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Chemo- and regioselective synthesis of 2-alkylidenetetrahydrofurans bearing a chiral sulfur atom by domino reactions of sulfoximines

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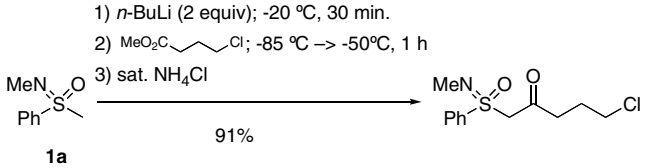
Abstract—The addition of the dianion of Johnson's sulfoximine to α,ω-halogenoesters evolves by an intramolecular heterocyclization to provide a direct access to 2-alkylidenetetrahydrofurans bearing a chiral sulfur atom via domino addition–elimination/S_N reactions.

The regio- and diastereoselective synthesis of 2-alkylidenetetrahydrofurans via anionic domino reactions has been developed in the past few years independently in our group[1] and the groups of Professors Zhao and coworkers,[2] Hagiwara et al.[3] and Langer and Freiberg.[4] These products are of pharmacological relevance and represent versatile building blocks for the synthesis of natural products.[3,5] The 2-alkylidenetetrahydrofurans bearing a conjugated electron withdrawing group such as a ketone, an ester, or a sulfone can undergo various transformations such as aromatization,[6] alkylation,[7] and bromination followed by palladium-catalyzed cross-coupling.[8] In the context of a study on β-ketosulfoximines connected with our work on anionic domino reactions, we have discovered that hitherto unknown sulfoximinyl 2-alkylidenetetrahydrofurans can be prepared stereoselectively via a domino addition–elimination/substitution sequence. The success of our methodology rests upon the sequential in situ preparation and selective trapping of a β-ketosulfoximine anion with readily available α,ω-halogenoesters.[9]

Addition of methyl 4-chlorobutyrate to a THF solution of the dianion of racemic Johnson's sulfoximine **1a**[10] at −85 °C, followed by hydrolysis with ammonium chloride at −50 °C, provides chemoselectively the corresponding ε-chloro-β-ketosulfoximine in 91% yield (Eq. 1).[11] When the same reaction mixture is hydrolyzed with 5% NaOH, the sulfoximinyl 2-alkylidenetetrahydrofurans **2a** (E:Z = 43:57) are formed chemo- and regioselectively in 83% yield by a domino addition–elimination/S_N2 sequence (Scheme 1).[12] Allowing the same reaction mixture to warm slowly to room temperature, and then to 68 °C resulted in the formation of the same sulfoximinyl 2-alkylidenetetrahydrofuran in 55% yield with better but reversed E/Z-stereoselectivity (E:Z = 86:14). The same procedure was applied to the racemic *N*-tosyl sulfoximine **1b**,[10c] which resulted in the formation of the corresponding *N*-tosyl sulfoximinyl 2-alkylidenetetrahydrofuran **2b** albeit in lower yield (17%) and selectivity (E:Z = 70:30).

In order to study the chiral induction of the sulfoximinyl group during the cyclization step, the dianion of racemic



(1)

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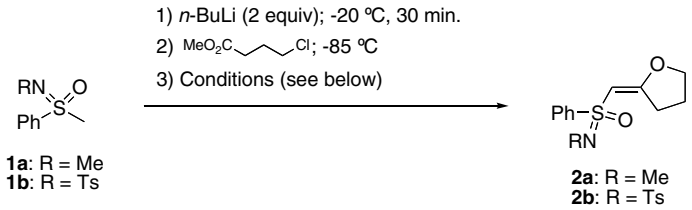


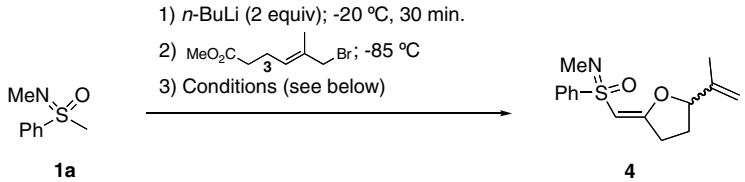
Sulfoximine	Conditions	Yield (%)	*E* / *Z*
1a	- 85 °C –> - 50 °C, 1 h then 5% NaOH, rt, 1 h	83	43:57
1a	- 85 °C –> rt, 2 h 68 °C, 1 h	55	86:14
1b	- 85 °C –> rt, 2 h 68 °C, 1 h	17	70:30

Scheme 1.

