FIRST SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME N-[4-(ETHOXYCARBONYL)-1-SUBSTITUTEDARYL-1,2,3-TRIAZOL-5-YL]N'-PHENYLCARBODIIMIDES AND THEIR DERIVATIVES

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Abstract: Some new N-[4-(ethoxycarbonyl)-1-substituted aryl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides were prepared starting from 1-substituted aryl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene) amino] -1, 2, 3 –triazoles 2 (iminophosphoranes) and phenyl isocyanate by using aza-Wittig reaction, which were reacted with alcohol or amine to give the compounds 4 in moderate or good yields. The new products were characterized by MS, NMR, ^{1}HNMR methods and elemental analysis.

Over past decades, the aza-Wittig methodology (1-4) has received increased attention for its utility in the formation of C=N bonds and heterocumulene bonds. As well as other workers recently demonstrated that the aza-Wittig reaction is powerful and useful tool for the synthesis of heterocycle (5-6), including nature products such as DC-81(7-8), l-vasicinone(9), (-)-benzomalvon A(10), and (+)-fumiquinazoline G(12)etc. On the other hand, the aza-Wittig reaction followed by electrocyclization, cyclization or heterocyclization, i. e., the tandem aza-Wittig methodology, has been utilized for the synthesis of many important heterocycles by Molina(3), Wamhoff(4), Quintela(13), Satio(14-15), and Noguchi(16-17) and coworkers. We were interested in the synthesis of heterocycles using iminophosphoranes derivatives and their biological activities,

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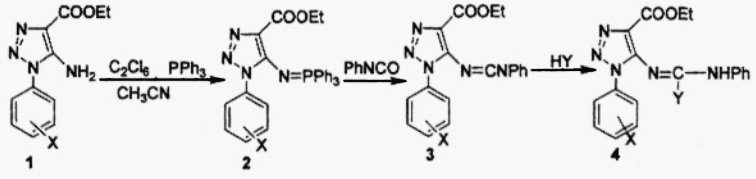
because they can react with carbonyl compounds to form Schiff base, carbon dioxide to give isothiocyanates and carbon disulfide to give isothiocyanates. They can also react with acids, alkylhalids, isocyanates, isothiocyanates and ozone etc(18). As a continuation of our study, in this paper, we report the synthesis of N- [4-(ethoxycarbonyl)-1- substituted phenyl-1, 2, 3 -triazol-5-yl] N'-phenylcarbodiimides and their derivatives from 1-substituted aryl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene) amino] -1, 2, 3 –triazoles 2.

The iminophosphoranes 2 serve as a good building block for heterocycles; they can be easily synthesized from the readily available 1-substituted aryl –4-ethoxycarbonyl –5-amino-1, 2, 3-triazole 1. The iminophosphoranes 2 were treated with phenyl isocyanate in refluxing acetonile to give N- [4-(ethoxycarbonyl) -1- substituted phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides 3 in 57-71% yield. The carbodiimides 3 were treated with alcohol or amine to give N-[4-(ethoxycarbonyl) -1- substituted phenyl-1, 2, 3-triazol-5-yl] -O-methyl-N'-phenylisourea etc. (compounds 4) in moderate to good yields (Scheme 1). The new products were characterized by MS, NMR, ^{1}HNMR methods and elemental analysis.



For compounds 1, 2, 3: a : X=H, b: 3'-NO_2, c: 4'-Cl, d: 3'-Br, e: 4'-CH_3, f: 4'-OCH_3, For 4a: X=4'-OCH_3, Y=$OCH(CH_3)_2$, 4b: X=CH_3, Y=OCH_3, 4c: X=3'-NO_2, Y=OCH_3, 4d: 3'-NO_2, Y=$N(C_2H_5)_2$, 4e: X=OCH_3, Y=OC_2H_5, 4f: X=3'-NO_2, Y=$OCH(CH_3)_2$

Further reactions of compound 3 and compound 4 are now in progress. We also tested their antibacterial activity of these new compounds. The antibacterial activity of a solution of compounds 3 in dimethyl sulfoxide (0.01%) was measured using paper plate method at 37℃(19). The experimental results show that propagation of a variety of bacteria was inhibited in varying degrees. The propagation of klebsiella pneumaniae ozaenae, Pseudomonas aeruginosa and Escherichia coli were weakly inhibited by compounds 3a-3k. Pseudomonas aeruginosa was stronger inhibited by3a-3k, 4d, 4e. A further experiment on the inhibition on bacteria is now in progress.

