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Review Article

SUCCINIMIDES: SYNTHESIS, REACTION AND BIOLOGICAL ACTIVITY

M. M. PATIL[1], S. S. RAJPUT[2]*

[1]Department of Chemistry, PSGVPM's ASC College, Shahada 425409, Maharashtra, India.[2]Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha 425408 Maharashtra, India.

Email: rajputss65@gmail.com

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ABSTRACT

This review summarizes the synthetic methods, reactions and biological application of important pharmacological succinimides and summarizes recent developments in their derivatives such as dichlorodiformyl, Schiff base, chalcone, Barbier type allylation etc. Over the last years. The biological activity of the cyclic imides is also briefly discussed. Formation of succinimidyl radicals and Single crystal studies on this type of compounds are beyond the scope of this review and will not be discussed. Nor referenced.

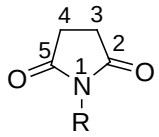
Keywords: Succinimides, Biological activity, Dichlorodiformyl, Cyclic imides.

INTRODUCTION

Substituted succinimides are important compounds of many drugs and drug candidates. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Cyclic imides and their derivatives contain an imide ring and the general structure –CO–N(R)–CO–, so they are cross biological membranes in vivo [1].

A diversity of biological activities and pharmaceutical uses have been attributed to them, such as succinimide is a part of many active molecules possessing activities such as CNS depressant [2], analgesic [3], antitumor [4], cytostatic [5], anorectic [6], nerve conduction blocking [7], antispasmodic [8], bacteriostatic [9], muscle relaxant [10], hypotensive [11], antibacterial [l2], antifungal [13], anti-convulsant [14] and anti-tubercular [15].

Substituted succinimide moiety **1** appears as an interesting precursor of many biologically active of the above class compounds.



1

where R= aliphatic or aromatic

This review provides an overview of the synthesis and reactivity of succinimides and derivatives. In the first part we intend to outline the general methods by which substituted succinimides are prepared. The second and third parts are devoted to the chemical reactivity of substituted succinimides.

Synthetic methods

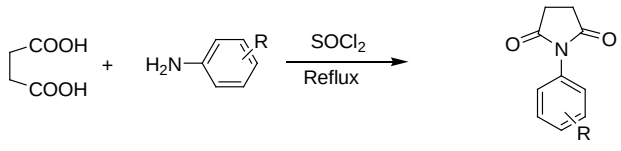
There have been a number of practically important routes to synthesize succinimides.

From succinic acid using $SOCl_2$

A well-established route for the synthesis of 1-substituted phenyl pyrrolidine-2,5-dione **4** was reported by condensation of succinic acid **2** and primary aromatic amine **3** using $SOCl_2$ under reflux condition (Scheme 1) [16].

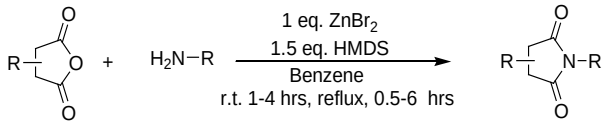
From cyclic anhydride using Lewis Acid

The convenient method was reported for the direct synthesis of substituted succinimides in which succinic anhydride **5** treated with amine **6** using Lewis acid catalyst in the presence of Hexamethyl disilazane (HMDS) in benzene afforded the substituted succinimides **7** (Scheme 2) [17].



2 **3** **4**

Scheme 1

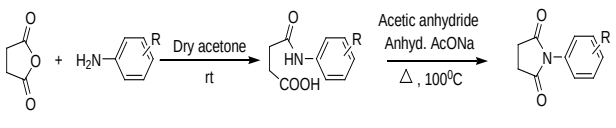


5 **6** **7**

Scheme 2

In dry acetone with acetic anhydride in anhydrous CH_3COONa

Reactions were studied and reported the synthesis in mild condition in which succinic anhydride **8** condensed with substituted aromatic amines **9** gives imic acid intermediate **10,** which on cyclization with the help of acetic anhydride in anhydrous sodium acetate at 100^{0}C gives N-phenyl succinimides **11** (Scheme 3) [18].

