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A Novel Stereoselective Route to γ-Butyrolactones

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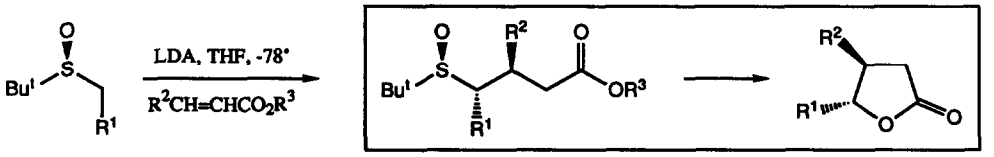
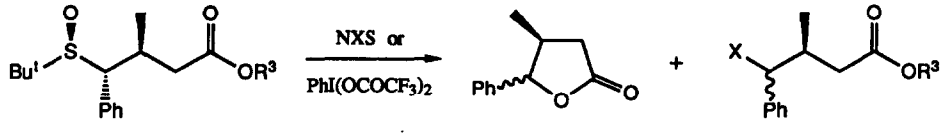
Abstract: *Treatment of the products obtained from conjugate additions of sulfoxides to α,β-unsaturated carbonyl compounds with soft electrophiles resulted in intramolecular displacement of the sulfinyl group by the carbonyl to give γ-butyrolactones. This novel cyclisation works best for benzylic sulfoxides and provides a concise route to* trans-*β,γ-disubstituted lactones with high stereoselectivity.*

Conjugate additions of sulfoxides to α,β-unsaturated esters proceed cleanly, with high stereoselectivity at the newly created chiral centres.[2,3] We now report that the resulting adducts can be transformed directly and stereoselectively into γ-butyrolactones, using a novel displacement reaction of the sulfinyl group.



It is known that halonium ions, can add to the sulfur atom of sulfoxides to produce intermediates which can fragment to give sulfinyl halides and carbonium ions.[4] We hoped that in the case of γ-sulfinyl carboxylic acid derivatives produced by conjugate additions, either the intermediate halosulfoxonium ions, or the stabilised benzylic carbonium ions formed by regioselective fragmentation, would undergo nucleophilic attack to furnish lactones. Accordingly, the conjugate adduct **1a**[3] was treated with N-chlorosuccinimide in dichloromethane at room temperature. The desired lactone **2** was indeed formed, but the major products were the chlorides **3** (X = Cl), arising from interception of the carbonium ion by chloride. It was encouraging that cleavage of the benzylic carbon-sulfur bond was greatly favoured over the alternative pathway to give *tert*-butyl carbonium ion. A survey of other reagents and conditions was then carried out in order to discover if the lactone could be produced selectively (Table 1).



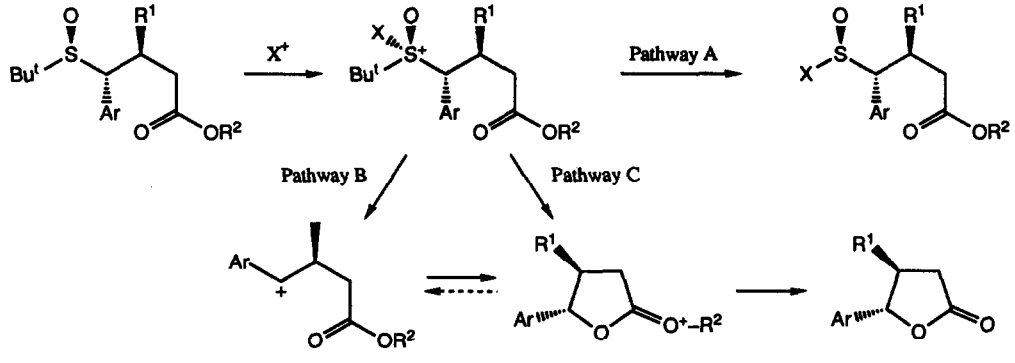
1a **2a** *trans*- **2b** *cis*- **3** (X = Cl, Br, I, $OCOCF_3$)

Table 1: Conditions for lactone formation.

