2016 中技社境外生研究獎學金
CTCI Science and Technology Research Scholarship

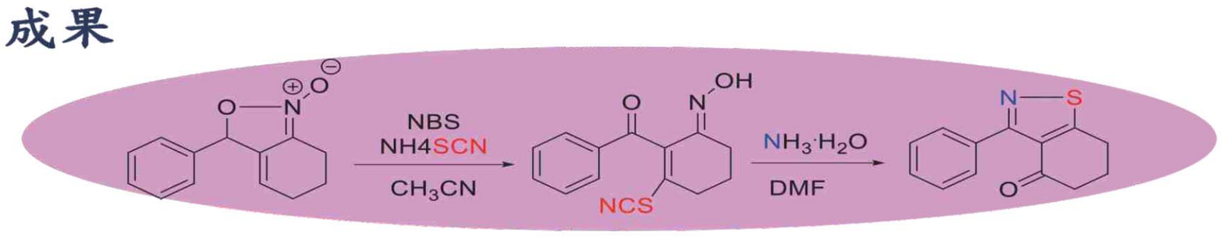
以 N-溴代丁二醯亞胺誘導環己烯並異噁唑啉-N-氧化物的硫腈化反應
N-Bromosuccinimide-Mediated Thiocyanation of Cyclohexene-Fused Isoxazoline N-Oxides

國立台灣師範大學 化學系
博士班三年級 Sachin S. Ichake 指導教授：姚清發

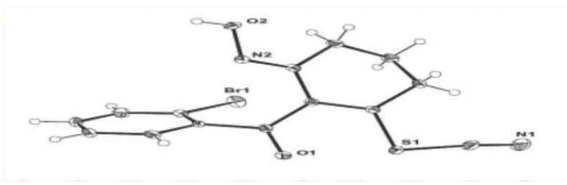
研究重點

An efficient, metal-free, NBS-mediated thiocyanation protocol has been developed for the synthesis of (6-(hydroxyimino)-2-thiocyanatocycloh ex-1-en-1-yl) (phenyl)methanone derivatives from cyclohexene-fused isoxazoline N-oxides under mild conditions. This rapid, one-pot transformation is achieved in acetonitrile, and provides access to diverse SCN-containing compounds bearing a wide range of functional groups in good to excellent yields. Moreover, an SCN containing product was further utilized for the synthesis of biologically important cyclohexanone ring-fused isothiazole derivatives

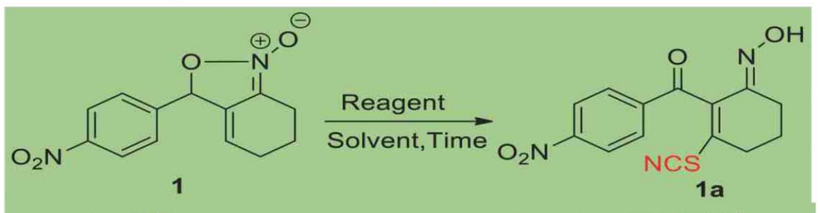
研究成果



crystal X-ray



Optimization Studies

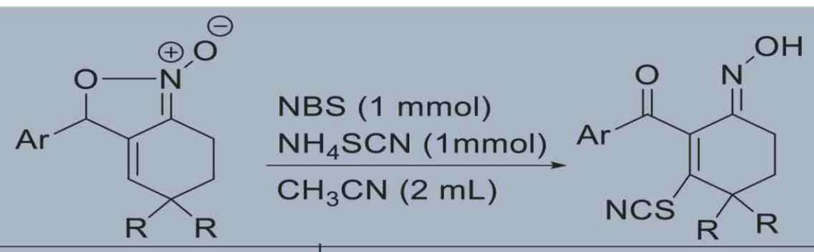


1 1a

Entry[a]	SCN Source	Solvent	Reagent	Time(h)	Yield(%)[b]
1	NH_4SCN	$CHCl_3$	NBS	1	31
2	NH_4SCN	THF	NBS	0.75	44
3	NH_4SCN	MeCN	NBS	0.25	78
4	NH_4SCN	CH_2Cl_2	NBS	12	20
5	NH_4SCN	MeOH	NBS	24	No reaction
6	NH_4SCN	H_2O	NBS	24	No reaction
7	NH_4SCN	DMF	NBS	0.5	46
8	NH_4SCN	DMSO	NBS	0.5	42
9	NH_4SCN	Dioxane	NBS	1	51
10	NaSCN	MeCN	NBS	12	34
11	KSCN	MeCN	NBS	12	42
12	NH_4SCN	MeCN	NCS	24	No reaction
13	NH_4SCN	MeCN	-	24	No reaction
14	NH_4SCN	MeCN	Selctfluor	12	-[c]
15	NH_4SCN	MeCN	TCCA	12	-[c]

[a]All the reactions were performed on 0.5 mmol scale. [b]NMR yields (CH2Br2 as an internal standard). [c] Desired product was not formed.

