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A NEW AND CONVENIENT ROUTE TO SYNTHESIS OF ENYNONES AND DIENONES FROM TosMIC

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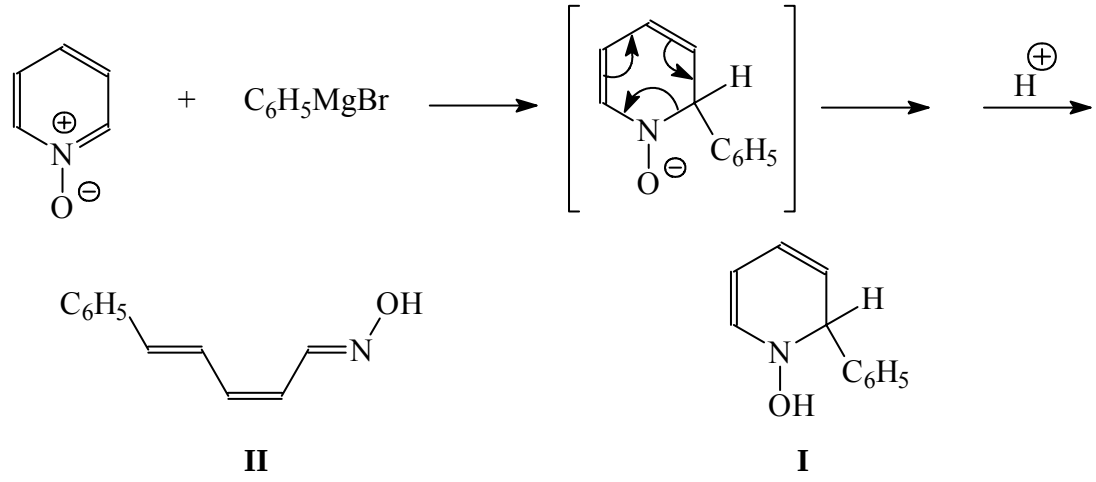
Abstract- Dilithio- and disodiotosylmethylisocyanides react with pyridine *N*-oxide and pyridazine *N*-oxide leading to formation of ring opened unsaturated products which on reaction with aralkyl halides and further hydrolysis result in formation of dienones and enynones respectively.

Enynones and dienones have been envisaged in recent years as intermediates for the synthesis of pharmacologically active compounds such as panaxytriol,[1] phomactin,[2] juncusol,[3] methylene-cyclopentenones,[4] spirocyclic methylenecyclopentenones,[5] 14-β-hydroxyandrost-15-en-17-ones,[6] 4 substituted 4-hydroxycyclohexa-2,5-dien-1-ones[7] and androst-5-en-7-ones.[8]

Tosylmethylisocyanide (TosMIC, **1**) has been extensively used as a useful reagent in organic synthesis and as a valuable synthon for heterocycles.[9] It has been used in various synthetic transformations.[10] Dilithio-tosylmethylisocyanide has been used for the synthesis of oxazoles and imidazoles[11] while monosodium and disodium salts of TosMIC have been used for synthesis of sex pheromones of common house fly.[12]

Both disodio- and dilithio-TosMIC react with pyridine *N*-oxide to form an unstable product (**1**) which could not be isolated. The structure of **1** was established on the basis of ^{1}H-NMR spectrum. The reaction of pyridine *N*-oxide with phenylmagnesium bromide was initially reported to yield 1, 2-dihydro- pyridine (**I**).[13] Later Kellogg and van Bergen established structure (**I**) to be incorrect and gave evidence for the ring opened structure, 5-phenyl-2,4-pentadienaldoxime (**II**)**.**[14] (**Figure 1**)

The stable dialkylated TosMIC derivative (**2**) was obtained by addition of aralkyl bromide to the reaction mixture of disodio or dilithio salt of TosMIC and pyridine *N*-oxide (**Scheme-1**). The structural assignment of **2** is based on spectral data and elemental analysis.

