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INTRODUCTION OF FUNCTIONALIZED SUBSTITUENTS INTO ACTIVE METHYLENE COMPOUNDS

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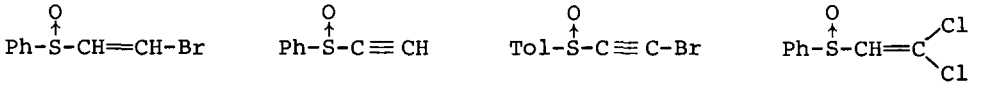
Condensation of active methylene compounds with variously functionalized carbon two unit Michael acceptors (1-5) afforded the corresponding adducts, respectively. Reaction of such Michael adducts with NBS to afford the vinyl (15, 16, and 17) and ethynyl (21) bromides will also be described.

In connection with the synthetic study of indole alkaloids, introduction of a keto group into an angular position activated by a carbonyl group was required. Since Michael acceptors are known to react with these hindered trisubstituted carbanions,[1] carbon two unit Michael acceptors[2] which after condensation can be convertible to an acetyl group were sought. As possible candidates, 2-bromovinyl phenyl sulfoxides (1, cis and 2, trans),[3] ethynyl phenyl sulfoxide (3),[4] bromoethynyl p-tolyl sulfoxide (4), and 2,2-dichlorovinyl phenyl sulfoxide (5)[5] were chosen.



