Electron-Deficient 3-Cyano-1-(*p*-toluenesulfonyl)-1,3-butadienes: Regio- and Stereoselective Synthesis of a Benzene Ring System by Michael-Type Addition-Cyclization with Enamines

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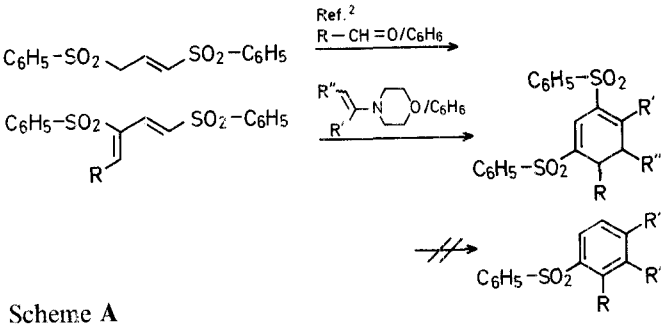
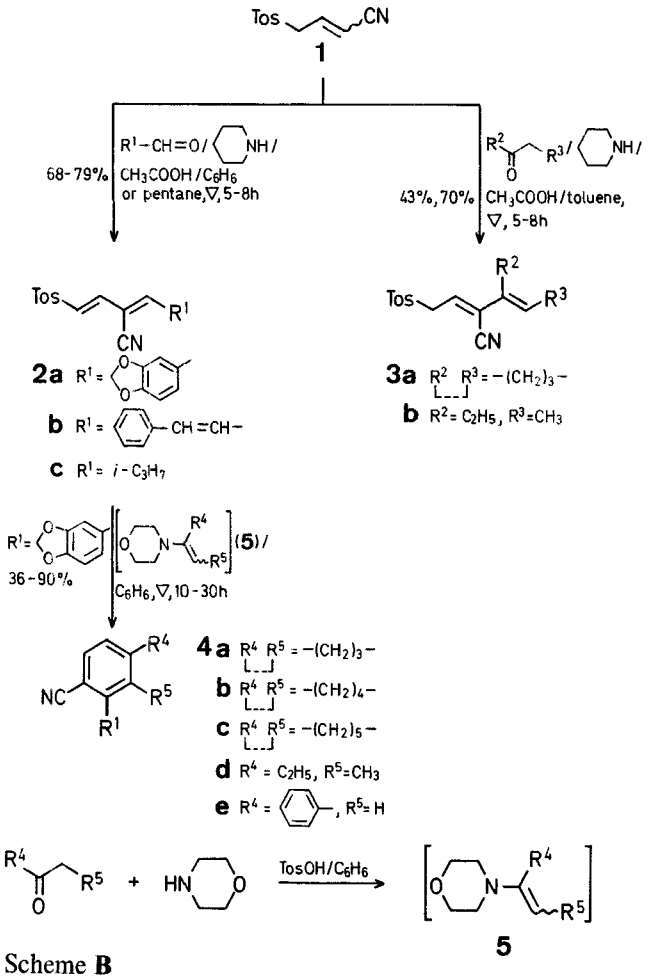
Knoevenagel-type condensation of 4-(*p*-toluenesulfonyl)-2-butenenitrile (**1**) with aldehydes provided electron-deficient 3-cyano-1-(*p*-toluenesulfonyl)-1,3-(*E,Z*)-butadienes **2**, and one of these dienes, **2a** was used in a Michael-type addition-cyclization with enamines to form the benzene ring system **4**.

Electron-deficient dienes offer a useful method for the formation of five- and six-membered ring systems by Michael-type addition-cyclization with nucleophiles such as sulfonium ylids and enamines[1]. We have reported that the benzenesulfonyl group is an efficient substituent for the synthesis of electron-deficient dienes and for the addition-cyclization with enamines[2].



