Oxidative Coupling of Aldehydes & Imines III. An Entry to the Synthesis of Highly Substituted Pyrrolidines

by

John C. Leffingwell

Leffingwell & Associates, Canton, GA 30115 USA
Email: leffingwell@leffingwell.com

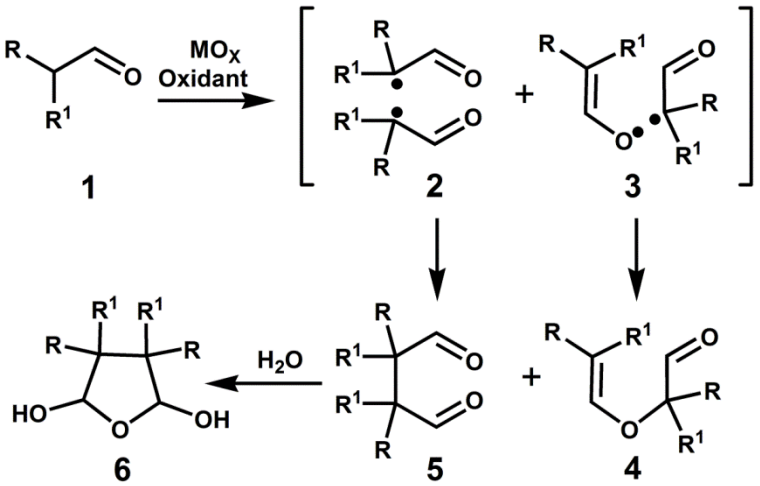
Abstract:

The oxidative coupling of selected aldehydes and imines (and ketones) with metal oxide oxidants, e.g. MnO_2, forms 2,2,3,3-tetraalkylsucinnaldehydes and aldimines to provide precursors for the synthesis of highly substituted pyrrolidines.

Background:

The discovery that selected aldehydes, imines (and ketones) are easily coupled with metal oxide oxidants such as manganese dioxide, lead dioxide and nickel peroxide to form products as shown in Figures 1 & 2 has been previously reported by us (1-6). Unpublished reports on this work are also referenced with links to the original research (7-12).

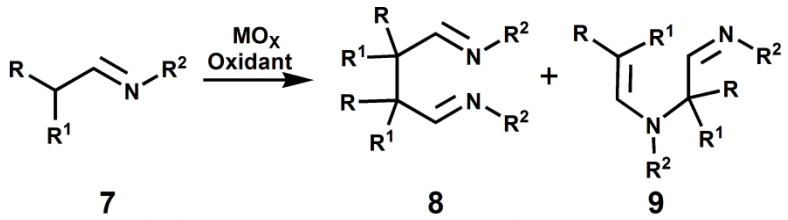
Figure 1. – Coupling of Aldehydes



***Note – R and R^1 = alkyl or Aryl and not –H**

Similarly, the metal oxide (e.g. MnO_2) oxidation of dialkyl-aldimines provides an analogous mixture of coupling products as shown in Figure 2.

Figure 2. – Coupling of Imines



***Note – In the coupling of imine 7, if R= alkyl and R^1= H, the corresponding pyrrole is formed (5).**

The N,N-di-substituted-2,2,3,3-tetra-substituted succinaldimines can be prepared either by the oxidative coupling of a 2-substituted aldehyde to a 2,2,3,3-tetra-substituted succinaldehyde (Figure 1) which is then converted to the diimine desired, or by oxidative coupling of a 2-substituted imine (see Figure 2). In practice, preparation from a 2,2,3,3-tetra-substituted succinaldehyde is often more convenient as the nitrogen substituent can be easily varied. .

This paper reviews the work of several colleagues (H.J. Bluhm, H.J Young & F.N. Wendelboe) in our group who utilized these findings to prepare a large number 1,3,3,4,4-penta- and 1,2,3,3,4,4,5-hepta- substituted pyrrolidines utilizing the 2,2,3,3-tetrasubstituted succinaldehydes **5** and N,N-disubstituted-2,2,3,3-tetrasubstituted succinaldimines **8** (as well as a ketimine coupling product) (25-26, 28-30).

Importance of Pyrrolidines:

The pyrrolidine moiety is found widely in naturally occurring bioactive molecules (e.g. nicotine, and atropine) as well as synthetic drugs such as Piracetam (2-oxo-1-pyrrolidine-acetamide) and Levetiracetam ((S)-2-(2-oxopyrrolidin-1-yl)butanamide). The pyrrolidine structure is also often found in illicit recreational drugs.

