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The Reactions of Tropone Tosylhydrazone Sodium Salt with Acetylene Derivatives Possessing Electron-Withdrawing Groups: A Novel Method of Synthesis of 1*H*-1,2-Benzodiazepine Derivatives

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Reactions of tropone tosylhydrazone sodium salt with dimethyl and diethyl acetylenedicarboxylate gave dimethyl and diethyl 1*H*-1,2-benzodiazepin-3,4-dicarboxylate, respectively. The same reactions, but using ethyl acetylenecarboxylate and 3-butyn-2-one, afforded ethyl 1*H*-1,2-benzodiazepin-4-carboxylate and 4-acetyl-1*H*-1,2-benzodiazepine, respectively, accompanied by 8-azaheptafulvene derivatives derived from the sodium salt and the acetylene derivatives, and *p*-toluenesulfinic esters formed from *p*-toluenesulfinic acid and the acetylene derivatives. Reactions of the sodium salt with ethyl 2-butynoate gave the corresponding sulfinic ester but afforded no diazepine derivative.

It is known that upon heating or irradiation, tropone tosylhydrazone sodium salt (**1**) generates nitrogen gas, sodium *p*-toluenesulfinate (**2**), and cycloheptatrienylidene (**3**), which is considered to be a singlet nucleophilic carbene[1] and to isomerize to an allene, cycloheptatetraene (**4**).[2] When heated in the presence of silver chromate, **1** affords 2-tosyl-2*H*-indazole (**6**) via a hydrazyl radical intermediate (**5**).[3]

The reactions of **1** with olefins have been well-studied and the following results are known. In reactions with ethylene derivatives **1** gives spiro[2.6]nonatriene derivatives (**7**) via the carbene (**3**),[1] on the other hand, in reactions with suitable dienes, such as anthracene, cyclopentadienone, or isobenzofuran derivatives, **1** affords the Diels-Alder-type addition products **8** via the allene (**4**).[2] However, papers concerning the reaction of **1** with acetylene derivatives are limited to reports concerning the reaction of **1** with phenylacetylene, where [2+2]-type adduct (**9**) and 2-phenylindene (**10**) are formed. The former is afforded via the allene-form (**4**) and the latter via an isomerization of **9**.[2]

As one part of the study on the reactivity of **1**, reactions of **1** with acetylene derivatives possessing electron-withdrawing groups were investigated to form benzo-1,2-diazepine derivatives, heptafulvene derivatives, and esters of *p*-toluenesufinic acid. Here, these results will be discussed.

Results

Tropone tosylhydrazone sodium salt (**1**) was allowed to react with two molar equivalents of dimethyl acetylenedicarboxylate (**11**) at 120 °C for 15 min in anhydrous diglyme. The ether extraction of the reaction mixture followed by silica-gel column chromatographic purification gave benzo-1,2-diazepine derivative (**12**) in a 34.0% yield. The same reaction, but using diethyl acetylenedicarboxylate (**13**), afforded the corresponding benzo-1,2-diazepine derivative (**14**)[4] in a 32.3% yield.

Reactions of **1** with ethyl acetylenecarboxylate (**15**) under analogous conditions as above afforded three products, benzo-1,2-diazepine derivative (**16**), 8-azaheptafulvene derivative (**17**), and ester of *p*-toluenesufinic acid (**18**) in the yields of 51.9, 1.5, and 24.8%, respectively. The same type of reaction of **1** with 3-butyn-2-one (**19**) gave benzo-1,2-diazepine derivative (**20**) and heptafulvene derivative (**21**) in the yields of 5.7 and 6.3%, respectively. The reaction of **1** with ethyl 2-butynoate (**22**) yielded sulfinic ester (**23**) in a 9.1% yield but gave no benzo-1,2-diazepine derivative. Reactions of **1** with diphenylacetylene (**24**) and 1-butyne (**25**) afforded no reaction product except **2** and polymeric resinous material.