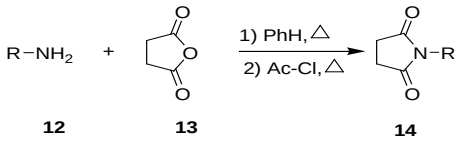


8 **9** **10** **11**

Scheme 3

From cyclic anhydride and amine in the presence of acetyl chloride

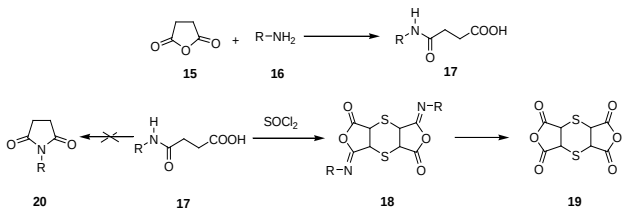
Treatment of amines **12** with succinic anhydride in the presence of benzene using acetyl chloride as dehydrating agent furnished succinimides **14** (Scheme 4) [19].



Scheme 4

Cyclic anhydride and $SOCl_2$

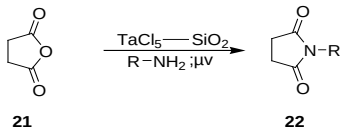
When imic acid **17** undergoes cyclization in the presence of $SOCl_2$, it gives product dithiin diisoimides **18** and diimides **19** instead of formation of N-substituted cyclic imides **20** (Scheme 5) [20].



Scheme 5

Solvent free synthesis in $TaCl_5$-Silica gel

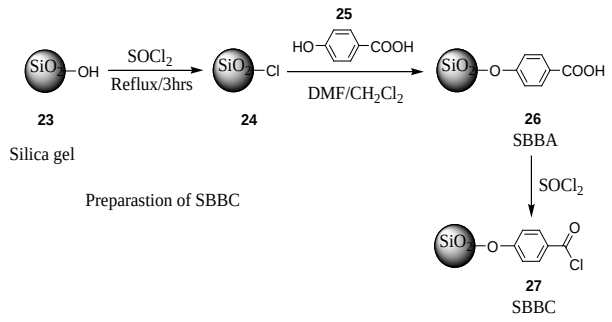
The new protocol developed for the synthesis of succinimide **22** from succinic anhydride **21** in solvent free condition using silica gel. The reaction is catalyzed by Lewis acid- $TaCl_5$. (Scheme 6) [21].



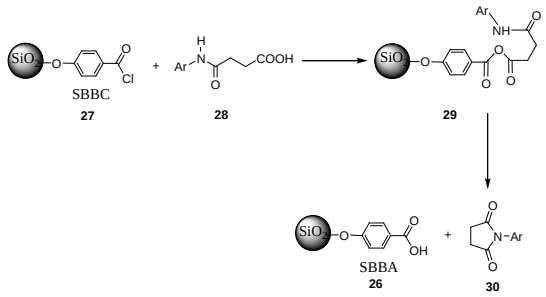
Scheme 6

Solid phase synthesis using SBBC

A new method upon adopting a solid-phase strategy for the synthesis of N-aryl succinimides **30** was described using the silica-bound benzoyl chloride (SBBC) **27** (Scheme 7) as dehydrating agent in reaction with N-arylsuccinamic acids **28** (Scheme 8) [22]. The main advantage of this method is the recyclability of SBBC.



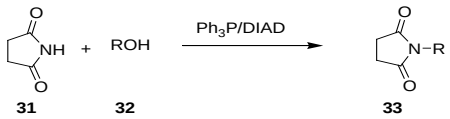
Scheme 7



Scheme 8

High Yield synthesis using a modification of Mitsunobu reaction

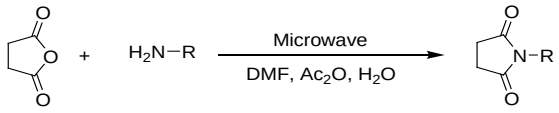
Modified Mitsunobu reaction used for the synthesis of N-substituted succinimide **33** using reaction between succinimide **31** and alcohol **32** in the presence of triphenyl phosphine and diisopropyl azodicarboxylate (DIAD) as a reagent. (Scheme 9) [23].



Scheme 9

Microwave assisted preparation of cyclic imides

Microwave-assisted preparation of substituted succinimide **36** was performed by reacting succinic anhydrides **34** and amine **35**. The reaction was carried out in solvent DMF, acetic anhydride or water. The yield reported by microwave assisted reaction was excellent as compared to conventional method. (Scheme 10) [24].