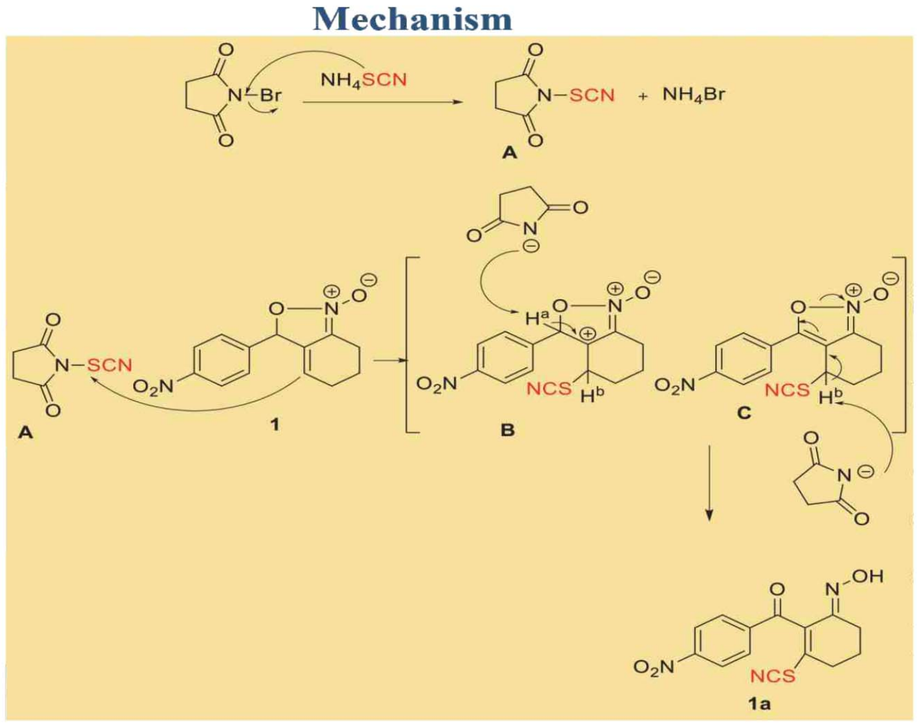
NBS mediated thiocyanation of various isoxazoline *N*-oxides.



Entry[a]	Ar	R	Time (min)	Yield (%)[b]	Entry[a]	Ar	R	Time (min)	Yield (%)[b]
1	$4\text{-}NO_2C_6H_4$	H	15	74	13	$3\text{-}ClC_6H_4$	H	18	64
2	$4\text{-}FC_6H_4$	H	17	65	14	$3\text{-}BrC_6H_4$	H	11	72
3	$4\text{-}ClC_6H_4$	H	25	71	15	$2,4\text{-}ClC_6H_3$	H	15	71
4	$4\text{-}BrC_6H_4$	H	20	72	16	$2,4\text{-}OMeC_6H_3$	H	13	61
5	$4\text{-}CNC_6H_4$	H	15	84	17	$3,4\text{-}MedioxyC_6H_3$	H	10	84
6	$4\text{-}MeC_6H_4$	H	13	58	18	C_6H_5	H	15	70
7	$4\text{-}OMeC_6H_4$	H	10	61	19	-Napth	H	11	74
8	$2\text{-}FC_6H_4$	H	15	80	20	C_6H_5	Me	15	94
9	$2\text{-}BrC_6H_4$	H	17	68	21	$4\text{-}ClC_6H_4$	Me	17	90
10	$2\text{-}IC_6H_4$	H	15	71	22	$3\text{-}NO_2C_6H_4$	Me	15	89
11	$3\text{-}NO_2C_6H_4$	H	15	66	23	$4\text{-}NO_2C_6H_4$	Me	15	88
12	$3\text{-}FC_6H_4$	H	13	69					

[a]All the reactions were performed on 0.5 mmol scale. [b]NMR yields (CH_2Br_2 as an internal standard). [c] Desired product was not formed.

Mechanism



Cyclohexanone ring-fused isothiazole derivatives

Conclusion

The broad substrate scope, mild reaction conditions, and moderate to excellent yield of products made this methodology interesting. The substrates bearing both electron withdrawing and electron donating groups on the phenyl ring were well tolerated in this method. Further, we utilized these newly synthesized thiocyano compounds for the synthesis of novel cyclohexanone ring fused isothiazole derivatives.

研究生活及心得：雖然做研究很辛苦，但是能夠看到想要的成果總是值得的。將來我會作為化學學者繼續努力，創造更美好的環境與將來。