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A Simple Approach to the Synthesis of 1,4-Bis(arylsulfonyl)tetrahydropyrazine-2,5-diones

Issa Yavari* and **Abdolali Alizadeh**

Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14115-175 Tehran, Iran

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Summary. The addition of triphenylphosphine to dimethyl acetylenedicarboxylate in the presence of arylsulfonylglycyl chlorides leads to 1,4-bis-arylsulfonyl-tetrahydropyrazine-2,5-diones and dimethyl (*E*)-2-chloro-2-butenedioate.

Keywords. Arylsulfonylglycyl chlorides; Dimethyl acetylenedicarboxylate; Dimethyl (*E*)-2-chloro-2-butenedioate; Tetrahydropyrazine-2,5-diones; Triphenylphosphine.

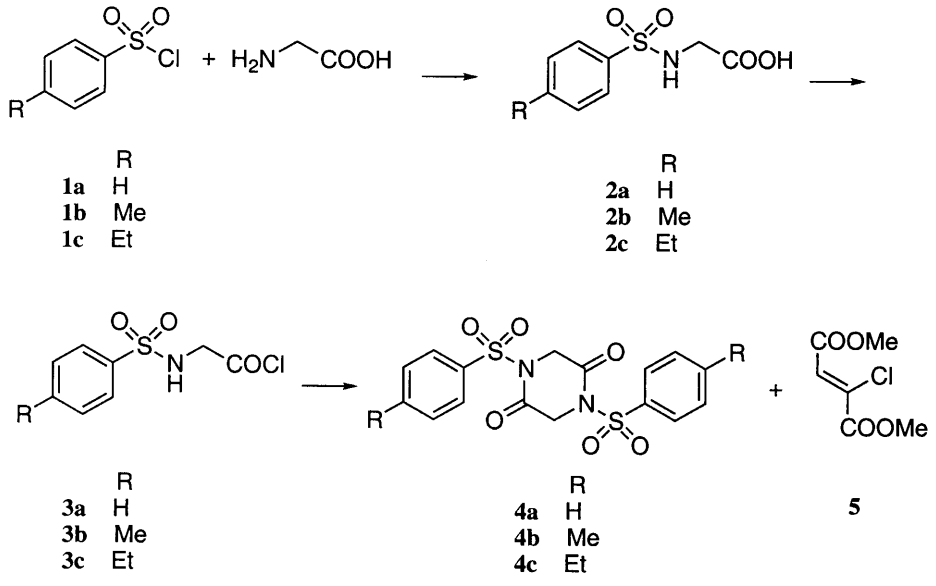
Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [1]. Diketopiperazines are used as advanced intermediates in the biosynthesis of ecteinascidins [2]. 2,5-Diketopiperazines have been utilized as chiral auxiliaries for asymmetric *Diels-Alder* reactions [3]. We report here an efficient synthetic route to 1,4-bis-arylsulfonyl-tetrahydropyrazine-2,5-diones (**4**) using triphenylphosphine, dimethyl acetylenedicarboxylate (*DMAD*), and arylsulfonylglycyl chlorides **3**.

Results and Discussion

The reaction of arylsulfonylglycyl chlorides **3** (prepared from **1** *via* **2**, see Scheme 1) with *DMAD* in the presence of triphenylphosphine proceeded spontaneously in dry tetrahydrofuran, and completed within a few minutes. ^{1}H and ^{13}C NMR spectra of the crude precipitate clearly indicated the formation of **4**. The presence of dimethyl (*E*)-2-chloro-2-butenedioate (**5**) in the liquid phase was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

