 2000) which had last been covered in this series in 1982. We acknowledge once again the extraordinary contributions of Dr. D. J. Brown, whose previous classics in heterocyclic chemistry in this series (*The Pyrimidines, The Pyrimidines Supplement I, The Pyrimidines Supplement II, Pteridines, Quinazolines Supplement I, The Pyrazines, Supplement I*) are now joined by the present exhaustive treatment of the last twenty years of pyrazine chemistry.

We extend once again our congratulations and our thanks to Dr. Brown for a further outstanding contribution to the literature of heterocyclic chemistry.

*Department of Chemistry*
*Princeton University*
*Princeton, New Jersey*

EDWARD C. TAYLOR

*Department of Chemistry*
*University of Pittsburgh*
*Pittsburgh, Pennsylvania*

PETER WIPF

# Preface

This supplement seeks to build on the solid foundation established by Dr. G. B. Barlin's original volume, *The Pyrazines*, that appeared within this series in 1982. That original book presented the first comprehensive review of pyrazines, embracing a mass of important historical material as well as a modern systematic treatment of pyrazine chemistry. Not surprisingly, it stimulated a great deal of research in all aspects of the field, resulting in the need for a supplementary volume to cover literature published between 1979 and 2000, inclusive.

In undertaking this task, the present author thought it wise to make certain changes in format to conform with recent trends. Thus pyrazine *N*-oxides and reduced pyrazines are no longer separated out from regular pyrazine derivatives; primary syntheses are now divided between two chapters, one involving aliphatic or carbocyclic substrates and the other involving heterocyclic substrates; and the many classified tables of pyrazine derivatives are replaced by a single alphabetical table of simple pyrazines that aims to list *all* such pyrazines (including those in the earlier tables). In view of these and other necessary changes, the essential status of the present volume as a *supplement* has been maintained by many sectional cross-references (e.g., *H* 28) to pages in the original volume (*Hauptwerk*), where earlier relevant information may be found; such cross-references are used also in the Table of Simple Pyrazines.

Chemical nomenclature used in this supplement follows current IUPAC recommendations [*Nomenclature of Organic Chemistry, Sections A–F, H* (eds. J. Rigaudy and S. P. Klesney, Pergamon Press, Oxford, 1970)] with one important exception: in order to keep "pyrazine" as the principal part of each name, those groups that would normally qualify as principal suffixes, but that are not attached directly to the nucleus, are rendered as prefixes. For example, 3-carboxymethyl-2 (1*H*)-pyrazinone is used instead of 2-(3-oxo-3, 4-dihydropyrazin-2-yl) acetic acid. Secondary and tertiary amino groups are rendered as prefixes. Ring systems are named according to Chemical Abstracts Service recommendations [*Ring Systems Handbook* (eds. anon., American Chemical Society, Columbus OH, 1998 edition)]. Many trivial names for pyrazines are listed in Section 5.6. In preparing this supplement, the patent literature has been largely ignored in the belief that useful factual information therein usually appears subsequently in the regular literature.

I am greatly indebted to my good friend and author of the original volume, Dr. Gordon Barlin, for invaluable consultation and advice; to the Dean of the Research School of Chemistry, Professor Denis Evans, for the provision of postretirement facilities within the School; to the branch Librarian, Mrs Joan Smith, for continual assistance in library matters; and to my wife, Jan, for much needed encouragement and her mighty help during indexing, proofreading, and the like.

*Research School of Chemistry* DES BROWN
*Australian National University, Canberra*

# Contents

CHAPTER 1

# Primary Syntheses from Aliphatic or Carbocyclic Synthons

Primary synthetic routes to pyrazines or hydropyrazines from aliphatic or carbocyclic synthons are so numerous and diverse that any system of classification cannot be satisfactory in all respects. The approach adopted here is based on the ways in which the six ring atoms of pyrazine can be supplied by synthons, as indicated in the Contents headings.

