AN EFFICIENT METHODS FOR THE SYNTHESIS OF SOME NEW 1-SUBSTITUTED ARYL-4- ETHOXYCARBONYL-5-DIMETHYLAMINOMETHYLENEAMIO-1, 2, 3-TRIAZOLE AND THEIR DERIVATIVES

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Abstract: A simple and efficient method has established for the synthesis of some 1-substituted aryl-4-ethoxycarbonyl-5-disubstituted aminomethyleneamino-1, 2, 3-triazoles. These compounds were first prepared from 1-substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazole and N, N-disubstituted formamides in the presence of phosphorus oxychloride under mild condition in moderate to good yields. The structures were characterized by IR, ^{1}H NMR, MS, and elemental analysis, and their inhibiting effects on various bacteria were also screened.

Heterocyclic β-enamino esters have been proved to be versatile synthons for the construction of manifold organic compounds(1). Among them, β-enamino esters containing 1,2,3-triazole are of great interest because of their high biological and pharmacological activity, such as antiflammatory and analgestic properties(2); antibacterial and antifungal activities; potential bacteriostats(3); antibiotic(4); antiviral activities and cytotoxicities; antitumour and antimicrobial activity(5), especially anti-HiV-1 activities(6). However, the reaction activity of the amino group in these compounds is relative low because v-triazole compounds possess a very extensive aromaticity. In this study, we attempt to improved the reaction activity of these compounds and obtain some new and useable 1, 2, 3-triazole derivatives which having better reaction activity under new procedure.

It is known that dimethyl formamidrazones are versatile synthetic intermediates and have been widely used for the construction of various heterocycles, such as triazoloquinolines and their salt(7), terazine (8), triazolopyrimidines(9), triazoles(10) and oxadiazoles(11). The structure of 1-Substituted aryl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1, 2, 3-triazoles 3 and their derivatives (4; 5) synthesized in this study is similar to that of dimethylformamidrones, therefore they might bearing similar reactivities.

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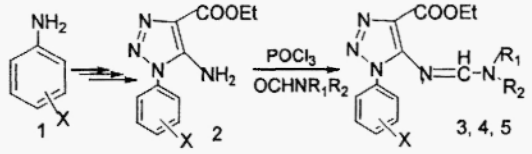
Here we report a direct and general method for the preparation of 1-substituted aryl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1, 2, 3-triazole and their derivatives starting from corresponding 1-substituted aryl-4-ethoxycarbonyl-5-amino 1, 2, 3-triazole. Compounds 2 were prepared from 1-substituted aniline by diazotization reaction and then treated with sodium azide, and [2+3] cylization with good yields(12). Typically, to prepare compounds 3, compounds 2 (2 mmol) was reacted with DMF (4mL) in presence of phosphorus oxychloride to form the product 3 in 41-88% yields. The desired product 3 is separated into its pure form by simple filtration and recrystalization. As we now, compounds 3; 4; 5 have not been reported in the literature. The structures of these products were characterized by IR, ^{1}H NMR, MS spectroscopy and also through elemental analysis. Synthetic route for compounds 3; 4; 5 are showed in **Scheme 1.** The results of the reaction are listed in **Table 1**, further study on the reactions of compound 3 ;4; 5 are now in progress.



X=H, p-CH_3, p-OCH_3, m-F, p-Cl, m-Br, m-CF_3, p-$COCH_3$, p-OC_2H_5, m-NO_2, p-NO_2

For 3: R_1=R_2=CH_3; for 4: R_1=CH_3, R_2==Ph; for 5: R_1=R_2=C_2H_5

Scheme 1

The antibacterial activity of a solution of compounds 3; 4; 5 in acetone (0.01%) was measured using paper plate method at 37^{0}C(14). The experimental results show that propagation of a variety of bacteria was inhibited in varying degrees. The propagation of klebsiella pneumaniae ozaenae was relatively strong inhibited by compounds3a, 3b, 3c, 3i; Escherichia coli by 3d, 3e, 3f; Pseudomonas aeruginosa by 3g, 3k and Proteus vulgaris by 3j respectively; Staphlococcus aureus was weakly inhibited by 3d, 3f. Further experiments on the inhibition on bacteria are now in progress.

