One-Pot Synthesis of Tetraalkyl Benzene-1,2,3,5-tetracarboxylates from a Four-Component Reaction of Alkyl Propiolates and Alkyl 2-Nitroethanoates Promoted by Ph_3P

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Alkyl 2-nitroethanoates react with alkyl propiolates in the presence of triphenylphosphine (Ph_3P) in a mechanistically unprecedented reaction to afford tetraalkyl benzene-1,2,3,5-tetracarboxylates in moderate yields (36–42%).

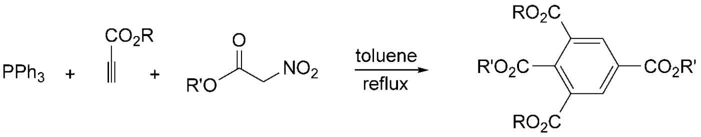
Introduction. – The chemistry of aromatic polycarboxylates has recently received considerable attention owing to the variety of bridging abilities of these compounds in the formation of inorganic–organic frameworks. In particular, multiple benzenecarboxylate ligands have been shown to be good building blocks in the design of metalorganic materials with desired topologies owing to their rich coordination modes [1–3]. Carbon nucleophiles (anions of carbon acids, organometallics, ylides, enamines, enol ethers, *etc.*) usually add to alkynes only in the presence of some activating substituent, reaction-facilitating solvents, specific coordination sites, or catalysts [4]. In many cases, cyclic products such as benzene derivatives are formed.

As part of our studies on the development of new routes to heterocyclic and carbocyclic systems [5], we herein report a simple one-pot synthesis of functionalized tetraalkyl benzene-1,2,3,5-tetracarboxylates **1** (see *Scheme 1* below).

Results and Discussion. – The reaction of alkyl propiolates **2** with alkyl 2-nitroethanoates **3** in the presence of triphenylphosphine (Ph_3P) under reflux in toluene was complete within a few hours (*Scheme 1*). The ^{1}H- and ^{13}C-NMR spectra of the crude reaction mixture clearly indicated the formation of the tetraalkyl benzene-1,2,3,5-tetracarboxylates **1a**–**d**. Products other than **1** could not be detected by NMR spectroscopy. The structures of compounds **1** were deduced from their elemental analyses and their IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopic data. For example, the ^{1}H-NMR spectrum of **1a** exhibited four sharp *singlets* readily recognized as arising from MeO (δ(H) 3.95, 4.00, 4.03) and aromatic (δ(H) 8.85) H-atoms. The ^{1}H-decoupled ^{13}C-NMR spectrum of **1a** showed ten distinct resonances, in agreement with the proposed structure. The ^{1}H- and ^{13}C-NMR spectra of **1b**–**d** were similar to those of **1a**, except for the alkoxy moieties, which exhibited characteristic signals with appropriate chemical shifts.

Unambiguous evidence for the structure of **1b** was obtained from single-crystal X-ray analysis. An ORTEP [6] diagram of **1b** is shown in the *Figure*. There are eight molecules of **1b** in the unit cell. The C=O group of the central carboxylate moiety is forced

