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Review

Recent development in the chemistry of 2,3-Dioxopyrrolidines

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ABSTRACT

The importance of 2,3-dioxopyrrolidines and related compounds comes from their potent biological activity. This review aims at highlighting the literatures that reported on the structure evidence, preparation, chemical properties and some applications of 2,3-dioxopyrrolidines. It is a trial to attract the attention of the chemists for exploring the synthetic potentialities of 2,3-dioxopyrrolidine derivatives as a key intermediate of the synthesis of new fused heterocycles with a 2,3-dioxopyrrolo moiety for applications in the different branches of applied chemistry.

KEYWORDS: 2,3-dioxopyrrolidine, structure, tautomerism, biological activity.

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1. Introduction

The biological activity of natural and synthetic compounds with a pyrrolidine moiety has been reported [1-10]. *N*-Substituted-4-(substituted benzylidene)-2,3-dioxopyrrolidines inhibit blood platelet aggregation [11] and aldose reductase [12]. A search of the literature showed that the condensed heterocycles having fused 2,3-dioxopyrrolo nucleus have attracted little attention, but some interest has come from physiologically active Amaryllidaceae [13], Erythrina [14] alkaloids and the antitumor agents [15, 16] (anthramycin, tomamycin, and neothramycins A and B) bearing this ring system. Moreover, 2,3-dioxo-5-(hetero)arylpyrrolidine derivatives were successfully converted to their respective 2,3-dioxo-5-(hetero) arylpyrroles [17]. These pyrrolidinones are promising intermediates for preparing various synthetically challenging and medicinally important alkaloids such as *dl*-vasicine [18], codonopsinine, anisomycin, and preussin [19-21]. Many groups have reported the synthesis of pyrrolidine-based iminosugars [22]. Zhang and co-workers reported the synthesis of iminosugars using D-glucose as a main precursor [23]. Doddi and co-workers reported the synthesis of azasugars, which have moderate inhibition against glycosidase enzyme utilizing pyrrolidine skeleton followed by regiospecific amination, ring closing metathesis, and diastereospecific dihydroxylations as the key reactions [24]. Recently, Hamzah, *et al*. reported the synthesis of pyrrolidine-based iminosugars in short steps *via* multi component reaction (MCR), amination, and stereoselective reduction [25]. A part of our laboratory studies [26] has focused on exploring the synthetic potentialities of 2,3-dioxopyrrolidine derivatives as key intermediates of the synthesis of fused heterocycles with a pyrrolo nucleus. A variety of 1,5- diaryl-2,3- dioxopyrrolidines could be readily obtained by adding the aromatic

amines to the arylidine derivatives of pyruvic acid [27, 28].

2. Preparation and Structure

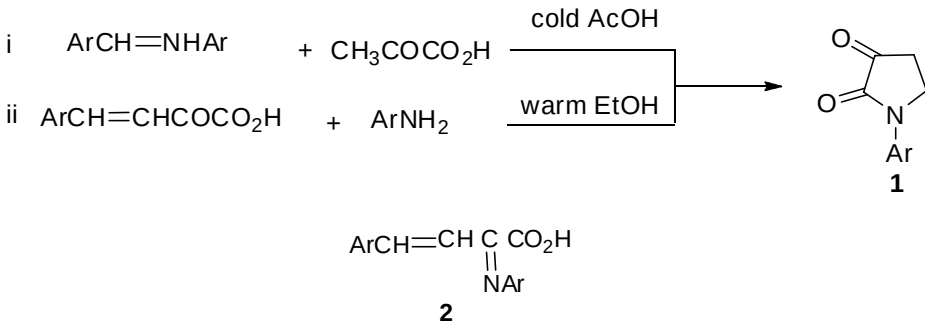
Several methods have been reported for the preparation 2,3-dioxopyrrolidines. In this context, this review will highlight the most important methods. Johnson and Adams reported that the thermal decomposition of l,5-diarly-2,3-dioxopyrrolidines evolved carbon dioxide [29]. As a result of this decarbonylation reaction, the other decomposition product which is cinnamylideneaniline was identified. The abnormal behavior of this "decarboxylation" reaction pushed Vaughan and Peters [30] to characterize the nature of the compound which undergoes such degradation and to study the reaction mechanism. Generally, l,5-diarly-2,3-dioxopyrrolidines **(1)** were mainly synthesized by the reaction of benzylideneaniline with pyruvic acid in cold glacial acetic acid or the benzylidenepyruvic acid with aniline in warm alcohol as shown in Scheme 1 [31]. Mechanisms of both reactions involved formation of the common intermediate 2-arylimino-3-benzylidenepropionic acids **(2)**, which underwent a cyclization rearrangement reaction to give compound **1** [32-34].

The structure of **1** as the condensation products from reactions i or ii was earlier assigned by Schiff and Bertini [35]. The presence of a carbonyl at position 3 was proved by the formation of 3-anils [36], which could not be hydrolyzed to the free 2,3-dioxopyrrolidines [31]. The nature of the reaction with phenyl hydrazine remained in doubt as various workers have reported divergent results [31, 32, 37]. Also, the cyclic nature of structures **1** was confirmed by the synthesis (Ar = Ph) of methyl 3-phenyl-3-(*N*-methoxalyl-*N*-phenylamino)propionate followed by hydrolysis and decarboxylation (cf. Scheme 2) [30].

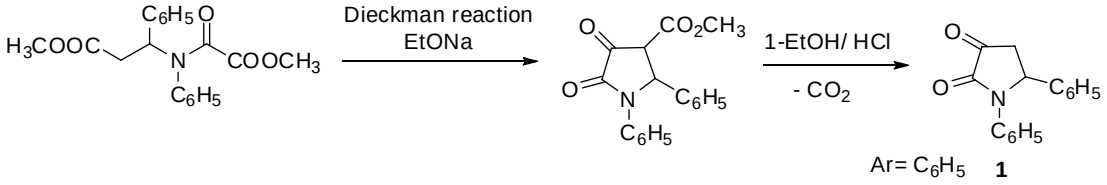
The 3-hydroxy-Δ^3-2-pyrrolinones' enol forms of 2,3-dioxopyrrolidines were supported by spectrographic evidence in both the infrared and ultraviolet regions [30, 31, 39-43].

3. Tautomeric rearrangement

The thermal decomposition of 1,5-diaryl-2,3-dioxopyrrolidine **(1)** to 3-arylidene-2-arylimino propionic acid **(2)** which was decarboxylated to cinnamylideneaniline **(3)** and CO_2 supported the fact that both compounds **1** and **2** are tautomeric forms (cf. Scheme 3) [30].



Scheme 1. Synthesis of 1,5-diaryl-2,3-dioxopyrrolidine **(1)**.



Scheme 2. Synthesis of 1,5-diphenyl-2,3-dioxopyrrolidine **(1)**.

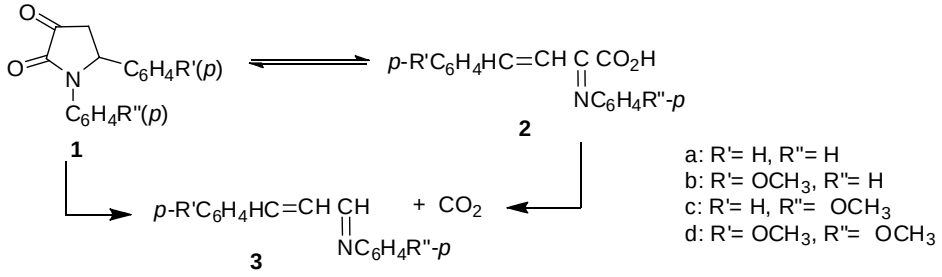
Thus, *N*-cinnamylideneaniline (**3a**) could be obtained by decarboxylation of 3-benzylidene-2-phenyliminopropionic acid (**2a**) in *o*-dichlorobenzene or thermal decomposition of l,5-diphenyl-2,3-dioxopyrrolidine **(1a)** under the same conditions. Both l,5-dianisyl-2,3-dioxopyrrolidine (**1d**) and 3-anisylidene-3-anisyliminopropionic acid (**2d**) afforded the same anil namely, *N*-(4-methoxycinnamylidene)-4-anisidine (**3d**), under identical conditions (cf. Scheme 4) [30].

The synthesis of 4-carbomethoxy-l,5-diphenyl-2,3-dioxopyrrolidine (**6**) gave an additional evidence that l,5-diaryl-2,3-dioxopyrrolidines are tautomers with 4-aryl-2-(arylamino)but-3-enoic acids which underwent thermal decarboxylation as shown in Scheme 5 [44, 45].

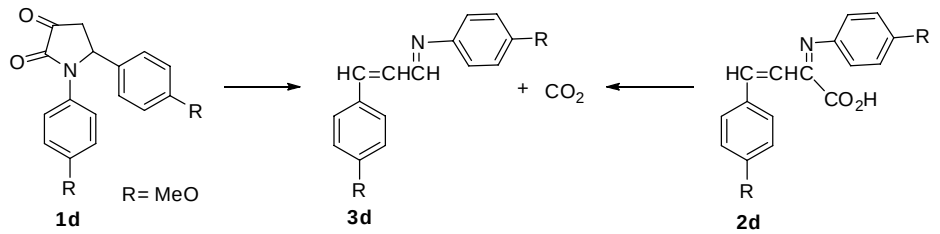
4. Methods of preparation

1,5-Diaryl-2,3-dioxopyrrolidines **(1)** could be synthesized by reacting the Schiff bases with pyruvic acid or adding anilines to a solution of pyruvic acid and benzaldehydes in ethanol or acetic acid (cf. Scheme 6) [32, 46-48].

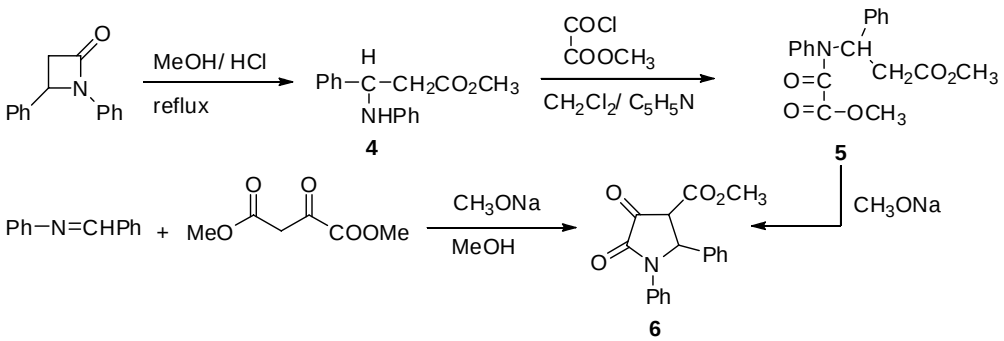
Heating of l-ethylimino-2-benzalpropionic acid with dilute hydrochloric acid gave 1,5-diphenyl-2,3-dioxopyrrolidine **(1)**. Phenylpyruvic acid was



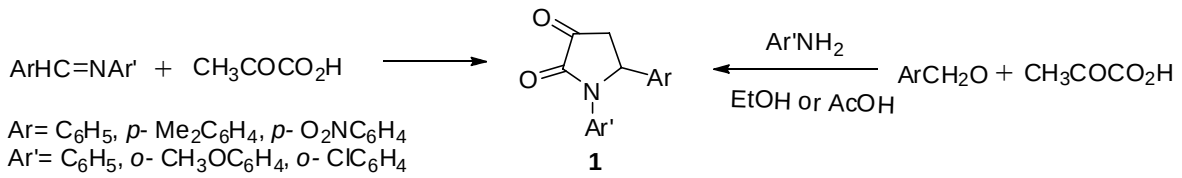
Scheme 3. Thermal decomposition of 1,5-diaryl-2,3-dioxopyrrolidine **(1)**.



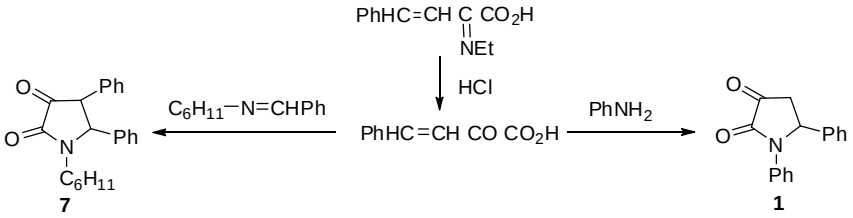
Scheme 4. Thermal decomposition of 1,5-dianisyl-2,3-dioxopyrrolidine **(1d)**.



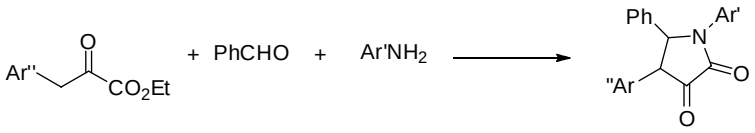
Scheme 5. Synthesis of 4-carbomethoxy-1,5-diphenyl-2,3-dioxopyrrolidine **(6)**.



