Synthesis and Antibacterial Activity of some Heterocyclic β–Enamino Ester Derivatives with 1, 2,3-triazole

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Abstract: Some new heterocyclic β-enamino ester derivatives with v-triazole were preparaed, and their inhibiting effects on various bacteria were also investigated.

Heterocyclic β–enamino esters have been proved to be versatile synthons for the construction of manifold heterocondensed systems(1). Among them, heterocyclic β-enamino containing 1,2,3-triazole are of great interest because of their high biologocal activity and pharmacological property. For example, as potential medicinal agents(2), they are currently used in research field on virus(3), in minishinflammatory(5), and used for antishock,anesthesia(4), especially in antitumor and antimicrobial activity(6).

We are interested in the design of new 1,2,3-triazole derivatives and their biological activities, and have prepared some heterocyclic β–enamino esters with 1,2,3-triazole core, an enamino double bond between an ester group and an adjacent amino . Because of their extensive aromaticity the activity of amino group on these molecules are sharply decreased. We attempt to obtain some new

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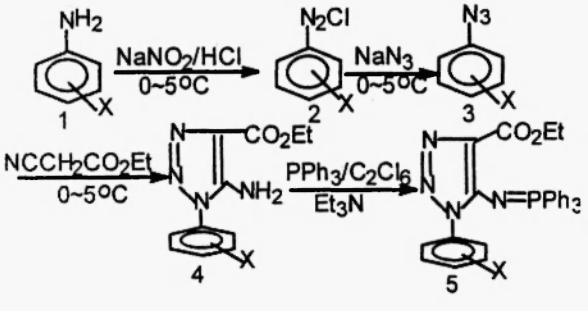
1,2,3-triazole derivatives (iminophosphoranes) with better reactivity through the reaction of the heterocyclic β–enamino ester with triphenylphosphine. These iminophosphoranes which are becoming more and more important in organic synthesis, can react with carbonyl compounds to form Schiff base, carbon dioxide to give isothiocyanates and carbon disulfide to give isothiocyanates. They can also react with acids, alkylhalids, isocyanates, isothiocyanates and ozone. They can be used in Dials-Alder reaction and in the synthesis of heterocyclic compounds(1). Therefore, we designed and sythesized some new heterocyclic β-enamino ester derivatves—iminophosphoranes and tested their antibacterial activity.

In this paper, we report the preparation of 1-substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazole (compounds 4), 1-substituted aryl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene) amino]-1,2,3-triazole(iminophosphorane) (compounds 5), and the results on their antibacterial activity. Compounds 4c-4f and compounds 5 have not report in the literature. The products were characterized by IR, HNMR, MS and also through elemental analysis.

The heterocyclic β-enamino esters 4a-4i were prepared from 1-substituted aniline by diazotization reaction, treated with sodium azide, and then [2+3]cylization with moderate to good yields. Subsequently, heterocyclic β-enamino esters were converted into the correspounding iminophosphorane dervatives 5a-5i by treatment with triphenyphosphorane, hexachloroethane and triethylamine system (the Wamhoff methed(8)) in good yields(**Scheme 1**).



Scheme 1: For X=4f, p-OC_2H_5; 4g, m-Br; 4h, p-$COCH_3$; 4i, m-F; 5a, p-OCH_3; 5b, m-NO_2; 5c, p-NO_2; 5d, p-CH_3; 5e, p-Cl; 5f, p-OCH_3; 5g, m-Br; 5h, p-$COCH_3$; 5i, m-F.

The antibacterial activity of a solution of compounds 4-5 in acetone(0.01%) was measured using

paper plate method at 37°C(9). The experimental results show that propagation of a variety of bacteria were inhibited in varying degrees. The propagation of klebsiella pneumaniae ozaenae was strongly inhibited by compounds 4h, 4f, 4g, 4i, 5d, 5g, 5c, 5f, Escherichia coli by 4f, 4g, 4h, 4i, 5b, 5c, 5d, 5f, 5h; Pseudomonas aeruginosa by 5a, 5b, 5c, 5d, 5g, 5h; and Proteus vulgaris by 5a, 5c, 5e, 5f, 5h, 5i, 5f respectively; Staphlococcus aureus was only inhibited by 5a; Pseudomonas aeruginosa was strongly inhibited by 5c, 5e, 5f, 5i. The inhibiting action of other compounds is very weak, further experments on the inhibition on bacteria is now in progress.

Expermental

Melting points were determined on micromelting point apparatus without correction. Microanalyses were performed on a CarloErba 1106 Elemental Analyzer. NMR spectra were recorded on a Bruker 400A instrument ($CDCl_3$, DMSO-d_6 with TMS as the internal reference. IR spectra were recorded (KBr) using a Nicolet10DXFT-IR spectrophotometer. Mass spectra were recorded on a QP-1000GS-MS. Acetonitrile was distilled over phosphorus pentaoxide, and toluene was distilled over lithium aluminum hydride and stored over activated 4A molecular sieves. All other reagents were purchased from the market and used without further purification.