Scheme A

However, the 1,3-bis[benzenesulfonyl]propene used did not react with ketones such as cyclohexanone, diethyl ketone, and acetophenone[2] (Scheme **A**). Further, elimination of benzenesulfinic acid to form a benzene ring system required rather severe reaction conditions and the yield was low. Hence, we have now developed this mehod into (a) an electron-deficient diene synthesis by regioselective Knoevenagel-type condensation of (*E*/*Z*)-4-(*p*-toluenesulfonyl)-2-butenenitrile (**1**), instead of 1,3-bis[benzenesulfonyl]propene, with aldehydes and ketones, and (b) a convenient synthesis of benzonitriles **4** by addition-cyclization of enamines to butadiene **2a** followed by elimination of *p*-toluenesulfinic acid (Scheme **B**).



Scheme **B**

The sulfone **1** [1:1 mixture of (*E*)- and (*Z*)-isomers] reacted with aldehydes at the α-position of cyano group to give 3-cyano-1-(*p*-toluenesulfonyl)-1,3-(*E*,*Z*)-butadienes **2**[3,4]. With ketones, the Knoevenagel-type condensation of **1** occurred with complete double-bond migration to give **3** (Table 1).

Using **2a**, the Michael-type addition-cyclization was investigated. Compound **2a** reacted regioselectively with enamines **5**, produced *in situ* by condensation of ketones and morpholine due to its instability towards oxygen, to give benzonitriles **4** (Table 2). Elimination of *p*-toluenesulfinic acid easily occurred in refluxing benzene, unlike in the case of the 1,3-bis[benzenesulfonyl]butadiene derivatives[2]. Aldehydes could not be used here because self-condensation occurred. the addition-cyclization of **3** did not occur under the same conditions.

4-(*p*-Toluenesulfonyl)-2-butenenitrile (1):
To a solution of 3-butenenitrile (3.4 g, 50 mmol) in chloroform (50 ml), a solution of bromine (8.0 g, 50 mmol) in chloroform (100 ml) is added dropwise during 1 h at 5°C. After stirring for 1 h, the solvent is evaporated. The residue is dissolved in dimethylformamide (100 ml). To the solution, sodium *p*-toluenesulfinate (8.9 g, 50 mmol) and then diisopropylethylamine (7.1 g, 55 mmol) are added at 5°C. After stirring for 3 h, the mixture is extracted with dichloromethane (2 × 100 ml). The extract is washed with water (3 × 50 ml) and dried with magnesium sulfate. Evaporation of dichloromethane and recrystallization (chloroform/hexane) give **1**; yield: 8.8 g (80%); m.p. 70–71°C; (*E*)/(*Z*) = 1:1 (by ^{1}H-N.M.R.).

M.S. (70eV): *m/e* = 221 (M^+).

H.R.M.S. (70eV): calc. for $C_{11}H_{11}NO_2S$: 221.0509; found: 221.0504.

I.R. (KBr): ν = 2220 (CN); 1310, 1140 (SO_2) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.44 (s, 3H, CH_3); 3.91, 4.12 (2d, *J* = 8 Hz, 2H, CH_2); 5.40, 5.54 (2d, *J* = 16, 10 Hz, 1H, C=CHCN); 6.49, 6.51 (2dt, *J* = 8 Hz, 10 Hz; 8 Hz, 16 Hz, 1H, C—CH=C); 7.34 (d, *J* = 8 Hz, 2H); 7.70, 7.72 ppm (2d, *J* = 8 Hz, 2H).

Table 1. Knoevenagel-Type Condensation of **1** with Aldehydes and Ketones

Product	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula	I.R. [cm^{-1}] (KBr or neat) $\nu_{C\equiv N}$	ν_{SO_2}	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity %)	H.R.M.S (70 eV) *m/e* (M^+) [calc. for M^+]
2a	5	73[a]	147–149°	$C_{19}H_{15}NO_4S$ (353.1)	2220	1315, 1140	2.42 (s, 3H); 6.02 (s, 2H); 6.80 (s, 1H); 6.89 (s, 1H); 7.16–7.41 (m, 4H); 7.49 (d, *J* = 8 Hz, 2H); 7.77 (d, *J* = 8 Hz, 2H)	353 (M^+, 43); 198 (47); 197 (100)	353.0743 [353.0721]
2b	6	68[a]	oil	$C_{20}H_{17}NO_2S$ (335.1)	2220	1320, 1145	2.38 (s, 3H); 7.04–8.33 (m, 14H)	335 (M^+, 8); 333 (100); 139 (96)	335.0987 [335.0978]
2c	8	79[b]	89–91°	$C_{15}H_{17}NO_2S$ (275.1)	2220	1315, 1140	1.11 (d, *J* = 7 Hz, 6H); 2.42 (s, 3H); 2.76–3.13 (m, 1H); 6.54 (d, *J* = 10 Hz, 1H); 6.62 (d, *J* = 15 Hz, 1H); 7.12 (d, *J* = 15 Hz, 1H); 7.30 (d, *J* = 8 Hz, 2H); 7.71 (d, *J* = 8 Hz, 2H)	275 (M^+, 5); 120 (100); 93 (30)	275.0970 [275.0979]