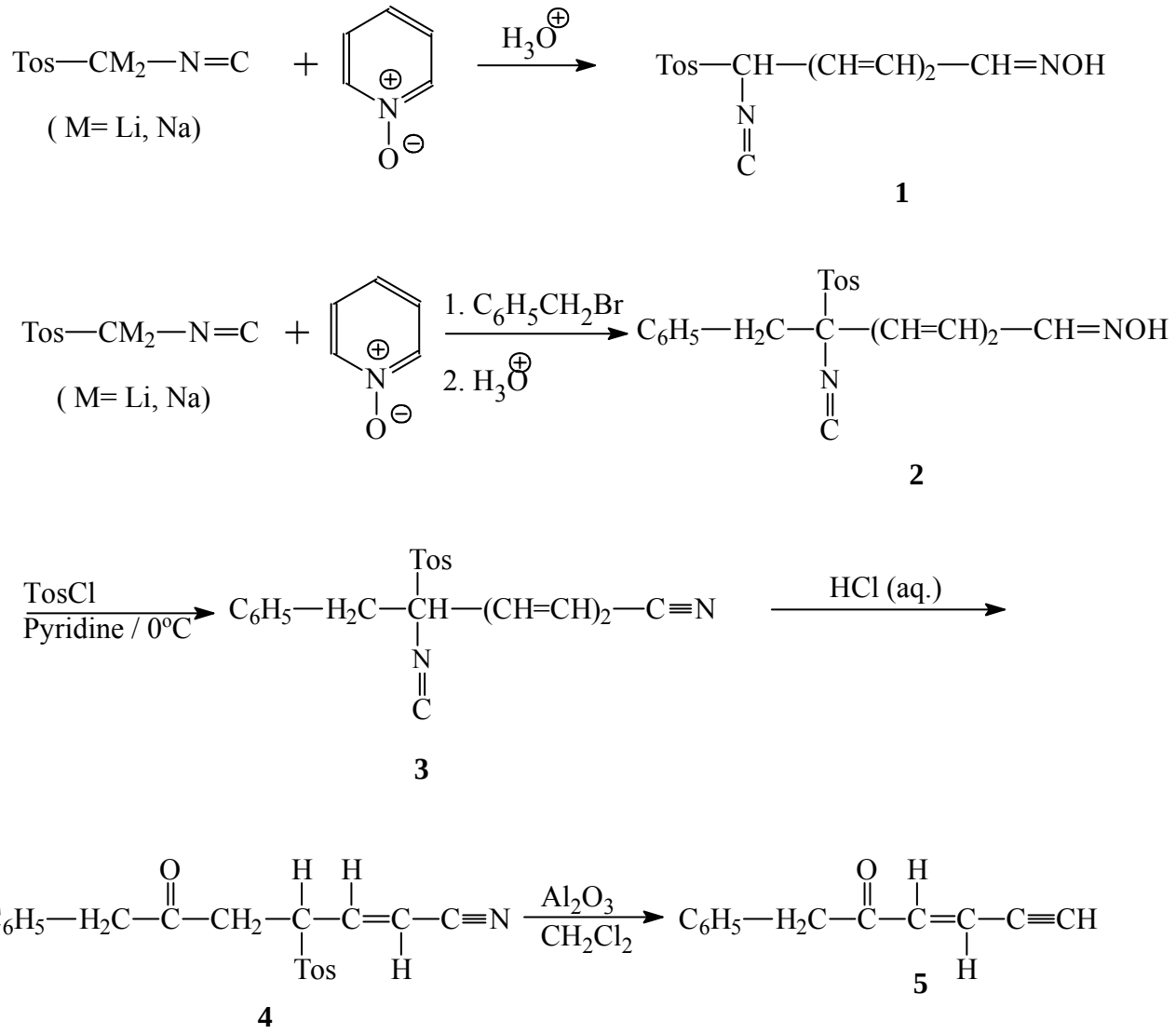


II **I**

Figure 1

In **2,** ^{1}H-NMR spectrum exhibits the alkene protons between δ 5.8 and δ 6.55 and characteristic resonance for the oxime proton at δ 10.4 in DMSO-d_6.[15] The methylene group adjacent to the asymmetric carbon atom in **2** appears as a singlet in $CDCl_3$. In ^{1}H-NMR spectrum of **2** in DMSO-d_6, the expected AB pattern for the methylene proton is observed. The IR spectrum (KBr) of **2** shows isocyano absorption at 2180 cm $^{-1}$ and oxime OH at 3400 cm $^{-1}$. The rationale for the formation of ring opened oxime (**2**) is comparable to the reaction of pyridine *N*-oxide with Grignard reagent (**Figure 1**).[14] The presence of only one sharp resonance at δ 10.4 in the ^{1}H-NMR spectrum shows presence of only one of the geometrical isomer, *syn* oxime (**2**)**. 2** on dehydration with tosyl chloride in pyridine at 0˚C yields 1-cyano-5-isocyano-6-phenyl-5-tosyl-hexadiene-1, 3. **3** on hydrolysis with aq. HCl in THF at room temperature undergoes an interesting 1, 3-shift of tosyl group along with expected replacement of isocyano group into keto group to yield 1-cyano-6-phenyl-4-tosylhexene-1-one-5 (**4**). The structure of **4** was established by ^{1}H-NMR double resonance (200 MHz). By irradiation at δ 4.6, multipletes at δ 3.0, 3.5 and 6.05 were resolved into doublets at δ 3.0 (J = 18 Hz), 3.5 (J = 18 Hz) and 6.05 (J = 11.0 Hz). Similarly irradiation at δ 6.05, δ 5.04 and δ 2.9 led to the evidence of *trans* stereochemistry across -CH=CH- in **3**. The IR spectrum (nujol) of **3** showed absorption bands at 1712 cm^{-1} for carbonyl and 2216 cm^{-1} for cyanide. **4** on rapid filtration through neutral Al_2O_3 in CH_2Cl_2 gave dienone (**5**) as the desired product. **5** in IR spectrum (neat) showed absorptions at 1685 