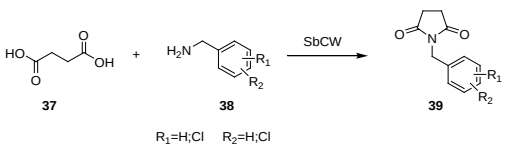


R=benzyl; R=$(CH_2)_6$; R=4-methyl phenyl; R=4,4'-methanediphenyl; R=1-naphthyl

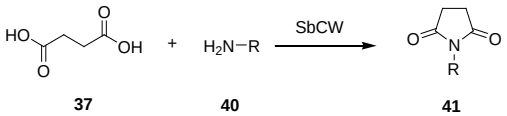
Scheme 10

Clean and efficient synthesis in sub critical water

An alternative, fast and clean method was reported using sub-critical water for the synthesis of substituted succinimide **41** by reaction of succinic acid **37** with aniline **40** in water at 280ºC in 30 min with high yield (Scheme 11 and 12) [25].



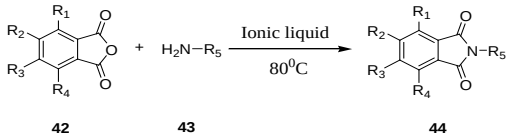
Scheme 11



Scheme 12

Synthesis using Ionic liquid

N-alkyl and N-arylimides **44** were synthesized from cyclic imides **42** and alkyl or aryl amine **43** efficiently under mild reaction conditions in the presence of ionic liquids. The use of ionic liquids offer improvements for the synthesis of cyclic imides with regard to the yield of products, simplicity in operation, short reaction times and green aspects by avoiding toxic catalyst and organic solvents (Scheme 13) [26].

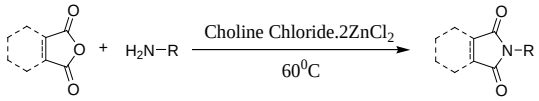


42 **43** **44**

Scheme 13

Synthesis using Lewis acid Choline Chloride.2ZnCl$_2$

The reaction of succinic anhydride **45** with aniline **46** using Lewis acidic ionic liquid Choline Cloride.2ZnCl$_2$ gave N-phenylsuccinimide **47** in good yield under mild condition (Scheme 14) [27].

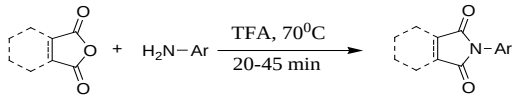


45 **46** **47**

Scheme 14

Facile synthesis using Trifluroacetic acid

A mixture of anhydride **48** and aromatic amine **49** in trifluoroacetic acid as reaction medium and promoter was refluxed at 70^{0}C for appropriate time to obtain succinimides **50** (Scheme 15) [28].

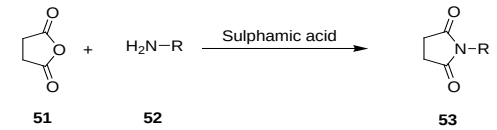


48 **49** **50**

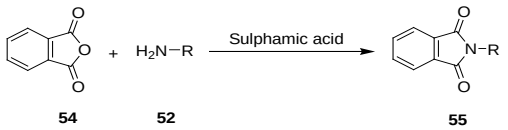
Scheme 15

One Pot Synthesis of N-alkyl and N-arylimides using Sulphamic Acid

One pot method was reported for the synthesis of succinimides **53** by reacting succinic anhydride **51** in situ with aromatic or aliphatic amines **52** using 10 % sulphamic acid as a catalyst (Scheme 16) [29].



51 **52** **53**

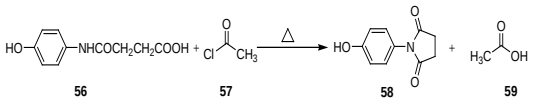


54 **52** **55**

Scheme 16

Synthesis using substituted succinamic acid and acetyl chloride

The synthesis of N(4-hydroxyphenyl)-succinimide **58** was prepared from N(4-hydroxyphenyl)- succinamic acid **56** using acetyl chloride **57** as dehydrating agent (Scheme 17) [30].



56 **57** **58** **59**

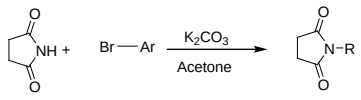
Scheme 17

Synthesis using aromatic halide and succinimide

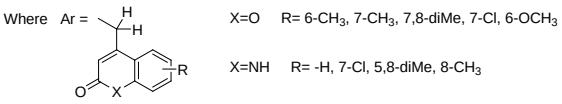
Marulashiddaiah et. al. reported the direct synthesis of N-substituted succinimides **62** from succinimide **60** and halide of coumarins and azocoumarins **61** under K_2CO_3 in acetone (Scheme 18) [31].

