One-Step Synthesis of Dialkyl 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates by Reaction of Acetylenedicarboxylates with 'Tosylmethyl Isocyanide' (TsMIC) and Triphenylphosphine

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The reactive 1:1 adducts in the reaction between Ph_3P and dialkyl acetylenedicarboxylates have been trapped with 'tosylmethyl isocyanide' (TsMIC; **1**) to yield dialkyl 2-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates **3** (*Scheme 1*). The structures of the highly functionalized compounds **3** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of cyclization is proposed (*Scheme 2*).

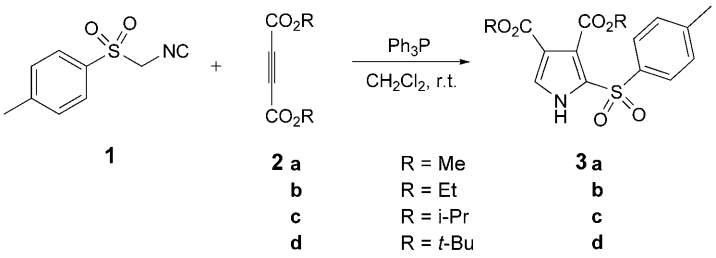
1. Introduction. – Isonitrile cyclization provides a useful alternative of the *Knorr*-type cyclization for pyrrole synthesis. In 1972, *van Leusen* and co-workers reported a pyrrole synthesis based on the reaction between 'tosylmethyl isocyanide' (TsMIC; **1**)[1]) with electron-deficient alkenes [1]. *Barton* and *Zard* found that the base-catalyzed reaction of nitroalkenes or β-nitroacetates with alkyl isocyanoacetate or TsMIC affords pyrrole-2-carboxylates or 2-sulfonylpyrroles, respectively [2][3]. TsMIC (**1**) and its substituted derivatives are being extensively used in the synthesis of 3,4-disubstituted and 2,3,4-trisubstituted pyrroles, respectively. With these results in mind, we decided to prepare 2,3,4-trisubstituted pyrroles from the reaction of **1** and dialkyl acetylenedicarboxylates in the presence of Ph_3P.

2. Results and Discussion. – When TsMIC (**1**) and dialkyl acetylenedicarboxylates **2** were mixed in the presence of Ph_3P in anhydrous CH_2Cl_2 at ambient temperature, a smooth 1:1 addition took place to produce the highly functionalized dialkyl 2-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylates **3** in 50–90% yield (*Scheme 1*). The ^{1}H- and ^{13}C-NMR spectra of the crude reaction mixtures clearly indicated the formation of the products. The structures of **3a**–**d** were deduced by IR, ^{1}H- and ^{13}C-NMR, MS, and elemental analysis. The mass spectra displayed the M^+ signals, and fragmentation always involved the loss of ester moieties.

The ^{1}H-NMR spectrum of **3a** exhibited three resonances at δ(H) 2.36 (*s*, Me), 3.77 (*s*, MeO), and 3.93 (*s*, MeO). The pyrrole H-atom resonated at δ(H) 7.44 ($^3J = 3.2$ Hz, H–C(5)), the pyrrole NH was observed at δ(H) 10.69 (br. *s*), and the aryl residues gave

[1]) Systematic name: 1-[(isocyanomethyl)sulfonyl]-4-methylbenzene.