cm^{-1} for carbonyl and 2224 cm^{-1} for cyanide and a broad singlet at δ 3.90 for two protons and multiplet between δ 5.0 - 7.6 for nine protons in ^{1}H-NMR spectrum. The reaction of pyridazine *N*-oxide with nucleophiles is known to yield ring opened product along with a small quantity of substitution product [16] (**Figure 2**). In these reactions ring opening takes place similar to pyridine *N*-

oxide. Reaction of disodio or dilithio salt of TosMIC with pyridazine *N*-oxide and further addition of aralkyl bromide to the reaction mixture leads to formation of diazonium hydroxide (**6**) (**Scheme-2**).



Scheme 1

Diazonium hydroxide (**6**) on prolonged standing at room temperature or heating forms enyne (**7**). The structure of **7** was assigned on the basis of its IR, ^{1}H-NMR and MS spectral data. Its IR spectrum shows absorptions at 2120 cm^{-1} (N=C) and at 3300 cm^{-1} (≡C-H). In the ^{1}H-NMR spectrum, the alkene proton signals and the alkyne proton signals show the expected coupling pattern. **7** on hydrolysis with 38% aq. HCl solution and further flash column chromatography over Al_2O_3 in CH_2Cl_2 yielded enynones (**8**). The IR spectrum (KBr) of **8** showed absorption at 1685 cm^{-1} for carbonyl and 3000 cm^{-1} for ≡C-H. In the ^{1}H-NMR spectrum the alkene and alkyne protons show pattern analogous to **7.**

The rationale for formation of **7** from **6** is due to loss of N_2 and H_2O from **6**, which is a known reaction for alkyldiazonium hydroxide.[17, 18] A possible mechanism for conversion of **6** into **7** involves an intramolecular reaction *via* a six membered cyclic intermediate as illustrated in **Figure 3**. The

stereochemistry around the double bond in **7** is *E*, as is evident from the coupling constant (J = 15 Hz) between the alkene protons.[19]