Table 1. The preparation of compound 3; 4; 5

Entry	X	Yield(%)[a]	m.p.(^{0}C)	State
3a	H	81	150~151	colorless crystal
3b	p-CH_3	74	118~120	colorless crystal
3c	p-Cl	69	158~159	colorless crystal
3d	m-NO_2	81	158~159	colorless crystal
3e	p-NO_2	84	181~183	colorless crystal
3f	m-Cl	76	95~96.5	colorless crystal
4a	H	54	138~139	colorless crystal
4b	p-CH_3	66	130~131	colorless crystal
4c	p-Cl	56	126~128	colorless crystal
4d	m-NO_2	49	128~130	yellow crystal
4e	p-NO_2	56	131~133	yellow crystal
4f	m-Cl	41	108~110	colorless crystal
5a	H	67	108~110	colorless crystal
5b	p-CH_3	61	112~114	colorless crystal
5c	p-Cl	44	168~170	colorless crystal
5d	m-NO_2	46	107~108	yellow crystal
5e	p-NO_2	43	179-180	yellow crystal
5f	m-Cl		136-137	colorless crystal

a: isolated yields

Experimental:

Malting 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. N, N-dimethylformamide, N-methylaniline, diethylamine, formic acid, phosphorus oxychloride were purchased from commercial suppliers and used without further purification.

General Procedure:

1-Substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazoles 2 were prepared according to the literature procedure(12).

Synthesis of 1-substituted aryl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1, 2, 3-triazoles **3**:

1-Substituted aryl-4-ethoxycarbonyl-5-amino-1,2,3-triazoles (2mmol) was dissolved in N, N-dimethylformamide (4mL), the reaction mixture was stirred and cooled to 0^0C, and phosphorus oxychloride (0.5mL) was added slowly. After the addition was complete, the mixture was stirred at 50-60^{0}C for 2 hours and then poured into stirring ice-water (50g), saturated solution of sodium hydroxide was added slowly, after adjustment to PH=7 with saturated solution of sodium hydroxide, a solid material slowly precipitated. It was collected by filtration, washed with water and recrystallization from ethanol.

3a 1-phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles:

colorless crystal, m.p.150~151^{0}C, $C_{14}H_{17}N_5O_2$, requires: C, 58.54; H, 5.92; N, 24.40. Found: C, 58.43; H, 5.86; N, 24.32. υ 1705 (C=O), 1635 (C=N), 997 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.43 (t, 3H, J=8Hz); 3.10 (d, 6H, J=5Hz); 4.36 (q, 2H, 6Hz); 7.42-7.75 (m, 5H); 8.50 (s, 1H)[13]. MS (m/z, %): 287 (33), 242 (16), 186 (34), 143 (8.5), 83 (100), 42 (81).

3b 1-(p-CH_3)phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles:

colorless crystal, m.p.118~120^{0}C, $C_{15}H_{19}N_5O_2$, requires: C, 59.80; H, 6.31; N, 23.26. Found: C, 59.62; H, 5.24; N, 23.18. υ 1710 (C=O), 1637 (C=N), 989 (-N=N-N-) cm^{-1}. δ H ($CDCl_3$),1.38 (t, 3H, J=7Hz); 2.40 (s, 3H); 3.03 (d, 6H); 4.32 (q, 2H, J=7Hz); 7.16-7.66 (m, 4H); 8.42 (s, 1H). MS (m/z, %): 301 (44), 256 (21), 200 (56), 158 (24.6), 83 (100), 42 (69).