Scheme 1



2	R
a	Me
b	Et

3	R'
a	Me
b	Et

1	R	R'	Yield [%]
a	Me	Me	42
b	Me	Et	36
c	Et	Me	38
d	Et	Et	39

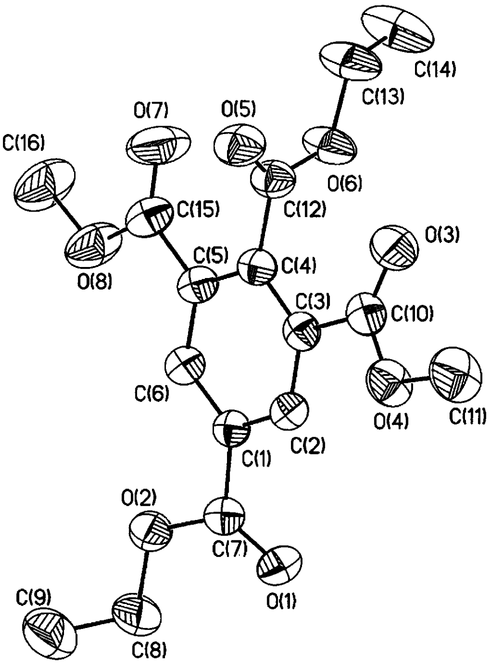
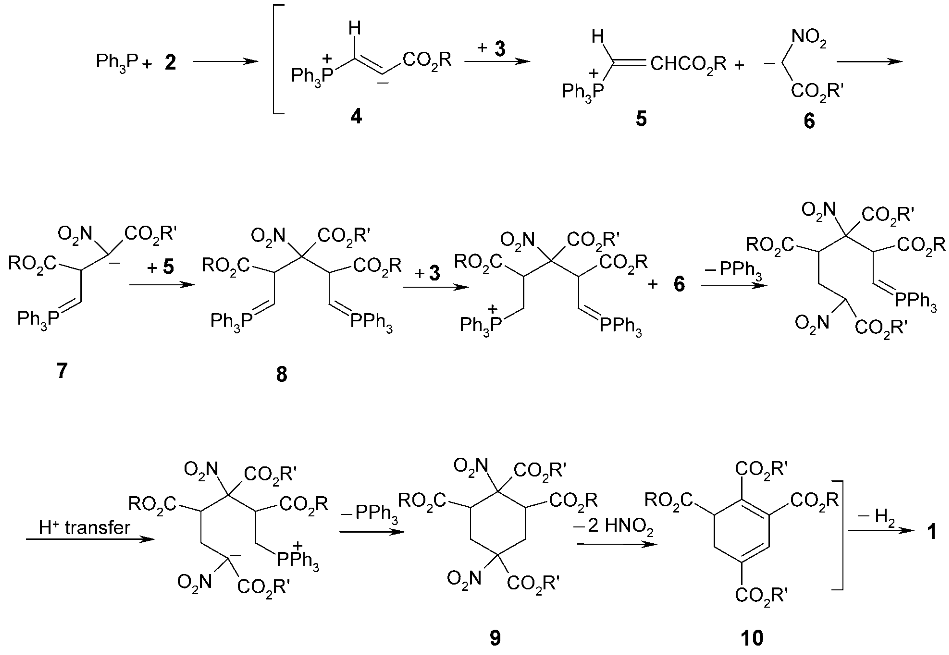


Figure. *X-Ray crystal structure of* **1b** (ORTEP-III Plot [6]). Arbitrary atom numbering.

out of the plane of the aromatic ring and it is twisted by *ca.* 88°. Details of the structure determination and refinement are described in the *Exper. Part.*

Although the mechanistic details of the above reaction are not known, a plausible mechanism may be advanced to rationalize product formation (*Scheme 2*). Presumably, a zwitterionic intermediate [7] of type **4**, formed from Ph_3P and alkyl propiolate, is protonated by **3** to furnish intermediate **5**, which is attacked by the carbanion **6** to produce ylide **7**. Further reaction of the latter with **5** leads to the bis-ylide **8**, which could undergo stepwise cyclization with **3** to produce the cyclohexane derivative **9** by elimination of Ph_3P. The cyclohexadiene **10**, produced by elimination of HNO_2, is finally converted to **1** by aromatization.

Scheme 2



In conclusion, we have discovered a novel transformation involving alkyl propiolates, alkyl 2-nitroethanoates, and $\mathrm{Ph_3P}$ that proceeds through a complex process affording tetraalkyl benzene-1,2,3,5-tetracarboxylates. The advantage of the present method is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

Experimental Part

General. Compounds **2** and **3** were obtained from *Fluka* and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in $\mathrm{cm^{-1}}$. ^{1}H- and ^{13}C-NMR Spectra: *Bruker DRX-500 AVANCE* instrument, in $\mathrm{CDCl_3}$ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430* mass spectrometer, at 70 eV; in m/z. Elemental analyses (C, H, N): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **1**. To a stirred soln. of $\mathrm{Ph_3P}$ (0.57 g, 2.2 mmol) and **3** (4 mmol) in anh. toluene (10 ml) was added dropwise compound **2** (4 mmol) in toluene (4 ml), and the mixture was heated at reflux for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography ($\mathrm{SiO_2}$; hexane/AcOEt 5 : 1) to afford the pure title compounds.

Tetramethyl Benzene-1,2,3,5-tetracarboxylate (**1a**). Yield: 0.25 g (42% rel. to **2**). Colorless powder. M.p. 120–122°. IR (KBr): 1723, 1726, 1731 (4 C=O); 1428; 1247. ^{1}H-NMR: 3.95 (*s*, 2 MeO); 4.00 (*s*, MeO); 4.03 (*s*, MeO); 8.85 (*s*, 2 CH). ^{13}C-NMR: 53.0 (2 MeO); 53.1 (MeO); 53.2 (MeO); 129.2 (C); 131.3 (C); 135.1 (2 CH); 140.4 (C); 164.4, 164.7, 166.3 (4 C=O). EI-MS: 310 (7, M^{+}), 240 (5), 212 (7), 168 (10), 140 (38), 112 (38), 68 (100), 57 (22). Anal. calc. for $\mathrm{C_{14}H_{14}O_8}$ (310.26): C 54.20, H 4.55; found: C 54.32, H 4.61.