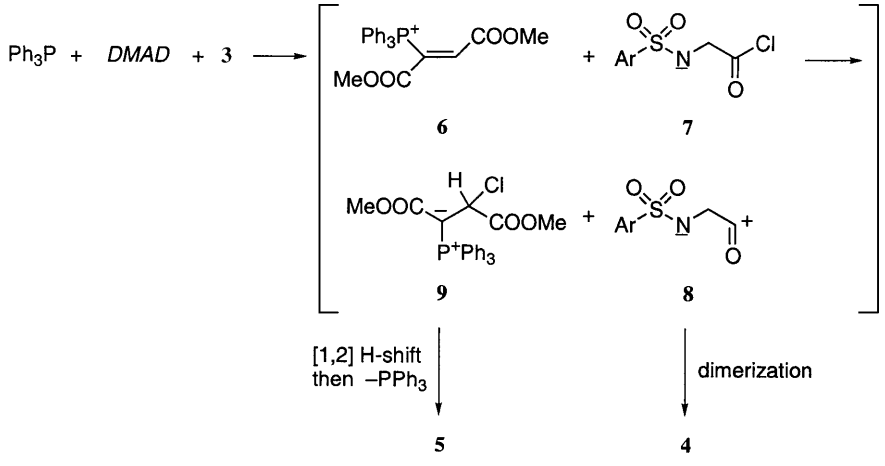
* Corresponding author. E-mail: isayavar@yahoo.com



Scheme 1

The structures of compounds **4a**–**4c** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion ($M^{+}+1$) peaks at $m/z = 395$, 423, and 451. The ^{1}H NMR spectrum of **4a** exhibited a single sharp line for the methylene ($\delta = 4.56$) protons. The ^{13}C NMR spectrum of **4a** showed six distinct resonances in agreement with the diketopiperazine structure. Partial assignment of these resonances is given in Experimental Section. The ^{1}H and ^{13}C NMR spectra of **4b** and **4c** are similar to those of **4a** except for the methyl and ethyl groups, which exhibit characteristic signals with appropriate chemical shifts.

Although the mechanism of the reaction between arylsulfonylglycyl chlorides **3** and *DMAD* in the presence of triphenylphosphine has not yet been established in an experimental manner, a possible mechanism is proposed in Scheme 2. On the



Scheme 2

basis of the well-established chemistry of trivalent phosphorus nucleophiles [4–12], it is reasonable to assume that the phosphorus ylide **9** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid. Then the positively charged ion is attacked by the chloride ion, to produce phosphorane **9**, which undergoes 1,2-H-shift and loss of Ph_3P to form the diester **5**. The product **4** apparently results from dimerization [13] of the intermediate **8** (see Scheme 2).

In conclusion, functionalized tetrahydropyrazine-2,4-diones **4a**–**4c** may be considered as potentially useful synthetic intermediates. The procedure described here may be an acceptable method for the preparation of tetrahydropyrazine-2,4-diones with variable functionalities. The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches [13].

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses (C, H, N) were performed using a Heraeus CHN–O-Rapid analyzer, the obtained values agreed favorably with the calculated ones. IR spectra were recorded on KBr discs on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500-Avance spectrometer at 500.1 and 125.7 in $CDCl_3$ or *DMSO-d*$_6$ using *TMS* as internal standard. Compounds **2** and **3** were prepared according to the published procedures [14–16]. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

1,4-Bis(phenylsulfonyl)tetrahydropyrazine-2,5-dione (**4a**, $C_{16}H_{14}N_2O_6S_2$)