Reagent	Solvent	Time	Ratio 2 : 3[a]	Ratio 2a : 2b[a,b]	Yield 2a
1.1 eq. NCS	CH_2Cl_2	5 days	40 : 60	>95 : <5	-
	CCl_4	9 days	43 : 57	-	-
	MeCN	7 days	42 : 58	-	-
1.2 eq. NBS	CH_2Cl_2	3 days	56 : 44	99 : 1	-
1.2 eq. NIS	CH_2Cl_2	18 days	90 : 10	92 : 8	73%
1.2 eq. PIFA[c]	CH_2Cl_2	3 days	5 : 95	-	-
3.0 eq. I_2	CH_2Cl_2	9 days	>95 : <5	93 : 7	84%

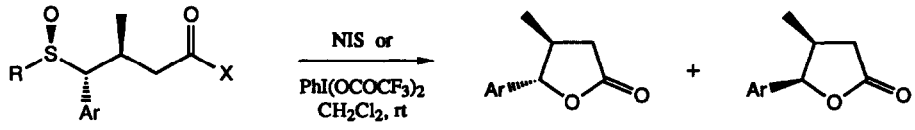
a The ratios of the products were determined by integration of the crude NMR spectra.
b The γ-H of the *trans*-lactone **2a** appears at δ4.90 (d, J 8Hz), that of the *cis*-lactone **2b** at δ5.55 (d, J 6Hz).[5]
c Phenyliodonium bistrifluoroacetate

Changing the solvent did not improve the selectivity, but use of reagents which gave less nucleophilic anions gave better selectivity for the lactone, as expected. NIS gave the lactone in 73% yield, but the best reagent proved to be molecular iodine, which gave an 84% yield of lactone. Both of these reagents furnished the trans-disubstituted lactone **2a** with high stereoselectivity. This stereochemical outcome could be the result of S_N2 displacement of the sulfinyl halide (pathway C, Scheme 1), or, more likely, formation of a carbonium ion followed by cyclisation to give the thermodynamically more stable product, either under kinetic or thermodynamic control (pathway B). We have not yet resolved these mechanistic uncertainties.



Scheme 1

A number of other conjugate adducts, and the corresponding acids and amides, were also converted into lactones as shown in Table 2. These results show that the carboxylic acids (obtained in essentially quantitative yields from the esters by hydrolysis using NaOH, H_2O, MeOH) cyclised faster than the esters, and that they gave the lactones highly stereoselectively using NIS or phenyliodonium bistrifluoroacetate (PIFA). Comparison of the results for the esters and the acids shows that it may sometimes be advantageous to carry out a hydrolysis of the ester prior to lactone formation. The amide (obtained in 83% yield by conjugate addition to *N,N*-dimethylcrotonamide) also cyclised relatively quickly, but PIFA was the only reagent which gave reproducible results in this case. The intermediate iminium ion could be observed by NMR, and it decomposed to the lactone on addition of water. The *p*-tolyl benzyl sulfoxide cyclised extremely cleanly, presumably because the halosulfoxonium ion undergoes highly regioselective fragmentation, but it must be noted that conjugate additions of *p*-tolyl sulfoxides are not very efficient.[3] The rapid high yielding lactonisation of the trimethoxybenzyl derivative presumably reflects the high stability of the corresponding carbonium ion.

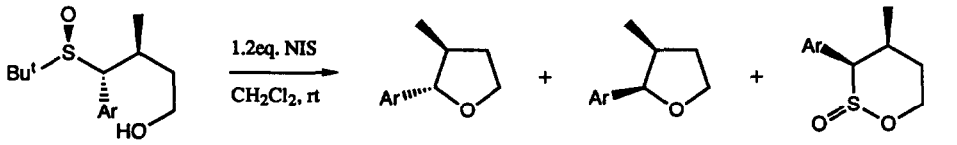


1 4a 4b

Table 2: Lactone formation from conjugate adducts **1**

R	Ar	X	Reagent	Time	Ratio 4a : 4b	Yield 4a
t-Bu	C_6H_5	OH	1.3eq. NIS	4 days	97 : 3	69%
			1.2eq. PIFA	3 days	100 : 0	71%
t-Bu	C_6H_5	NMe_2	1.2eq. NIS	7 days	-	23%
			1. eq. PIFA	3 days	95 : 5	72%
p-Tol	C_6H_5	OMe	1.2eq. NIS	2 days	98 : 2	98%
t-Bu	3,4,5-$(MeO)_3C_6H_2$	OH	1.2eq. NIS	14h	91 : 9	89%

