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Regio- and Stereoselectivity of Intramolecular Nitrile Oxide Cycloaddition to Furan.

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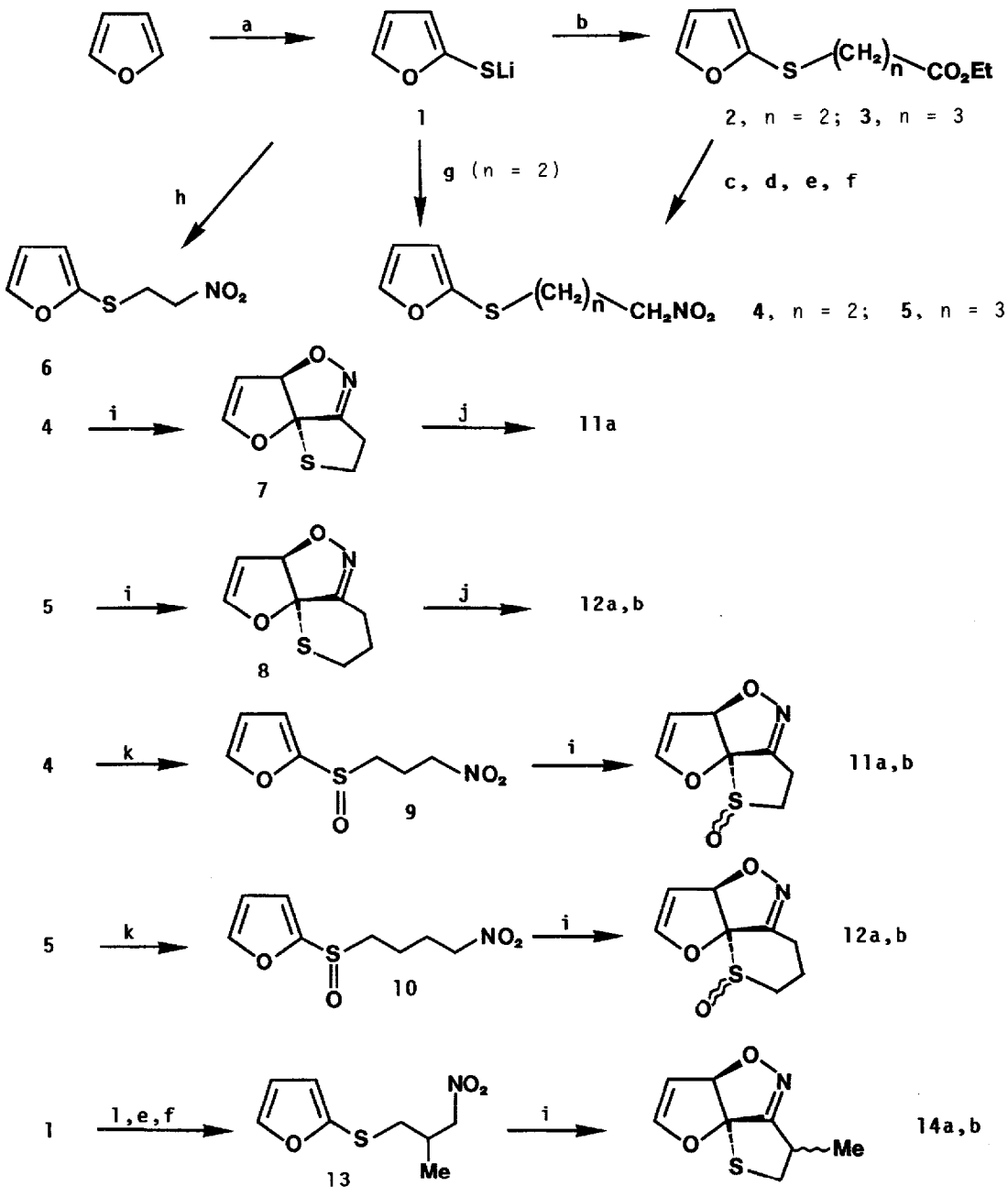
Abstract. Intramolecular nitrile oxide cycloaddition to functionalized furans occurs with complete regiochemical control but low diastereoselectivity.

