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REACTIONS OF DIAZO COMPOUNDS OF HETEROCYCLIC ALDEHYDES WITH PHENYLACETYLENE: FORMATION OF PYRAZOLES COMBINED WITH HETEROCYCLES

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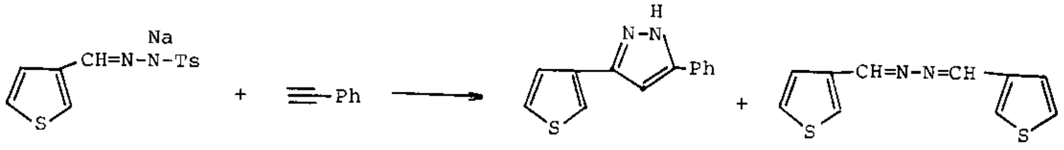
Abstract —— Reactions of sodium salts of 2- and 3-thiophenecarbaldehyde tosylhydrazone and furfural tosylhydrazone with phenylacetylene afforded pyrazoles combined with thiophene and furan moieties via 1,3-dipolar cycloadditions of the corresponding diazo compounds.

It is known that sodium salts of tosylhydrazones generate carbenes via diazo compounds by thermolysis or photolysis.[1] The reactivities of diazo compounds are known to be influenced by conjugation with unsaturated moieties.[2] The chemistry of diazo compounds conjugated with heterocyclic moieties, however, does not seem to have been well clarified yet. Previously, Shechter documented that diazo compounds combined with thiophene or furan moieties generated the corresponding carbenes, which then rearranged to the acetylene derivatives.[3] Maas reported the addition reactions of these carbenes with styrene derivatives to give cyclopropane derivatives.[4]

Recently, we published that the tosylhydrazones combined with thiophene, furan, or pyrrole moieties underwent 1,3 N→C migration of the tosyl group releasing nitrogen and that the corresponding carbenes added to olefins stereospecifically by nucleophilic manner.[5] We investigated reactions of these tosylhydrazones with phenylacetylene to obtain pyrazoles combined with heterocycles. Compounds containing pyrazole and/or thiophene groups have attracted much attention not only because of the pharmaceutical activity but also because of the recent finding that the polymers of thienylpyrrole have improved the natures of organic conductors.[6] These facts prompted us to report the recent result of our research.

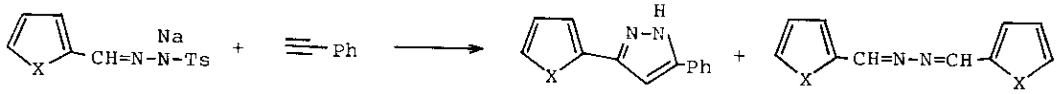
When sodium salt of 3-thiophenecarbaldehyde tosylhydrazone (1a) was allowed to react with an equimolar amount of phenylacetylene in anhydrous diglyme at 130°C for 30 min a pyrazole derivative 2a and a ketazine derivative 3a were afforded in 21.3 and 16.2% yields, respectively. The yield of 2a was improved by using a large excess amount of phenylacetylene. Thus, the reaction of 1a with ten-molar equivalent amount of phenylacetylene afforded 2a as a sole isolable product in 60.8% yield. The reaction of sodium salt of 2-thiophenecarbaldehyde tosylhydrazone (1b) and an equimolar amount of phenylacetylene gave 2b and 3b in 3.6 and 15.1% yields, respectively, and the same reaction with ten-molar equivalent amount of phenylacetylene formed 2b in 13.0% yield, but afforded no ketazine derivative 3b.



1a

2a

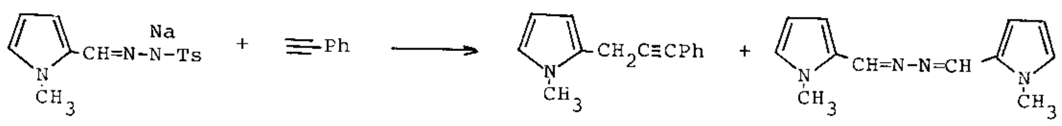
3a



1b: X=S
1c: X=O

2b: X=S
2c: X=O

3b: X=S
3c: X=O



1d

4d

3d

The reaction of sodium salt of furfural tosylhydrazone (1c) with an equimolar amount of phenylacetylene gave 3c in 7.4% yield, but the reaction with ten-molar equivalent amount of phenylacetylene afforded 2c in 8.5% yield. The reaction of sodium salt of 1-methyl-2-pyrrolecarbaldehyde tosylhydrazone (1d) with an equimolar amount of phenylacetylene formed the ketazine derivative 3d in 14.4% yield while the reaction with ten-molar equivalent amount of phenylacetylene afforded 8.7% yield of the acetylene derivative 4d.

