

Chemistry of Thiophene 1,1- Dioxides

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November 26, 2014

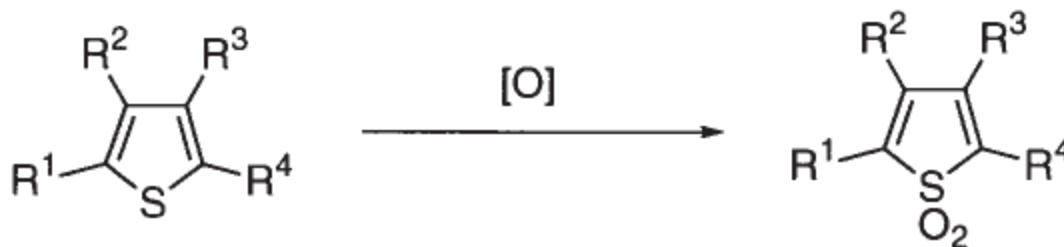
Contents

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- **Reactivities**
- Cycloadditions and Related Reactions
- Nucleophilic Addition
- Ring Opening Reactions
- Ring Alkylation
- SN2 Reactions
- Steglich Reagent
- Reduction and Oxidation
- Pyrolysis

Thiophene 1,1-dioxides

- Thiophene 1,1-dioxides are most commonly prepared by oxidation of thiophenes. Thiophene oxides, where two pairs of lone pair electrons are consumed for bond formation with oxygen atoms, are no longer aromatic.
- As unsaturated sulfones, they serve as dienophiles, 1,3-dipolarophiles, and Michael acceptors.
- They, as dienes, undergo a wide variety of synthetically useful Diels-Alder reactions and occasionally undergo even [4+6] cycloadditions.

Synthesis: *By Oxidation of Thiophenes*



• **For synthesis, organic peracids are the most common reagents.**

Such as *peracetic, perbenzoic, m-chloroperbenzoic, and trifluoroperacetic acids, and, in rare cases, p-nitroperbenzoic and monoperphthalic acids*

• **Dimethyldioxirane has been shown to be very useful for this oxidation.**

• **Many inorganic oxidizing reagents**

NaBO₃ · 4H₂O/AcOH and F₂/H₂O/CH₃CN produce a variety of thiophene dioxides in better yields

Synthesis: *By Oxidation of Thiophenes*

Table 5. Preparation of thiophene 1,1-dioxides by oxidation with *m*-CPBA

The structure shows a five-membered thiophene ring with a sulfur atom at the bottom position. The sulfur atom is bonded to two oxygen atoms, forming a 1,1-dioxide group. The ring carbons are numbered 2, 3, 4, and 5 starting from the sulfur. Substituents are labeled as follows: R¹ at position 2, R² at position 3, R³ at position 4, and R⁴ at position 5.

R ¹	R ²	R ³	R ⁴	Yield (%)	Reference
Me	H	H	Me	52	33
<i>t</i> -Bu	H	H	<i>t</i> -Bu	70	33
<i>t</i> -Bu	H	<i>t</i> -Bu	H	56	33
Ph	H	H	Ph	74	33
Me	Me	Me	Me		34
Me	Ph	Ph	Me		34
Cl	Cl	Cl	Cl	50	35
C _n H _{2n+1} ^a	H	H	C _n H _{2n+1} ^a	35–51	36
H	<i>t</i> -Bu	<i>t</i> -Bu	H	93	37
<i>t</i> -Bu	<i>t</i> -Bu	H	H	79	38
H	1-ad ^b	1-ad ^b	H	75	39
H	neop ^c	neop ^c	H	68	40
<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	75	41

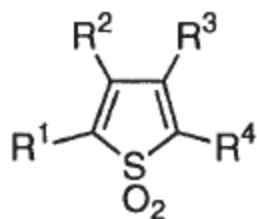
^a n = 6–11,

^b 1-ad = 1-adamantyl,

^c neop = neopentyl.

Synthesis: *By Oxidation of Thiophenes*

Table 6. Preparation of thiophene 1,1-dioxides by oxidation with dimethyldioxirane

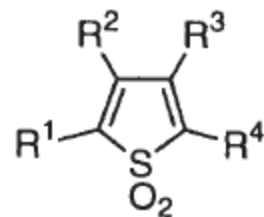


R ¹	R ²	R ³	R ⁴	Yield (%)
Me	H	H	Me	93
PhCH ₂	H	H	PhCH ₂	93
Ph	Ph	Ph	Ph	99
Br	H	H	Br	27
COPh	Ph	Ph	COPh	76
Et	H	H	COMe	53

- The oxidation is carried out under neutral conditions.
- In addition, workup procedure is very simple since the dimethyldioxirane is converted into acetone.
- The oxidation is applicable to thiophenes carrying electron-withdrawing substituent(s), which resist oxidation with peracids

Synthesis: *By Oxidation of Thiophenes*

Table 7. Preparation of thiophene 1,1-dioxides by oxidation with inorganic oxidizing reagents



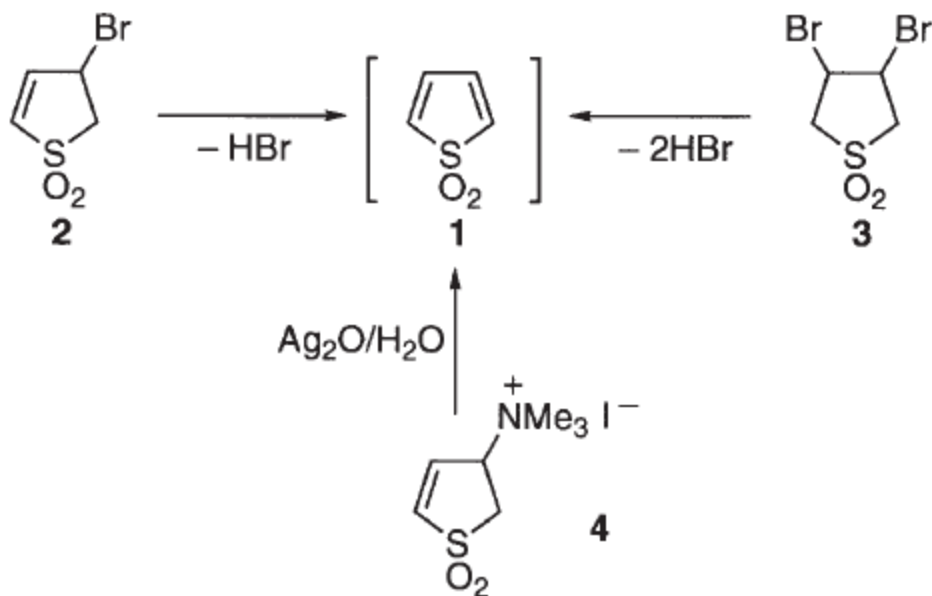
R ¹	R ²	R ³	R ⁴	Yield (%)	Method ^a
Me	H	H	Me	78	A
C ₉ H ₁₉	H	H	C ₉ H ₁₉	65	A
-CH=CH-CH=CH-		H	H	95	A
-CH=CH-CH=CH-		-CH=CH-CH=CH-		95	A
Me	H	H	Me	95	B
Br	H	H	Br	95	B
Cl	H	H	Cl	70	B
Me	H	H	CO ₂ Et	90	B
-CH=CH-CH=CH		H	H	100	B

^a Method A: NaBO₃ · H₂O, AcOH, 45–50°C. Method B: F₂, H₂O, CH₃CN, –10°C.

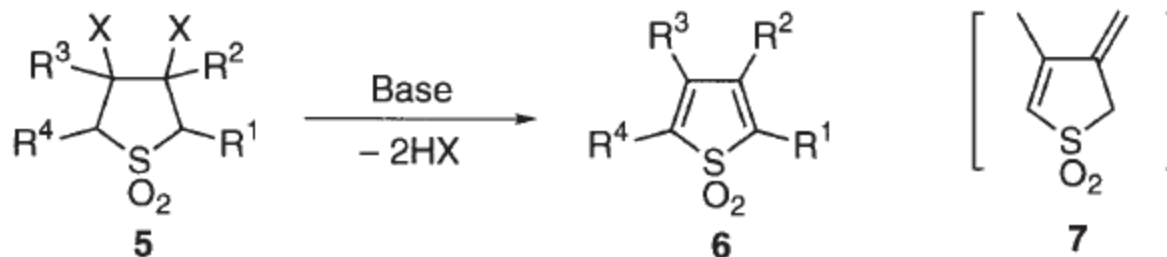
McKillop, A, Kemp, D. *Tetrahedron*(**1989**) 45,3299

Rozen, S, Bareket, Y. *J. Chem. Soc. Chem. Commun.* (**1994**) 1959

Synthesis: *From Dihydrothiophene and Tetrahydrothiophene 1,1-dioxide*



Synthesis: *From Dihydrothiophene and Tetrahydrothiophene 1,1-dioxide*

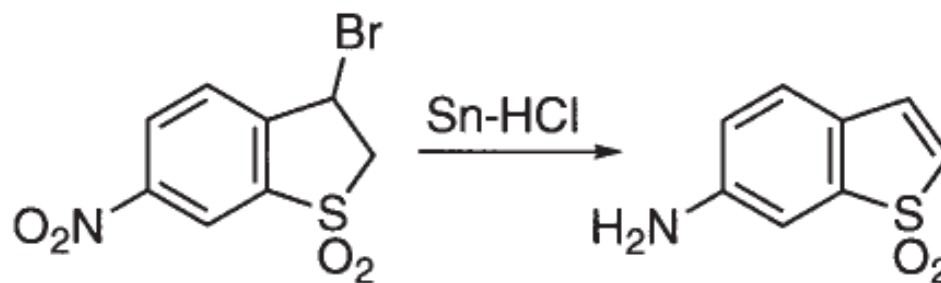
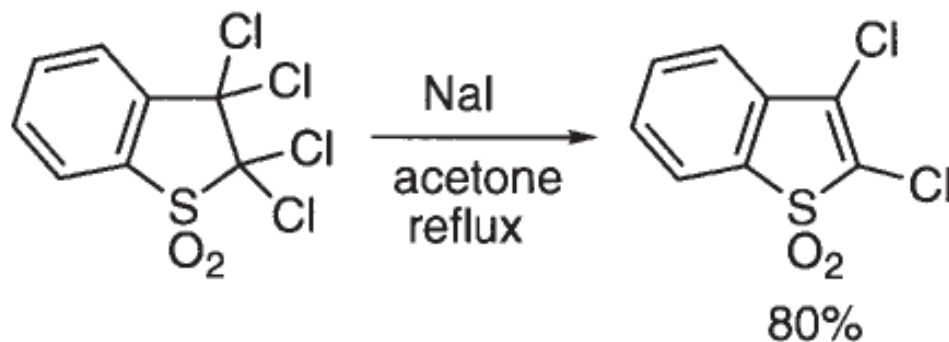


X = Cl or Br

- a: $R^2 = R^4 = H, R^1 = R^3 = t\text{-butyl}$
- b: $R^1 = R^4 = H, R^2 = R^3 = Cl$; 82%
- c: $R^1 = R^4 = H, R^2 = R^3 = Me$
- d: $R^1 = R^2 = R^3 = R^4 = Me$

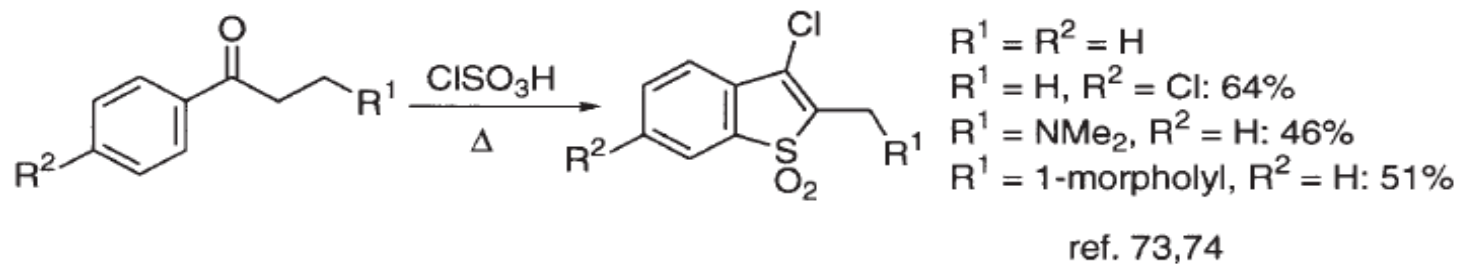
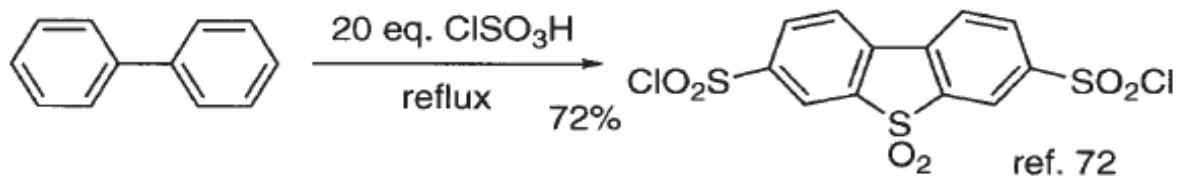
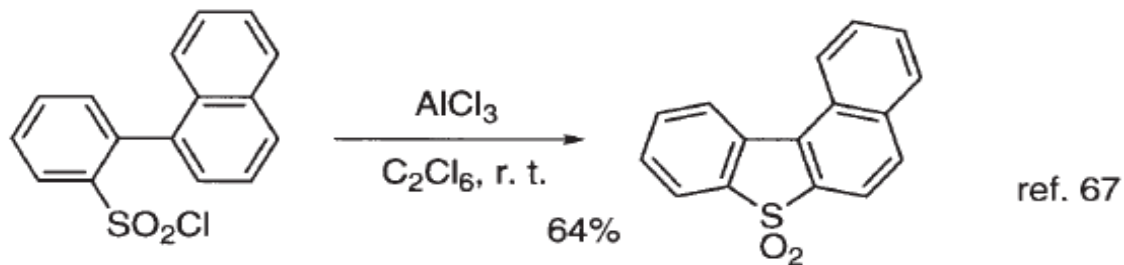
Synthesis: *From Dihydrothiophene and Tetrahydrothiophene 1,1-dioxide*