Table 1. (continued)

Product	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula	I.R. [cm^{-1}] (KBr or neat) $\nu_{C\equiv N}$	ν_{SO_2}	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity %)	H.R.M.S (70 eV) *m/e* (M^+) [calc. for M^+]
3a	7	43[a]	101–104°	$C_{16}H_{17}NO_2S$ (287.1)	2205	1290, 1135	1.74–2.14 (m, 2H); 2.22–2.60 (br, 4H); 2.42 (s, 3H); 4.11 (d, J = 8 Hz, 2H); 6.02 (t, J = 8 Hz, 1H); 6.07–6.18 (br, 1H); 7.31 (d, J = 8 Hz, 2H); 7.69 (d, J = 8 Hz, 2H)	287 (M^+, 6); 142 (42); 132 (100); 105 (36); 104 (38)	287.0986 [287.0979]
3b	25	70[a]	oil	$C_{16}H_{19}NO_2S$ (289.1)	2210	1310, 1135	0.89 (t, J = 7 Hz, 3H); 1.64 (d, J = 7 Hz, 3H); 2.17 (q, J = 7 Hz, 2H); 2.32 (s, 3H); 4.13 (d, J = 8 Hz, 2H); 5.93 (q, J = 7 Hz, 1H); 6.12 (t, J = 8 Hz, 1H); 7.23 (d, J = 7 Hz, 2H); 7.67 (d, J = 7 Hz, 2H)	289 (M^+, 9); 146 (44); 134 (100); 107 (33)	289.1122 [289.1135]

[a] Solvent: benzene.

[b] Solvent: pentane.

Table 2. Michael-Type Addition-Cyclization to **2a** with Enamines

Product	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula	I.R. (KBr) $\nu_{C\equiv N}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (relative intensity %)	H.R.M.S. (70 eV) *m/e* (M^+) [calc. for M^+]
4a	18	76	110–111°	$C_{17}H_{13}NO_2$ (263.1)	2210	1.80–2.20 (m, 2H); 2.67–3.07 (m, 4H); 5.91 (s, 2H); 6.69–6.82 (m, 3H); 7.16 (d, J = 8 Hz, 1H); 7.41 (d, J = 8 Hz, 1H)	263 (M^+, 100)	263.0932 [263.0945]
4b	19	66	144–145°	$C_{18}H_{15}NO_2$ (277.1)	2205	1.53–1.91 (br, 4H); 2.31–2.58 (br, 2H); 2.69–2.96 (br, 2H); 5.94 (s, 2H); 6.63 (d, J = 8 Hz, 1H); 6.67 (s, 1H); 6.84 (d, J = 8 Hz, 1H); 7.07 (d, J = 8 Hz, 1H); 7.38 (d, J = 8 Hz, 1H)	277 (M^+, 100)	277.1090 [277.1101]
4c	10	90	126–127°	$C_{19}H_{17}NO_2$ (291.1)	2210	1.33–2.02 (br, 6H); 2.49–2.76 (br, 2H); 2.80–3.00 (br, 2H); 5.98 (s, 2H); 6.56–6.71 (m, 2H); 6.84 (d, J = 8 Hz, 1H); 7.11 (d, J = 8 Hz, 1H); 7.37 (d, J = 8 Hz, 1H)	291 (M^+, 100)	291.1266 [291.1258]
4d	29	44	101–102°	$C_{17}H_{15}NO_2$ (265.1)	2210	1.22 (t, J = 7 Hz, 3H); 2.08 (s, 3H); 2.47 (q, J = 7 Hz, 2H); 5.94 (s, 2H); 6.64 (d, J = 8 Hz, 1H); 6.68 (s, 1H); 6.86 (d, J = 8 Hz, 1H); 7.18 (d, J = 8 Hz, 1H); 7.44 (d, J = 8 Hz, 1H)	265 (M^+, 100)	265.1105 [265.1102]
4e	23	36	107–109°	$C_{20}H_{13}NO_2$ (299.1)	2200	5.97 (s, 2H); 6.78–7.24 (m, 3H); 7.33–7.83 (m, 8H)	299 (M^+, 100)	299.0948 [299.0946]