The poor reactivity of furan as 2 π component in the 1,3-dipolar cycloaddition with nitrile oxide[1] greatly limited its practical use in this reaction.[2,3] This is particularly unfortunate since the furan-nitrile oxide cycloaddition definitely offers the best entry to C-4 oxygenated isoxazolines, and to a number of amino sugars derivatives thereof, as demonstrated by Jäger's pioneering work.[4] Entropically favoured intramolecular processes[5,6] could represent an effective alternative to the sluggish intermolecular reaction. In this line we here report an intramolecular nitrile oxide cycloaddition to furan that features an easily removable sulphur atom in the tether connecting dipole and dipolarophile.[7]

Synthetic route to the desired nitrile oxide precursors is outlined in Scheme 1.[8] Esters **2** and **3** were obtained in a one-pot reaction from furan by lithiation,[9] reaction with sulphur[10] to give lithium 2-furyl thiolate 1, and quenching with ethyl 2-bromopropionate and ethyl 2-bromobutyrate, respectively. Standard synthetic manipulations involving reduction, tosylation, conversion to the iodide, and reaction with $AgNO_2$ afforded nitrosulphides **4** and **5**. Alternatively, compound **4** was obtained in 40% yield by reacting **1** with 1-iodo-3-nitropropane. For sake of comparison nitrosulphide **6** was also prepared by addition of **1** to nitroethylene generated in situ from 2-acetoxynitroethane.[7]

Intramolecular cyclization (Table 1) was achieved by refluxing a 0.02M benzene solution[11] of **4** and **5** in the presence of p-chlorophenylisocyanate and catalytic triethylamine, to give fused[12] tricyclic products **7** and **8**, respectively, as single regioisomers, as demonstrated by high field ^1H and ^{13}C NMR spectroscopy.[13] As expected compound **6** did not undergo cycloaddition.

We next turned our attention to the possibility of controlling the absolute stereochemistry of the reaction by inserting a stereogenic centre along the chain connecting dipole and dipolarophile.[14] To this goal, compounds **3** and **4** were oxidized with $NaIO_4$ to the corresponding chiral, but racemic, sulphoxides **9** and **10**.[15] Their cyclization afforded



Scheme 1. Reagents (yields): a, n-BuLi, THF; then S_8; b, $Br(CH_2)_2COOEt$ (68%) or $Br(CH_2)_3COOEt$ (77%); c, $LiAlH_4$, Et_2O (quantitative); d, TosCl, Et_3N, CH_2Cl_2 (80%, n = 2; 82%, n = 3); e, KI, $^nBu_4NI$, benzene, H_2O (93%, n = 2; 85%, n = 3); f, $AgNO_2$, Et_2O (56%, n = 2; 53%, n = 3); g, $I(CH_2)_3NO_2$ (40%); h, $AcO(CH_2)_2NO_2$ (57%); i, p-Cl-C_6H_4-NCO, Et_3N, benzene; j, mCPBA, CH_2Cl_2; k, $NaIO_4$, MeOH, H_2O (80%, n = 2; 87%, n = 3); l, $BrCH_2CH(Me)CH_2Cl$ (66%).

isoxazoline **11a,b** and **12a,b** as 75:25 and 70:30 mixture of diastereoisomers, respectively. These products were also obtained by a highly stereoselective mCPBA oxidation of **7** and **8**; indeed, from **7**, **11a** was obtained exclusively, while **8** afforded an 85:15 mixture of epimeric sulphoxides **12a** and **12b**.

Finally, compound **13** was prepared and its intramolecular cycloaddition examined. The reaction affords a 66:34 mixture of diastereoisomers **14a,b**, in line with the low degree of stereocontrol generally observed in the reaction of chiral nitrile oxides.[14]

Table 1. Synthesis of isoxazolines **7, 8, 11a,b, 12a,b,** and **14a,b.**

Compound	Yield %[a]	m.p.°C (n_D^{25})	Diastereoisomeric[b] ratios **a:b**
7	79[c]	76-77	-
8	75[c]	(1.5578)	-
11a,b	63	150-151(dec.)[d]	75:25
11a,b[e]	70	150 (dec.)	97: 3
12a,b	60	128-129/120-121[f]	70:30
12a,b[g]	76	128-129/120-121[f]	85:15
14a,b	73[c]	(1.5561)[h]	66:34

[a] Isolated yields after flash chromatography. [b] As determined by high field NMR spectroscopy. [c] The unreacted nitrosulphide was partially recovered. [d] M.p. of **11a**; **11b** was isolated impure of **11a**. [e] By oxidation of **7**. [f] M.p. of **12a** and **12b**, respectively. [g] By oxidation of **8**. [h] Of the 66:34 isomer mixture.

In conclusion the intramolecular cycloaddition of nitrile oxides derived from **4, 5, 9, 10,** and **13** is a highly regioselective but poorly diastereoselective process. Work is in progress to improve the stereocontrol of this reaction, and to explore the synthetic opportunities offered by the polyfunctionalized cycloadducts **7, 8, 11, 12,** and **14.**

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