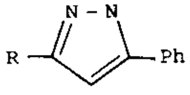
The spectral properties of the products are as follows:

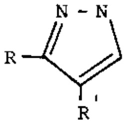
2a: mp 183 °C. Hrms: 226.0570. Calcd for $C_{13}H_{10}N_2S$: 226.0565. Mass m/z (rel intensity): 226 (M^+, 18), 225 (100), 196 (14). Ir (KBr): 3100, 1600, 1575, 1495 cm^{-1}. Uv (EtOH): 244 nm (sh, log ε, 4.44), 251 nm (log ε, 4.60), 260 nm (sh, log ε , 4.27). ^{1}HNmr (Acetone-d_6) δ ppm: 3.05 (broad s, 1H), 7.03 (s, 1H), 7.40 (m, 3H), 7.59 (m, 2H), 7.87 (m, 3H). ^{13}CNmr ($CDCl_3$) δ ppm: 100.3, 121.0, 125.6, 125.8, 126.4, 128.3, 128.9, 131.0, 132.8, 145.1, 148.3.

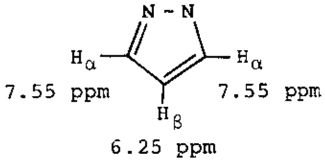
2b: mp 212°C. Hrms: 226.0565. Calcd for $C_{13}H_{10}N_2S$: 226.0565. Mass m/z (rel intensity): 226 (M^+, 16), 225 (100), 197 (15). Ir (KBr): 3110, 1570, 1490 cm^{-1}. Uv (EtOH): 258 nm (log ε , 4.83). ^{1}HNmr ($CDCl_3$) δ ppm: 6.64 (s, 1H), 6.96 (dd, 1H, J=3.5 and 4.7 Hz), 7.22 (m, 5H), 7.63 (m, 2H), 9.26 (broad s, 1H). ^{13}CNmr ($CDCl_3$) δ ppm: 100.0, 124.1, 124.8, 125.6, 127.5, 128.4, 128.9, 130.1, 134.9, 145.3, 146.9.

2c: mp 180 °C. Hrms: 210.0782. Calcd for $C_{13}H_{10}N_2O$: 210.0793. Mass m/z (rel intensity): 210 (M^+, 13), 209 (100), 180 (18), 151 (16), 126 (6). Ir (KBr): 3150, 1600, 1580, 1500 cm^{-1}. Uv (EtOH): 260 nm (log ε, 4.47). ^{1}HNmr ($CDCl_3$) δ ppm: 6.32 (dd, 1H, J=2.0 and 3.8 Hz), 6.54 (dd, 1H, J=0.7 and 3.8 Hz), 6.65 (s, 1H), 7.24 (m, 3H), 7.30 (dd, 1H, J=0.7 and 2.0 Hz), 7.63 (m, 2H), 10.65 (broad s, 1H). ^{13}CNmr ($CDCl_3$) δ ppm: 99.2, 106.2, 111.3, 125.6, 128.1, 128.7, 130.6, 141.2, 141.9, 147.0, 147.7.

4d: mp 54 °C. Hrms: 195.1007. Calcd for $C_{14}H_{13}N$: 195.1047. Mass m/z (rel intensity): 195 (M^+, 100), 194 (100), 193 (88), 164 (20), 117 (20). Ir (KBr): 2815, 1660, 1500, 1490 cm^{-1}. Uv (EtOH): 238 nm (log ε , 4.38). ^{1}HNmr ($CDCl_3$) δ ppm: 3.51 (s, 3H), 3.65 (s, 2H), 6.06 (m, 2H), 6.52 (m, 1H), 7.23