The structure of **14** was determined on the basis of

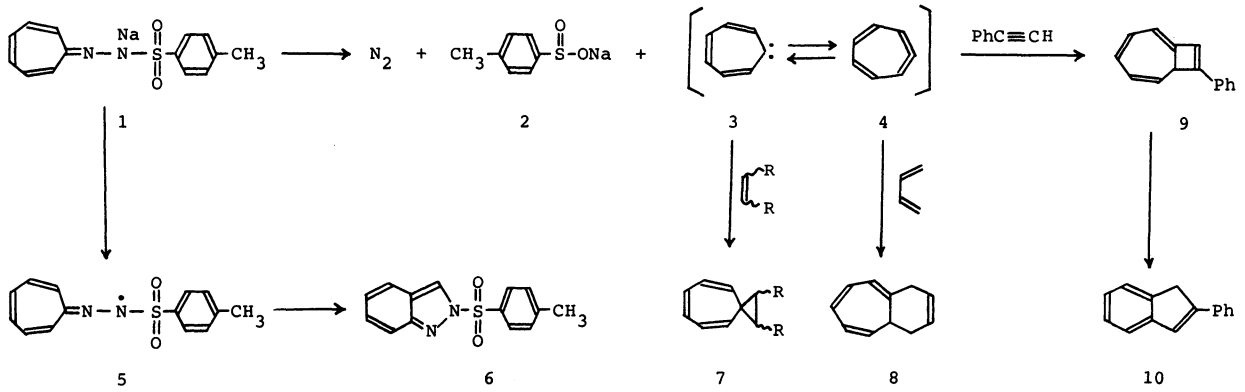

Fig. 1.

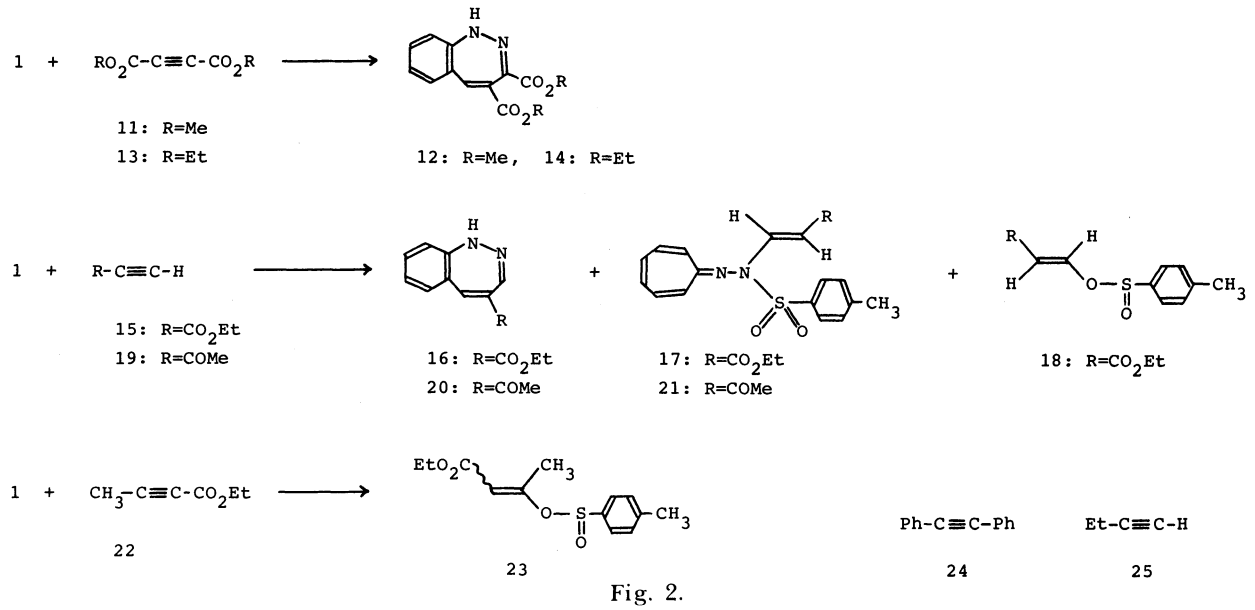

Fig. 2.

