RING OPENING REACTIONS OF SUCCINIMIDES

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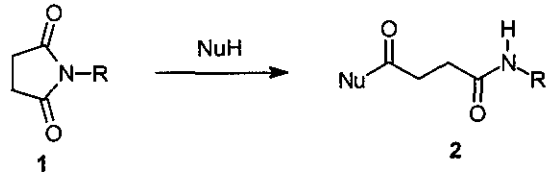
Abstract - This review describes recent examples of inter- and intra-molecular nucleophilic ring opening of succinimides, including aminolysis, alcoholysis, and reactions with carbon nucleophiles.

I. INTRODUCTION

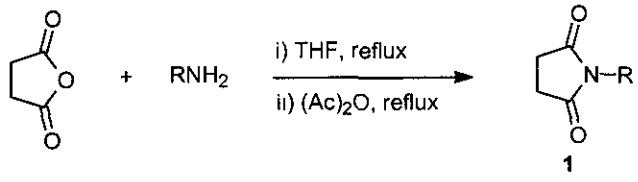
Succinimide and its *N*-substituted derivatives are key structural units in many important compounds[1] including plant growth stimulators,[2] additives for lubricating oils,[3] corrosion inhibitors,[4] psychoanaleptic agents,[5] drugs for memory enhancement,[6] antitumor agents such as epipodophyllotoxin glycoside[7] and for

other purposes.[1,8] *N*-Hydroxysuccinimide (**1**, R = OH) is used in peptide chemistry to activate carboxyl groups. The chemistry of succinimides and other similar cyclic imides was last reviewed almost 30 years ago,[1] the present discussion is focused on developments since then. We consider particularly nucleophilic ring opening reactions of succinimides (Scheme 1) and consider sequentially inter- and intra-molecular reactions with each classified according to the nucleophile: nitrogen-, oxygen-, and carbon-linked, and hydride.



Scheme 1

N-Alkyl-substituted succinimides have usually been prepared from primary amines and succinic anhydride (Scheme 2);[9] other methods are discussed in the earlier review,[1] and will not be considered in detail here.



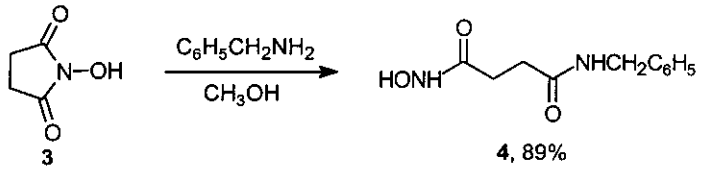
Scheme 2

II. INTERMOLECULAR REACTIONS

a) Nitrogen-linked nucleophiles

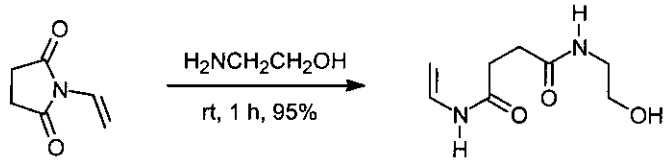
The activating effects of the two carbonyl groups enable a succinimide to react easily with amines, as disclosed in early work.[1] More examples of this reaction have been reported recently using simple amines, diamines and hydrazines as nucleophiles. For instance, benzylamine reacts easily with *N*-hydroxysuccinimide (**3**) to give diamide (**4**) in high yield (Scheme 3).[10] The condition used for this reaction also shows the higher reactivity of nitrogen nucleophiles (amines) toward succinimide over oxygen nucleophiles (methanol).[10]

When both amino and hydroxy groups are present in the same nucleophile, the amino group reacts selectively with a succinimide: thus *N*-vinylsuccinimide (**5**) and ethanolamine produce diamide (**6**) in almost quantitative yield at room temperature (Scheme 4).[11]



3 **4**, 89%

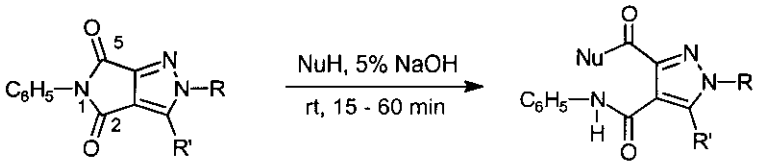
Scheme 3



5 **6**

Scheme 4

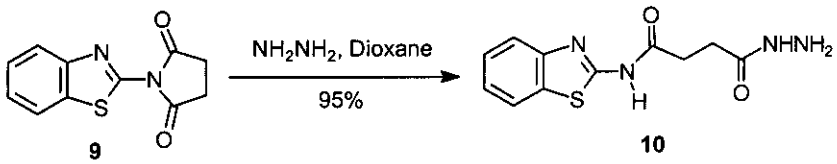
Anilines and secondary amines are also more reactive than hydroxide or alkoxide anions; although the latter can open the succinimide ring (*cf.* next section). Treatment of compound (**7**) with amines in 5% NaOH solution at room temperature, gave diamides (**8**) selectively and in good yields which were generally higher for primary amines than for secondary amines (Scheme 5).[12] In this reaction, the amine attacked the less hindered 5-position carbonyl group.



