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Reactions of 1-Methylpyrrole Derivatives by Benzyne

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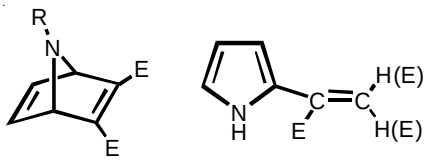
In general, benzyne is known that it reacts additionally by using-additional reaction on electrophilicity and pyrrole derivatives causes Diel-Alder reaction or Michael type addition reaction. Our study synthesized various Michael-type adducts **3a**,**b**, **4a**,**b**, **8** by the reaction of 1-methylpyrroles and dimethyl acetylenedicarboxylate (DMAD) (or diethyl acetylenedicarboxylate or diethyl azodicarboxylate) with $AlCl_3$ as a acid-catalyst. We have performed benzyne chemistry of 2- or 3-substituted pyrroles. Products are **6a-d**. Those results indicate that due to electrophilicity of benzyne, a wide variety of anionic and unchanged nucleophilic readily add to pyrrole to generate substituted pyrroles.

Keywords: Pyrrole, Benzyne, Diels-Alder reaction, Michael-type reaction, Electrophilicity.

INTRODUCTION

Benzynes are fascinating species that engage in a variety of interesting transformations, including nucleophilic addition reactions, [2+2] cycloadditions, Diels-Alder reactions and click chemistry[1-8]. Generally, pericyclic cyclo additions with benzyne, such as Diels-Alder reaction, are one of the most important methods for the construction of polyaromatic compounds[9-14]. Due to its extraordinary reactive ability, the reaction is observed with a very wide range of dienes including simple benzyne derivatives or other aromatic compounds. Due to its electrophilicity as the other important property, a wide variety of anionic and uncharged nucleophiles readily add to arynes to generate substituted arenes. Typical examples include addition of amines, sulfonamides, carbamates, phenols, carboxylic acid[15], β-keto-esters, malonate esters[16] and α-cyanocarbonyl compounds[17]. We here designed reaction of substituted pyrroles with benzyne through 2-(trimethylsilyl)phenyl trifluoromethane-sulfonate and cesium fluoride. Moreover the reactions of substituted pyrroles with electron-poor acetylenes (or azodicarboxylates) usually follow two different pathways: (a) a Diels-Alder cyclo addition of the pyrrole ring at both of its positions (C2/C5) to yield a 7-azabicyclo[2.2.1]heptane derivative or (b) a Michael-type addition of the pyrrole derivative at one of its positions(C2 or C5) to yield a vinyl-substituted pyrrole (**Scheme-I**)[18].

As part of our ongoing interest in diverse biologically active antibiotics, we sought to explore the use of benzyne(1,2-didehydrobenzene) for the elaboration of 1*H*-pyrrolylbut-2-enedioic acid dimethyl esters from 1*H*-pyrrolylfumarates.



E : $COOCH_3$

Scheme-I

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and uncorrected. Infrared spectra were recorded on a Perkin-Eimer 683 spectrophotometer. Ultraviolet and visible spectra were recorded on a Shimadzu double-beam spectrophotometer. NMR spectra were recorded on a Varian EM 360-A spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. Mass spectra were obtained by using a Finnigan model 3300 mass spectrometer.

General procedure for the reaction of N-methylpyrrole and dimethyl acetylenedicarboxylate (DMAD): A mixture of N-methylpyrrole (0.24 g, 3 mmol) and dimethyl acetylenedicarboxylate (0.43 g, 3 mmol) with $AlCl_3$ (1.33 g, 10 mmol) and CH_2Cl_2 (10 mL) was refluxed for 4 h. After 4 h, the reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was neutralized with 20 mL of $NaHCO_3$ and extracted with dichloromethane (30 mL × 2 times). The combined dichloromethane fractions were dried over Na_2SO_4 and concentrated

under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product. After flash chromatography, dimethyl 2-(1-methyl-*1H*-pyrrol-2-yl)fumarate (**3a**) (0.12 g, 28 %) and dimethyl 2-(1-methyl-1*H*-pyrrol-3-yl)fumarate (**4a**) (8.79×10^{-2}, 21 %) were obtained.