Johnson's sulfoximine **1a** was allowed to react under the previously described conditions with methyl ester **3** bearing an allylic bromide as a second electrophilic position (Scheme 2). When the reaction medium is hydrolyzed at −40 °C with 5% NaOH, the sulfoximinyl 2-alkylidenetetrahydrofurans **4** (*E*:*Z* = 40:60) are formed regioselectively in substantial yield by a domino addition–elimination/S_N2' sequence. However, almost no chiral induction was observed, and (*E*)-**4** and (*Z*)-**4** were isolated as near (1:1) mixtures of diastereomers. If the reaction medium is allowed to warm to room temperature and stirred 4 h before hydrolysis, the sulfoximinyl 2-alkylidenetetrahydrofurans **4** is isolated with good *E*/*Z* selectivity (*E*:*Z* = 9:91), but still with extremely poor chiral induction.

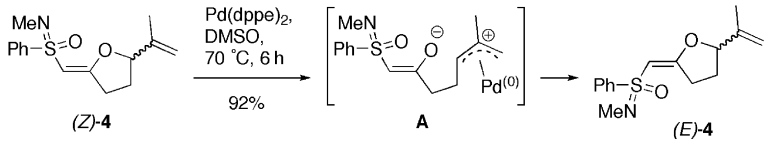
It is worthy of note that good *E*/*Z*-selectivity can only be achieved in the cases where heterocyclization precedes hydrolysis. The thermodynamically more stable *E*-isomer (thermodynamic product) is favoured in the domino addition–elimination/S_N2 reaction leading to **2**, while the *Z*-isomer (kinetic product), most probably derived from a lithium chelated β-ketosulfoximinate intermediate (i.e., **E**), is favoured in the domino addition–elimination/S_N2' reaction leading to **4**. Indeed, for **4**, the cyclization step was carried out at lower temperature (kinetic reaction control) and thus, almost no isomerization to the thermodynamically more stable (*E*)-isomer occurred. However, (*Z*)-**4** (dr = 1.1:1) is slowly converted to the more stable isomer (*E*)-**4** (dr = 1.1:1) on standing neat at room temperature over several months (together with a significant decomposition). This isomerization is better conducted via the π-allyl palladium complex **A**, which undergoes chemo- and regioselective *O*-cyclization to give almost exclusively (*E*)-**4** (dr > 25:1) without significant change in the diastereomeric ratio (dr = 1.1:1, Scheme 3).[13,14]

By extrapolation of the work of Professors Gais et al. on the α,*ortho* to α,α transmetallation of dilithiated alkylphenylsulfones,[15] and considering the more recent work of Professor Müller on dilithiosulfoximines,[16] one can postulate the mechanism depicted in Scheme 4 for the observed results. The initially formed α,*ortho* dilithiosulfoximine **B** would undergo transmetallation to the α,α dilithiosulfoximine **C**, which reacts chemoselectively with the α,ω-halogenoester to give the α-sulfoximinylcarbanion **D**, or alternatively the acylation of the sulfone can precede the translithiation via **C**′. The α-lithio-β-ketosulfoximine **D** in turn rearranges to the chelated enolate **E**, precursor of (*Z*)-**2** and (*Z*)-**4**, the isomerization of which provides the more stable isomers (*E*)-**2** and (*E*)-**4**. The chelated enolate **E** places the bulky phenyl group in the plane of the C=C double

