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Unusual Reversal of Stereoselectivity of 1,3-Dipolar Cycloaddition in the Presence of Lewis Acids

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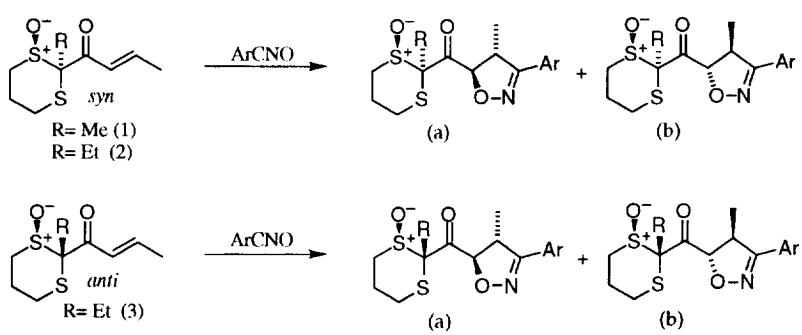
Abstract: The addition of Lewis acids to dipolar cycloaddition reactions of mesityl nitrile oxide with α,β-unsaturated 2-acyl-1,3-dithiane 1-oxides affects and can even reverse the sense of induced stereoselectivity. © 1997 Elsevier Science Ltd.

We have recently reported the use of α,β-unsaturated 2-acyl-1,3-dithiane 1-oxide derivatives as dipolarophiles which give complete regiocontrol in dipolar cycloaddition reactions with nitrile oxides.[1] The reactions also exhibit a moderate degree of stereocontrol, induced by the asymmetry of the dithiane oxide (DiTOX) unit. We now wish to report the effect on these reactions of the addition of Lewis acids, which can alter and even reverse the induced stereochemistry, an unusual feature for this type of process.

We have investigated the effect of the addition of several Lewis acids upon the induced stereoselectivity in reactions of 2,4,6-trimethylphenyl nitrile oxide with the *syn*-2-methyl-2-crotyl-1,3-dithiane 1-oxide (1) and the *syn*- (2) and *anti*- (3) isomers of 2-ethyl-2-crotyl-1,3-dithiane 1-oxide (Scheme 1). The reactions are completely regioselective, with only the 5-acyl dihydroisoxazoles being isolated, in marked contrast to literature reports, where electron-deficient 1,2-disubstituted alkenes tend to give mixtures of regioisomers with poor selectivity.[2] The two product diastereoisomers are labelled as (a) and (b) throughout, where (a) has the new carbon-oxygen bond in a *syn* relationship to the sulfoxide, as shown.[3]



Scheme 1

The enone substrates were prepared as previously described by us from 1,3-dithiane in one pot by alkylation with iodomethane or iodoethane followed by hydroxyalkylation with crotonaldehyde, using butyl lithium as base.[1] Oxidation to the ketone and finally sulfur oxidation led to enones (1) to (3).

2,4,6-Trimethylphenyl nitrile oxide is a stable compound which is easily prepared over two steps from mesitaldehyde, in our hands in 58% yield.[4] Cycloadditions were performed in either diethyl ether or dichloromethane solution at room temperature, and were allowed to reach completion. Attempts to accelerate the reaction by heating led to a loss of stereo- and regioselectivity, and to the formation of a small amount of the alternative regioisomers.

The reactions were first carried out with the *syn*-2-methyl substrate (1) in the absence of any Lewis acids.[1] Subsequently, a variety of Lewis acids were screened, initially with a view to improving the observed stereoselectivities (Table). Several Lewis acids, including tin and titanium tetrachlorides, boron trifluoride etherate, ethyl aluminium chloride, and, perhaps less surprisingly, ethyl magnesium bromide, led to decomposition, an observation in accord with our work on Lewis acid catalysed hetero-Diels-Alder reactions.[5] The introduction of an appropriate Lewis acid, however, particularly zinc halides, reduced and in some cases even reversed the sense of induced stereoselectivity of the reaction without compromising yields, which were generally very good to excellent. As far as we are aware, this reversal of the sense of induced stereoselectivity is remarkable in that such effects have only rarely been observed previously in dipolar cycloaddition processes,[6] although similar effects are of course familiar from other transformations, for example aldol reactions.[7] The reversal of stereoselectivity presumably results from the imposition of a chelated transition state in the presence of Lewis acid with a different geometry from that obtaining in the absence of Lewis acid, perhaps as a result of dipole–dipole interaction.