7 **8**

R	R'	Nu	yield (%)
p-$NO_2C_6H_4$	CH_3S	morpholino	45
p-$NO_2C_6H_4$	CH_3S	C_6H_5NH	44
C_6H_5	CH_3S	C_6H_5NH	88
p-$NO_2C_6H_4$	C_6H_5NH	morpholino	66
p-$NO_2C_6H_4$	C_6H_5NH	C_6H_5NH	96

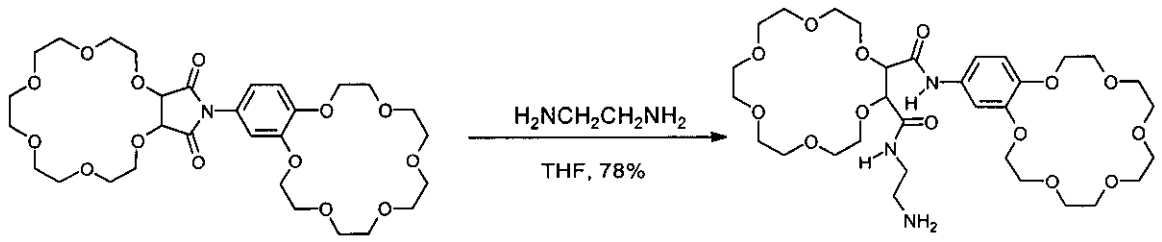
Scheme 5



9 10

Scheme 6

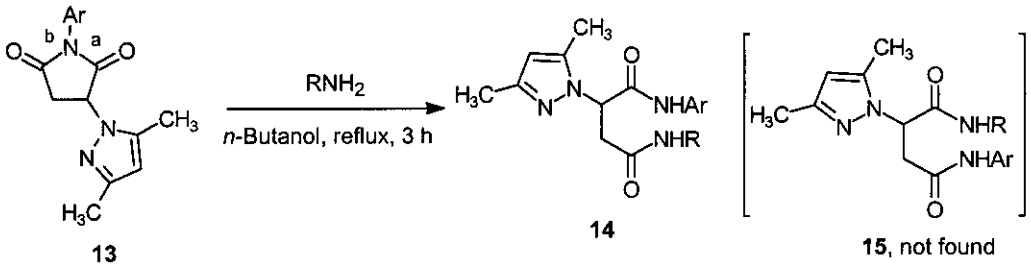
Succinimide derivative (**9**) reacts with one equivalent of hydrazine to give 1,4-diamide (**10**) as the ring opened product in good yield under milder conditions (Scheme 6).[13]



11 12

Scheme 7

Nucleophiles containing two amino groups proceed efficiently to give monoacylated products. The reaction of crown ether (**11**) at room temperature with ethylenediamine forms diamide (**12**) (78%), a bis-crown ether ionophore that behaves as a pH-modulated ion transporter (Scheme 7).[14]



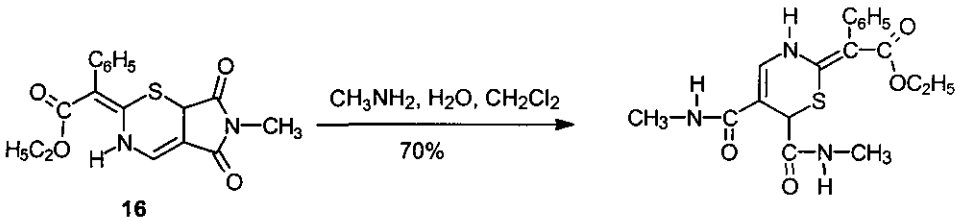
13 14 15, not found

R: C_6H_5, *p*-$CH_3C_6H_4$

Ar: C_6H_5, *p*-$CH_3C_6H_4$, 3,5-$Cl_2C_6H_3$ Scheme 8

When substituents are present on the succinimide ring amines will attack the less hindered side. Thus compound (**13**) (Scheme 8, *cf.* Scheme 5) gives diamide (**14**) selectively, the other isomer (**15**) was not detected in the reaction mixture by TLC. However, the authors argued that this high chemoselectivity was based on the HSAB (Hard-Soft Acid Base) concept,[15] the carbonyl group (b) being relatively softer than

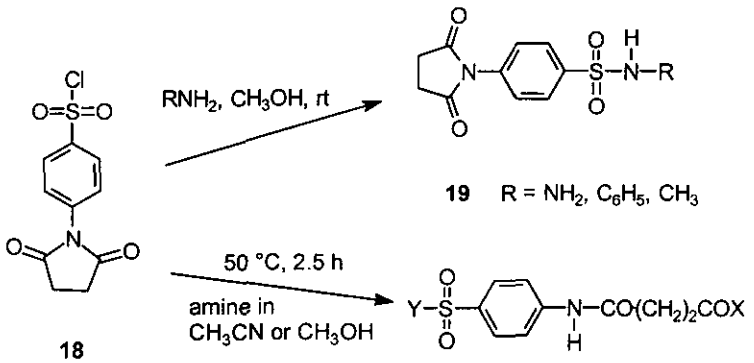
the carbonyl group (a) in **13**. Thus, the amino groups (amine is softer than alcohol[16]) attack the carbonyl group (b) in **13** (Scheme 8).[15]



16 **17**

Scheme 9

Under these aminolysis conditions, other functional groups, such as the carboxylic ester in the succinimide (**16**), are unaffected (Scheme 9).[17]