Scheme 6. Synthesis of 1,5-diphenyl-2,3-dioxopyrrolidine (**1**).

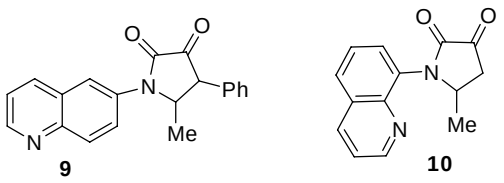


Scheme 7. 1,5-diphenyl-2,3-dioxopyrrolidine (**1**) **&** 1-cyclohexyl-4,5-diphenyl-2,3-dioxopyrrolidine **(7)**.



Ar'= Ph, 2-naphthyl, 2-naphthyl, 3-quinolyl,
5-quinolyl, 4-MePh, β-Naphthyl,4-MePh
Ar''= Ph, $PhCH_2$, 2-furoyl, 2-quinolyl, 4-quinolyl,6-methoxy-8-quinolyl,
2-quinoxalyl, 2-quinoxalyl, 2-benzoxazolyl, 2-benzothiazolyl

Scheme 8. Synthesis of 1,4,5-trisubstituted-2,3-dioxopyrrolidines **(8)**.



Scheme 9. l- (6-quinolyl) **and** l- (8-quinolyl)-2,3-dioxopyrrolidines **(9, 10).**

reacted with benzalcyclohexylamine to afford 1-cyclohexyl-4,5-diphenyl-2,3-dioxopyrrolidine **(7)** (cf. Scheme 7) [33].

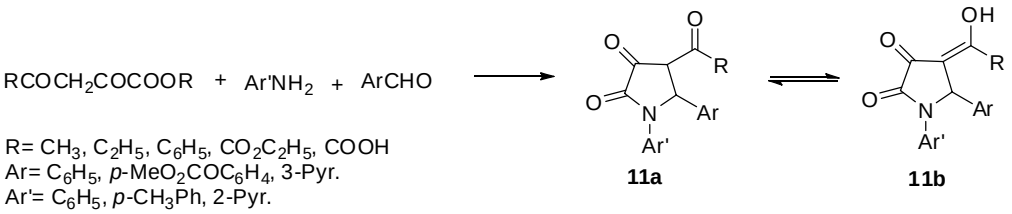
On the other hand, the 1,4,5-trisubstituted-2,3-dioxopyrrolidines **(8)** having a heterocyclic ring could be obtained by heating the derivatives of ethyl pyruvate with the Schiff bases or a mixture of benzaldehyde and amines (cf. Scheme 8) [49-56].

Treatment of 6-aminoquinoline with acetaldehyde and phenyl pyruvic acid afforded 5-methyl-4-phenyl- l-(6-quinolyl)--2,3-dioxopyrrolidine **(9)** [52], while heating 8- aminoquinoline under reflux with acetaldehyde and pyruvic acid in hot absolute ethyl alcohol gave 5-methyl-l-(8-quinolyl)-2,3-dioxopyrrolidine **(10)** (cf. Scheme 9) [53].

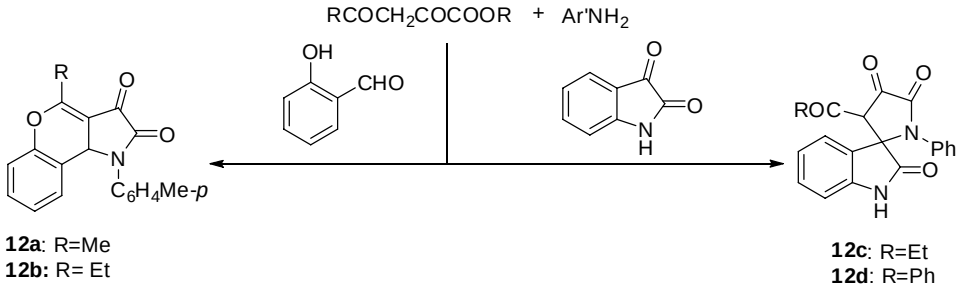
The ethyl esters of 2,4-diketoacids condensed simultaneously with aromatic amines ($ArNH_2$) and aldehydes (ArCHO) to yield 2,3-dioxopyrrolidines consisting of an equivalent mixture of the keto **11a** and enol **11b** forms (cf. Scheme 10) [37, 57-59].

Afsah *et al*. [58] have reported the synthesis of new derivatives of 2,3- dioxopyrrolidines **12** following the reaction sequence in Scheme 11.

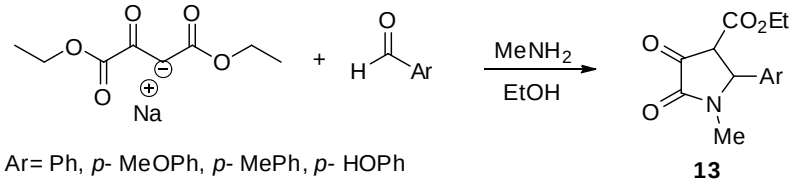
Sodium diethyl oxaloacetate was condensed with an aldehyde and methyl amine in equimolar ratio in refluxing ethanol to afford 5-aryl-4-carbethoxy-1-methyl-2,3-dioxopyrrolidines **13** (cf. Scheme 12) [2].



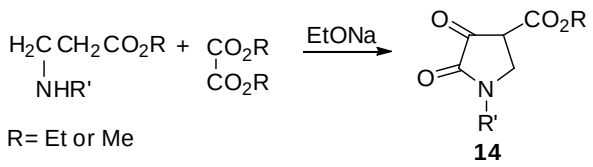
Scheme 10. Synthesis of 2,3-dioxopyrrolidines **(11a&b)** from ethyl esters of 2,4-diketoacids.



Scheme 11. Synthesis of 4-acyl-5-pyridyl-2,3-dioxopyrrolidines (**12**).



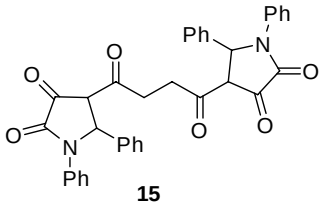
Scheme 12. Synthesis of 5-aryl-4-carbethoxy-1-methyl-2,3-dioxopyrrolidines **(13)**.



Scheme 13. Synthesis of 1-substituted-4-carbalkoxy -2,3-dioxopyrrolidines **(14)**.

The oxalic acid esters were condensed with a different 3-arylaminopropanoic acid ester to yield a series of l-aryl-4-carbalkoxy -2,3-dioxopyrrolidines **(14)** (cf. Scheme 13) [60].

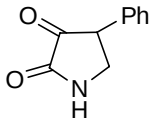
When a mixture of diethyl α,α', γ,γ'-tetraoxosebacate and benzalaniline was heated for half hour on a water bath at 50 °C, the fluid mass became viscous and hardened at 95 °C. Three crystallization from acetic acid gave succinyl-4,4'-bis (2,3-dioxo-l,5-diphenylpyrrolidine) **(15)** [61].



Diethyl alkyl oxalacetate and benzalaniline in ether gave 4-alkyl-4-carbethoxy-l,5-diphenyl-2,3-dioxopyrrolidine **(16)** which was saponified in methanol containing one equivalent KOH and acidified to give the corresponding 4- substituted of **1** which is **17** (cf. Scheme 14) [62].

Ethyl oxalacatate, NH_3 and ketones yielded 5,5-dialkyl-4-carbethoxy-2,3-dioxopyrrolidine **(18)** (cf. Scheme 15) [63].

The reduction of ethyl cyanopyroracemate with nickel as catalyst goes as far as the primary amine which splits off ethyl alcohol with closing of the five membered ring and gives 4-phenyl-2,3-dioxopyrrolidine (**19**) [64].



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Several 2,3-dioxopyrrolidines **(20)** could be obtained by refluxing the esters of 2-oxosuccinic, 2-oxopropanoic and/ or 2-oxo-3-phenylpropanoic acids with different carbonyl compounds (aldehydes or ketones) and amines (cf. Scheme 16) [65, 66].

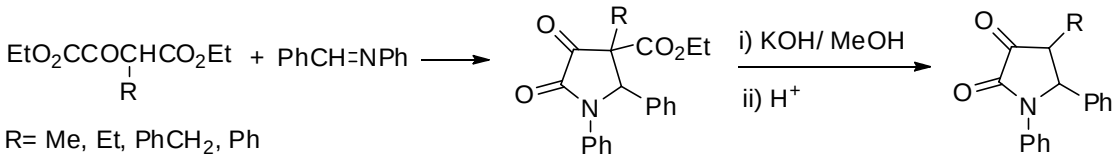
Hydrolysis of $Cl_3CCOCMe_2CH(CCl_3)$ NMe_2 in refluxing 99% ethanol for 8 hours gave 40% $Cl_3CCOCMe_2CH(COCl)NMe_2$ and 45% pyrrolidinedione **(21)** (cf. Scheme 17) [67].

2,3-Dioxopyrrolidine **(24)** could be prepared by utilization of Jones reagent following the Scheme 18 [69].

5. Condensation with aldehydes

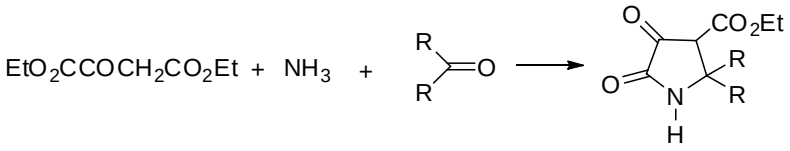
l-Substituted-4-benzylidene-2,3-dioxopyrroldines (**27)** could be conveniently prepared by condensing substituted benzaldehydes with 1-substituted-2,3-dioxopyrrolidines (**26)** or the readily available l-substituted-4-carbethoxy-2,3-dioxopyrrolidine **(14)** after its acid hydrolysis and decarboxylation in a single operation (cf. Scheme 19) [70-73, 74].

Diethyl oxalate was reacted with ethyl acrylate and 3-aminopropanoic acid or 4-aminobutanoic acid in a molar ratio by one-pot synthesis to form 3-(4-(ethoxycarbonyl)-2,3-dioxopyrrolidin-1-yl)propanoic acid **(28a)** and 4-(4-(ethoxycarbonyl)-2,3-dioxopyrrolidin-1-yl)butanoic acid **(28b)** respectively. The β-ketoesters **28** were refluxed with



16 **17**

Scheme 14. Synthesis of 4-alkyl-l,5-diphenyl-2,3-dioxopyrrolidine **(17)**.



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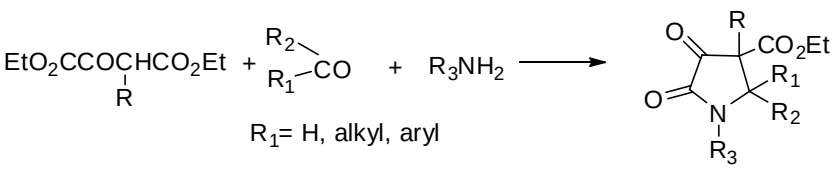
Scheme 15. Synthesis of 5,5-dialkyl-4-carbethoxy-2,3-dioxopyrrolidine **(18)**.



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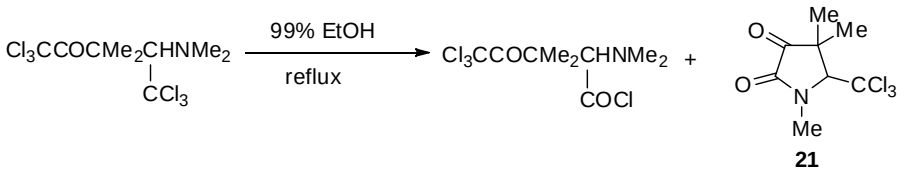
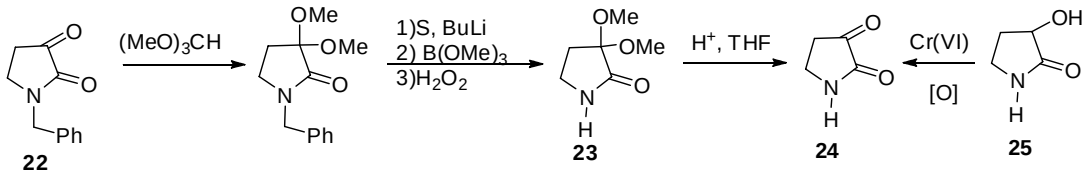
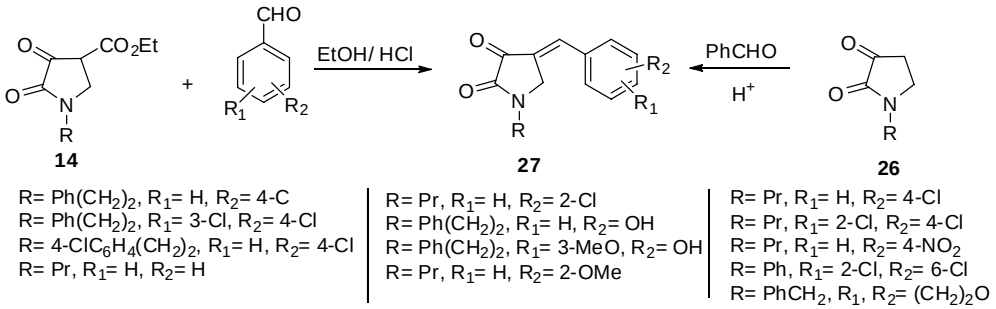
Scheme 16. Synthesis of 2,3 dioxopyrrolidine drivatives **(20)**.