Dimethyl 2-(1-methyl-1*H*-pyrrol-2-yl)fumarate (3a): Isolated yield: 28 %; R_f: 0.41 (TLC eluent; EtOAc:*n*-hexane = 1:3, v/v); Mass (70 eV), *m/z* (rel. Int. %): 223 (98), 164 (100), 105 (69), 75 (22), 59 (19), 51 (13); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01 (s, 1H), 6.72 (t, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 2.4, 3.8 Hz, 1H), 6.15 (dd, *J* = 2.2, 3.4 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.64, 165.56, 135.30, 130.06, 125.10, 124.44, 111.95, 107.96, 52.98, 51.96, 34.46. Anal. calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.31; H, 5.82; N, 6.35.

Dimethyl 2-(1-methyl-1*H*-pyrrol-3-yl)fumarate (4a): Isolated yield: 21 %; R_f: 0.32 (TLC eluent; EtOAc:*n*-hexane = 1:3, v/v); Mass (70 eV), *m/z* (rel. Int. %): 223 (19), 164 (46), 105 (100), 75 (40), 59 (47), 51 (32); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.78 (t, *J* = 2.1 Hz, 1H), 6.44 (dd, *J* = 1.7, 3.9 Hz, 1H), 6.17 (dd, *J* = 2.7, 3.8 Hz, 1H), 5.98 (s, 1H), 3.94 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.08, 165.94, 140.78, 129.78, 126.73, 116.30, 110.97, 109.12, 52.79, 51.95, 36.67. Anal. calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.28; H, 5.83; N, 6.34.

Diethyl 2-(1-methyl-1*H*-pyrrol-2-yl)fumarate (3b): Isolated yield: 21 %; R_f: 0.33 (TLC eluent; EtOAc: *n*-hexane = 1:5, v/v); Mass (70 eV), *m/z* (rel. Int. %): 251 (10), 178 (9), 150 (16), 134 (10), 105 (59), 82 (83), 77 (46), 63 (57), 51 (100); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.00 (s, 1H), 6.71 (t, *J* = 2.04 Hz, 1H), 6.16 (dd, *J* = 1.72, 3.80 Hz, 1H), 6.13 (dd, *J* = 2.72, 3.76 Hz, 1H), 4.27 (q, *J* = 7.16 Hz, 2H), 4.10 (q, *J* = 7.16 Hz, 2H), 3.47 (s, 3H), 1.31 (t, *J* = 7.16 Hz, 3H), 1.15 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.09, 165.32, 135.25, 130.56, 125.34, 124.15, 111.81, 107.84, 61.93, 60.87, 34.43, 14.12, 13.98. Anal. calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.19; H, 6.77; N, 5.52.

Diethyl 2-(1-methyl-1*H*-pyrrol-3-yl)fumarate (4b): Isolated yield: 22 %; R_f: 0.22 (TLC eluent; EtOAc: *n*-hexane = 1: 5, v/v); Mass (70 eV), *m/z* (rel. Int. %): 251 (6), 178 (7), 150 (16), 134 (10), 105 (100), 82 (97), 77 (60), 63 (67), 51 (86); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.77 (t, *J* = 2.04 Hz, 1H), 6.44 (dd, *J* = 1.72, 3.76 Hz, 1H), 6.16 (dd, *J* = 2.72, 3.76 Hz, 1H), 5.95(s, 1H), 4.40 (q, *J* = 7.16 Hz, 2H), 4.21 (q, *J* = 7.16 Hz, 2H), 3.75 (s, 3H), 1.38 (t, *J* = 7.16 Hz, 3H), 1.30 (t, *J* = 7.16 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.59, 165.40, 140.71, 129.51, 126.93, 116.01, 111.51, 108.98, 61.86, 60.59, 36.68, 14.20, 13.94. Anal. calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.17; H, 6.78; N, 5.50.

Diethyl 1-(1-methyl-1*H*-pyrrol-3-yl)hydrazine-1,2-dicarboxylate (8): Isolated yield: 40 %; R_f: 0.35 (TLC eluent; EtOAc: *n*-hexane = 1: 5, v/v); Mass (70 eV), *m/z* (rel. Int. %): 255 (4), 182 (8), 136 (6), 95 (100), 67 (80), 53 (41); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (br s, 1H), 6.53 (t, *J* = 2.04 Hz, 1H), 6.08 (m, 2H), 4.23 (q, *J* = 7.16 Hz, 4H), 3.61 (s, 3H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 155.92, 129.19, 120.08, 106.54, 104.65, 63.24, 62.05, 32.78, 14.38, 14.34. Anal. calcd. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.75; H, 6.67; N, 5.51.