3c 1-(p-Cl)phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles:

colorless crystal, m.p.158~159 ^{0}C, $C_{14}H_{16}ClN_5O_2$, requires: C, 52.26; H, 4.98; N, 21.77. Found: C, 52.15; H, 4.93; N, 21.69. υ 1703 (C=O), 1632 (C=N), 986 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.41 (t, 3H, J=7Hz); 3.05 (d, 6H, J=6Hz); 4.43 (q, 2H, J=7Hz); 7.35-7.80 (m, 4H,); 8.50 (s, 1H). MS (m/z, %): 321 (37), 292 (3), 276 (10), 220 (14), 191 (7.5), 83 (91.4), 42 (100).

3d 1-(m-NO_2)phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles:

colorless crystal, m.p.134~136 ^{0}C, $C_{14}H_{16}N_6O_4$, requires: C, 50.60; H, 4.82; N, 25.30. Found: C, 50.48; H, 4.77; N, 25.22. υ 1698 (C=O), 1642 (C=N), 973 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.45 (t, 3H, J=6Hz); 3.15 (d, 6H, J=6Hz); 4.38 (q, 2H, J=7Hz); 7.77-8.40 (m, 4H,); 8.70 (s,

1H). MS (m/z, %): 332 (27), 287 (4), 231 (16), 202 (13), 173 (14), 83 (100), 42 (75).

3e 1-(p-NO_2)phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles: colorless crystal, m.p.181~183 ^{0}C, $C_{14}H_{16}N_6O_4$, requires: C, 50.60; H, 4.82; N, 25.30. Found: C, 50.47; H, 4.76; N, 25.21. υ 1704 (C=O), 1632 (C=N), 987 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.34 (t, 3H, J=6Hz); 3.04 (d, 6H, J=5Hz); 4.27 (q, 2H, J=8Hz); 8.11-8.21 (m, 4H,); 8.51 (s, 1H). MS (m/z, %): 332 (25), 287 (11), 231 (21), 202 (11), 173 (17), 83 (100), 42 (81).

3f: 1-(m-Cl)phenyl-4-ethoxycarbonyl-5-dimethylaminomethyleneamino-1,2,3-triazoles: colorless crystal, m.p.95~96.5 ^{0}C, $C_{14}H_{16}ClN_5O_2$, requires: C, 52.26; H, 4.98; N, 21.77. Found: C, 52.15; H, 4.93; N, 21.69. υ 1703 (C=O), 1632 (C=N), 986 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.41 (t, 3H, J=7Hz); 3.05 (d, 6H, J=6Hz); 4.43 (q, 2H, J=7Hz); 7.35-7.80 (m, 4H,); 8.50 (s, 1H). MS (m/z, %): 321 (37), 292 (3), 276 (10), 220 (14), 191 (7.5), 83 (91.4), 42 (100).

4a:1-phenyl-4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.138~139 ^{0}C, $C_{19}H_{19}N_5O_2$, requires: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.20; H, 5.40; N, 19.97. υ 1701 (C=O), 1634 (C=N), 989 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.42 (t, 3H, J=6Hz); 3.47 (s, 3H); 4.40 (q, 2H, 6Hz); 7.22-7.83 (m, 10H); 8.81 (s, 1H). MS (m/z, %): 349 (38), 275(4.8), 248(46), 118 (100), 77 (85), 42 (36).

4b:1-(p-CH_3)phenyl-4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.130~131^{0}C, $C_{20}H_{21}N_5O_2$, requires: C, 66.10; H, 5.82; N, 19.27. Found: C, 65.98; H, 5.76; N, 19.20. υ 1700 (C=O), 1633 (C=N), 990 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.41 (t, 3H, J=6Hz); 2.43(s, 3H); 3.45(s, 3H); 4.44 (q, 2H, J=6Hz); 7.21-7.69 (m, 9H); 8.96 (s, 1H). MS (m/z, %): 363 (31), 289 (6.6), 262(42), 118 (100), 77 (85), 42 (36).