3-Cyano-1-(*p*-toluenesulfonyl)-1,3-butadienes 2; General Procedure:
A solution of 4-(*p*-toluenesulfonyl)-2-butenenitrile (**1**; 0.44 g, 2 mmol), aldehyde (2 mmol), and catalytic amounts of piperidine and acetic acid in benzene (20 ml) is refluxed for 5–8 h in a Dean-Stark apparatus. The mixture is extracted with ether (50 ml), the extract is washed with water (30 ml), and dried with magnesium sulfate. The residue obtained on evaporation of the solvent is crystallized from chloroform/hexane or chromatographed on a column of silica gel using hexane/ethyl acetate (3/1) as eluent to isolate the product (Table 1).

Benzonitriles 4; General Procedure:
A solution of 2-cyano-1-[3,4-(methylenedioxyphenyl)]-4-(*p*-toluenesulfonyl)-1,3-butadiene (**2a**; 0.35 g, 1 mmol), ketone (1.2 mmol), morpholine (0.10 g, 1.2 mmol), and a catalytic amount of *p*-toluenesulfonic acid in benzene (20 ml) is refluxed for 10–30 h in a Dean-Stark apparatus. The mixture is extracted with diethyl ether (50 ml). The extract is washed with water (2 × 30 ml) and dried with magnesium sulfate. Evaporation of the solvent and column chromatography on silica gel using hexane/ethyl acetate (5/1) as eluent give the product (Table 2).

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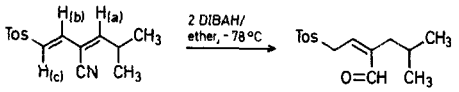
[2] Masuyama, Y., Sato, H., Kurusu, Y. *Tetrahedron Lett.* **1985**, *26*, 67.

[3] For stereochemistry in Knoevenagel reaction see: House, H.O., *Modern Synthetic Reactions*, 2nd Edn., W.A. Benjamin Inc., Menlo Park, California, 1972, p. 646.
Tanikaga, R., Tamura, T., Nozaki, Y., Kaji, A. *J. Chem. Soc. Chem. Commun.* **1984**, 87.

[4] For determination of the regiochemistry of **2**, reduction of **2c** was carried out with double the molar quantity of diisobutylaluminium hydride (DIBAH) in ether at −78 °C to give the corresponding α,β-unsaturated aldehyde (see below). The ^{1}H-N.M.R. spectrum of the aldehyde showed a singlet for the formyl proton at $\delta = 9.71$ ppm; for the reduction of olefinic nitrile using DIBAH see: Bohlmann, F., Fiedler, L. *Chem. Ber.* **1981**, *114*, 227.



2c

The stereochemistry of **2c** was tentatively determined by the measurement of the Nuclear Overhauser Effect (N.O.E.). The N.O.E. enhancement was measured on a 3 % solution of **2c** in chloroform-*d* using a Jeolco FX-200 spectrometer (200 MHz). Irradiation of $H_{(a)}$ enhanced the intensity of the $H_{(b)}$ signal by 7.8 %; for the Nuclear Overhauser Effect, see: Bell, R.A., Saunders, J.K. *Top. Stereochem.* **1973**, *7*, 1. The coupling constant between $H_{(b)}$ and $H_{(c)}$ is 14.9 Hz. These results suggest the structure **2c**.