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SUCCINAMIDES AND N- SUBSTITUTED SUCCINAMIDES A REVIEW ON THEIR SYNTHESIS

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ABSTRACT

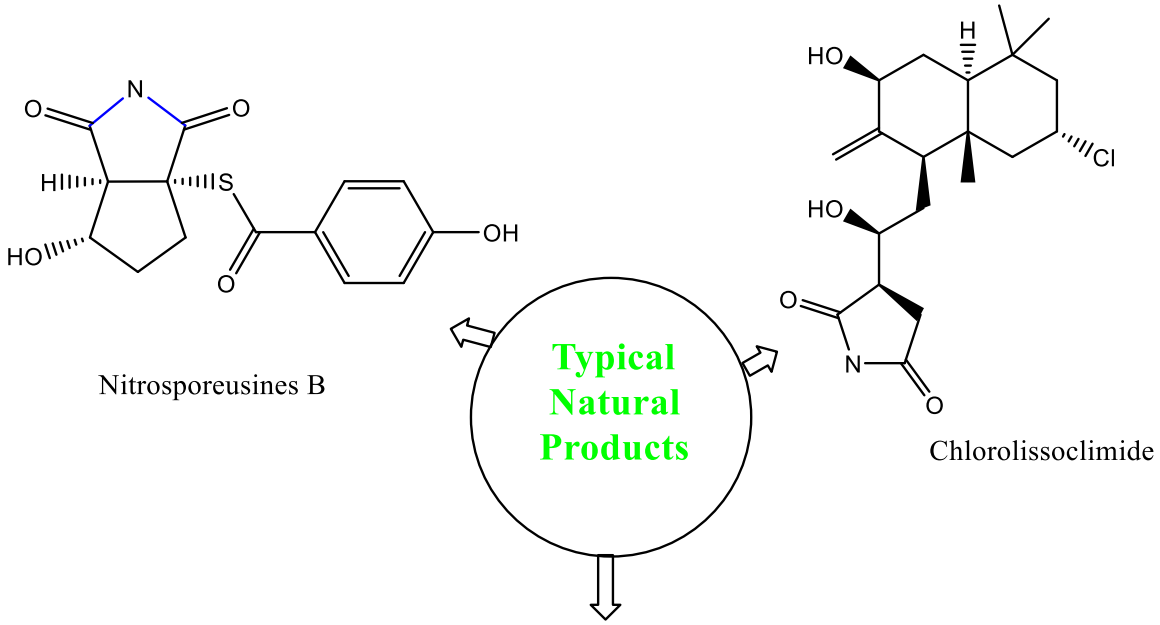
This review deals with synthesis of cyclic imides particularly focuses on succinamide derivatives. Succinamides are important scaffolds in organic synthesis out of them nitrogen substituted succinamides are attracted attention of synthetic organic community. In modern era and in the world of AI synthetic organic chemistry has become important part of drug discovery by considering this aspect in this work attempt to review of some important synthetic methods of synthesis of particularly N-substituted succinamide derivatives.

KEYWORDS: Succinamide, N-substituted phenyl succinamide.

INTRODUCTION

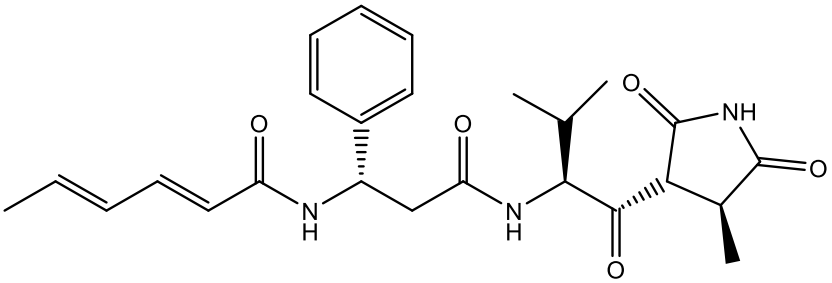
Cyclic imides are important class of nitrogen containing compounds there are many important member of this class like maliamide, Pthalamide, Glutarimide and Succinamide. The succinamides are five membered cyclic imide comprise nitrogen atom adjacent to two carbonyl carbon make them synthetically very imperative. The succinamide is biologically significant molecule as their derivatives used in synthesis of neurotransmitter analogue.[1] The some of its derivatives used in treatment of multiple myeloma[2] succinamide has significant anticonvulsant activity[3-7] that is helpful for measurement of this property by electroshock seizer model.[8] The succinamide is act as neuroprotective agent.[9] and it has found to have Antileptic property[10-11] it also shows human T-type channel blocker activity[12] The N-substituted succinamide derivatives have numerous synthetic applications such as chemo selective trimethylation[13], Use of reusable catalyst for N-protection of amine groups[14],

Catalyst for synthesis of xanthenes type of dyes in solvent free condition.[15] The derivatives of Succinamide have incredible contribution in field of pharmacy and drugs that used for treatment of epilepsy[16] and in the study of neuroscience[17] it has analgesic[18-19] and anti-inflammatory activities.[20] It is used in treatment of diabetic complications[21] and showed anticancer activity[22-23], antitumor activity[24] and found to have broad spectrum against human Carcinoma Cell.[25] The molecule incorporated succinamide moiety showed Antimicrobial[26-27], Cytotoxic and DNA binding and Apoptotic inducing Activity[28], Protophorperinogen oxidase inhibitor[29], CNS depressant activity[30], Hypoglycemic activity[31], Hypolipidemicactivity.[32] Some important molecules possessing succinamide nucleus have quoted here showing incredible structural modifications.

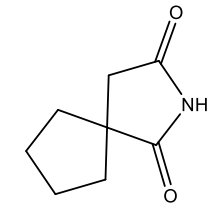


Nitrosporeusines B

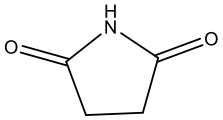
Chlorolissoclimide



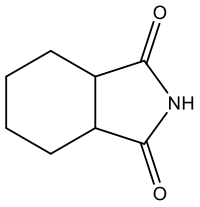
Molramide B



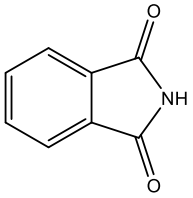
2- Azaspiro[4,4]nonane-1,3-dione



Succinamide



Hexahydro thalamide

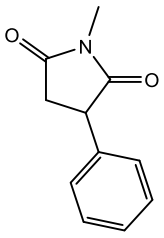


Pthalamide

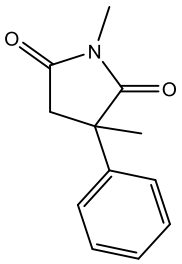
Broad Pharmacological Activities

- Anticonvulsant
- 5-HT ligands
- Anti-inflamatory
- Antitumor
- Antimicrobial
- Antiviral
- Enzyme inhibitors