General procedure for the reaction of benzyne: To a solution of MeCN (5 mL), dimethyl 2-(1-methyl-*1H*-pyrrol-2-yl)fumarate (4.7×10^{-2}, 0.2 mmol) and 2-(trimethylsilyl) phenyl trifluoromethanesulfonate (1.43×10^{-1} g, 0.48 mmol) was added CsF (0.4 mmol, 2eq). The reaction mixture was allowed to stir at room temperature and monitored by TLC to establish completion of the reaction. After the reaction mixture was filtered by celite, it was extracted with H_2O (10 mL) and CH_2Cl_2 (30 mL). The combined CH_2Cl_2 fractions were dried over Na_2SO_4 and concentrated under reduced pressure.

Products were purified by column chromatography (EtOAc:*n*-hexane = 1:5, v/v) to give the corresponding pyrrole derivatives **6a** and **6b**.

Dimethyl 2-(1-methyl-3,5-diphenyl-1*H*-pyrrol-2-yl)fumarate (6a): Isolated yield: 28 %; R_f: 0.58 (TLC eluent; EtOAc: *n*-hexane = 1: 3, v/v); Mass (70 eV), *m/z* (rel. Int. %): 375 (100), 315 (47), 301 (13), 284 (20), 256 (28), 241 (39), 215 (6), 150 (7), 120 (6), 106 (6), 77 (7); ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.33 (dd, *J* = 1.4, 7.84 Hz, 1H), 7.65 (dd, *J* = 1.36, 7.52 Hz, 1H), 7.44 (m, 2H), 7.36 (d, *J* = 7.52 Hz, 1H), 7.31 (d, *J* = 7.52 Hz, 1H), 7.30 (s, 1H), 7.17 (m, 2H), 6.75 (t, *J* = 7.52 Hz, 1H), 6.65 (dd, *J* = 1.04, 8.88 Hz, 2H), 3.78 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 166.90, 165.02, 149.99, 145.90, 143.81, 132.99, 131.02, 130.71, 130.42, 128.91, 127.02, 126.65, 126.27, 125.30, 124.32, 124.16, 117.45, 113.81, 53.06, 51.81, 40.30. Anal. calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.59; H, 5.61; N, 3.68.

2-(1-Methyl-5-phenyl-1*H*-pyrrol-2-yl)-but-2-enedioic acid dimethyl ester (6b): Isolated yield: 11 %; R_f: 0.33 (TLC eluent; EtOAc:*n*-hexane = 1: 3, v/v); Mass (70 eV), *m/z* (rel. Int. %): 299 (100), 239 (93), 255 (53), 208 (41), 181 (80), 152 (37), 139 (51), 59 (13); ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.80 (dd, *J* = 3.76, 6.16 Hz, 1H), 7.50 (m, 3H), 7.42 (dd, *J* = 3.08, 6.16 Hz, 1H), 7.21 (d, *J* = 7.84 Hz, 1H), 6.59 (d, *J* = 7.84 Hz, 1H), 6.18 (s, 1H), 3.72 (s, 3H), 3.51 (s, 3H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 167.81, 165.54, 145.22, 144.61, 132.06, 127.99, 126.16, 125.46, 124.62, 123.04, 121.56, 120.19, 102.76, 52.88, 51.72, 30.79. Anal. calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.23; H, 5.68; N, 4.63.