From succinic acid using EDC

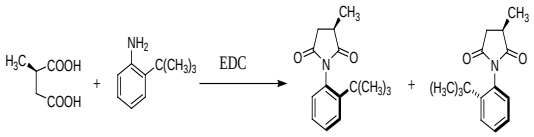
A novel approach of asymmetric deprotonation strategy to the synthesis of chiral succinimides results atroposomeric imides **65** and **66** was reported, starting from (R)-2-methyl succinic acid **63** and orthoisobutylaniline using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (Scheme 19) [32].



60 **61** **62**



Scheme 18

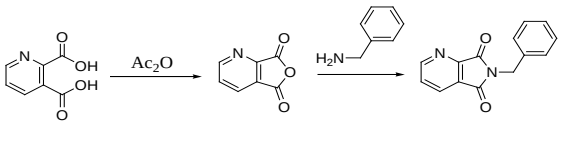


63 **64** **65** **66**

Scheme 19

Using aromatic dicarboxylic acid

The synthesis of C7 side chain began with the formation of anhydride **68** from pyridine-2,3-dicarboxylic acid **67** and acetic anhydride (Scheme 20) [33].

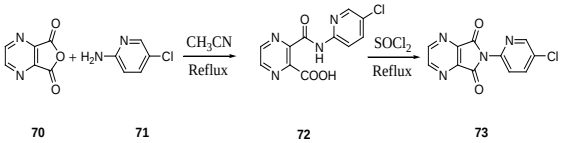


67 **68** **69**

Scheme 20

Using pyrazine anhydride and 2-amino-5-chloropyridine

The treatment of pyrazine anhydride **70** with 2-amino-5-chloropyridine **71** gave amide **73** in good yield (Scheme 21) [34].



70 **71** **72** **73**

Scheme 21

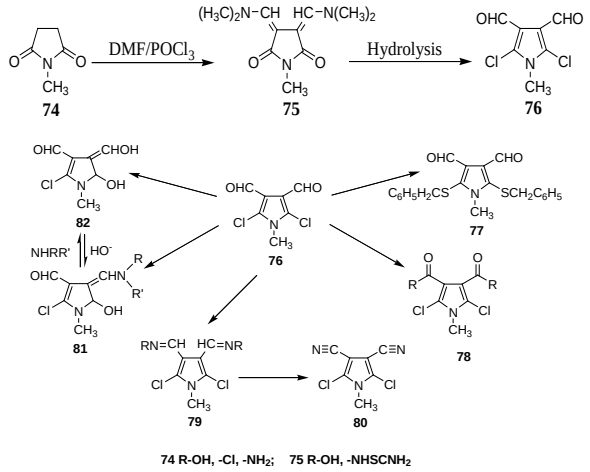
Chemical reactions

Chloroformylation

N-substituted succinimide on dichloro diformylation give halovinyl derivatives. in the presence of dimethylformamide and phosphorus oxycloride.

Chloroformylation of N-substituted succinimide

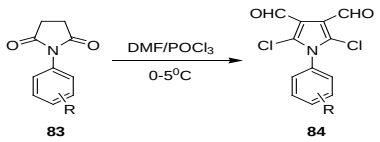
N-alkyl substituted succinimide **74** underwent dichloro diformylation in the presence of dimethylformamide and phosphorus oxycloride leads to aromatization of ring and formation of N-substituted dichlorodiformylpyrroles **76** via intermediate **75**, which was used as synthone for the preparation of derivatives **77-82** (Scheme 22) [35].



Scheme 22

Chloroformylation of N-phenyl succinimide

Halovinyl aldehyde derivative, N-phenyl-2,5-dichloro-3,4-diformyl succinimide **84** was obtained by successive reaction of **83** with Vilsmeier-Haack reagent ($DMF/POCl_3$) at 0-5^{0}C (Scheme 23) [36].



Scheme 23

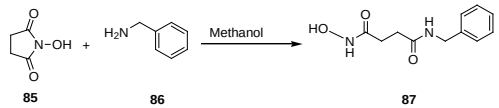
Ring opening reactions

The nucleophilic ring opening reaction of succinimides shows inter and intra molecular reaction. Each reaction is classified according to nucleophile: Nitrogen, Oxygen, Carbon linked and hybrid.