In each subsection, any examples of syntheses that lead directly to pyrazines usually precede any that afford di-, tetra-, or hexahydropyrazines (piperazines) in that order. Examples of any pre-1978 syntheses in each broad category may be located from the cross-references (e.g., *H* 49) to appropriate subsections in Barlin's parent volume.[1686] Less comprehensive reviews of primary syntheses in the pyrazine series have appeared in recent years.[743, 1287, 1426, 1677]

## 1.1. FROM A SINGLE SIX-ATOM SYNTHON

Because of symmetry in the pyrazine ring, there are only two ways in which a pyrazine can be formed from a six-atom synthon: by completion of the N1—C2 bond or the C2—C3 bond. In most examples, the synthon has been isolated but not necessarily characterized prior to ring closure.

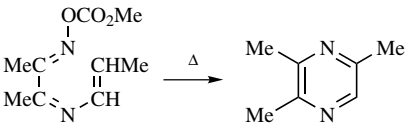
### 1.1.1. By Completion of the N1—C2 Bond

The cyclization of an N—C—C—N—C—C synthon has been used widely to make pyrazines and hydropyrazines. Because the terminal nitrogen atom is usually an amino or related group, examples are classified according to the substituent (or unsaturation) at the terminal carbon atom of the synthon: The nature of the synthon naturally determines the degree of aromaticity in the product.

#### *1.1.1.1. From Appropriate ω-Unsaturated Azaalkylamines (H 358)*

This unusual synthesis is exemplified by the cyclization of methyl [1-methyl-2-(prop-2-enylimino)propylideneamino]carbonate (**1**) to 2,3,5-trimethylpyrazine

(**2**) in 63% yield by brief thermolysis in toluene at 300°C;[839] several analogues were prepared from comparable substrates.[839, 1534]

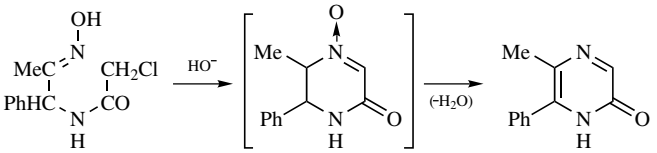


(**1**) (**2**)

### *1.1.1.2. From Appropriate ω-Halogeno(azaalkylamines)*

Such cyclizations are illustrated in the following examples:

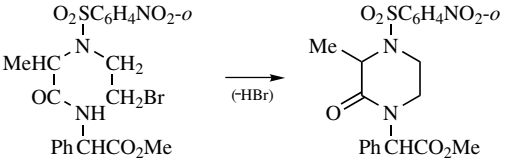
1-(2-Chloroacetamido)-1-phenylacetone oxime (**3**) gave 5-methyl-6-phenyl-2(1*H*)-pyrazinone (**5**) via the *N*-oxide (**4**) (NaOH, dioxane, 20°C, 20 h: 86%); several analogues of (**4**) and (**5**) were made similarly.[544]



(**3**) (**4**) (**5**)

Methyl 2-{2-[*N*-(2-bromoethyl)-*o*-nitrobenzenesulfonamido]propionamido}-2-phenylacetate (**6**) gave 1-(α-methoxycarbonylbenzyl)-3-methyl-4-*o*-nitrobenzenesulfonyl-3.4.5.6-tetrahydro-2(1*H*)-pyrazinone (**7**) [1,8-diazabicyclo [5,4,0]undec-7-ene, tetrahydrofuran(THF): > 95%].[1622]

Also other examples.[863, 1493, 1772]

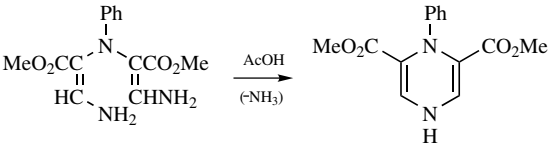


(**6**) (**7**)

### *1.1.1.3. From Appropriate α,ω-Diamino(azaalkanes)*

This rare synthesis has been used to advantage in the conversion of *N*,*N*-bis (2-amino-1-methoxycarbonylvinyl)aniline (**8**) into dimethyl 1-phenyl-1,4-dihydro-

2,6-pyrazinedicarboxylate (**9**) (74%) by simply boiling in acetic acid for 20 min; analogues were made similarly.[810] Related examples have been reported.[1767]

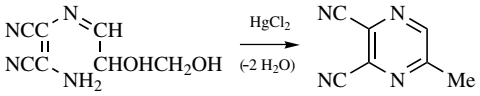



(**8**) (**9**)