In conclusion, we describe an synthesis of carbodiimides 3 and their derivatives 4 from readily

available starting materials such as iminophosphoranes and phenyl isocynates. New compounds may be useful compounds in biochemistry and synthetic chemistry since these products display a range of biological activities and synthesis potential.

Experimental

Melting points were determined on X4 micromelting point apparatus (China) and uncorrected. Microanalyses were performed on Vario EL Elemental Analyzer. ^{1}H NMR spectra were recorded on a Bruker 400A instrument ($CDCl_3$, DMSO-d_6) with TMS as internal reference. IR spectra were recorded (KBr) using Bruker IFS 120 HP spectrophotometer. Mass spectra were recorded on HP6890/5373GS/MC. Acetonitrile was distilled over phosphorus pentaoxide; All other reagents were purchased from the market and purification by standard methods.

General Procedure

1-Substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazoles 1 was prepared according to the literature procedure(20). The iminophosphoranes 2 were prepared according to the literature procedure (19)in high yields.

Synthesis of N-[4-(ethoxycarbonyl)-1- substituted phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides

To a stirred solution of compounds 2 (0.5mmol) in anhydrous acetonitrile (15mL) was added phenyl isocyanate (0.6mmol) at room temperature under N_2. After the mixture was refluxed for 4h, the solvent was removed under reduced pressure; the residue was purified on a silica gel TCL column (EtOAC/hexane) to give compounds 3.

3a: N-[4-(ethoxycarbonyl)-1-phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides: m.p. 197-199℃, ^{1}H NMR (DMSO-d_6) δ 1.28(t, *J*=6.2 Hz, 3H), 4.27 (q, *J*=6.4 Hz, 2H), 6.95-7.67 (10H, m); 8.63(1H, s), IR (KBr) v: 3286 (N-H), 1697 (C=O), 1648(C=N), 998 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):333 (12.4), 304 (16.3), 183 (9.7), 143 (23.6), 108 (100) 77(69.6). Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86, H, 4.50, N, 21.02; Found C, 64.76, H, 4.45, N, 20.95.

3b: N-[4-(ethoxycarbonyl)-1-(3'-nitro) phenyl-1, 2, 3-triazol-5-yl] N' – phenylcarbodiimides: m.p. 202-203 ℃, ^{1}H NMR (DMSO-d_6) δ 1.21(t, *J*=6.2 Hz, 3H), 4.20 (q, *J*=6.4 Hz, 2H), 7.03-8.20 (9H, m); 9.08(1H, s), IR (KBr) v: 3276 (N-H), 1687 (C=O), 1627(C=N), 1003 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 378 (10.8), 349 (11.8), 333 (17.4), 143 (34), 108 (100) 77(45). Anal. calcd for $C_{18}H_{14}N_6O_4$: C, 57.14, H, 3.70, N, 22.22; Found C, 57.03, H, 3.64, N, 22.15.

3c: N-[4-(ethoxycarbonyl)-1-(4'-chloro) phenyl-1, 2, 3-triazol-5-yl] N'- phenylcarbodiimides: m.p. 217-218℃, ^{1}H NMR (DMSO-d_6) δ: 1.31(t, *J*=6.2 Hz, 3H), 4.32 (q, *J*=6.4 Hz, 2H), 6.95-7.83 (9H, m); 9.0 (1H, s), IR (KBr) ν: 3278 (N-H), 1688 (C=O), 1625(C=N), 987 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):368(11.7), 339 (17.5), 323 (10.7), 183 (37.2), 143 (44), 108 (100), 77 (53.1); Anal. calcd for $C_{18}H_{14}ClN_5O_2$: C, 58.78, H, 3.81, N, 19.05; Found C, 58.65, H, 3.75, N, 18.97.