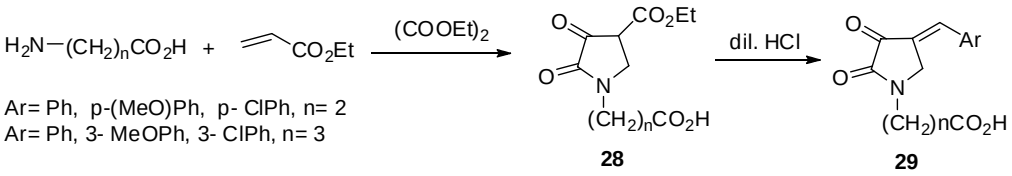
Scheme 17. Synthesis of 5-trichloromethyl-1,4,4-trimethyl-2,3-dioxopyrrolidine **(21)**.



Scheme 18. Synthetic route of 2,3-dioxopyrrolidine **(24)**.



Scheme 19. Synthesis of 1-substituted-4-benzylidene-2,3-dioxopyrrolidines **(27)**.



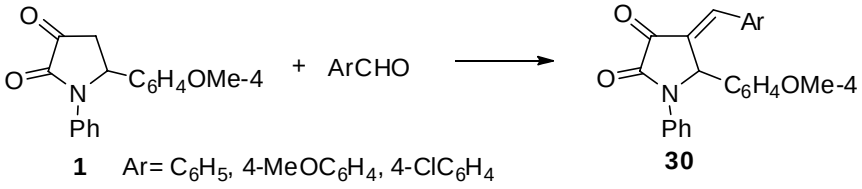
Scheme 20. Synthesis of l-(ω-Carboxyalkyl)-4-carbethoxy-2,3-dioxopyrrolidines **(28)**.

hydrochloric acid to be hydrolyzed and decarboxylated to the parent 4-(2,3-dioxopyrrolidin-1-yl) derivatives of propanoic and butanoic acids, which were directly reacted with aromatic aldehydes to synthesize the 4-arylidene- l-(ω-carboxyalkyl)-2,3- dioxopyrrolidines **(29)** (cf. Scheme 20) [73].

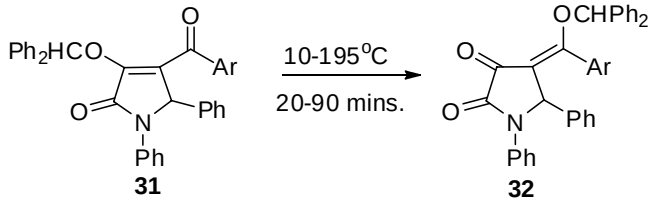
The 4-arylidene-5-(*p*-methoxyphenyl)-1-phenyl-2,3-dioxopyrrolidines **(30)** could be synthesized by direct condensation of 4-(4-methoxyphenyl)-1-phenyl-2,3-dioxopyrrolidine (**1**) with benzaldehyde, *p*-anisaldehyde, and/or *p*-chlorobenzaldehyde (cf. Scheme 21) [26f].

Moreover, 1,5-diphenyl-4- [aryl (diphenylmethoxy) methylidene]-2,3-dioxopyrrolidenes **(32)** were prepared by heating l,5-diphenyl-3-(diphenyl methoxy)- 4-aroyl-2,5-dihydropyrrol-2-ones **(31)** at 170-195 °C for 20-90 minutes (cf. Scheme 22) [75].

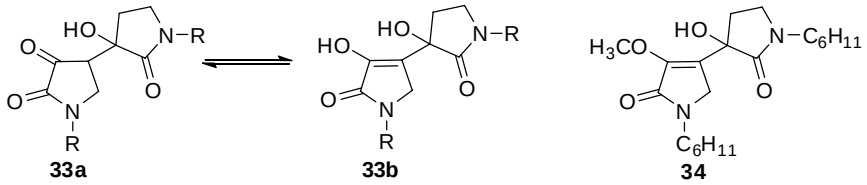
The l-substituted-2,3-dioxopyrrolidines underwent rapid self-condensation of the aldol type to form 1,1'-diaryl(dialkyl)-3-hydroxy-[3,3'-bipyrrolidine]-



Scheme 21. 4-arylmethylene-5-(*p*-methoxyphenyl)-1-phenyl-2,3-dioxopyrrolidines **(30)**.

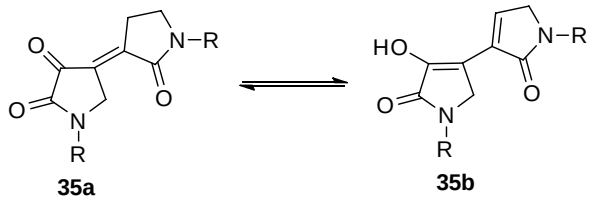


Scheme 22. 1,5-diphenyl-4- [aryl (diphenylmethoxy) methylidene]-2,3-dioxopyrrolidenes **(32)**.



2,4',5'-trione **(33a)** (or its enol tautomer **33b**) [76]. 1-cyclohexyl-4-(1-cyclohexyl-3-hydroxy-2-oxopyrrolidin-3-yl)-3-methoxy-1H-pyrrol-2(5H)-one **(34)** was obtained when cyclohexyl compound reacted with diazomethane [76].

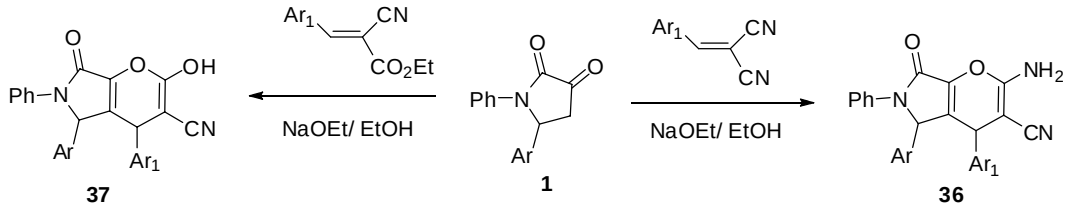
The self-condensation products are readily dehydrated to yield the compounds, which could be identified as l,l'-disubstituted-2,4',5'-trioxo-3,3'-bipyrrolidylidenes **(35)** [76]. The l,5-diaryl-2,3-dioxopyrrolidine apparently exhibits the same aldol dimerization behavior [77].



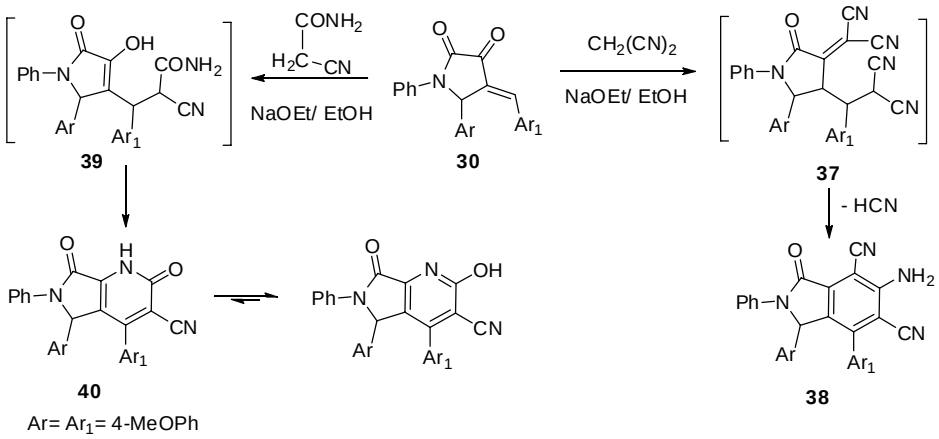
6. Michael addition reaction

1,5-Diaryl-2,3-dioxopyrrolidines underwent Michael-Addition reaction as a cyclic ketone containing an active methylene group. Thus, treatment of 5-aryl-1-phenyl-2,3-dioxopyrrolidine (**1**) with 2-benzylidenemalononitriles and/or ethyl α-cyanocinnamates in the presence of sodium ethoxide as a basic catalyst under the conditions of Michael-Addition reaction afforded 4,5-diaryl-2-amino-7-oxo-6-phenyl-4,5,6,7-tetrahydropyrano [2,3-*c*]pyrrole-3-carbonitrile **(36)** and 4,5-diaryl- 2-hydroxy-7-oxo-6-phenyl-4,5,6,7-tetrahydropyrano [2,3-*c*]pyrrole-3-carbonitrile (**37)** respectively (cf. Scheme 23) [26f].

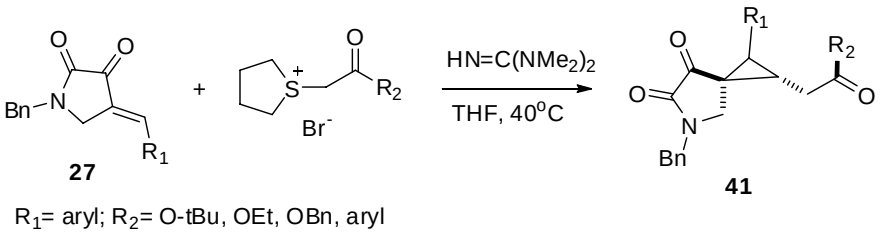
On the other hand, the malononitrile was added to the active methylene compound namely 5-aryl-4-benzylidene-1-phenylpyrrolidine-2,3-dione under Michael-type condensation reactions and 5-amino-1,7-diaryl-3-oxo-2-phenylisoindoline-4,6-dicarbonitrile **(38**) has been identified as the reaction product by cyclization of the unstable adduct **(37)** [26f]. Also, the formation of the 5*H*-pyrrolo[3,4-*b*]pyridine-3-carbonitrile derivative **(40)** was performed by the Michael-addition reaction of ethyl cyanoacetamide with 4-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-1-phenyl-2,3-dioxopyrrolidine **(30)** to form the



Scheme 23. 5-Aryl-2,3-dioxopyrrolidine (**1**) with α-cyanocinnamonitriles & ethyl α-cyanocinnamates.



Scheme 24. Michael addition reaction of 4-arylidene-2,3-dioxopyrrolidines **(30)** with malononitrile.



Scheme 25. The Michael addition of Sulfonium salts to 4-arylidene-2,3-dioxopyrrolidines **(27)**.

adduct **39**, which readily cyclized to a product that characterized as **40** (cf. Scheme 24) [26f].

Michael addition of Sulfonium salts containing an active methylene group led to formation of a *trans*/*cis* mixture of polysubstituted spirocyclopropane derivatives of 2,3-dioxopyrrolidine (41) in good yields in a ratio of up to >20:1 (cf. Scheme 25) [78].

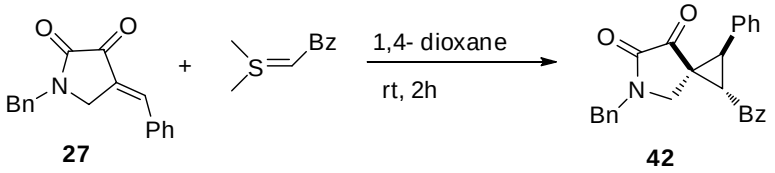
Also, the cyclopropanation of 4-arylidene-2,3-dioxopyrrolidines **27** with sulfur ylide in 1,4-dioxane afforded spirocyclopropanes **42** at room temperature in excellent yields and with promising diastereoselectivity (cf. Scheme 26) [79].

The spirocyclopropanes **43** containing amide groups could be obtained following Scheme 27 [79].

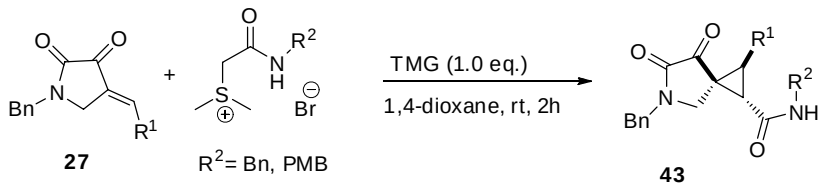
Chiral spirocyclopropane **44** was synthesized by the reaction sequence in Scheme 28 [79].

Also, the chiral dispiro[indoline-3,1'-cyclopropane-2',3"-pyrrolidine]-2,4",5"-triones **(45)** was formed accordingly (cf. Scheme 29) [80].