### *1.1.1.4. From Appropriate ω-Amino(azaalkanols) (H 372)*

This synthesis usually gives hydropyrazines but appropriate substituents in the substrate can ensure autooxidation to pyrazines, as illustrated in the first of the following examples:

2-Amino-3-(2,3-dihydroxypropylideneamino)maleonitrile (**10**) gave 5-methyl-2,3-pyrazinedicarbonitrile (**11**) ($HgCl_2$, $Me_2SO$, 25°C, 3 h: 60%).[76]

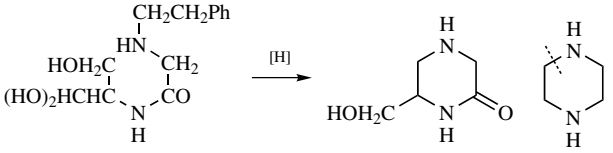



(**10**) (**11**)

2-[2-(Benzyloxycarbonylamino)acetamido]-3-hydroxypropionaldehyde hydrate (**12**) gave 6-hydroxymethyl-3,4,5,6-tetrahydro-2 (1*H*)-pyrazinone (**13**) (Pd/C, MeOH, $H_2$, 50 atm, 20°C, 24 h: 96%).[1061]

2-(2-Aminoethylamino)ethanol gave piperazine (**14**) (Cu—$Al_2O_3$ catalyst, continuous flow, 200°C: 95%).[1064]

Also other examples.[1330, 1641]

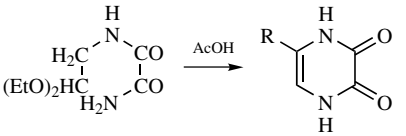



(**12**) (**13**) (**14**)

### *1.1.1.5. From Appropriate ω-Amino(azaalkanals) (H 49)*

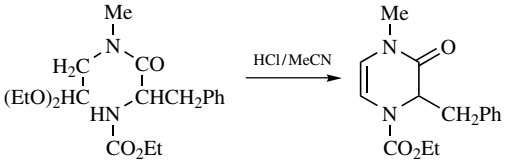
In this type of synthesis, the substrate's aldehydo group is usually present as an acetal and its amino group may sometimes form part of a terminal amido group. Such possibilities are illustrated in some of the following examples:

*N*-(2,2-Diethoxyethyl)oxamide (**15**) gave 2,3(1*H*,4*H*)-pyrazinedione (**16**, R = H) (AcOH, reflux: 68%);[1562] 5-methyl-2,3 (1*H*, 4*H*)-pyrazinedione (**16**, R = Me) was made somewhat similarly.[812]




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

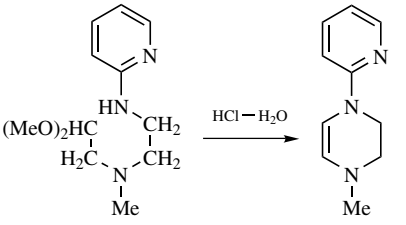
Ethyl *N*-{1-[(*N*-(2,2-diethoxyethyl)-*N*-methylcarbamoyl]-2-phenylethyl}amino-formate (**17**) gave ethyl 2-benzyl-4-methyl-3-oxo-1,2,3,4-tetrahydropy-razinecarboxylate (**18**) [HCl, MeCN, 20°C, 1 h: yield unstated (?%)]; analogues likewise.[248]




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

2-{2-[*N*-(2,2-Dimethoxyethyl)-*N*-methylamino]ethylamino}pyridine (**19**) gave 1-methyl-4-(pyridin-2-yl)-1,2,3,4-tetrahydropyrazine (**20**) (3 M HCl, 80°C, 2 h: 65%).[1404]

Also other examples.[36, 122, 123, 339, 665, 822, 1095, 1774]

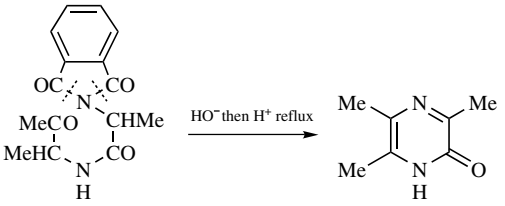



(**19**) (**20**)

