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STUDIES ON THE ANTITUMOR AGENT CC-1065

1-Phenylsulfonyl-1,3-Butadiene. An Electrophilic Equivalent to 1,3-Butadiene for the Synthesis of 3,3'-Bipyrroles.

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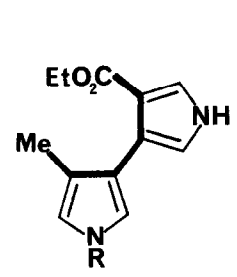
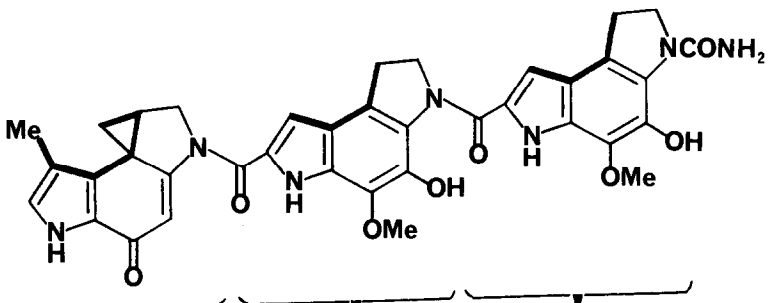
SUMMARY: Sequential conjugate additions of methyl TOSMIC anion and TOSMIC anion to 1-phenylsulfonyl-1,3-butadiene provides a direct route to 3,3'-bipyrroles, and illustrates that 1-phenylsulfonyl-1,3-butadiene can function as an electrophilic 1,3-butadiene equivalent.

Recently we reported the synthesis of the rare 3,3'-bipyrrole 1 as part of a strategy directed towards the synthesis of the potent antitumor agent CC-1065 2.[1] The central reaction used to make 1 is the sequential conjugate addition of TOSMIC anion to ethyl sorbate.[2] This approach



1



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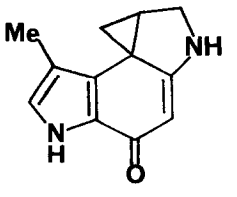

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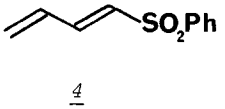

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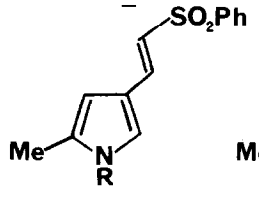
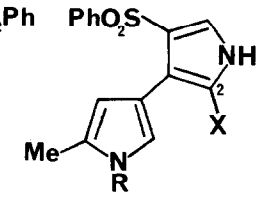