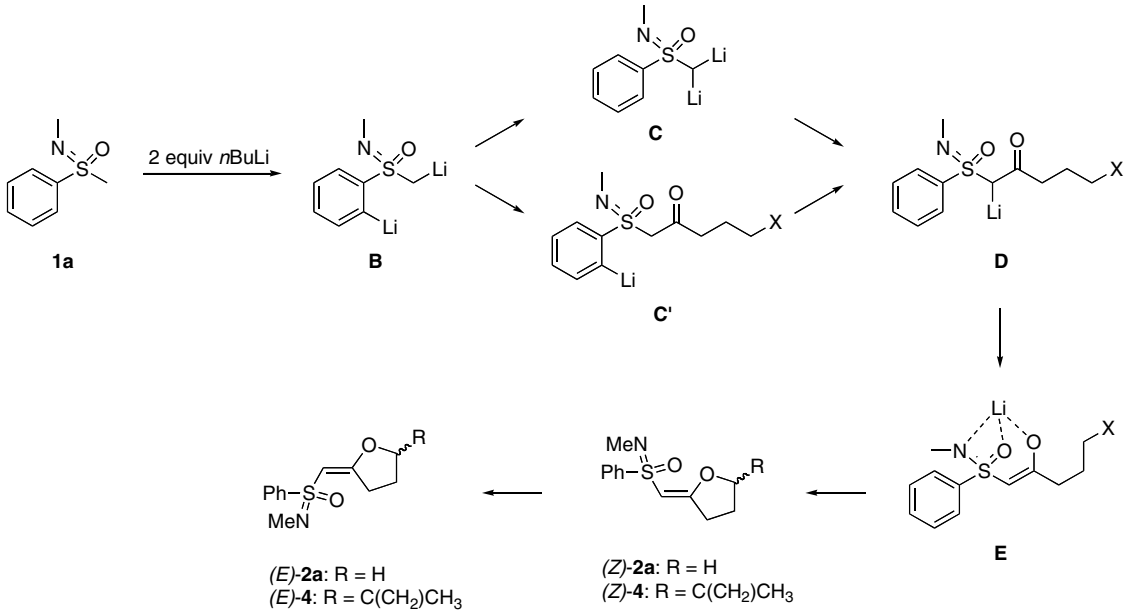


Conditions	Yield (%)	*E* / *Z*	dr_E	dr_Z
- 85 °C –> - 40 °C, 1 h then 5% NaOH, rt, 0.25 h	46	40:60	1.1:1	1.1:1
- 85 °C –> - 40 °C, 1 h then rt, 4 h	43	9:91	1.05:1	1.05:1

Scheme 2.



Scheme 3.



Scheme 4.

bond, and thus the observed extremely poor chiral induction would result from the low steric difference between the *N*-methyl and the oxygen groups. The domino reaction described herein is one of the rare examples of a reaction of a chiral heteroatom stabilized dilithiocarbanion in which both lithium atoms are attached to the same carbon atom.[16]

In summary, 2-alkylidenetetrahydrofurans bearing a chiral sulfoximine group have been prepared in substantial yields and with manageable good *E*/*Z*-selectivity via chemo- and regioselective anionic domino addition–elimination/substitution sequences. The scope and applications of this new process are under investigation.

Acknowledgements

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12. The configuration of compounds **2** and **4** was unambiguously determined by 2D NMR NOESY experiments. (*Z*)-**2** and (*Z*)-**4** show strong NOE correlations between the vinyllic proton and the allylic protons, whereas no correlation is observed for the (*E*)-configured isomers. Analytical data: Compound (±)-(*Z*)-**2a**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 7.83–7.88 (m, 2H), 7.37–7.45 (m, 3H), 5.37 (br s, 1H), 4.28 (ddd, $J = 13.9$, 8.7, 6.9 Hz, 1H), 4.16 (ddd, $J = 13.9$, 8.6, 7.0 Hz, 1H), 2.55–3.63 (m, 2H), 2.60 (s, 3H), 1.80–2.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 168.0 (C), 141.2 (C), 131.6 (CH), 128.4 (2 CH), 128.3 (2 CH), 97.4 (CH), 74.5 (CH_2), 31.6 (CH_2), 29.2 (CH_3), 23.0 (CH_2); MS (ESI+) *m*/*z* 278 (100%, $[M+H]^+$). Compound (±)-(*E*)-**2a**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 7.71–7.80 (m, 2H), 7.33–7.43 (m, 3H), 5.67 (t, $J = 1.5$ Hz, 1H), 3.98–4.14 (m, 2H), 3.05 (dddd, $J = 17.6$, 8.6, 6.9, 1.6 Hz, 1H), 2.64 (dddd, $J = 17.6$, 8.6, 6.8, 1.5 Hz, 1H), 2.56 (s, 3H), 1.80–2.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 173.2 (C), 141.6 (C), 131.6 (CH), 128.7 (2 CH), 127.6 (2 CH), 99.1 (CH), 71.8 (CH_2), 29.1 (CH_3), 28.5 (CH_2), 23.6 (CH_2); MS (ESI+) *m*/*z* 278 (100%, $[M+H]^+$).
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