General procedure: Synthesis of heterocyclic β-enamino esters: 1-substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazoles were prepared according to the literature procedures(8).

Synthesis of iminophosphorane--1-substituted aryl -4-ethoxycarbonyl-5-[(triphenylphosphoran ylidene)amino]-1,2,3-triazoles: triphenylphosphine (12mmol), triethylamine (10mmol) and hexachloroethane (10mmol) were added to a solution of 1-sustituted aryl-4-ethoxycarbonyl-5-amino-1,2,3-triazole (10mmol) in anhydrous acetonitrile (30mL) . The mixture was stirred at room temperature for more than 12 hours. The solvent was removed under reduced pressure, 10mL dry toluene was added to the residue, and refluxed with stirring for 15minutes. After cooling to room temperature, triethylamonium salt was filtered off and the solvent was evaporated under reduced pressure, the residue was recrystallized from benzene.

4f: 1-(*p*-ethoxyl)phenyl-4-ethoxycarbonyl-5-amino]-1,2,3-triazole: mp 172~173°C, $C_{13}H_{16}N_4O_3$, Found: C, 56.40, H, 5.74, N, 20.20. requires: C, 56.52, H, 5.79, N, 20.28.$\nu_{max/cm-1}$(KBr): 3285,3452, 1682, 987. $\delta_H(CDCl_3)$: 1.44(t, 6H, *J* 6.4Hz); 4.31(q, 2H, *J* 6.4Hz); 5.24(s, 2H); 7.36-7.49(m, 4H). MS EI (m/z, %): 276(44), 247(15.9), 231(38.1), 185(78.3), 108(100).

4g: 1-(*m*-bromo)phenyl-4-ethoxycarbonyl-5-amino-1,2,3-triazole: mp 125~126°C, $C_{11}H_{11}BrN_4O_2$, Found: C, 42.35, H, 3.48, N, 17.03; requires: C, 42.44. H, 3.54, N, 18. $\nu_{max/cm-1}$(KBr):3435, 3308. 1697, 991. $\delta_H(CDCl_3)$: 1.44(t, 3H, *J* 7.2Hz), 4.40(q, 2H, *J* 6Hz), 5.31(s, 2H), 7.50-7.75(m, 4H). MS EI (m/z, %): 311(66.4), 282(10.4), 266(41.2), 231(56.4), 185(71.2), 108(69.3).

4h: 1-(*p*-acetyl)phenyl-4-ethoxycarbonyl-5-amino-1,2,3-triazole: mp 213~214°C, $C_{13}H_{14}N_4O_3$, Found: C, 56.82, H, 5.05, N, 20.36, requires: C, 56.93, H, 5.11, N, 20.44. $\nu_{max/cm-1}$(KBr): 3458, 3294, 1716, 1684, 983. $\delta_H(CDCl_3)$:1.45(t, 3H, *J* 7.2Hz), 2.61(s, 3H), 4.45(q, 2H, *J* 10.8Hz), 504(s, 2H). 8.12-8.22(m, 4H). MS EI (m/z, %): 274(82.1), 245(66.7), 231(33.1), 229(54.8), 185(44), 108(88).

4i: 1-(*m*-fluoro)phenyl-4-ethoxycarbonylethoxycarbonyl-5-amino-1,2,3-triazole: mp 119~120°C. $C_{11}H_{11}FN_4O_2$, Found: C, 52.61, H, 4.34, N, 23.16, requires: C, 52.8, H, 4.40, N, 22.4. $\nu_{max/cm-1}$(KBr): 3439, 3316, 1713, 978. $\delta_H(CDCl_3)$:1.44(t, 3H, *J* 7.2Hz), 4.44(q, 2H, *J* 6.4Hz), 5.36(s, 2H), 7.26-7.54(m, 4H). MS EI (m/z, %): 250(24), 231(44), 221(57.6), 185(79), 108(77).

5a:1-(*p*-methoxyl)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene) amino] -1,2,3-triazole: mp 179~181°C, $C_{30}H_{27}N_4O_3P$, Found: C, 68.65, H, 5.12, N, 10.79, requires: C, 68.96, H, 5.17, N, 10.73. $\nu_{max/cm-1}$(KBr): 1690, 1330, 997. $\delta_H(CDCl_3)$: 1.06(t, 3H, *J* 7.2), 3.85-3.95(m, 5H, CH_2, OCH_3), 7.36-7.56(m, 19H),. MS EI (m/z, %): 522(11.3), 493(4.4), 262(96.8), 185(44.6), 108(84).

5b: 1-(*m*-nitro)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1,2,3-triazole: mp 176~177°C, $C_{29}H_{24}N_5O_4P$, Found: C, 64.85, H, 4.53, N, 13.12, requires: C, 64.80, H, 4.47, N, 13.04. $\nu_{max\,cm-1}$(KBr): 1699, 1332, 997. $\delta_H(CDCl_3)$: 1.08(t, 3H, *J* 7.2Hz), 3.98(q, 2H, *J* 6.4Hz), 7.49-7.62(m, 19H). MS EI (m/z, %): 537(12), 508(17.4), 492(3.5), 262(100)., 185(61), 108(33).