4c:1-(p-Cl)phenyl-4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.126~128^{0}C, $C_{19}H_{18}ClN_5O_2$, requires: C, 59.45, H, 4.73; N, 18.25. Found: C, 59.35; H, 5.06; N, 18.18. υ 1702 (C=O), 1635 (C=N), 991 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.40 (t, 3H, J=6Hz); 3.48 (s, 3H); 4.38 (q, 2H, 6Hz); 7.23-7.81 (m, 9H); 9.01 (s, 1H). MS (m/z, %): 384 (38), 310 (11.6), 281(41), 145(34), 118 (92), 77 (100), 42 (39), 29 (46)

4d:1-(m-NO_2)phenyl- 4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.128~130^{0}C, $C_{19}H_{18}N_6O_4$, requires: C, 57.86, H, 4.60; N, 21.31. Found: C, 57.75; H, 4.55; N, 21.23. υ 1703 (C=O), 1636 (C=N), 992 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.44 (t, 3H, J=6Hz); 3.57 (s, 3H); 4.36 (q, 2H, J=6Hz); 7.29-8.37 (m, 9H); 9.1 (s, 1H). MS (m/z, %): 394 (38), 320 (31), 291 (11.6), 276(43), 145(34), 118 (62), 77 (100), 42 (32), 29 (36)

4e:1-(p-NO_2)phenyl-4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.131~133^{0}C, $C_{19}H_{18}N_6O_4$, requires: C, 57.86, H, 4.60; N, 21.31. Found: C, 57.75; H, 4.55; N, 21.23. υ 1704 (C=O), 1636 (C=N), 993 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.45 (t, 3H, J=6Hz); 3.58(s, 3H); 4.37 (q, 2H, J=6Hz); 7.30-8.47 (m, 9H); 9.2 (s, 1H). MS (m/z, %): 394 (41), 320 (30), 291 (13.5), 276(42), 145(44), 118 (59), 77 (100), 42 (31), 29 (33)

4f: 1-(m-Cl)phenyl-4-ethoxycarbonyl-5-[methyl(phenyl)amino]methyleneamino-1,2,3-triazole: colorless crystal, m.p.108~110 ^{0}C, $C_{19}H_{18}ClN_5O_2$, requires: C, 59.45, H, 4.73; N, 18.25. Found: C, 59.35; H, 5.06; N, 18.18. υ 1701 (C=O), 1634 (C=N), 989 (-N=N-N-) cm^{-1}. δ

H($CDCl_3$), 1.43 (t, 3H, J=6Hz); 3.45 (s, 3H); 4.39 (q, 2H, 6Hz); 7.28-7.81 (m, 9H); 8.99 (s, 1H). MS (m/z, %): 384 (33), 310 (6.6), 281(31), 145(39), 118 (72), 77 (100), 42 (31), 29 (34)

5a:1-phenyl- 4-ethoxycarbonyl-5-(diethylamino)methyleneamino -1,2,3-triazole:
colorless crystal, m.p.108~110 ^{0}C, $C_{16}H_{21}N_5O_2$, requires: C, 60.94, H, 6.71; N, 22.21. Found: C, 60.83; H, 6.65; N, 22.13. υ 1700 (C=O), 1635 (C=N), 990 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.18(t, 3H, J=4Hz), 1.29(t, 3H, J=4Hz), 1.45 (t, 3H, J=6Hz); 3.39 (q, 2H, J=5Hz); 3.98 (q, 2H, J=5Hz); 4.42(q, 2H, J=6Hz), 7.28-7.96 (m, 4H); 8.41 (s, 1H). MS (m/z, %): 315(41), 72(6.7), 214(55), 157(26), 77(12), 57(100), 28(60)