18 **19** **20**

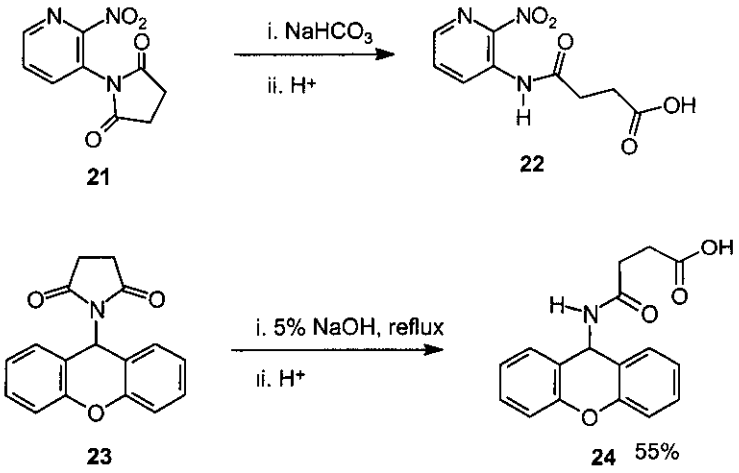
20	X	Y
a	$N(CH_3)_2$	$N(CH_3)_2$
b	morpholino	morpholino
c	$NHNH_2$	$NHNH_2$
d	$NHN{=}C(CH_3)_2$	$NHN{=}C(CH_3)_2$
e	OCH_3	$N(CH_3)_2$

Scheme 10

However, sulphonyl chlorides have higher reactivities toward amines than succinimides. *N*-(*p*-Chlorosulphonylphenyl)succinimide (**18**) reacted with two equivalents of amine in methanol at room temperature to give the sulphonamides (**19**). However, with four equivalents of amine in acetonitrile at higher temperature (50 °C), **18** was also ring-opened to yield **20a-d** (yields unreported). The same

reaction with four equivalents of dimethylamine in warm methanol gave a mixture of **20a** and **20e** (Scheme 10).[18]

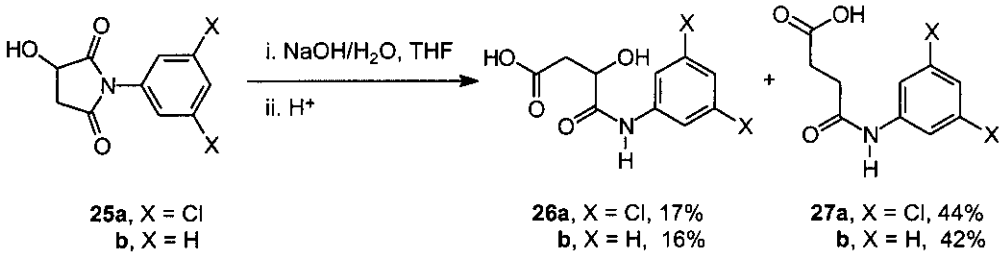
In summary, reactions between succinimides and amines (including hydrazines) proceed under mild conditions to give diamides in high yields. Moreover, oxygen nucleophiles (*e. g.* HO^-, MeOH) do not interfere with the aminolysis reaction at room temperature.



Scheme 11

b) Oxygen-linked nucleophiles

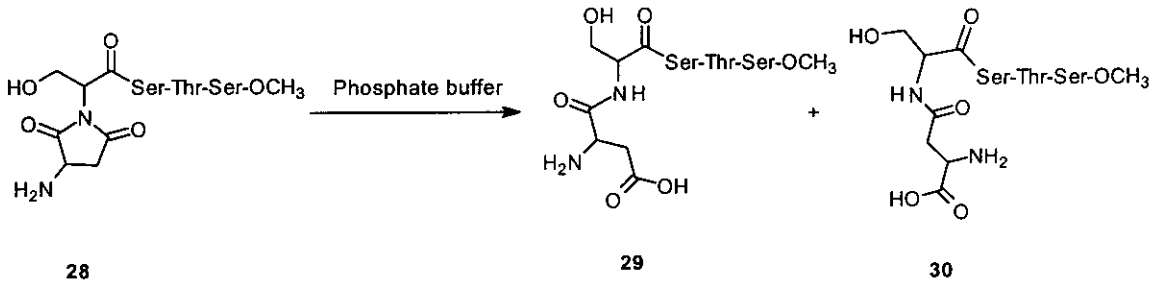
In contrast to ordinary amides, succinimides (*e. g.* **21**, **23**) can be hydrolyzed to carboxylic acids under weakly basic conditions (Scheme 11).[19]



Scheme 12

The regioselectivity for the hydrolysis of succinimides is lower than that for the amination reactions discussed in the previous section. When *N*-aryl-2-hydroxysuccinimides (**25a,b**) were hydrolyzed with