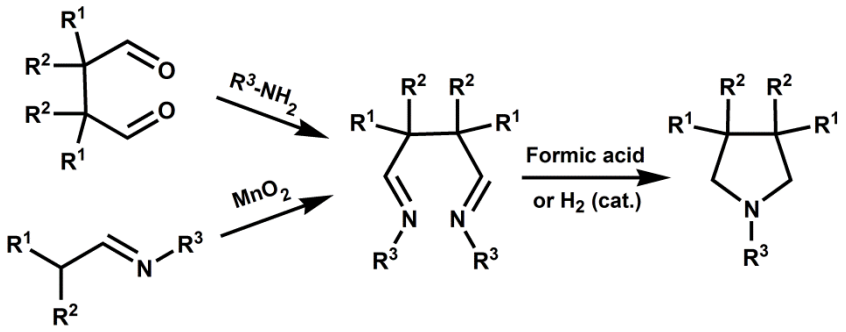
Pyrrolidines are commonly used as building blocks for pharmaceutical, agrochemicals and other fine chemical manufacturing.

Various synthetic procedures for the production of substituted pyrrolidines have been reviewed (13-25), but no simple procedures for the preparation of 1,3,3,4,4-penta-substituted pyrrolidines have been reported other than that by Bluhm et al. (25-26).

A. Syntheses of 1,3,3,4,4-penta-substituted pyrrolidines from N,N-disubstituted-2,2,3,3-tetra-substituted succinaldimines:

The general procedure for constructing the penta-substituted pyrrolidines when R^1, R^2 and R^3 = alkyl and/or aryl is depicted in Figure 3.

Figure 3.



This section will focus on the research reported by H.J. Bluhm (25-26).

Bluhm studied the reduction of the tetra-substituted succinaldimines with a series of reducing agents (including $LiAlH_4$, $NaBH_4$, and hydrogenation using various catalysts & solvents, as well as formic acid).

Sodium borohydride in ethanol resulted in approximately 60% yields of the pyrrolidine along with the diamine and other products. However, lithium aluminum hydride in either ether or refluxing tetrahydrofuran was found to favor formation of the 1,4-diamine with only small amounts of the pyrrolidine produced.

Reduction using 5% platinum on carbon, 5% palladium on charcoal and 5% rhodium on carbon all gave excellent yields, while Raney Nickel and 5% ruthenium on carbon were less satisfactory. The hydrogenation products were influenced to a considerable extent by the solvent used. Glacial acetic acid was the most satisfactory medium in that the pyrrolidine was the only product obtained. When ether or ethanol containing two equivalents of acetic acid was used, lower yields of the pyrrolidine were obtained along with the corresponding 1,4-diamine and other unidentified products which appeared to be polymeric in nature.

The most convenient method for preparing the pyrrolidines was by the reaction with formic acid. The diimine is stirred with at least two equivalents of 88% formic acid at room temperature. The evolution of carbon dioxide during the initial stages of the

reaction requires some cooling as a means of controlling the reaction rate. Yields obtained were as high as 91% using this method.

Table 1 provides examples.

Table 1. – Reduction of N,N-disubstituted-2,2,3,3-Tetrasubstituted Succinaldimines to Pentasubstituted-pyrrolidines

R^1	R^2	R^3	$NaBH_4$	H_2-AcOH[a]	88% HCO_2H[b]
Methyl	Methyl	Methyl	75%[e]	-	-
Methyl	Methyl	Ethyl	-	-	65%
Methyl	Methyl	i-Propyl	-	-	91%
Methyl	Methyl	i-Butyl	-	82%	-
Methyl	Methyl	n-Butyl	-	85%	90%
Methyl	Methyl	n-Dodecyl	-	67%[c]	-
Methyl	Methyl	CH_2CH_2OH	-	82%[c]	-
Methyl	Methyl	Me-N-Me	-	62%[d]	-
Methyl	Methyl	Cyclohexyl	-	63%	90%
Methyl	Methyl	Phenyl	-	26%[c]	42%[c]
Methyl	Methyl	Benzyl	-	27%	72
Methyl	Methyl	3-PyrCH_2	-	26%[e]	-
Methyl	Methyl	Phenylethyl	-	14%[c]	-
Ethyl	Butyl	i-Butyl	-	58%[f]	-
Methyl	Phenyl	n-Butyl	-	68%[e,f]	50%[e]
Methyl	i$PrC_6H_5CH_2$	n-Butyl	-	39%[e,f?]	-
Phenyl	Phenyl	i-Propyl	-	-	trace

a - hydrogenation of diimine in AcOH over 5% Pt on C

b - reduction with 88% formic acid

c - Yield based on crude diimine produced from the succinaldehyde

d - Yield based on the succinaldehyde bis(dimethyldihydrazone)