Benzo[b]thiophen 1,1-dioxides:



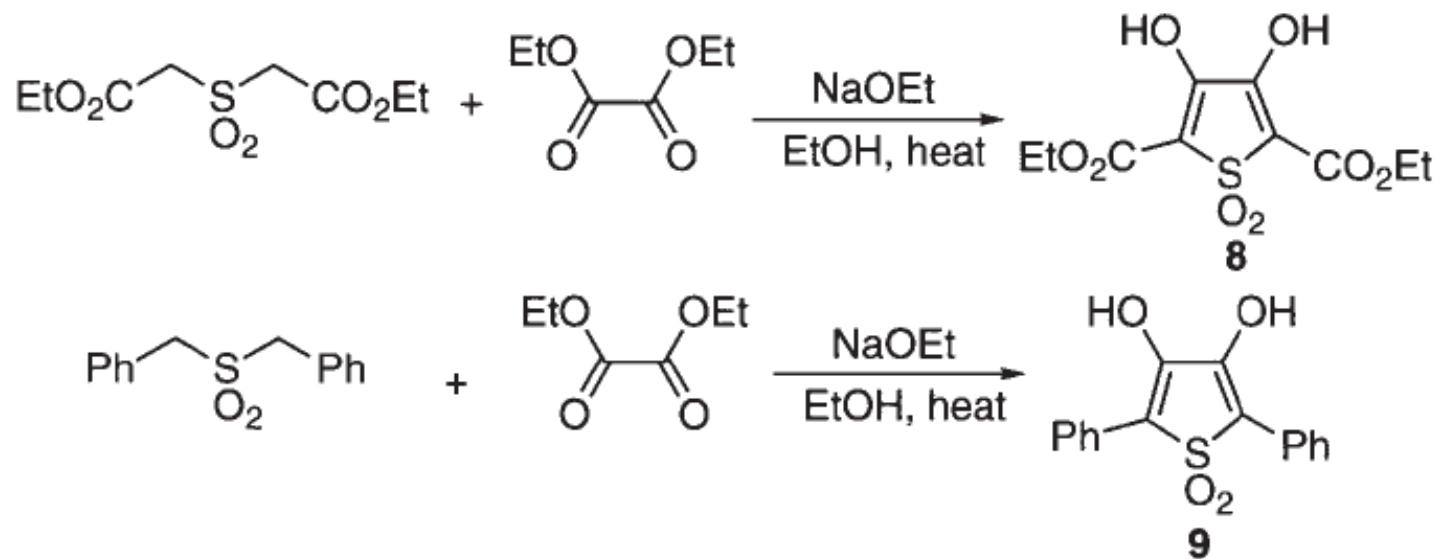
Synthesis: *By Intramolecular Cyclization*

Friedel-Crafts type reactions

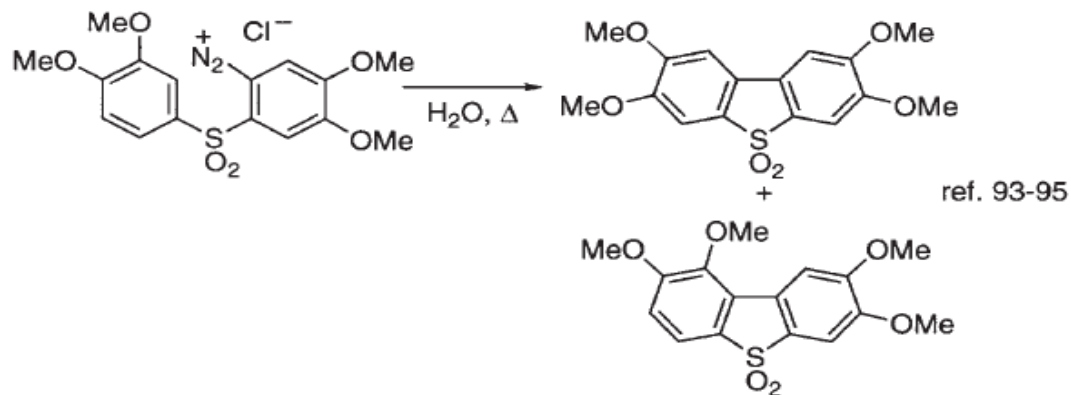
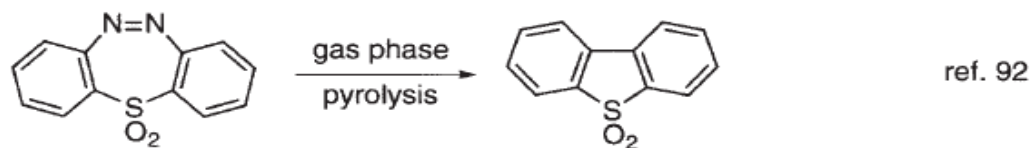
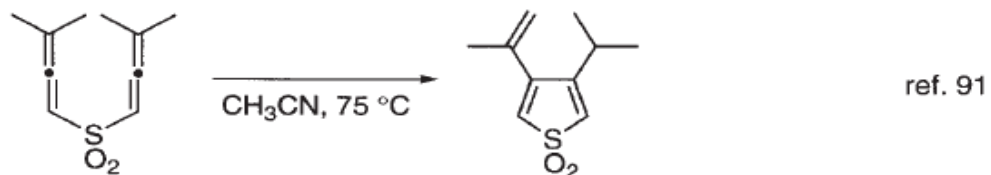
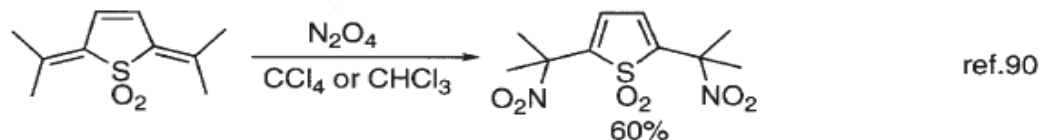


Synthesis: *By Intramolecular Cyclization*

Hinsberg type condensation:



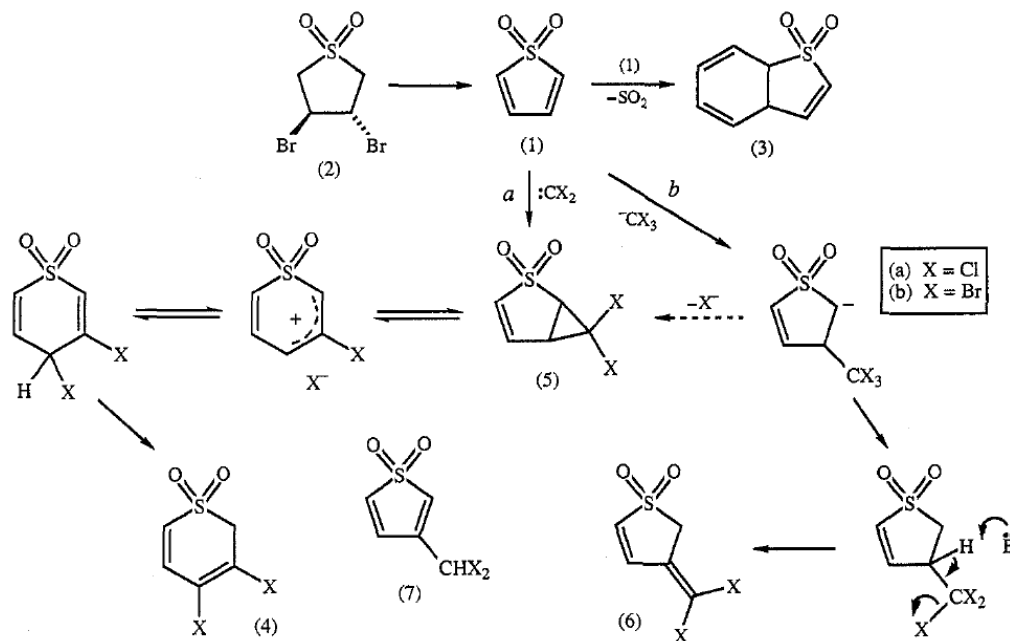
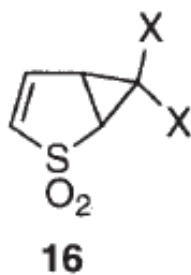
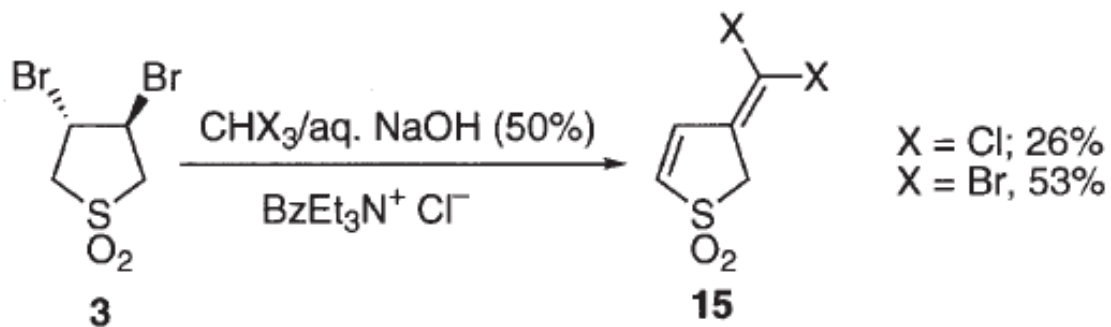
Synthesis: Miscellaneous



Reactivities:

- *As unsaturated sulfones, many of them are thermally labile .because of easy dimerization and are highly reactive toward other substrates.*
- *Monocyclic thiophene dioxides and benzo[b]thiophene dioxides serve as a 2π -component toward dienes and 1,3-dipoles, and monocyclic derivatives also act as dienes toward numerous 2π - and 6π -components.*
- *In addition, they undergo a wide variety of reactions with many other reagents. These are the very properties that make them synthetically most versatile.*