3d: N-[4-(ethoxycarbonyl)-1-(3'-bromo) phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides: m.p. 205-206℃, ^{1}H NMR (DMSO-d_6) δ: 1.26(t, *J*=6.2 Hz, 3H), 4.29 (q, *J*=6.4 Hz, 2H), 6.98-7.63 (9H, m); 9.2 (1H, s), IR (KBr) ν: 3280 (N-H), 1692 (C=O), 1630(C=N), 993 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 412(11.4), 383(9.8), 367(13.5), 183(24.7), 108(100) 77(41.5); Anal. calcd for $C_{18}H_{14}BrN_5O_2$: C, 52.43, H, 3.40, N, 17.00; Found C, 54.34, H, 3.34, N, 16.92.

3e: N-[4-(ethoxycarbonyl)-1-(4'-methyl) phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides: m.p. 197-199℃, ^{1}H NMR (DMSO-d_6) δ: 1.26(t, *J*=6.2 Hz, 3H), 2.33(s, 3H), 4.13 (q, *J*=6.4 Hz, 2H), 7.04-7.63 (9H, m); 8.64(1H, s), IR (KBr) ν: 3285 (N-H), 1690 (C=O), 1629(C=N), 993 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 347(19.2), 318 (6.8), 302 (14.2), 183(26.4), 108(100), 77(72.1);Anal. calcd for $C_{19}H_{17}N_5O_2$: C, 65.70, H, 4.90, N, 20.17; Found C, 65.60, H, 4.84, N, 20.10.

3f: N-[4-(ethoxycarbonyl)-1-(4'-methoxyl) phenyl-1, 2, 3-triazol-5-yl] N'-phenylcarbodiimides: m.p. 216-217℃, ^{1}H NMR (DMSO-d_6) δ: 1.16(t, *J*=6.2 Hz, 3H), 3.8(s, 3H), 4.12 (q, *J*=6.4 Hz, 2H), 6.92-7.64 (9H, m); 8.9 (1H, s), IR (KBr) ν: 3285 (N-H), 1691 (C=O), 1628(C=N), 992 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 363(11.3), 334(9.6), 318(14.2), 183(23.6), 108(100), 77(33); Anal. calcd for $C_{19}H_{17}N_5O_3$: C, 62.81, H, 4.68, N, 19.28; found C, 62.69, H, 4.62, N, 19.20.

Synthesis of compounds 4:

To a stirred solution of compounds 2 (0.5mmol) in anhydrous acetonitrile (15mL) was added phenyl isocyanate (0.6mmol) at room temperature under N_2. After the mixture was refluxed for 4h, the solvent was removed under reduced pressure, 15mL anhydrous alcohol or amine was added to the residue, and refluxed with stirring 1h, excess alcohol and amine was evaporated under reduced pressure, the residue was purified on a silica gel TCL column (EtOAC/hexane) to give compounds 4

4a: N-[4-(Ethoxycarbonyl)-1-(4'-methoxyl) phenyl-1, 2, 3-triazol-5-yl]-O-isopropyl- N'-phenylisourea: m.p. 188-190℃, ^{1}H NMR (DMSO-d_6) δ: 1.08(d, *J*=6.2 Hz, 6H), 1.23(t, J=6.2, 3H), 3.9 (s, 3H), 4.14 (q, *J*=6.4 Hz, 2H), 5.0(m, 1H), 7.15-7.64 (9H, m); 8.6 (1H, s), IR (KBr) ν: 3288

(N-H), 1722 (C=O), 1641(C=N), 990 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 423(14.6), 394(17.7), 378 (9.9), 183(34.1), 108(100), 77(69.4). Anal. calcd for $C_{22}H_{25}N_5O_4$: C, 62.41 H, 5.91, N, 16.55; Found C, 62.30, H, 5.85, N, 16.47.