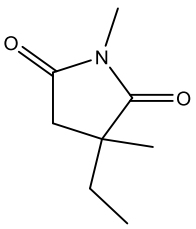
Approved drug and clinical candidates



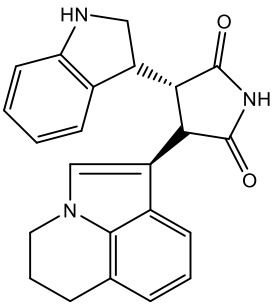
Phensuximide



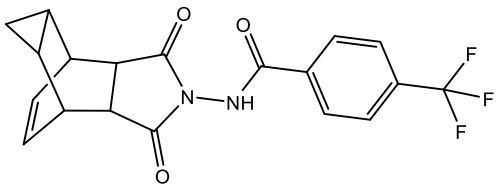
Methsuximide



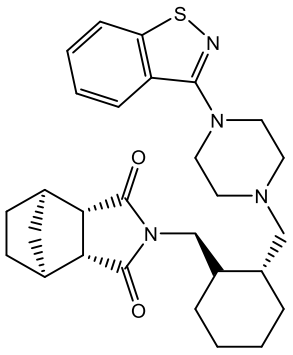
Ethsuximide



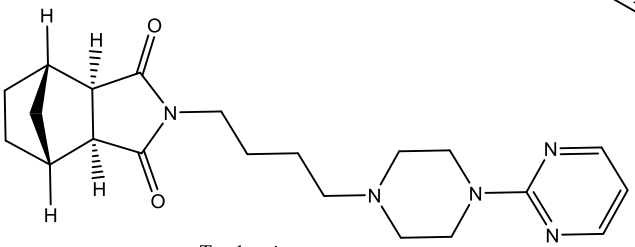
Tivantinib



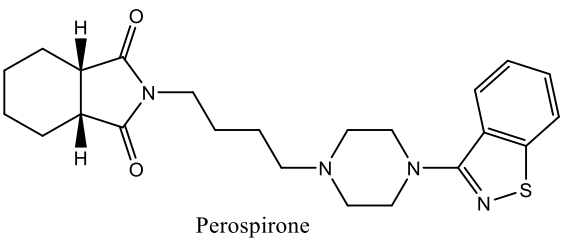
Tecovirimat



Lurasidone



Tandospirone

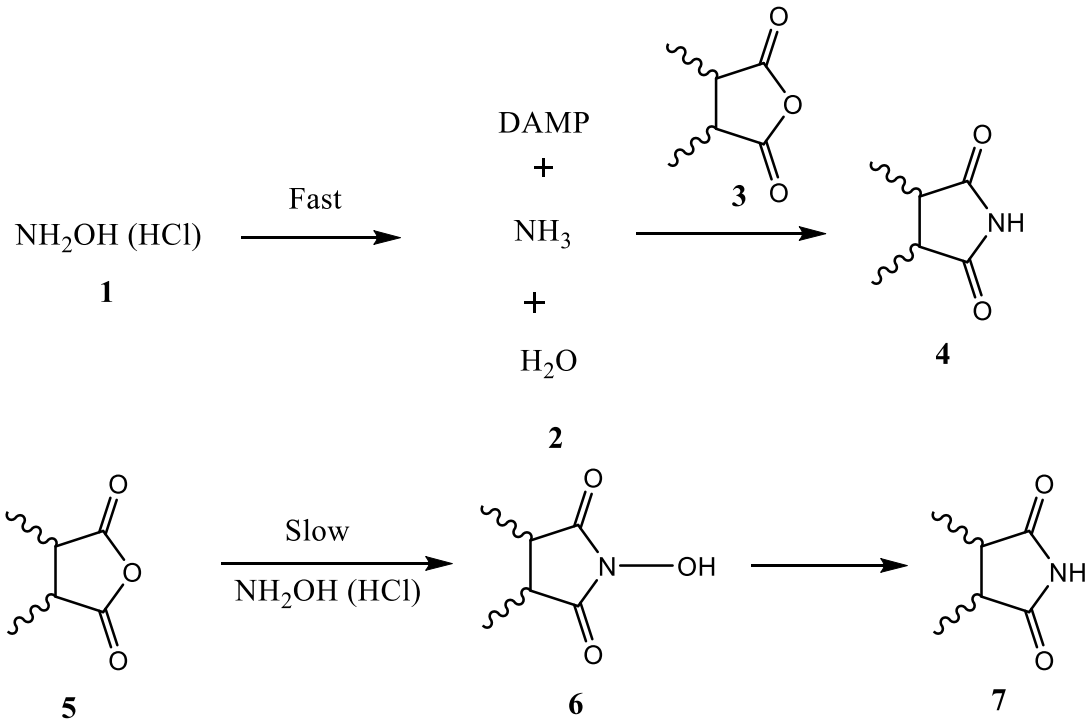


Perospirone

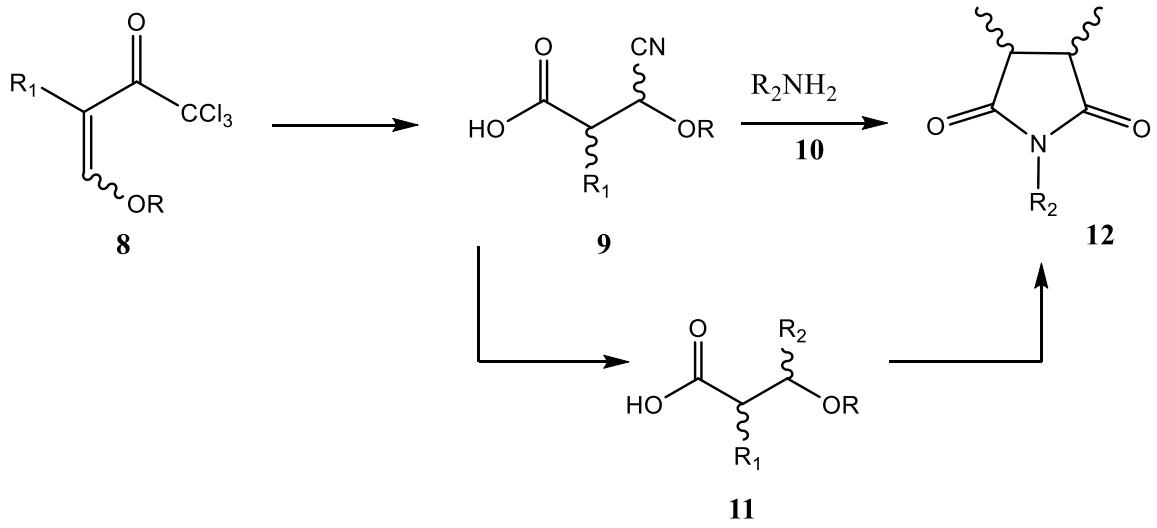
On account of such useful properties huge numbers of derivatives of succinamide have been formulated in view of all above applications some important method of synthesis of succinamide have summarized here and reviewed in following schemes.

Synthesis of N-Substituted Succinamide

Ellis Benjamin, Yousef Hijji et al[33] reported synthesis of succinamide (4) from hydroxyl amine hydrochloride reacted with ammonia and dimethyl amino pyridine further treatment with succinic anhydride (3) (Scheme 1)

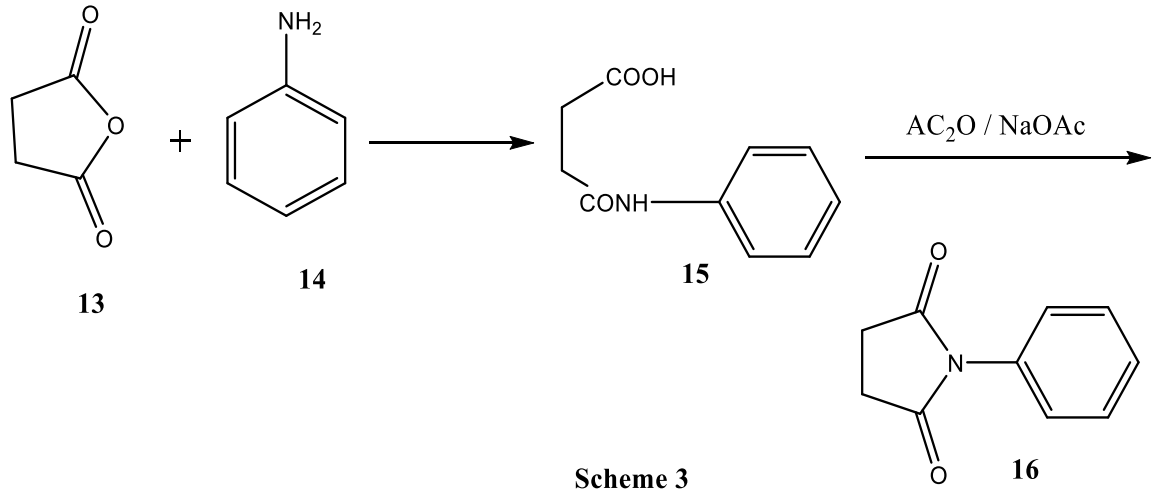


Nilo Zannata, Fabio M. Da silva et al[34] attempted synthesis of N- substituted succinamide by conversation of comp (8) to cyano carboxylic acid (9) which on condensed with primary amine (10) afforded to N- substituted succinamide (12) It was also formulated by other route in which comp (9) converted to dicarboxylic acid and reacted with primary amine converted to N- substituted succinamide (Scheme 2)



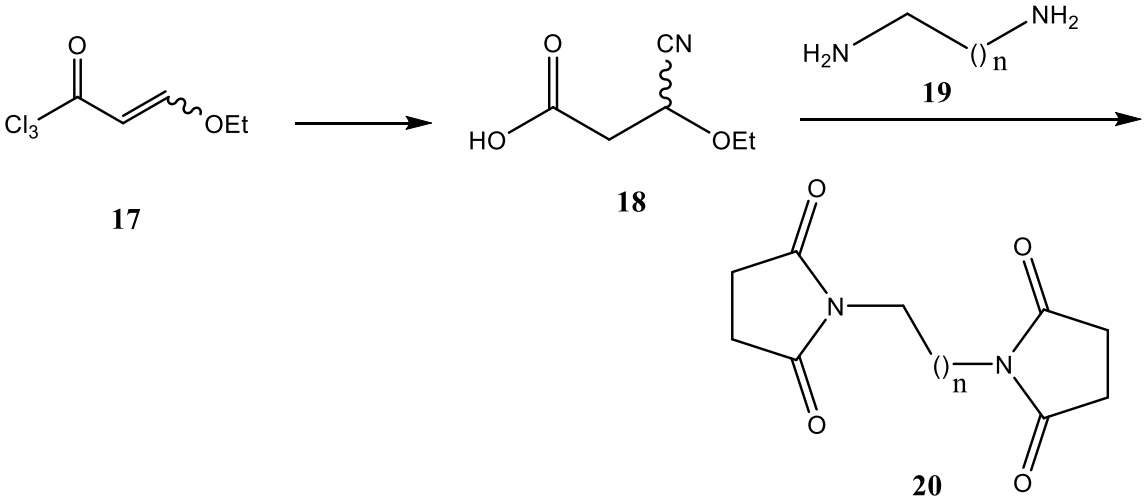
Scheme 2

AlhamMarouf Al-azzawi et al[35] formulated an efficient method of synthesis of N phenyl substituted succinamide from succinic anhydride (13) on treatment with aniline (14) resulted formation of intermediate 15 which further refluxed in acetic anhydride and sodium acetate(Scheme 3)