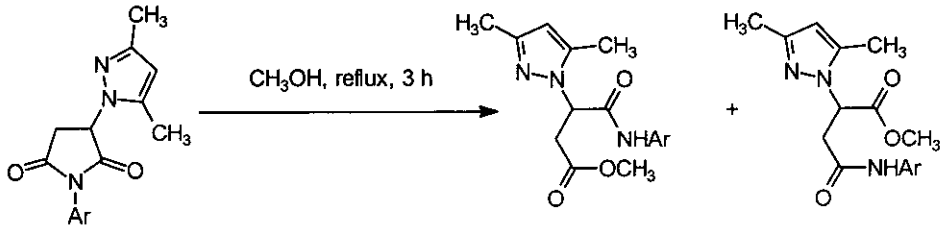
aqueous NaOH solution (0.2 N) at room temperature for 12 h, pairs of compounds (**26a,b**) and (**27a,b**) were obtained with low selectivity (Scheme 12).[20]



28 **29** **30**

Scheme 13

Succinimides containing ester or amide groups can be hydrolyzed selectively under mild conditions (Scheme 13), without affecting the ester or amide group. Thus, **28** gave two products (**29**) and (**30**), unfortunately in unreported ratio and yield.[21]

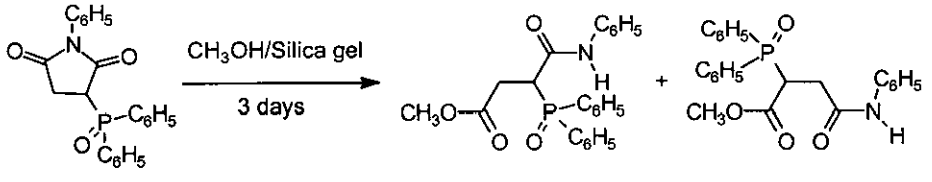


13 **31** **32**

Ar: C_6H_5, *p*-$CH_3C_6H_4$, 3,5-$Cl_2C_6H_3$

Scheme 14

Succinimides are ring opened by methanol under mild conditions into methyl esters. When substituents are present on the succinimide ring, mixtures are formed, *e. g.* the methanolysis of **13** gave products (**31**) and (**32**) (Scheme 14).[16]

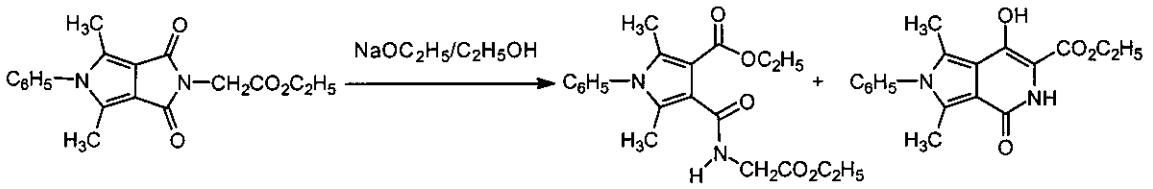


33 **34** **35**

Scheme 15

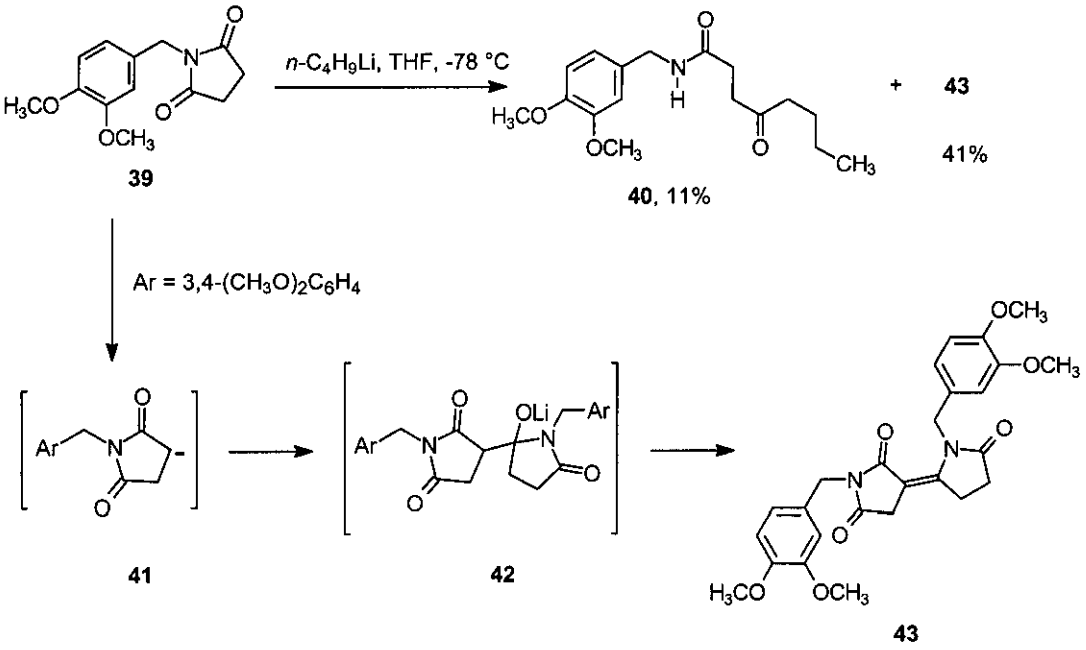
The methanolysis of compound (**33**) occurs on silica gel at room temperature after several days to give esters (**34**) and (**35**) (Scheme 15),[22] again in unreported ratio and yield.