Intermolecular reactions

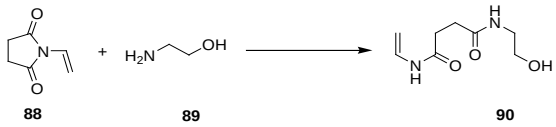
Nitrogen linked nucleophile

The activating effects of the carbonyl groups enable a succinimide to react easily with amine. The reactions have been recently reported using simple amines, diamines and hydrazine as nucleophiles. Benzylamine **86** react easily with N-hydroxy succinimides **85** to gives diamide **87** in high yield (Scheme 24) [37].



Scheme 24

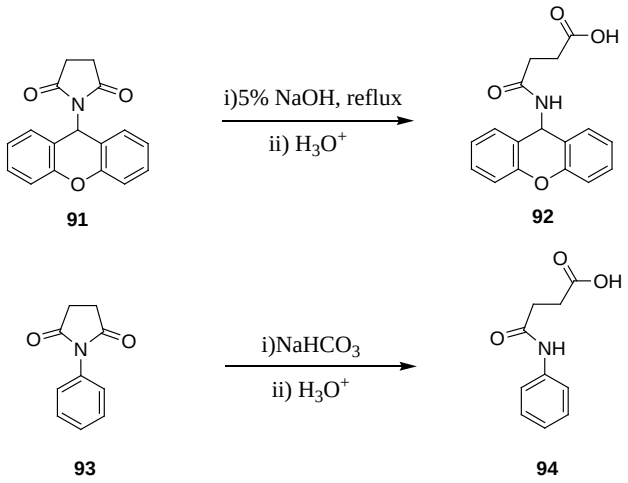
When both amino and hydroxyl groups are present in the same nucleophile, the amino group reacts selectively with succinimide. Thus N-vinyl succinimide **88** and ethanolamine **89** produce diamide **90** in almost quantitative yield at room temperature (Scheme 25) [38].



Scheme 25

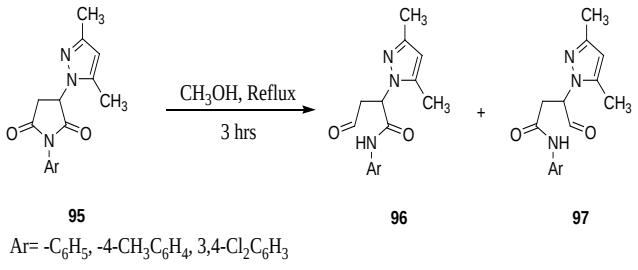
Oxygen linked nucleophile

In contrast to ordinary amides, succinimides **91** and **93** were hydrolyzed to carboxylic acids **92** and **94** under weakly basic condition (Scheme 26) [39].



Scheme 26

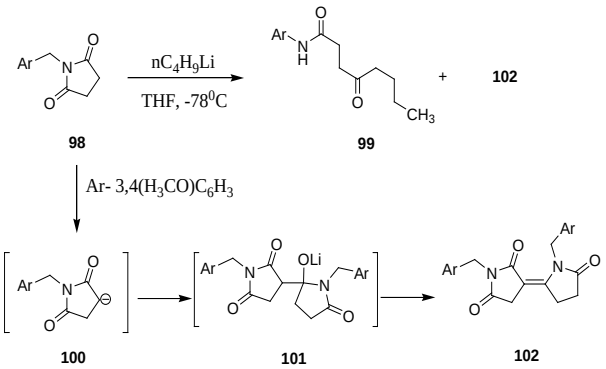
Succinimide **95** underwent ring opening reaction by methanolysis under mild condition into methyl ester **96** and **97** (Scheme 27) [40].



Scheme 27

Carbon linked nucleophile

Reaction between succinimide and lithium reagent produce low yield of ketones (e. g. **98→99**, Scheme 28). Since lithium reagents act as strong base, abstract one proton from the succinimide to formimic enolate **100**, which then undergoes intermolecular nucleophilic addition to another molecule of succinimide to produce dimeric product (Scheme 28) [41].



