

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.

by

John C. Leffingwell

Leffingwell & Associates, Canton, GA 30115 USA

Email: leffingwell@leffingwell.com

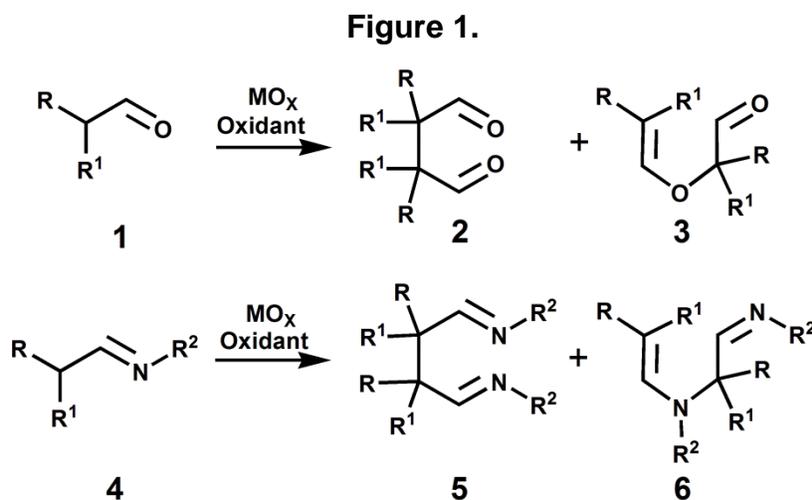
Abstract:

The oxidative coupling of selected aldehydes and imines with metal oxide oxidants, e.g. MnO_2 , forms 2,2,3,3-tetraalkylsuccinaldehydes and aldimines to provide precursors for the novel syntheses of various di- & triazabicyclo-[3.2.1]octan-3-ones tropane alkaloid analogs via dipolar additions.

Background:

The discovery that selected aldehydes, imines (and ketones) are easily coupled with metal oxide oxidants such as manganese dioxide, lead dioxide or nickel peroxide to form products (as shown in Figure 1.) has been previously reported by us (1-6).

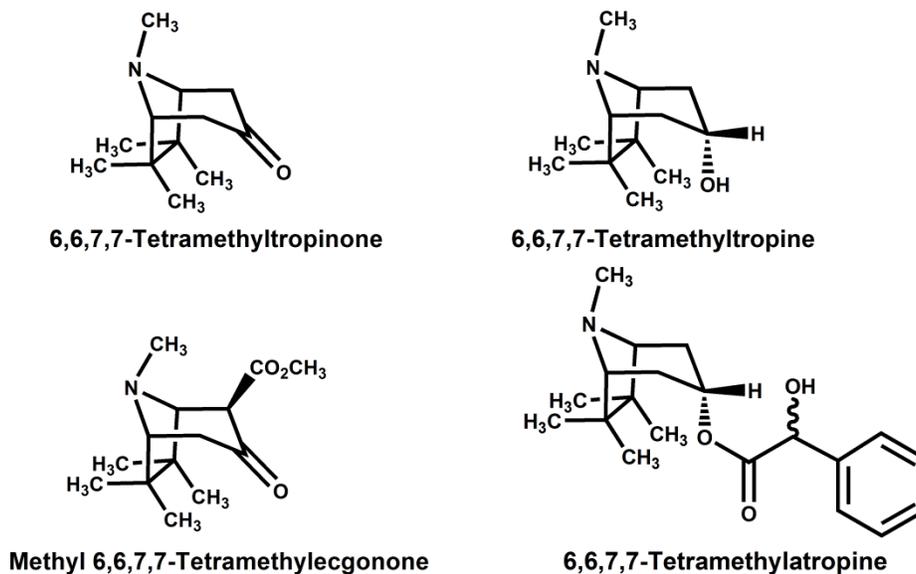
Unpublished reports on this work are also referenced with links to the original research (7-11).



Note – In the coupling of imine **4**, if R= alkyl and R¹= H, the corresponding pyrrole is formed (**6**).

In our first paper in this series (1), we reported on the utility of the 2,2,3,3-tetramethylsuccinaldehydes **2** and dialdimines **5** in the syntheses of the tropane analogs of tropinone and related alkaloids, e.g. 6,6,7,7-tetramethyltropinone, 6,6,7,7-tetramethyltropine Methyl 6,6,7,7-tetramethylecgonone and 6,6,7,7-tetramethylatropine (Figure 2).