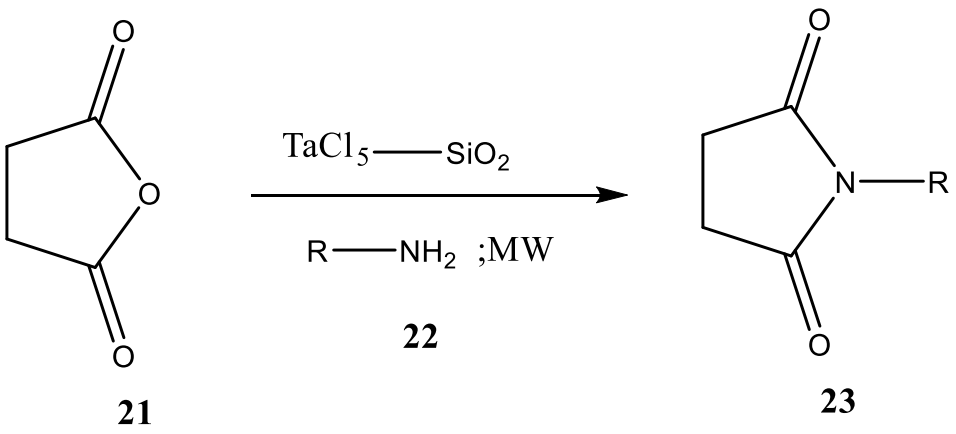
Scheme 3

Zantta N, Da Silva, et al[36] have studied and device synthesis of N-subtituted di succinamide derivatives from comp (17) converted to compound (18) which is condensed with diamine (19) furnished to N-substituted di-succinamide (20) (Scheme 4)



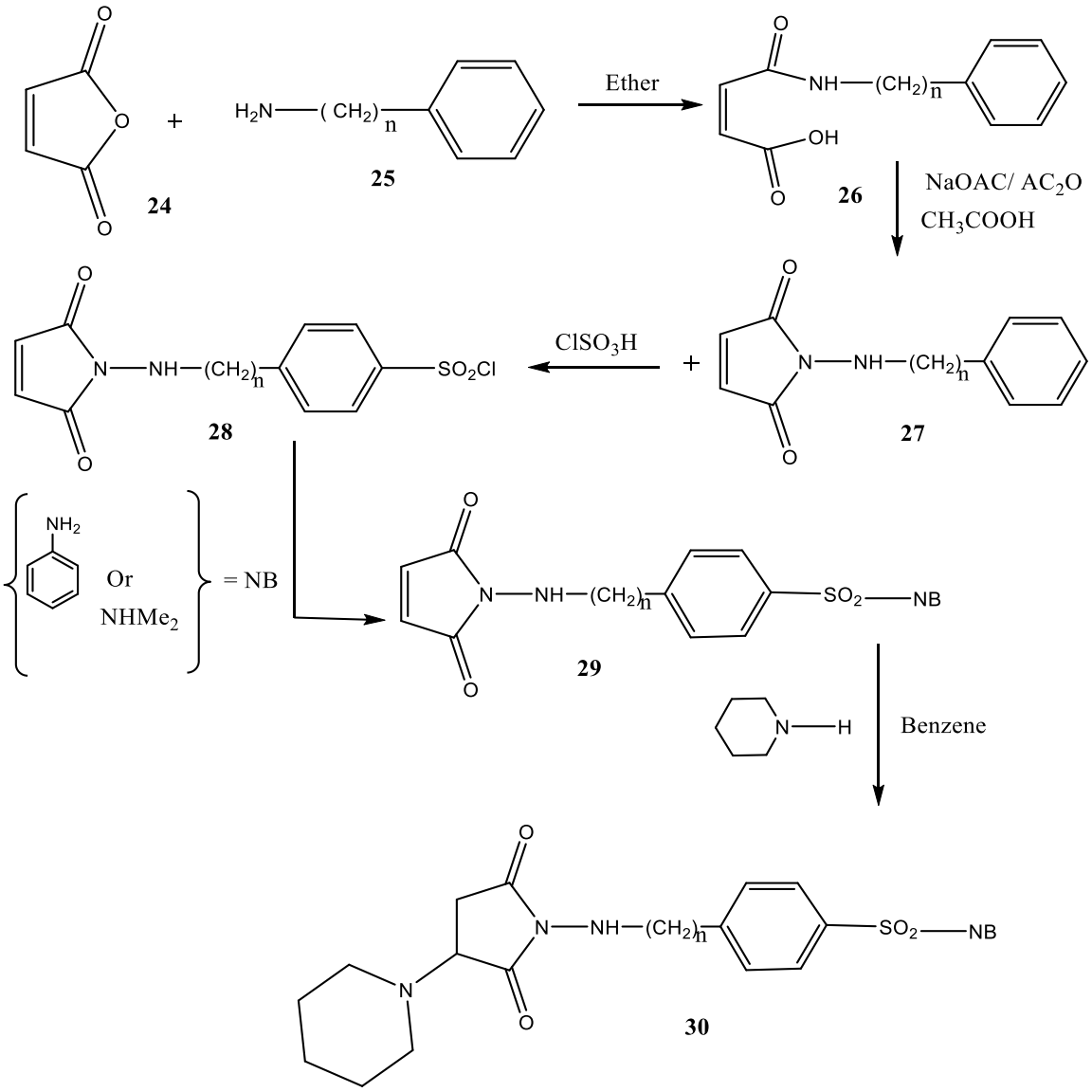
Scheme 4

Chandrasekhar S, Takhi M, et al[37] developed new microwave assisted synthesis of N-phenyl substituted succinamide (23) from Succinic anhydride (21) and primary amine (22) incorporated Tantalum pentachloride with silica (Scheme 5)



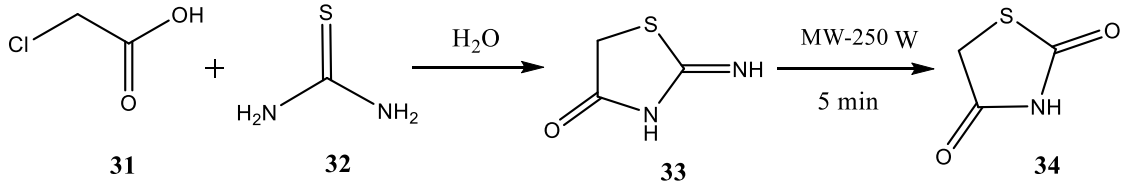
Scheme 5

R Correa, V. CechinfelFilho, et al[38] carried out Synthesis of succinamide from malic unhydride (24) and primary amine (25) refluxed in ether afforded to intermediate (26) which on further cyclised in presence of sodium acetate and acetic acid furnished into N-substitued maliamide (27) which on treatment with chloro sulphonic acid converted in to compound (28) which reacted with nitrogen base compound (29) obtained it on treatment with piperidine in presence of benzene furnished in to N-phenyl substituted succinamide (30) (Scheme 6)