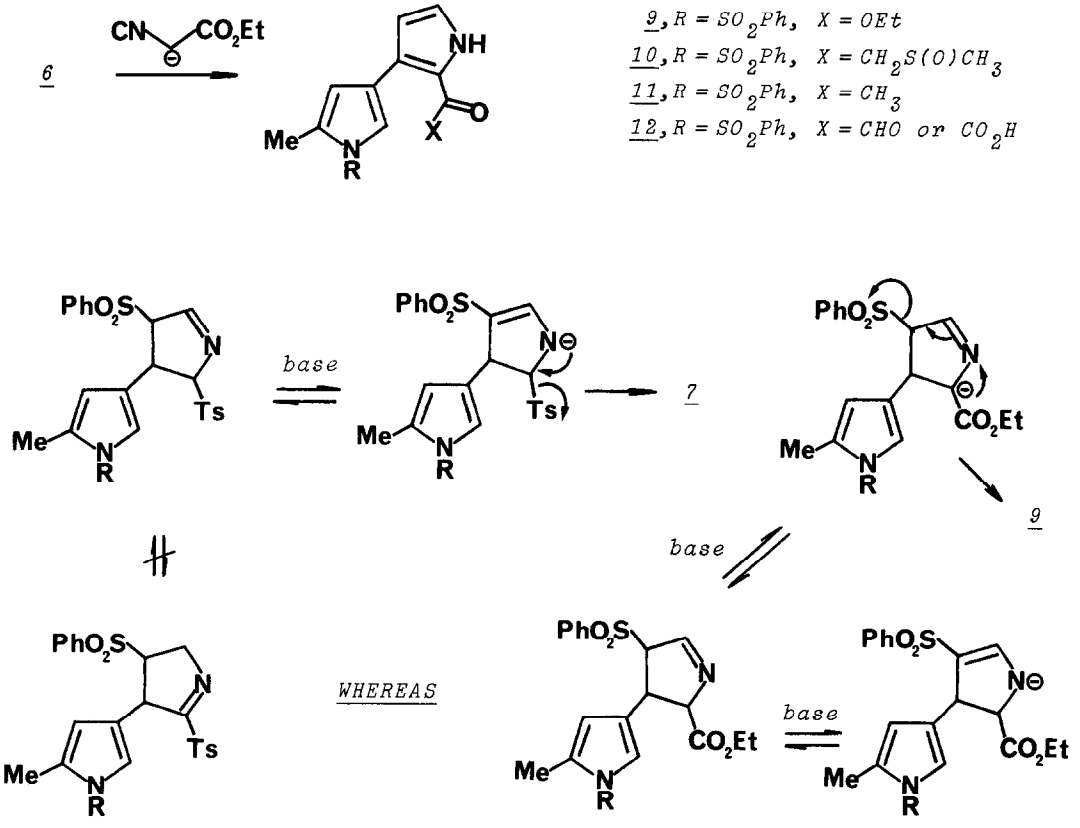
5, R = H
6, R = SO_2Ph



7, X = H
8, X = Et

(R = -SO_2Ph unless otherwise stated)

has been vindicated by the subsequent conversion of 1 *into the A-portion* 3 *of CC-1065;*[3] *Thus the carbon atoms of sorbic acid comprise the thickened bonds in* 1 *and* 2. *For a similar strategy to be applicable to the synthesis of the B/C-portion of CC-1065 an electrophilic equivalent to 1,3-butadiene was required that would undergo similar sequential conjugate additions of TOSMIC anion.*



SCHEME 1

1-Phenylsulfonyl-1,3-butadiene 4[4] *was treated with TosCHMeNC/NaH/THF/DMSO/20°C to give the 2,4-disubstituted pyrrole* 5, *64%. This result is remarkable considering the extreme ease with which* 4 *undergoes anionic polymerization when exposed to bases. The pyrrole* 5 *was converted into*

the N-phenylsulfonyl derivative 6, m.p. 169-170°C, and treated with $TosCH_2NC/NaH/THF/DMSO/20°C$ to give the 3,3[1]-bipyrrole 7, 72%, m.p. 193-194°C. Similarly, treatment of 6 with TosCHEtNC/NaH/HMDS/THF/20°C gave the ethyl analog 8, 95%. The bipyrrole 7 was not amenable to selective acylation, and reduction (Raney Nickel) removed the N-phenylsulfonyl group rather than the C-phenylsulfonyl group. Consequently, we required a method for selectively removing the C-phenylsulfonyl group, which would at the same time introduce a useful functional group at C-2 (see structure 7). Treatment of 6 with $EtO_2CCH_2NC/NaH/HMDS/DMSO/THF/20°C$[5] gave the desired 3,3[1]-bipyrrole 9, 70%, m.p. 119-121°C. A contrast should be noted, since the conversion of 6 into 7 involves the elimination of the -Ts group rather than the $-SO_2Ph$ group, whereas, conversion of 6 into 9 involves the elimination of the $-SO_2Ph$ group. SCHEME 1 rationalizes these observations. It should be noted that the ethyl isocyanoacetate procedure normally produces an oxazole, whereas, pyrroline compounds are only observed under drastic conditions. Undoubtedly, the $PhSO_2$- leaving group leading to aromatization provides the driving force for the pyrrole annulation to take place under very mild conditions.

Treatment of 9 with $LiCH_2S(O)CH_3$ gave 10 (90%), which on Zn/AcOH reduction lead to the methyl ketone 11 (80%). All attempts to oxidize 11 to the glyoxal or glyoxalic acid 12[6] resulted in decomposition. Attempted intramolecular Pummerer reaction of 10, using a variety of electrophilic conditions, also lead to decomposition.[7] Currently, we are examining the regioselective electrophilic substitution chemistry of the 3,3[1]-bipyrrole 7.[8]

The ability to construct 3,3[1]-bipyrroles, having an electrophilic substituent either at the 2- or 3- positions, illustrates the flexibility of this type of strategy for the synthesis of functionally differentiated 3,3[1]-bipyrroles. The use of 1-phenylsulfonyl-1,3-butadiene in Michael reactions that form C-C bonds should find wider use in synthesis.

In summary, 1-phenylsulfonyl-1,3-butadiene can function as a viable electrophilic butadiene equivalent for the synthesis of unsymmetrical 3,3[1] bipyrroles.

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8. *This will be reported at a later date. All new compounds were characterized by standard spectroscopic and micro-analytical/M.S. techniques.*

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