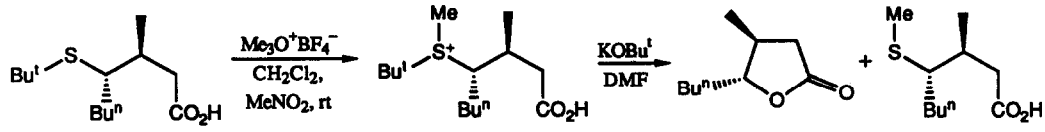
Reduction of a conjugate adduct (LAH, 93%) furnished the alcohol **5**. When this was subjected to the cyclisation conditions, the tetrahydrofuran **6** (2-H: 4.18, d, J 8Hz) was formed in moderate yield, along with the *cis*-isomer **7** (2-H: 4.85, d, 6Hz),[6] and a crystalline byproduct, tentatively identified as the sultine **8**.[4] The sultine could be formed by attack of the alcohol at the sulfur atom of the iodosulfoxonium salt, followed by loss of the tertiary butyl carbonium ion, or by loss of the *tert*-butyl cation followed by cyclisation of the hydroxy sulfinyl iodide. The formation of the sultine provides direct evidence of the competition between two fragmentation pathways (Scheme 1), to give either a benzyl (pathway B) or a tertiary carbocation (pathway C), which may be responsible for the moderate yields observed in many of these cyclisations. This novel cyclisation method should prove useful for the stereoselective preparation of heavily substituted tetrahydrofurans.



5 Ar = 3,4,5-$(MeO)_3C_6H_2$ **6** 65% **7** ~5% by NMR **8** ~10% by NMR

We have also carried out some preliminary studies to determine if the method could be extended to alkyl sulfoxides. A multistep route for intramolecular substitution of alkyl sulfoxides, comprising reduction to the sulfide, *S*-alkylation, and displacement of the sulfonium salt, has been used for the preparation of epoxides,[7,8] and lactones.[9] A brief study of this method ran into an obvious problem. Sulfide **9**[10] was alkylated with trimethyloxonium tetrafluoroborate, and the sulfonium salt **10** was treated with potassium *tert*-butoxide. A low yield of the lactone **11** (*quercus* lactone-a[11]) was isolated, but the major product was the methyl sulfide **12**, arising from elimination of isobutene from the intermediate sulfonium salt **10**. Although an overall yield of 39% of the lactone (in 4 steps from the sulfoxide) was eventually obtained, and further optimisation should be possible, this procedure seems unlikely to be competitive with direct cyclisation, and it was abandoned.

The results for one-step conversion of sulfoxides **13**, bearing three different 'spectator' groups, into the *quercus* lactone **11**[11] are presented in Table 3. Cyclisation of the *tert*-butyl sulfoxide gave a very poor yield, presumably because of competitive loss of *tert*-butyl carbonium ion. The *p*-tolyl derivative has no such facile



alternative pathway available to it, and it gave a moderate (53%) yield of the lactone, with good stereoselectivity (>9:1). Unfortunately however, *p*-tolyl conjugate adducts cannot be obtained with good stereoselectivity.[2] We then turned to imidazolyl sulfoxides, which can be obtained from conjugate additions with high yields and excellent stereoselectivity.[12] The resulting esters or acids did not give the lactone under a variety of conditions, but the amide did cyclise, albeit with very variable results. It is clear that the cyclisation of alkyl derivatives is still an unsatisfactory process, but we are optimistic that further work on heteroaryl sulfoxides will provide a solution to this problem.

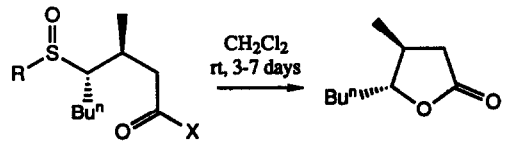


Table 3: Cyclisations of alkyl sulfoxides

R	X	Reagent	Yield of 11
Bu^t	OH	PIFA	20%
p-Tol	OH	NIS	53%
Im[a]	NMe_2	PIFA	25-50%

a Im = *N*-Methyl-2-imidazolyl

To the best of our knowledge, this is a novel one-step method for the intramolecular displacement of sulfinyl groups.[13] It's development means that sulfoxides can be added to the list of "chemical chameleons", groups which confer the potential for both nucleophilic and electrophilic behaviour at the carbon to which they are attached.[14] The use of enantiomerically pure sulfoxides in this highly stereoselective conjugate addition/sulfur displacement sequence should provide a convenient method for the asymmetric synthesis of lactones and tetrahydrofurans, and work on synthetic applications is in progress.

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