Succinimides can also be transformed into esters under basic conditions. Compound (**36**) was heated with one equivalent of $NaOC_2H_5$ in ethanol at room temperature for one hour to give a mixture of **37** and **38**. Compound (**37**) underwent subsequent cyclization to **38** (34%) upon heating in ethanol with an excess of $NaOC_2H_5$ (Scheme 16).[23]



Scheme 16

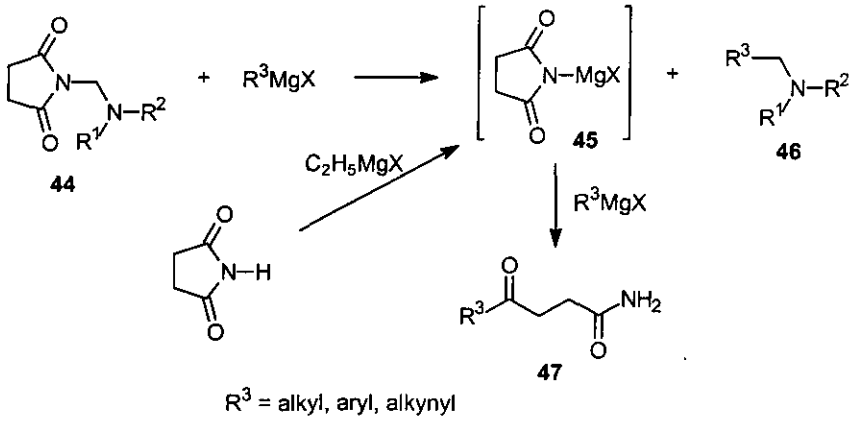
The above examples demonstrate that the hydrolysis and esterification of succinimides proceed under mild conditions, but the yields and regioselectivity are relatively low, compared to the aminolysis reaction.



Scheme 17

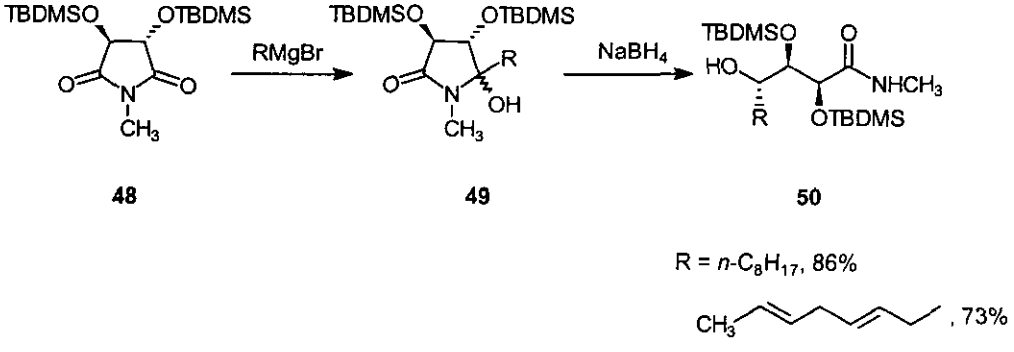
c) Carbon-linked nucleophiles

Reactions between succinimides and lithium reagents produce low yields of ketones (*e. g.* **39** → **40**, Scheme 17). Since lithium reagents are strong bases, they abstract one proton from the succinimide to form an imidic enolate (**41**), which then undergoes intermolecular nucleophilic addition to another molecule of succinimide to produce dimeric products (**43**) (Scheme 17).[24]



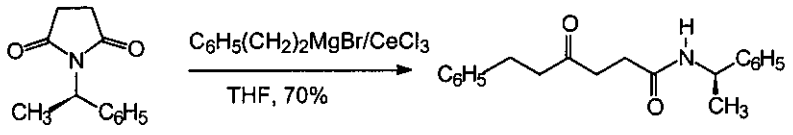
Scheme 18

Reactions of *N*-(aminomethylene)succinimides (**44**) with two equivalents of Grignard reagents afforded ring opening products γ-keto amides (**47**) and tertiary amines (**46**) (Scheme 18).[25] The reaction involves a salt-like succinimidomagnesium halide intermediate (**45**). By a similar reaction sequence, succinimide itself can be treated with ethylmagnesium halide to form intermediate (**45**), which reacts further with various Grignard reagents to give γ-keto amides (**47**) in 35-69% yields (Scheme 18).[26]



Scheme 19

If C-deprotonation of the succinimide ring CH_2 as shown in **41** is blocked by suitable substitution, *e. g.* **48**, the addition of Grignard reagents led smoothly to the formation of labile hydroxy lactams (**49**) easily reduced to amides (**50**) (Scheme 19).[27,28]



51 **52**

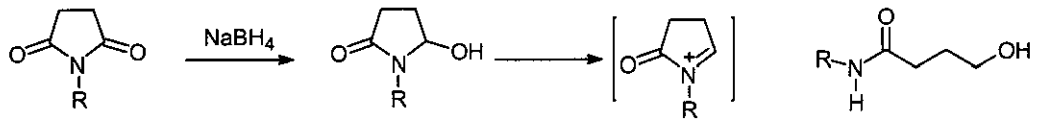
Scheme 20

In the general case, formation of the enolate as in **41** can be avoided by converting the basic lithium or Grignard reagents into organocerium reagents, which can be generated *in situ* from Grignard reagents and cerium (III) chloride. Organocerium reagents can react with succinimides (*e. g.* **51**, Scheme 20) to produce the desired amido ketones (*e. g.* **52**) in moderate yields.[29] Without cerium chloride, only dimeric products were produced in this reaction.