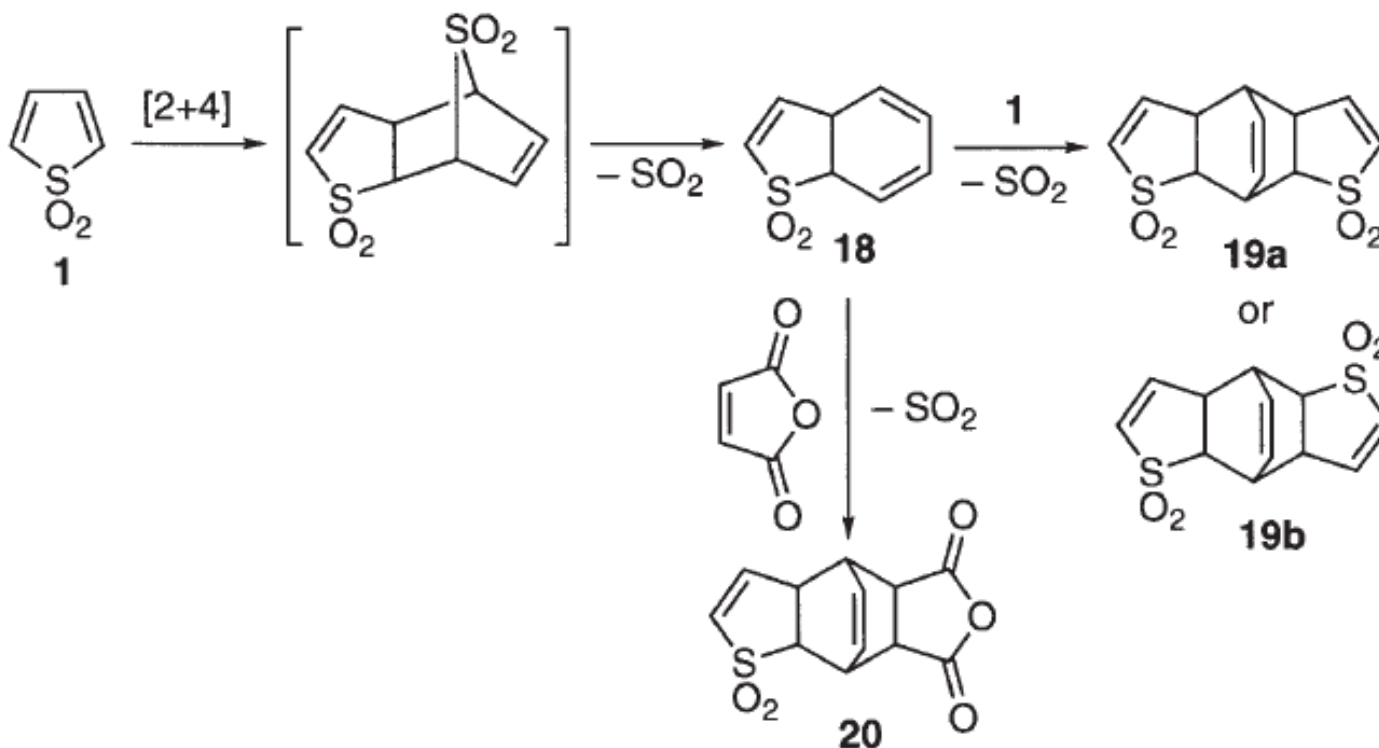
Reactivities: $[1+2]$ Cycloaddition



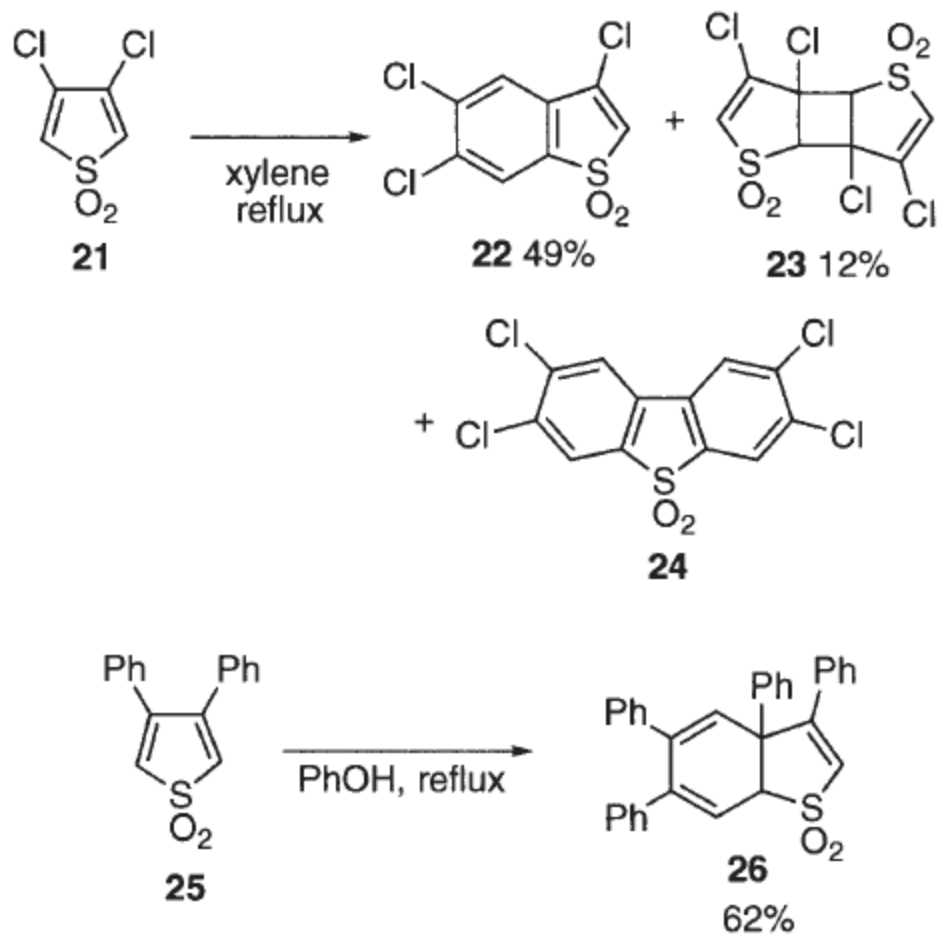
Reactivities: $[2+2]$ and $[2+4]$ Cyclodimerization

Thiophene 1,1-dioxides undergo cyclodimerization in two ways.

- Thermally labile anthiophene 1,1-dioxides undergo $[2+4]$ dimerization, one molecule acting as a dienophile and the other acting as a diene;
- Thermally stable thiophene 1,1-dioxides undergo $[2+2]$ dimerization on photoirradiation.



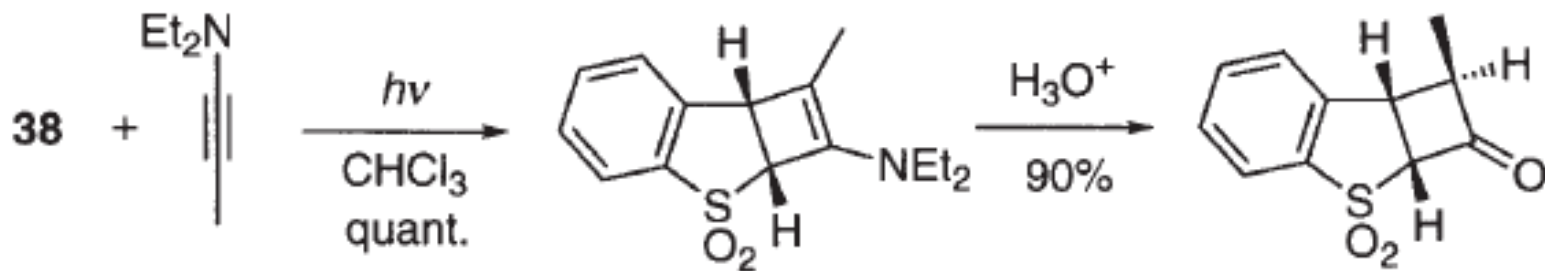
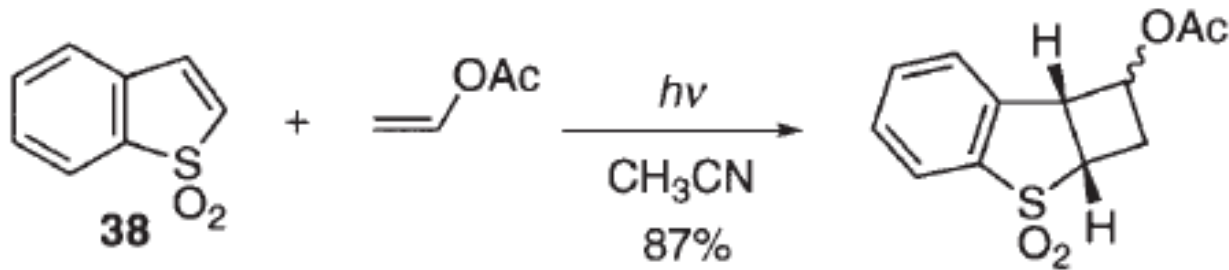
Reactivities: $[2+2]$ and $[2+4]$ Cyclodimerization



Bluestone. H, Bimber. R, Berkley. R, Mandel .Z. *J Org Chem* (1960) 26:346

Overberger. CG, Whelan. JM. *J Org Chem* (1961) 26:4328

Reactivities: $[2+2]$ Photocycloaddition

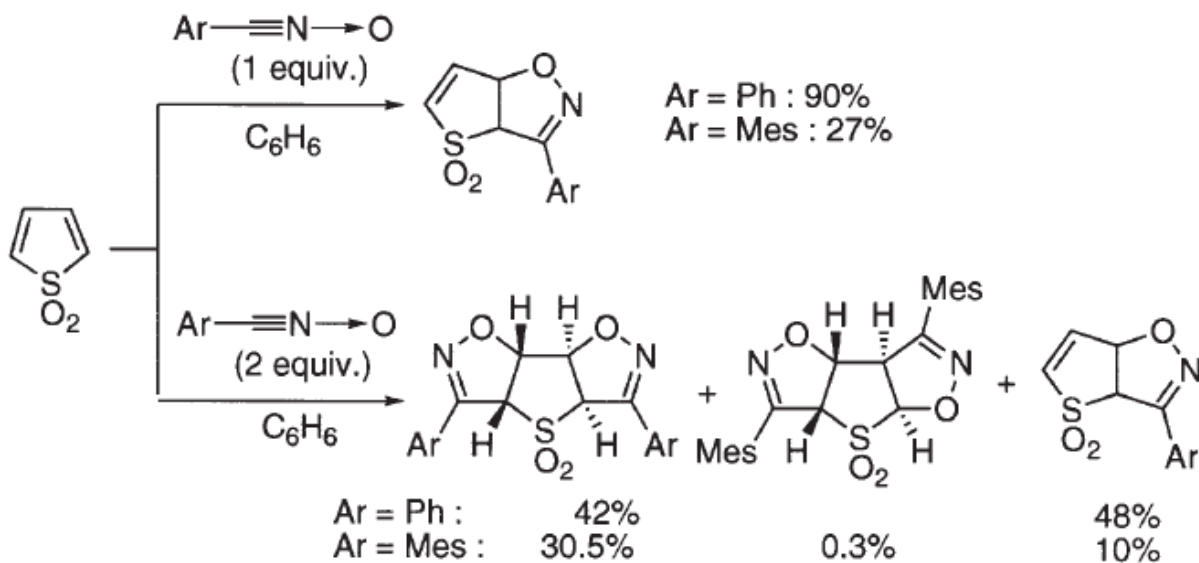
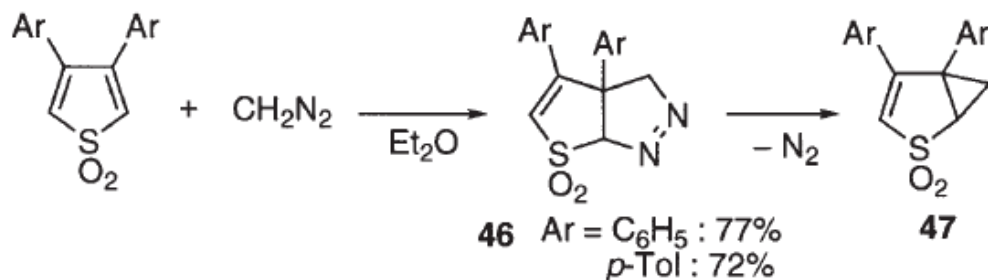


Ikeda, M, Uno, T, Homma, K, Ono, K, Tamura, Y. *Synth Commun* (1980) 10:437

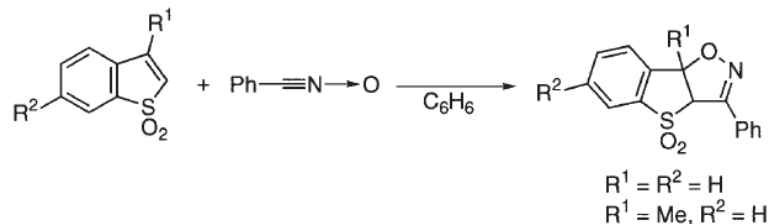
Eisch, J.J, Galle, J.E, Hallenbeck, L.E. *J Org Chem* (1982) 47:1608

Reactivities: 1,3-Dipolar Cycloaddition

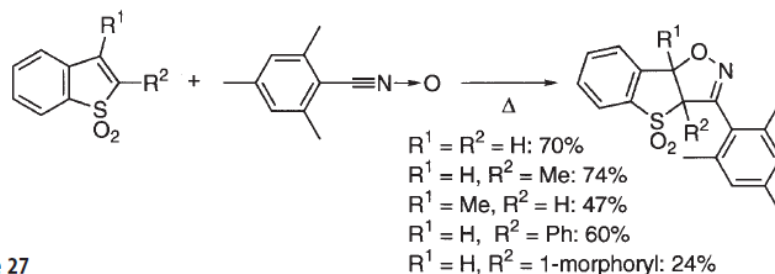
In most cases, 1,3-dipolar cycloadditions is regioselective



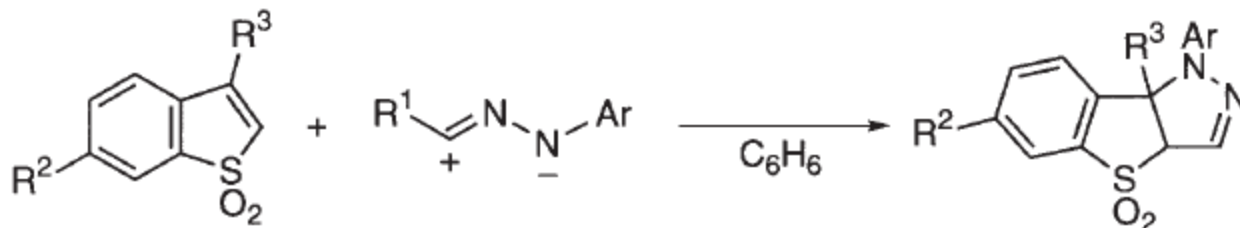
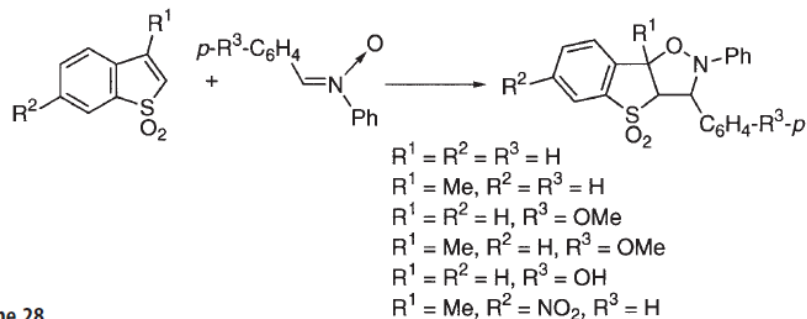
Reactivities: *1,3-Dipolar Cycloaddition*