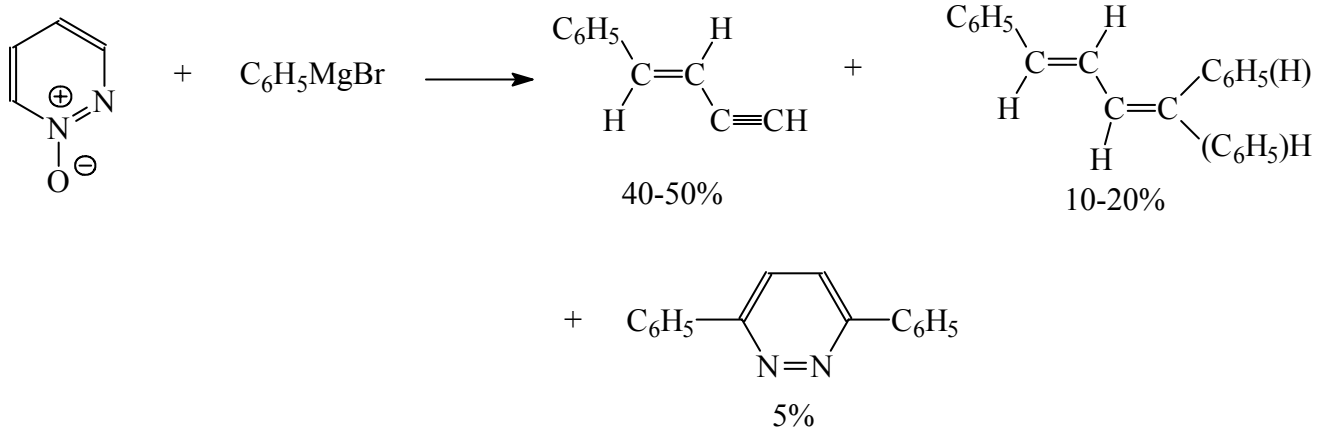
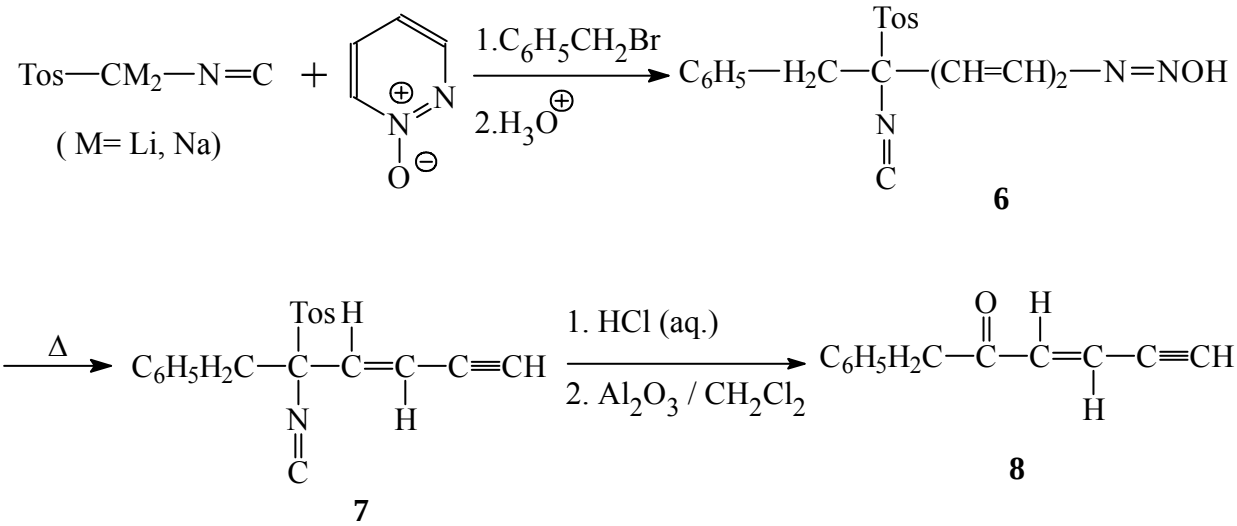