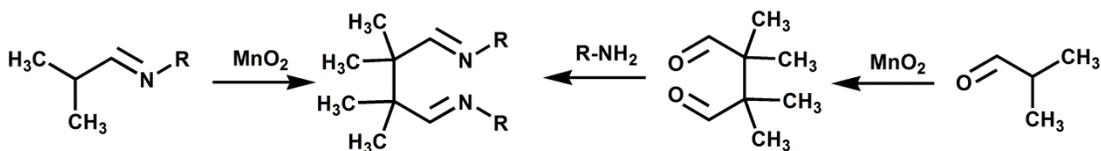
Figure 2.



A. Syntheses of 2,4,8-substituted-6,6,7,7-tetramethyl-2,4,8-triaza-bicyclo[3.2.1]octan-3-ones (and thiones) by 1,4-Dipolar addition of isocyanates and thioisocyanates to N,N-Dimethyl-2,2,3,3-tetramethylsuccinaldimine.

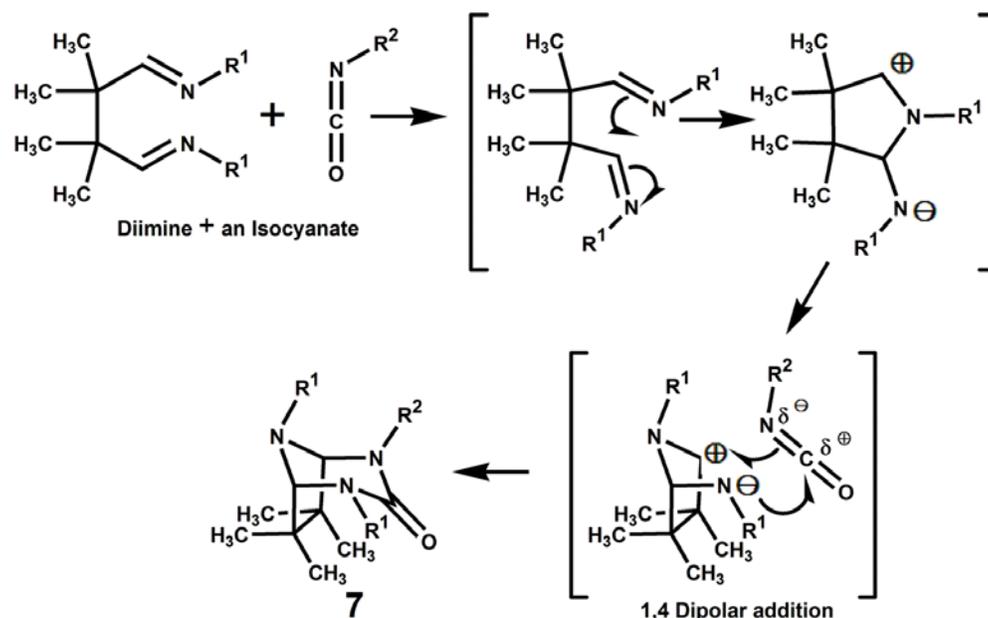
The tetramethylsuccinaldimines can be prepared either by the oxidative coupling of isobutyraldehyde to 2,2,3,3-tetramethylsuccinaldehyde which is then converted to the diimine desired or by oxidative coupling of an imine of isobutyraldehyde (see Figure 3). In practice, preparation from the tetramethylsuccinaldehyde was usually used, as a large quantity of this material was available from pilot scale preparation.

Figure 3.



As part of the studies on the possible utility of the tetraalkyl-succinaldehydes and dialdimines, the potential synthesis of tropane analogs was suggested (9). This paper reviews the previously unpublished work of Harvey Young in our group who undertook a study on the preparation of a number of 6,6,7,7-Tetramethyl-tropane type compounds (12). Young discovered that isocyanates (and thioisocyanates) would undergo a facile 1,4-polar addition (a [4+2] cycloaddition) with 2,2,3,3-tetramethylsuccindialdimines (with a concomitant ring closure) to form 2,4,8-substituted-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one compounds with the general structure **7** as shown in Figure 4.