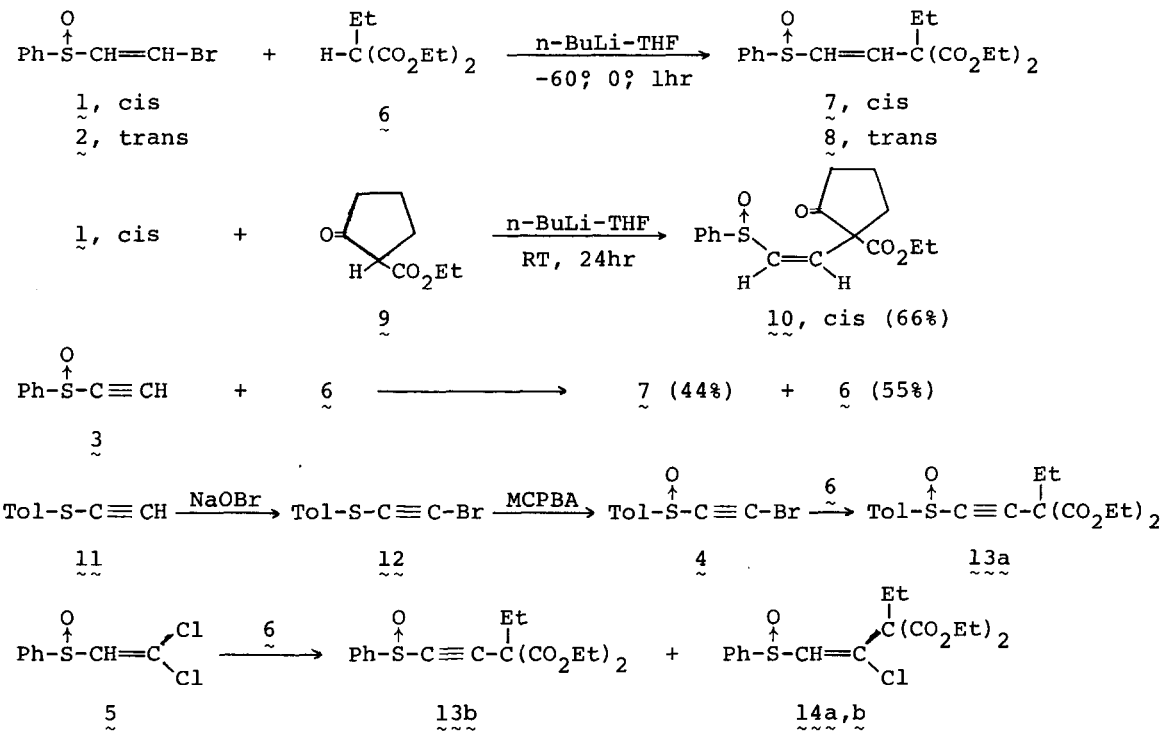
1, cis; 2, trans — 3 — 4 — 5

The reaction of 3 and vinyl and iodovinyl sulfones with organocopper(I) reagents has been published[6] but the reaction with active methylene compounds which is essential to achieve our primary purpose has not been reported so far.[7] When 1 (1.0 equiv) and 2 (1.0 equiv) were subjected to the reaction with diethyl ethylmalonate (6) (1.1 equiv) in the presence of n-BuLi (1.0 equiv), the adducts, 7 [cis, NMR(CCl_4) δ 6.18(1H, d, J=10.8Hz), 6.54(1H, d, J=10.8Hz)] and 8 [trans, NMR(CCl_4) δ 6.67(1H, d, J=15.6Hz), 6.90(1H, d, J=15.6Hz)] were obtained in quantitative yields, respectively. In the same way, 9 produced 10 [cis, NMR(C_6D_6) δ 6.06(1H, d, J=10.2Hz), 6.31(1H, d, J=10.2Hz)] although the reaction proceeded much slower in this case. These data show that the condensation proceeded with retention of configuration, which accords quite well with the reaction of organocopper(I) reagents with (E)-2-iodo-1-alkenyl sulfones to give 2-alkylated products with retained configuration.[6c,d] Addition of 6 to the ethynyl sulfoxide (3) proceeds again stereospecifically in a trans fashion affording 7 in 44% yield

although the cis stereoselectivity of the addition of the organocopper(I) reagents to acetylenic sulfoxides has been established.[6b,d]

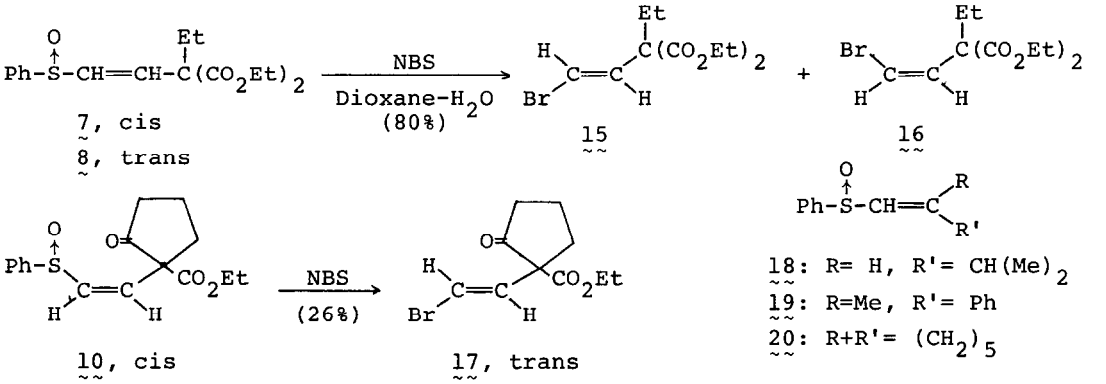
Then, the reaction of the bromoethynyl sulfoxide (4) was investigated expecting the direct introduction of the acetylenic sulfoxide which was presumed to be a still more effective precursor for a methyl ketone. The ethynyl sulfide (11)[4] was brominated with NaOBr to afford bromoacetylene (12)[IR(neat) 2140cm^{-1}], which without purification oxidized with MCPBA in CH_2Cl_2. The resultant sulfoxide (4) [73%, IR(neat) 2135cm^{-1}] was found to be extremely unstable but can be purified by a rapid passage of a short Silica Gel column. Addition of 4 (1.3 equiv) thus obtained in CH_2Cl_2 to a mixture of 6 (1.0 equiv) in THF and n-BuLi (1.0 equiv) produced quite smoothly the expected acetylenic sulfoxide (13a) [IR (neat) 2180cm^{-1}] in 72% yield. The present method would be extended to a general method for the introduction of an acetylenic group to an angular position.

Considering a rather unstable nature of 4, the reaction of 2,2-dichlorovinyl sulfoxide (5) which presumed to have an analogous reactivity with 4 was also investigated. As was expected, 5 afforded 13b [IR(neat) 2180cm^{-1}] in 55% yield along with a stereoisomeric mixture of the chlorovinyl sulfoxides, 14a [NMR (CCl_4) δ 6.48(1H, s)] and 14b [NMR(CCl_4) δ 7.11(1H, s)](35% yield).