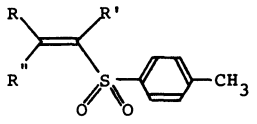

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Fig. 3.

its spectral properties and was confirmed by a comparison of its melting point and spectral properties with those of the authentic sample.[4] The structures of the another benzo-1,2-diazepines were determined by the resemblance of their spectral properties to those of the analogous benzo-1,2-diazepines containing **14**.[4] The structures of **17** and **21** were determined as follows. The molecular ion peaks in their mass spectra and the elemental analyses show that **17** and **21** are the addition products of tropone tosylhydrazone and the corresponding acetylene derivatives (**15** and **19**), respectively. The multiplet signals corresponding to six protons at around δ 6.5—7.1 in the NMR spectra[5] and the absorption maximum at long wavelength in the UV spectra[6] suggest the existence of the 8-azaheptafulvene moiety in these products. The coupling constants (14 Hz) between the olefinic protons show that the configuration of these two protons is trans-configuration.[7]

The structures of **18** and **23** were determined on the basis of their spectral properties as follows. The coupling constant (15 Hz) between the olefinic protons shows that these two protons in **18** are in trans-configuration each other.[7] The absorption at 1150 cm^{-1} in the IR spectra demonstrates that the SO_2 groups of these products are sulfinyl groups and not sulfonyl groups such as **26**.[8]

Discussion

The formation of benzo-1,2-diazepine derivatives can be explained to be as follows. The thermal decomposition of the sodium salt (**1**) generates diazotropilidene (**27**).[9] The Michael-type addition of the anionic nitrogen atom of **27** to the acetylene derivatives[10] forms an ionic intermediate (**28**),[9e,11] which gives the bicyclic intermediate (**29**) by intramolecular cyclization. The valence tautomerization in the tropylidene moiety of **29** affords the norcaradiene-type intermediate (**30**),[12] which then forms the final products, benzo-1,2-diazepine derivatives via the cleavage of the three-membered ring.

The formation of the 8-azaheptafulvene dereivatives (**17**, **21**) and the sulfinic esters (**18**, **23**) are considered to proceed through Michael-type additions of the anions of tropone tosylhydrazone and *p*-toluenesulfinic acid to the corresponding acetylene derivatives, respectively.

There is an evident difference between reactions of **1** with acetylenes and reactions of **1** with olefins. It was clarified that reactions of **1** with acetylenes possessing electron-withdrawing groups proceed via diazotropilidene but that reactions with olefins proceed via carbene (**3**) or the allene (**4**). For example, the reaction of **1** with dimethyl acetylenedicarboxylate gives the benzo-1,2-diazepine derivative via diazotropilidene (**27**); on the other hand, reactions of **1** with dimethyl fumarate or maleate afford the spiro compounds **7** via the carbene (**3**).[1] No such product as **31** has ever been formed.

These differences in the reactivity can be explained as follows. The primary product of the decomposition of **1** is diazotropylidene (**27**).[9,13] In the case of the existence of acetylenes possessing electron-withdrawing groups, **27** reacts with the acetylenes to form **29** [Path A]. It is known that the nucleophilic reactions of reagents such as amines or imines with acetylene derivatives proceed easily more than do reactions with ethylene derivatives.[10] If there are no suitable acetylenes, **27** further decomposes to the carbene (**3**) or the allene (**4**) [Path B]. Probably, this decomposition of **27** proceeds more quickly than the reaction of **27** with olefins