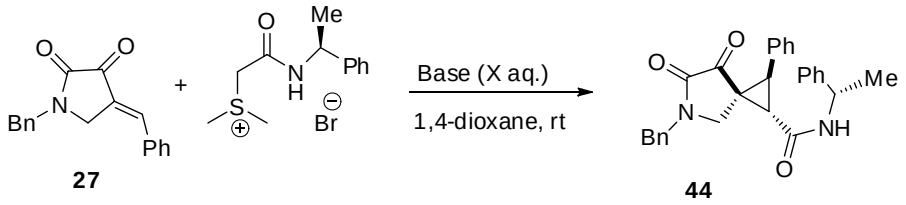
The reaction of 1,4-Michael addition reaction of 4-arylidene-2,3-dioxopyrrolidines **(27)** with nitroalkane catalyzed by a chiral copper complex (L-Cu(OTf)$_2$-*N*-ethylmorpholin) in aqueous media afforded nitro-containing pyrrolidones **(46)** in high



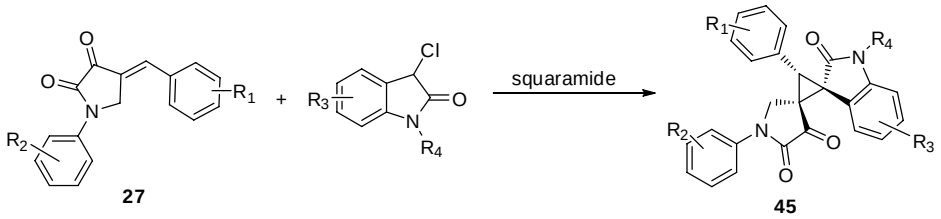
Scheme 26. The cyclopropanation of 4-arylidene-2,3-dioxopyrrolidines **49** with sulfur ylide.



Scheme 27. The cyclopropanation of 4-arylidene-2,3-dioxopyrrolidines **27** with amidic sulfonium salts.



Scheme 28. The cyclopropanation of 4-aryldene-2,3-dioxopyrrolidines **27** with *N*-phenylethyl sulfur ylide.



Scheme 29. Formation of dispiro[indoline-3,1'-cyclopropane-2',3"-pyrrolidine]-2,4",5"-triones **(45)**.

yields with excellent diastereoselectivities (cf. Scheme 30) [81].

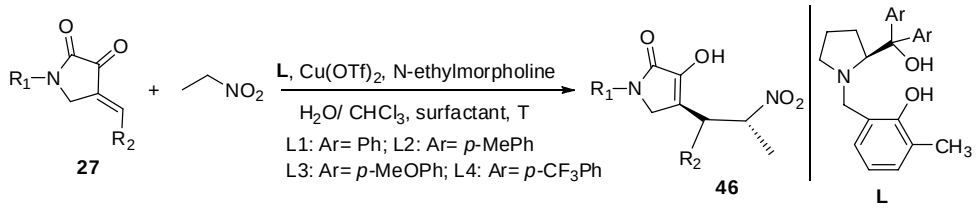
7. Cycloaddition reactions

When the 4-arylidene-1-benzyl-2,3-dioxopyrrolidines **(27)** was subjected to the reaction with heterocyclic ketene aminals in ethanol, it gave a series of imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines **47** in good to excellent yields (cf. Scheme 31) [82].

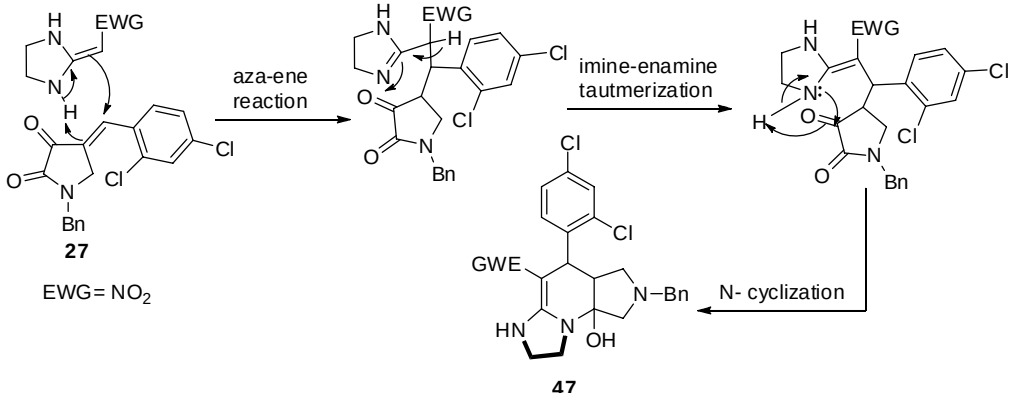
The 4-arylidene-2,3-dioxopyrrolidine derivatives **27** are readily added to allene ketones **48** in an asymmetric [4+2] cycloaddition reaction yielding 4-alky-6-benzyl-2-(2-oxoalkyl)-5,6-dihydropyrano [2,3-c]pyrrol-7(4H)-one derivatives **49** in moderate to high yields with good enantioselectivities (cf. Scheme 32) [83].

Moreover, the chiral *N*,*N*-dioxide/Ni(OTf)$_2$ complex catalyzed the addition of 4-arylidene-2,3-dioxopyrrolidines **27** to cyclopentadiene under the conditions of asymmetric Diels–Alder reaction and produced the corresponding chiral-bridged compounds **50** in high yields (cf. Scheme 33) [84].

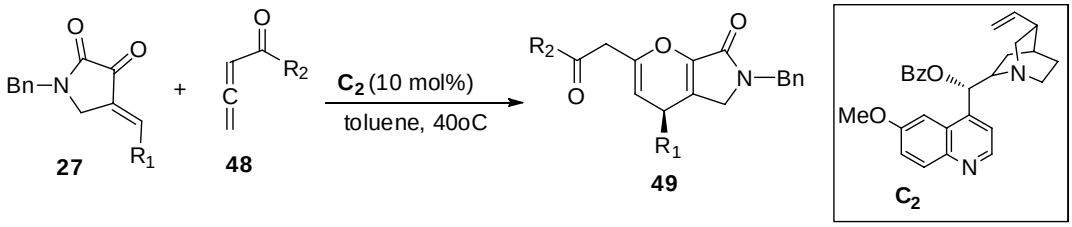
Also, a series of isoindolinone derivatives **52** were obtained in excellent yields. The reaction proceeded



Scheme 30. Michael addition reaction of 4-arylidene-2,3-dioxopyrrolidines **(27)** to nitroalkane.



Scheme 31. Cycloaddition reaction 4-arylidene-2,3-dioxopyrrolidines **(27)** with heterocyclic ketene aminals.



Scheme 32. Cycloaddition reaction of 4-arylidene-2,3-dioxopyrrolidine **27** with allene ketones **48**.

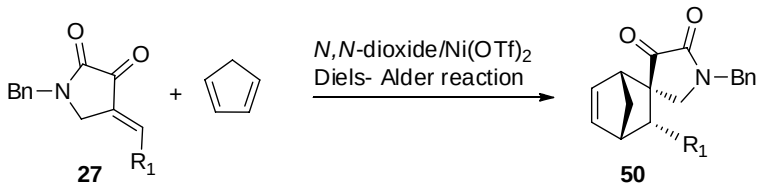
via cascade conjugate addition, intramolecular carbonyl addition, and desulfonative aromatization (cf. Scheme 34) [85].

8. Acylation and Alkylation

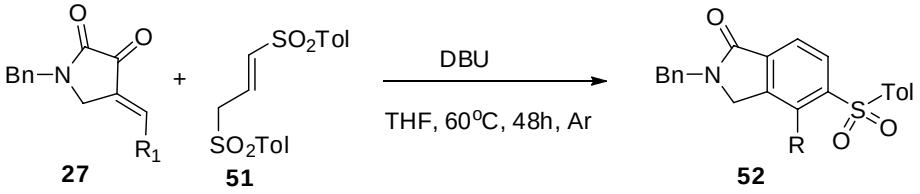
The acetylation of ethyl 1-alkyl-4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (enol structure) **(14)** with ketene produced 3-acetoxy-4-carbethoxy-2-oxo-3-pyrroline **(53)**, which could be used as an acetylating agent. The methyl derivative (**53**, R=CH_3) in the aqueous solution acetylated the sodium *p*-aminobenzoate to sodium 4-acetamidobenzoate (cf. Scheme 35) [76].

The treatment of the enol form **14** with diazomethane led to the methylation of the OH-3 and gave the 3-methoxy derivative **54** in a high yield [67]. Also, dimethyl sulfate methylated 4-carbmethoxy-5-methyl-2,3-dioxopyrrolidines **(13)** yielding the corresponding 3-methoxy-Δ^3- pyrroline **(55)** (cf. Scheme 36) [86].

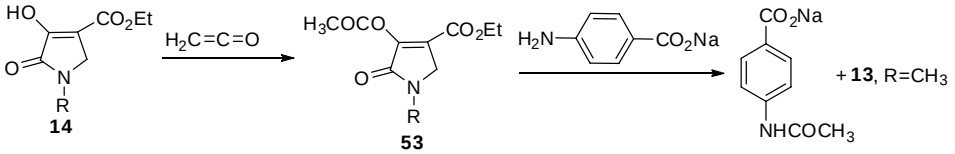
The potassium salt of 1-cyclohexyl-2,3-dioxo-4,5-diphenylpyrrolidine **(7)** and methyl iodide gave 1-cyclohexyl-2,3-dimethoxy-4,5-diphenylpyrrole **(56)** [33]. The alkylation of l,4-dibenzyl-2,3-dioxopyrrolidine **(57)** afforded l,4,4'-tribenzyl-2,3-dioxopyrrolidine **(58)** (cf. Scheme 37) [70].



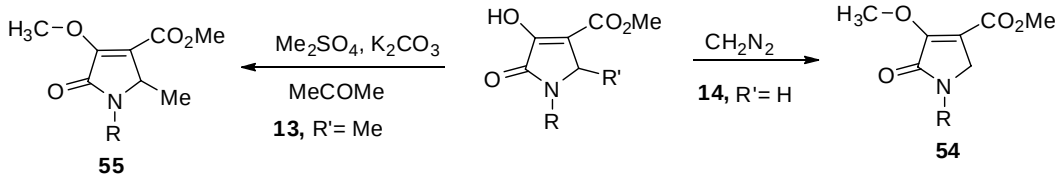
Scheme 33. The reaction **of** 4-arylidene-2,3-dioxopyrrolidines **27** with cyclopentadiene.



Scheme 34. Synthesis of isoindolinones **52** from 4-arylmethylene-2,3-dioxopyrrolidines **27**.



Scheme 35. The acetylation of ethyl 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(14)** with ketene.



Scheme 36. The methylation of the ethyl 4-hydroxy-5-oxo-1*H*-pyrrole-3-carboxylates **(14 & 56)**.

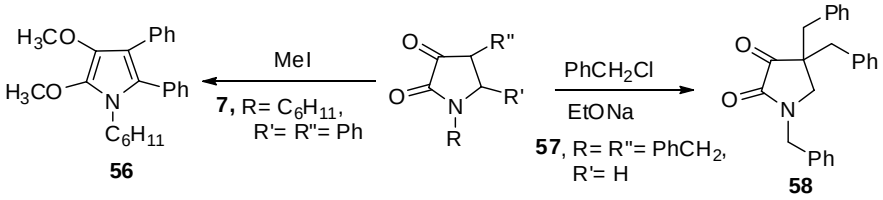
9. Hydrolysis

The 4-carbomethoxy-l-benzyl-2,3-dioxopyrrolidine **(14)** (or the corresponding ethyl ester) was hydrolyzed and decarboxylated by boiling with 20% hydrochloric acid to yield the corresponding 1-benzyl-2,3-dioxopyrrolidine **(22)** [60] and had been used for the preparation of other simple 2,3-dioxopyrrolidines (cf. Scheme 38 [76].

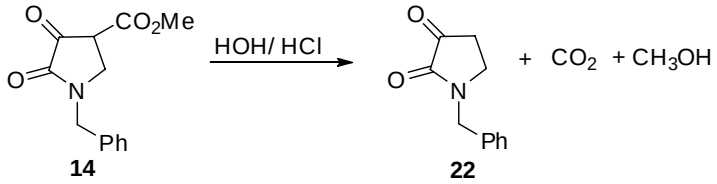
4-Carbethoxy-5-(4-methoxyphenyl)-1-methyl-2,3-dioxopyrrolidine **(13)** (or its enol form) was hydrolyzed and decarboxylated to the parent 2,3-diketone **59** with 68% yield**.** The dioxopyrrlidine **59** was treated with various hydrazine salts to synthesize 2-oxo-5-aryl-3-hydrazone **60** [1, 2], where the hydrazone derivatives of pyrrolidine displayed a variety of interesting biological activities (cf. Scheme 39) [87].