scheme 27

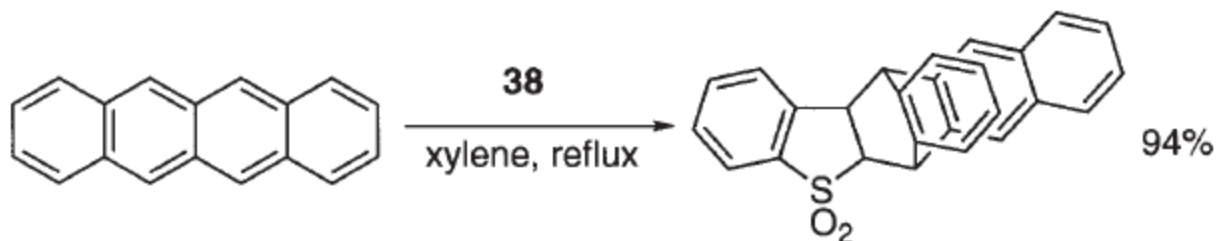
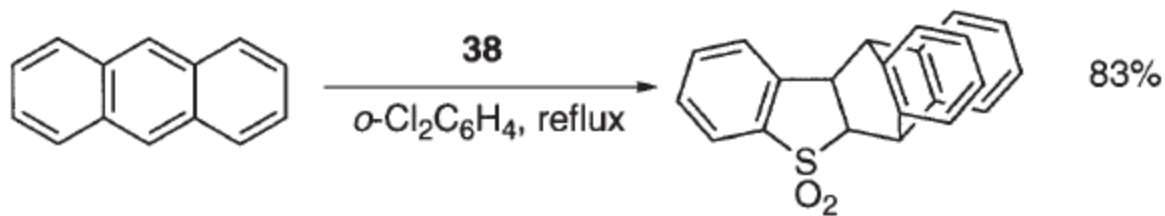
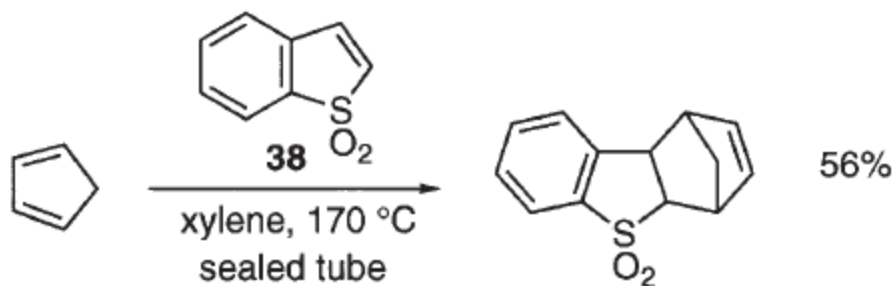


scheme 28



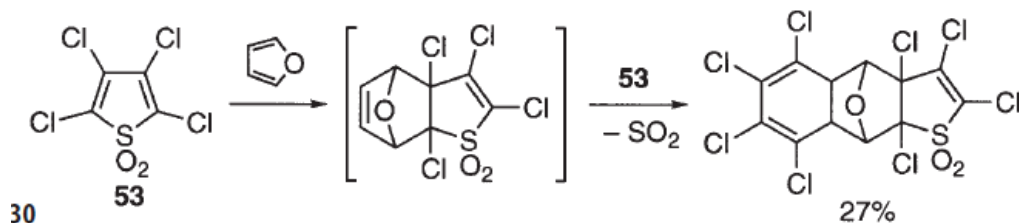
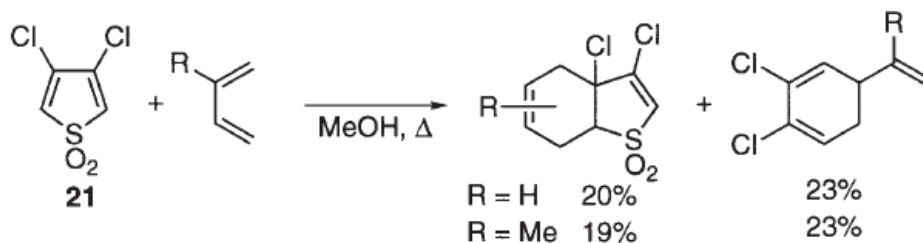
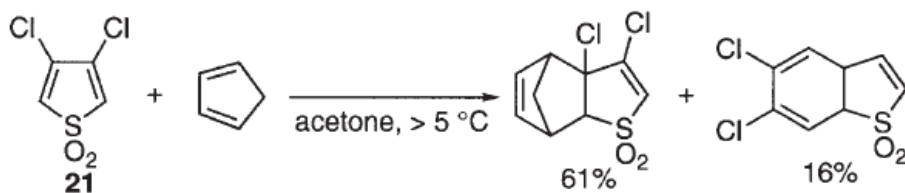
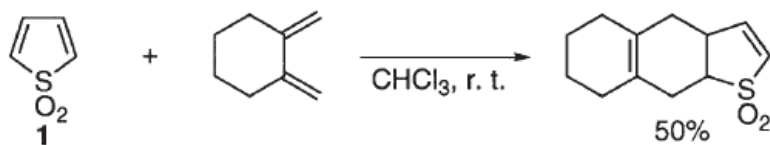
Reactivities: [2+4] Cycloaddition (Thiophene Dioxides as 2 π Component)

As a 4 π component toward dienophiles



Reactivities: [2+4] Cycloaddition (Thiophene Dioxides as 2π Component)

Behave as a dienophile toward 4π components



Reactivities: $[4+2]$ Cycloaddition (Thiophene Dioxide as 4π Component)

Thiophene dioxides act as a 4π component toward a wide variety of dienophiles.

- Due to the electron-withdrawing properties of the sulfonyl group, they are rather electron-deficient dienes. Therefore, dienophiles do not necessarily require activation by electron-withdrawing group(s) in order to undergo cycloaddition with most thiophene dioxides.
- The electron demand of the Diels-Alder reactions of thiophene dioxides often becomes inverse to that of common Diels-Alder reactions. Even electron-rich alkenes can then take part in the Diels-Alder reactions with thiophene dioxides. This is one of the features that makes thiophene dioxides synthetically important.
- Although the Diels-Alder reactions of many thiophene dioxides have been examined in great detail, the most extensively investigated are those with tetrachlorothiophene 1,1-dioxide. **This** is easily obtainable by oxidation of tetrachlorothiophene and is thermally stable, but is very reactive and can react with a wide variety of alkenic dienophiles.
- $[4+2]$ cycloadditions with alkenic dienophiles are classified for convenience into six categories according to the structures of the final products.

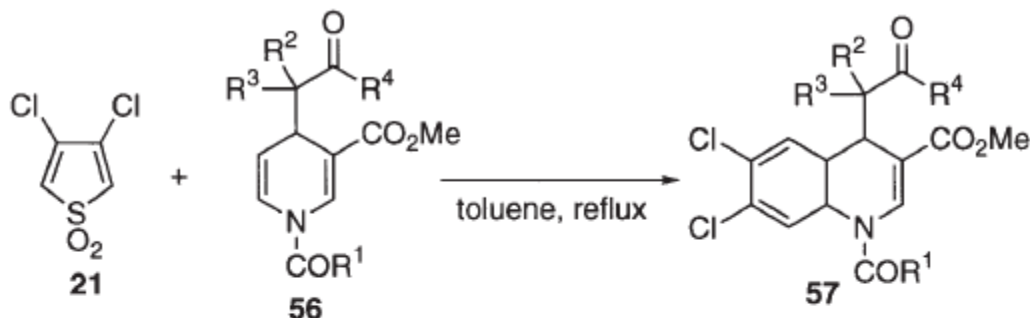
Table 8 (continued)

Dienophiles	Products	Yields
		R, R = CH ₂ CH ₂ CH ₂ :75 % R, R = CH ₂ (CH ₂) ₃ CH ₂ :73 % R, R = CH ₂ CH ₂ C(=CH ₂)CH ₂ CH ₂ :75 %
		74 %
		27 %
		80 %
		91 %
		65 %
		R = CH ₂ CH ₂ C ^o CH:70 % R = CH ₂ (CH ₂) ₈ CH ₃ :88 % R = CH ₂ (CH ₂) ₃ C = CH ₂ :69 % R = CH ₂ (CH ₂) ₄ C = CH ₂ :69 % R = CO ₂ H:68 % R = CO ₂ Me:91 % R = CN:83 % R = CH ₂ CO ₂ H:78 % R = CH ₂ (CH ₂) ₇ CO ₂ H:78 % R = CH ₂ Br:88 % R = CH ₂ NCS:55 % R = 4-(1,2-methylenedioxy)benzyl:75 % R = 2-pyridyl:75 % R = N-pyrrolidonyl:84 %

Reactivities:

[4+2] Cycloaddition with Alkenic Dienophiles

Category A: 1,3-Cyclohexadiene-Forming Reactions



$R^1 = \text{OEt}, R^2 = R^3 = \text{H}, R^4 = \text{Ph} : 21\%$

$R^1 = \text{OEt}, R^2 = \text{H}, R^3 = \text{Ph}, R^4 = \text{OMe} : 52\%$

$R^1 = \text{OEt}, R^2 = R^3 = \text{Me}, R^4 = \text{OMe} : 36\%$

$R^1 = \text{NMe}_2, R^2 = \text{H}, R^3 = \text{Ph}, R^4 = \text{OMe} : 54\%$

$R^1 = \text{NMe}_2, R^2 = R^3 = \text{Me}, R^4 = \text{OMe} : 36\%$

$R^1 = \text{OEt}, R^2 = R^3 = \text{H}, R^4 = \text{Ph} : 61\%^a$

$R^1 = \text{OEt}, R^2 = R^3 = \text{H}, R^4 = p\text{-MeOC}_6\text{H}_4 : 21\%^a$

$R^1 = \text{OMe}, R^2 = \text{H}, R^3 = \text{Me}, R^4 = \text{Et} : 55\%^a$

$R^1 = \text{OMe}, R^2 = \text{H}, R^3 = \text{Me}, R^4 = \text{Ph} : 31\%^a$

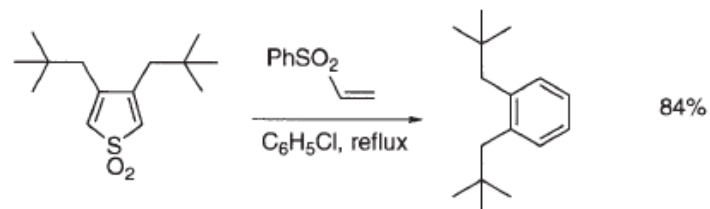
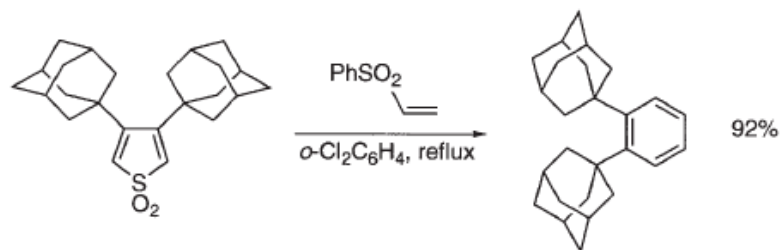
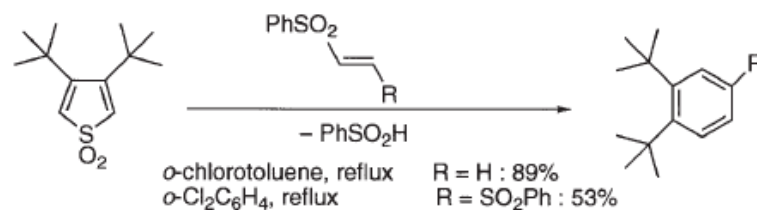
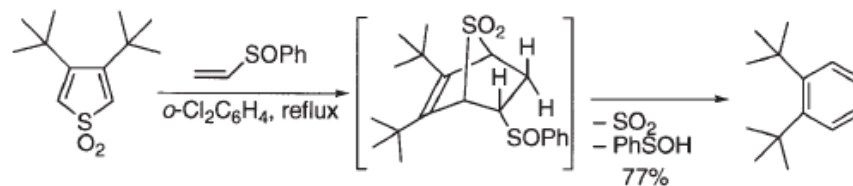
$R^1 = \text{OMe}, R^2 = R^3 = R^4 = \text{Me} : 22\%^a$

$R^1 = \text{NMe}_2, R^2 = R^3 = R^4 = \text{Me} : 22\%^a$

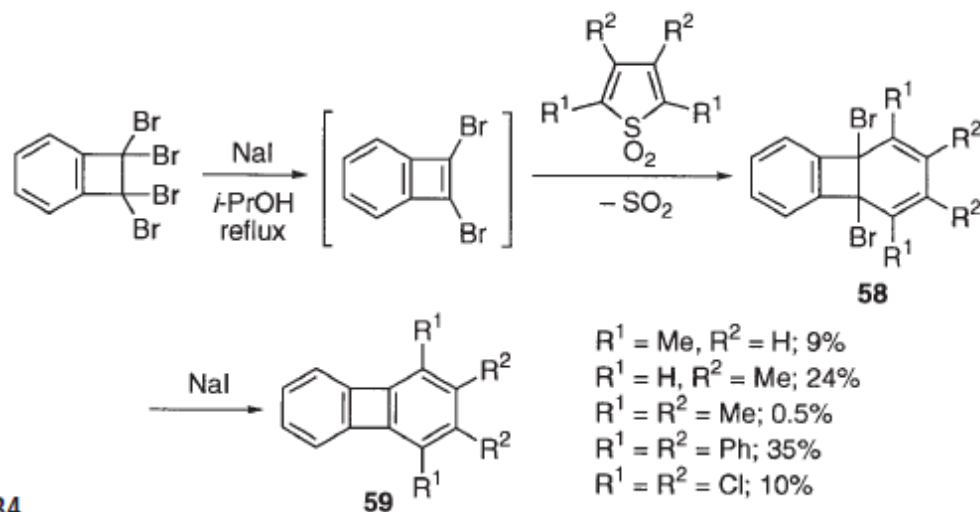
^a Results in the presence of 2,6-lutidine

Reactivities: [4+2] Cycloaddition with Alkenic Dienophiles

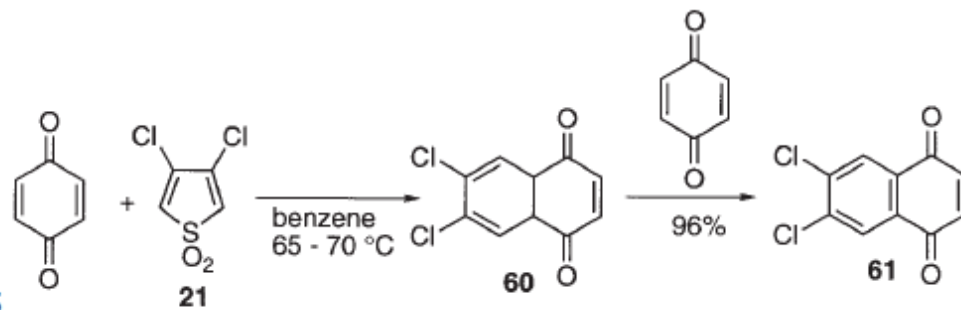
Category B: Benzene Ring-Forming Reactions by Removal of a Small Molecule from Initial Adducts



