

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

Mingdong Chen, Shijie Lu*, Guangpu Yuan, Shiyang Yang and Xiaoli Du

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000 China

Abstract: Some new heterocyclic β -enamino ester derivatives with 1,2,3-triazole were prepared, 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 biological 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).

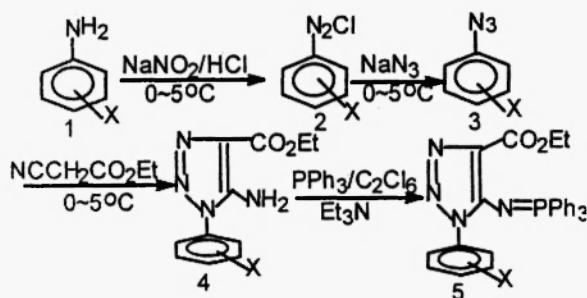
We are interested in the design of new 1,2,3-triazole derivatives and their biological activities, and have prepared some heterocyclic β -enamino esters with 1,2,3-triazole core, an enamino double bond between an ester group and an adjacent amino . Because of their extensive aromaticity the activity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

*To receive any correspondence

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, alkylhalides, isocyanates, isothiocyanates and ozone. They can be used in Dials-Alder reaction and in the synthesis of heterocyclic compounds(1). Therefore, we designed and synthesized some new heterocyclic β -enamino ester derivatives—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]cyclization with moderate to good yields. Subsequently, heterocyclic β -enamino esters were converted into the corresponding iminophosphorane derivatives **5a-5i** by treatment with triphenylphosphorane, hexachloroethane and triethylamine system (the Wamhoff method(8)) in good yields(**Scheme 1**).



Scheme 1: For X=4f, p-OC₂H₅; 4g, m-Br;

4h, p-COCH₃; 4i, m-F; 5a, p-OCH₃;

5b, m-NO₂; 5c, p-NO₂; 5d, p-CH₃; 5e, p-Cl;

5f, p-OCH₃; 5g, m-Br; 5h, p-COCH₃; 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 pneumoniae 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; *Staphylococcus 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 experiments on the inhibition on bacteria is now in progress.

Experimental

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 (CDCl₃, DMSO-d₆ 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. $\nu_{\max/\text{cm}^{-1}}$ (KBr):

3285, 3452, 1682, 987. $\delta_H(\text{CDCl}_3)$: 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, $C_{11}H_{11}BrN_4O_3$,

Found: C, 42.35, H, 3.48, N, 17.03; requires: C, 42.44, H, 3.54, N, 18. $\nu_{\max/\text{cm}^{-1}}$ (KBr): 3435, 3308.

1697, 991. $\delta_H(\text{CDCl}_3)$: 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. $\nu_{\max/\text{cm}^{-1}}$ (KBr): 3458, 3294.

1716, 1684, 983. $\delta_H(\text{CDCl}_3)$: 1.45(t, 3H, J 7.2Hz), 2.61(s, 3H), 4.45(q, 2H, J 10.8Hz), 5.04(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-ethoxycarbonyl-5-amino-1,2,3-triazole: mp 119~120°C.

$C_{11}H_{11}FN_4O_3$, Found: C, 52.61, H, 4.34, N, 23.16, requires: C, 52.8, H, 4.40, N, 22.4. $\nu_{\max/\text{cm}^{-1}}$ (KBr):

3439, 3316, 1713, 978. $\delta_H(\text{CDCl}_3)$: 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. $\nu_{\max/\text{cm}^{-1}}$ (KBr): 1690, 1330, 997. $\delta_H(\text{CDCl}_3)$: 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.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1699, 1332, 997. $\delta_H(\text{CDCl}_3)$: 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. C₂₉H₂₄N₅O₄P. Found: C, 64.85, H, 4.53, N, 13.12, requires: C, 64.80, H, 4.47, N, 13.03.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1699, 1332 997. δ_{H} (CDCl₃): 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 C₃₀H₂₇N₄O₃P, Found: C, 71.20, H, 5.25, N, 11.1 requires: C, 71.01, H, 5.17, N, 11.05.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1707, 1329, 997. δ_{H} (CDCl₃): 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, C₂₉H₂₄ClN₄O₃P, Found: C, 66.17, H, 4.64, N, 10.70, requires: C, 66.1, H, 4.59, N, 10.64.

$\nu_{\max/\text{cm}^{-1}}$ (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, C₃₁H₂₉N₄O₃P, Found: C, 69.38, H, 5.44, N, 15.70, requires: C, 69.27, H, 5.40, N, 15.64.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1690, 1325, 997. δ_{H} (CDCl₃): 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, C₂₉H₂₄BrN₄O₃P, Found: C, 64.19, H, 4.26, N, 9.9. requires: C, 60.94, H, 4.20, N, 9.81.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1703, 1328, 997. δ_{H} (CDCl₃): 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 C₃₁H₂₇N₄O₃P, Found: C, 69.78, H, 5.10, N, 10.61. requires: C, 69.66, H, 5.06, N, 10.49.

$\nu_{\max/\text{cm}^{-1}}$ (KBr): 1701, 1685, 1331, 996. δ_{H} (CDCl₃): 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-(4-fluorophenyl)-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. δ_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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