### *1.1.1.6. From Appropriate ω-Amino(azaalkanones) (H 64, 358)*

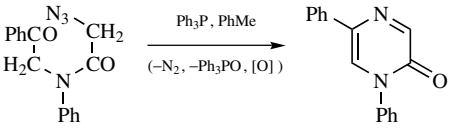
In some of the following examples, the terminal amino group of the substrate is initially protected or even replaced by an azido group:

*N*-(1-Acetylethyl)-2-phthamimidopropionamide (**21**) gave 2,5,6-trimethyl-2(1*H*) -pyrazinone (**22**) (KOH—$H_2O$, 20°C, 30 min; then AcOH ↓ , pH 4–5, reflux, 10 h: 65%); also homologues.[1099]



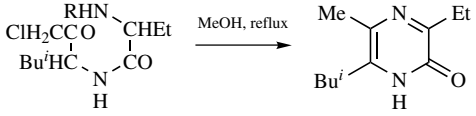

(**21**) (**22**)

2-Azido-*N*-phenacyl-*N*-phenylacetamide (**23**) gave 1,5-diphenyl-2(1*H*)-pyrazinone (**24**) ($Ph_3P$, PhMe, 20°C, 20 h: 35%; the evident oxidation was not aerial); analogues likewise.[555]




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

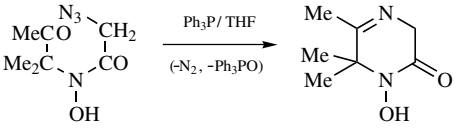
2-Amino-*N*-(1-chloroacetyl-3-methylbutyl)butyramide (**25**, R = H), prepared *in situ* as hydrochloride by treatment of its *N*-*tert*-butoxycarbonyl derivative (**25**, R = $CO_2Bu^t$) in HCl–dioxane, gave 3-ethyl-6-isobutyl-5-methyl-2(1*H*)-pyrazinone (**26**) (MeOH, reflux, 2 h: 90%);[389] many analogues were made similarly.[118, 121, 175, 389, 1452, 1491]




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

*N*-(1-Acetyl-1-methylethyl)-2-azido-*N*-hydroxyacetamide (**27**) gave 1-hydroxy-5,6,6-trimethyl-3,6-dihydro-2 (1*H*)-pyrazinone (**28**) ($Ph_3P$, THF, 20°C, 24 h: 79%).[424]

Also other examples.[416, 1031, 1101, 1386, 1628, 1743]

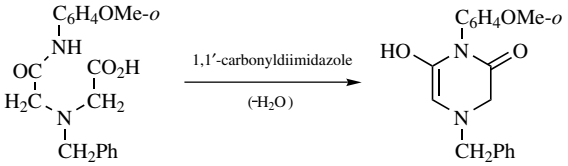



(**27**) (**28**)

### *1.1.1.7. From Appropriate ω-Amino(azaalkanoic) Acids*

Such substrates have been used occasionally, as illustrated in the following examples:

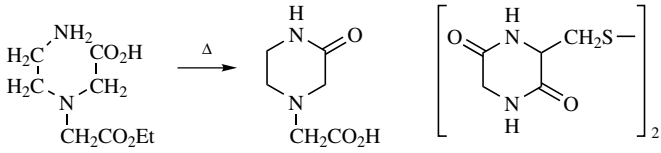
*N*-Benzyl-*N*-[(*N*-*o*-methoxyphenylcarbamoyl)methyl]glycine (**29**) underwent dehydrative cyclization to 4-benzyl-6-hydroxy-1-*o*-methoxyphenyl-3,4-dihydro-2(1*H*)- pyrazinone (**30**) (1,1′-carbonyldiimidazole, THF, −30 → 65°C, 17 h: 83%; other reagents gave lower yields).[487]




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

*N*-(2-Aminoethyl)-*N*-carboxymethylglycine (**31**) gave 4-carboxymethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrazinone (**32**) ($Me_2NCHO$, reflux: ?%).[820]

Also the formation of bis(3,6-dioxopiperazin-2-ylmethyl)disulfide (**33**)[1440] and other examples.[671, 1748, 1759, 1770]

