Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5755-5758, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01176-8

Synthesis of Chiral Non-racemic 2-Arylpyrrolines by a [3+2] Cycloaddition Route[1]

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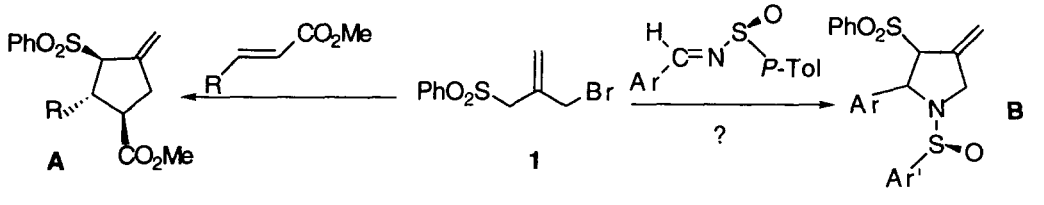
Abstract : A new and efficient diastereoselective (upto 76% de) synthesis of 2-aryl-3-pyrroline derivatives **3a-f** has been achieved by [3+2] cycloaddition of allylsulfone **1** and non-racemic sulfinimines **2**. Separation of the diastereomers led to optically pure 2(R)-pyrrolines (62-72% yield). The N-sulfinyl auxiliary can be removed with TFA. Copyright © 1996 Elsevier Science Ltd

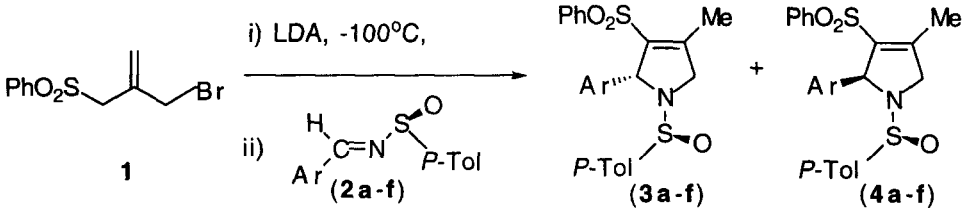
Many naturally occuring alkaloids and biologically active compounds posses the pyrrolidine moiety as a basic skeleton.[2] Numerous reports have described the application of pyrrolidine or pyrroline derivatives as chiral ligands,[3] chiral auxiliaries,[4] chiral bases,[5] and chiral building blocks for supramolecular chemistry.[6] A wide variety of synthetic approaches to the pyrroline or pyrrolidine skeleton are available. Most of the syntheses of chiral pyrrolidines emerge from natural amino acids as chiral auxiliaries[7] or are based on diastereoselective alkylation[8] or asymmetric hydrogenation[9] of an existing pyrroline moiety.

Herein, we describe a general approach to chiral non-racemic 2-arylpyrrolidine derivatives employing a [3+2] cycloaddition strategy[10] that involves the anion of allyl sulfone **1** and non-racemic sulfinimines[11] **2** as the chiral source. Based on our studies of **1** with unsaturated esters to afford **A**[12] we visualised that reaction of 3-(benzenesulfonyl)-2-bromomethyl-1-propene **1** , a 1,3-dipole equivalent of trimethylenemethane (TMM), with electrophilic imines **2** could lead, hopefully in a diastereoselective manner, to functionalized 4-methylenepyrrolidines **B**.



The required chiral sulfinimines (**2a-f**) were prepared employing the method of Davis *etal.*[13]Though, initially reaction of the anion of **1** with sulfinimine (S)-**2a** led to a mixture of ill-defined products, optimization (LDA at -100° C and utilization of HMPA) led to isolation of a cycloadduct in 70% yield. The adduct was shown by NMR to be a pyrroline formed as a 7.3:1 mixture of two diastereomers, **3a** and **4a**, separable by chromatography on silica gel. The ^{1}H NMR spectrum of **3a** showed a broad singlet at δ 2.26(3H), two *ddd* at δ 4.28 and 4.56(each 1H) and *dq* at δ 5.74(1H). The corresponding signals in ^{13}C NMR at δ 13.0(*q*), 60.3(*t*),

67.7(*d*) further confirmed the assigned structure. All our attempts to isolate an 4-exomethylene derivative(see **B**) were unsuccessful; apparently under the basic conditions isomerisation of the *exo* to the *endo* double bond occurs readily[14] due to the presence of the neighbouring sulfone function. The reaction was found to be general with other aryl sulfinimines (**2b-f**) giving rise to the corresponding 3-pyrroline derivatives (**3b-f** and **4b-f**)[15] in good yield and with a diastereomeric ratio of 3:1 to 7:1(Table I). The observed diastereoselection is presumably attributable to Li^+ chelation in the transition state between the sulfone and sulfinimine oxygens.



Scheme 1

Table I: Formation of chiral pyrrolines **3a-f** and **4a-f** and yields of **3** by reaction of **1** with **2a-f** at -100°C

