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ELECTROPHILIC QUENCHING OF DIANIONS OF 4-[5'-SULFONYLMETHYLISOXAZOLYL]-1,4-DIHYDROPYRIDINES. A DIRECT ROUTE TO FUNCTIONALIZED HANTZSCH ESTERS†

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Abstract: *An expedient entry into the preparation of Hantzsch Esters is presented. The method involves dilithiation and selective electrophilic quenching of 4-[5'-sulfonylmethylisoxazolyl]-1,4-dihydropyridines.*

The calcium antagonist activity of the 4-aryl-1,4-dihydropyridines (DHPs) has been found to correlate with certain key electronic and structural features.[1] A Quantitative Structure Activity Relationship (QSAR) study was reported by Triggle's group, who found that pharmacology for 46 DHPs was correlated by log $1/C = 0.62\,\pi + 1.96\,\sigma - 0.44\,L_{meta} - 3.26\,B_{1para} - 1.51\,L_{meta'} + 14.23$, which had a correlation coefficient of 0.90. The correlations indicate that pharmacological data for nifedipine analogues is dependent on lipophilicity, an electronic term, and separate steric terms for each position of the aromatic ring.[1c] Of particular importance is the correlation of negative ionotropic activity[2] with the Verloop steric parameter B_1,[3] for ortho substituents on the phenyl ring, which has focused interest on the conformational preferences of the DHPs.[4] We had reported earlier on the synthesis, structure and biology of isoxazolyl-1,4-dihydropyridines (IDHPs),[5a,b] which present the opportunity for probing the role of substituents oriented in this B_1 direction. We have recently found that 4-isoxazolyl-1,4-dihydropyridines (IDHPs) containing chiral substituents at C-5 of the isoxazole moiety exhibit pronounced enantioselectivity in the displacement of [^{3}H] calcium antagonists from cardiac membrane preparations, which is a measure of specific binding to the protein which serves as the putative calcium channel.[5c] We desired a direct entry into the modification of IDHPs in this C-5 lateral position. We herein report the reactions of C-5 sulfonyl isoxazoles,[6,7] which allows convergent entry into rational substitution at this position in the corresponding IDHPs.

The requisite starting materials were prepared from the C-5 sulfonyl isoxazole **1**, (R^1=R^2=Ph, mp 119-120°C),[7] followed by selective deprotection of the C-4 functional group to the aldehyde, **2**, and Hantzsch pyridine synthesis. Using aqueous ammonia and standard Hantzsch pyridine conditions, significant quantities of benzisoxazoles, **3**, were observed for the C-3' phenyl isoxazole. In fact, the benzisoxazole, **3**, R^1=R^2=Ph, mp 154-156°C whose structure was determined by single crystal x-ray diffractometry, was the major product (75%). The 4-sulfonylmethylisoxazoles-1,4-dihydropyridines (SIDHPs), **4**, could be separated by simple flash chromatography (15%). In the case of R^1=CH_3, R^2=Ph, in contrast, the SIDHP **4** was isolated as the major