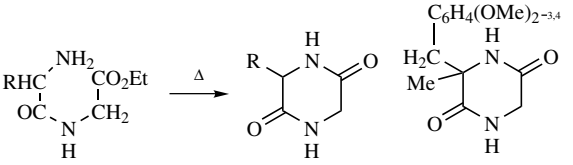



(**31**) (**32**) (**33**)

### *1.1.1.8. From Appropriate ω-Amino (azaalkanoic) Esters (H 363, 369)*

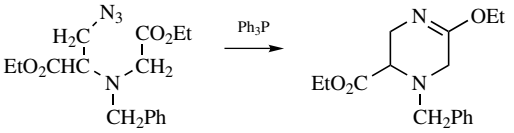
Such cyclizations have been used extensively, especially to prepare hydropyrazines. The amino group of the substrate may be replaced by an azido group or it may be used (especially for chiral syntheses) in a protected form: In the latter case, deprotection is usually done prior to cyclization albeit in a one-pot sequence; the ester group of the substrate may be replaced by a terminal lactonic grouping.[813] The following examples illustrate some such possibilities:

Ethyl *N*-(2-amino-3-methylbutyryl)glycinate (**34**, R = $Pr^i$) gave 3-isopropyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**35**, R = $Pr^i$) (PhMe, reflux, 24 h: 79%);[1351] similar procedures afforded the 3-isobutyl homologue (**35**, R = $Bu^i$) (71%)[193] and 3-(3,4-dimethoxybenzyl)-3-methyl-3,6-dihydro-2,5(1*H*,4*H*) -pyrazinedione (**36**) (81%).[188]



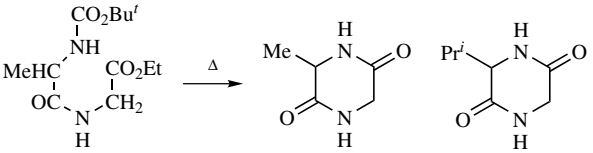
(**34**) (**35**) (**36**)

Ethyl *N*-(2-azido-1-ethoxycarbonylethyl)-*N*-benzylglycinate (**37**) gave ethyl 1-benzyl-5-ethoxy-1,2,3,6-tetrahydro-2-pyrazinecarboxylate (**38**) ($Ph_3P$, PhMe, 100°C, 9 h: 58%).[1468]



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

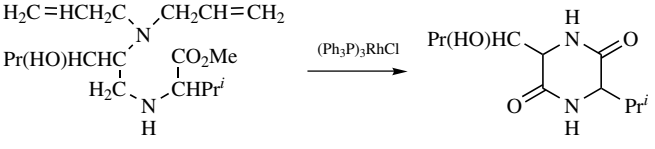
Ethyl *N*-[2-(*tert*-butoxycarbonylamino)propionyl]glycinate (**39**) gave 3-methyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**40**) (200°C, A, 30 min: > 95%; mechanism?);[1616] an homologous product, 3-isopropyl-3,6-dihydro-2,5(1*H*,4*H*)-pyrazinedione (**41**) was made somewhat similarly but in two stages (Pd/C, MeOH—$CH_2Cl_2$, $H_2$, 24 h; then PhMe, reflux, 12 h: 65%).[50]



(**39**) (**40**) (**41**)

Methyl *N*-(2-diallylamino-3-hydroxyhexyl)-2-isopropylglycinate (**42**) gave 6-(1-hydroxybutyl)-3-isopropyl-3,4,5,6-tetrahydro-2(1*H*)-pyrazinone (**43**) [$(Ph_3P)_3$ RhCl, MeCN—$H_2O$, distillation (see original for details), 5 h: 47%].[404]

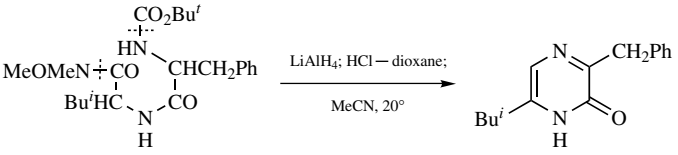
Also other examples.[182, 189, 229, 703, 813, 843, 1347, 1465, 1495, 1498, 1535, 1750]