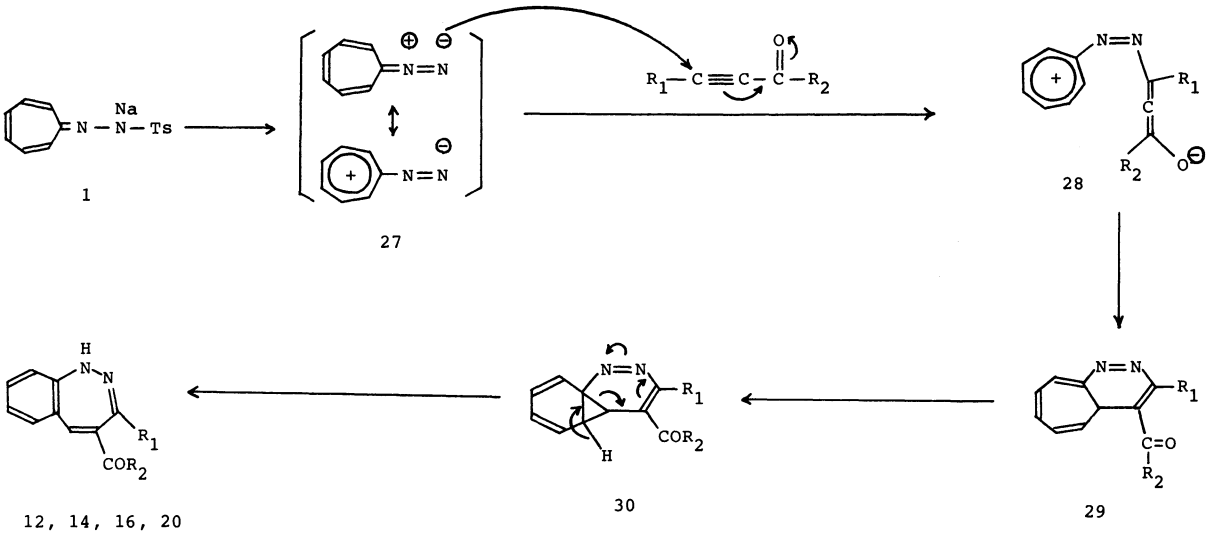

Fig. 4.

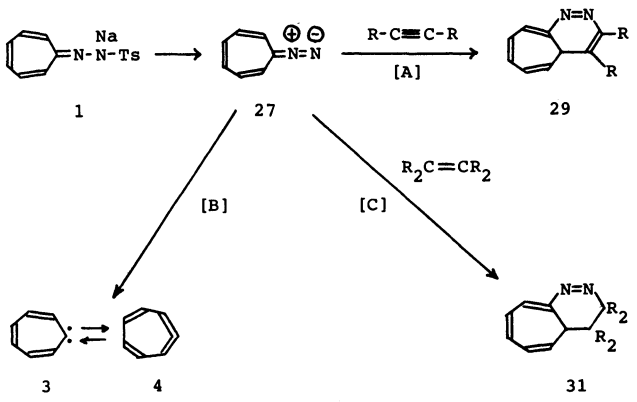

Fig. 5.

to give **31** [Path C].

The fact that reactions of **1** with the acetylene derivatives **22** and **25**, which have electron-donating groups do not afford the benzo-1,2-diazepine derivatives seems to partially support the above considerations. The inactivity of **27** toward diphenylacetylene (**24**) can be attributed to the fact that **24** have no strong electron-withdrawing groups.

Experimental

All melting points were uncorrected. NMR spectra were measured with Varian XL 200 or Hitachi R-20B spectrometers with tetramethylsilane as an internal standard. UV and IR spectra were measured with Hitachi 220A and DS-701G spectrometers, respectively. Mass spectra were measured with Hitachi M-52 or JMS-DX300 spectrometers. Wako gel C 200 and Wako gel B5F were used for column and thin-layer chromatography, respectively. Diglyme was dried over Molecular Sieves 3A 1/16.

Reaction of Tropone Tosylhydrazone Sodium Salt (1) with Dimethyl Acetylenedicarboxylate (11). A mixture of **1** (14.80 g, 50 mmol) and **11** (14.60 g, 100 mmol) in anhydrous diglyme (70 ml) was heated at 120 °C for 15 min. The reaction mixture was poured into water, extracted with ether, washed with water and brine, and dried over anhydrous sodium sulfate. After filtration the solvent was removed on a rotary evaporator to give a mixture of crystals of **12** and an oil. The crystals of **12** (4.010 g) were removed by filtration and the filtrate was column-chromatographed on silica gel to give the crystals of **12** (405 mg) by the use of benzene-ether 8:2. The total yield of **12** was 4.415 g, 34.0%. The crystals were recrystallized from cyclohexane to give pure crystals **12**.