Table. Influence of Lewis acids on dipolar cycloaddition

Entry	Substrate	Solvent	Lewis acid	Yield/% (a+b)	Ratio a:b
1	(1) *syn*	Et_2O	—	72	3.5:1
2	(1) *syn*	CH_2Cl_2	—	90	2:1
3	(1) *syn*	Et_2O	$ZnCl_2$	100	2:1
4	(1) *syn*	CH_2Cl_2	$ZnCl_2$	96	1:1.5
5	(1) *syn*	CH_2Cl_2	ZnI_2	91	1:2
6	(1) *syn*	Et_2O	$MgBr_2.OEt_2$	25 (75)‡	1:2
7	(1) *syn*	CH_2Cl_2	$Ti(O^iPr)_4$	14 (83)‡	2:1
8	(1) *syn*	CH_2Cl_2	$BF_3.OEt_2$	§	—
9	(1) *syn*	CH_2Cl_2	$EtAlCl_2$	§	—
10	(1) *syn*	CH_2Cl_2	$TiCl_4$	§	—
11	(1) *syn*	CH_2Cl_2	$SnCl_4$	§	—
12	(1) *syn*	CH_2Cl_2	EtMgBr	§	—
13	(2) *syn*	Et_2O	—	85	1:1
14	(2) *syn*	CH_2Cl_2	$ZnCl_2$	89	1:1.2
15	(3) *anti*	Et_2O	—	79	1:1
16	(3) *anti*	Et_2O	$ZnCl_2$	95	1:1
17	(3) *anti*	CH_2Cl_2	$ZnCl_2$	56 (28)‡	1:1

‡ Figure in parentheses is % of starting material recovered

§ No product or starting material isolated

It is interesting that the highest induced stereoselectivity is exhibited in each sense by the *same* dipolarophile, the *syn*-2-methyl derivative (1), both in the absence of any Lewis acid and in the presence of zinc iodide. It is also noteworthy that, in accordance with literature reports,[8] ether gave the highest stereoselectivity, for isomer (a) in the absence of Lewis acid,[1] but that dichloromethane was the most effective solvent for formation of isomer (b) when a Lewis acid was used.

In conclusion, we can report completely regioselective 1,3-dipolar cycloaddition reactions of mesityl nitrile oxide, with only the 5-acyl dihydroisoxazoles being isolated, both in the presence and absence of Lewis acids. This behaviour is in marked contrast to literature reports. In addition, the modest stereoselectivities observed are affected and even reversed by the addition of Lewis acids to the reaction mixtures. Behaviour of this type also appears to be rare in the literature.

Experimental Section

General Experimental Details

Purification of Solvents

Petroleum ether refers to petroleum ether b.p. 40-60 °C. Petroleum ether and ethyl acetate were distilled prior to use. Diethyl ether was freshly distilled under an atmosphere of nitrogen from the sodium/benzophenone ketyl radical immediately prior to use. Dichloromethane was dried by distillation from calcium hydride under an inert atmosphere.

Reagents

Zinc chloride was purchased as a 1 M solution in diethyl ether in 100 ml bottles. Other reagents were used as supplied.

Preparation of Glassware

All reactions were carried out in round bottomed flasks which were either baked at 150 °C for a minimum of two hours or dried in a Bunsen burner flame. The flasks were allowed to cool in a desiccator, and were purged with nitrogen prior to being stopped with septum caps. Other apparatus such as syringes, needles, cannulas and magnetic stirrer bars were dried under similar conditions and allowed to cool in a desiccator.