Saponification of 4-carbethoxy-2,3-dioxopyrrolidines **(61)** with 1.0 N aqueous alkali or with alcoholic alkali afforded *N*-oxalyl-β-aminobutyric acid derivatives **62** *via* opening of the pyrrolidine ring (cf. Scheme 40) [63, 86].

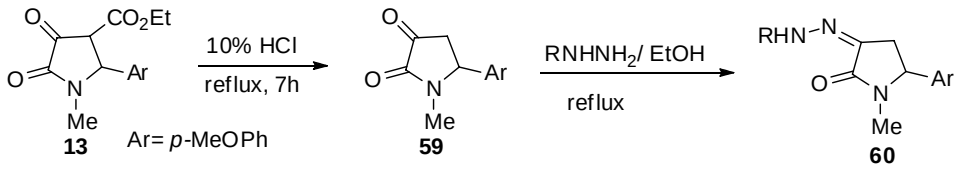
In most cases, the acidic hydrolysis of dioxopyrrolidines under ordinary conditions of temperature was unsuccessful and the starting reactants were obtained again. The 1.0 N (20%)



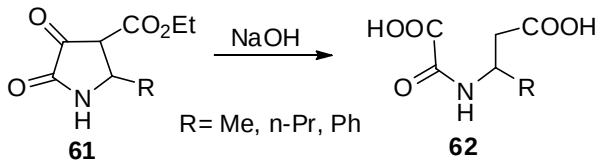
Scheme 37. The alkylation of 2,3-dioxopyrrolidines.



Scheme 38. The preparation of l-benzyl-2,3-dioxopyrrolidine **(22)**.



Scheme 39. The acid hydrolysis and decarboxylation of 4-carbethoxy -2,3-dioxopyrrolidine **(13)**.



Scheme 40. Saponification of 4-carbethoxy-2,3-dioxopyrrolidines **(62)**.

hydrochloric acid as well as 20% hydrochloric acid failed to hydrolyze the dioxopyrrolidine at 100 ºC. The hydrolysis with concentrated hydrochloric acid by heating for 30 minutes was incomplete and most of the original material was unchanged. The parent 4-carbethoxy-5-methyl-2,3-dioxopyrrolidine **(61)** was the only derivative that could be hydrolyzed on heating with concentrated hydrochloric acid and yielded oxalic and β-aminobutyric acids (Scheme 41) [86].

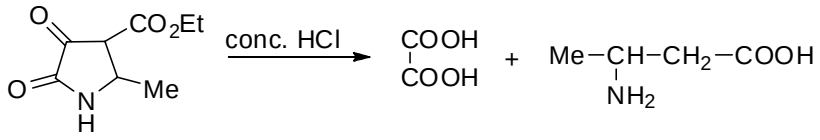
The hydrolysis of the ethyl 5-methyl-2-oxo-3-methoxy-Δ^3-pyrroline-4-carboxylate enol ether **(63)** with alkali led to the formation of 4-carboxy-2-oxo-3-methoxy-5-methyl-Δ^3- pyrroline **(64)**, which was decarboxylated to 2-oxo-3-methoxy-5-methyl-Δ^3-pyrroline **(65)** in the presence of glass powder (cf. Scheme 42) [86].

The removal of the ester group (COOEt) of ethyl 4,5-dioxo-1,2-diphenylpyrrolidine-3-carboxylate **(6)** could be achieved by heating under reflux with nitrobenzene at about 200 °C [62, 87] or methyl benzoate in the presence of some water, followed by cooling and dilution with petroleum-ether (cf. Scheme 43) [88].

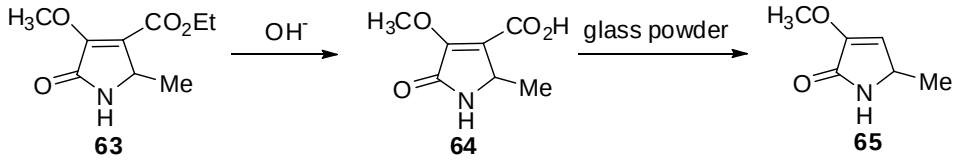
On the other hand, 4-carbethoxy-1,5-diphenyl-2,3-dioxopyrrolidine **(6)** was refluxed with NaH_2PO_2. H_2O and 47% HI in acetic acid to produce 3-hydroxy-1,5-diphenyl-2-pyrrolidone **(66)** (Scheme 44) [89].

10. Halogenation

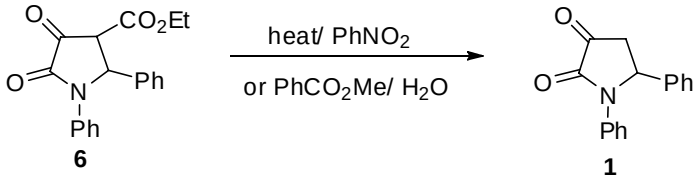
Bromination of 1-substitued-2,3-dioxopyrrolidine **(22)** afforded **74** and/or **75** according to the reaction sequence in Scheme 45 [90].



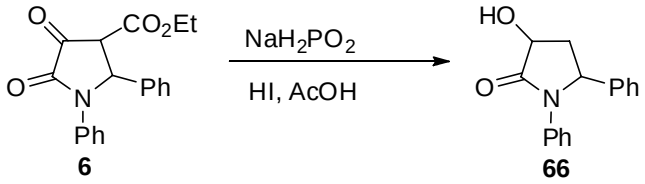
Scheme 41. The acid hydrolysis of 4-carbethoxy-5-methyl-2,3-dioxopyrrolidine **(61)**.



Scheme 42. The hydrolysis of 4-carbethoxy- 5-methyl -3-methoxy-2-oxo -Δ^3-pyrroline **(63)**.



Scheme 43. Preparation of 1,5-diphenylpyrrolidine-2,3-dione **(6)**.



Scheme 44. Hydrolysis, decarboxylation and reduction of 4-carbethoxy-1,5-diphenyl-2,3-dioxopyrrolidine **(6)**.

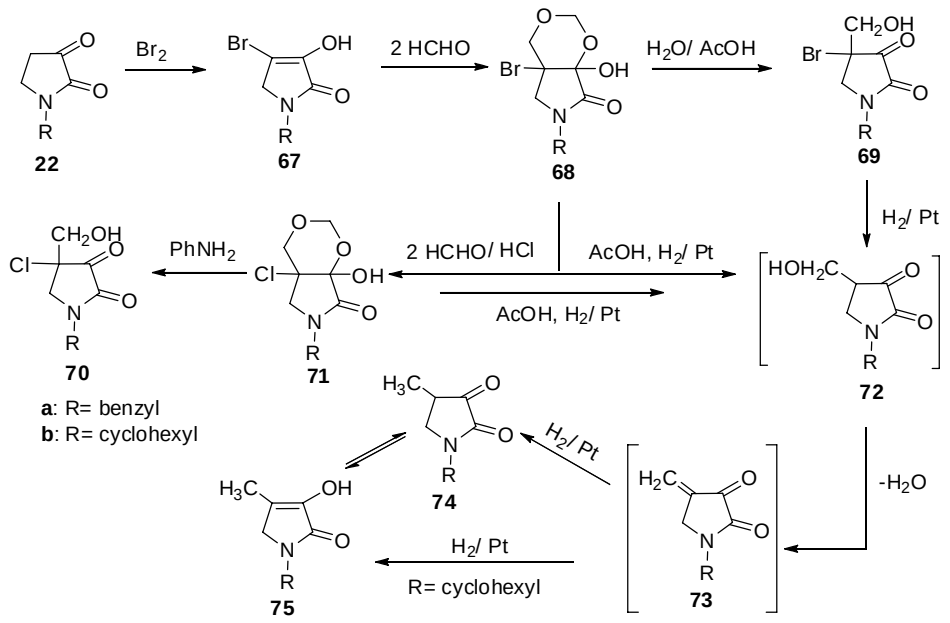
11. Condensation with amines

The 2,3-dioxopyrrolidine cyclic ketones were condensed with the amines giving the expected anil derivatives, which may be produced in the tautomeric anil-enamine forms. Thus, 2,3-dioxopyrrolidines **(22)** reacted with aniline and afforded the corresponding anils of the type **76** [88-91]. However, the reaction with 1-cyclohexyl-2,3-dioxopyrrolidine produced the enamine **76** [76]. Vaughan [32, 45] had proposed the Doebner's "anil-anilide" analogous structure **77** for the reaction of l,5-diphenyl-2,3-dioxopyrrolidine **(1)** and/or its derivatives with aniline (cf. Scheme 46).

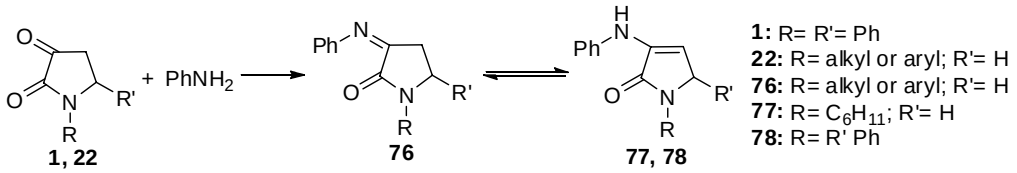
On the other hand, Southwick *et al.* [92] p repared 3,4-dihydroquinazoline alkaloidal system **81** according to the reaction sequence in Scheme 47.

On the same manner the 2-chloro-6-nitrotoluene has been used in the synthesis of DL-chlorovasicine (7-chloro-3-hydroxypeg-9-ene) **(84)** [93] *via* its conversion to 2.3-dioxopyrrolidine **82**, which was hydrolyzed and decarboxylated to the diketone **83** (cf. Scheme 48).

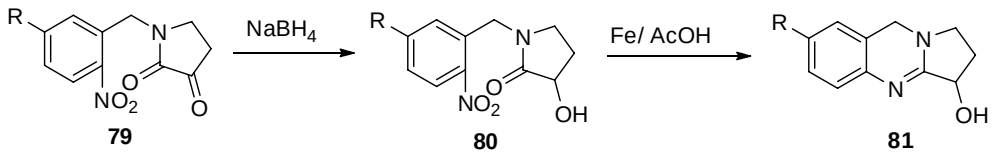
The reaction of the appropriate arylidene pyruvic acid with a primary aromatic amine according to the method of Vaughan and Peters [94] led to the formation of 1,5-diphenyl-3-(phenylamino)-1*H*-pyrrol-2(5*H*)-one **(86)** by treatment with an aromatic amine *via* a simple amine exchange reaction [88].



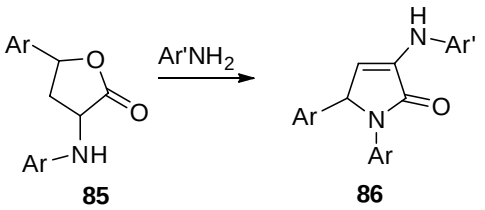
Scheme 45. Bromination of 1-substitued-2,3-dioxopyrrolidine **(22)** and reactions of the product.



Scheme 46. The reaction of 2,3-dioxopyrrolidines **(1, 22)** with aniline.



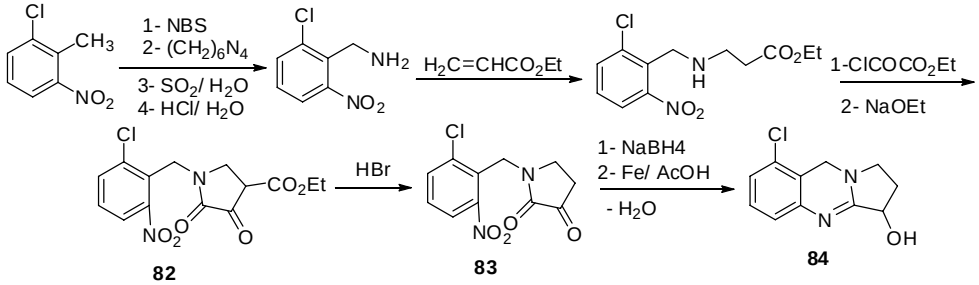
Scheme 47. Synthesis of 3,4-dihydroquinazoline alkaloidal system **81**.



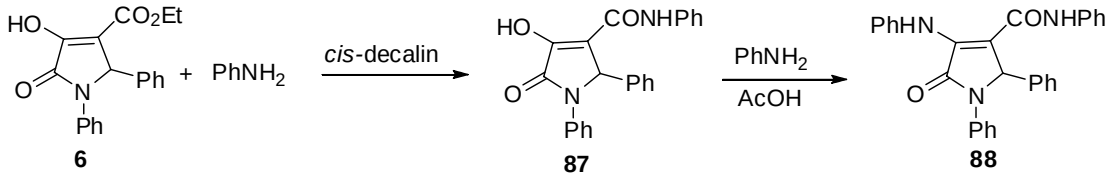
On the other hand, the synthesis of the enamines namely, 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one **(88)** could be achieved by the thermal hydrolytic decarboxylation of ethyl 4,5-dioxo-1,2-diphenylpyrrolidine-3-carboxylate **(6)** in the presence of the amines (cf. Scheme 49) [88].