5c: 1-(*p*-nitro)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1, 2, 3-triazole: mp 223~225°C, $C_{29}H_{24}N_5O_4P$. Found: C, 64.85, H, 4.53, N, 13.12, requires: C, 64.80, H, 4.47, N, 13.03. $\nu_{max/cm-1}$(KBr): 1699, 1332 997. $\delta_H(CDCl_3)$: 1.03(t, 3H, *J* 7.2Hz), 3.88 (q, 2H, *J* 4Hz), 7.26-8.23(m, 19H). MS EI (m/z, %): 538(M+1, 100), 508(90.9), 492(13.2), 262(100), 185(62.5), 108(100).

5d: (*p*-methyl)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1, 2, 3-triazole: mp 173~175°C $C_{30}H_{27}N_4O_2P$, Found: C,71.20, H, 5.25, N, 11.1 requires: C,71.01, H,5.17, N, 11.05. $\nu_{max/cm-1}$(KBr): 1707, 1329, 997. $\delta_H(CDCl_3)$: 1.1(t, 3H, *J* 7.2Hz), 2.16(s, 3H), 3.89(q, 2H, *J* 6.4Hz), 7.63-7.4(m, 19H), MS EI (m/z, %): 507(100), 462(9.9), 434(3.8), 262(100), 185(22), 108(19).

5e: (*p*-chloro)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene) amino]-1,2,3-triazole: mp 227~228°C, $C_{29}H_{24}ClN_4O_2P$, Found: C,66.17, H, 4.64, N, 10.70, requires: C, 66.1, H, 4.59, N, 10.64. $\nu_{max/cm-1}$(KBr): 1705, 1327, 997. δ_H(DMSO): 1.05(t, 3H, *J* 7.2Hz), 3.9(q, 2H, *J* 6.0Hz), 7.35-7.79(m, 19H). MS EI (m/z, %): 529(43), 500(17.9), 428(4.3), 262(100), 185(56), 108(71).

5f:1-(*p*-ethoxyl)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1, 2, 3-triazole: mp 191~193°C, $C_{31}H_{29}N_4O_3P$, Found: C. 69.38, H, 5.44, N, 15.70, requires: C, 69.27, H, 5.40, N, 15.64. $\nu_{max/cm-1}$(KBr): 1690, 1325, 997. $\delta_H(CDCl_3)$: 1.08(t, 3H, *J* 7.2Hz), 1..48(t, 3H, *J* 6.4Hz), 3.88-4.04(m, 4H), 7.26-7.53(m, 19H). MS EI (m/z, %): 537(44.2), 508(31.6), 492(5.1), 262(100), 185(17), 108(29).

5g: 1-(*m*-bromo)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1,2,3-triazole: mp 172~173°C, $C_{29}H_{24}BrN_4O_2P$, Found: C, 64.19, H, 4.26, N, 9.9. requires: C,60.94, H, 4.20, N, 9.81. $\nu_{max/cm-1}$(KBr): 1703, 1328, 997. $\delta_H(CDCl_3)$: 1.03(t, 3H, *J* 7.2), 3.90(q, 2H,*J* 6.4Hz), 7.27-7.62(m, 19H). MS EI (m/z, %): 573(30.8), 543(56.5), 262(100), 185(50.7), 108(100).

5h: 1-(*p*-acetyl) phenyl–4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1, 2, 3-triazole: mp 191~192°C $C_{31}H_{27}N_4O_3P$, Found: C, 69.78, H, 5.10, N, 10.61. requires: C, 69.66, H, 5.06, N, 10.49. $\nu_{max/cm-1}$(KBr): 1701, 1685, 1331, 996. $\delta_H(CDCl_3)$:1.06(t, 3H, *J* 7.2Hz), 2.64(s, 3H), 3.90(q,

2H, *J* 6.2Hz), 7.26-8.019m, 19H). MS EI (m/z, %): 534(100), 505(16.1), 489(15.4), 262(100), 185(52.7), 108(100).

5i:1-(m-fluoro)phenyl-4-ethoxycarbonyl-5-[(triphenylphosphoranylidene)amino]-1,2,3-triazole: mp 169~171°C, $C_{29}H_{24}FN_4O_2P$, Found: C, 68.34, H, 4.74, N, 11.07. requires: C, 68.23, H, 4.70, N, 10.98. $\nu_{max/cm-1}$(KBr): 1685, 1331, 996. $\delta_H(CDCl_3)$: 1.14(t, 3H, *J* 7.2Hz), 3.91(q, 2H, *J* 6.4Hz), 7.26-8.71(m, 19H). MS EI (m/z, %): 510(32), 491(54.5), 481(62.5), 465(56.4), 262(100), 185(61), 108(100).

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