NOVEL PREPARATION AND REACTION OF N-BENZENESULFONYL- AND N-METHANESULFONYLTROPONIMINES. NEW ENTRY TO 1-AZAAZULENE DERIVATIVES

Tohru Takayasu, Hiroshi Katayama, and Makoto Nitta*

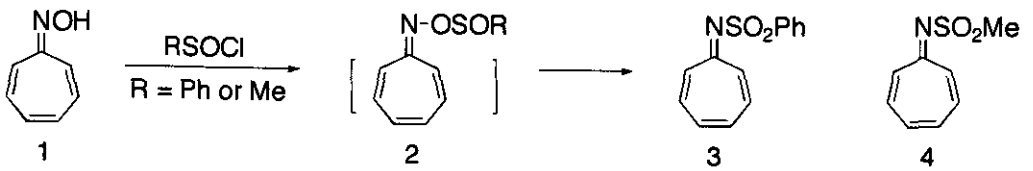
Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169, Japan

Abstract -- N-Benzenesulfonyl- and N-methanesulfonyl-troponimines were prepared through the reaction of tropone oxime with benzenesulfinyl- and methanesulfinyl chloride. The troponimines reacted with enamines to give formal [8 + 2] cycloadducts, which subsequently underwent elimination-dehydrogenation sequences to give 1-azaazulene derivatives in modest yields.

The chemistry of azaazulenes has attracted considerable attention for several decades.[1-7] In a series of studies concerning (vinylimino)phosphoranes,[4] we have demonstrated a convenient method synthesizing 1-azaazulene derivatives[4-6] and 5-azaazulene derivatives.[7] Although (vinylimino)phosphoranes are easily available by the Staudinger reaction[4,8] of azidoethylene derivatives and several azidoarenes with tertiary phosphines,[4] simple 1-azidocycloalkenes are not readily available.[9] Thus the methodology has a limited applicability for the preparation of a variety of azaazulenes. Since 1-azaazulenes and 1-azaazulen-2(H)-ones have also attracted much attentions from the view point of their pharmacological activities,[10] we have embarked on the exploration of methodology synthesizing versatile 1-azaazulenes. Although the cycloaddition reaction of simple troponimines has been studied for an electron-

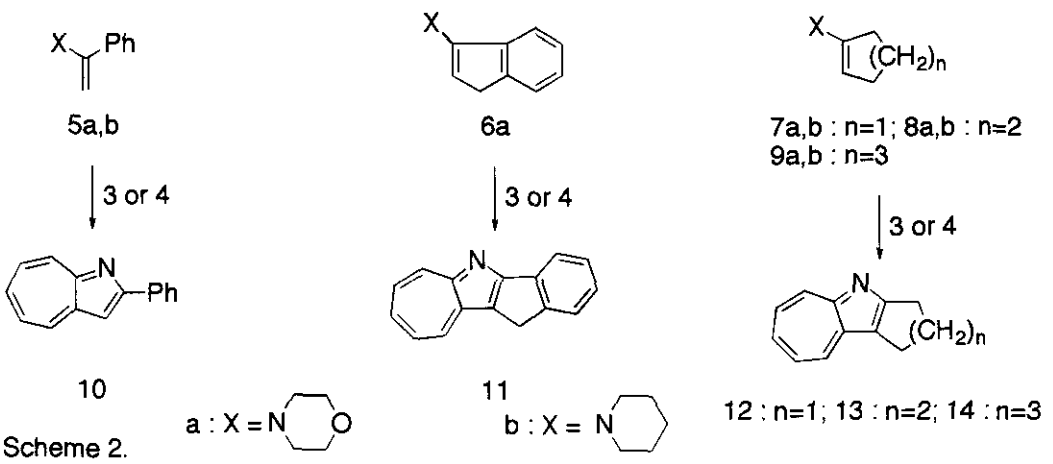
deficient acetylene[11a] and cumulenes,[11b-i] no reaction of troponimine with electron-rich olefins is reported. The reaction of tropone with enamines[12] is known to give formal [8 + 2] cycloadducts. Thus, our strategy for preparation of 1-azaazulene is to obtain the troponimines having electron-withdrawing substituent on the nitrogen atom, because such troponimines are expected to have low lying HOMO, LUMO, and highly polarized nature like tropone. We describe here novel preparation and the reaction of N-benzenesulfonyl- and N-methanesulfonyltroponimines (3) and (4) with enamines to give 1-azaazulenes, albeit in modest yields.