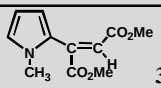
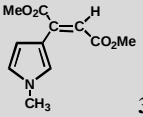
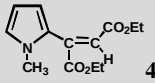
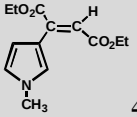
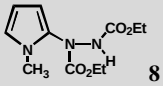
Dimethyl 2-(1-methyl-2,5-diphenyl-1*H*-pyrrol-3-yl)fumarate (6c) and dimethyl 2-(1-methyl-4,5-diphenyl-1*H*-pyrrol-3-yl)fumarate (6d) (isomer): Isolated yield: 43 %; R_f: 0.38 (TLC eluent; EtOAc:*n*-hexane = 1:3, v/v); Mass (70 eV), *m/z* (rel. Int. %): 375 (3), 315 (5), 256 (7), 241 (15), 150 (11), 121 (11), 106 (13), 77 (33), 59 (100). The mixture exists as a 3:2 mixture of isomer: Signals corresponding to the major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 8.18 (d, *J* = 8.56 Hz, 1H), 7.94 (d, *J* = 8.88 Hz, 1H), 7.57-7.15 (m, 6H), 6.76 (t, *J* = 7.52 Hz, 1H), 6.65 (d, *J* = 7.88 Hz, 2H), 6.24 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.39 (s, 3H). Representative signals corresponding to the minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 1.40 Hz, 1H), 7.65 (m, 1H), 7.57-6.64 (m, 10H), 3.78 (s, 3H), 3.51 (s, 3H), 6.76 (t, *J* = 7.52 Hz, 1H), 6.65 (d, *J* = 7.88 Hz, 2H), 6.24 (s, 1H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 168.01, 166.89, 165.21, 165.00, 149.97, 149.80, 147.45, 147.10, 145.90, 143.81, 132.97, 132.50, 131.39, 131.00, 130.88, 130.69, 130.40, 128.95, 128.91, 127.22,

127.03, 126.69, 126.63, 126.26, 125.78, 125.29, 124.39, 124.31, 124.22, 124.15, 124.09, 53.05, 52.81, 52.18, 51.80, 40.30. Anal. calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.56; H, 5.60; N, 3.71.

RESULTS AND DISCUSSION

1-Methylpyrrole examined in our laboratory gave two 1:1 Michael-type adducts with acetylenedicarboxylate (DMAD) under the conditions specified in Table-1. Instead of [4+2] cycloadducts or 1:2 Michael-type adduct, Michael-type adducts **3a** (28 %) and **4a** (21 %) added at C-2(α position) or C-3(β position) were produced. But, in case of 1-phenylpyrrole with dimethyl acetylenedicarboxylate in ether solvent without $AlCl_3$,1:1 (23 %) and 1:2 (26 %) [4+2] cycloadducts were obtained. The specific outcome of two reactions is strongly dependent on the substituent at the nitrogen atom.

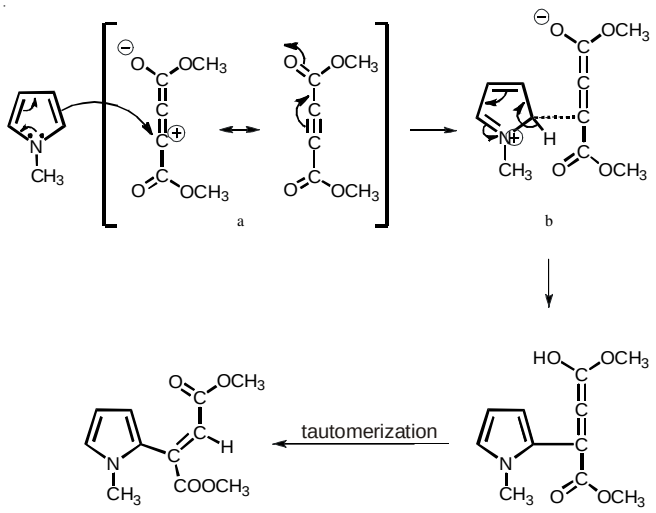
TABLE-1
REACTION AND YIELDS OF MICHAEL-TYPE ADDUCTS **3**, **4**, **8**

Entry	1:1 adduct	Time (h)	Yield* (%)
1	 **3a**	4	28
2	 **3b**	4	21
3	 **4a**	4	22
4	 **4b**	4	21
5	 **8**	4	42