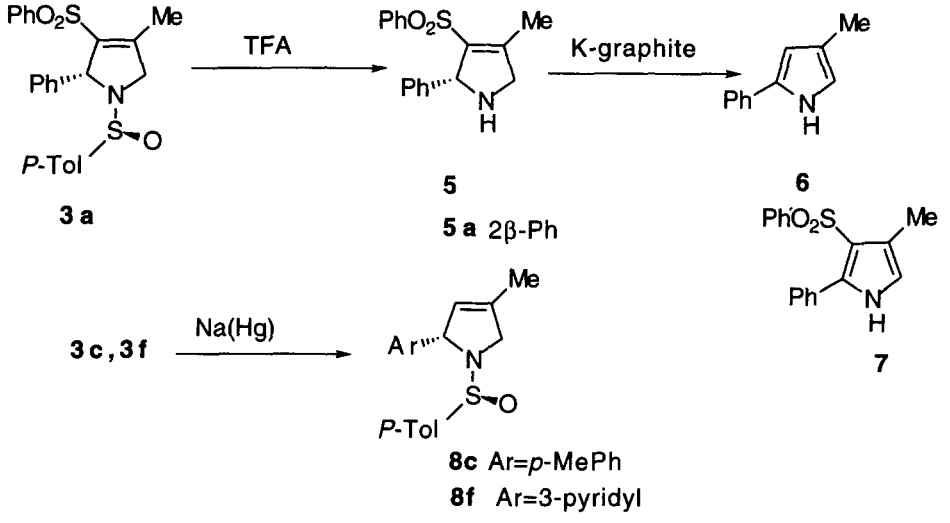
Entry	Ar	Ratio[a] **3**:**4**	Yield[b] (%)	$[\alpha]_D^{25}$ of **3**
a	Ph	88:12	70	-81.8(c 1.1,$CHCl_3$)
b	*p*-MeOPh	75:25	62	-92.8(c 1.2, $CHCl_3$)
c	*p*-MePh	86:14	72	-83.8(c0.84, $CHCl_3$)
d	*p*-ClPh	83:17	68	-130(c 1,$CHCl_3$)
e	2-Furyl	88:12	70	-38(c 1.05, MeOH)
f	3-Pyridyl	86:14	66	-70(c 1, $CHCl_3$)

(a) based on ^{1}H NMR of crude product (b) Isolated yield of the major diastereomer **3**. The minor diastereomer **4** was isolated in 10-20% yield.

In a typical experiment, 1 mmol of **1** in 1mL of THF was added to a solution of LDA (1.2 equiv.) in THF at -100°C. After 10 min, sulfinimine (S)-**2a** (1.1 equiv.) was added slowly and the solution was stirred at -100°C for 30 min. HMPA was added and the mixture was stirred at -90°C for further 2h (Scheme 1). Quenching of the reaction mixture with saturated aq. NH_4Cl solution and work up afforded the crude 1-*p*-toluenesulfinyl-4-methyl-2-phenyl-3-benzenesulfonyl-3-pyrroline as a 7.3:1 mixture of two diastereomers **3a** and **4a**. The two diastereomers were easily separated by silica gel flash chromatography using 4:6 ethyl acetate:pet.ether. X-ray crystallographic analysis of **3a** establishes the absolute configuration as 2(R), S(S).[16]

The N-sulfinyl group in **3a** was removed by treating with 2-equiv. of TFA in methanol at 0°C for 3-4 h and pyrroline **5** was isolated in 90% yield [$[\alpha]_D^{25}$=-42° (c 0.95, MeOH)]. Removal of the sulfinyl group from **4a**, gave pyrroline **5a**, the enantiomer of **5** [$[\alpha]_D^{25}$=+50° (c 1.0, MeOH)] indicating the diastereomeric

relationship between (R,S) **3a** and (S,S) **4a**. Attempts to desulfonate **3a** cleanly using Na(Hg) were unsuccessful and refluxing of **3a** with sodium dithionite and sodium hydrogencarbonate in aqueous methanol[17] afforded compounds **6** and **7** in 80% yield in a 3:1 ratio. We succeeded in obtaining pyrrolines **8c** and **8f** by reaction of **3c** and **3f** respectively with Na(Hg). Treatment of **5** with potassium on graphite[18] in THF at 20°C yielded 2-phenyl-4-methylpyrrole **6** as the only isolable product in 60% yield (Scheme 2). Hence, this methodology can serve as a short route to 2-arylpyrrole derivatives[19] starting from **1** and racemic sulfinimines.



Scheme 2

In summary, this methodology based on Michael addition of **1** to (S)-sulfinimines **2** serves as a novel and efficient stereoselective route to optically active 2(R)-arylpyrroline derivatives. Starting from (R)(-) sulfinimines **2** and **1**, the antipode of **3** can be prepared. Further elaboration of these chiral pyrrolines is in progress.

Acknowledgement: We are grateful to the US-Israel Binational Science Foundation and the Israel Science Foundation for support of this research. We thank Dr.H.E.Gottlieb for help with the NMR spectra, Dr.M. Cojocaru for help with the mass spectra, and Professor E.Ghera for helpful discussions.

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14. Similar results were also obtained in the absence of HMPA but the reaction has to be slowly warmed to 0°C for an overall period of 6h.
15. All compounds were characterized by ^{1}H and ^{13}C NMR, mass spectroscopy. Data for compound **3a**: mp. 186-188°C, ^{1}H NMR ($CDCl_3$) (300 MHz) δ 2.26(*bs*, 3H), 2.3(*s*, 3H), 4.28(ddd, J-16,2,1 Hz, 1H), 4.56(ddd, J=16,5.5,1.5 Hz, 1H), 5.74(dq, J=5,1.5 Hz, 1H), 6.64-6.68(m, 2H), 6.84-7.08(m, 4H), 7.14-7.44(m, 8H) ^{13}C NMR ($CDCl_3$) δ 149.3(s), 141.0(s), 140.9(s), 138.8(s), 136.3(s), 132.6(d), 128.9(d), 128.3(d), 128.2(d), 127.5(d), 127.3(d), 126.9(d), 125.7(d), 67.7(d), 60.3(t), 21.0(q), 13.0(q). ms 438(MH^+), 332, 298(100), 222, 143. Observed mass= 438.1095 (for MH^+, calculated value= 438.1197).
16. We thank Professor A.I.Meyers, Colorado State University, for providing the X-ray analysis of **3a**. Details will be published in a full paper.
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(*Received in UK* 30 *April* 1996; *revised* 12 *June* 1996; *accepted* 14 *June* 1996)