Reactivities: *Category B: Benzene Ring-Forming Reactions by Removal of a Small Molecule from Initial Adducts*

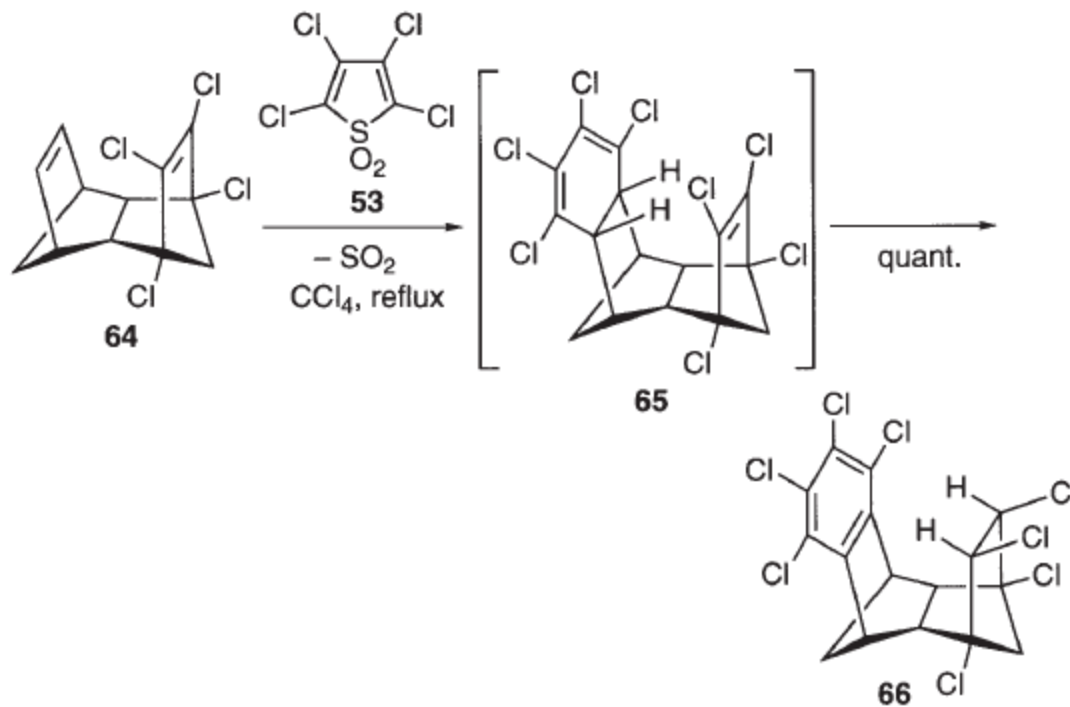


Scheme 34



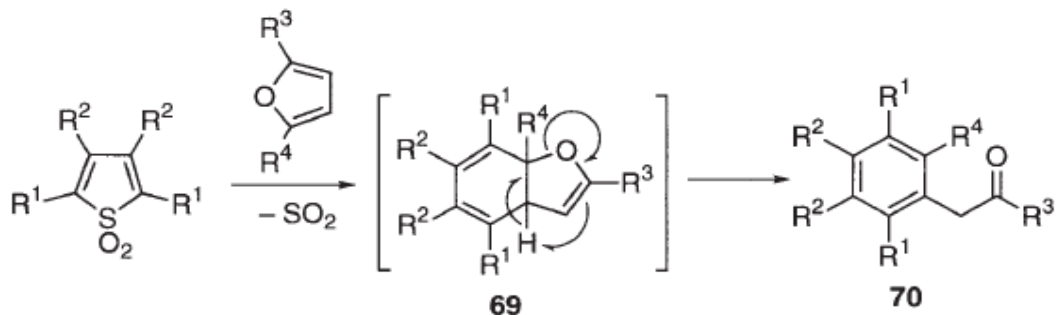
Scheme 35

Reactivities: *Category B: Benzene Ring-Forming Reactions by Removal of a Small Molecule from Initial Adducts*



Reactivities:

Category C: Benzene Ring-Forming Reactions by Ring Opening of Initial Adducts



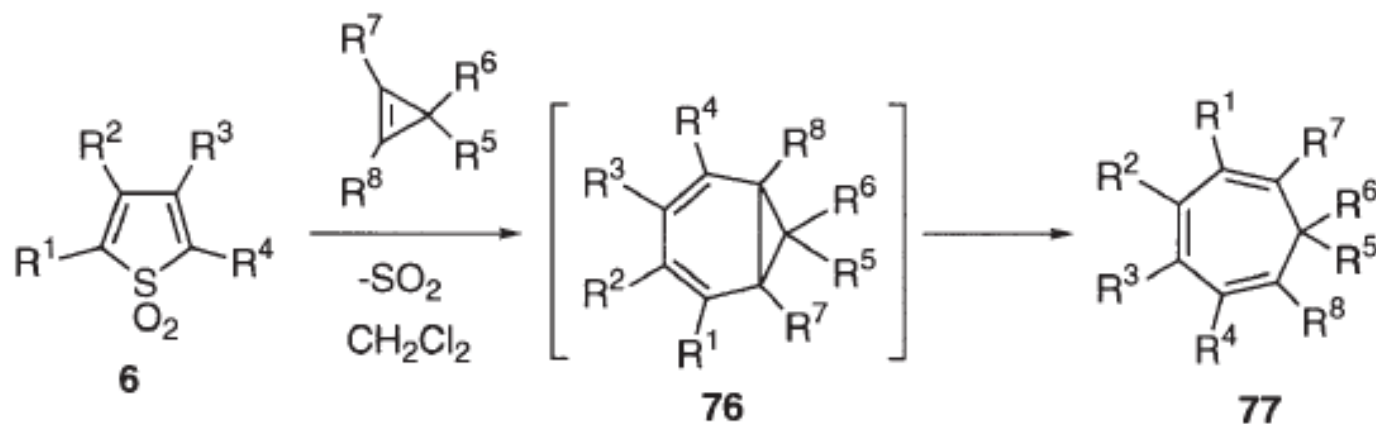
hexane, 65 °C, 30 min	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{Me}, \text{R}^4 = \text{H}: 92\%$
hexane, 65 °C, 30 min	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{Bu}, \text{R}^4 = \text{H}: 93\%$
93 °C, 30 min	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{R}^4 = \text{Me}: 90\%$
93 °C, 30 min	$\text{R}^1 = \text{R}^2 = \text{Br}, \text{R}^3 = \text{R}^4 = \text{Me}: 90\%$
93 °C, 30 min	$\text{R}^1 = \text{Cl}, \text{R}^2 = \text{H}, \text{R}^3 = \text{R}^4 = \text{Me}: 77\%$
$\text{ClCH}_2\text{CH}_2\text{Cl}$, 83 °C, 1 h	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{CH}_2\text{OAc}, \text{R}^4 = \text{H}: 74\%$
$\text{ClCH}_2\text{CH}_2\text{Cl}$, 83 °C, 1 h	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{CH}_2\text{NHAc}, \text{R}^4 = \text{H}: 74\%$
CH_2Cl_2 , 30 °C	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{OMe}, \text{R}^4 = \text{H}: 77\%$
100 °C, 22 h	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{CO}_2\text{Me}, \text{R}^4 = \text{H}: 62\%$ (enol form)
125 °C, 1 h	$\text{R}^1 = \text{R}^2 = \text{Cl}, \text{R}^3 = \text{COMe}, \text{R}^4 = \text{H}: 37\%$ (enol form)

Raasch,MS. *J Org Chem* (1980) 45, 867

Nakayama J, Yamaoka S, Nakanishi T, Hoshino M. *J Am Chem Soc.* (1988) 110:6598

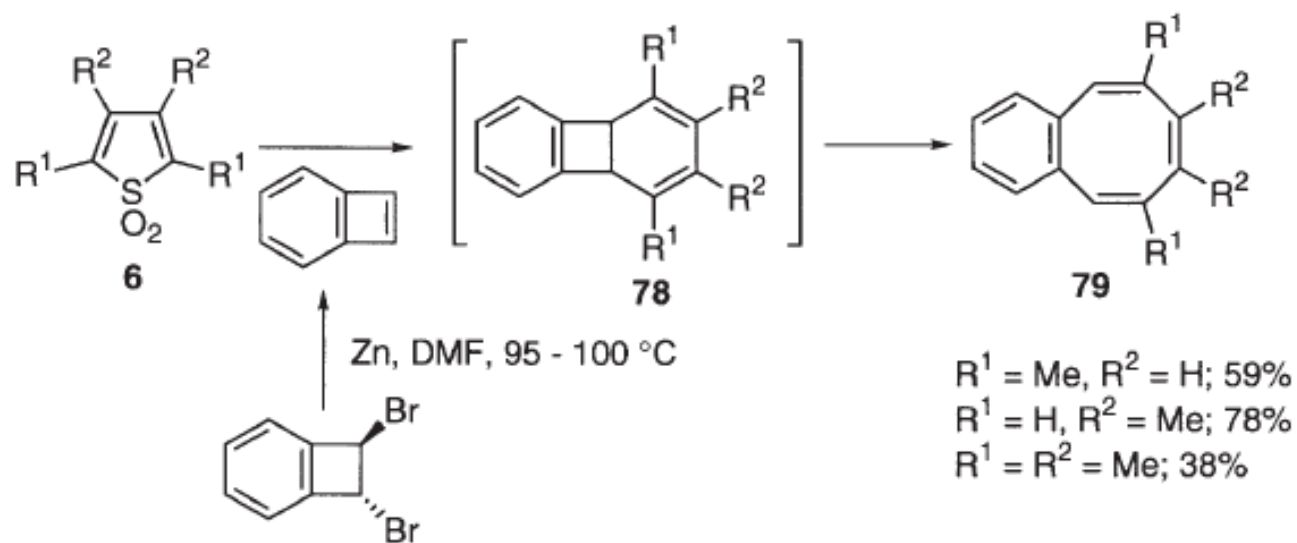
Reactivities:

Category D: Seven- and Eight-Membered Ring-Forming Reactions

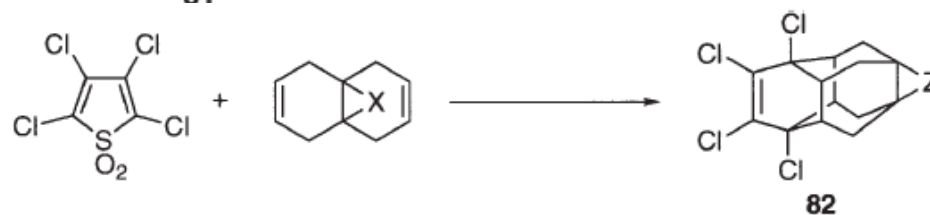
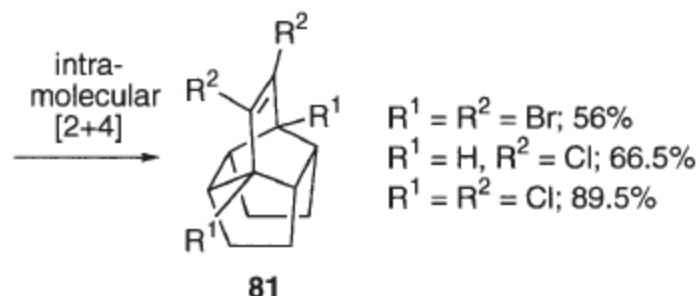
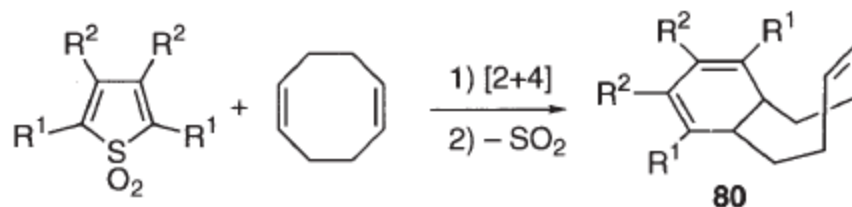


Reactivities:

Category D: Seven- and Eight-Membered Ring-Forming Reactions

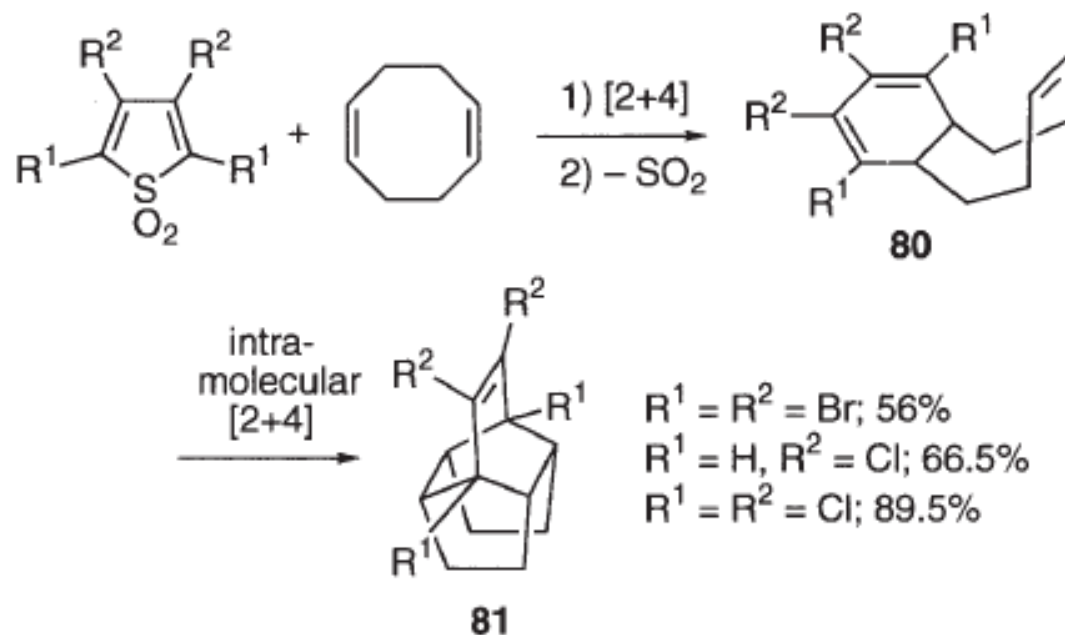


Reactivities: *Category E: [4+2] Cycloaddition Followed by Intramolecular [4+2] Cycloaddition*



