The Synthesis of (4*E*)-*N*-(4-chlorophenyl)-5-substituted-2-diazo-3-oxopent-4-enoic Acid Amides

Heng-Shan Dong* (董恒山), Dong-Dong Wang (王棟東) and Chi-Qiong Jin (金池瓊)
State Key Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, P. R. China

The (*4E*)-*N*-(4-chlorophenyl)-5-(3-chlorophenyl)-2-diazo-3-oxopent-4-enoic acid amides **5a~j** were synthesized with *N*-(4-chlorophenyl)-2-diazo-3-oxobutyramide **4** from *p*-chloroaniline and various arylaldehydes. The yielded products **5a~j** were investigated with NMR, MS, IR, and X-ray crystallographic techniques.

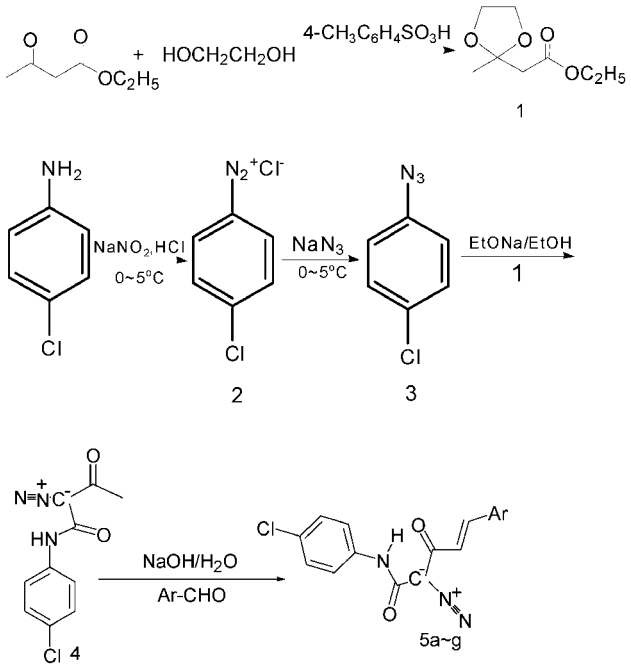
Keywords: α-Diazodicarbonyl compound; 2-Diazo-3-oxopent-4-enoic acid amide; Synthesis; Ethyl(acetoketal)acetate; (2-Methyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester.

INTRODUCTION

In recent years in various publications, certain compounds having a 1,2,3-triazole nucleus have been reported as antibacterials,[1] antifungals,[2] antivirals,[3] anti-inflammatories, and analgesics.[4] Recently, some new 1,3,4-triazole derivatives have been synthesized as possible anticonvulsants[5] and plant growth regulators;[6] 1,2,3-triazole derivatives have been synthesized to inhibit tumor proliferation, invasion, metastasis,[7] and have shown anti-HIV activity.[8-13] Likewise, pyrone nucleus derivatives have been synthesized which have shown anti-HIV activity.[14-19] We have reported the crystalline structure of 5-[5-amino-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]-2-(3-bromoanilino)-1,3,4-thiodiazole and their derivatives,[20-22] and the crystalline structure of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazole.[23] We figure the synthesis of 4-acetyl-1-(*p*-chlorophenyl)-5-hydroxyl-1,2,3-triazole by reaction of *p*-chlorophenyl azide with ethyl(acetoketal)acetate or (2-methyl-[1,3]-dioxolan-2-yl)-acetic acid ethyl ester, *N*-(4-chlorophenyl)-2-diazo-3-oxobutyramide is gotten by the triazole ring opening in the medium of acid water, subsequently reacting the compound with arylaldehydes. We obtained (4*E*)-*N*-(4-chlorophenyl)-5-substituted-2-diazo-3-oxopent-4-enoic acid amide. A great deal of interest has been focused on the α-diazocarbonyl compounds.[24] When properly substituted, they can be useful materials for photoresist. This has inspired us to extend our work on α-diazodicarbonyl compounds *N*-(4-chlorophenyl)-2-diazo-3-oxo-butyramide with heterocyclic openings in order to study the synthesis and potential applications of (4*E*)-*N*-(4-chlorophenyl)-5-substituted-2-diazo-3-oxopent-4-enoic acid amides.

