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Syntheses of Enantiomerically Pure Furyl and Thienyl p-Tolyl Sulfoxides

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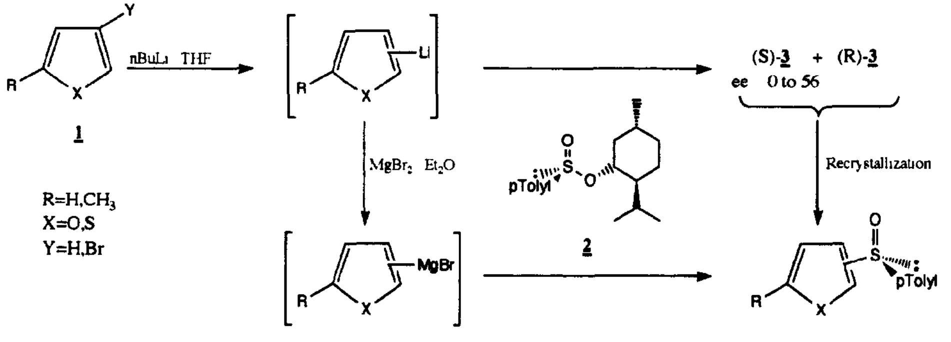
Abstract : *We report a highly enantioselective reaction of Grignard reagents, derived from simple furans or thiophene, with (−)-(S)-menthylsulfinate to give in high yield enantiomerically pure furyl and thienylsulfoxides.*

In connection with synthetic studies on unsaturated sulfoxides, we became interested in the preparation of optically active p-tolylsulfinylfurans or thiophenes. These molecules, that have not been described yet, belong to the very small enantiomerically pure sulfinyl diene family (1).

The well-known Andersen methodology (2) was chosen. Owing to the availability of 2- or 3- lithiofurans and thiophenes, our first procedure was as follows :

Optically pure (−)-menthyl-(S)-p-toluenesulfinate in THF or ether was added dropwise to a cold solution of the lithium derivative of furan or thiophene, at -78 °C under nitrogen. The reaction mixture was stirred at -78 °C for one hour before quenching with saturated aqueous ammonium chloride (scheme 1).



Scheme 1

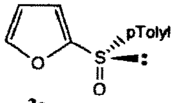
By this way, the crude product showed a low, if any, e.e. (3) (see Table, method A). We noticed that the inverse addition, conceptually better, in which the organometallic was added to the sulfinate, improved the e.e. (see Table, method B).

In contrast, it was found that the Grignard's reagents obtained from the bromo compounds (Table, method C), or issued from the lithium derivatives, by adding freshly prepared magnesium bromide (4) before addition of menthylsulfinate, gave enantiomeric pure (S)-Sulfoxides (Table, method D).

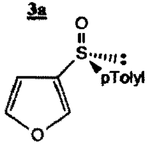
This dramatic dependance between metal used and e.e. cannot be explained by subsequent racemization of the final sulfoxide. A test was made at room temperature, mixing BuLi or 2-lithiofuran to enantiomerically pure sulfoxide 3a. After four hours, no racemisation occured, in agreement with reports that the pyramidal inversion at sulfur is not affected by strong bases. The most obvious explanation for the difference between Li and Mg intermediates is that with Mg clean S_N2 reaction occurs, perhaps favored by chelation of the metal, instead of a rather ionic S_N1, encountered with Li. In summary the sequence studied demonstrates the interest of the exchange Li ⟶ Mg, before the reaction with menthylsulfinate.

Currently, work is in progress in order to study the synthetic applications of these optically active dienes.

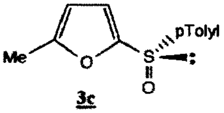
Table



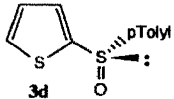
3a



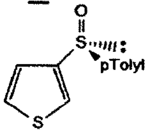
3b



3c



3d



3e

entry	compound	method(6)	yield(5)	crude e.e.(3)	[α](7)
1	3a	A	95	0	
2	3a	B	95	30	
3	3a	D	91	100	106
4	3b	A	71	56	
5	3b	D	76	100	31
6	3c	A	77	9	
7	3c	B	92	50	
8	3c	D	91	100	165
9	3d	A	86	4	
10	3d	C	56	95(3)	
11	3d	D	74	100	110
12	3e	A	37	56	
13	3e	D	90	100	40

Methods : A : 1) n-BuLi/THF, 2) (-)-(S)-menthyl-p-Toluenesulfinate
B : inverse addition (Lithium salt is added to the (-)-(S)-menthyl-p-Toluenesulfinate)
C : 1) Mg/THF, 2) (-)-(S)-menthyl-p-Toluenesulfinate
D : 1) n-BuLi/THF, 2) $MgBr_2/Et_2O$, 3) (-)-(S)-menthyl-p-Toluenesulfinate

References and Notes

(1) E.Bonfand, P.Gosselin and C.Maignan, ***Tetrahedron Letters***, 1992, 33(17), 2347 and references 2-5 cited therein.
(2) K.K.Andersen, ***J. Org. Chem.***, 1964, 29, 1953.
(3) reaction mixtures were analyzed by NMR [Eu(hfc)$_3$ shift reagent] and HPLC (DAICEL, Chiralcel, OB 250mm, 254 nm UV detector); for 3d (entry 10), by NMR only.
(4) L.Brandsma, H.Verkruijsse, ***Preparative Polar Organometallic Chemistry 1***, p. 158, Springer-Verlag, 1987.
(5) all furans and thiophenes used are commercially available (Aldrich). 3-bromofuran was also synthesized according to J.Srogl, M.Janda and I.Stibor, ***Coll. Czedroslov. Chem. Commun.***, 1970, 35, 3478.
(6) the physical and spectrometric data were in good agreement with literature values.
(7) the optical purification of partially resolved mixtures of 3b, 3d and 3e was conveniently effected by recrystallization in ether (entries 4,9 and 12).