Moreover, the 1,5-diphenyl-3-phenylamino-4-carboxypiperdido-2(5*H*)-pyrrolone **(91)** could be prepared following the sequence in Scheme 50 [88].

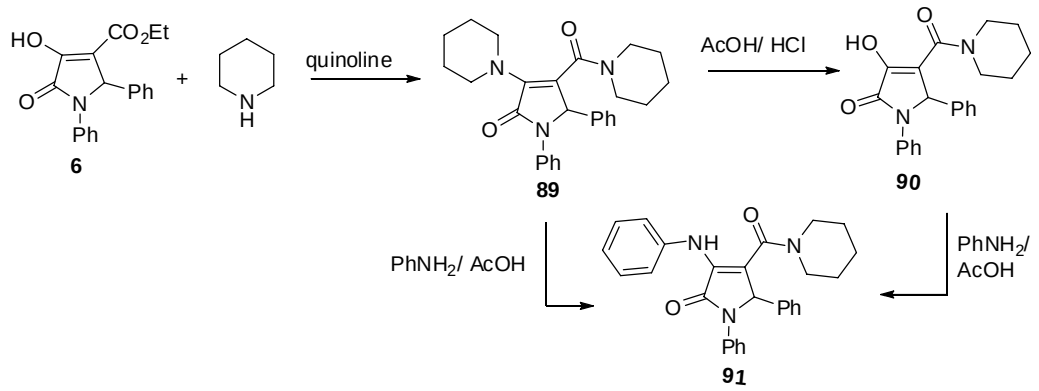
On the other hand, 4-carbomethoxy-2,3-dioxopyrrolidine **(14)** was fused in an oil bath at 90-110 ºC with primary aromatic amines and gave



Scheme 48. Synthesis of DL-chlorovasicine **(84)**.



Scheme 49. The reaction of 4-carbethoxy-1,5-diphenyl-2,3-dioxopyrrolidene **(6)** with aniline.



Scheme 50. Formation of l,5-diphenyl-3-phenylamino-4-carboxypiperdido-2(5*H*)-pyrrolone **(91)**.

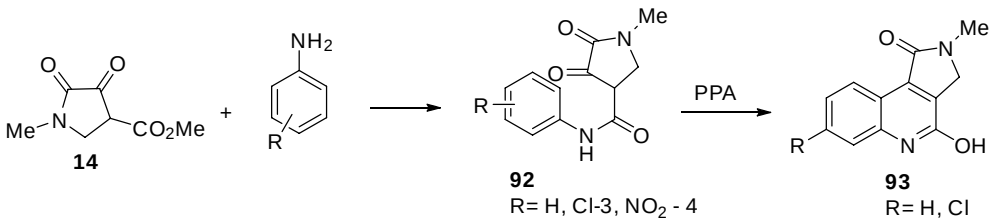
the 4-carbamoyl derivatives **(92)** which were cyclized to pyrrolo [3,4-*c*]quinolines **93** by heating with polyphosphoric acid (PPA) (Scheme 51) [26b].

The diaza-steriodal system **95** was obtained by treatment of compound **14** with α-naphthylamine to produce 4-(1-naphthylcarbamoyl) dioxopyrrolidine **94** followed by cyclization with PPA (Scheme 52) [26b].

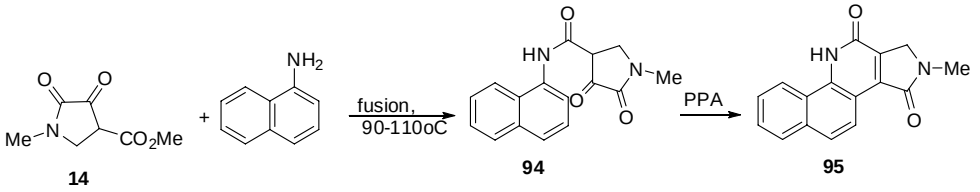
The methyl β-ketoester **14** was condensed with 4*H*-1,2,4-triazol-3-amine and/or 1*H*-tetrazol-5-amine to result in the formation of the pyrrolo[3,4:4,5] 1,2,4-triazolo[2,3-*b*]pyrimidin-8- one **(96)** and pyrrolo [3,4:4,5]tetrazolo[5,1-*b*]pyrimidin-8-one **(97)**, respectively according to their correct analytical and spectral data. Essentially under the same reaction conditions, the condensation of 2,3-dioxopyrrolidine **14** with 2-aminobenzimidazole was carried out to produce the pyrrolo[4,4:4,5]benzimidazo[1,2-*b*]pyrimidin-9-one **(98)** (Scheme 53) [26b].

In addition, the condensation of **14** with 2-amino-5-ethylthiazole and/ or 3-amino-1-phenyl-2- pyrazolin-5-one afforded the linearly fused pyrroloheterocycles **99** and **100**, respectively (Scheme 54) [26g].

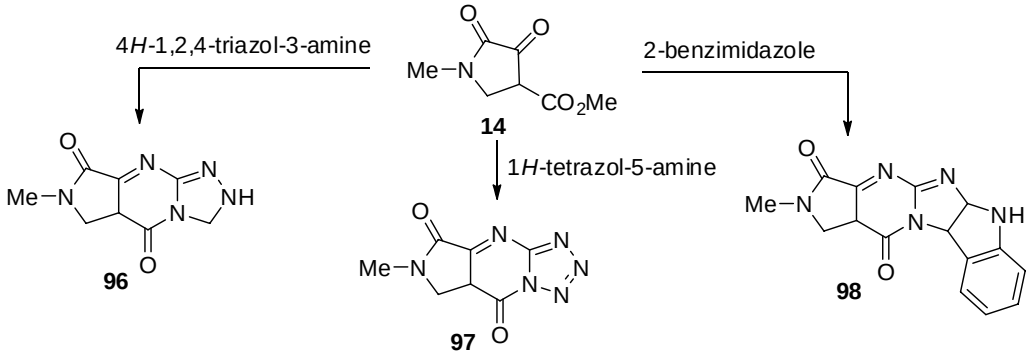
Also, 6-aryl-2-phenyl-7,7a-dihydro-5*H*-pyrazolo [1,5-*a*]pyrrolo[3,4-*d*]pyrimidine-5,8(6*H*)-dione **(102)**



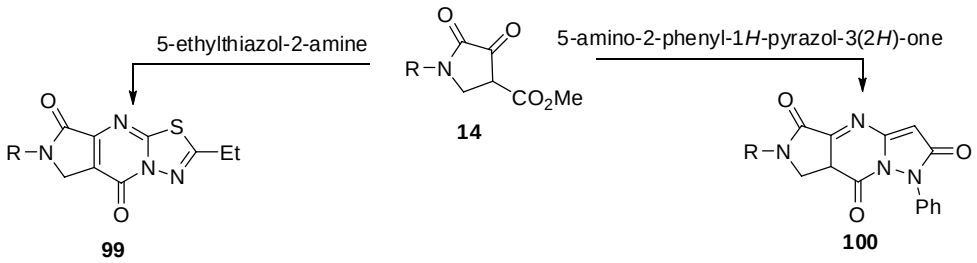
Scheme 51. Formation of 1*H*-pyrrolo[3,4-*c*]quinoline derivatives **(93)**.



Scheme 52. Synthesis of 2-methyl-1H-benzo[h]pyrrolo[3,4-c]quinoline-3,11(2*H*,10*H*)-dione **(95)**.



Scheme 53. Reaction of 4-carbomethoxy-2,3-dioxopyrrolidine **(14)** with aminoazols.

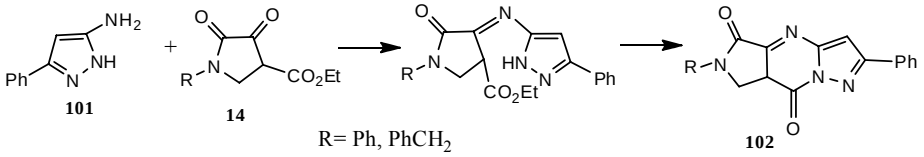


Scheme 54. Reaction of 4-carbomethoxy-2,3-dioxopyrrolidine **(14)** with aminoazols.

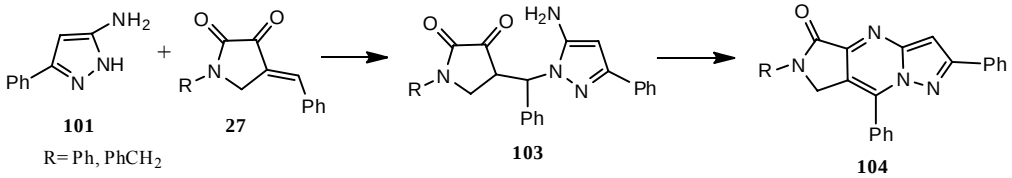
could be synthesized by refluxing of 5-amino-3-phenylpyrazole **(101)** with 1-aryl-4-carbethoxy-2,3-dioxopyrrolidine **(14)** (Scheme 55) [95].

In continuation to this work, the 5-amino-3-phenylpyrazole **(101)** was added to 1-aryl-4-benzylidene--2,3-dioxopyrrolidene **(27)** to form the Michael adduct **103** which spontaneously cyclized and aromatized to the pyrazolopyrimidines **104** (Scheme 56) [95].

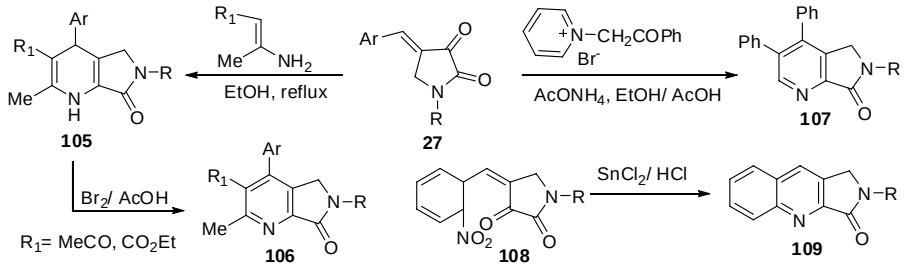
On the other hand, pyrrolo[3,4-*b*]pyridines **106** is



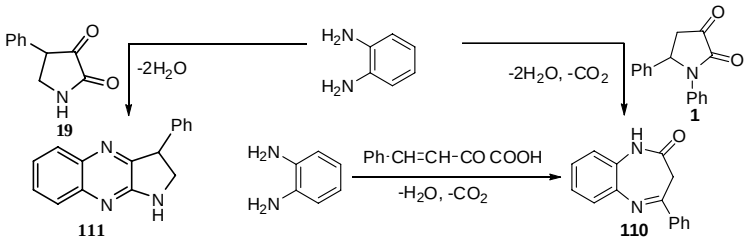
Scheme 55. Reaction of **14** with 5-amino-3-phenylpyrazole.



Scheme 56. Michael addition of 5-amino-3-phenylpyrazole to 4-benzylidenedioxopyrroline **(27)**.



Scheme 57. Synthesis of pyrrolo[3,4-*b*]pyridines **106** & 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-ones**109**.



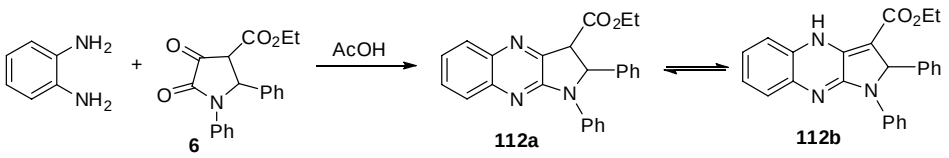
Scheme 58. The reaction of l,5-diphenyl-2,3-dioxopyrrolidine **(1)** with *o*- phenylenediamine.

synthesized according to the reaction sequence in Scheme 57. Moreover, 4-(2-nitrobenzylidene) pyrrolidine-2,3-diones **(108)** spontaneously cyclized to 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-ones**109** upon reducing with stannous chloride at ambient temperature [96].

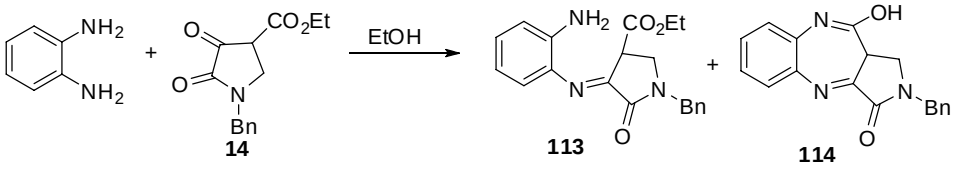
12. Condensation with diamines

The condensation reaction of l,5-diphenyl-2,3-dioxopyrrolidine **(1)** and/or benzylidene pyruvic acid with *o*- phenylenediamine led to the formation of the same product, which was assigned as 4-phenyl-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one **(110)** [32]. In contrast to this behavior, it has been reported that the reaction of *o*-phenylenediamine with 4-phenyl-2,3-dioxopyrrolidine **(19)** resulted in the formation of the quinoxaline derivative **111** (cf. Scheme 58) [64].