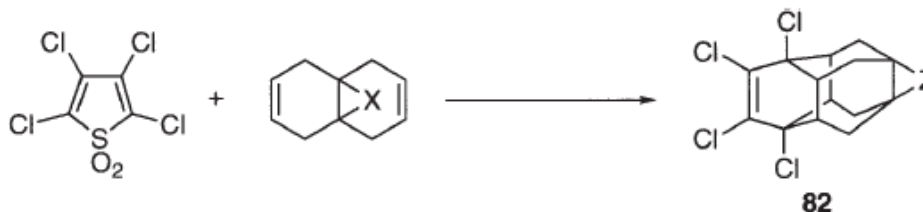
	X = O	2,6-di- <i>t</i> -butyl-4-methylphenol, NaHCO ₃ , CCl ₄ , reflux	
	X = CCl ₂	neat, 120 °C	33%
	X = NHCO	1,2-dichloroethane, reflux	66%
	X = CO ₂ CO	toluene, reflux	70%
	X = CH ₂ OCH ₂	toluene, reflux	40%
eme 48	X = OC(CH ₃)O	K ₂ CO ₃ , toluene, reflux	41%

Reactivities: *Category E: [4+2] Cycloaddition Followed by Intramolecular [4+2] Cycloaddition*



Reactivities: *Category E: [4+2] Cycloaddition Followed by Intramolecular [4+2] Cycloaddition*

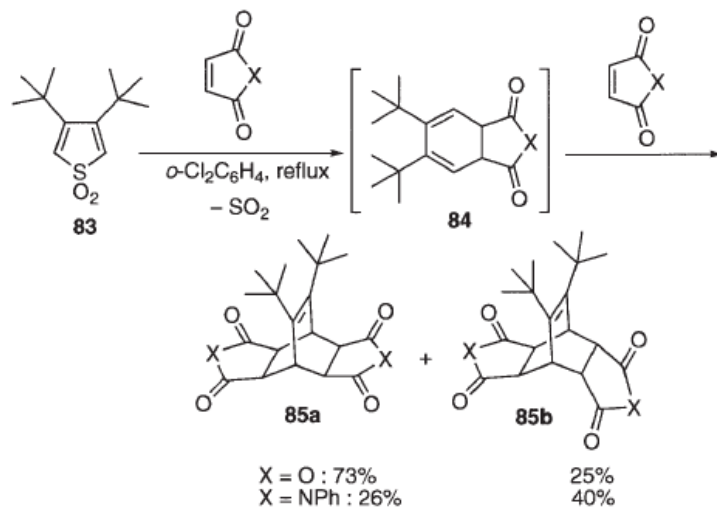
The reaction was applied to the preparation of structurally interesting cage compounds



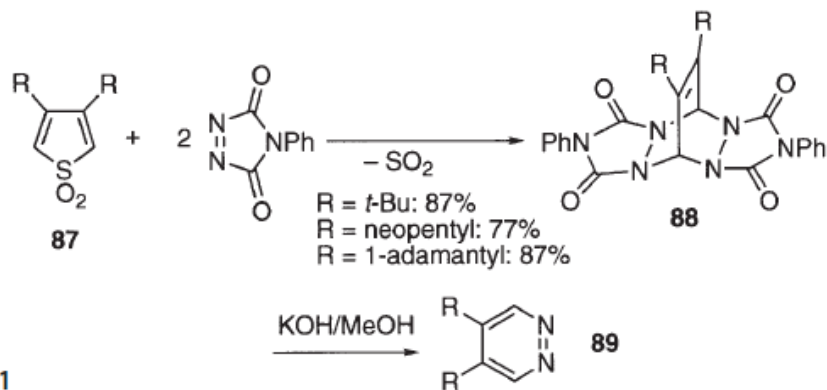
eme 48	X = O	2,6-di- <i>t</i> -butyl-4-methylphenol, NaHCO ₃ , CCl ₄ , reflux	
	X = CCl ₂	neat, 120 °C	33%
	X = NHCO	1,2-dichloroethane, reflux	66%
	X = CO ₂ CO	toluene, reflux	70%
	X = CH ₂ OCH ₂	toluene, reflux	40%
	X = OC(CH ₃)O	K ₂ CO ₃ , toluene, reflux	41%

Reactivities:

Category F: Bis-Adduct Formation



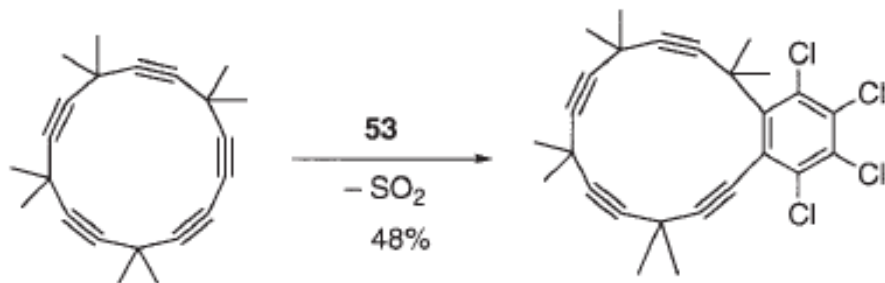
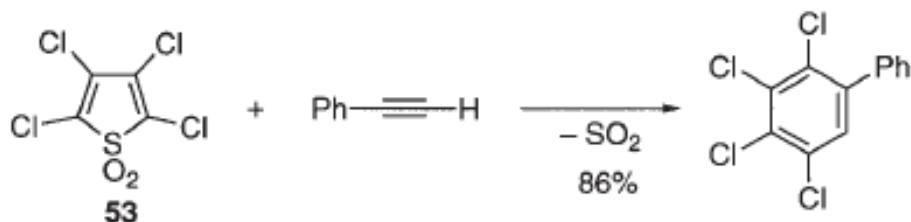
Nakayama J, Hirashima A. *J Am Chem Soc* (1990) 112:7648



Reactivities:

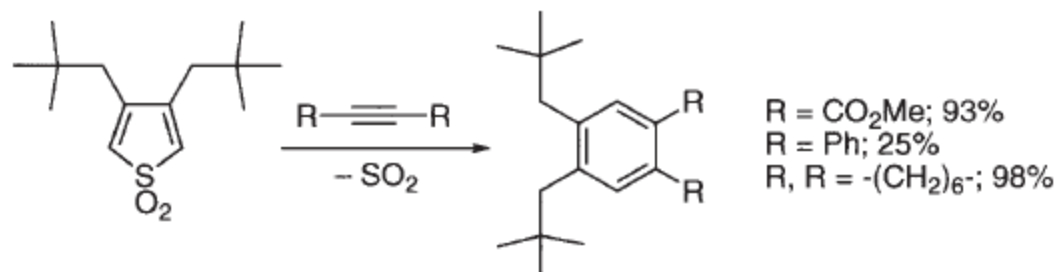
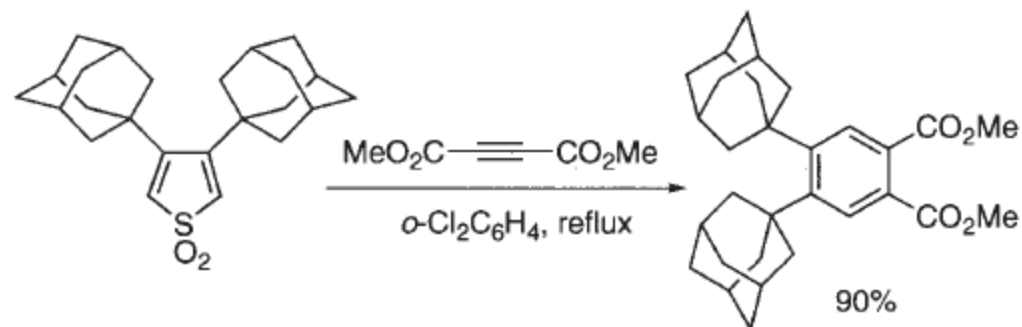
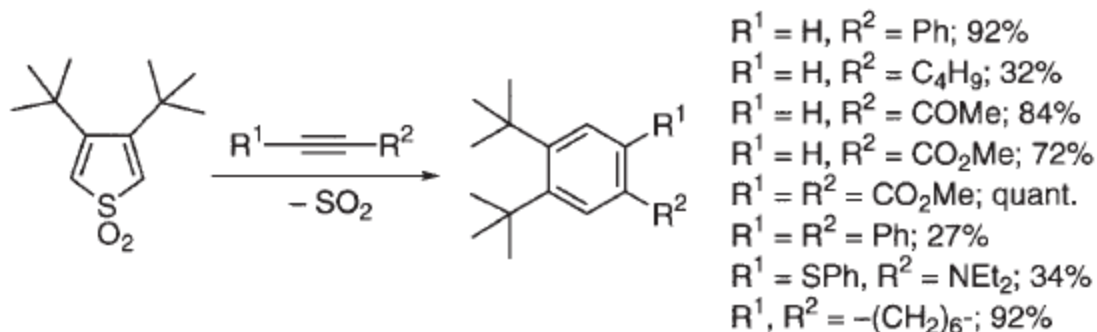
[4+2] Cycloaddition with Alkynic Dienophiles

[4+2] Cycloaddition of thiophene 1,1-dioxides with alkynic dienophiles leads to the formation of benzene derivatives with elimination of sulfur dioxide



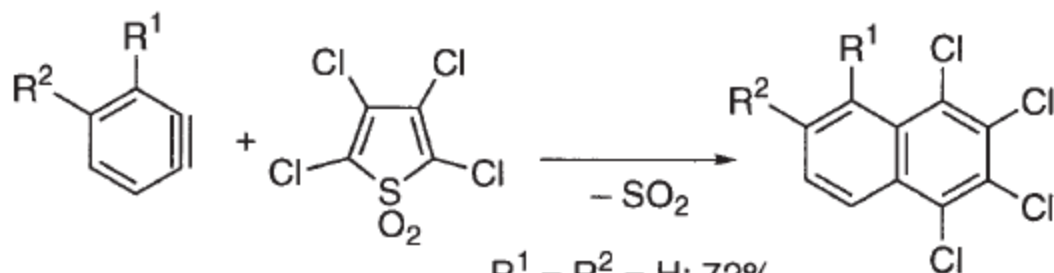
Reactivities:

[4+2] Cycloaddition with Alkynic Dienophiles

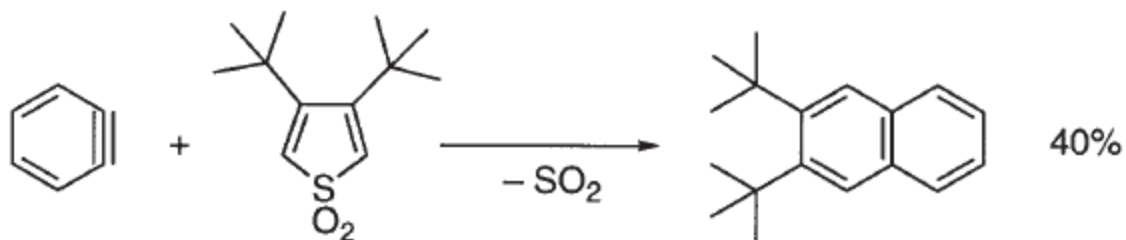


Reactivities:

[4+2] Cycloaddition with Alkynic Dienophiles

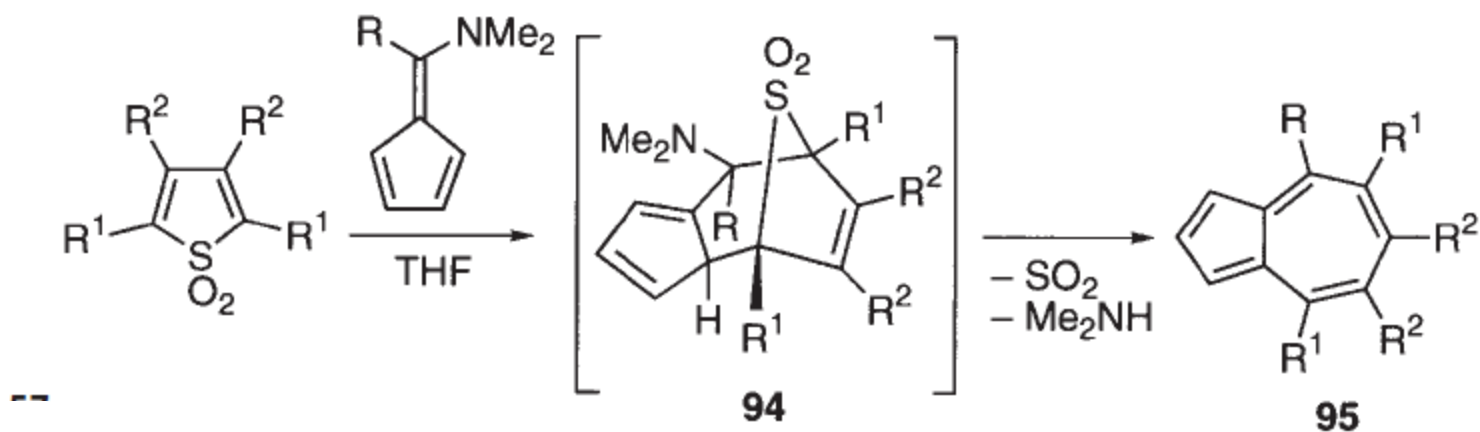


$R^1 = R^2 = \text{H}; 72\%$
 $R^1 = \text{Me}, R^2 = \text{H}; 65\%$
 $R^1 = \text{H}, R^2 = \text{Me}; 40\%$