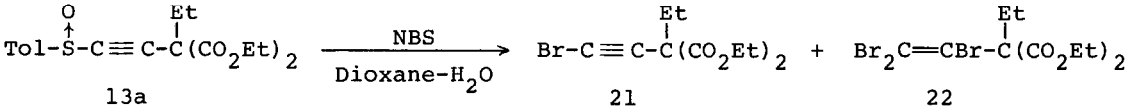
In an effort to convert the functionalized substituents thus introduced to an acetyl group, the reaction of 7, 8, and 10 with aqueous NBS was carried out since Tsuchihashi et al. have reported the successful formation of 1-bromo-2-hydroxy-2-phenylethyl p-tolyl sulfoxide by the reaction of the 2-styryl p-tolyl

sulfoxide with aqueous NBS.[8] Treatment of the cis adduct (7) (1.0 equiv) with NBS (2.0 equiv) in dioxane - H_2O (1.2 : 1) afforded unexpectedly a mixture of trans (15) [NMR(CCl_4) δ 6.26(1H, d, J=14.4Hz), 6.62(1H, d, J=14.4Hz)] and cis (16) [NMR(CCl_4) δ 6.29(1H, d, J=7.8Hz), 6.87(1H, d, J=7.8Hz)] bromovinyl derivatives (80%) along with $PhSO_2Br$, the trans isomer being much favoured (9 : 1). None of the expected bromohydrin could be isolated. The same mixture of 15 and 16 was obtained (80%) in the same ratio from the trans adduct (8). Analogous reaction was observed with the cis adduct (10) affording again the corresponding trans bromovinyl derivative (17) [26%, NMR(CCl_4) δ 6.16(1H, d, J=14.4Hz), 6.62 (1H, d, J=14.4Hz)]. On the other hand, with 18, 19, and 20, a diastereomeric mixture of 1-bromo-2-hydroxy derivatives was obtained in each case.[9] Here, it became apparent that bromovinyl derivatives were obtained only when R (or R') is a bulky trisubstituted methyl group.[10]



7, cis
8, trans
15
16
10, cis
17, trans
18: R= H, R'= $CH(Me)_2$
19: R=Me, R'= Ph
20: R+R'= $(CH_2)_5$

Then, the reaction of the ethynyl sulfoxide (13a) with NBS in dioxane - H_2O was investigated expecting the direct formation of the desired β-keto sulfoxide. However, products actually obtained were a mixture of the bromoacetylene (21)[11] and the tribromoethylene (22) along with TsBr when 1.4 - 1.7 equiv of NBS were used. Around half of 13a was recovered unchanged. The use of excess NBS (3.5 equiv) produced only 22 in 72% yield.



13a
21
22

Further work for the introduction of oxygen function to the Michael adducts is being continued.

ACKNOWLEDGMENTS: We thank Prof. M. Hoshino for his helpful discussion and also thank Messrs. Y. Nemoto, H, Nomura, and K. Gamo for their technical assistance.

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4. a) W. E. Parham, P. L. Stright, J. Am. Chem. Soc., 78, 4783 (1956). b) W. E. Parham, R. F. Motter, G. L. O. Mayo, ibid., 81, 3386 (1959). c) H. J. Boonstra, and J. F. Arens, Rec. Trav. Chim. Pays-Bas, 79, 866 (1960) and also see ref. 6d).
5. The corresponding sulfide is known; S. L. Cristol, and B. B. Jarvis, J. Am. Chem. Soc., 88, 3095 (1966). The sulfoxide (5) was prepared by a standard method using MCPBA in $CHCl_3$.
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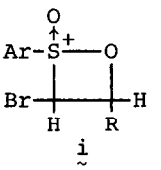
7. Condensation of 1-bromovinyl p-chlorophenyl sulfoxide with 2-nitropropane and subsequent dehydrobromination has been published; R. Tanikaga, H. Sugihara, K. Tanaka, and A. Kaji, Synthesis, 299, 1977. Addition of MeOH to the product and the subsequent thermolysis has also been reported.
8. G. Tsuchihashi, S. Mitamura, and K. Ogura, Tetrahedron Lett., 455, 1974.
9. In the cases of 2,2-disubstituted vinyl sulfoxides (19) and (20), the isomeric 1-hydroxy-2-bromo derivatives were also obtained.
10. The bromovinyl derivatives are presumably produced by the cleavage of the cyclic sulfoxonium salt (i) formed from initially produced bromohydrin by taking into account of the mechanism of the related reactions; F. Jung, N. K. Sharma, and T. Durst, J. Am. Chem. Soc., 95, 3420 (1973). However, a



i

different cleavage pattern of cyclic sulfoxonium salts has been reported; H. Taguchi, H. Yamamoto, and H. Nozaki, Tetrahedron Lett., 2463, 1973. Bromine present in i must be playing an important role in the present reaction but the exact mechanism is still open for discussion.
11. Separation of 21 from 22 was unsuccessful and so its structure was deduced from IR spectrum of this mixture showing apparent peak due to an acetylene [IR(neat) 2220cm^{-1}] and GC-MS exhibitting distinct peaks at 291 and 293 (M^++ 1) corresponding to 21. The "M^++ 1" peaks were observed for all substituted diethyl ethylmalonates (6, 7, 8, 13a,b, and 15) we examined.

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