Tropone oxime (1)[13] was obtained in 90% yield through the modified reaction of tropone with hydroxylamine hydrochloride in MeOH for 1 week. According to the well-known procedure converting oximes to N-arenesulfonyl- and N-alkanesulfonyl-imines,[14] the N-benzenesulfonyltroponimine (3) was prepared by the reaction of oxime (1) with benzenesulfinyl chloride in the presence of NEt_3. The imine (3) is stable and easily purified by column chromatography on Florisil to give pure sample of 3. In a similar fashion, reaction of 2 with methanesulfinyl chloride afforded N-methanesulfonyltroponimine (4) (Scheme 1). Since the compound (3) was previously obtained in a trace amount through the reaction of tropone with benzenesulfonyl isocyanate,[15] the structure was assigned by comparison of the physical data with those reported in the literature.[15] The structure of 4 was assigned on the basis of the physical data.



Scheme 1.

General procedure for the reactions of 3 and 4 with enamines was as follows. A mixture of 3 or 4, enamines (5a,b-9a,b), and 10% Pd/C was heated under reflux until almost all of 3 or 4 disappeared. The separation of the products was performed through TLC on silica gel. The reaction conditions and the yield of the products are summarized in Table 1.



Scheme 2.

Table 1. The reaction of troponimines (3) and (4) with enamines (5a,b-9a,b)

			Reaction conditions			
Entry	Compd	Enamine[a]	Solvent[b]	Time/h	Product	Yield/%[c]
1	3	5a	Xylene	6	10	58
2	3	5b	Xylene	1	10	33
3	3	6a	Xylene	10	11	31
4	3	7a	Xylene	12	12	25
5	3	7b	Xylene	1	none	--
6	3	8a	Xylene	3.5	13	28
7	3	8b	Xylene	0.7	13	24
8	3	9a	Xylene	3	14	48
9	3	9b	PhMe	1	14	38
10	4	5a	PhH	6	10	26
11	4	6a	PhH	5	11	8
12	4	8a	PhH	6	13	31
13	4	9a	Xylene	5.5	14	11

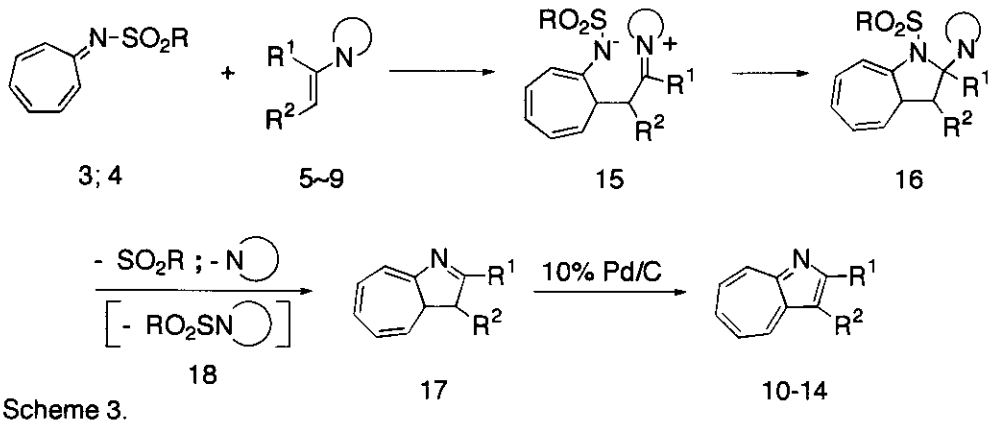
a. Two molar equivalent amounts of enamines were used. b. Reactions were carried out under refluxing. c. Based on 3 or 4 used.