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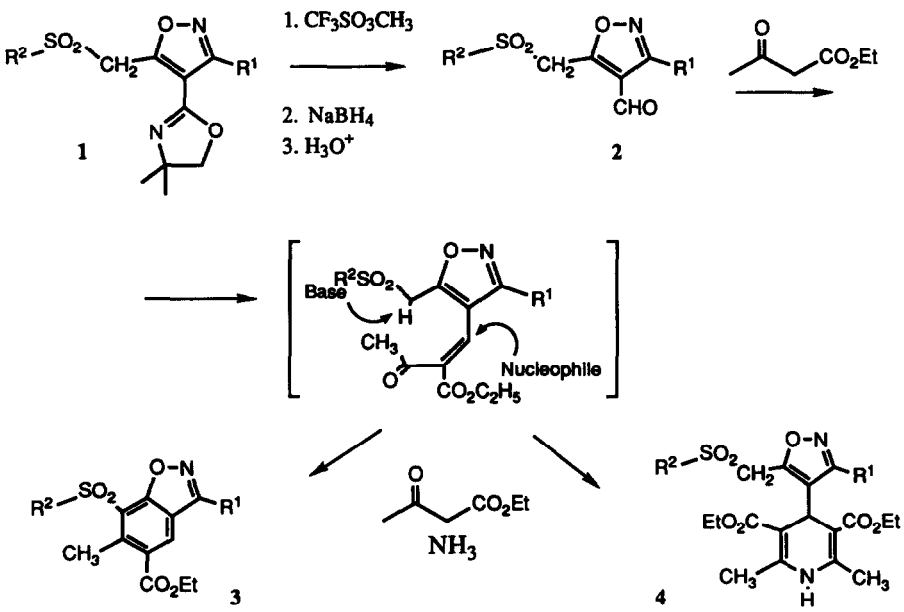
product (70%, mp 151-153°C, again, this structure was confirmed by single crystal x-ray determination) along with 10% benzisoxazole **3** . For **4**, R^1=R^2=CH_3, only DHP product was observed (60% isolated yield). We attribute this reactivity to (1) enhanced acidity of the methylene group adjacent to the sulfonyl for **2**, R^1=R^2=Ph, and (2) the steric effect of the R^2=Ph during the critical Michael addition step of the Hantzsch pyridine synthesis. Thus in cases with R^2=CH_3 the SIDHP **4** predominates in useful yield.

We then turned our attention to deprotonation of SIDHP **4**. We anticipated the possible complication of deprotonation at the C-2 methyl of the DHP - a vinylogous urethane.[8] Metalation of the SIDHPs, **4**, proceeds to the dianion with two equivalents of LDA at -78°C, followed by quenching to produce electrophile incorporation in the C-5 lateral position of the isoxazole, **5**. Apparently, the sulfonyl moiety increases the acidity at this position sufficiently to allow for clean deprotonation adjacent to the isoxazole, as established readily by the disappearence of the $PhSO_2CH_2$- signal found in the ^1H NMR ($CDCl_3$, 200 MHz) of **4** [at δ 4.459 (s, 2H)], and the subsequent appearence in **5a** of a pattern characteristic of the CH_3CH- group [δ 4.505 (q, 1H, J = 7 Hz; 1.526 (d, 3H, J = 7 Hz)]. Typical results are shown in **Table I**.



The use of other bases to effect deprotonation has been explored. Potassium t-butoxide can deprotonate the SIDHP **4**, however, with very reactive electrophiles, such as iodomethane, electrophilic quenching at the nitrogen is observed competitive with that at the position lateral to the isoxazole moiety. This process was also found to occur quite efficiently, and with excess electrophile, the N,C-5'-***di*** methyl product can be obtained in over 60% yield after isolation and purification.

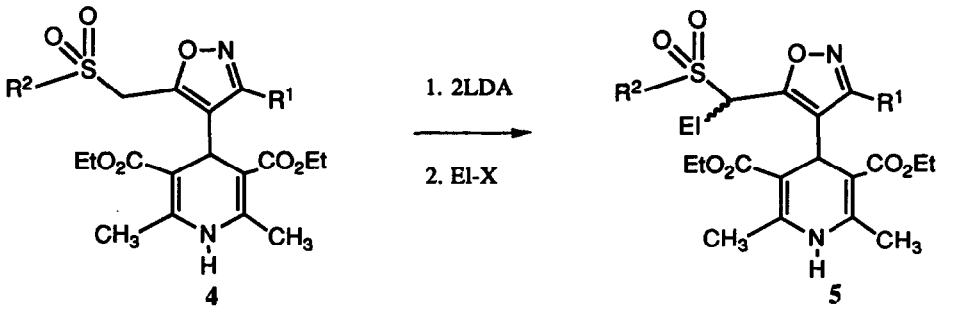
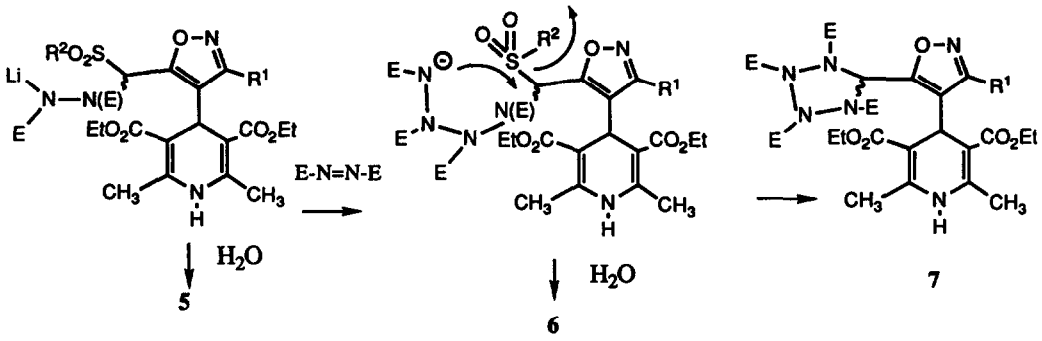