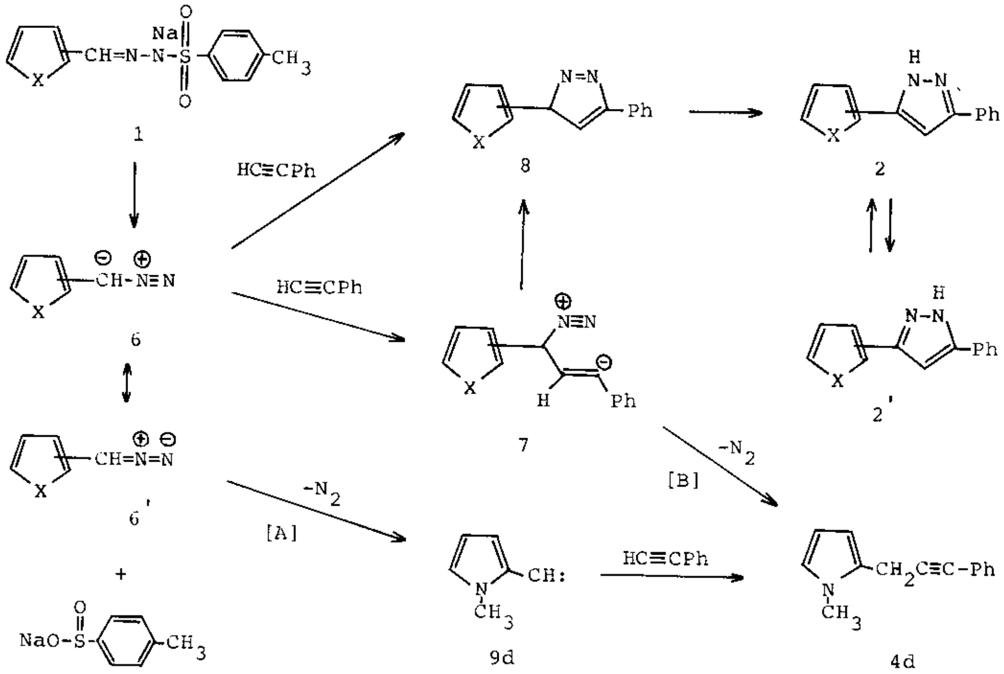




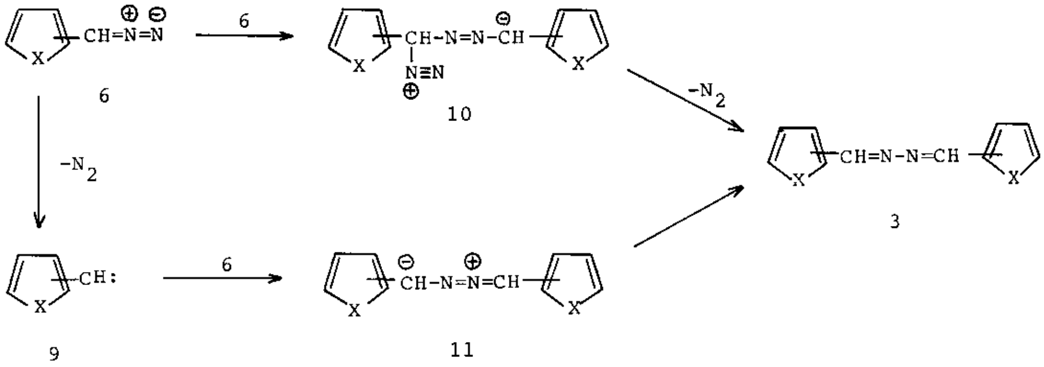


(m, 3H), 7.40 (m, 2H). ^{13}CNmr ($CDCl_3$) δ ppm: 17.7, 33.7, 81.5, 86.2, 106.7, 107.1, 122.1, 123.5, 127.0, 127.8, 128.2, 131.5.

The structures of ketazines (3) were determined by coincidences of their spectral properties with those of the authentic samples.[5] The structures of the other products were deduced on the basis of their spectral, especially nmr spectral properties and confirmed by their resemblances to those of the analogous compounds.[7] The substitution pattern of the pyrazole derivatives was decided by the comparison of their nmr spectral properties with those of pyrazole, as follows.[8] The chemical shifts of the pyrazole ring protons of 2 are ca. 6.25 ppm, which correspond to the H proton of pyrazole as shown in the figure. This fact shows that 2 must have the substituents at the α and α' positions not at the α and β positions such as 5.