Figure 2



Scheme 2

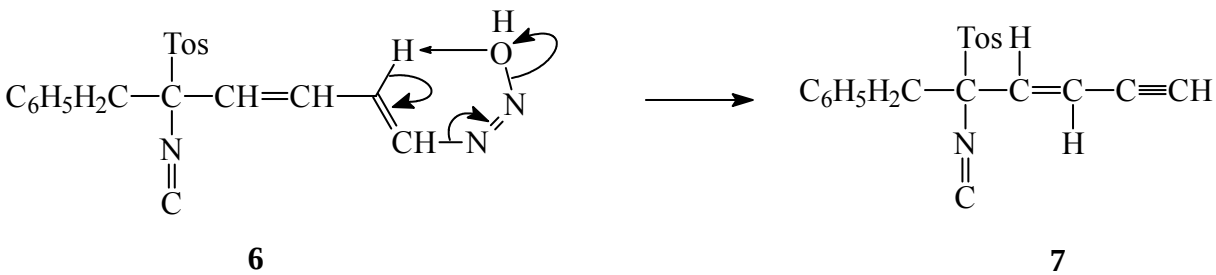


Figure 3

EXPERIMENTAL

All experiments were carried out under N_2 unless indicated otherwise. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 100 MHz Varian XL-100 or 200 MHz Nicolet spectrometer in δ units downfield from internal TMS. Unicam SP-200 (IR), AEI 902 (MS spectra), Varian 1400 (GLC) instruments were used in routine analyses.

Preparation of dilithio TosMIC [11]

To a solution of TosMIC (1.95 g, 0.01 mol) in dry THF (40 mL) was added 1.6 N solution of n-BuLi in hexane (13 mL, 0.021 mol) at –70˚C. The orange solution was stirred for 10 min at -70˚C. The dilithio-TosMic (0.01 mol) in THF-hexane thus prepared can be used for further reaction under nitrogen atmosphere at this temperature.

Preparation of disodio-TosMIC [12]

To a suspension of pre-washed NaH (0.528 g, 0.022 mol) in DMSO-ether (1:5, 18 mL) was added TosMIC (1.95 g, 0.01 mol) in dry ether (15 mL) at rt and stirred for 10 min at this temperature. The disodio-TosMIC (0.01 mol) in DMSO-ether was used for further reaction.

6-Isocyano-7-phenyl-6-tosyl-2, 4-heptadienaldoxime (2)

(a) From dilithio-TosMIC:

To a stirred solution of dilithio-TosMIC, prepared as described above from TosMIC (1.95 g, 0.01 mol) in THF (40 mL), was added all at once a solution of pyridine *N*-oxide (0.95 g, 0.01 mol) in THF (10 mL) at –70˚C. The cooling mixture was removed and the reaction mixture allowed to warm up till the temperature reached to 0˚C. Benzyl bromide (2.4 mL, 0.02 mol) was added to the reaction mixture at 0˚C and stirring continued at 0˚C for 1 h, followed by 1 h at rt. Acetic acid (2 mL) was added and the reaction mixture poured onto ice cold water (40 mL). After extraction with CH_2Cl_2, drying (Na_2SO_4) and concentration *in vacuo*, a brown viscous oil was obtained. It was crystallized with MeOH-cyclohexane to yield **2** as colorless crystals (2.70 g, 64%); mp 135 - 137˚C; IR (KBr): 1150, 1330, 2180 and 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.40 (s, 6H, cyclohexane), 2.45 (s, 3H), 3.45 (s, 2H), 5.8 - 6.55 (m, 4H), 7.0 - 8.0 (m, 10H), 8.60 (s, 1H); ^{1}H-NMR (DMSO-d_6): δ 1.40 (s, 6H, cyclohexane), 2.45 (s, 3H), 3.40 and 3.75 (ABq, 2H, J = 12 Hz), 6.0 - 6.5 (br s, 4H), 7.10 - 8.05 (m, 10H), 10.40 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 21.5, 38.4, 84.2, 124.9, 125.1, 125.3, 127.1, 127.6, 128.1, 129.4, 129.7, 133.1, 133.8, 144.2, 146.6, 166.5; MS m/z 362 [M^+- 60 (½ C_6H_{12} + H_2O)]; Anal. Calcd for $C_{21}H_{2O}N_2O_3S$. ½ C_6H_{12}: C, 68.25; H, 6.16; N, 6.64; S, 7.58. Found: C, 68.2; H; 6.1; N, 7.0; S, 7.6.