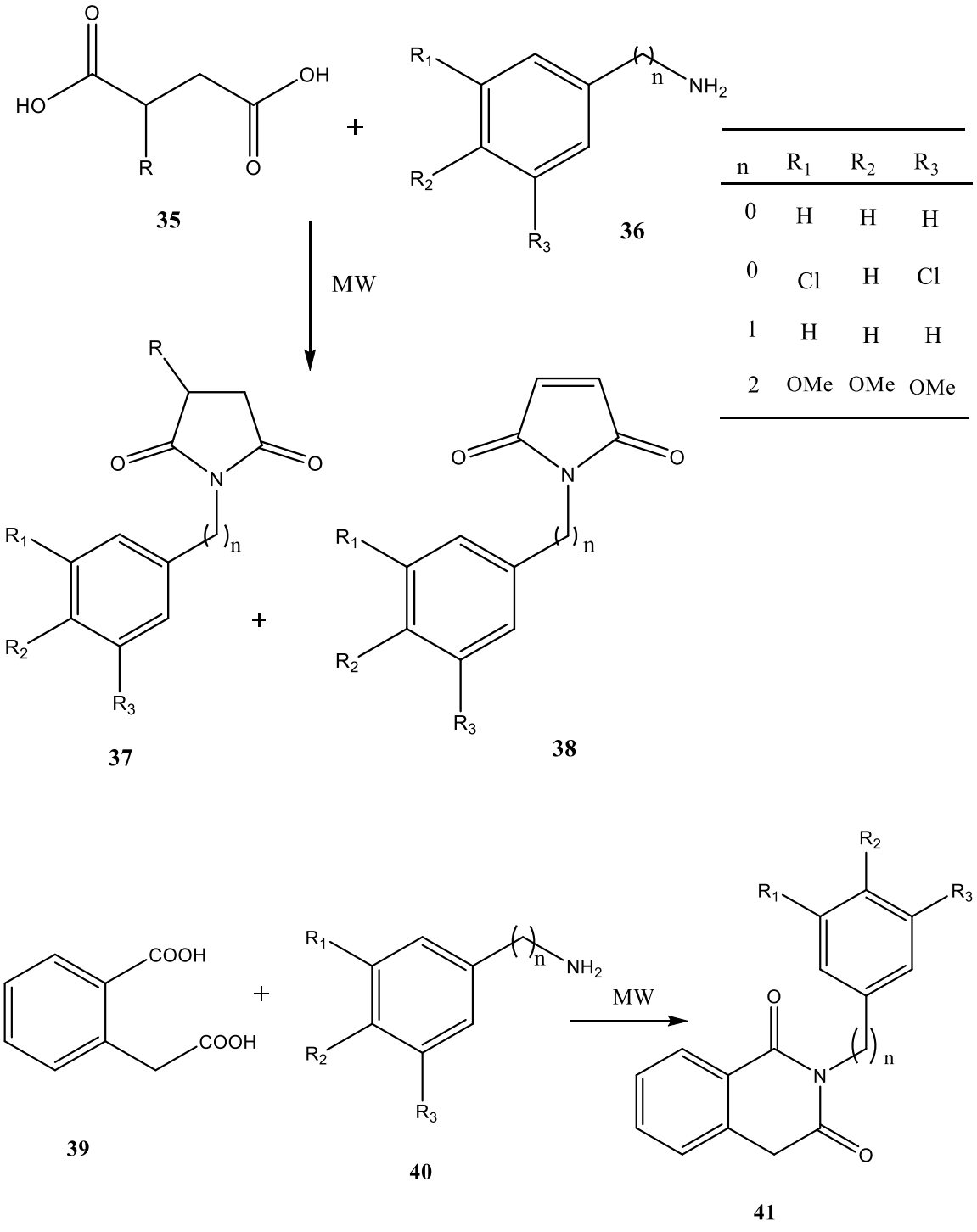
Scheme 6

Chanda N et al[39] extensively studied and reported synthesis of sulphur containing succinamide (34) green protocol by use of microwave radiation and initiated with reaction of chloro acetic acid and thiourea at lower temp in presence of water converted in to compound (33) which further irradiated in microwave radiation afforded to thiazolidine 2,5 dione (34) (Scheme 7)



Scheme 7

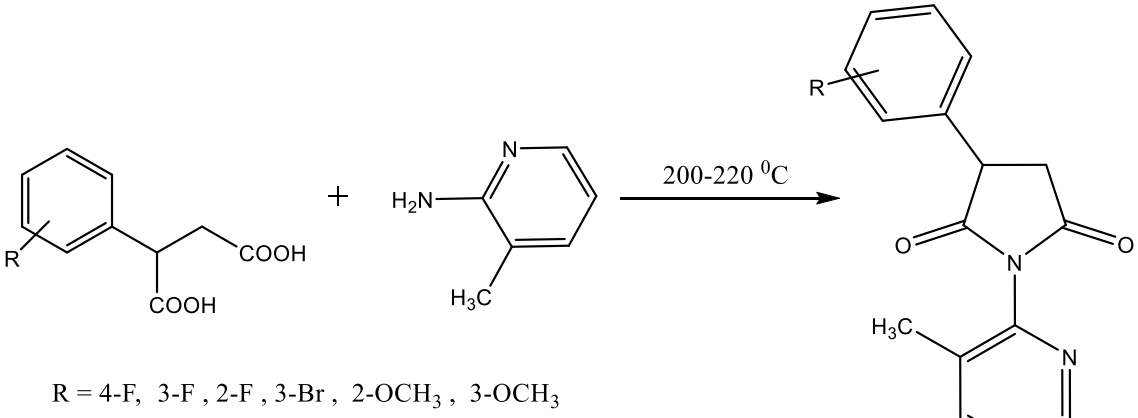
Julio A. Seijas, M. pilar Vazquez tato, et al[40] have extended their work and formulated new methodology for synthesis of N-substituted succinamide (37) and N substituted maliamide (38) from substituted succinic acid (35) substituted primary amine (36) upon microwave irradiation. The N-substituted glutariamide (41) have synthesized by reaction of dicarboxylic acid (39) with substituted primary amine (40) in microwave irradiation. (Scheme 8)



n	R_1	R_2	R_3
0	H	H	H
0	Cl	H	Cl
1	H	H	H
2	OMe	OMe	OMe

Scheme 8

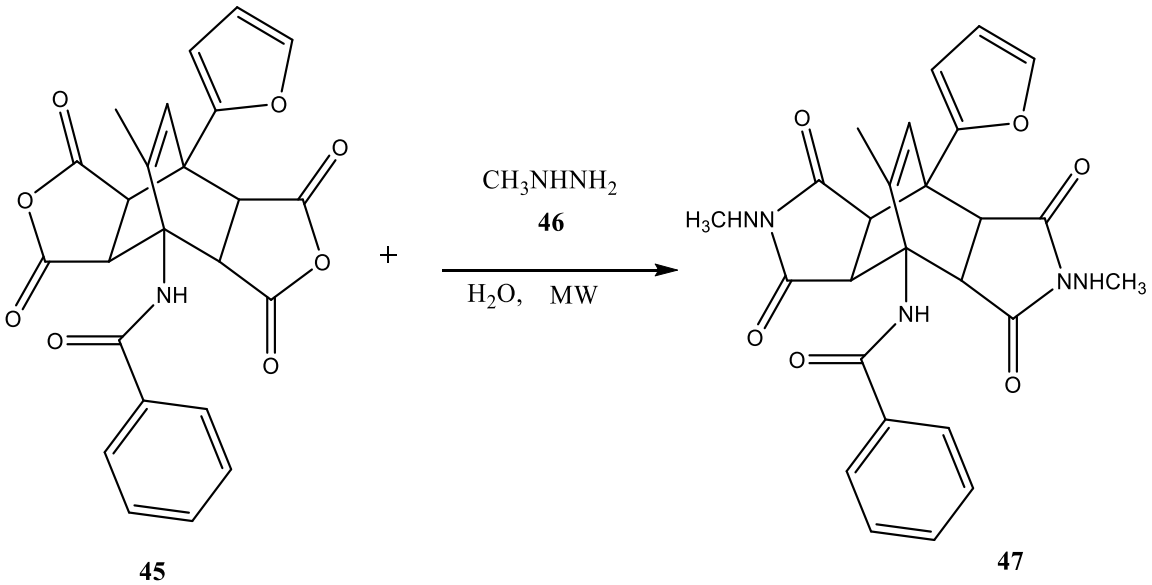
Jolantaobanska, Alfred zejc, et al[41] Attempted synthesis of N-pyridinyl substituted succinamide by condensation of phenyl substituted succinic acid (42) with amino pyridine (43) at 200 0C afforded to compound (44) (Scheme 9)



R = 4-F, 3-F , 2-F , 3-Br , 2-OCH_3 , 3-OCH_3

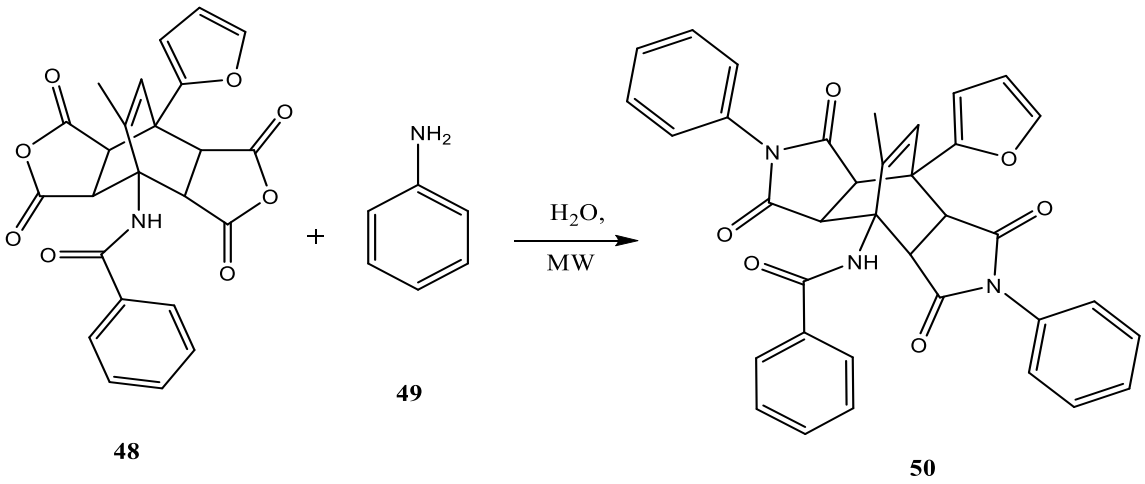
Scheme 9

VivekPolshettiwer, Rajendra S.Verma, et al[42] Formulated green and microwave assisted method of synthesis of novel spiro di N-phenyl substituted succinamide derivatives. The spirofuranyl substituted di-succinic unhydride (45) irradiated with methyl hydrazine (46) converted in to N-substituted succinamide (47). The compound (48) reacted with aniline (49) in microwave radiation furnished to di N-phenyl substituted succinamide (50)(Scheme 10 &11)