The reaction of 3 with 1-phenyl-1-(N-morpholinyl)- and 1-phenyl-1-(N-piperidinyl)ethylenes (5a and 5b) afforded 2-phenylcyclohepta[b]pyrrole (2-phenyl-1-azaazulene) (10) in modest yields (Scheme 2, Table 1, Entries 1 and 2). The reaction of 3 with 3-(N-morpholinyl)indene (6a) and 1-(N-morpholinyl)cyclopentene (7a) gave 2,3-ring-annulated 1-azaazulenes, 11H-cyclohept[b]indeno[2,1-d]pyrrole (11) and 2,3-dihydro-1H-cyclohepta[b]cyclopenta[d]pyrrole (12) (Entries 3 and 4), respectively. Similarly, the cyclic enamines, 1-(N-morpholinyl)- and 1-(N-piperidinyl)cycloalkenes (8a and 8b) and (9a and 9b), afforded 2,3-ring-annulated 1-azaazulenes, 1,2,3,4-tetrahydrocyclohept[b]indole (13) and 2,3,4,5-tetrahydro-1H-dicyclohepta[b,d]pyrrole (14), in modest yields (Entries 6-9). Although the reaction using morpholine enamines proceeded slowly as compared with those of piperidine enamines, the yields of the products are slightly better for the reaction of morpholine enamines (Entries 1, 4, 6, and 8) than those for piperidine enamine (Entries 2, 5, 7, and 9). Thus the reaction of 4 with morpholine enamines (5a), (6a), (8a), and (9a) were carried out, and the products (10), (11), (13), and (14) were obtained in slightly lower yields as compared with the corresponding reactions for 3, except for Entry 12.

The compounds (10)[4a,16], (11)[5b], (13),[17] and (14)[17] are known and their structures were confirmed by comparison of the physical data with those reported in the literatures. The structure of compound (12) was unequivocally assigned on the basis of the physical data.

The HOMO and LUMO energies of 3 and 4 were obtained by the MNDO method.[16] The calculation suggests that HOMO and LUMO energies of 3 (LUMO: -1.40; HOMO: -9.50) are lower than those of 4 (LUMO: -1.22; HOMO: -9.58), respectively, but both of them are lower than those of tropone (LUMO: -0.82; HOMO: -9.25). The high charge density on the nitrogen atom of 3 (-0.52) and 4 (-0.57) as compared with that on the oxygen atom of tropone (-0.31) suggests a polarized nature of 3 and 4, thus the reactivity of them toward enamines is similar to that of tropone (Scheme 3).[12] The enamine alkylation process onto troponimines (3) and (4) gives the intermediate 15, which undergoes cyclization to give 16. The present reactions did not proceed to give 1-azaazulene derivatives in the absence of Pd/C. Thus, we propose that elimination of sulfonyl

and amino groups occurs to give 17, which is easily dehydrogenated in the presence of 10% Pd/C to give 1-azaazulenes. One may consider the elimination of sulfonamide (18) to give 17. However, attempted isolation of eliminating species such as sulfonamide



Scheme 3.

through TLC was unsuccessful in the case of Entry 1, and benzenesulfinic and benzenesulfonic acids were isolated in trace amounts. The elimination process in 16 may be complicated and may cause the modest yields of the 1-azaazulene derivatives. Thus, further modification of the substituent on the nitrogen atom of troponimine would be required.

In summary, we have presented that the readily available N-benzenesulfonyl- and N-methanesulfonyltroponimines reacted with enamines to give phenyl-substituted and 2,3-ring-annulated 1-azaazulenes, albeit in modest yields. Further synthetic applicabilities of troponimines are underway in our laboratory.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR were recorded on a Hitachi R-90 and a JEOL JNM-GSX 400 spectrometers, in $CDCl_3$, and chemical shifts were given in ppm (δ) relative to internal $SiMe_4$ standard. IR spectra were recorded on a Shimadzu IR-400 spectrophotometer. Mass spectral and high resolution mass spectral studies were conducted by using a Shimadzu GCMS QP-1000 and a JEOL JMS-DX300 spectrometers. Mps were recorded on a Yamato MP-21 apparatus and are uncorrected. All the reactions were carried out under anhydrous conditions and dry nitrogen atmosphere.