(**42**) (**43**)

### *1.1.1.9. From Appropriate ω-Amino(azaalkanamides)*

Such substrates are seldom used but *tert*-butyl {1-[1-(*N*-methoxy-*N*-methylcarbamoyl)-3-methylbutyl]carbamoyl -2-phenylethyl}aminoformate (**44**) gave 3-benzyl-6-isobutyl-2(1*H*)-pyrazinone (**45**) (21%) by two deprotections ($LiAlH_4$; and HCl—dioxane) and a final cyclization in acetonitrile during 13 h.[1510]

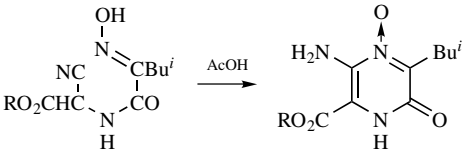



(**44**) (**45**)

### *1.1.1.10. From Appropriate ω-Amino (azaalkanenitriles) (H 49, 344)*

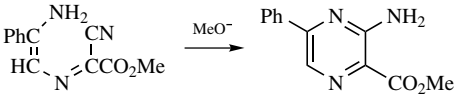
These nitriles are usually employed to afford aromatic pyrazinamines but they can be used to produce hydropyrazinamines, chloropyrazinamines, or even pyrazines without an amino substituent. The following cyclizations illustrate some of these uses:

Methyl 2-cyano-*N*-(2-hydroxyimino-4-methylvaleryl)glycinate (**46**, R = Me) gave methyl 3-amino-5-isobutyl-6-oxo-1, 6-dihdyro-2-pyrazinecarboxylate 4-oxide (**47**, R = Me) (AcOH, 70°C, 3 h: > 32%);[337] the ethyl ester (**47**, R = Et) (> 62%) was made similarly.[848]



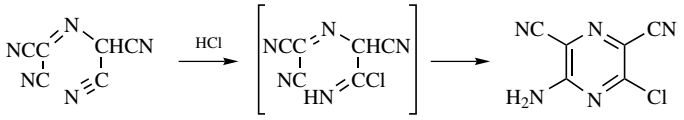

(**46**) (**47**)

Methyl 2-(β-aminostyrylimino)-2-cyanoacetate (**48**) gave methyl 3-amino-5-phenyl-2-pyrazinecarboxylate (**49**) (MeONa, MeOH—$CH_2Cl_2$, 20°C, 15 min: 70%).[941]




(**48**) (**49**)

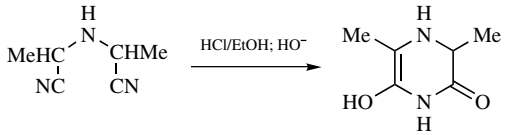
α-(Dicyanomethyleneamino)malononitrile (**50**) underwent addition of hydrogen chloride to afford the unisolated iminonitrile (**51**) and thence 3-amino-5-chloro-2,6-pyrazinedicarbonitrile (**52**) (HCl—AcMe, reflux, 10 min: 43%).[447]




(**50**) (**51**) (**52**)

2,2′-Iminodipropiononitrile (**53**) gave 6-hydroxy-3,5-dimethyl-3,4-dihydro-2(1*H*)-pyrazinone (**54**) (HCl/EtOH, 0°C, 12 h; then $Na_2CO_3$—$H_2O$: 18%; by a yet unconfirmed mechanism).[577]

Also other examples.[436, 747, 749, 1180, 1284]

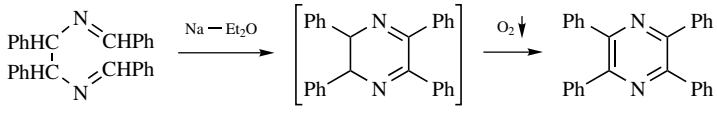



(**53**) (**54**)

## 1.1.2. By Completion of the C2-C3 Bond

Not unnaturally, the synthesis of a pyrazine or hydropyrazine from a single C—N—C—C—N—C synthon is rare. However, the cyclization of *N*,*N*′-dibenzylidene or *N*,*N*′-diacyl derivatives of ethylenediamines has proven possible, as indicated in the following examples:

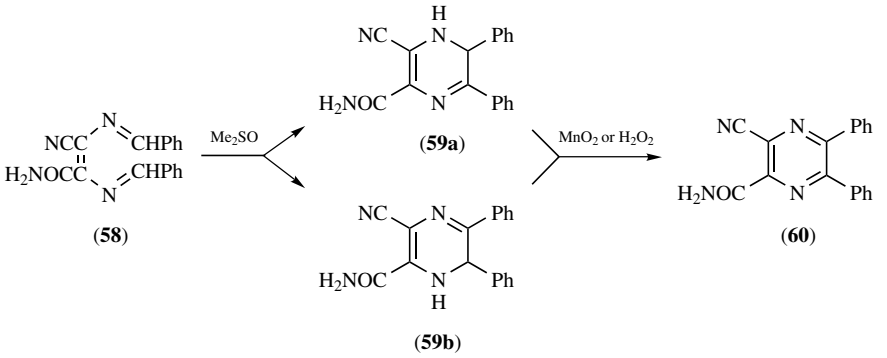
1,2-Bis (benzylideneamino)-1,2-diphenylethane (**55**) gave 2,3,5,6-tetraphenylpyrazine (**57**), via the unisolated 2,3-dihydro derivative (**56**) (Na—$Et_2O$, reflux, $N_2$, 6 h; then $O_2 \downarrow$, 20°C, 10 min: 90%).[138]




(**55**) (**56**) (**57**)

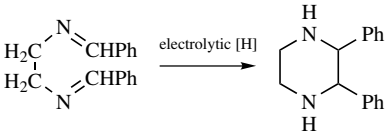
2,3-Bis(benzylideneamino)-2-cyanoacrylamide (**58**) gave a separable mixture of 3-cyano-5,6-diphenyl-4,5-dihydro- (**59a**) and 3-cyano-5,6-diphenyl-1,6-dihydro-2-pyrazinecarboxamide (**59b**) ($Me_2SO$, 80°C, 10 min: 10 and 68%, respectively);

oxidation of either product gave 3-cyano-5,6-diphenyl-2-pyrazinecarboxamide (**60**) ($MnO_2$, $Me_2NCHO$, 60°C, 12 h: 80%; or $H_2O_2$, MeOH, 55°C, 8 h: 30%); several substituted-phenyl derivatives were made likewise.[752]



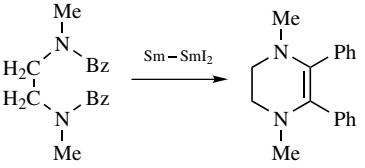

(**58**) (**59a**) (**59b**) (**60**)

1,2-Bis(benzylideneamino)ethane (**61**) afforded 2,3-diphenylpiperazine (**62**) ($TsONEt_4$, MsOH, $Me_2NCHO$, Pb cathode, 0.5 amp: 95%); analogues likewise.[845]




(**61**) (**62**)

1,2-Bis(*N*-methylbenzamido)ethane (**63**) gave 1,4-dimethyl-2,3-diphenyl-1,4,5,6-tetrahydropyrazine (**64**) (Sm—$SmI_2$, THF, 67°C, 3 h: 62%).[463]




(**63**) (**64**)

## 1.2. FROM TWO SYNTHONS

Most of the primary syntheses from aliphatic or carbocyclic substrates fall into this category, which is subdivided successively according to the number and the type of ring atoms supplied by each synthon.

## 1.2.1. By Using a One-Atom and a Five-Atom Synthon

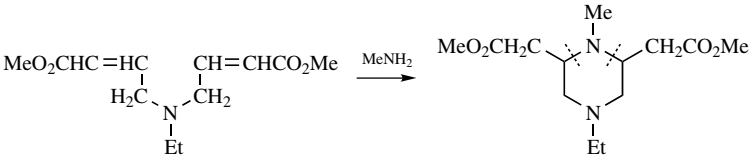
The one-atom synthon may supply either N1 or C2 but nearly all known examples fall into the first of these subcategories.