12: Mp 153—154 °C. Found: C, 60.10; H, 4.95; N, 10.85%. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.95; N, 10.77%. Mass *m/z* (rel intensity) 260 (M^+, 22), 175 (12), 143 (100), 142 (30), 139 (29), 115 (34). IR (KBr) 3350, 3020, 2950, 1730, 1640, 1600 cm^{-1}. UV (EtOH) 204 nm (log ε, 4.21), 257 (4.16), 285 (sh, 4.02). ^1H NMR (CD_3COCD_3) δ=3.70 (3H, s), 3.71 (3H, s), 6.8—7.4 (4H, m), 7.86 (1H, s), 8.10 (1H, broad s).

Reaction of Tropone Tosylhydrazone Sodium Salt (1) with Diethyl Acetylenedicarboxylate (13). A mixture of **1** (5.92 g, 20 mmol) and **13** (17.00 g, 100 mol) in anhydrous diglyme (50 ml) was heated at 120 °C for 15 min. The reaction mixture was treated as usual and chromatographed on silica gel to give crystals of **14** (1.86 g, 32.3%, mp 113—114 °C, lit,[4] 114° C) by the use of benzene-ether 8:2.

14: ^1H NMR (CD_3COCD_3) δ=1.28 (6H, two triplets), 4.15 (4H, two quartets), 6.75 (4H, m), 7.45 (1H, s), 7.80 (1H, broad s).

Reaction of Tropone Tosylhydrazone Sodium Salt (1) with Ethyl Acetylenecarboxylate (15). A mixture of **1** (5.92 g, 20 mmol) and **15** (9.80 g, 100 mmol) in anhydrous diglyme (50 ml) was heated at 120 °C for 15 min and the reaction mixture was treated as usual. The resulted oily material was column-chromatographed on silica gel to give crystals of **18** (1.26 g, 24.8%) by the use of benzene, crystals of **17** (110 mg, 1.5%) by the use of benzene-ether 50:1, and crystals of **16** (3.02 g, 51.9%) by the use of benzene-ether 50:1. The crystals of **16**, **17**, and **18** were recrystallized from cyclohexane to give pure compounds, respectively.

16: Mp 93—94 °C. Found: C, 66.59; H, 5.49; N, 13.09%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%. MS *m/z* (rel intensity): 216 (M^+, 63), 171 (14), 144 (18), 143 (100). IR (KBr) 3320, 3020, 2950, 1710, 1630. 1595 cm^{-1}. UV (EtOH): 211 nm (log ε, 4.13), 258 (4.22), 303 (sh, 3.45). ^1H NMR (CD_3COCD_3) δ=1.30 (3H, t), 4.24 (2H, q), 6.7—7.2 (4H, m), 7.32 (1H, d, J=1.5 Hz), 7.68 (1H, broad s), 7.78 (1H, d, J=1.5 Hz).

17: Mp 125—126 °C. Found: C, 61.33; H, 5.32; N, 7.41%.

Calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52%. MS *m/z* (rel intensity): 372 (M^+, 2), 327 (3), 217 (100), 190 (3), 189 (5). IR (KBr) 3060, 2970, 1712, 1615, 1360, 1160 cm^{-1}. UV (EtOH): 235 nm (log ε, 4.39), 277 (4.18), 315 (4.05), 346 (sh, 3.95). ^1H NMR ($CDCl_3$) δ=1.25 (3H, t), 2.40 (3H, t), 4.11 (2H, q), 4.93 (1H, d, *J*=14 Hz), 6.5—7.2 (6H, m), 7.24 (2H, d, *J*=8 Hz), 7.74 (2H, d, *J*=8 Hz), 8.08 (1H, d, *J*=14 Hz).