(b) The disodio-TosMIC prepared from TosMIC (1.95 g, 0.01 mol) was reacted with pyridine *N*-oxide and benzyl bromide under similar conditions as described above for (a). **2** was obtained in 70% yield as colorless crystals.

1-Cyano-5-isocyano-6-phenyl-5-tosylhexadiene -1, 3 (3)

p-Toluenesulfonyl chloride (1.90 g, 0.01 mol) was added to a stirred solution of oxime (**2**) (4.22 g, 0.01 mol) in pyridine (10 mL) at 0˚C. The reaction mixture was kept at 0˚C for 12 h and pyridine was distilled off at 40 - 50˚C at reduced pressure. Dark brown syrup was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (3 x 30 mL), brine (30 mL), dried (Na_2SO_4) and the solvent concentrated *in vacuo*. Brown solid after animal charcoal treatment in CH_2Cl_2 yielded colorless solid. After two crystallizations from CH_2Cl_2-hexane, **3** was obtained as colorless needles (3.10 g, 83%); mp 128 -129˚C (decomp); IR (Nujol): 1150, 1325, 2134, 2216 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.57(s, 2H), 5.30 (m, 1H), 6.22 (m, 2H), 6.72 (m,1H), 7.0 - 8.0 (m, 9H); ^{13}C-NMR ($CDCl_3$): δ 21.5, 38.5, 83.7, 101.2, 114.5, 128.0 to 147.1 (12 aromatic carbons and 4 olefinic carbons), 167.7; exact MS m/z found, 362 .112 (Calcd; 362 .109); Anal. Cacld for $C_{21}H_{18}N_2O_2S$: C, 69.61; H, 4.97; N, 7.73; S, 8.83. Found: C, 69.41; H, 4.94; N, 7.70; S, 8.75.

1-Cyano-6-phenyl-4-tosylhexene-1 (4)

To a stirred solution of **3** (3.62 g, 0.01 mol) in THF (80 mL) was added conc. HCl (38% aq. solution, 6 mL). The reaction mixture was stirred at rt for 2.5 h, H_2O (150 mL) added and extracted with ether (150 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield viscous brown syrup. Crystallization with CH_2Cl_2-hexane gave **4** as colorless crystals (2.48 g, 70%); mp 139 - 139.4˚C; IR (Nujol): 1150, 1308, 1712, 2224 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.00 (m, 1H), 3.50 (m, 1H), 3.77 (s, 2H), 4.60 (m, 1H), 5.40 (d, J = 16Hz, 1H), 6.05 (m, 1H), 7.0 - 7.8 (m, 9H); ^{13}C-NMR ($CDCl_3$): δ 21.4, 38.2, 49.8, 62.5, 106.5, 113.6, 143.3, 127.0 to 142.2 (12 aromatic carbons), 202.0; MS m/z 353 (M^+); Anal. Calcd for $C_{2O}H_{19}NO_3S$: C, 67.98; H, 5.38; N, 3.96; S, 9.06. Found: C, 67.80; H, 5.50; N, 3.96; S, 8.98.

1-Cyano-6-phenyl-1-hexadiene-1, 3-one-5 (5)

4 (353 mg, 0.00l mol) was dissolved in dry CH_2Cl_2 (20 mL) and rapidly filtered through a neutral alumina (activated) column and eluted with 100 mL of dry CH_2Cl_2. **5** was obtained as colorless oil. (171 mg, 87%); IR (Neat): 1685, 2220 cm^{-1}; ^{1}H-NMR ($CDCl_3$); δ 3.90 (s, 2H), 5.0 - 7.6 (m, 9H); MS m/z 197 (M^+); Anal. Calcd for $C_{13}H_{11}NO$: C, 79.18; H, 5.58; N, 7.10. Found: C, 79.30; H, 5.62; N, 7.22.