Scheme 1

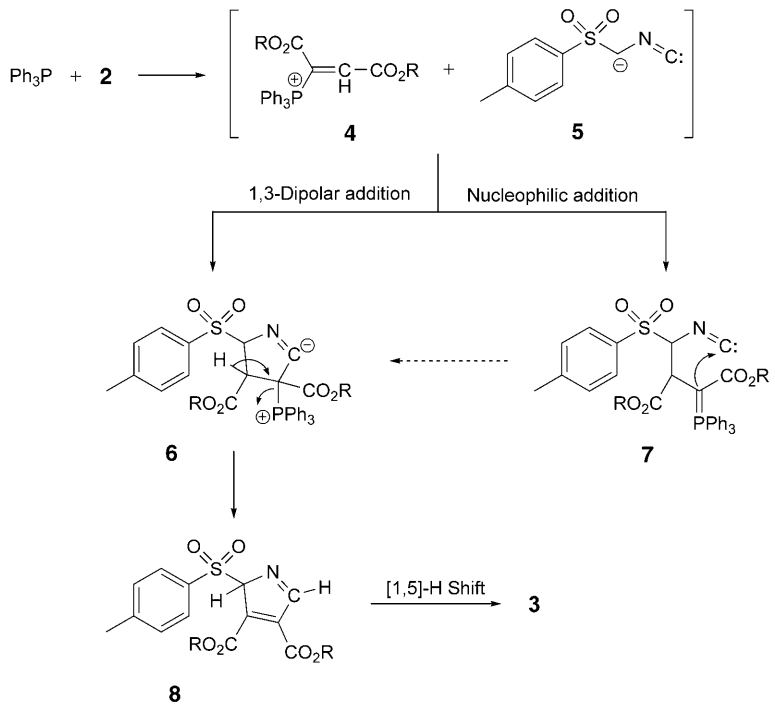


rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 13 distinct resonances, in agreement with the pyrrole structure. The ^{1}H- and ^{13}C-NMR spectra of **3b**–**d** were similar to those of **3a**, except for the ester resonances, which exhibited characteristic signals with appropriate chemical shifts (see *Exper. Part*).

The mechanism of the reaction between TsMIC (**1**) and acetylene-1,2-dicarboxylates in the presence of Ph_3P has not yet been fully established experimentally. A possible pathway is shown in *Scheme 2*.

On the basis of the well-established chemistry of trivalent-phosphorus nucleophiles [4–11], it is reasonable to assume that the pyrroles **3** in the above reaction result from

Scheme 2



nucleophilic addition of Ph_3P to the acetylenic esters **2**, followed by protonation of the 1:1 adduct by TsMIC (**1**). Then, the positively charged ion **4** and the TsMIC anion **5** undergo a 1,3-dipolar cycloaddition to produce the betain **6**. Alternatively, the positively charged ion **4** is attacked in a nucleophilic reaction by **5** to produce the ylide **7**, which, under the reaction conditions employed, may cyclize to the betain **6**. Finally, loss of Ph_3P under formation of **8** and a [1,5]-H shift give rise to the observed pyrroles **3**.

In summary, we have established a simple one-pot procedure for the preparation of trisubstituted pyrroles carrying a sulfonyl group in 2-position. The reaction can be performed under neutral conditions, and the reagents can be mixed without any pre-activation or modification, in contrast to multistep approaches.

Experimental Part

General. Dimethyl-, diethyl- and di(*tert*-butyl) acetylene-1,2-dicarboxylate, and *tert*-butyl isocyanide were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. Diisopropyl acetylenedicarboxylate was prepared according to lit. procedures [12][13]. Column chromatography (CC): *Merck* silica gel (230–240 mesh). Melting points (m.p.): *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^1H-, ^{13}C-, and ^{31}P-NMR Spectra: *Bruker DRX 500-AVANCE* instrument, at 500.1, 125.7, and 202.4, MHz, resp., in $CDCl_3$ soln.; δ in ppm, J in Hz. EI-MS (70 eV): *Finnigan MAT-8430* mass spectrometer; in m/z (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **2** (exemplified for **2a**). To a magnetically stirred soln. of Ph_3P (0.26 g, 1 mmol) and TsMIC (**1**; 0.19 g, 1 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise a soln. of **2a** (0.14 g, 1 mmol) in anh. CH_2Cl_2 (3 ml) at r.t. over 10 min. The mixture was stirred for 48 h, the solvent was removed under reduced pressure, and the residue was separated by CC (SiO_2; hexane/AcOEt).

*Dimethyl 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate* (**3a**). Yield: 300 mg (90%). Colorless crystals. M.p. 107–108°. IR (KBr): 3255 (NH); 1710 (COO); 1284, 1128 (SO_2); 1210, 1166 (ester C–O). ^1H-NMR (500 MHz, $CDCl_3$): 2.36 (*s*, 3 H); 3.77 (*s*, 3 H); 3.93 (*s*, 3 H); 7.25 (*d*, J=8.0, 2 H); 7.44 (*d*, J=3.2, 1 H); 7.82 (*d*, J=8.0, 2 H); 10.96 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.21; 51.84; 52.92; 116.43; 121.77; 127.19; 127.69; 128.63; 129.91; 137.68; 144.95; 162.89; 164.43. EI-MS: 337 (9, M^+), 306 (41), 274 (33), 242 (100), 183 (69), 139 (16), 107 (12), 91 (61), 65 (47), 39 (16). Anal. calc. for $C_{15}H_{15}NO_6S$ (337.34): C 53.41, H 4.48, N 4.15; found: C 53.3, H 4.5, N 4.2.