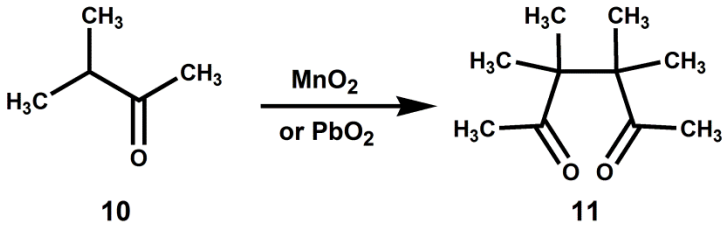
e - Yield based on crude diimine from coupling reaction

f - 2 isomers cis/trans

B. Synthesis of 2,5-Dimethylene-3,3,4,4-tetramethyl-N-n-butyl-pyrrolidine and derivatives from N-(3-methyl-2-butylidene)-n-butylamine:

The oxidative coupling of 2-methyl-3-butanone **10** to the dimeric product 3,3,4,4-tetramethylhexane-2,5-dione **11** (Figure 4) has previously been reported by Leffingwell using manganese dioxide (3), and by Wolf using lead dioxide (27).

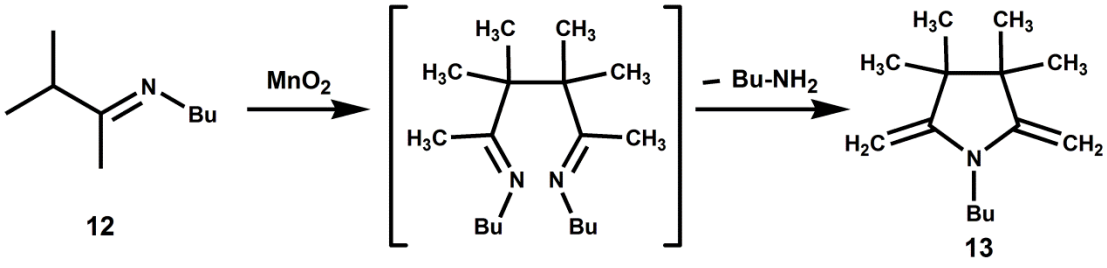
Figure 4.



10 11

Young extended this type reaction by the oxidative coupling of N-(3-methyl-2-butylidene)-n-butylamine **12** (28). Although the "normal coupling" took place as expected, a concomitant ring closure ensued giving rise to the novel 1-butyl-3,3,4,4-tetramethyl-2,5-dimethylenepyrrolidine **13** in 29% yield, after distillation, as shown in Figure 5.

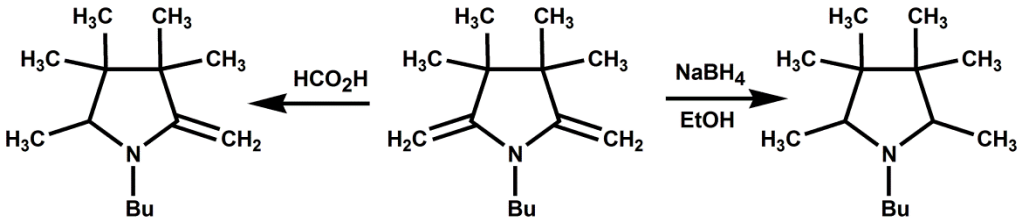
Figure 5.



12 13

Reduction of **13** with 97% formic acid gave about 75% of crude 1-butyl-2,3,3,4,4-pentamethyl-5-methylenepyrrolidine **14** (55% of pure material after distillation) while reduction with sodium borohydride gave about 90% crude 1-butyl-2,3,3,4,4,5-hexamethylpyrrolidine **15** (50% of pure material after distillation).

Figure 6.



The 2,5-dimethyl stereochemistry of the heptaalkyl-pyrrolidine **15** was not determined.