Figure 4.

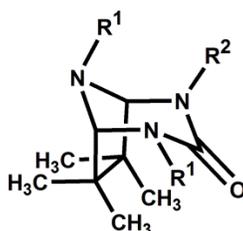


Experimentally, the synthesis procedure utilized for producing the 2,4,8-substituted-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-ones (and thiones) by 1,4-Dipolar addition was to add 1 mole equivalent of the isocyanate (or thioisocyanate) dropwise to 1 mole equivalent of a N,N-dialkyl-2,2,3,3-tetramethylsuccinaldimine in refluxing benzene.

We believe this is the first report of such 1,4-dipolar of additions of isocyanates (and thioisocyanates) to form 2,4,8-triaza-bicyclo[3.2.1]octan-3-ones (and thiones).

Table 1. provides the results and yields.

Table 1.



Isocyanate Used	R ¹	R ²	C3 >=O or >=S	Product	Yield (%)
phenyl isocyanate	n-butyl	Phenyl	>=O	2,8-dibutyl-6,6,7,7-tetramethyl-4-phenyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	~100
p-tolyl isocyanate	n-butyl	p-tolyl	>=O	2,8-dibutyl-6,6,7,7-tetramethyl-4-(4-methylphenyl)-2,4,8-triazabicyclo[3.2.1]octan-3-one	96
3,4-dichlorophenyl isocyanate	n-butyl	3,4-dichlorophenyl	>=O	2,8-dibutyl-4-(3,4-dichlorophenyl)-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	95
2,5-dichlorophenyl isocyanate	n-butyl	2,5-dichlorophenyl	>=O	2,8-dibutyl-4-(2,5-dichlorophenyl)-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	76
ethyl isocyanatoacetate	methyl	-CH ₂ CO ₂ C ₂ H ₅	>=O	ethyl 2-{4,6,6,7,7,8-hexamethyl-3-oxo-2,4,8-triazabicyclo[3.2.1]octan-2-yl}acetate	75
ethyl isocyanatoacetate	n-butyl	-CH ₂ CO ₂ C ₂ H ₅	>=O	ethyl 2-{4,8-dibutyl-6,6,7,7-tetramethyl-3-oxo-2,4,8-triazabicyclo[3.2.1]octan-2-yl}acetate	66
ethyl isocyanate	ethyl	ethyl	>=O	2,4,8-triethyl-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	62
butyl isocyanate	n-butyl	n-butyl	>=O	2,4,8-tributyl-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	57
allyl isocyanate	n-butyl	allyl	>=O	2,8-dibutyl-6,6,7,7-tetramethyl-4-(prop-2-en-1-yl)-2,4,8-triazabicyclo[3.2.1]octan-3-one	54
9-decenyl isocyanate	n-decyl	9-decenyl	>=O	2-(dec-9-enyl)-4,8-didecyl-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	54
methyl isocyanate	methyl	methyl	>=O	2,4,6,6,7,7,8-heptamethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	38
propyl isocyanate	n-propyl	n-propyl	>=O	2,4,8-tripropyl-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	32
4-ethoxyphenyl isocyanate	n-butyl	4-ethoxyphenyl	>=O	2,8-dibutyl-4-(4-ethoxyphenyl)-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	87
4-chlorophenyl isocyanate	n-butyl	4-chlorophenyl	>=O	2,8-dibutyl-4-(4-chlorophenyl)-6,6,7,7-tetramethyl-2,4,8-triazabicyclo[3.2.1]octan-3-one	96
Phenyl thioisocyanate	n-butyl	Phenyl	>=S	2,8-dibutyl-6,6,7,7-tetramethyl-4-phenyl-2,4,8-triazabicyclo[3.2.1]octane-3-thione	65