### *1.2.1.1. Where the One-Atom Synthon Supplies N1 (H 49)*

Such one-atom synthons are normally ammonia or a primary or secondary amine. The following examples are therefore classified according to the type of five-atom cosynthon used:

**With 1,5-Dialkylidene-3-azapentanes**

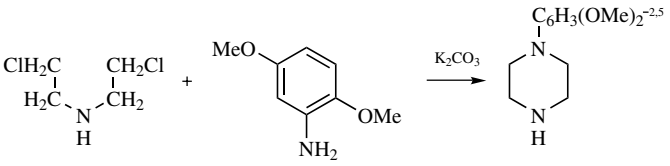
N-Ethyl-*N*,*N*-bis(3-methoxycarbonylallyl)amine (**65**) gave 1-ethyl-3,5-bis(methoxycarbonylmethyl)-4-methylpiperazine (**66**) ($MeNH_2$, MeOH, 0 → 25°C, ? h: 69%); homologues likewisa.[1494]




(**65**) (**66**)

**With 1,5-Dihalogeno-3-azapentanes**

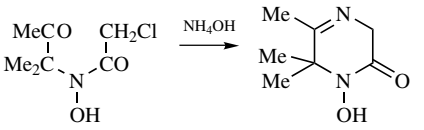
Bis(2-chloroethyl)amine (**67**) and 2,5-dimethoxyaniline gave 1-(2,5-dimethoxyphenyl)piperazine (**68**) ($K_2CO_3$, $MeOCH_2CH_2OCH_2CH_2OMe$, reflux, 48 h: 62%).[610]




(**67**) (**68**)

**With 5-Halogeno-3-azapentanyl Ketones or Aldehydes**

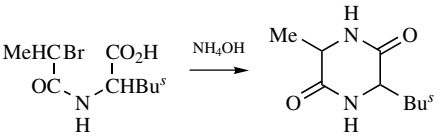
*N*-(1-Acetyl-1-methylethyl)-2-chloro-*N*-hydroxyacetamide (**69**) gave 1-hydroxy-5,6,6-trimethyl-3,6-dihydro-2(1*H*)-pyrazinone (**70**) ($NH_4OH$—EtOH—dioxane, 20°C, 3 days: 8%); likewise one homologue.[424] Aldehydes gave better results under reductive conditions.[1768]



(**69**) (**70**)

### With 5-Halogeno-3-azapentanoic Acids or Esters

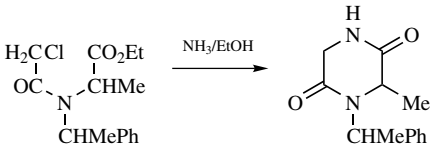
2-(2-Bromopropionamido)-3-methylvaleric acid (**71**) gave 3-*sec*-butyl-6-methyl-3,6-dihydro-2,5 (1*H*,4*H*)-pyrazinedione (**72**) ($NH_4OH$, 20°C, 7 days, volatiles ↑ ; PhOH, 145°C, 2 h: 73%).[317]



(**71**) (**72**)

Ethyl 2-[2-chloro-*N*-(1-phenylethyl)acetamido]propionamide (**73**) gave 3-methyl-4-(1-phenylethyl)-3,6-dihydro-2,5 (1*H*,4*H*)-pyrazinedione (**74**) (7 M $NH_3$/EtOH, 20°C, 24 h: ?%).[1349]

Also other examples.[890]



(**73**) (**74**)

### With 3-Aza-1,5-pentanediols

A neat mixture of diethanolamine hydrochloride and aniline hydrochloride gave 1-phenylpiperazine (**75**) (microwave irradiation, Dean–Stark, 12 min: 50%);[1197] also related examples.[1066, 1197]

Diethanolamine and *m*-(trifluoromethylthio)aniline gave 1-[*m*-(trifluoromethylthio)phenyl]piperazine (**76**) (HCl gas ↓, ~ 190°C, 1 h; then 240°C, 90 min: 33%); analogues likewise.[592]

Also other examples.[814, 894]

*Note:* It seems relevant that aqueous solutions of *N*-methyldiethanolamine (**77**), employed to remove $H_2S$ from hydrocarbon gases, gradually accumulate *inter alia* 1,4-dimethyl-, 1-(2-hydroxyethyl)-4-methyl-, and 1,4-bis(2-hydroxyethyl)piperazine.[1583]