The reaction is considered to proceed as follows. Decomposition of the tosylhydrazone (1) forms the diazo compound 6, which then adds to phenylacetylene to give the intermediate 8 via the ionic intermediate 7 or via a concerted 1,3-dipollar cycloaddition. Hydrogen migration in 8 affords the final product 2. Although two possible paths are considered for the formation of 4d (path A involves carbene 9d while path B contains an ionic intermediate 7d), path A is more plausible as path B proceeds via an unfavorable hydride shift process. Ketazines are considered to be formed through the dimerization of 6 via a releasing of nitrogen from the intermediate 10 or through a coupling of 6 and 9. The different yields of 2a-c from 1a-c can be attributed to the different stabilities of 6a-c. The ir spectra demonstrated that the absorbance of the diazo group (2072 cm^{-1}, in $CHCl_3$) of 6b disappears within 2 h at room temperature. On the other hand the corresponding absorbance of 6a did not show any change even after 24h. This fact is considered to show that under the reaction conditions 6a outlives enough to react with phenylacetylene to give pyrrazoles whereas 6b decomposes to the corresponding carbene which then rearranged to the unstable acetylene derivatives.[3]



EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and were uncorrected. Nmr spectra were measured with a Varian XL 200 or Hitachi R-20B spectrometers with tetramethylsilane as an internal standard. Ir and uv spectra were measured with a JASCO A-102 and Hitachi 200-10 spectrophotometers, respectively. Mass spectra were measured with a Hitachi M-52 or JMX-DX300 spectrometers. Wako gel B5F and Wako gel C 200 were used for thin-layer and column chromatography, respectively. Diglyme was dried over Molecular Sieves 3A 1/16.

Only a typical reaction is mentioned bellow and the other reactions are summarized in the Table.

Reaction of 1a with an Equimolar Amount of Phenylacetylene. To a solution of 3-

thiophenecarbaldehyde tosylhydrazone (2.80 g, 10 mmol) in anhydrous diglyme (30 ml) was added sodium hydride (440 mg, 18 mmol). After evolution of hydrogen gas had ceased, phenylacetylene (1.02 g, 10 mmol) was added and the mixture was heated at 130°C for 30 min. After filtration, the filtrate was poured into water, extracted with ether, washed with water and brine, and dired over anhydrous sodium sulfate. After filtration, the solvent was removed on a rotary evaporator to give crude crystals, which were recrystallized from chloroform to give crystals 2a (308 mg, 13.6%). The filtrate was subjected to thin-layer chromatography on silica gel using hexane-ethyl acetate (4:1) to give crystals 2a (174 mg, 7.7%, R_f=0.80) and 3a (301 mg, 16.2%, R_f=0.70).

Amount		Temperature	Time	Products
Tosylhydrazone	$PhC\equiv CH$			(Eluent Solvent)
1a 2.80g (10 mmol)	10.2g (100 mmol)	150°C	50 min	2a 1.37g (60.8%) (hexane-ethyl acetate 4:1)
1b 2.80g (10 mmol)	1.02g (10 mmol)	95°C	15 min	2b 81mg (3.6%) (benzene-ether 7:3) 3b 236mg (15.1%) (benzene)
1b 2.80g (10 mmol)	10.2g (100 mmol)	98°C	13 min	2b 294mg (13.0%) (benzene)
1c 2.64g (10 mmol)	1.02g (10 mmol)	100°C	8 min	3c 114mg (7.4%) (benzene-ether 4:1)
1c 2.64g (10 mmol)	10.2g (100 mmol)	100°C	20 min	2c 179mg (8.5%) (benzene-ether 4:1)
1d 2.77g (10 mmol)	1.02g (10 mmol)	95°C	15 min	3d 175mg (14.4%) (benzene-ether 19:1)
1d 2.77g (10 mmol)	10.2g (100 mmol)	100°C	15 min	4d 170 mg (8.7%) (hexane-benzene 3:2)

Measurement of IR Spectra. To a solution of 2-thiophenecarboxyhydrazone[4] (0.26g, 2 mmol) in chloroform (5 ml) was added active manganese dioxide (1.00g) and stirred at 0 °C for 4h. Immediately after filtration the filtrate was set to an ir spectrophotometer JASCO A-102 and the change of the intensity of the peak at 2072 cm^{-1} with the passage of time was measured. 3-Thiophenecarboxyhydrazone was measured in the same way as above.

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