45 47

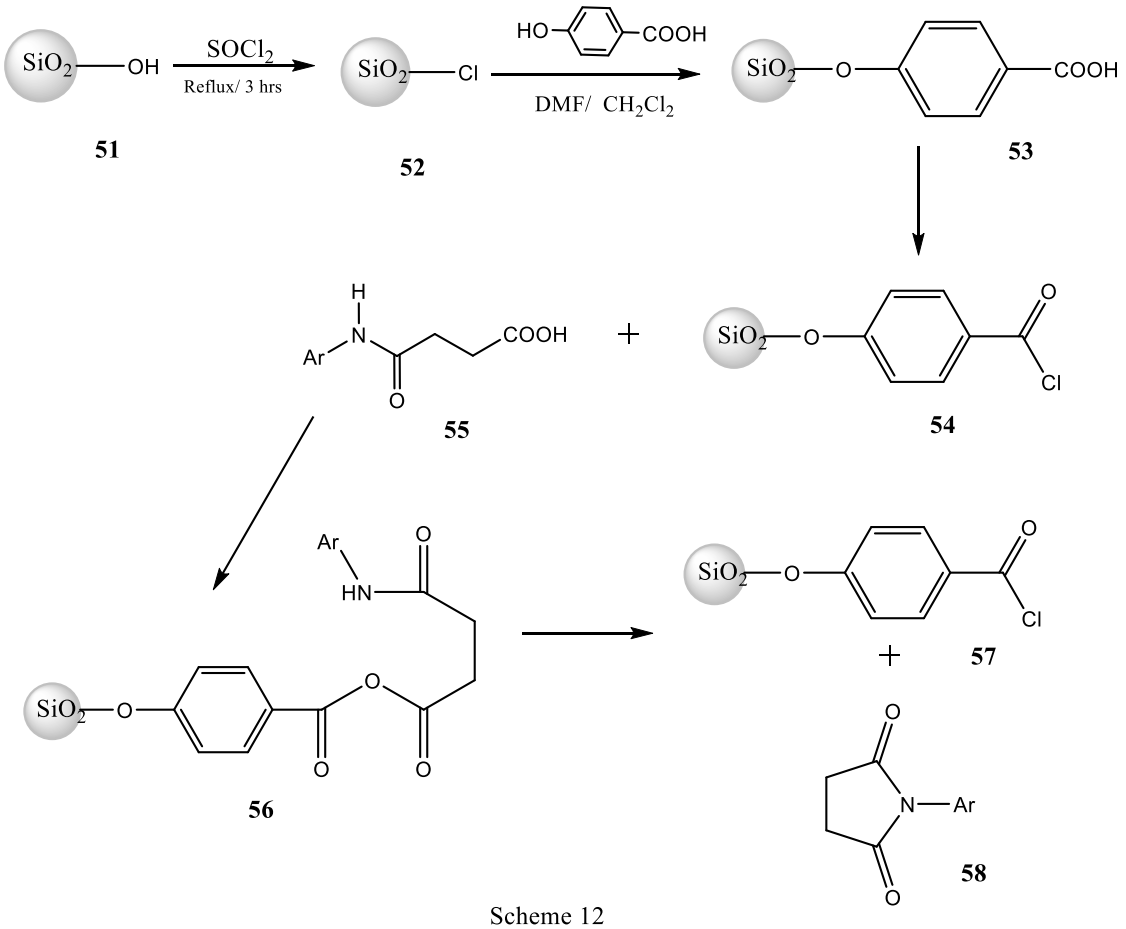
Scheme 10



48 49 50

Scheme 11

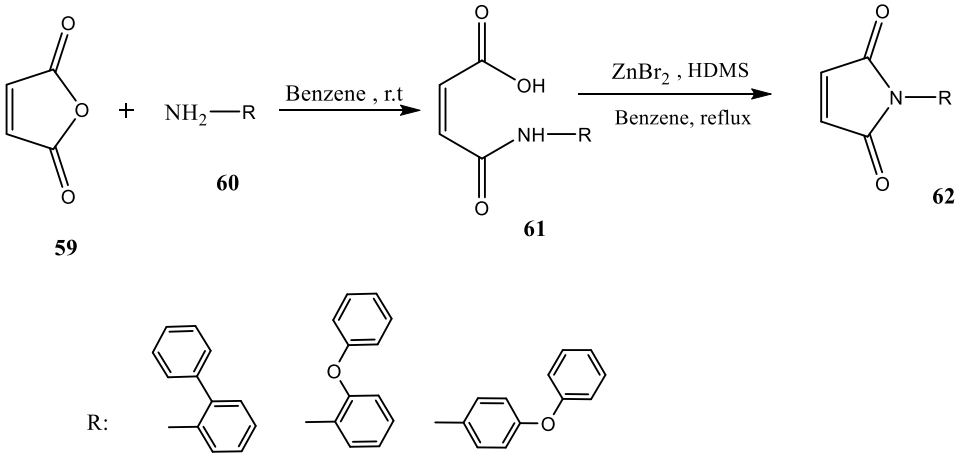
Red-Moghadam k, Kheyrkhan L, et al[43] Attempted synthesis of N-aryl substituted succinamide by using silica gel as a solid phase and it has converted in to silica substituted benzoyl chloride (54) which further condensed with N-aryl amidio carboxylic acid (55) afforded to compound (56) which on dehydration regenerated silica substituted benzoyl chloride with formation of N-aryl substituted succinamide (58) (Scheme 12)



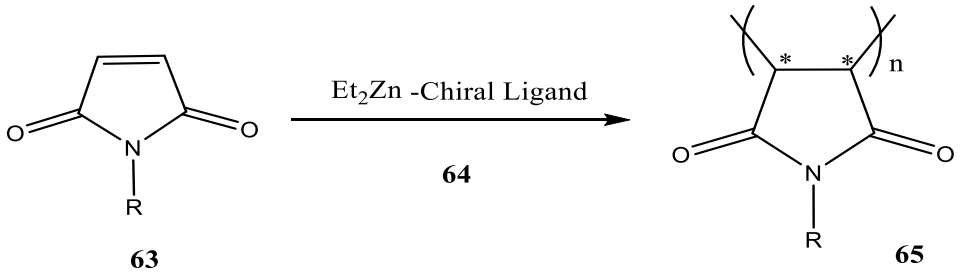
51 52 53 55 54 56 57 58

Scheme 12

Tsutoma Oishi, Yukio Isboe, et al[44] have studied and reported synthesis of N substituted maliamide (62) by reaction of malic unhydride (59) with amine (60) afforded intermediate (61) which underwent ring closure upon refluxed in presence of zinc bromide.(Scheme 13&14)