In summary, the reaction of carbon nucleophiles with succinimides depends on the organometallic reagents being used. For basic organolithium and magnesium reagents, proton abstraction and subsequent dimerization are always observed along with the nucleophilic substitution. Fortunately, selective nucleophilic substitution could be attained using less basic organocerium reagents.

d) Reduction

Generally, succinimides can be reduced to give hydroxy lactams (*e. g.*, **1** → **53**, Scheme 21), which are precusors to α-acyliminium salts (**54**) and other functional groups.[27] Under certain conditions, hydroxy lactams (**53**) can be reduced further to give ring opened ω-hydroxy amide (**55**) as product (Scheme 21, *cf.* Scheme 19).[28, 30]



1 **53** **54** **55**, R = *p*-$O_2NC_6H_4$

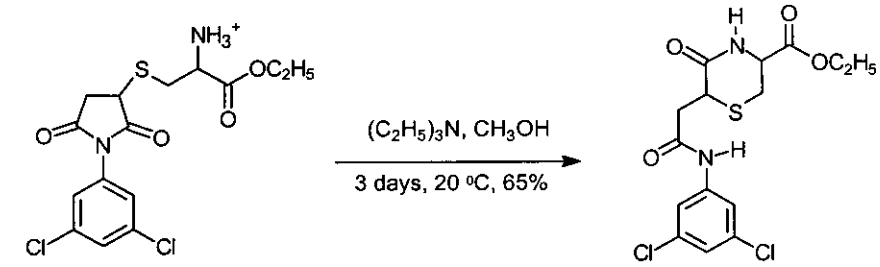
Scheme 21

III. INTRAMOLECULAR REACTIONS

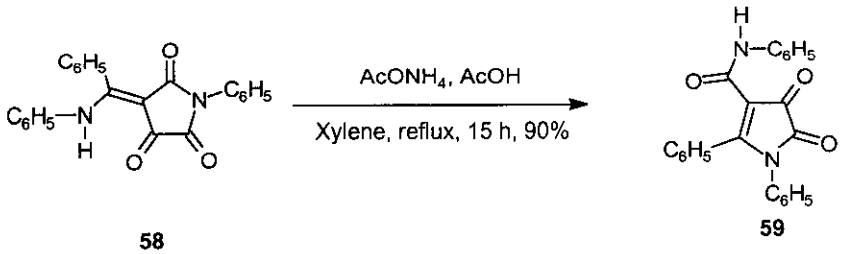
c) Nucleophilic substitution

When an amino group is tethered to a succinimide (*e. g.*, **56** and **58**), it will react to form preferentially a five or six-member ring product (**57**) and (**59**) (Scheme 22).[31]

A tethered amido group can also react with succinimides to form a new succinimide ring (*e. g.*, **60** → **64**, Scheme 23).[32] The first step is the hydrolysis of **60** to give compound (**61**), then the amide reacts intramolecularly *via* an intermediate of **62** to give **64** in high yield. Hydrogen bonding between the amide nitrogen and the imide carbonyl, as shown in **60** probably controls the site of attack by base.



56 **57**

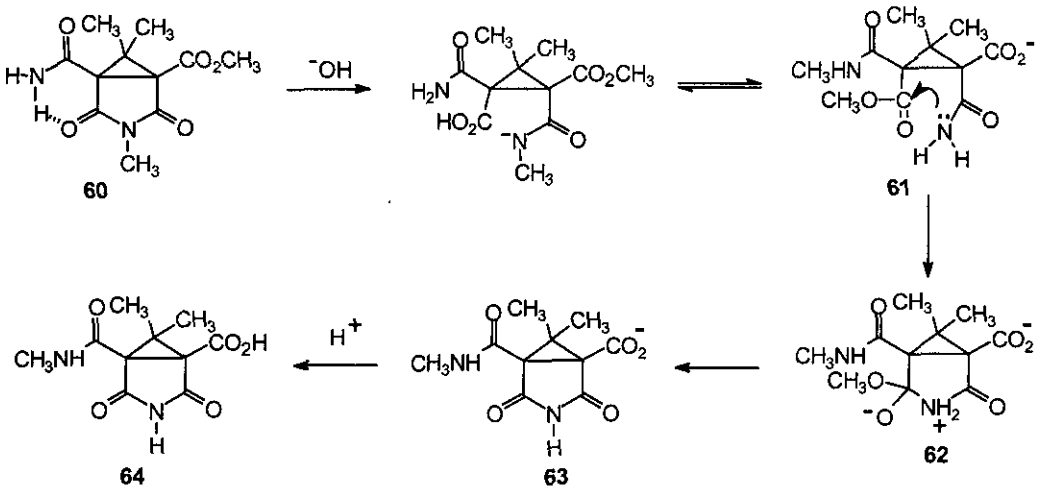


58 **59**

Scheme 22

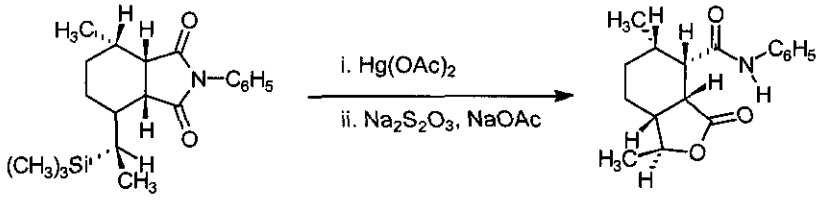
Similar to amino groups, tethered hydroxy group can react with succinimides to form a new five or six membered ring by opening of the succinimide moiety. In the sequence shown in Scheme 24, the silane group in **65** is the precursor of a hydroxy group.[33]