5b:1-(p-CH_3)phenyl-4-ethoxycarbonyl-5-(diethylamino)methyleneamino-1,2,3-triazole:
colorless crystal, m.p.112~114 ^{0}C, $C_{17}H_{23}N_5O_2$, requires: C, 61.99, H, 7.04; N, 21.26. Found: C, 61.88; H, 6.98; N, 21.19. υ 1699 (C=O), 1631 (C=N), 989 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.17(t, 3H, J=4Hz), 1.28(t, 3H, J=4Hz), 1.43 (t, 3H, J=6Hz); 2.40(s, 3H), 3.38 (q, 2H, J=5Hz); 3.97 (q, 2H, J=5Hz); 4.40(q, 2H, J=6Hz), 7.24-7.66 (m, 4H); 8.44 (s, 1H). MS (m/z, %): 329(41), 286(12), 228(52), 171(24), 111(59), 77(12), 57(100), 28 (60)

5c:1-(p-Cl)phenyl- 4-ethoxycarbonyl-5-(diethylamino)methyleneamino -1,2,3-triazole:
colorless crystal, m.p.168~170^{0}C, $C_{16}H_{20}ClN_5O_2$, requires: C, 54.94, H, 5.76; N, 20.02. Found: C, 54.83; H, 5.70; N, 20.17. υ 1702 (C=O), 1635 (C=N), 990 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.40-1.48(m, 9H,), 4.41-4.53 (m, 6H); 7.27-7.78 (m, 4H); 8.21 (s, 1H). MS (m/z, %): 349(29), 306(31), 248(13), 191(31), 131(14), 77(13), 57(100), 28 (59)

5d:1-(m-NO_2)phenyl-4-ethoxycarbonyl-5-(diethylamino)methyleneamino-1,2,3-triazole:
colorless crystal, m.p.107~108^{0}C, $C_{16}H_{20}N_6O_4$, requires: C, 53.33, H, 5.59; N, 23.32. Found: C, 53.22; H, 5.54; N, 23.25. υ 1705 (C=O), 1636 (C=N), 993 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.41-1.478(m, 9H,), 3.46 (q, 2H, J=5Hz); 3.58 (q, 2H, J=5Hz); 4.42(q, 2H, J=6Hz), 7.65-8.70 (m, 4H); 9.01 (s, 1H). MS (m/z, %): 360(29), 287(11), 259(20.1), 201(12.5), 111(53), 77(58), 56(100), 28(59)

5e:1-(p-NO_2)phenyl-4-ethoxycarbonyl-5-(diethylamino)methyleneamino-1,2,3-triazole:
colorless crystal, m.p.179-180^{0}C, $C_{16}H_{20}N_6O_4$, requires: C, 53.33, H, 5.59; N, 23.32. Found: C, 53.22; H, 5.54; N, 23.25. υ 1705 (C=O), 1637 (C=N), 994 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.27(t, 6H, J=5Hz), 1.478(t, 3H, J=6Hz), 3.76 (q, 4H, J=5Hz); 4.51 (q, 2H, J=6Hz); 7.64-7.67 (m, 4H); 8.48 (s, 1H). MS (m/z, %): 360(21), 287(16), 259(21.1), 201(10.5), 111(49), 77(51), 56(100), 28(64)

5f:1-(m-Cl)phenyl- 4-ethoxycarbonyl-5-(diethylamino)methyleneamino -1,2,3-triazole:
colorless crystal, m.p.136~137^{0}C, $C_{16}H_{20}ClN_5O_2$, requires: C, 54.94, H, 5.76; N, 20.02. Found: C, 54.83; H, 5.70; N, 20.17. υ 1700(C=O), 1634 (C=N), 987 (-N=N-N-) cm^{-1}. δ H($CDCl_3$), 1.40-1.49(m, 9H,), 4.41-4.54 (m, 6H); 7.27-7.79 (m, 4H); 8.31 (s, 1H). MS (m/z, %): 349(21), 320(19), 291(14.5), 236(13.5), 77(55), 56(100), 28 (55).

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