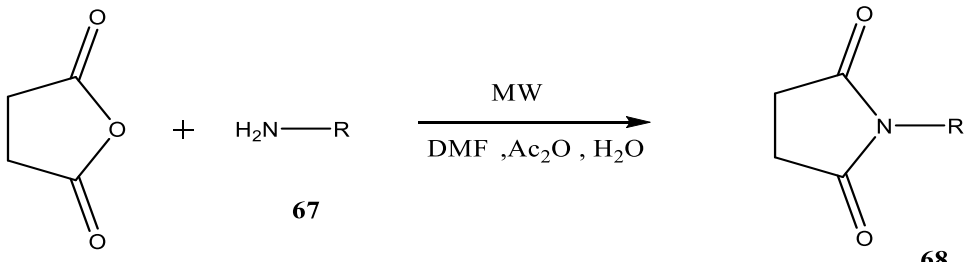


Scheme 13



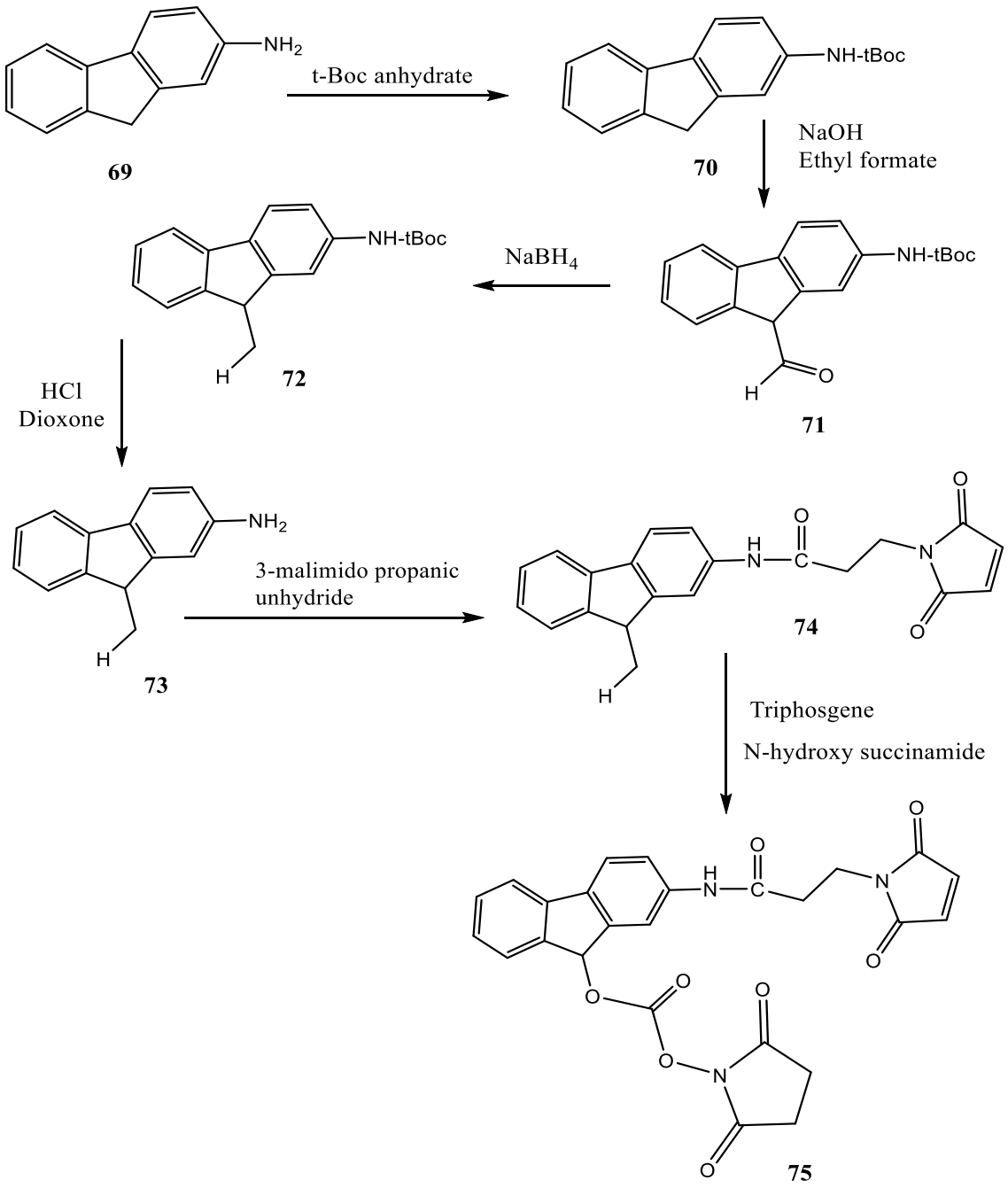
Scheme 14

Upadhay SK, Pingali Subramanya R k, et al[45] carried out microwave assisted synthesis of N-substituted succinamide (68) from treatment succinic unhydride (66) with amine (67) upon microwave irradiation. (Scheme 15)



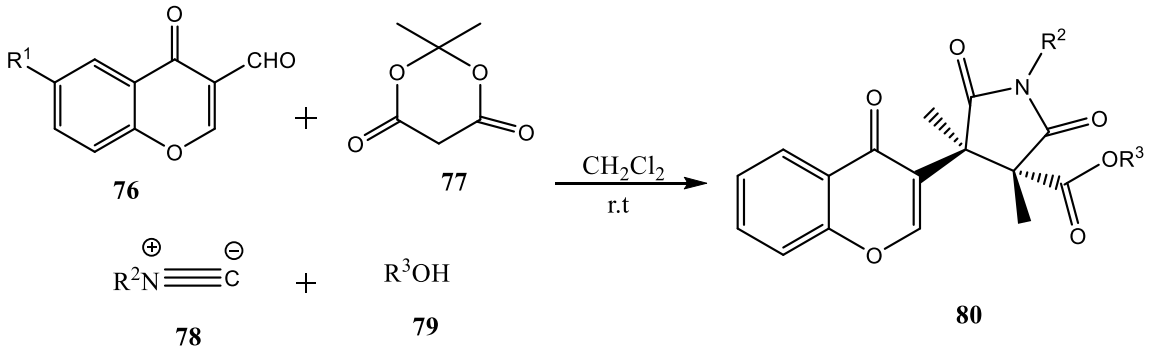
Scheme 15

HaimTsubery, Marina Mironchik, et al[46] extended their work and synthesized biologically important derivative of N-substituted succinamide incorporated with maliamide moiety (79) from series of reaction. Initiated from amine formylated with protection of amino group resulted formyl derivative which further reduced to alcohol by sodium borohydride further deprotection of amino group and condensed with malimado propanic unhydride converted to compound (74) which further treatment with N-hydroxyl succinamide in presence of triphosgene furnished to compound (75) (Scheme 16)



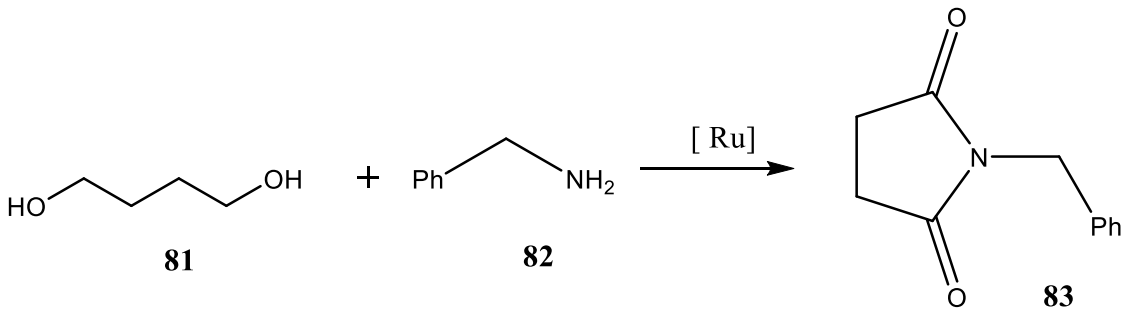
Scheme 16

M.B Teimouri et al[47] studied and reported synthesis of chiral substituted succinamide derivatives from multi component reaction of compound (76), (77), (78) and (79) in presence of dichloro methane at room temperature resulted in to compound (80) (Scheme 17)

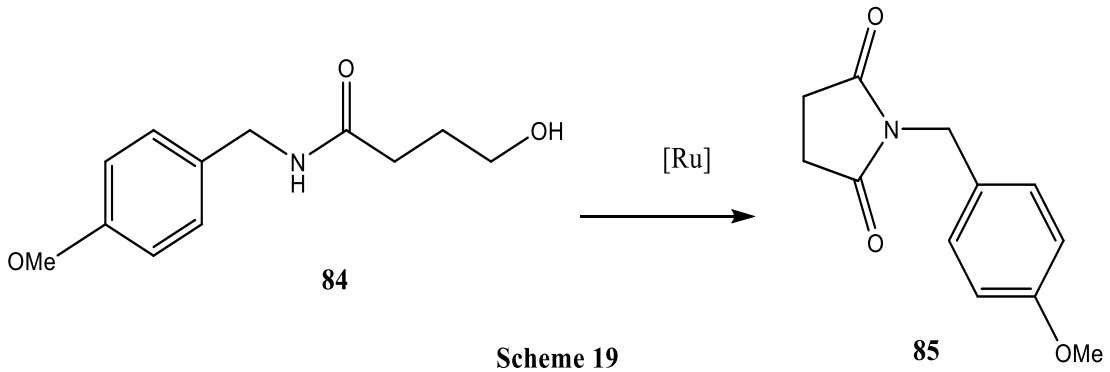


Scheme 17

Jiang Zang, Muthaiah Senthilkumar, et al[48] have synthesized N-substituted succinamide from 1,4 butanediol and phenyl substituted methylamine in presence of Ruthenium catalyst afforded to succinamide (83) (Scheme 18) The applicability of catalysis reaction extended to Ruthenium catalyzed reaction of N (4-methoxybenzyl)-4-hydroxybutanamide (84) furnished to succinamide (85) (Scheme 19)