Preparation of N-benzenesulfonyltroponimine (3). To a stirred solution of tropone oxime (1) (605 mg, 5 mmol) and NEt_3 (505 mg, 5 mmol) in ether (10 mL) was added a solution of benzenesulfinyl chloride (805 mg, 5.02 mmol) in ether (5 mL) at 0 °C, and the mixture was stirred for 30 min. The reaction mixture was filtered to remove Et_3NHCl, and the filtrate was stirred for 5 h at rt. After the ether was evaporated, the residue was chromatographed on Florisil using hexane-AcOEt: 1/1 to give 3 (598 mg, 49%): mp 94-95 °C (from CCl_4) (lit.,[15] mp 94 °C); ^{1}H-NMR (400 MHz) δ 7.09-7.11 (2H, m), 7.21-7.27 (4H, m), 7.48-7.57 (3H, m), 8.00-8.03 (2H, m); ^{13}C-NMR (100.4 MHz) δ 126.7, 128.7, 132.2, 136.8, 139.1, 142.3, 170.6; IR ($CHCl_3$) 3070, 3017, 1630, 1596, 1522, 1508, 1477, 1404, 1284, 1144, 1083, and 860 cm^{-1}; MS (m/z) 245 (M^+, 100%). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.66; H, 4.52; N, 5.71. Found: C, 63.46; H, 4.33; N, 5.63.

Preparation of N-methanesulfonyltroponimine (4). To a stirred solution of tropone oxime (1) (1.22 g, 10.1 mmol) and NEt_3 (1.27 g, 12.5 mmol) in CH_2Cl_2 (10 mL) was added a solution of methanesulfinyl chloride (1.2 g, 12.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h and another 5 h at rt. After the reaction mixture was filtered, and the filtrate was concentrated, the residue was separated by column chromatography on silica gel using hexane-AcOEt: 1/1 to give 4 (925 mg, 50%): yellow oil; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 3.11 (3H, s), 7.07-7.24 (6H, m); ^{13}C-NMR ($CDCl_3$, 100.4 MHz) δ 43.2, 135.1, 136.5, 138.8, 170.3; IR ($CHCl_3$) 3027, 3024, 1632, 1597, 1526, 1510, 1478, 1422, 1401, 1286, 1258, 1120, 969, and 866 cm^{-1}; MS (m/z) 183 (M^+, 85%), 104 (100%); High resolution MS Calcd for $C_8H_9NO_2S$: 183.0354. Found: 183.0342.

General procedure for the reaction of 3 or 4 with enamines. A mixture of 3 (1 mmol) or 4 (1 mmol), 10% Pd/C (10 mg), and enamines (5a,b), (6a), (7a,b-9a,b) (2 mmol) in the solvent indicated in Table 1 was heated under reflux for a period listed in Table 1. After the reaction mixture was filtered through Celite, the filtrate was concentrated, and the resulting residue was separated by TLC (silica gel; hexane-AcOEt: 1/3) to give the products. The reaction conditions and the yields of the products are summarized in Table 1. For 12: orange oil; ^{1}H-NMR (400 MHz) δ 2.64 (2H, tt, J=7.3, 7.3 Hz), 3.06 (2H,

t, J=7.3 Hz), 3.18 (2H, t, J=7.3 Hz), 7.49 (1H, dd, J=9.7, 10.1 Hz), 7.60 (1H, dd, J=9.5, 9.9 Hz), 7.68 (1H, dd, J=9.7, 9.9 Hz), 8.19 (1H, d, J=10.1 Hz), 8.45 (1H, d, J=9.5 Hz); ^{13}C-NMR ($CDCl_3$, 100.4 MHz) δ 23.8, 28.5, 29.1, 127.3, 128.3, 132.1, 133.6, 135.6, 136.4, 138.5, 163.5, 183.2; MS (m/z) 169 (M^+, 66%), 168 (100%); High resolution MS Calcd for $C_{12}H_{11}N$: 169.0892. Found: 169.0900. Picrate: mp 193-196 °C (from MeOH). Anal. Calcd for $C_{18}H_{14}N_4O_7$: C, 54.28; H, 3.54; N, 13.76. Found: C, 54.49; H, 3.54; N, 13.76.

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