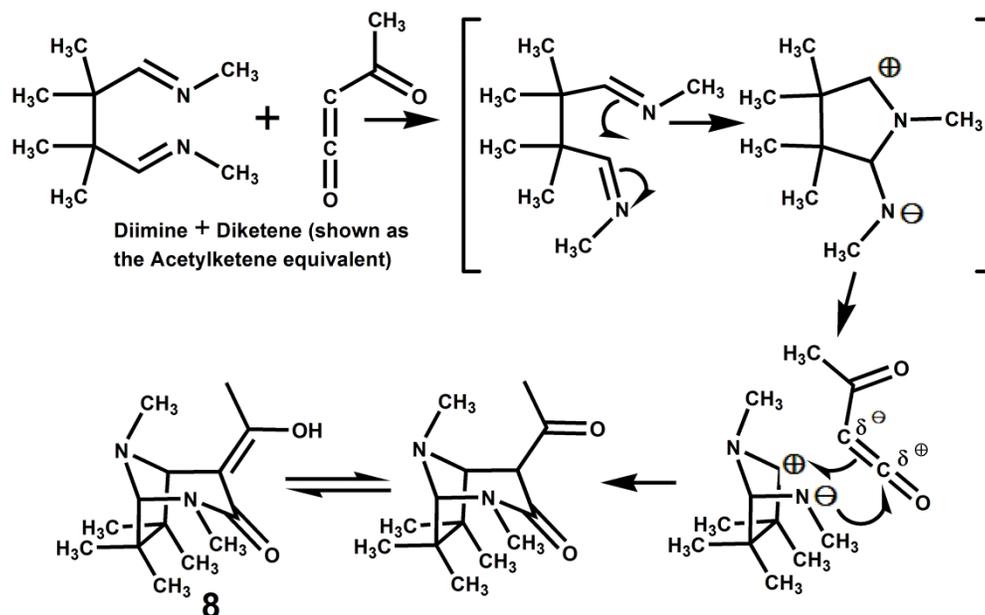
B. Syntheses of 4-(1-hydroxyethylidene)-2,6,6,7,7,8-hexamethyl-2,8-diazabicyclo[3.2.1]octan-3-one by addition of Diketene with N,N-Dimethyl-2,2,3,3-tetramethylsuccinaldimine.

The reaction of diketene with N,N-dimethyl-2,2,3,3-tetramethylsuccinaldimine in water at 80° C. produces 4-(1-hydroxyethylidene)-2,6,6,7,7,8-hexamethyl-2,8-diazabicyclo[3.2.1]-octan-3-one **8** in 44% yield (13). As diketene acts chemically as an acetylketene

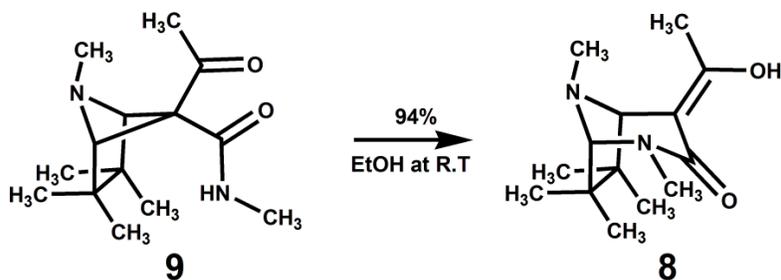
equivalent, at first glance one might assume the reaction proceeds in a manner analogous to the isocyanate 1,4-dipolar cycloadditions, *vide supra*.

Figure 5.

Theoretical Formation of Compound 8 by 1,4-Dipolar Addition



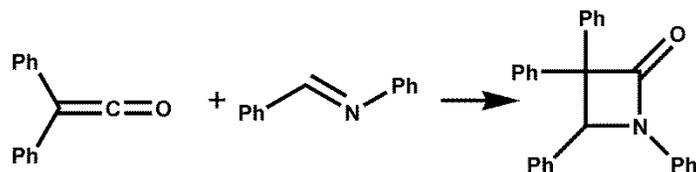
This assumption, however is complicated by the fact that the same reaction conducted in ether at room temperature produced 6-acetyl-N,2,2,3,3,5-hexamethyl-5-azabicyclo[2.1.1]hexane-6-carboxamide 9 in 45% yield. Further, when 9 is stirred for 23 hours in ethanol at room temperature it forms 8 in 94% yield.



Thus another mechanism must be in play.