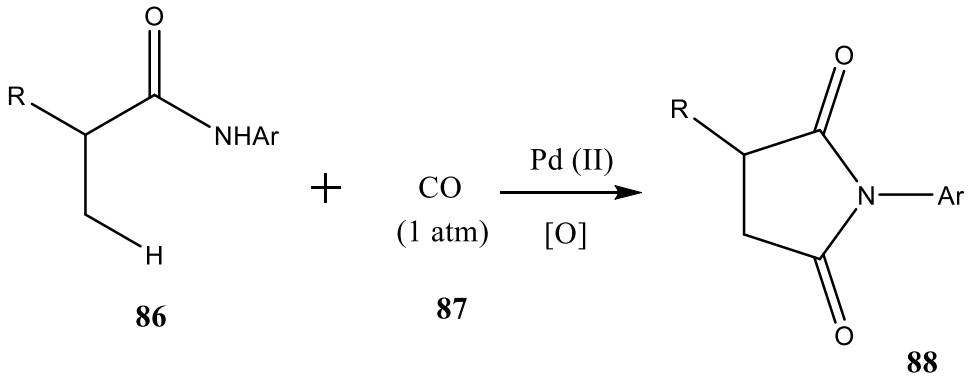


Scheme 18



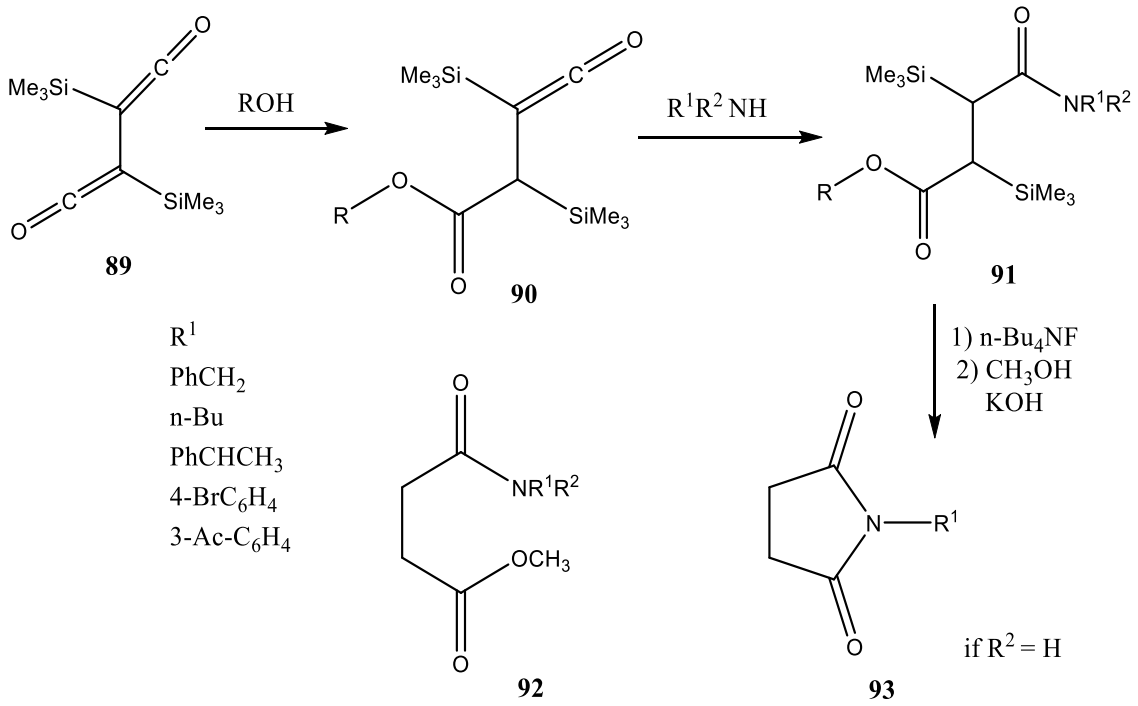
Scheme 19

EunJeongYoo, Masayuki Wasa, et al[49] have developed palladium catalyzed synthesis of N-aryl substituted succinamide (88) from reaction N-aryl substituted amide (86) with carbon monoxide (Scheme 20)



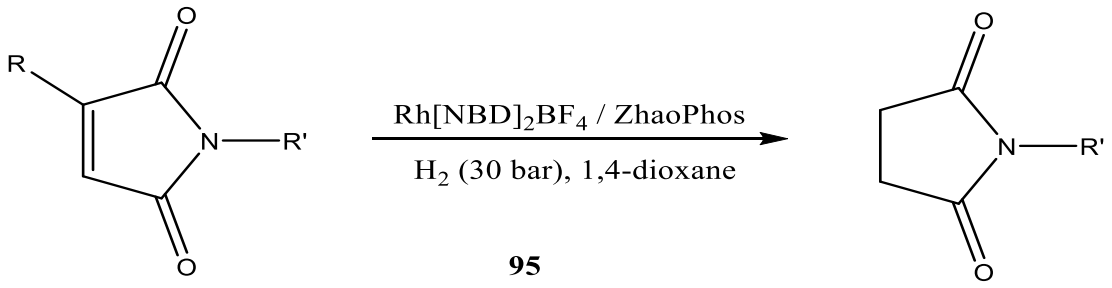
Scheme 20

Adel Rafai far, Thomas T. Tidwell, et al[50] have reported synthesis of N-substituted succinamide (93) by series of reaction initiated from trimethyl sillyl diketene (89) which treated with alcohol converted to ester (90) which further reacted with secondary amine afforded compound (91) which refluxed in ethanol in presence of tetra butyl ammonium fluoride cyclised in to N-substituted succinamide (Scheme 21)



Scheme 21

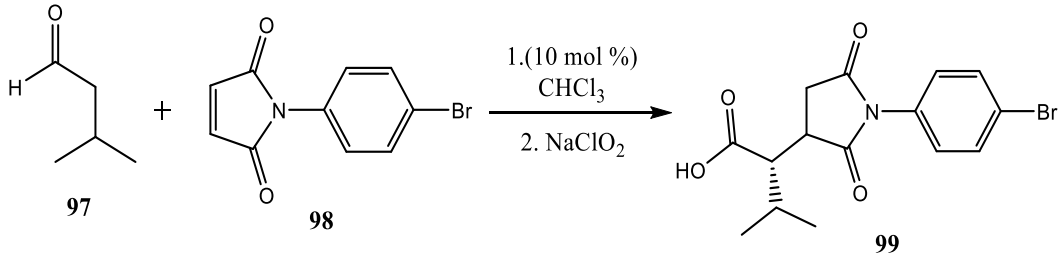
Zhengyun Han, pan Li, et al[51] have expansively studied and develop new catalytic method formulation of N-substituted succinamide (96). The N-substituted maliamide (94) have reduced in presence of Rhodium salt as catalyst (95) furnished in to N substituted succinamide (96) (Scheme 22)



94 95 96

Scheme 22

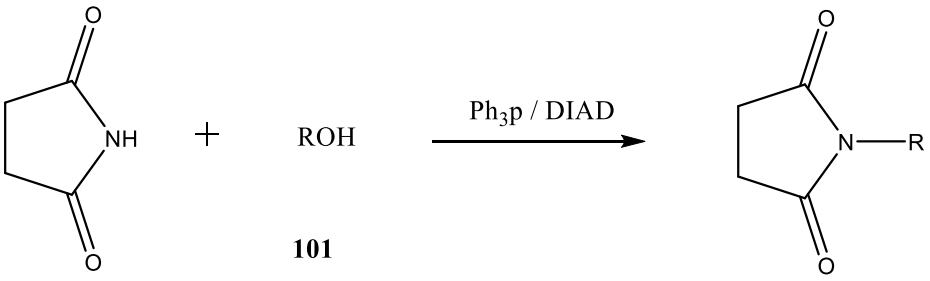
Gui-Ling zaho, YongmeiXu, HenrikSunden, et al[52] have carried out synthesis of succinamide 99 by condensation of aldehyde (97) and maliamide (99) in presence of sodium oxy chloride and chloroform (Scheme 23)



97 98 99

Scheme 23

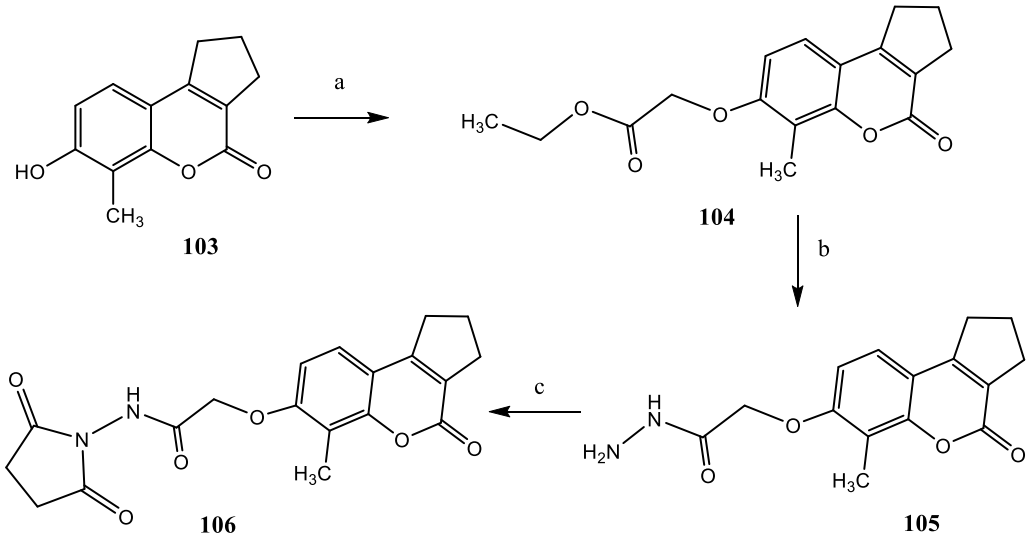
Walker MA, et al[53] have develop triphenylphosphenecatalysed synthesis of N substituted succinamide from condensation of imide (100) with alcohol (101) furnished to compound (102). (Scheme 24)



100 101 102

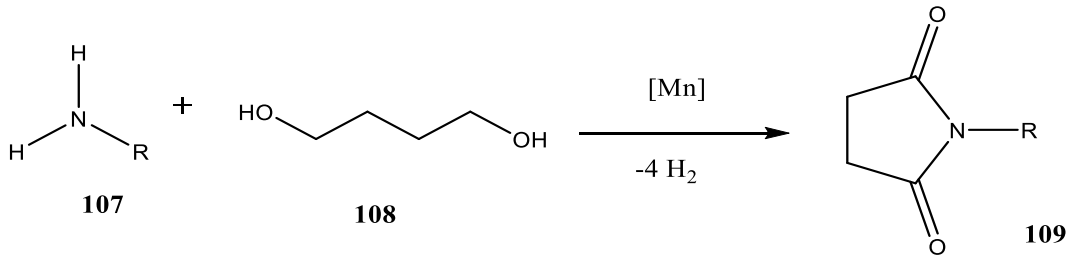
Scheme 24

Sohair L El-Ansary, GhaneyaS.Hassan, et al[54] have broadly studied and reported novel biologically active succinamide derivative (106) for this purpose compound (103) treated with ethyl acetoacetate in presence of dry ether afforded to compound (104) which further condensed with Hydrazine hydrate in presence of ethanol converted in to compound (105) finally it was refluxed with succinic anhydride in presence of glacial acetic acid finished in to compound (106). (Scheme 25)