Table I. Isolated, Purified Yields and partial characterization data for products **5**.

Entry	R^1	R^2	El-X	Yield (%)[a]	Empirical Formula	MS (% RI)[b]	HPLC-CSP[e] α
a	CH_3	C_6H_5	CH_3-I	62	$C_{25}H_{30}N_2O_7S$	503 (19.5)	1.16
b	CH_3	C_6H_5	$C_6H_5CH_2$-Br	75	$C_{31}H_{34}N_2O_7S$	579 (37.1)[c]	1.29
c	CH_3	C_6H_5	m-$BrC_6H_4CH_2$-Br	72	$C_{31}H_{34}BrN_2O_7S$	659(3.5) 657(4.3)	1.14
d	CH_3	C_6H_5	m-$CH_3OC_6H_4CH_2$-	83	$C_{32}H_{36}N_2O_8S$	609 (40)[c]	1.25
e	CH_3	C_6H_5	TBOC-N=N-TBOC	42	$C_{44}H_{63}N_6O_{15}S$	948(63)[c,d]	n.d.
f	CH_3	CH_3	$C_6H_5CH_2$-Br	56	$C_{26}H_{32}N_2O_7S$	515(68.9)[c]	1.32

[a] Yield of isolated product after purification by chromatography. [b] Fast Atom Bombardment., $[M+1]^+$ unless otherwise noted. [c] Chemical Ionization. [d] Two Equivalents of El were incorporated, see text. TBOC = $CO_2C(CH_3)_3$. [e] Chiralcel OJ, hexane-isopropanol (9:1), 0.5 mL /min.

It is noteworthy that the di-t-butylazodicarboxylate (**Table I**, entry **5e**) gave incorporation of two electrophiles, even with short reaction times (5 min). Extended reaction time with the corresponding diethylazodicarboxylate electrophile (DEAD, 12h) produced *two* products which both had incorporated two equivalents of the diazodicarboxylate were isolated, **6** (45%) and **7**(28%). Moreover, one of these products, **7**, also lacked the phenylsulfonyl moiety (Mass spectrum m/z 694 [5% rel. intensity], corresponds to $C_{30}H_{42}N_6O_{13}$). We postulate that this product arises by an intramolecular displacement of the phenylsulfonyl group, via lithio-**6**, well known for its "chemical chameleon"[10] reactivity. This observation demonstrates that the sulfonyl group, once it serves its role to direct the metalation and electrophile quenching, can be removed.



This route to chiral SIDHPs is convergent and efficient, and allows for systematic substituent variation towards the end of the synthetic route. The regiochemistry observed herein is complementary to that reported by Poindexter for the 4-aryl-DHPs.[8] We are currently using this methodology to prepare SIDHPs to test the validity of current drug-receptor interaction hypotheses,[9] and will report on our progress in due course.

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