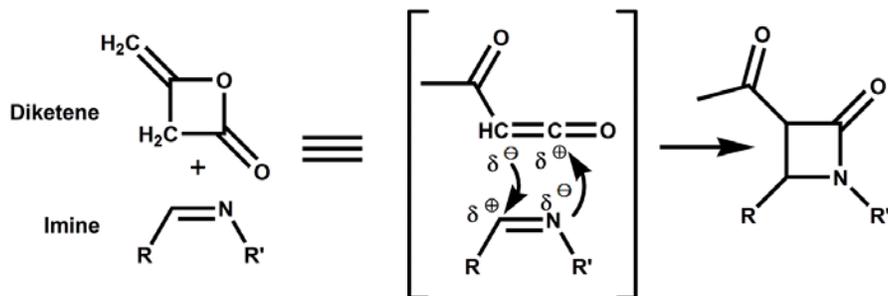
The literature shows that the reaction of ketenes with Schiff bases (i.e. imines) were found to form β -lactams as early as 1907 by Staudinger (14,15) who reacted diphenylketene with benzylideneaniline to form the β -lactam, 1,3,3,4-tetraphenylazetid-2-one (Figure 6).

Figure 6.



Further Kato et al. (16) and Goo et al. (17) have demonstrated that diketene reacts with imines to yield acetylazetid-2-ones by a [2+2] cycloaddition as shown below.

Figure 7.

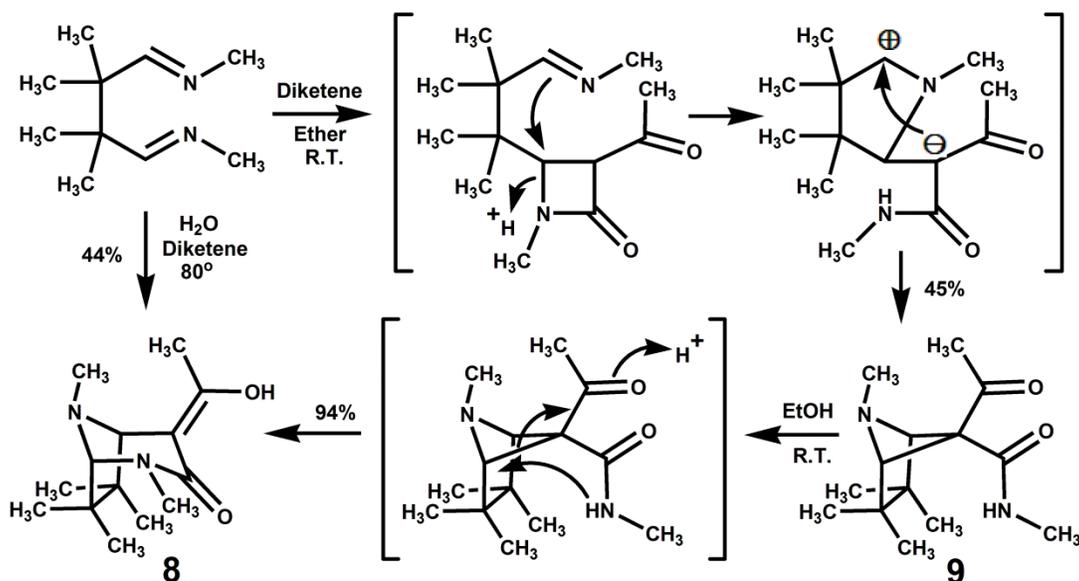


This information suggests another possible route may be occurring in Young's synthesis of 4-(1-hydroxyethylidene)-2,6,6,7,7,8-hexamethyl-2,8-diazabicyclo[3.2.1]octan-3-one, **8**. That is, the possibility that the reaction proceeds via an acetylazetid-2-one intermediate formed by an initial [2+2] cycloaddition.

A speculative possible mechanism is shown below in Figure 8.

Figure 8.

Alternative Mechanistic Route to **8** via an Acetylazetidione First Step



Conclusions:

Dipolar additions of isocyanates and thioisocyanates to 2,2,3,3-tetramethylsuccinaldimines are effective in producing novel substituted triazabicyclo[3.2.1]octan-3-ones (and thiones).

While the reaction of diketene with N,N-dimethyl-2,2,3,3-tetramethylsuccinaldimine produces 4-(1-hydroxyethylidene)-2,6,6,7,7,8-hexamethyl-2,8-diazabicyclo-[3.2.1]octan-3-one, the mechanism of formation remains speculative.

The procedures described provide easy access to di- and triazabicyclo[3.2.1]octan-3-one tropane analogs.

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