Scheme-25

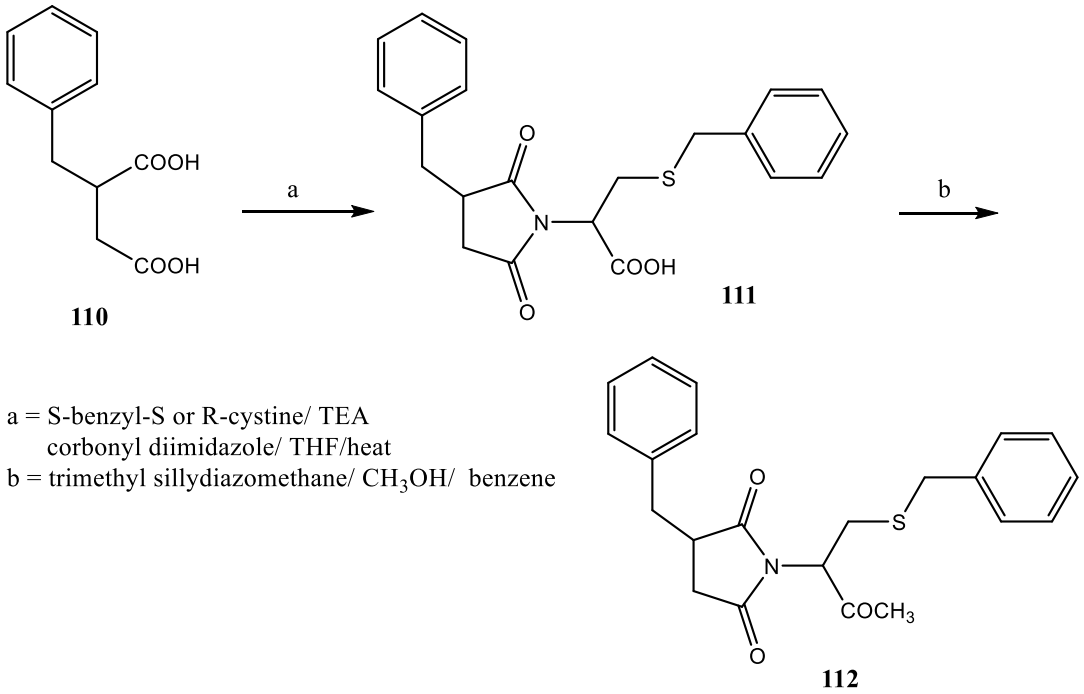
Noel angel Espinosa-jalpa, Amitkumar, et al[55] have devised Mangene catalyzed synthesis of N-substituted succinamide (109) from reaction of Secondary amine with butanediol (Scheme 26)



Scheme 26

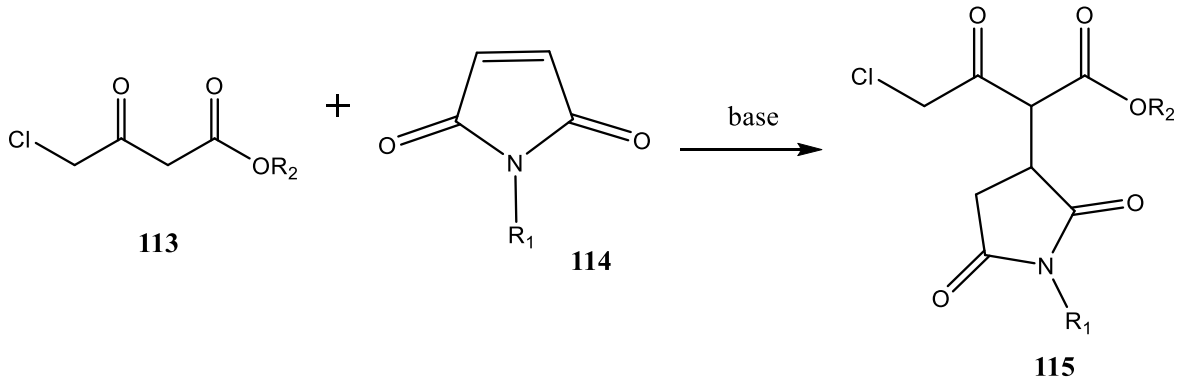
William C. Groutas, Michael J.Brubaker, et al[56] extensively studied and reported synthesis of biologically active human leukocyte enzyme inhibitor derivative of N substituted succinamide (112) have achieved compound (110) with Cysteine afforded to N-substituted

succinamide (111) which further esterification with the help of trimethyllsillyl diazomethane (Scheme 27)



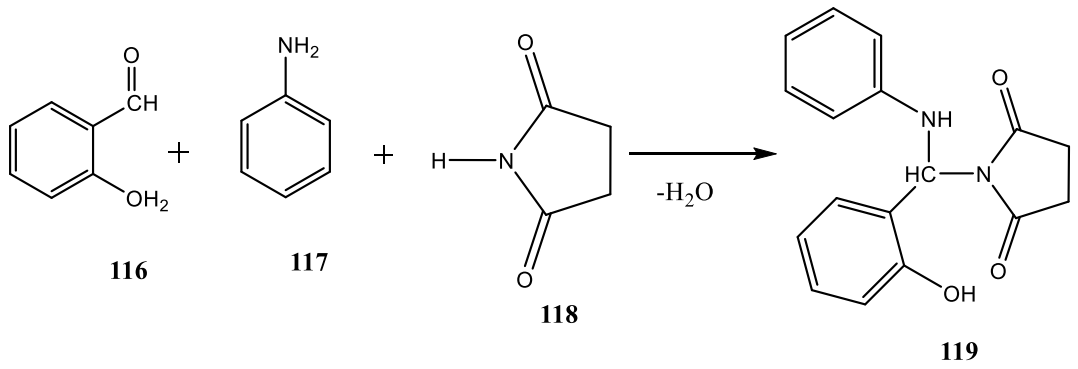
Scheme- 27

Jhon.j, Hopf. H, et al[57] have reported synthesis by using Michael type addition reaction of Dicarbonyl compound (113) with Maliamide (114) in presence of base transformed to novel N-substituted succinamide derivative (115). (Scheme 28)



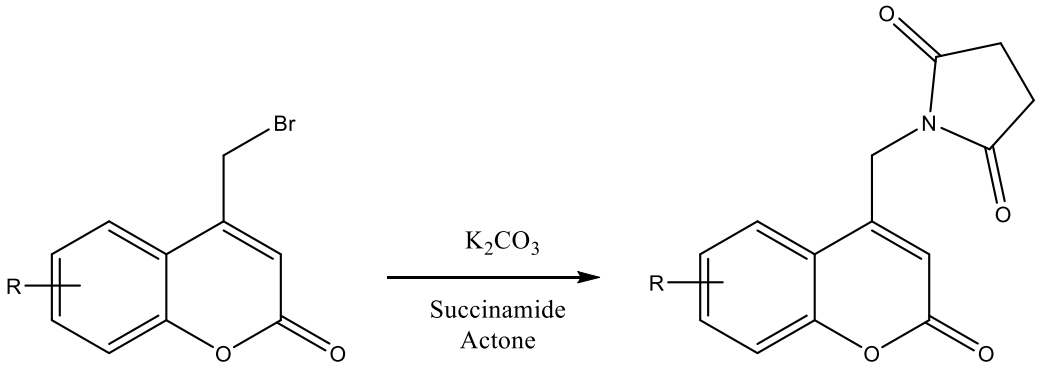
Scheme 28

M.paulJohnpeter, A. Paluraj, et al[58] has attempted synthesis of N-substituted succinamide (119) by multicomponant reaction of Orthohydroxybenzaldehyde, Aniline and Succinamide. (Scheme 29)



Schem 29

R. Marulasiddaiah, Rajesh G. Kalhambkar, et al[59] have reported synthesis of biologically important cumarine substituted succinamide from condensation of compound (120) with succinamide in presence of potassium carbonate and acetone converted in to compound (121). (Scheme 30)



R = 6-CH_3, 7-CH_3, 7-Cl, 8-CH_3, 6-OCH_3

Scheme 30

The N-substituted succinamides have been synthesized from various routs by using dicorboxylic acid, from diols, from amide, from succinic anhydride and also by use of maliamide this revels that N-substituted sucinamide is an important class of cyclic imide in the midst of different imides it has incredible biological activities such as Plant growth regulator.[60] The N-substituted succinamide shown numerous synthetic applications some of them are summarized here

CONCLUSION

This review thrown light on various synthetic methods of succinamide synthesis. Various protocols have been suggested for formulation of succinamide derivatives. Ranging from

conventional to non- conventional methods of synthesis of succinamides gaves an opportunity to develop important drug candidates and active pharmaceutical ingradients.

Especially various substituents on nitrogen substituted makes the molecule more versatile and applicability towards various field of research. The stereo chemical induction within the succinamide moiety is an important strategy for development of diverse drug properties in the molecule. The succinamide molecule have huge application so many researcher have paid attention and studied their synthesis and properties still many of its possible applications have not been discovered yet so further in investigation and research in this molecule extended more possibility in future.

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