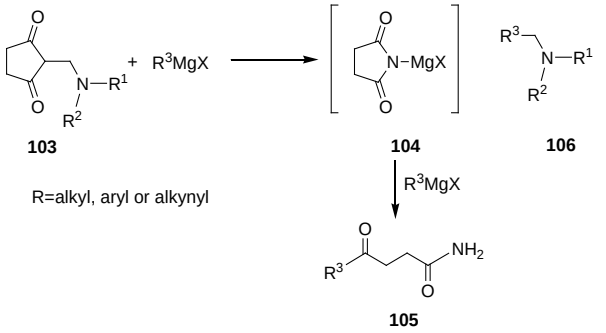
Scheme 28

Reaction of N-(aminomethylene) succinimide **103** with two equivalents of Grignard reagents afforded ring opening product γ-keto amines **105** and tertiary amines **106**. The reaction involves a salt like succinimidomagnesium halide intermediate **104**, which reacts further with various Grignard reagents to give γ-keto amines **105** (Scheme 29) [42].

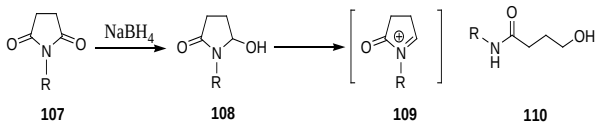
Reduction

Generally, succinimide can be reduce to give hydroxyl lactums (e. g. **107→108**, Scheme 30), which are precursors to α-acyliminium salt **109** and other functional groups.

Under certain conditions hydroxyl lactams **108** can be reduced further to give ω-hydroxy amide **110** as a product (Scheme 30) [43].



Scheme 29



Scheme 30

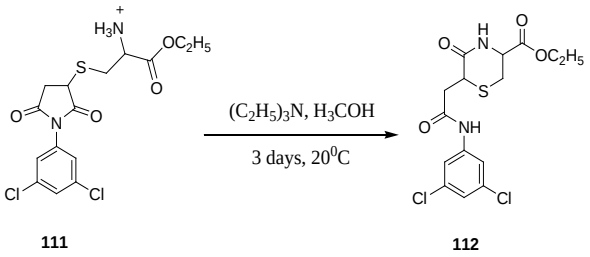
Intermolecular reactions

Nucleophilic substitution

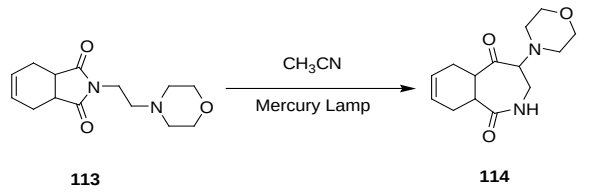
When succinimide **111** is reacting with the amino group, it forms preferentially a six member ring product **112** (Scheme 31) [44].

Photochemical ring opening

Succinimide can undergo ring opening and intramolecular cyclization under photochemical conditions. When compound **113** was irradiated in the presence of methyl Nitrile, a product **114** was obtained (Scheme 32) [45].



Scheme 31

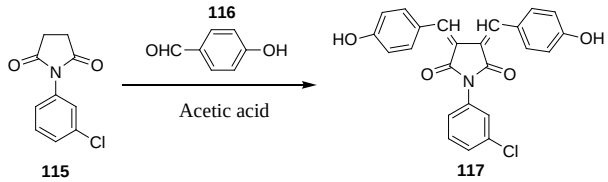


Scheme 32

Bis-heterocyclic derivatives

Bis-chalcones

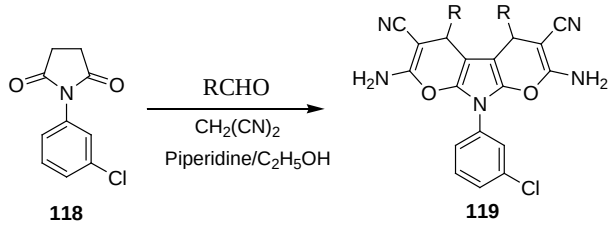
Bis chalcone **117** was obtained by reaction of N-(3-chlorophenyl) succinimide **115** and 4-hydroxy benzaldehyde **116** using glacial acetic acid. The bis chalcone separate as colored crystals (Scheme 33) [46].



Scheme 33

Azo flurorene

A mixture of N-(3-chlorophenyl) succinimide **118** refluxed with aldehyde in the presence of malononitrile in piperidine/ethanol for 4-5 hrs give azo flurorene **119** (Scheme 34) [47].



Scheme 34

CONCLUSION

Succinimides are easily available and have high chemical reactivity due to the presence of both carbonyl and methylene groups. Substituted succinimides are important compounds of many drugs and drug candidates. This survey was attempted to summarize the synthetic methods and reactions of succinimides.

CONFLICT OF INTERESTS

Declared None.

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