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Synthesis of Ethylenetetracarboxylic Acid Derivatives

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Summary. The three-component reaction of the zwitterions generated from dialkyl acetylenedicarboxylate and isocyanides with isocyanates is described. The reaction afforded the corresponding special type of ethylenetetracarboxylic acid derivatives in good yields.

Keywords. Alkyl isocyanide; Dialky acetylenedicarboxylate; Arylsulfonyl isocyanate; Multicomponent reaction; Sulfonamide.

Introduction

An important goal in the preparation of relevant organic compounds, such as natural products and analogues, drugs, and diagnostics is the improvement of synthetic efficiency. Moreover, other essential issues are the care of our environment, the preservation of our resources, and economical advantages. A general way to improve synthetic efficiency and also to address the other criteria is the development of multicomponent reactions [1]. In 1969 *Winterfeldt et al.* first described the reaction of isocyanides and acetylenes [2]. This early finding forms the basis for a large class of new backbones thus accessible. The chemistry is based upon the initial formation of a zwitterionic adduct of the isocyanide with the acetylene. Isocyanides, by virtue of their carbenic character, react readily with most common multiple bonds [3].

Sulfonamide-containing compounds have a high potential as pharmaceutical and agricultural agents due to their diverse biological profiles. The ability to serve as amide surrogates, with unique physical properties, have made them ideal functional groups for the development of novel peptidomimetics [4]. In addition, sulfonamides have served as key functional groups in the development of novel nonpeptidal HIV protease inhibitors, matrix metalloproteinase inhibitors, thrombin inhibitors, and fibrinogen receptor antagonists. The sulfonamide structural motif is widely found in molecules of medicinal interest, particularly antibacterial agents [5–9]. More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as *Alzheimer*'s disease, arthritis, and cancer [10, 11].

Ethylenetetracarboxylic acid derivatives are versatile building blocks for conversion to other tetrafunctionalized olefins, such as ethylenetetracarboxylic dianhydride, and is used in *Diels-Alder* reaction as a dienophile, and also can be converted to methyl propiolate by controlled pyrolysis [12–14].

Recently, we have reported and developed the multicomponent reaction mediated by zwitterionic intermediates produced by a variety of nuclephiles [15–20]. Although the trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylate and isocyanides with activated alkenes, aldehydes, imines, and isothiocyanides has been studied, trapping of the initially formed 1:1 intermediate with isocyanates has not been reported [21–25]. In this paper, we present the results of an extended investigation of the reactivity of the zwitterion with arylsulfonyl

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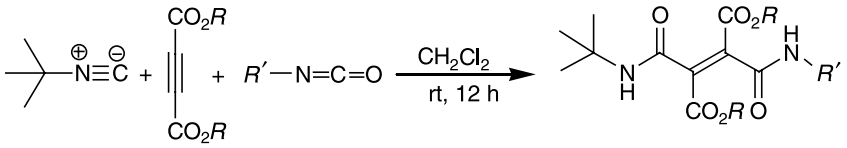
isocyanates or aryl isocyanates in CH_2Cl_2 leading to the formation of the corresponding ethylenetetracarboxylic acid derivatives.

Results and Discussion

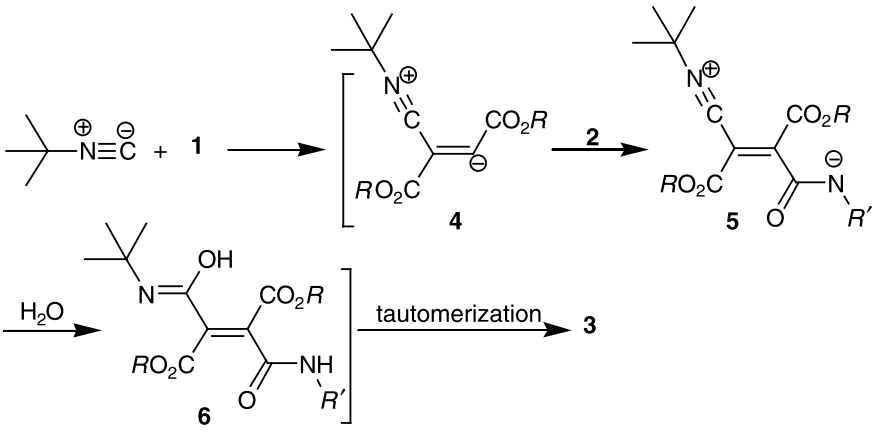
Arylsulfonyl isocyanates offer sp carbon electrophilic sites, and therefore it was of interest to examine the reactivity profile of the zwitterion towards sulfonamide derivatives. Thus, when arysulfonyl- or aryl isocyanate **2** were treated with the *in situ* generated zwitterion from *DMAD* and *tert*-butyl isocyanide in CH_2Cl_2 at room temperature, the ethylenetetracarboxylic acid derivatives **3** were obtained in 65–80% yield after 12 h (Scheme 1).