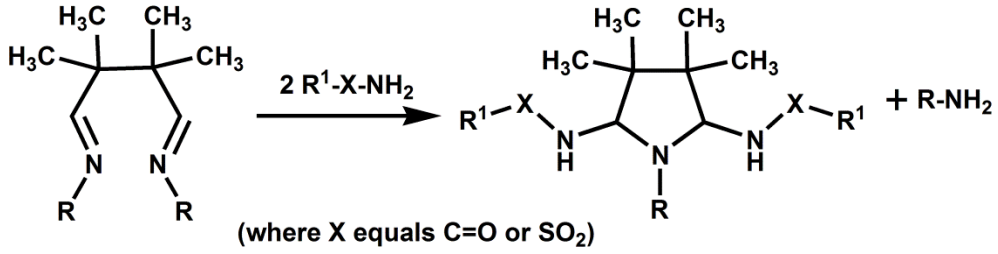
It should be noted that no attempt was made to optimize these reactions.

C. Syntheses of 1,2,3,3,4,4,5-hepta-substituted pyrrolidines from N,N-disubstituted-2,2,3,3-tetra-substituted succinaldimines:

a. Reaction of amides and sulfonamides with N,N-disubstituted-2,2,3,3-tetramethylsuccinaldimines to form 1-alkyl-3,3,4,4-tetramethyl-2,5(bis-amido or sulfamido)pyrrolidines:

Young also disclosed the synthesis of 2,5-bis(amido and sulfonarnido)-pyrrolidine derivatives by the reaction of N,N-1-dialky1-2,2,3,3-tetramethylsuccinaldimines with amides and sulfonamides (29) as shown in Figure 7.

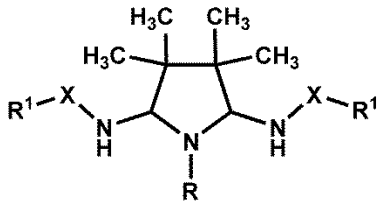
Figure 7.



The reaction was conducted by refluxing one mole equivalent of the N,N-1-dialky1-2,2,3,3-tetramethylsuccinaldimines with two mole equivalents of the amide or sulfonamide in benzene for 3-10 hours. Upon cooling, the product was isolated by crystallization.

Table 2 shows the results.

.**Table 2. - 1-alkyl-3,3,4,4-tetramethyl-2,5(bis-amido or sulfamido)pyrrolidines**



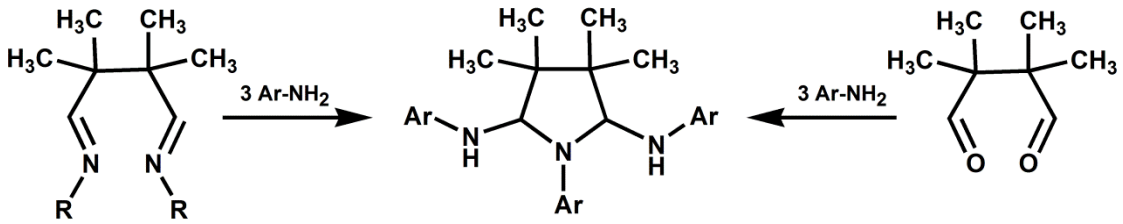
R	R^1	X	Product	Yield
methyl	acetamido	C=O	N-(5-acetamido-1,3,3,4,4-pentamethylpyrrolidin-2-yl)acetamide	72.5%
methyl	prop-2-enamido	C=O	N-[1,3,3,4,4-pentamethyl-5-(prop-2-enamido)pyrrolidin-2-yl]prop-2-enamide	90.2%
methyl	cyclopropaneamido	C=O	N-(5-cyclopropaneamido-1,3,3,4,4-pentamethyl-pyrrolidin-2-yl)cyclopropanecarboxamide	72.5%
methyl	2-hydroxy-2-methylpropanamido	C=O	2-hydroxy-N-[5-(2-hydroxy-2-methylpropanamido)-1,3,3,4,4-pentamethylpyrrolidin-2-yl]-2-methylpropanamide	62.0%
methyl	pyridine-3-amido	C=O	N-[1,3,3,4,4-pentamethyl-5-(pyridine-3-amido)pyrrolidin-2-yl]pyridine-3-carboxamide	86.5%
methyl	benzamido	C=O	N-(5-benzamido-1,3,3,4,4-pentamethylpyrrolidin-2-yl)benzamide	59.0%
methyl	3,4-dimethylbenzamido	C=O	N-[5-(3,4-dimethylbenzamido)-1,3,3,4,4-pentamethyl-pyrrolidin-2-yl]-3,4-dimethylbenzamide	53.2%
methyl	benzenesulfonamido	SO_2	N-(5-benzenesulfonamido-1,3,3,4,4-pentamethyl-pyrrolidin-2-yl)benzenesulfonamide	81.0%
ethyl	benzenesulfonamido	SO_2	N-(5-benzenesulfonamido-1-ethyl-3,3,4,4-tetramethyl-pyrrolidin-2-yl)benzenesulfonamide	93.5%
methyl	4-chlorobenzenesulfonamido	SO_2	4-chloro-N-[5-(4-chlorobenzenesulfonamido)-1-ethyl-3,3,4,4-tetramethylpyrrolidin-2-yl]benzene-1-sulfonamide	72.7%