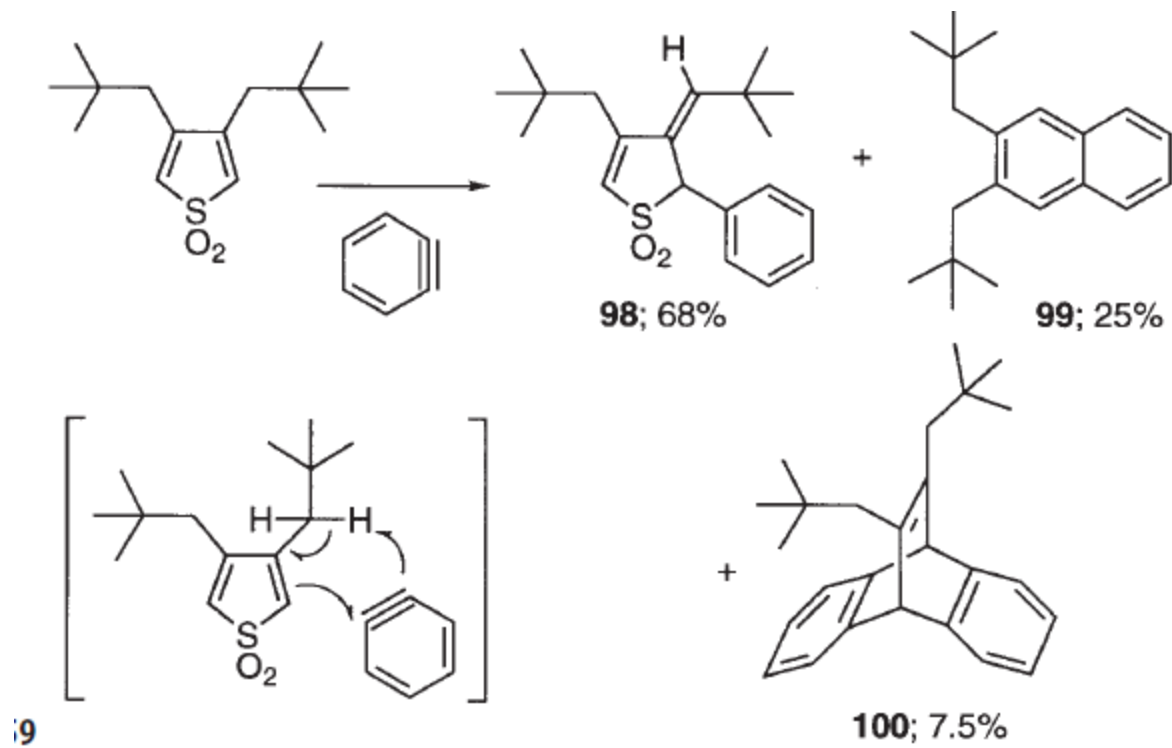


Reactivities:

[4+6] Cycloaddition

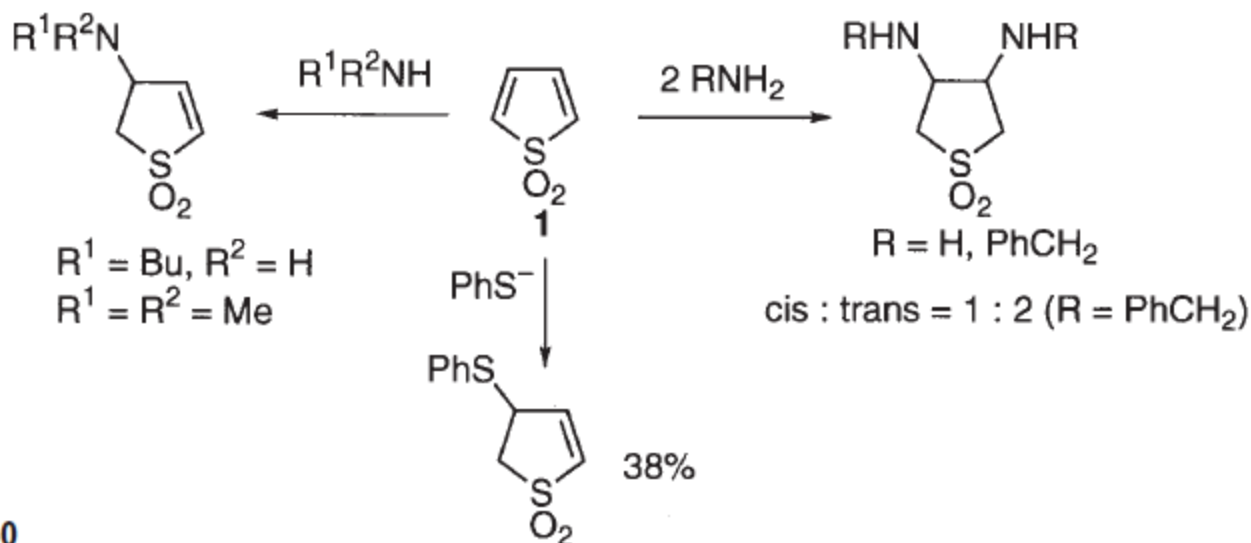


Reactivities: *Ene Reaction*



Reactivities: Nucleophilic Addition

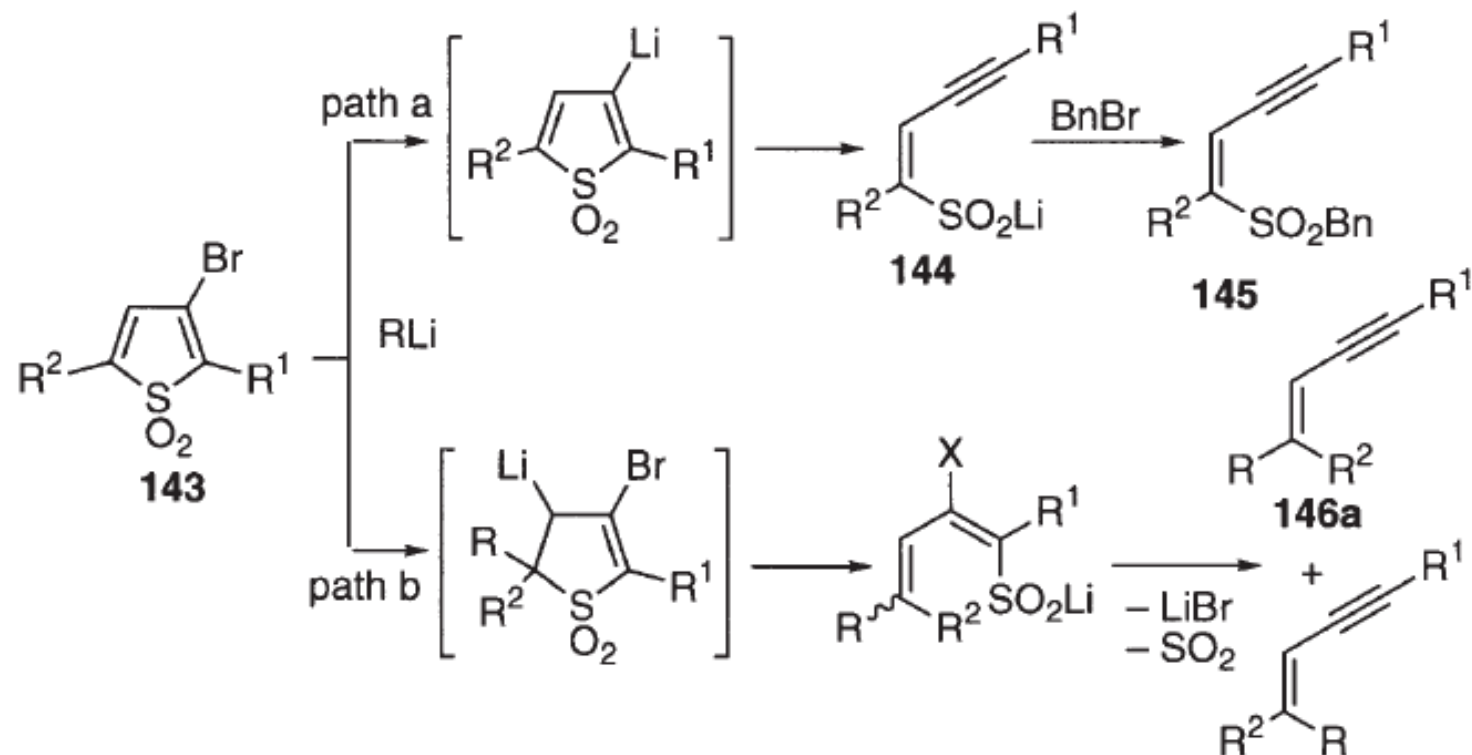
Thiophene 1,1-dioxides are typical α,β -unsaturated sulfones and take part in a nucleophilic 1,4-addition acting as Michael acceptors



50

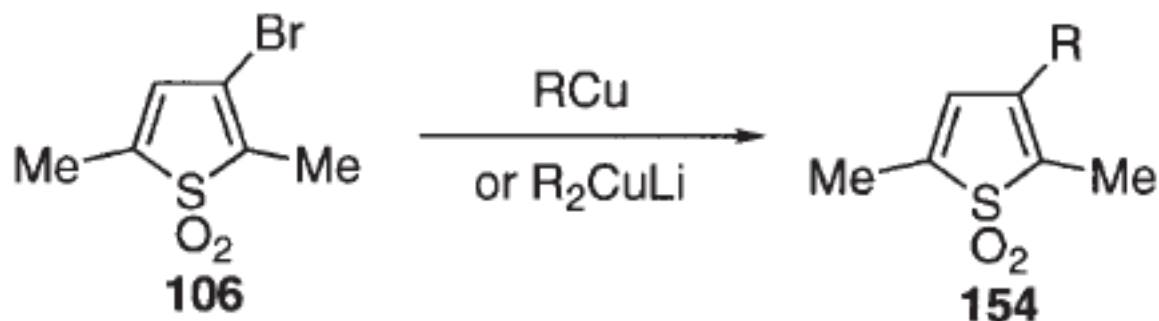
Chou T-S, Chen M-H. *Heterocycles*(1987) 26:2829
Bailey WJ, Cummins EW. *J Am Chem Soc* (1954) 76:1932
Bates HA, Smilowitz L, Lin J. *J Org Chem* (1985) 50:899

Reactivities: *ring opening reaction*



Reactivities: *ring alkylation*

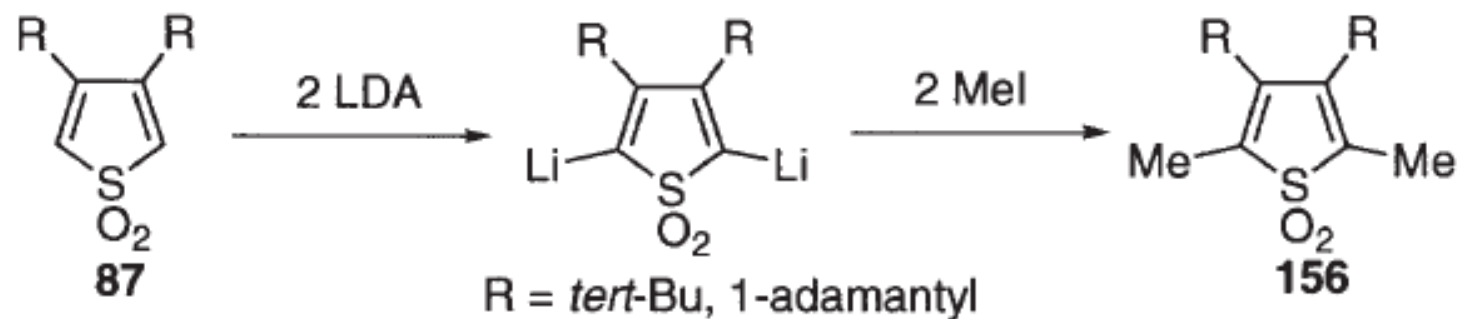
Ring alkylation of thiophene 1,1-dioxides was performed in two ways



RCu: R = Me, 100%; R = Et, 100%; R = Bu, 100%; R = *tert*-Bu; 47%
R₂CuLi: R = Me, 78%; R = Et, 83%; R = Bu, 53%; R = *tert*-Bu; 11%