Analogous reactions were observed with other arylsulfonyl isocyanates, *DMAD*, and *tert*-butyl isocyanides. The structures of compounds **3a**–**3d** were deduced from their elemental analyses, IR, and high-field ^1H and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion peak at $m/z = 426$, which is consistent with the 1:1:1:1 adduct of *tert*-butyl isocyanide:dimethyl acetylenedicarboxylate: benzenesulfonyl isocyanate:water. The IR spectrum of **3a** exhibited absorption bands due to the carbonyl group of esters at 1727 cm^{-1}, and NH groups at 3400 and 3295 cm^{-1}, the absorption bands of the sulfonyl moiety appeared at 1363 and 1142 cm^{-1}. The ^1H NMR spectrum of **3a** exhibited three single sharp singlets readily recognized as arising from *tert*-butyl ($\delta = 1.43$ ppm) and methoxy ($\delta = 3.56$ and 3.84 ppm), protons along with two NH triplets ($\delta = 7.43$ ppm, $J = 6.8$ and $\delta = 7.59$ ppm, $J = 7.0$ Hz). The aryl moiety exhibited characteristic signals in the aromatic



	R	R′	% Yield of **3**
3a	*Me*	$C_6H_5SO_2$	65
3b	*Me*	*p*-*Me*$C_6H_4SO_2$	70
3c	*Me*	*m*-*Me*C_6H_4	80
3d	*Et*	*m*-*Me*C_6H_4	65

Scheme 1



$R' = C_6H_5SO_2$, *p*-*Me*$C_6H_4SO_2$, *m*-*Me*C_6H_4

Scheme 2

region of the spectrum. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 14 distinct resonances in agreement with the dimethyl 2-[(*tert*-butylamino)-carbonyl]-3-[[[(phenyl)sulfonyl]amino]carbonyl]-2-butenedioate structure. Partial assignment of these resonances is given in the Experimental Section. The ^{1}H and ^{13}C NMR spectra of compound **3b**–**3d** are similar to those of **3a** except for the ester groups and the aryl moiety which exhibit characteristic signals with appropriate chemical shifts (see Experimental Section).

Although we have not established the mechanism of the reaction between the isocyanides and the acetylenic esters in the presence of the isocyanate **2** in an experimental manner, a possible explanation is proposed in Scheme 2.

On the basis of the well-established chemistry of isocyanides [26–31], it is reasonable to assume that the functionalized ethylenetetracarboxylic acid derivatives **3** apparently result from initial addition of the isocyanide to the acetylenic ester and subsequent attack of the resulting zwitterion **4** at the arylsulfonyl isocyanate or aryl isocyanate **2** to yield zwitterion **5**, followed by attack of H_2O on the zwitterion **5** to form **6** as intermediate. Then the latter rearranges under the reaction condition employed to produce the ethylenetetracarboxylic acid derivatives **3** (Scheme 2).

Experimental

Dimethyl-, diethyl acetylenedicarboxylates, and *tert*-butyl isocyanide were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-rapid analyzer; their results were in good agreement with the calculated data. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 meshes.