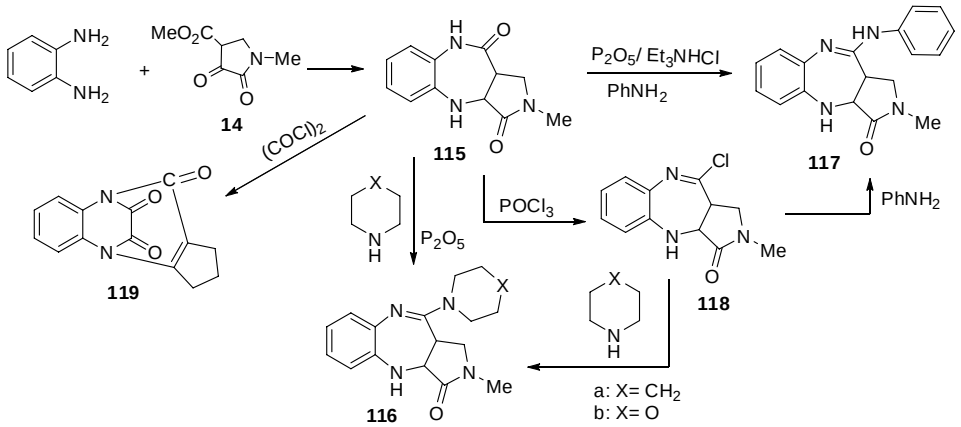
According to the interpretation of the IR spectrum of the reaction product, which showed the



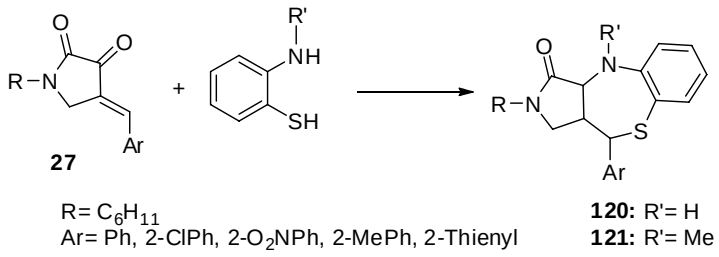
Scheme 59. Formation of 3-carbethoxy-2,3-dihydro-1,2-diphenyl-1-pyrrolo[2,3 -*b*]quinoxaline **(112)**.



Scheme 60. Condensation of l-Benzyl-4-carbethoxy-2,3-dioxopyrrolidine **(14)** with *o*- phenylenediamine.



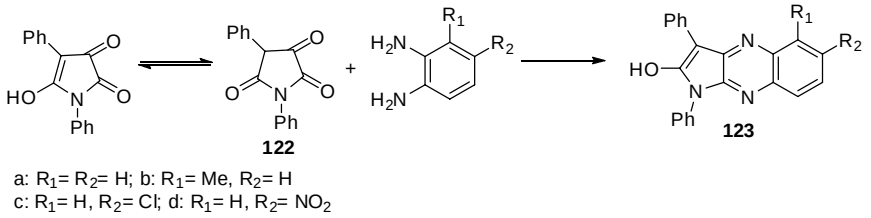
Scheme 61. Reactions of the pyrrolo[3,4-*b*][1,5]benzodiazepinedione derivative **115**.



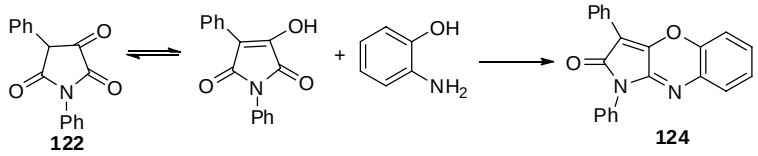
Scheme 62. Synthesis of pyrrolo[3,4-*b*][1,5]benzodiazepinediones **120** and **121**.

absorption bands at 3360 (NH) and 1675 (conjugated ester carbonyl) cm^{-1}, the condensation of 4-carbethoxy-l,5-diphenyl-2,3-dioxopyrrolidine **(6)** and *o*-phenylenediamine under reflux in glacial acetic acid produced 3-carbethoxy-2,3-dihydro-1,2-diphenyl-1-pyrrolo[2,3 -*b*] quinoxaline **(112a)**, or its tautomer **(112b)** (cf Scheme 59) [88].

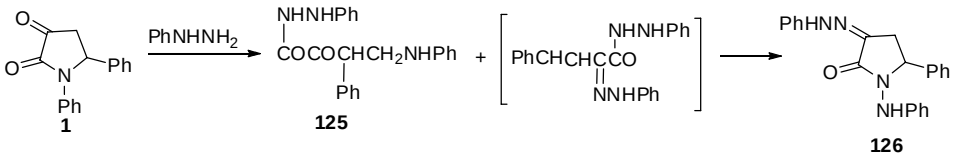
l-Benzyl-4-carbethoxy-2,3-dioxopyrrolidine **(14)** was reacted with *o*- phenylenediamine in ethanol



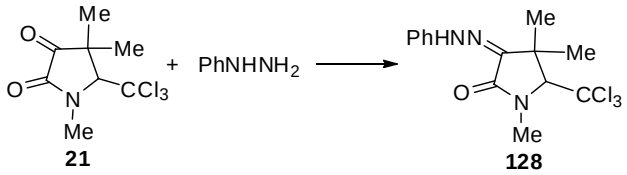
Scheme 63. Synthesis of 1,3-diphenyl-1H-pyrrolo[2,3-b]quinoxalin-2-ols **(123)**.



Scheme 64. Synthesis of 1,3-diphenylbenzo[b]pyrrolo[2,3-e][1,4]oxazin-2(1H)-one **(124)**.



Scheme 65. The action of phenyl hydrazine on1,5-diphenyl-2,3-dioxopyrrolidine **(1)**.



Scheme 66. Formation of 1,4,4-trimethyl-3-(2-phenylhydrazono)-5-(trichloromethyl)pyrrolidin-2-one **(162)**.

giving a mixture of pyrrolobenzodiazepinedione **114** and ethyl 4-((2-aminophenyl)imino)-1-benzyl-5-oxopyrrolidine-3-carboxylate **(113)**, which was converted to **114** on heating (cf Scheme 60) [97].

Sofan [26d] reported on some chemical studies on the pyrrolo[3,4-*b*][1,5]benzodiazepinedione derivative **115**, which could be converted to **116-119** following the reaction sequence in Scheme 61.

The dehydrative cyclization concomitant to the reaction of 2-aminothiophenol with 4-arylidene-1-cyclohexyl-2,3-dioxopyrrolidenes **(27)** under the condition of Michael reaction afforded the pyrrolo [3,4-*c*][1,5]benzothiazepines **(120)**. The synthesis of the methyl derivatives of **(121)** *via* the methylation of **120** with MeI failed; however, these compounds could be prepared by the treatment of 2-methylaminothiophenol as a Michael donor with the arylidene derivatives of 1-substituted-2,3-dioxopyrrolidine (cf Scheme 62) [98].

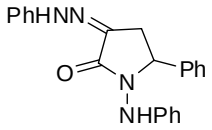
1,4-Diphenyl-2,3,5-trioxopyrrolidine **(122)** was also condensed with *o*-phenylenedianime and its derivatives to yield 1,3-diphenyl-1H-pyrrolo[2,3-b]quinoxalin-2-ol **(123)**, depending on the data of the IR and ^{1}H NMR spectra (cf Scheme 63) [26e].

In the same direction, the benzopyrroloxazine **(124)** could be formed in quantitative yield by condensing **122** with *o*-aminophenol in glacial acetic acid (cf Scheme 64) [26e].

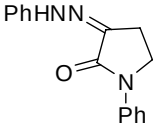
13. Reaction with hydrazines

It has been reported that the condensation reaction of the ketonic carbonyl at C-3 in 1,5-diphenyl-2,3-dioxopyrrolidine **(1)** with phenyl hydrazine led to the formation of the two compounds which were identified as 2-dioxo-*N*',3-diphenyl-4-(phenylamino) butanehydrazide **(125;** dec. at 132°) and 5-phenyl-1-(phenylamino)-3-(2-phenylhydrazono) pyrrolidin-2-one **(126;** melted at 230 °C) as the reaction products (cf Scheme 65) [31, 32, 36, 44, 99, 100].

According to the conclusion of Southwick *et al*. [76], most of the l-substituted-2,3-dioxopyrrolidines condensed with phenylhydrazine to give products corresponding in composition to the formula "1-phenyl-3-(2-phenylhydrazono)pyrrolidin-2-one" 127. However, Vaughan and McCane [45], reported that treatment of 1,5-diphenylpyrrolidine-2,3-dione with phenyl hydrazine gave 5-phenyl-1-(phenylamino)-3-(2-phenylhydrazono)pyrrolidin-2-one 126 as the reaction product.



126



127

The condensation reaction of 5-trichloromethyl-1,4,4-trimethyl-2,3-dioxopyrrolidine **(21)** with phenylhydrazine resulted in the formation of the expected C-3 mono(phenylhydrazone) **128** (cf Scheme 66) [67].

14. Conclusion

This review showed the most important methods for the synthesis of pharmaceutically potent 2,3-dioxopyrrolidines, which also form the main moiety in a variety of bioactive compounds. In spite of the presence of literature reports that describe many types of natural or unnatural dioxopyrrolidines and their modification, the reports that investigated the condensed heterocycles having fused 2,3-dioxopyrrolo nucleus are infrequent. Therefore, this review has focused on the preparation and exploration of 2,3-dioxopyrrolidines's synthetic potentialities as key intermediates for the synthesis of fused heterocycles with a pyrrolo nucleus that have medicinal and industrial interest.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

REFERENCES

1. Mohammat, M. F., Najim, N., Mansor, N. S., Sarman, S., Shaameri, Z., Zain, M. M. and Hamzah, A. S. 2011, ARKIVOC, ix, 429-438.
2. Mohammat, M. F., Shaameri, Z. and Hamzah, A. S. 2009, Molecules, 14, 250-256.
3. Shorvon, S. 2001, Lancet, 358, 1885.
4. Pandeya, S. N., Sriram, D., Nath, G. And De Clereq, E. 1999, Farmaco (Societa Chimica Italiana, 54(9), 624-628.
5. El-Masry, A. H., Fahmy, H. H. and Abdel wahed, S. H. A. 2000, Molecules, 5(12), 1429-1438.
6. Watson, A. A., Fleet, G. W. J., Asano, N., Molyneux, R. J. and Nash, R. J. 2001, Phytochemistry, 56, 265-295.
7. Asano, N. 2003, Curr. Top. Med. Chem., 3, 471.
8. Asano, N., Nash, R. J., Molyneux, R. J. and Fleet, G. W. 2000, Tetrahedron Asymmetry, 11(8), 1645-1680.
9. Khanov, M. T., Sultamov, M. B. and Egorova, T. A. 1971, 210; Chem Abstr 1972, 135091r.
10. Winchester, B. and Fleet, G. W. 1992, Glycobiology, 2, 199.
11. Mylari, B. L., Beyer, T. A. and Siegel, T. W. 1991, J. Med. Chem., 34(3), 1011-8
12. Makani, S. H. S. and Sugden, J. K. 1980, Arzneium-Forsch Drug Res., 30(11), 1135-37.
13. (a) Tsuda, Y. and Isobe, K. J. 1971, Chem. Soc. D, 1555-1556. (b) Tsuda, Y., Ukai, A. and Isobe, K. 1972, Tetrahedron Lett., 13, 3153.
14. (a) Sano, T., Toda, J. and Tsuda, Y. Heterocycles 1982, 18(1), 229-232. (b) Sano, T., Horiguchi, Y., Tsuda, Y., Furuhata, K., Takayanagi, H. and Ogura, H. 1987, Chem Pharm Bull, 35(1), 9-22.
15. (a) Hurley, L. H., Reck, T., Thurstan, D. E., Langley, D. R., Holden, K. G., Hertzberg, R. P., Hoover, J. R. E., Gallagher Jr, G. and Faucette, L. F. 1988, Chem. Res. Toxicol., 1, 5, 258-268. (b) Remers, W. A. 1988, John Wiley: New York, Vol. 2, 28-92.
16. Hurley, L. H. and Thurston, D. E. 1984, Pharm. Res., 1, 52-59.
17. (a) Metten, B., Kostermans, M., Van Baelen, G., Sment, M. and Dehaen, W. 2006,