2,5-Diethyl 1,3-Dimethyl Benzene-1,2,3,5-tetracarboxylate (**1b**). Yield: 0.24 g (36%). Colorless crystals. M.p. 99–101°. IR (KBr): 1730, 1728, 1727 (4 C=O); 1433; 1242. ^{1}H-NMR: 1.41 (*t*, $^3J = 7.2$, Me), 1.44 (*t*, $^3J = 7.2$, Me); 3.94 (*s*, 2 MeO); 4.45 (*q*, $^3J = 7.2$, CH_2O); 4.89 (*q*, $^3J = 7.2$, CH_2O); 8.82 (*s*, 2 CH). ^{13}C-NMR: 13.9 (Me); 14.3 (Me); 52.9 (2 MeO); 62.0 (CH_2O); 62.2 (CH_2O); 129.2 (C); 131.5 (C); 135.0 (2 CH); 140.4 (C); 164.3, 164.5, 167.5 (4 C=O). EI-MS: 338 (4, M^+), 293 (100), 265 (33), 149 (51), 71 (39), 57 (91). Anal. calc. for $C_{16}H_{18}O_8$ (338.32): C 56.80, H 5.36; found: C 56.71, H 5.40.

1,3-Diethyl 2,5-Dimethyl Benzene-1,2,3,5-tetracarboxylate (**1c**). Yield: 0.26 g (38%). Colorless powder. M.p. 87–89°. IR (KBr): 1722, 1725, 1729 (4 C=O); 1461; 1299. ^{1}H-NMR: 1.34 (*t*, $^3J = 7.2$, 2 Me); 3.95 (*s*, MeO); 4.10 (*s*, MeO); 4.32 (*q*, $^3J = 7.2$, 2 CH_2O); 8.93 (*s*, 2 CH). ^{13}C-NMR: 14.0 (Me); 53.4 (MeO); 53.5 (MeO); 61.7 (2 CH_2O); 128.4 (C); 128.5 (C); 129.5 (2 CH); 154.4 (C); 159.2, 159.8, 162.8 (4 C=O). EI-MS: 338 (7, M^+), 230 (8), 212 (4), 168 (2), 140 (4), 94 (2), 57 (100). Anal. calc. for $C_{16}H_{18}O_8$ (338.32): C 56.80, H 5.36; found: C 56.72, H 5.39.

Tetraethyl Benzene-1,2,3,5-tetracarboxylate (**1d**). Yield: 0.28 g (39%). Colorless powder. M.p. 74–76°. IR (KBr): 1716, 1719, 1724 (4 C=O); 1454; 1244. ^{1}H-NMR: 1.26 (*t*, $^3J = 7.1$, Me); 1.40 (*t*, $^3J = 7.2$, 2 Me); 1.45 (*t*, $^3J = 7.2$, Me); 4.34 (*q*, $^3J = 7.1$, CH_2O); 4.41 (*q*, $^3J = 7.2$, 2 CH_2O); 4.46 (*q*, $^3J = 7.2$, CH_2O); 8.80 (*s*, 2 CH). ^{13}C-NMR: 13.9 (Me); 14.1 (2 Me); 14.3 (Me); 62.0 (CH_2O); 62.1 (C); 62.2 (2 CH_2O); 129.7 (C); 131.4 (C); 134.8 (2 CH); 140.2 (C); 164.2, 164.4, 167.4 (4 C=O). EI-MS: 257 (3, M^+), 212 (4), 226 (6), 154 (8), 126 (84), 82 (18), 59 (100). Anal. calc. for $C_{18}H_{22}O_8$ (366.37): C 59.01, H 6.05; found: C 58.94, H 6.01.

X-Ray Crystal-Structure of **1b**[1]). Structure-determination and refinement data: $C_{16}H_{18}O_8$, M_r 338.30, crystal size 0.22×0.20×0.05 mm, monoclinic, $a = 9.1177(6)$, $b = 9.7933(7)$, $c = 26.7605(18)$ Å; $\alpha = 90$, $\beta = 92.635(5)$, $\gamma = 90°$; space group $C\ 2/c$, $Z = 8$, $V = 3331.7(10)$ Å^3, $D_{calc.} = 1.349$ g cm^{-3}; $R = 0.0845$, $R_w = 0.1354$; $-31 \le h \le 32$; $-13 \le k \le 14$; $-18 \le l \le 20$; MoK_α radiation ($\lambda = 0.71073$ Å); $T = 120(2)$ K.

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Received July 23, 2006

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[1] The crystallographic data of **1b** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-299058. Copies of the data can be obtained, free of charge, at http://www.ccdc.cam.ac.uk/data_request/cif.