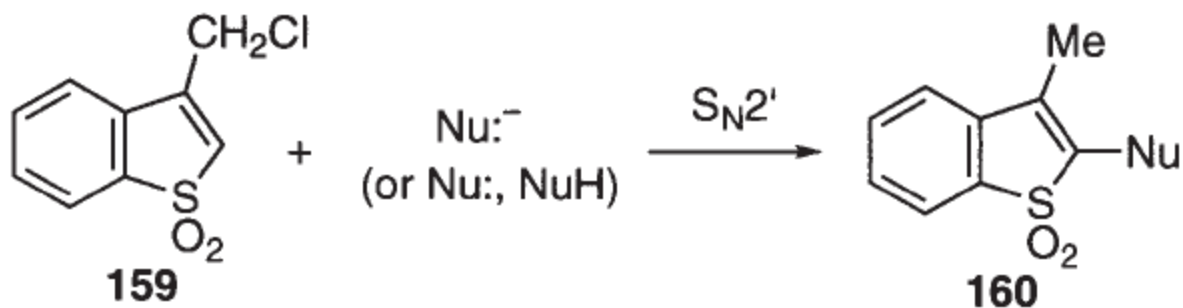
Reactivities: *ring alkylation*

On the another hand

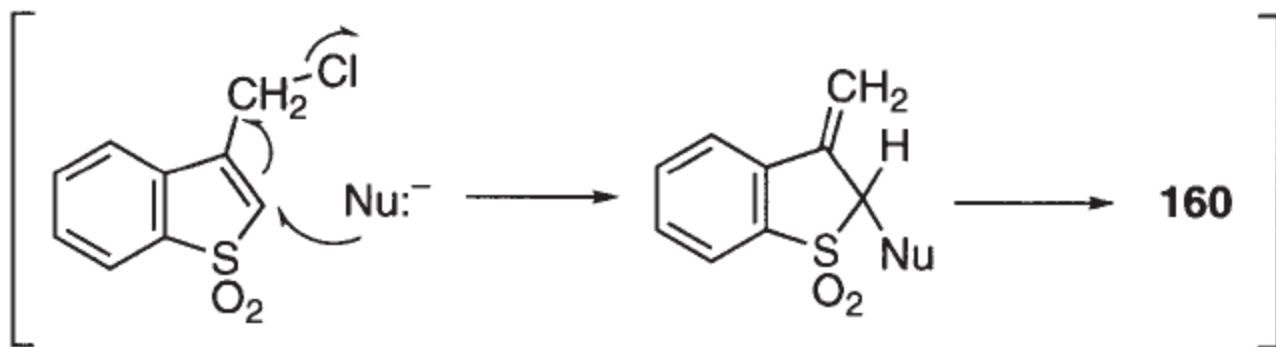


Kamiyama H, Nakayama J, unpublished results. See also: Kamiyama H, Hasemi R, Nakayama J. *Heteroatom Chem.* (1993) 4:445

Reactivities: S_{N2} reaction

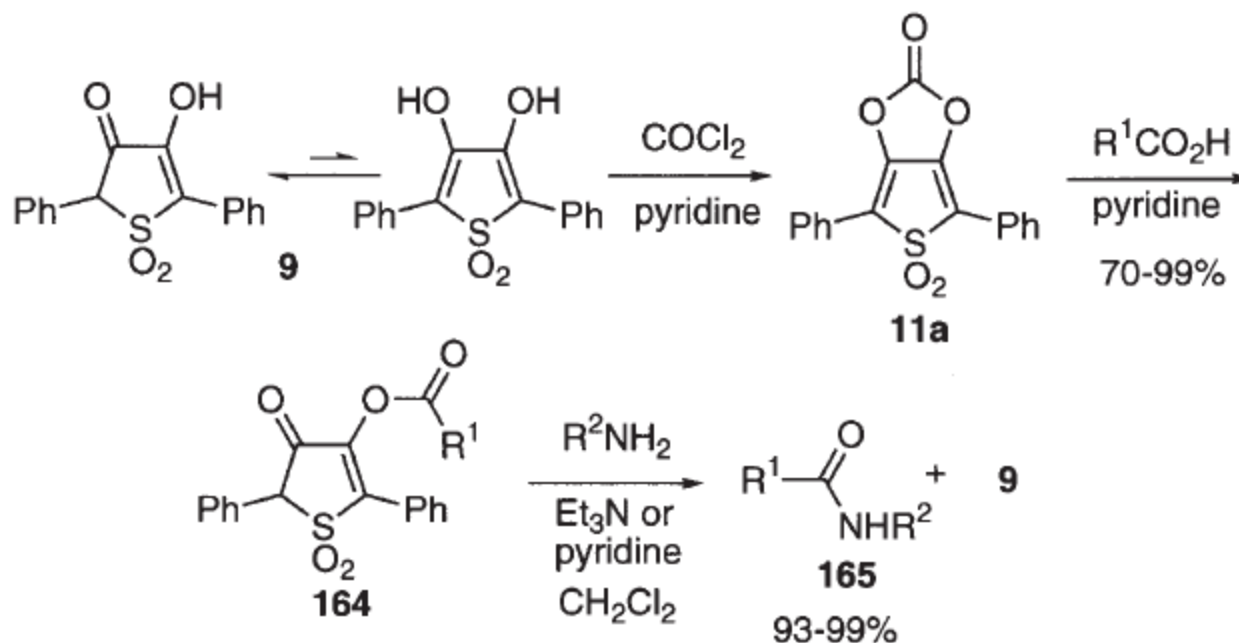


$Nu = NC_5H_{10}$ (49%), NC_4H_8O (25%), SPh (89%), $[S=C(NH_2)_2]^+$ (90%)



Reactivities: *steglich reagent*

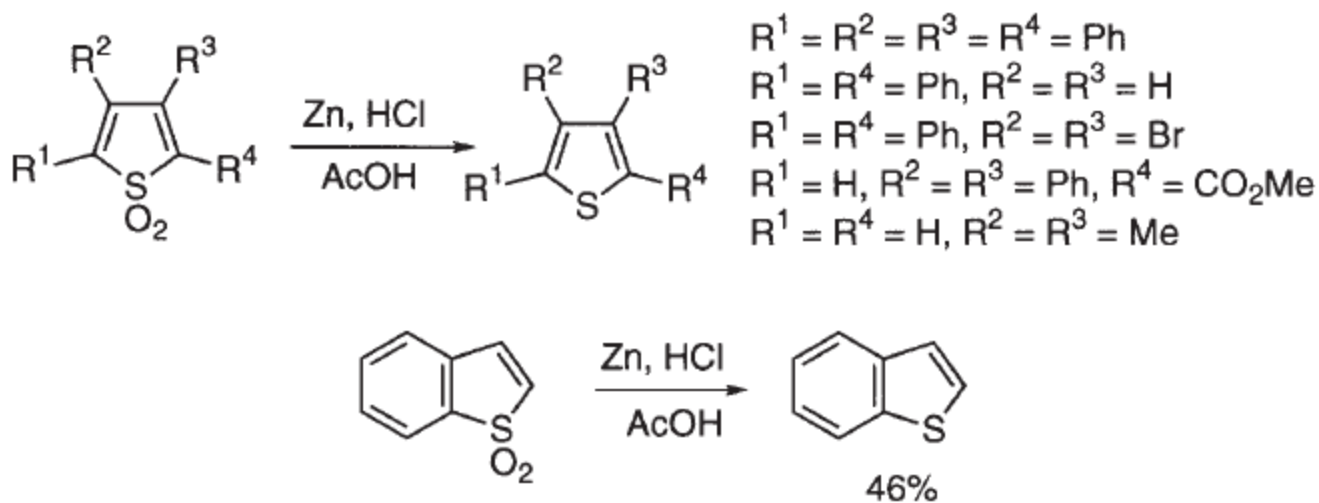
a strongly activating reagent in many condensation reactions



$\text{R}^1\text{CO} = \text{EtCO}, t\text{-BuCO}, \text{Cbz-Val}, \text{Cbz-Pro}, \text{Boc-Pro}, \text{Boc-Phe}, \text{Boc-Met}$

$\text{R}^2\text{NH}_2 = \text{Val-OMe}, \text{Val-O-}t\text{-Bu}$

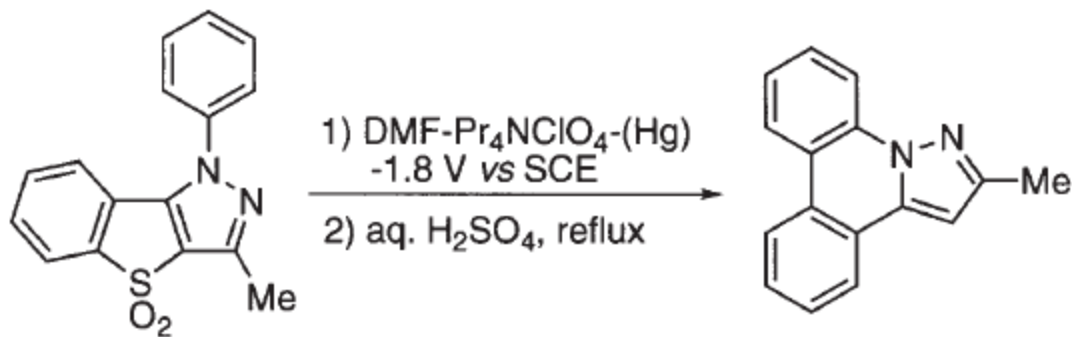
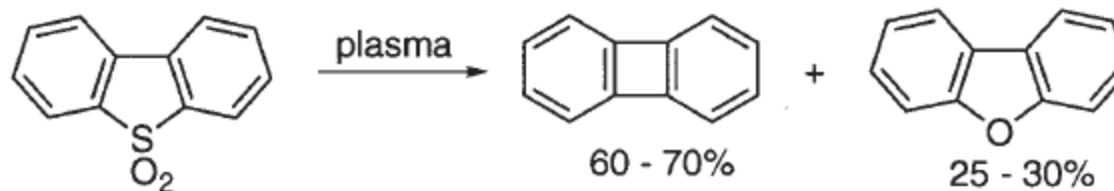
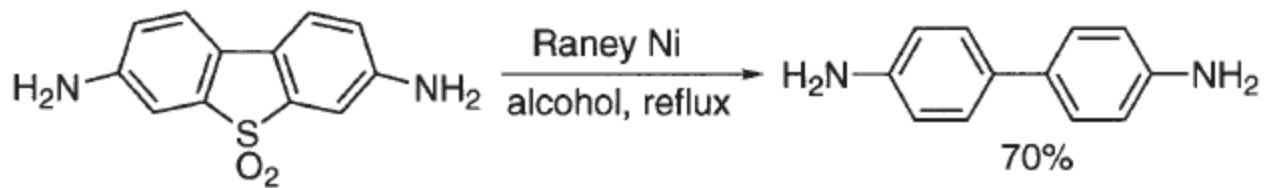
Reactivities: *reduction*



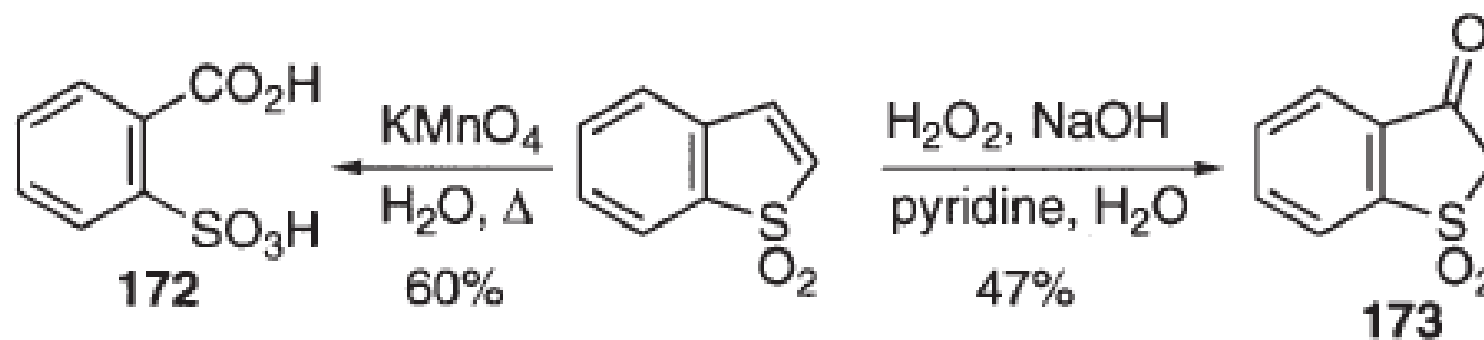
Monocyclic thiophene 1,1-dioxides [186, 232] and benzo[*b*]thiophene 1,1- Dioxide are reduced to the corresponding thiophenes by zinc in a mixture of acetic acid and hydrochloric acid

Reactivities: *reduction*

Some examples :



Reactivities: *Oxidation*

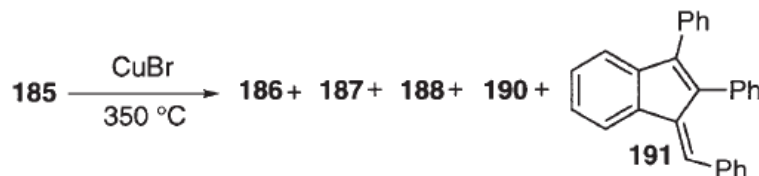
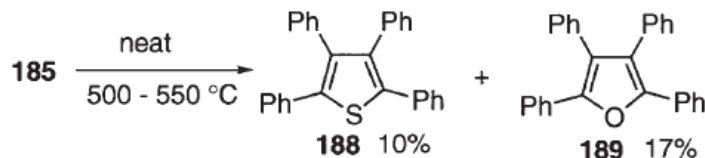
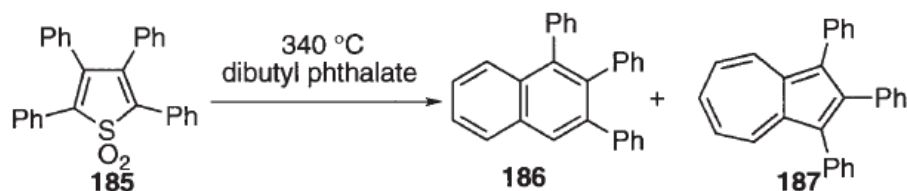


Bordwell FG, McKellin WH (1950) *J Am Chem Soc* 72:1985

Marmor S. *J Org Chem.* (1977) 42:2927

Reactivities: *Pyrolysis*

Pyrolysis products of thiophene 1,1-dioxides are much dependent on reaction conditions.



HAPPY THANKSGIVING!



Dong Group 2014.11