5-Isocyano-6-phenyl-5-tosyl-1, 3-hexadien-1-diazonium hydroxide (6)

(a) From dilithio-TosMIC

To a stirred solution of dilithio-TosMIC, prepared as described above from TosMIC (1.95 g, 0.01 mol) was added all at once a solution of pyridazine *N*-oxide (0.96 g, 0.01 mol) in THF (2 mL). The cooling mixture was removed and when the reaction mixture reached at 0˚C, it was allowed to stir at 0˚C for 15 min. A dark red paste was formed in the reaction mixture. The reaction mixture was allowed to cool at -20˚C and benzyl bromide (2 mL, 0.0017 mol) was added all at once. After stirring for 2 h at -10˚C, acetic acid (2 mL) was added and the reaction mixture poured onto H_2O (100 mL). After extraction with CH_2Cl_2, drying (Na_2SO_4) and evaporation of CH_2Cl_2 between 0 to 20˚C, an oil was obtained which was dissolved in ether (100 mL). The suspension formed was filtered, filtrate concentrated at rt to yield **6** as an oil (2.4 g, 63%). The oil was unstable even at rt as gas bubbles were visible in the oil. ^{1}H-NMR ($CDCl_3$); δ 2.40 (s, 3H), 3.50 (s, 2H), 5.70 - 6.95 (m, 4H), 7.0 - 7.6 (m, 7H), 7.85 (half ABq, 2H, J = 8 Hz), 9.10 (br s, 1H). **(b)** The disodio-TosMIC prepared from TosMIC (1.95 g, 0.01 mol) was reacted with pyridazine *N*-oxide and benzyl bromide under similar conditions as described for (a). **6** was obtained in 60% yield as an oil.

5-Isocyano-6-pheny-5-tosylhexene-3(*E*)-yn-1 (7)

6 (1.90 g, 0.005 mol) was dissolved in MeOH (5 mL) and the solution heated at 30 - 40˚C. A violent evolution of gas was observed. When the evolution of gas stopped the solution was cooled, colorless crystals thus obtained were collected by filtration and washed with MeOH and ether affording **7.** Crystallization with CH_2Cl_2-hexane gave **7** as colorless crystals. (1.38 g, 52%); mp 133 - 134˚C; IR (KBr): 1150, 1320, 2120, 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.00 (d, 1H, J = 2 Hz), 3.50 (s, 2H), 5.25 (dd, 1H, J = 2 Hz, J = 15 Hz), 6.30 (d, 1H, J =15 Hz), 7.20 (s, 5H), 7.30 and 7.75 (ABq, 4H, J = 8 Hz); MS m/z, 335 (M^+); Anal. Calcd for $C_{20}H_{17}NO_2S$: C, 71.62; H, 5.11; N, 4.17; S, 9.56. Found: C, 71.50; H, 5.10; N, 4.20; S, 9.50.

6-Phenyl-hexene-3(*E*)-yn-1-one-5 (8)

7 (335 mg, 0.001 mol) was dissolved in dry CH_2Cl_2 (15 mL) and rapidly filtered through a neutral alumina (activated) column and eluted with 100 mL of dry CH_2Cl_2. **8** was obtained as viscous oil; (135 mg, 81%); IR (Neat): 1691, 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.02 (d, 1H, J = 2 Hz), 3.75 (s, 2H), 6.45 (d, 1H, J = 15 Hz), 6.60 (d, 1H, J = 15 Hz), 7.20 (s, 5H); MS m/z, 170 (M^+); Anal. Calcd for $C_{12}H_{10}O$: C, 84.70; H, 5.88. Found: C, 84.82; H, 5.90.

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