Normal Work-up Procedure

Unless otherwise stated, reactions were worked up by the addition of saturated aqueous ammonium chloride, followed by extraction of the aqueous phase with dichloromethane. The combined organic extracts were washed with water and dried over anhydrous magnesium sulphate, which was removed by filtration. The filtrate was reduced in volume on a rotary evaporator to give the crude product.

Chromatography

Flash column chromatography was performed using Merck 9385 silica gel or Merck neutral alumina; compressed air was used to supply any necessary pressure to the column. Thin layer chromatography was carried out on glass backed plates coated with a 0.25 mm layer of silica gel or neutral alumina. UV inactive compounds were visualized by exposure to iodine mixed with silica gel, or by spraying with aqueous potassium permanganate (10 g in 1 litre of water containing 5 g Na_2CO_3) followed by heating.

Spectroscopy

^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 (200 MHz) instrument. All spectra were recorded using tetramethylsilane (TMS) as the internal reference. Infra-red spectra were recorded in the range 4000 to 600 cm^{-1} using a PerkinElmer 298 instrumen; solid samples were run as Nujol mulls and liquids as thin films, on sodium chloride plates, unless otherwise

indicated. Electron impact (EI) and chemical ionization (CI) mass spectra were recorded on VG Analytical 7070E or Trio 1000 Quadrupole GCMS instruments.

Other Analytical Data
Microanalyses were performed using a Carlo Erba elemental analyser by the Department of Chemistry microanalysis service. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Experimental Procedures
(±)-(4(R),5(R)-Dihydro-4-methyl-3-(2,4,6-trimethylphenyl)isoxazol-5-yl) (2(S)-methyl-1,3-dithian-2-yl) methanone (R)-*S*-oxide (4a) and (±)-(4(S),5(S)-dihydro-4-methyl-3-(2,4,6-trimethylphenyl)isoxazol-5-yl) (2(S)-methyl-1,3dithian-2-yl) methanone (R)-*S*-oxide (4b)

To a solution of (1) (0.089 g, 0.408 mmol) in diethyl ether (5 ml) at room temperature was added a solution of 2,4,6-trimethylbenzonitrile oxide (0.131 g, 0.816 mmol) in diethyl ether (5 ml). The resulting mixture was stirred at room temperature for 7 days. The solvent was removed *in vacuo* and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the separable cycloadducts, (4a) as a colourless solid and (4b) as colourless crystals (0.111 g, 72%, 3.5: 1).
For (4a): mp 98-99 °C; ν_{max} (dichloromethane) 1712, 1611 and 1040 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.18 (3H, d, *J* 7.15 Hz), 2.10 (3H, s), 2.25-2.50 (3H, m), 2.27 (6H, s), 2.30 (3H, s), 3.15-3.25 (2H, m), 3.35-3.45 (1H, m), 4.07 (1H, quintet, *J* 7.15 Hz, H-C4), 5.11 (1H, d, *J* 7.15 Hz), 6.89 (2H, s); *m/z* (EI) 379.12770 (M^+); $C_{19}H_{25}NO_3S_2$ requires 379.12759.
For (4b): mp 140-141 °C; ν_{max} 1710, 1610 and 1040 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.15 Hz), 2.00 (3H, s), 2.20-2.40 (1H, m), 2.27 (6H, s), 2.30 (3H, s), 2.45-2.55 (2H, m), 2.75-2.85 (1H, m), 3.1-3.15 (1H, m), 3.55-3.65 (1H, m), 3.95 (1H, quintet, *J* 7.15 Hz, H-C4), 5.26 (1H, d, J 7.15 Hz), 6.90 (2H, s); *m/z* (EI) 379.12733 (M^+); $C_{19}H_{25}NO_3S_2$ requires 379.12759.