18: Mp 89—90 °C: Found: C, 56.89, H, 5.52%. Calcd for $C_{12}H_{14}O_4S$: C, 56.69; H, 5.55%. MS *m/z* (rel intensity): 254 (M^+, 13), 145 (10), 139 (100), 97 (19). IR (KBr): 3050, 2970, 1720, 1595, 1310, 1240, 1150 cm^{-1}. UV (EtOH): 246 nm (log ε, 3.99). ^1H NMR ($CDCl_3$) δ=1.28 (3H, t), 2.47 (3H, s), 4.26 (2H, q), 6.26 (1H, d, *J*=15 Hz), 7.34 (2H, d, *J*=8 Hz), 7.36 (1H, d, *J*=15 Hz), 7.77 (2H, D, *J*=8 Hz).

Reaction of Tropone Tosylhydrazone Sodium Salt (1) with 3-Butyn-2-one (19). A mixture of **1** (5.92 g, 20 mmol), **19** (6.80 g, 100 mmol) in anhydrous diglyme (50 ml) was heated at 120 °C for 15 min. After the usual workup, the resulted oily material was column-chromatographed on silica gel to give an oily material, which was then thin-layer-chromatographed on silica gel using ether as a developing solvent to give an oil of **20** (210 mg, 5.7%, R_f=0.80) and an oil of **21** (430 mg, 6.3%, R_f=0.55).

20: Found: *m/z* 186.0814. Calcd for $C_{11}H_{10}N_2O$: *m/z* 186.0793. MS *m/z* (rel intensity) 186 (M^+, 100), 171 (18), 144 (58), 116 (25). IR (oil): 3350, 3020, 2960, 1670, 1600, 1465 cm^{-1}. UV (EtOH): 258 nm (log ε, 4.21, 310 (sh, 3.58). ^1H NMR (CD_3COCD_3) δ=2.41 (3H, s), 6.7—7.2 (4H, m), 7.45 (1H, d, *J*=1.5 Hz), 7.60 (1H, bs), 7.73 (1H, d, *J*=1.5 Hz).

21: Found: *m/z* 342.1027. Calcd for $C_{18}H_{18}N_2O_3S$: *m/z* 342.1038. MS *m/z* (rel intensity) 342 (M^+, 2), 230 (100), 215 (90), 187 (83), 135 (69). IR (oil): 3030, 2970, 1680, 1535, 1365, 1160 cm^{-1}. UV (EtOH): 237 nm (log ε, 4.32), 282 (4.15), 331 (sh, 3.80). NMR ($CDCl_3$) δ=2.3 (3H, s), 5.20 (1H, d, *J*=14 Hz), 6.5—7.0 (6H, m), 7.16 (2H, d, *J*=8 Hz), 7.60 (2H, *J*=8 Hz), 7.90 (1H, d, *J*=14 Hz).

Reaction of Tropone Tosylhydrazone Sodium Salt (1) with Ethyl 2-Butynoate (22). A mixture of **1** (5.92 g, 20 mmol) and **22** (4.48 g, 40 mmol) in anhydrous diglyme (30 ml) was heated at 120 °C for 15 min. After the usual treatment the resulted oily material was column-chromatographed on silica gel to give an oily material (1.04 g) by the use of benzene-ether 9:1. The oily material was thin-layer-chromatographed on silica gel using benzene-ether 9:1 as a developing solvent to give an oil of **23** (490 mg, 9.1%, R_f=0.8).

23: Found: *m/z* 268.0794. Calcd for $C_{13}H_{16}O_4S$: *m/z* 268.0770. MS *m/z* (rel intensity) 268 (M^+, 16), 222 (30), 139 (38), 103 (100). IR (oil): 3030, 2970, 1720, 1595, 1320, 1200, 1150 cm^{-1}. UV (EtOH) 247 nm (log ε , 4.07). ^1H NMR ($CDCl_3$) δ=1.23 (3H, t), 2.20 (3H, s), 2.36 (3H, s), 4.12 (2H, q), 6.23 (1H, s), 7.18 (2H, d), 7.58 (2H, d).

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