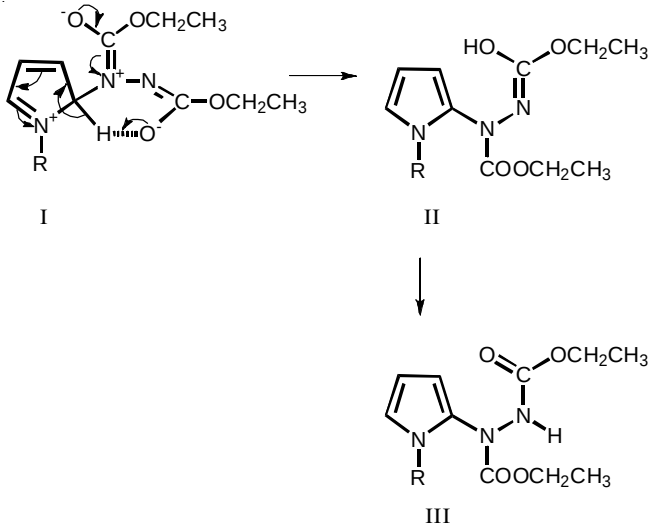
*Isolated yield

1-Substituted pyrroles bearing aryl or electron withdrawing substituents at the nitrogen atom react with dimethyl acetylenedicarboxylate to give [4+2] cycloadducts. In contrast, when the 1-substituent is an alkyl group, as in 1-methylpyrrole, Michael-type adducts are formed. The reaction of 1-phenylpyrrole and diethyl azodicarboxylate (DADC) with $AlCl_3$ in dichloromethane was formed no [4+2] cycloadduct but 1:1 Michael-type adduct **8** (42 %). Plausible mechanisms for the formation of Michael-type adduct from dimethyl acetylenedicarboxylate or diethyl azodicarboxylate are shown in **Schemes II** and **III**. The addition of dimethyl acetylenedicarboxylate or diethyl azodicarboxylate to 1-methyl pyrrole is considered initially to form a zwitterionic intermediate I and b (**Schemes II** and **III**).

An α-hydrogen may then be transferred intramolecularly through a six-membered transition state in the aprotic solvent as shown in **Schemes I** and **II**. The facile solvation or intermolecular protonation by the protic solvent may be an explanation for the better yield. Thus, in protic solvents, it is proposed that the protonated dimethyl acetylenedicarboxylate (**Scheme-II**) or diethyl azodicarboxylate (**Scheme-III**) formed by



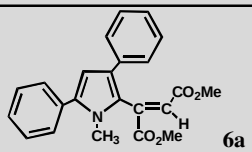
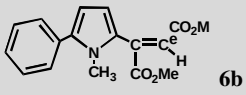
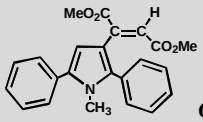
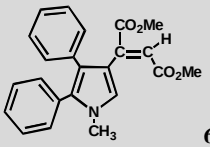
Scheme-II: Plausible mechanism for formation of Michael-type adduct by using dimethyl acetylenedicarboxylate



Scheme-III: Plausible mechanism for formation of Michael-type adduct by using diethyl azodicarboxylate

protonation of carbony of oxygen of dimethyl acetylenedicarboxylate or diethyl azodicarboxylate facilitates nucleophilic attack of π electron of pyrrole ring. To elucidate exact reactivity of dimethyl 2-(1-methyl-1*H*-pyrrol-2-yl)fumarate (**3a**) or dimethyl 2-(1-methyl-1*H*-pyrrol-3-yl)fumarate (**4a**) with 2-(trimethylsilyl)phenyltrifluoro-methanesulfonate, we have performed benzyne chemistry of 2- or 3-substituted pyrroles. The reaction of dimethyl 2-(1-methyl-1*H*-pyrrol-2-yl)fumarate (**3a**) and 2-(trimethylsilyl)-phenyltrifluoromethanesulfonate with cesium fluoride was formed dimethyl 2-(1-methyl-3,5-diphenyl-1H-pyrrol-2-yl)fumarate (**6a**) and 2-(1-methyl-5-phenyl-1H-pyrrol-2-yl)-but-2-enedioic acid dimethyl ester (**6b**). And also the reaction of dimethyl 2-(1-methyl-1*H*-pyrrol-3-yl)fumarate (**4a**) was formed dimethyl 2-(1-methyl-2,5-diphenyl-1*H*-pyrrol-3-yl)fumarate (**6c**) and dimethyl 2-(1-methyl-4,5-diphenyl-1*H*-pyrrol-3-yl)fumarate (**6d**) (Table-2). Those results indicate that due to electrophilicity of benzyne, a wide variety of anionic and uncharged nucleophiles readily add to pyrrole to generate sunstituted pyrroles.

TABLE-2
REACTION TIME AND YIELDS OF **6a-d**

Entry	1:1 adduct	Product	Time (h)	Yield* (%)
1	**3a**	 **6a**	24	28
2	**3b**	 **6b**	24	11
3	**4a**	 **6c**	24	43
4	**4b**	 **6d**	Isomers	

*Isolated yield

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