*Diethyl 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate* (**3b**). Yield: 180 mg (50%). Colorless crystals. M.p. 157–159°. IR (KBr): 3330 (NH); 1735, 1703 (COO); 1323, 1140 (SO_2); 1269, 1186 (ester C–O). ^1H-NMR (500 MHz, $CDCl_3$): 1.26 (*t*, J=7.1, 3 H); 1.37 (*t*, J=7.1, 3 H); 2.41 (*s*, 3 H); 4.23 (*q*, J=7.1, 2 H); 4.41 (*q*, J=7.1, 2 H); 7.44 (*d*, J=8.0, 2 H); 7.65 (*d*, J=3.2, 1 H); 7.94 (*d*, J=8.3, 2 H); 11.98 (br., 1 H). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 14.02; 14.15; 21.12; 60.56; 61.77; 116.58; 123.19; 127.81; 128.09; 128.82; 130.35; 139.22; 145.30; 162.36; 164.00. EI-MS: 366 (3, $[M+1]^+$), 334 (3), 298 (17), 242 (37), 224 (20), 186 (23), 167 (77), 123 (13), 97 (30), 57 (100). Anal. calc. for $C_{17}H_{19}NO_6S$ (365.39): C 55.88, H 5.24, N 3.83; found: C 55.9, H 5.2, N 3.9.

*Diisopropyl 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate* (**3c**). Yield: 330 mg (85%). Colorless crystals. M.p. 132–134°. IR (KBr): 3255 (NH); 1711 (COO); 1280, 1146 (SO_2); 1209, 1179 (ester C–O). ^1H-NMR (500 MHz, $CDCl_3$): 1.26 (*d*, J=6.2, 6 H); 1.41 (*d*, J=6.2, 6 H); 2.35 (*s*, 3 H); 5.12 (*quint.*, J=6.2, 1 H); 5.30 (*quint.*, J=6.2, 1 H); 7.24 (*d*, J=8.0, 2 H); 7.42 (*d*, J=3.2, 1 H); 7.86 (*d*, J=7.5, 2 H); 10.78 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.57; 21.73; 21.85; 68.27; 70.10; 116.90; 122.80; 127.20; 127.58; 127.63; 129.89; 137.98; 145.75; 161.99; 163.75. EI-MS: 394 (7, $[M+1]^+$), 352 (5), 335 (4), 310 (4), 292 (100), 244 (18), 226 (86), 201 (43), 183 (37), 155 (20), 139 (49), 108 (29), 91 (86), 43 (61). Anal. calc. for $C_{19}H_{23}NO_6S$ (393.45): C 58.00, H 5.89, N 3.56; found: C 58.0, H 5.9, N 3.5.

*Di(*tert*-Butyl) 2-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrole-3,4-dicarboxylate* (**3d**). Yield: 400 mg (95%). Colorless crystals. M.p. 144–146°. IR (KBr): 3185 (NH); 1696 (COO); 1329, 1296 (SO_2); 1249, 1145 (ester C–O). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.5 (*s*, 9 H); 1.61 (*s*, 9 H); 2.39 (*s*, 3 H); 7.28 (*d*, *J* = 8.5, 2 H); 7.31 (*d*, *J* = 3.2, 1 H); 7.88 (*d*, *J* = 8.3, 2 H); 10.03 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.62; 28.07; 28.28; 81.19; 82.98; 118.85; 123.64; 126.20; 127.21; 127.51; 129.86; 138.14; 144.67; 161.43; 162.53. EI-MS: 277 (14), 138 (27), 11 (11), 91 (55), 58 (100), 41 (86), 39 (84). Anal. calc. for $C_{21}H_{27}NO_6S$ (421.50): C 59.84, H 6.46, N 3.32; found: C 59.9, H 6.5, N 3.3.

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