Tethered phenolic groups also undergo intramolecular nucleophilic substitutions to form six-membered ring products in high yields (*e. g.*, **67** → **68**, Scheme 25).[34] The first step of this reaction is the



Scheme 23

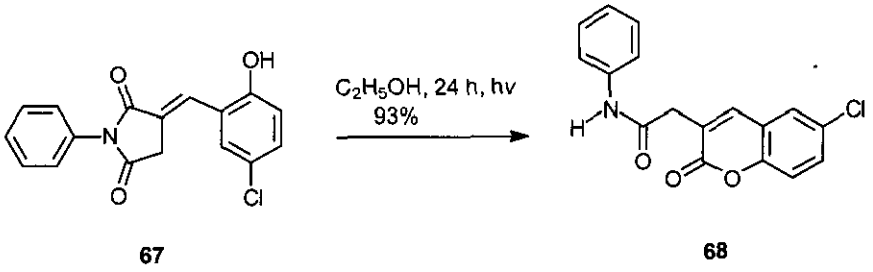
isomerisation of the *trans*- to a *cis*-double bond in **67** under photochemical conditions, then the *cis*-intermediate undergoes intramolecualr nucleophilic substitution to give **68**.



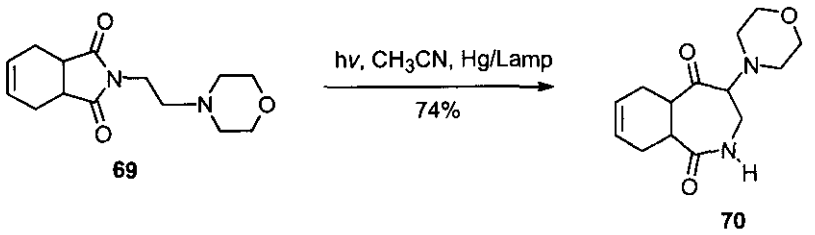
Scheme 24

b) Photochemical ring opening

Succinimides can undergo ring-opening and intramolecular cyclization under photochemical conditions.



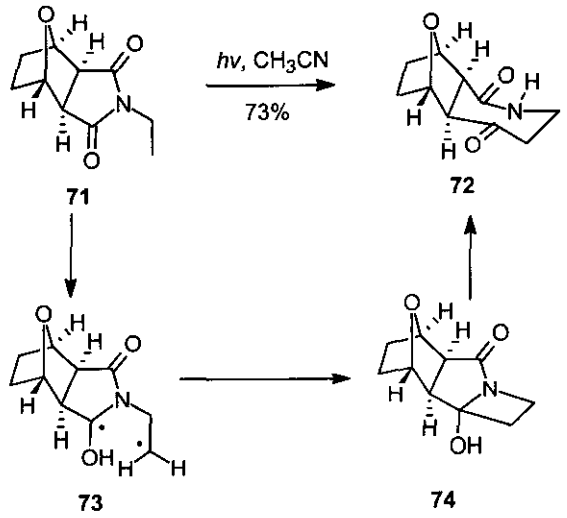
Scheme 25



69 70

Scheme 26

When compound (**69**) was irradiated, compound (**70**) was obtained in 74% yield (Scheme 26).[35] Under the same conditions, irradiation of *N*-ethylsuccinimide (**71**) gave **72** (73%) (Scheme 27).[36] The first step of the photochemical reaction is the 1,5-hydrogen shifts (the Norrish type II photochemical reaction) to give a biradical intermediate (**73**), followed by the formation of an aza-cyclobutanol (**74**), subsequent ring opening afforded **72** (Scheme 27).[37]



71 72 73 74

Scheme 27

In summary, intramolecular reactions of succinimide with oxygen or nitrogen nucleophiles give five or six member ring product. The photochemical reaction can be used to prepare seven member ring lactam.

IV. CONCLUSIONS

The above examples illustrate the reactivity of succinimides towards nucleophiles which makes them useful synthetic intermediates. Such reactions usually result in ring opening which is sometimes followed by cyclization to form a new heterocyclic ring. Reactive nucleophiles include amines (primary and

secondary, aliphatic and aromatic), amides, hydrazines, alcohols, and organometallic reagents. High selectivity is generally observed towards nitrogen- as compared with oxygen- nucleophiles.