***IUPAC Nomenclature**

b. Reaction of Arylamines with N,N-disubstituted-2,2,3,3-tetramethylsuccinaldimines (or 2,2,3,3-tetramethylsuccinaldehyde) to form 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines:

In a somewhat analogous manner to the work described above by Young, F.N. Wendelboe (30) produced a series of 1-aryl-2,2,3,3-tetramethyl-2,5(bis-arylamino)pyrrolidines. In this case, however, he reacted one mole equivalent of the N,N-dialkyl-2,2,3,3-tetramethylsuccinaldimines (or the 2,2,3,3-tetramethylsuccinaldehyde) with approximately three mole equivalents of the arylamine as shown in Figure 8.

Figure 8.



Procedure A.

The procedure utilized for preparing the 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines from 2,2,3,3-tetramethylsuccinaldehyde was:

> In a flask equipped with Dean-Stark trap and condenser were placed 2,2,3,3-tetramethylsuccinaldehyde, the arylamine and either benzene or toluene. These were refluxed for various lengths of time ranging from 4 to 24 hours. The solvent was then stripped off, resulting in a solid product which was purified by recrystallization.

Yields are provided in Table 3.

Table 3. – 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines from 2,2,3,3-tetramethylsuccinaldehyde

Ar	Product	Yield
4-methylphenyl	3,3,4,4-tetramethyl-1,N2,N5-tris(4-methylphenyl)-pyrrolidine-2,5-diamine	53.1%
4-chlorophenyl	1,N2,N5-tris(4-chlorophenyl)-3,3,4,4-tetramethyl-pyrrolidine-2,5-diamine	17.4%
4-(dimethylamino)phenyl	1,N2,N5-tris[4-(dimethylamino)phenyl]-3,3,4,4-tetramethylpyrrolidine-2,5-diamine	29.2%

***IUPAC Nomenclature**

Procedure B.

The procedure utilized for preparing the 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines from N,N'-diisopropyl-2,2,3,3-tetramethylsuccinaldimine was:

> In a flask fitted with a condenser, the arylamines were mixed with N,N'-diisopropyl-2,2,3,3-tetramethylsuccinaldimine (II) and heated in an oil bath at approximately

100° C. with stirring. The isopropyl amine was stripped off and the resulting solid purified by recrystallization.

Yields are provided in Table 4.

Table 4. – 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines from N,N'-diisopropyl-2,2,3,3-tetramethylsuccinaldimine

R	Ar	Product	Yield
isopropyl	2-methylphenyl	3,3,4,4-tetramethyl-1,N2,N5-tris(2-methylphenyl)-pyrrolidine-2,5-diamine	82.5%
isopropyl	3-methylphenyl	3,3,4,4-tetramethyl-1,N2,N5-tris(3-methylphenyl)-pyrrolidine-2,5-diamine	75.0%
isopropyl	4-(ethoxycarbonyl)phenyl	ethyl 4-[2,5-bis({[4-(ethoxycarbonyl)phenyl]amino})-3,3,4,4-tetramethylpyrrolidin-1-yl]benzoate	99.0%
isopropyl	4-chlorophenyl	1,N2,N5-tris(4-chlorophenyl)-3,3,4,4-tetramethyl-pyrrolidine-2,5-diamine	90.0%
isopropyl	4-(dimethylamino)phenyl	1,N2,N5-tris[4-(dimethylamino)phenyl]-3,3,4,4-tetramethylpyrrolidine-2,5-diamine	84.0%
isopropyl	4-methoxyphenyl	1,N2,N5-tris(4-methoxyphenyl)-3,3,4,4-tetramethyl-pyrrolidine-2,5-diamine	72.0%
isopropyl	4-phenylphenyl	3,3,4,4-tetramethyl-1,N2,N5-tris(4-phenylphenyl)-pyrrolidine-2,5-diamine	77.0%
isopropyl	pyridin-3-yl	3,3,4,4-tetramethyl-1,N2,N5-tris(pyridin-3-yl)pyrrolidine-2,5-diamine	85.0%