Dimethyl (E)-2-[(tert-butylamino)carbonyl]-3-[[(phenyl)-sulfonyl)amino]carbonyl]-2-butenedioate (**3a**, $C_{18}H_{22}N_2O_8S$)
Typical procedure: To a magnetically stirred solution of 0.14 g dimethyl acetylenedicarboxylate (1 mmol) and 0.18 g benzenesulfonyl isocyanate (1 mmol) in 3 cm^3 dry CH_2Cl_2 was added dropwise a solution of 0.08 g *tert*-butyl isocyanide (1 mmol) in 3 cm^3 dry CH_2Cl_2 at room temperature over 10 min. The reaction mixture was then stirred for 12 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using *n*-hexane:ethyl acetate mixture (4:1) as eluent to give **3a** as yellow crystals, mp 110–112°C, yield 0.28 g, 66%; IR (KBr): $\bar{\nu} = 3400$, 3295 (NH), 1727 (C=O), 1600 (C=C), 1547, 1433 (*Ar*), 1363, 1142 (SO_2), 1208, 1142, 1086, 1018 (C–O) cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.43$ (9H, s, ^{t}Bu), 3.56 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 7.43 (1H, t, $^{3}J_{HH} = 6.8$ Hz, NH), 7.51 (1H, t, $^{3}J_{HH} = 7.1$ Hz, 1CH of *Ar*), 7.59 (1H, t, $^{3}J_{HH} = 7.0$ Hz, NH), 7.83 (2H, t, $^{3}J_{HH} = 7.1$ Hz, 2CH of *Ar*), 7.97 (2H, d, $^{3}J_{HH} = 6.9$ Hz, 2CH of *Ar*) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta =$ 28.02 (CMe_3), 49.49 (O*Me*), 52.20 (O*Me*), 53.40 (CMe_3), 126.24 (C=C), 126.56 (2CH of *Ar*), 127.42 (2CH of *Ar*), 129.12 (C=C), 140.84 (C_{ipso} of SO_2), 156.75 ($CON^{t}Bu$), 157.68 (CO_2Me), 163.38 (CO_2Me), 168.69 (*C*ON) ppm; MS (EI, 70 eV): m/z (%) = 426 (M^+, 2), 353 (6), 299 (12), 241 (32), 196 (4), 141 (43), 138 (6), 105 (7), 77 (100), 57 (35), 41 (26).

Dimethyl (E)-2-[(tert-butylamino)carbonyl]-3-[[[(4-methyl-phenyl)sulfonyl]amino]carbonyl]-2-butenedioate
(**3b**, $C_{19}H_{24}N_2O_8S$)
Yellow crystals, mp 108–110°C, yield 0.31 g, 70%; IR (KBr): $\bar{\nu} = 3320$, 3315 (NH), 1733 (C=O), 1667 (C=C), 1585, 1430 (*Ar*), 1369, 1168 (SO_2), 1277, 1250, 1168, 1080 (C–O) cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.40$ (9H, s, ^{t}Bu), 2.43 (3H, s, *Me*), 3.38 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 7.28 (1H, t, $^{3}J_{HH} = 8.3$ Hz, NH), 7.32 (1H, t, $^{3}J_{HH} = 7.6$ Hz, NH), 7.73 (2H, d, $^{3}J_{HH} = 8.3$ Hz, 2CH of *Ar*), 8.04 (2H, d, $^{3}J_{HH} =$ 8.3 Hz, 2CH of *Ar*) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 21.65$ (*Me*), 27.92 (Me_3C), 52.87 (O*Me*), 53.58 (O*Me*), 56.68 (Me_3C), 129.49 (2CH of *Ar*), 129.91 (2CH of *Ar*), 133.75 (C=C), 136.71 (C=C), 145.06 (C_{ipso} of SO_2), 147.06 (C_{ipso} of CH_3), 156.71 ($CON^{t}Bu$), 158.26 (CO_2Me), 160.89 (CO_2Me), 161.83 (*C*ON) ppm; MS (EI, 70 eV): m/z (%) = 440 (M^+, 2), 407 (5), 343 (3), 299 (3), 270 (2), 238 (2), 197 (5), 155 (3), 108 (5), 91 (100), 77 (9), 57 (54), 41 (43).