V. REFERENCES

1. M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, 1970, **70**, 439.
2. J. Hudec, M. Polievka, S. Polacek, and V. Macho, Czech. CS 237,122, 1987 (*Chem. Abstr.*, 1988, **108**, 17770x).
3. R. H. Walsh, PCT Int. Appl. WO 87 02,663, 1987 (*Chem. Abstr.*, 1987, **107**, 137365v); L. Ziemianski, W. Stanik, Z. Lukasik, E. Przyluska, J. Lewandowski, A. Cacha, T. Surawski, R. Kacki, and K. Naruszewicz. Pol. Pl 167,129, 1995 (*Chem. Abstr.*, **124**, 121806e).
4. O. L. Mikhailova, E. A. Paron'kina, and B. V. Shchekin, *Khim. Tekhnol. Topl. Masel* 1990, *20*; S. L. Wang, G. R. Meyer, and K. C. Brinkman, U.S. US 5024677, 1996 (*Chem. Abstr.*, 1991, **115**, 117603h).
5. E. Toja, C. Gorini, C. Zirotti, F. Barzaghi, and G. Galliani, *Eur. J. Med. Chem.* 1991, **26**, 403.
6. G. Galliani, F. Barzaghi, C. Zirotti, and E. Toja, Eur. Pat. Appl. EP 296,979, 1988 (*Chem Abstr.*, 1989, **110**, 173082w).
7. D. M. Vyas, M. G. Saulnier, and J. F. Kadow, Eur. Pat. Appl. EP 291,957, 1988 (*Chem. Abstr.*, 1989, **111**, 23896w).
8. S. Souda, N. Ueda, S. Miyazawa, K. Tagami, S. Nomoto, M. Okita, N. Shimomura, T. Kaneko, and M. Fujimoto *Eur. Pat. Appl. EP* 268956, 1988 (*Chem. Abstr.*, 1989, **110**, 23889a).
9. A. K. Bose, *Org. Synth., Coll. Vol. 5*, 1973, 973.
10. V. B. Ranadive and S. D. Samant, *Indian J. Chem., Sect B*, 1995, **34B**, 102.
11. K. Kato, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1736.
12. M. Augustin and P. Jeschke, *J. Prakt. Chemie,* 1987, **329**, 607.
13. V. I. Kabachnyi, O. F. Kochinova, L. A. Porokhnyak, and A. M. Brizitskaya, *Farm. Zh.* (Kiev), 1991, 42.
14. H. Dugas and J. Vaugeois, *Synthesis*, 1991, 420.
15. M. S. Abd El Halim, A. Nada, and W. A. Gad, *Monatsh. Chem.*, 1994, **125**, 1437.
16. R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, 1967, **89**, 1827.
17. F. Reliquet, A. Reliquet, and J. C. Meslin, *Phosphorus Sulfur,* 1994, **89**, 63.
18. R. Cremlyn and R. Nunes, *J. Chem. Soc. Pak.*, 1987, **9**, 611; R. Cremlyn and R. Nunes, *Gazz. Chim. Ital.*, 1987, **117**, 183.
19. L. Bukowski and M. Janowiec, *Pharmazie*, 1989, **44**, 267; I. Zeid, S. El-Kousy, A. M. El-

Torgoman, and A. H. Ismail, *Liebigs Ann. Chem.*, 1987, 163.

20. H. Shih and G. O. Rankin, *Synthesis*, 1989, 866.
21. Y. Okada and S. Iguchi, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2129.
22. J. J. G. S. Van Es, K. Jaarsveld, and A. van der Gen, *J. Org. Chem.*, 1990, **55**, 4063.
23. W. Malinka and T. Bodalski, *Pol. J. Chem.*, 1995, **69**, 95.
24. M. I. Collado, E. Lete, N. Sotomayor, and M. J. Villa, *Tetrahedron*, 1995, **51**, 4701.
25. M. Sekiya and Y. Terao, *Chem. Pharm. Bull.*, 1970, **18**, 947.
26. M. Sekiya and Y. Terao, *Chem. Pharm. Bull.*, 1971, **19**, 391.
27. W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367.
28. H. Yoda, T. Katagiri, and K. Takabe, *Tetrahedron Lett.*, 1991, **32**, 6771.
29. P. D. Bailey, K. M. Morgan, D. I. Smith, and J. M. Vernon, *Tetrahedron Lett.*, 1994, **35**, 7115.
30. J. C. Hubert, J. B. P. A. Wijnberg, and W. N. Speckamp, *Tetrahedron*, 1975, **31**, 1437.
31. B. Zaleska, *J. Prakt. Chemie*, 1988, **330**, 841.
32. H. Hart and F. Freeman, *J. Am. Chem. Soc.*, 1963, **85**, 1161.
33. I. Fleming, A. K. Sarkar, M. J. Doyle, and P. R. Raithby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2023.
34. R. G. Gailey and H. Zimmer, *Tetrahedron Lett.*, 1970, 2839.
35. L. R. B. Bryant and J. D. Coyle, *Tetrahedron Lett.*, 1983, **24**, 1841.
36. Y. Kanaoka, H. Okajima, Y. Hatanaka, and M. Terashima, *Heterocycles*, 1978, **11**, 455.
37. Y. Kanaoka, Y. Migita, and K. Koyama, *Tetrahedron Lett.*, 1973, **14**, 1193; P. J. Wagner, *Acc. Chem. Res.*, 1971, **4**, 168; Y. Kanaoka *Acc. Chem. Res.*, 1978, **11**, 407.

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