Tetrahedron, 62(25), 6018-6028. (b) Mohammat, M. F., Shaameri, Z., Hamzah, A. S., Fun, H. K. and Chantrapromma, S. 2008, Acta crystallographica. Section E, Structure Reports Online, 64(Pt 4), o661-2.
18. (a) Southwick, P. L. and Cremer, S. E. 1959, The Journal of Organic Chemistry 24(6), 753-755. (b) Southwick, P. L. and Casanova, J. Jr. 1958, Journal of the American Chemical Society, 80(5), 1168-1173
19. Veeresa, G. and Datta, A. 1998, Tetrahedron, 54(51), 15673-15678.
20. Huang, P.-Q. and Zheng, X. 2003, ARKIVOC, 2003(ii), 7-14.
21. Wang, Y. and Ma, D. 2001, Tetrahedron Asymmetry, 12(5), 725-730.
22. (a) Mohammat, M. F., Mansor, N. S., Shaameri, Z. and Hamzah, A. S. 2015, J. Korean Chem. Soc., 59(1), 31-35. (b) Kotkar, S. P., Chavan, V. B. and Sudalai, A. 2007, Org. Lett., 9(6), 1001-1004. (c) Sugiyama, M., Hong, Z., Liang, P. H., Dean, S. M., Whalen, L. J., Greenberg, W. A. and Wong, C. H. 2007, J. Am. Chem. Soc., 129(47), 14811-14817. (d) Tsou, E. L., Chen, S. Y., Yang, M. H., Wang, S. C., Cheng, T. R. and Cheng, W. C. 2008, Bioorg. Med. Chem., 16(24), 10198-10204.
23. Zhang, E., Bai, P. Y., Sun, W., Wang, S., Wang, M-M. and Xu, S-M. 2016, Carbohydr. Res., 434, 33-36.
24. Doddi, V. R. and Vankar, Y. D. 2007, Eur. J. Org. Chem., 33, 5583-5589.
25. Bacho, M. Z., Mohammat, M. F., Shaameri, Z., Wibowo, A., Kamarulzaman, F. and Hamzah, A. S. 2020, Orient. J. Chem., 36(2), 309-319.
26. (a) Sofan, M. A., Fouda, A. M. and Afsah, E. M. 2004, Polish J. Chem., 78, 837-842. (b) Sofan, M. A. 1997, Pharmazie, 52(4), 276-278. (c) Sofan, M. A., Mashaly, M. M., El-Shamy, N. Y. and El-Hossini, M. S. 1997, Polish J.Chem., 71(2), 196-200. (d) Sofan, M. A. 1996, Pharmazie, 51(8), 548-550. (e) Metwally, M. A. and Sofan, M. A. 1990, Zeitschrift für Naturforschung B., 45(3), 382-384. (f) El-Ablak, F. Z., Abu-Elenein, N. S. and Sofan, M. A. 2016, J. Heterocyclic Chem., 53, 1999. (g) Sofan, M. A., Etman, H. A. and Metwally, M. A. 1988, Pakistan J. Sci. Ind. Res., 31, 471. (h) Sofan, M. A. 1985, Ph. D. Thesis, Fac. of Sci.Mansoura University, Egypt.
27. Vaughan, W. R. and Peters L. R. 1953, J. Org. Chem., 18, 382-392.
28. El-Maati, T. M. 1999, Boll. Chim. Farm., 138(6), 272-9.
29. Johnson, J. R. and Adams, R. 1923, J. Am. Chem. Soc., 45(5), 1307-1315.
30. Vaughan, W. R. and Peters L. R. 1953, J. Org. Chem., 18(4), 405-421.
31. Bucherer, H. T. and Russischwili, R. 1930, J. Prakt. Chem., 128, 89.
32. Bodforss, S. 1927, Ann., 455, 41-69, 1927, Chem. Abstr., 21, 2902.
33. Skita, A. and Wulff, C. 1927, Ann., 455, 17.40; 1927, Chem. Abstr., 21, 2882.
34. Doebner, O. 1887, Ann. 242, 265, 1899, Ber., 20, 278; Doebner, O. and GiesKe, M., 1887, Ann., 242, 290.
35. Schiff, R. and Bertini, C. 1897, Ber., 30, 601.
36. Borsche, W. 1908, Chem. Ber., 41(3), 3884-3894.
37. Dohrn, M. and Thielee, A. 1931, Ber., 64B, 2863-5. 1932, Chem. Abstr. 26, 1928.
38. Schiff, R. and Gigli, L., 1898, Ber., 31, 1306.
39. Borsche, W. 1909, Chem. Ber., 42(3), 4072-4088.
40. Braude, E. A. 1945, Ann. Repts. on progress Chem. (Chem. Soc. London), 42, 105-30.
41. French, H. S. and Holden, M. E. T. 1945, J. Am. Chem. Soc., 67(8), 1239-1242
42. Gillam, A. E. and West, T. F. 1942, J. Chem. Soc., 486-488
43. Meyer, W. L. and vaughan, W. R. 1957, J. Org. Chem., 22(1), 98-99. https://doi.org/10.1021/jo01352a618
44. Garzarolli-Thumlackh, 1899, Monatsh, 20, 480.
45. Vaughan, W. R. and McCane, D. I. 1955, J. Org. Chem., 20(2), 143-154.
46. Mlle, W., Jakobson, R. and Dawidowicz, B. 1929, Roczniki Chem., 9, 661-5; 1930, Chem. Abstr. 24, 3017.
47. Minchilli, M. 1948, accad. Atti e relaz Pugliese Sci., 6, 511-16; 1952, Chem. Abstr.,46, 113.
48. Di fonzo, M. Saracini, C., 1955, It. Farmco. (Pavia) Ed. Sci. 10, 528-31, 1956, Chem. Abstr., 50, 8639b.

49. Musante, C. and Fatutta, S. 1958, Gazz. Chim. Ital. 88, 879-98. 1959, Chem. Abstr. 53, 18943g.
50. Borsche, W. and Manreuffel, R. 1937, Ann., 526, 22-46, Chem. Abstr., 31, 405.
51. Borsche, W. and Butschli, L. 1937, Ann., 529, 266-73, Chem Abstr., 31, 5363.
52. Borsche, W. and Wagner - Roemmich, M. 1940, Ann., 544, 280-6, 1941, Chem. Abstr., 35, 118.
53. Misani, F. and Bogert, M. T. 1945, J. Org. Chem., 10, 458-63.
54. Borsche, W. and Doeller W. 1944, Ber. 76B, 1176-9; 1945, Chem. Abstr. 39, 1413.
55. Borsche, W. and Doeller, W. 1938, Ann., 537, 39-52; 1939, Chem. Abstr. 33, 1738.
56. Borsche, W. And Doeller, W. IV. 1938, Ann., 537, 53-66; 1939, Chem. Abstr., 33, 1739.
57. Keskin, H. 1946, Rev. Faculte Sci. Univ. Istanbul,11A, 112, 1-23; 1946, Chem. Abstr., 40, 5427.
58. Afsah, E. M., Etman, H. A. Hamama, W. S. and Sayed, A. F. 1995, Boll. Chim. Farm., 134, 281-284.
59. Schering A. – G. 1939, Ger., 678, 152, 11, 1939 (Cl. 12 P.2); 1939, Chem. Abstr., 33, 7963
60. Southwick, P. L. and Crouch, R. T. 1953, J. Am. Chem. Soc., 75(14), 3413-3417.
61. Musante, C. And Stener, A. 1956, Gazz. Chim Ital., 86, 1111-23; 1958, Chem. Abstr., 52, 3770e.
62. Vaughan, W. R. and Covey, I. S. 1958, J. Am. Chem. Soc., 80, 2197-2201.
63. Ustik, A. and Duranti, E. 1958, Ricera Sci., 28, 259-2. 1959, Chem. Abstr., 53, 17999.
64. Rupe, H. and Pieper, B. 1929, Helv. Chim. Acta, 12, 637-49; 1929, Chem. Abstr., 23, 4463.
65. Merchant, J. R. and Bhandarkar, R. M. 1963, J. Indian. Chem. Soc., 40(5), 353-58.
66. Merchant, J. R. and Srinivasan, V. 1962, Recueil, 81, 144-155.
67. Morimoto, T. and Sekiya, M. 1979, Chem. Pharm. Bull., 27(7), 1697-700.
68. Sundberg, R. J., Pearce, B. C. and Laurino, J. P. 1986, J. Heterocycl. Chem., 23, 537-539.
69. Goel, O. P., Krolls, U. and Lewis, E. P. 1985, Org. Prep. Proced. Int., 17, 91-97.
70. Southwick, P.L., Barnas, E.F. 1962, J. Org. Chem., 27(1), 98-106.
71. Singh, M. and Sugden, J. K. 1968, Chem. & Ind., 845.
72. Makani, S. H. S., Sugden J. K. R., Snyder C. A. and Southwick, P. L. 1980, J. Heterocyclic Chem., 17, 1231.
73. Madhav R., Snyder, C. A. and Southwick, P. L. 1980, J. Heterocyclic Chem., 17, 1231.
74. Singh, M. and Sugden, J. K. 1971, J. Med. Chem., 14(1), 76-78.
75. Andreichikov, Yu. S., Gein, V. L. and Anikina. I. N. U.S.S.R.S.U 1,121, 258 (Cl. Co. 7D. 207144, 1984, Otkrytiya Izobret. 40, 64, 1985, Chem. Abstr., B 102, 203871g.
76. Southwick, P. L., Previc, E. F., Casanova, JR. J. and Carlson, E. H. 1956, J. Org. Chem., 21(10), 1087-1095.
77. Meyer, W. L. and Vaughan, W. R. 1957, J. Org. Chem., 22(12), 1554-1560.
78. Zhang, S., Hu, X.-Q., Wang, Z.-Q. and Xu, P.-F. 2015, Synthesis, 47(17), 2529- 537.
79. Li,Y., Li, Q.-Z., Huang, L., Liang, H., Yang, K.-C., Leng, H.-J., Liu, Y., Shen, X.-D., Gou, X.-J., Li, J.-L. 2017, Molecules, 22, 328.
80. Wen, J.-B. and Du, D.-M. 2020, Org. Biomol. Chem., 18, 1647.
81. Huang, Y., Zha, Z. and Wang, 2020, Z. Org. Lett., 22, 2512-2516.
82. Chen, X., Zhu, L., Fang, L., Yan, S. and Lin, 2014, J. RSC Adv., 4, 9926-9934.
83. Zhang, S., Luo, Y.-C., Hu, X.-Q., Wang, Z.-Y, Liang, Y.-M. and Xu, P.-F. 2015, J. Org. Chem., 80(14), 7288-7294.
84. Lu, Y., Zhou, Y., Lin, L., Zheng, H., Fu. K., Xiaohua Liu, X. and Xiaoming Feng, X. 2016, Chem. Commun., 52, 8255.
85. Tang, X.-z., zhou, J.-x., Liang, H.-j., Xue-jing Zhang, X.-j., Yan, M. and Chan, A. S. C. 2019, Tetrahedron Letters, 60(2), 147-149.
86. Merchant, J. R., Srinivasan, V., and Bhandarkar, R. M. 1963, Indian J. Chem. l, 165-167.
87. Wang, C. L. J. and Calabrese, J. C. 1991, J. Org. Chem., 56(14), 4341-4343.
88. Vaughan, W. R. and Tripp, R. C. 1960, J. Am. Chem. Soc., 82, 4370-6.
89. Wasserman, H. H. And Koch, R. C. 1962, J. Org. Chem., 27(1), 35-39
90. Soduthwick, P. L. and Vida, J. A. 1962, J. Org. Chem., 27(9), 3075-3079
91. Cassaday, S. A. and Bogert, M. T. 1941, J. Am. Chem. Soc., 63(3), 703-708

92. Southwick, P. L. and Casanova, Jr. J. 1958, J. Am. Chem. Soc., 80(5), 1168-1173
93. Southwick P. L. and Cremer, S. E. 1959, Org. Chem., 24(6), 753-755.
94. Meiwald, J. and Chapman, O. L. 1950, J. Am. Chem. Soc., 72, 633.
95. Sofan, M. A., El-Taweel, F. M. A., Abu El- Maati. and El- Agamey, A.- G. 1994, Indian J. Chem., 33B, 738-741.
96. Madhav R. 1974, J. Chem. Soc., Perkin Trans., 1, 2108-2110.
97. Morosawa, S. 1958, Bull Chem. Soc. Japan, 31, 418-22.
98. Keizo, M., Mariko K. and Sachiko, U. 1993, Chem. Express, 8(9), 773-776.
99. Ciusa, A. 1911, Gazz. Chim.Ital., 44, 144.
100. (a) Vejdelk, Z. J., Protiva, M. 1964, Cesk. Farm., 13(76), 1964, Chem Abstr., 10, 10662. (b) Armarego, W. L. F., Milloy, B. A. and Sharma. 1972, Chem. Soc., Perkin Trans., 1, 2485-2490.