To a solution of (1) (0.028 g, 0.128 mmol) in dichloromethane (3 ml) at room temperature was added a solution of 2,4,6-trimethylbenzonitrile oxide (0.041 g, 0.256 mmol) in dichloromethane (2 ml). The resulting mixture was stirred at room temperature for 7 days. The solvent was removed *in vacuo* and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the cycloadducts (4a,b) (0.044 g, 90%, 2: 1).

To a solution of (1) (0.023 g, 0.106 mmol) in diethyl ether (2 ml) at room temperature was added a solution of zinc chloride in diethyl ether (1.0 M, 0.106 ml, 0.106 mmol). The mixture was stirred for ten minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.034 g, 0.212 mmol) in diethyl ether (5 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the cycloadducts (4a,b) (0.040 g, 100%, 2: 1).

To a solution of (1) (0.030 g, 0.138 mmol) in dichloromethane (3 ml) at room temperature was added a solution of zinc chloride in diethyl ether (1.0 M, 0.138 ml, 0.138 mmol). The mixture was stirred for ten minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.044 g, 0.276 mmol) in dichloromethane (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the cycloadducts (4a,b) (0.50 g, 96%, 1: 1.5).

To a solution of (1) (0.029 g, 0.133 mmol) in diethyl ether (3 ml) at room temperature was added solid magnesium bromide etherate (0.034 g, 0.133 mmol). The mixture was stirred for ten

minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.034 g, 0.266 mmol) in diethyl ether (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give starting material (0.014 g, 47%) and the cycloadducts (4a,b) (0.014 g, 28%, 1: 2).

To a solution of (1) (0.024 g, 0.11 mmol) in dichloromethane (3 ml) at room temperature was added solid zinc iodide (0.035 g, 0.11 mmol). The mixture was stirred for ten minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.035 g, 0.22 mmol) in dichloromethane (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the cycloadducts (4a,b) (0.038 g, 91%, 1: 2).

To a solution of (1) (0.033 g, 0.151 mmol) in dichloromethane (3 ml) at room temperature was added titanium (IV) isopropoxide (0.045 ml, 0.151 mmol). The mixture was stirred for ten minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.048 g, 0.302 mmol) in dichloromethane (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give starting material (0.027 g, 83%) and the cycloadducts (4a,b) (0.007 g, 14%, 2: 1).

(±)-(4(R),5(R)-Dihydro-4-methyl-3-(2,4,6-trimethylphenyl)isoxazol-5-yl) (2(S)-ethyl-1,3-dithian-2-yl) methanone (R)-*S*-oxide (5a) and (±)-(4(S),5(S)-Dihydro-4-methyl-3-(2,4,6-trimethylphenyl)isoxazol-5-yl) (2(S)-ethyl-1,3-dithian-2-yl) methanone (R)-*S*-oxide (5b)

To a solution of (2) (0.174 g, 0.75 mmol) in diethyl ether (10 ml) at room temperature was added a solution of 2,4,6-trimethylbenzonitrile oxide (0.242 g, 1.50 mmol) in diethyl ether (10 ml). The mixture was stirred at room temperature for 7 days. The solvent was removed *in vacuo* and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the separable cycloadducts, (5a) as a yellow oil and (5b) as a colourless solid (0.251 g, 85%, 1: 1).
For (5a): ν_{max} (neat) 1708, 1610, and 1034 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.15 Hz), 1.24 (3H, d, *J* 7.15 Hz), 2.24 (9H, s), 2.25-2.50 (4H, m), 2.75-2.85 (1H, m), 3.05-3.25 (3H, m), 3.97 (1H, quintet, *J* 7.15 Hz), 5.21 (1H, d, *J* 7.15 Hz), and 6.88 (2H, s); *m/z* (EI) 393.14343 (M^+); $C_{20}H_{27}NO_3S_2$ requires 393.14325.
For (5b): mp 122-123 °C; ν_{max} (dichloromethane) 1710, 1612, and 1040 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.15 Hz), 1.23 (3H, d, *J* 7.15 Hz), 2.28 (9H, s), 2.25-2.55 (4H, m), 2.75-2.85 (1H, m), 3.00-3.20 (2H, m), 3.25-3.42 (1H, m), 3.85 (1H, quintet, *J* 7.15 Hz), 5.32 (1H, d, *J* 7.15 Hz), and 6.88 (2H, s); *m/z* (EI) 393.14343 (M^+); $C_{20}H_{27}NO_3S_2$ requires 393.14325.