Dimethyl (E)-2-[(tert-butylamino)carbonyl]-3-(3-toluidino-carbonyl)-2-butenedioate (**3c**, $C_{19}H_{24}N_2O_6$)
Brown powder, mp 168–170°C, yield 0.3 g, 80%; IR (KBr): $\bar{\nu} = 3425$, 3245 (NH), 1723 (CO_2Me), 1650 (CON), 1635 (CON), 1588 (C=C), 1540, 1444 (*Ar*) cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.30$ (9H, s, ^{t}Bu), 2.33 (3H, s, *Me*), 3.82 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 6.48 (1H, s, NH), 6.96 (1H, d, $^{3}J_{HH} = 7.5$ Hz, CH of *Ar*), 7.21 (1H, t, $^{3}J_{HH} = 7.8$ Hz, CH of *Ar*), 7.38 (1H, d, $^{3}J_{HH} = 7.9$ Hz, CH of *Ar*), 7.42 (1H, s, CH of *Ar*), 8.78 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 21.44$ (CH_3), 28.36 (Me_3C), 52.96 (Me_3C), 53.34 (O*Me*), 53.37 (O*Me*), 117.21 (CH of *Ar*), 120.68 (CH of *Ar*), 125.98 (CH of *Ar*), 128.86 (CH of *Ar*), 135.53 (C=C), 136.80 (C=C), 137.10 (C_{ipso} of NHCO), 138.98 (C_{ipso} of CH_3), 160.32 (*C*ON*Ph*), 161.69 ($CON^{t}Bu$), 164.29 (CO_2Me), 164.46 (CO_2Me) ppm; MS (EI, 70 eV): m/z (%) = 377 (M^+, 1), 304 (1), 270 (6), 244 (1), 214 (68), 182 (6), 171 (3), 107 (100), 91 (4), 77 (3), 57 (18), 53 (3), 41 (10).

Diethyl (E)-2-[(tert-butylamino)carbonyl]-3-(3-toluidinocarbonyl)-2-butenedioate (**3d**, $C_{21}H_{28}N_2O_6$)

Colorless crystals, mp 171–173°C, yield 0.26 g, 64%; IR (KBr): $\bar{\nu} = 3335$ (NH), 1727 (CO_2Me), 1656 (CON), 1670 (CON), 1617 (C=C), 1525, 1446 (*Ar*) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.29$ (9H, s, ^tBu), 1.30 (3H, t, $^3J_{HH} = 7.0$ Hz, OCH_2CH_3), 1.31 (3H, t, $^3J_{HH} = 6.9$ Hz, OCH_2CH_3), 2.32 (3H, s,CH_3), 4.27 (2H, q, $^3J_{HH} = 7.0$ Hz, OCH_2CH_3), 4.30 (3H, q, $^3J_{HH} = 6.9$ Hz, OCH_2CH_3), 6.34 (1H, s, NH), 6.94 (1H, d, $^3J_{HH} = 7.5$ Hz, CH of *Ar*), 7.19 (1H, t, $^3J_{HH} = 7.7$ Hz, CH of *Ar*), 7.33 (1H, d, $^3J_{HH} = 8.1$ Hz, CH of *Ar*), 7.39 (1H, s, CH of *Ar*), 8.59 (1H, s, NH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.77$ (OCH_2CH_3), 13.85 (OCH_2CH_3), 21.42 (CH_3), 28.36 (Me_3C), 52.92 (Me_3C), 62.67 (OCH_2CH_3), 62.69 (OCH_2CH_3), 117.17 (CH of *Ar*), 120.64 (CH of *Ar*), 125.96 (CH of *Ar*), 128.86 (CH of *Ar*), 136.01 (C=C), 136.45 (C=C), 136.99 (C_{ipso} of NHCO), 139.00 (C_{ipso} of CH_3), 160.24 (*C*O*Ph*), 161.99 (*C*ON^tBu), 163.84 (CO_2Et), 163.96 (CO_2Et) ppm; MS (EI, 70 eV): m/z (%) = 404 (M^+, 1), 336 (6), 335 (15), 334 (31), 298 (11), 242 (51), 186 (10), 168 (9), 142 (6), 107 (100), 91 (8), 77 (6), 57 (45), 41 (20).

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