General Procedure

To a magnetically stirred solution of 0.46 g benzenesulfonylglycyl chloride (2 mmol) and 0.28 g dimethyl acetylenedicarboxylate (2 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise a mixture of 0.52 g triphenylphosphine (2 mmol) in 10 cm^3 CH_2Cl_2 at $-5°C$ over 20 min. After 2 h the product was filtered, washed with 2×5 cm^3 cold CH_2Cl_2 and dried in vacuum. The filtrate residue was purified by silicagel (Merck 230–400 mesh) column chromatography by a hexane–ethyl acetate mixture as eluent. The compound eluted using a mixture of hexane–ethyl acetate (5:1) and was identified as dimethyl (*E*)-2-chloro-2-butenedioate (**5**) [17]. **5**: ^1H NMR (90 MHz, $CDCl_3$): $\delta = 3.82$ (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.20 (1H, s, CH) ppm; ^{13}C NMR (23 MHz, $CDCl_3$): $\delta = 54.0$ (OCH_3), 55.8 (OCH_3), 127.9 (CH), 135.2 (C–Cl), 162.23 (*C*O_2Me), 163.95 (*C*O_2Me) ppm. **4a**: White powder; yield: 0.64 g (82%); mp 294–296°C (decomp.); IR (KBr) $\nu_{max} = 1706$ (C=O), 1579 (Ph), 1356 and 1173 (SO_2) cm^{-1}; ^1H NMR (500.1 MHz, *DMSO-d*$_6$): $\delta = 4.56$ (4H, s, $2CH_2$), 7.63 (4H, t, $^3J = 7.7$ Hz, $4CH_{meta}$ of $2C_6H_5$), 7.80 (2H, sextet, $^3J = 7.5$ Hz, $^4J = 1.0$ Hz, $2CH_{para}$ of $2C_6H_5$), 7.98 (4H, d, $^3J = 8.0$ Hz, $4CH_{ortho}$ of $2C_6H_5$) ppm; ^{13}C NMR (125.7 MHz, *DMSO-d*$_6$): $\delta = 49.42$ ($2CH_2$), 128.83 ($4CH_{meta}$ of $2C_6H_5$), 129.72 ($4CH_{ortho}$ of $2C_6H_5$), 135.22 ($2CH_{para}$ of $2C_6H_5$), 137.66 ($2C_{ipso}$ of $2C_6H_5$), 161.8 (2C=O) ppm; MS: m/z (%) = 395 (1), 330 (5), 266 (13), 141 (42), 107 (21), 77 (100), 51 (42).

1,4-Bis[(4-methylphenyl)sulfonyl]tetrahydropyrazine-2,5-dione (**4b**, $C_{18}H_{18}N_2O_6S_2$)

White powder; yield 0.71 g (85%); mp 282–284°C (decomp.); IR (KBr) $\nu_{max} = 1700$ (C=O), 1591 (Ph), 1364 and 1180 (SO_2) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 2.47$ (6H, s, $2CH_3$), 4.49 (4H, s, $2CH_2$), 7.35 (4H, d, $^3J = 8.17$ Hz, 4CH of C_6H_4), 7.89 (4H, d, $^3J = 8.3$ Hz, 4CH of C_6H_4) ppm; ^{13}C NMR (125.7 MHz, *DMSO-d*$_6$): $\delta = 21.00$ ($2CH_3$), 49.35 ($2CH_2$), 128.90 ($4CH_{meta}$ of $2C_6H_5$),

130.13 ($4CH_{ortho}$ of $2C_6H_5$) 134.71 ($2C–SO_2$), 146.08 ($2C–CH_3$), 163.69 (2C=O) ppm; MS: m/z (%): 423 (2), 358 (25), 294 (SO_2), 155 (39), 120 (21), 91 (100), 65 (52).

1,4-Bis[(4-ethylphenyl)sulfonyl]tetrahydropyrazine-2,5-dione (**4c**, $C_{20}H_{22}N_2O_6S_2$)

White powder; yield 0.72 g (80%); mp 272–274°C (decomp.); IR (KBr): $\nu_{max} = 1701$ (C=O), 1584 (Ph), 1350 and 1165 (SO_2) cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.28$ (6H, t, $^3J = 7.5$ Hz, $2CH_3$), 2.76 (4H, q, $^3J = 7.5$ Hz, $2CH_2$), 4.49 (4H, s, $2CH_2$–N), 7.38 (4H, d, $^3J = 7.9$ Hz, 4CH of C_6H_4), 71.92 (4H, d, $^3J = 8.0$ Hz, 4CH of C_6H_4) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.45$ ($2CH_3$), 28.53 ($2CH_2CH_3$), 48.07 ($2CH_2$–N), 128.23 ($4CH_{meta}$ of 2Ar–SO_2), 128.60 ($4CH_{ortho}$ of 2Ar–SO_2), 133.59 ($2C–SO_2$), 151.91 (2C–Et), 161.84 (2C=O) ppm; MS: m/z (%) = 451 (4), 386 (44), 322 (25), 217 (17), 169 (58), 153 (13), 105 (100), 79 (65), 56 (33).

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