4b: N-[4-(ethoxycarbonyl)-1-(4'-methyl) phenyl-1, 2, 3-triazol-5-yl] -O-methyl- N'-phenylisourea: m.p. 186-188℃, ^{1}H NMR (DMSO-d_6) δ: 1.17 (t, *J*=6.2 Hz, 3H), 2.3 (s, 3H), 3.80 (s, 3H) , 4.2 (q, *J*=6.4 Hz, 2H), 6.95-7.50 (m ,9H); 9.1(s ,1H), IR (KBr) ν: 3291 (N-H), 1712 (C=O), 1648(C=N), 992 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 379(23.4), 350 (9.6), 334 (12), 183(51.3), 108(100), 77(46.5);Anal. calcd for $C_{20}H_{21}N_5O_3$: C, 63.32, H, 5.54, N, 18.47; found C, 63.20, H, 5.48, N, 18.40.

4c: N- [4-(ethoxycarbonyl)-1-(3'-nitro) phenyl-1, 2, 3-triazol-5-yl]-O-methyl -N'-phenylisourea: m.p. 194-195 ℃, ^{1}H NMR (DMSO-d_6) δ: 1.21(t, *J*=6.2 Hz, 3H), 3.92(s, 3H), 4.25 (q, *J*=6.4 Hz, 2H), 7.19(s, 5H), 7.81-8.32 (4H, m); 9.26(s, 1H), IR (KBr) ν: 3314 (N-H), 1724 (C=O), 1639(C=N), 1012 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 410 (24.2), 381 (11.5), 365 (23.1), 183(52.1), 108(100), 77(58.3); Anal. calcd for $C_{19}H_{18}N_6O_5$: C, 55.61, H, 4.39, N, 20.49; Found C, 55.50, H, 4.33, N, 20.41.

4d: N-[4-(ethoxycarbonyl)-1-(3'-nitro) phenyl-1, 2, 3-triazol-5-yl]-N", N"-diethylamino-N' -phenylisourea: m.p. 203-205℃, ^{1}H NMR (DMSO-d_6) δ: 1.17(m, 9H), 3.6(q, J=6.4Hz, 4H), 4.28 (q, *J*=6.4 Hz, 2H), 6.56-8.09(m, 9H), 8.44(s, 1H), IR (KBr) ν: 3309 (N-H), 1692 (C=O), 1637(C=N), 1014 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 451 (10.3), 422 (13.4), 406 (42.1), 334 (33.4), 183(23), 108(100), 77(45); Anal. calcd for $C_{22}H_{25}N_7O_4$: C, 58.54, H, 5.54, N, 21.73; Found C, 58.43, H, 5.48, N, 21.65.

4e N-[4-(ethoxycarbonyl)-1-(4'-methoxyl) phenyl-1, 2, 3-triazol-5-yl]-O- ethyl-N' –phenylisourea: m.p. 215-217℃, ^{1}H NMR (DMSO-d_6) δ: 1.14 (t, *J*=6.2 Hz, 3H), 3.76 (s, 3H), 3.80(s, 3H), 4.2 (q, *J*=6.4 Hz, 2H), 7.01-7.63 (m ,9H); 9.01(s ,1H), IR (KBr) ν: 3294 (N-H), 1693 (C=O), 1628(C=N), 991 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 409 (8.8), 380(24.1), 364(13.1), 183(26.6), 108(108), 77(66.4); Anal. calcd for $C_{21}H_{23}N_5O_4$: C, 61.61, H, 5.62, N, 17.11; found C, 61.49, H, 5.56, N, 17.03.

4f: N-[4-(ethoxycarbonyl)-1-(3'- nitro) phenyl-1, 2, 3-triazol-5-yl]-O-isopropyl -N'-phenylisourea: m.p. 195-197 ℃, ^{1}H NMR (DMSO-d_6) δ: 1.24(m, 9H), 4.20 (q, *J*=6.4 Hz, 2H), 5.2(m, 3H), 7.12-8.20 (m, 9H); 9.0(s, 1H), IR (KBr) ν: 3266 (N-H), 1718 (C=O), 1640(C–N),

1000 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 438 (17.2), 409 (11), 393 (9.7), 183(45), 108(100), 77(68). Anal. calcd for $C_{21}H_{22}N_6O_5$: C, 57.53, H, 5.02, N, 19.18; Found C, 57.42, H, 4.96, N, 19.10.

Acknowledgment: This work was supported by National Natural Science Foundation of China (No. 29933050) and Educational Committee Foundation of Tianjin

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Received on May 6, 2003