***IUPAC Nomenclature**

In general, Procedure B using N,N'-diisopropyl-2,2,3,3-tetramethylsuccinaldimine appeared to provide better yields.

It should be noted that in a some cases (e.g. when the Aryl was 2-pyridyl, 4-pyridyl, 4-(diethylamino)phenyl, 4-benzoylphenyl or (4-acetylphenyl)amino) the reaction stopped after adding two mole equivalents of the arylamine to yield the 1-isopropyl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidine.

Although the stereochemistry at the 2,5-bis positions of the 1-aryl-3,3,4,4-tetramethyl-2,5(bis-arylamino)pyrrolidines was not determined, preliminary thermodynamic calculations using the Chemaxon Marvin conformer calculator plugin indicates that the trans isomers are favored.

Conclusions:

Use of the dimeric oxidative coupling products such as the 2,2,3,3-tetraalkylsucinnaldehydes and aldimines provides a simple entry point for the synthesis of a variety of highly substituted penta- and hepta- substituted pyrrolidines.

This is the 3d paper in our series on the Oxidative Coupling of Aldehydes & Imines (31-32).

References:

(1.) Leffingwell, John C., "The oxidative coupling of aliphatic aldehydes." *Journal of the Chemical Society D: Chemical Communications* 6 (1970): 357-358.

(2.) Leffingwell, John C., “Preparation of monomeric or dimeric imines and pyrroles”, U.S. Patent No. 3,598,827, issued August 10, 1971

(3.) Leffingwell, John C., "Process of coupling aldehydes and ketones." U.S. Patent 3,609,193, issued September 28, 1971.

(4.) Leffingwell, John C., " Treatment of 2-substituted aldehydes with lead dioxide." U.S. Patent No. 3,658,849, issued April 25, 1972.

(5.) Leffingwell, John C., "Process for the preparation of dimeric imines and pyrroles." U.S. Patent 3,709,890, issued January 9, 1973.

(6.) Leffingwell, John C., “Oxidative Coupling of Aldehydes & Imines I. An Entry to the Synthesis of 6,6,7,7-Tetraalkyl Tropane Alkaloid Analogs.” Leffingwell Reports, Vol 6. (No 1), 1-18, June 2014

(7.) Leffingwell, John C., An improved process for the oxidative coupling of isobutyraldehyde - a method for the separation and purification of the two isomeric coupling products, RJRT Concept of Invention 1967, No. 1, January 20, 1967; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/aat58d00/pdf

(8.) Leffingwell, John C., The oxidative coupling of aldehydes with manganese dioxide, RJRT Concept of Invention 1966, No. 4, January 24, 1966; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/glt58d00/pdf

(9.) Leffingwell, John C., The oxidative coupling of activated methylene compounds by metal oxides, RJRT Research Dept. Report 1966, No. 22, May 23, 1966; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/pll59d00/pdf

(10.) Leffingwell, John C., Oxidative coupling reactions in organic chemistry II. Oxidation of ketones, aldehydes and Schiff bases with lead dioxide, RJRT Research Dept. Report 1968, No. 5, January 23, 1968; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/aol59d00/pdf

(11.) Leffingwell, John C., Oxidation of aldehydes, ketones, amines and Schiff bases with lead peroxide, RJRT Concept of Invention 1967, No. 3, February 3, 1967; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/cat58d00/pdf

(12.) Blum, H. J., The oxidative coupling of imines, RJRT Research Dept. Report 1968, No. 30, July 23, 1968; accessed June 5, 2014 from http://legacy.library.ucsf.edu/tid/apl59d00/pdf

(13.) Hameed, Shahid, and Tashfeen Akhtar. "Recent Advances in the Synthesis of Five-Membered Heterocycles." Current Organic Chemistry 15, no. 5 (2011): 694-711.