To a solution of (2) (0.034 g, 0.15 mmol) in dichloromethane (10 ml) at room temperature was added a solution of zinc chloride in diethyl ether (1.0 M, 0.15 ml, 0.15 mmol). The mixture was stirred for 10 minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.047 g, 0.30 mmol) in dichloromethane (10 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the separable cycloadducts (5a,b) (0.046 g, 87%, 1: 1.2).

(±)-(4(R),5(R)-Dihydro-4-methyl-3-phenylisoxazol-5-yl) (2(R)-ethyl-1,3dithian-2-yl) methanone (R)-*S*-oxide (6a) and (±)-(4(S),5(S)-Dihydro-4methyl-3-phenylisoxazol-5-yl) (2(R)-ethyl-1,3-dithian-2-yl) methanone (R)*S*-oxide (6b)

To a solution of (3) (0.155 g, 0.67 mmol) in diethyl ether (10 ml) at room temperature was added a solution of 2,4,6-trimethylbenzonitrile oxide (0.215 g, 1.34 mmol) in diethyl ether (10 ml). The mixture was stirred at room temperature for 7 days. The solvent was removed *in vacuo* and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give a mixture of starting material (0.019 g, 12%) and the separable cycloadducts (6a) and (6b), both as clear oils (0.207 g, 79%, 1: 1).
For (6a): ν_{max} (neat) 1703, 1612, and 1054 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.15 Hz), 1.25 (3H, d, *J* 7.15 Hz), 1.55- 1.80 (2H, m), 2.05-2.60 (4H, m), 2.30 (9H, s), 3.00-3.20 (2H, m), 3.90 (1H, quintet, *J* 7.15 Hz), 5.32 (1H, d, *J* 7.15 Hz), and 6.92 (2H, s); *m/z* (EI) 393.14343 (M^+), $C_{20}H_{27}NO_3S_2$ requires 393.14325.
For (6b): ν_{max} (neat) 1703, 1611, and 1042 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.15 Hz), 1.20 (3H, d, *J* 7.15 Hz), 1.60-2.03 (2H, m), 2.30 (9H, s), 2.35-2.45 (3H, m), 2.95-3.15 (3H, m), 3.91 (1H, quintet, *J* 7.15 Hz), 5.23 (1H, d, *J* 7.15 Hz), and 6.92 (2H, s); *m/z* (EI) 393.14343 (M^+), $C_{20}H_{27}NO_3S_2$ requires 393.14325.

To a solution of (3) (0.033 g, 0.14 mmol) in diethyl ether (3 ml) at room temperature was added a solution of zinc chloride in diethyl ether (1.0 M, 0.14 ml, 0.14 mmol). The mixture was stirred for 10 minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.046 g, 0.29 mmol) in diethyl ether (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give the cycloadducts (6a,b) (0.053 g, 95%, 1: 1).

To a solution of (3) (0.235 g, 1.01 mmol) in dichloromethane (12 ml) at room temperature was added a solution of zinc chloride in diethyl ether (1.0 M, 0.14 ml, 0.14 mmol). The mixture was stirred for 10 minutes before the addition of a solution of 2,4,6-trimethylbenzonitrile oxide (0.326 g, 2.02 mmol) in diethyl ether (3 ml). The resulting reaction mixture was stirred at room temperature for 7 days, the solvent removed *in vacuo*, and the material purified by column chromatography using 75% ethyl acetate/petroleum ether as the eluent to give a mixture of starting material (0.066 g, 28%) and the cycloadducts (6a,b) (0.223 g, 56%, 1: 1).

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