(14.) Baltazzi, Evan, and Lewis I. Krimen. "Recent Advances in the Chemistry of Pyrrole." Chemical Reviews 63, no. 5 (1963): 511-556.

(15.) Li, J. J. and Corey, E. J. (eds) (2011) Pyrroles and Pyrrolidines, in Name Reactions in Heterocyclic Chemistry II, John Wiley & Sons, Inc., Hoboken, NJ, USA

(16.) Zeni, Gilson, and Richard C. Larock. "Synthesis of heterocycles via palladium-catalyzed oxidative addition." Chemical reviews 106, no. 11 (2006): 4644-4680.

(17.) Candeias, Nuno R., Luis C. Branco, Pedro M. P. Gois, Carlos AM Afonso, and Alexandre F. Trindade. "More Sustainable Approaches for the Synthesis of N-Based Heterocycles." Chemical reviews 109, no. 6 (2009): 2703-2802.

(18.) Stanley, Levi M., and Mukund P. Sibi. "Enantioselective copper-catalyzed 1, 3-dipolar cycloadditions." Chemical reviews 108, no. 8 (2008): 2887-2902.

(19.) Sukhorukov, Alexey Yu, and Sema L. Ioffe. "Chemistry of six-membered cyclic oxime ethers. application in the synthesis of bioactive compounds." Chemical reviews 111, no. 8 (2011): 5004-5041.

(20.) Alvarez-Corral, Miriam, Manuel Munoz-Dorado, and Ignacio Rodriguez-Garcia. "Silver-mediated synthesis of heterocycles." Chemical reviews 108, no. 8 (2008): 3174-3198.

(21.) Coldham, Iain, and Richard Hufton. "Intramolecular dipolar cycloaddition reactions of azomethine ylides." Chemical reviews 105, no. 7 (2005): 2765-2810.

(22.) Muller, Thomas E., Kai C. Hultzsch, Miguel Yus, Francisco Foubelo, and Mizuki Tada. "Hydroamination: direct addition of amines to alkenes and alkynes." Chemical reviews 108, no. 9 (2008): 3795-3892.

(23.) O'Hagan, David. "Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids." Natural product reports 17, no. 5 (2000): 435-446.

(24.) Bellina, Fabio, and Renzo Rossi. "Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions." Tetrahedron 62, no. 31 (2006): 7213-7256.

(25.) Bluhm, Herbert J. "Preparation of substituted pyrrolidines", RJRT Research Dept. Report 1968, No. 31, July 25, 1968; accessed July 9, 2014 from http://legacy.library.ucsf.edu/tid/bpl59d00/pdf

(26.) Bluhm, Herbert J., and Eugene R. Fluck. "1,3,3,4,4-Pentasubstituted pyrrolidines." U.S. Patent 3,674,806 issued July 4, 1972.

(27.) Wolf, Anton. "Verfahren zur Herstellung von Kondensationsprodukten." German Patent 876237 issued May11, 1953.

(28.) Young, Harvey J. "Oxidative coupling of n-2-(3-methylbutylidene)-n-butylamine with manganese dioxide. The preparation of a novel 2,5-dimethylene-pyrrolidine." RJRT Research Dept. Memorandum 1969, No. 29, May 9, 1969; accessed July 9, 2014 from http://legacy.library.ucsf.edu/tid/ekw69d00/pdf

(29.) Young, Harvey J. "The reaction of succinaldimines with amides and sulfonamides." RJRT Research Dept. Report 1970, No. 20, April 22, 1970; accessed July 9, 2014 from http://legacy.library.ucsf.edu/tid/qej59d00/pdf

(30.) Wendelboe, Frederick N. "Synthesis of substituted phenylpyrrolidines." RJRT Research Dept. Report 1969, No. 16, May 13, 1969; accessed July 9, 2014 from http://legacy.library.ucsf.edu/tid/kql59d00/pdf

(31.) Leffingwell, John C. "Oxidative Coupling of Aldehydes & Imines I. An Entry to the Synthesis of 6,6,7,7-Tetraalkyl Tropane Alkaloid Analogs." Leffingwell Reports, Vol 6. (No 1), 1-18, June 2014

(32.) Leffingwell, John C. "Oxidative Coupling of Aldehydes & Imines II. An Entry to the Synthesis of Tropane Alkaloid Analogs (di & triazabicyclo[3.2.1]octan-3-ones) by Dipolar Additions." Leffingwell Reports, Vol. 6 (No. 2), 1-9, July 2014