In this paper, we report the synthesis of (4*E*)-*N*-(4-chlorophenyl)-5-substituted-2-diazo-3-oxopent-4-enoic acid amides **5a~j**. The route of synthesis is in Scheme I.

Scheme I



5a Ar=ph; **5b**, 3-chlorophenyl; **5c**, 3,4-dimethoxyphenyl; **5d**, 3,4-methylenedioxyphenyl; **5e**, 4-methoxyphenyl; **5f** 2-furanyl; **5g**, 4-*N,N*-dimethylaminophenyl; **5h**, 4-hydroxyphenyl; **5i**, 2-hydroxyphenyl; **5j**, 4-hydroxy-3-methoxyphenyl.

EXPERIMENTAL SECTION

Melting points were uncorrected and determined on an XT_4-100x microscopic melting point apparatus. IR spectra were obtained in KBr discs on a Nicolet 170SX FT-IR spectrometer. MS were performed on an HP-5988A spectrometer (EI at 70 eV). ^{1}H NMR spectroscopy ($CDCl_3$) were recorded on an Avance Mercury plus-300 instrument with TMS as an internal standard. Uv spectra were obtained on a Shimadzu Uv-260 spectrometer.

(2-Methyl-[1,3]-dioxolan-2-yl)-acetic acid ethyl ester 1 was prepared following a method reported in the literature[25]

Compound **1** (in 90% yield). ^{1}H NMR δ_H: 4.039-4.164 (q, 2H, *J* = 7.2 Hz, OC$\underline{H}_2$CH$_3$); 3.933 (s, 4H, -OC$\underline{H}_2$C$\underline{H}_2$O-); 2.616 (s, 2H, -CC$\underline{H}_2$CO$_2$-); 1.455 (s, 3H, CH$_3$-); 1.185-1.256 (t, 3H, *J* = 7.2 Hz, CH$_2$-C$\underline{H}_3$) ppm.

***N*-(4-chlorophenyl)-2-diazo-3-oxo-butyramide was prepared from *p*-chloroaniline following a method reported in the literature**[26]

The solution of sodium ethoxide [3.5 g (1.5 mol) of sodium in 50 mL of ethanol] was added to a solution of 15.3 g (0.1 mol) *p*-chlorophenyl azide and 12.0 mL (0.1 mol) ethyl (acetoketal)acetate **1** in 80 mL absolute ethanol in one portion under an ice bath. Then the reaction mixture was heated under reflux for 48 hours. The solution was cooled to room temperature and the solvent was removed in vacuo to give a syrup mixture. This mixture was dissolved in 100 mL water and acidified to pH = 1~2 with hydrochloric acid (4 M). After stirring in an ice bath for one hour the resulting precipitate was filtered off and washed with water and recrystalized from ethanol to give 16 g of compound **4**. Yield 65%, mp 145-146 °C (Lit. 143 °C),[27] IR υ_{max}: 3236, (b, -N-H), 3069 (Ar-H), 3027, 2938, (w, CH$_3$), 2125 (s, diazo), 1670, 1638 (s, C=O, -CONH-), 1596, 1548, 1488 (s, Ar), 953, 841, 820 (m, Ph-1,2H), 722 (C-Cl) cm^{-1}. ^{1}H NMR δ_H: 10.216 (b, 1H, NH); 7.521-7.545 (d, 2H, *J* = 7.2 Hz, Ph-2,6H); 7.296-7.271 (d, 2H, *J* = 7.2 Hz, Ph-3,5H); 2.425 (s, 3H, CH$_3$-) ppm. MS *m/z*: 237($M^{+\cdot}$, 21), 239 (M+2, 7), 194 (4), 181 (9), 167 (10), 153 (6), 138 (54), 127 (14), 111 (28), 99 (21), 83 (44), 75 (28), 69 (5), 63 (19), 55 (14), 50 (11), 43 (100), 39 (10). Uv ($CHCl_3$, c = 10^{-3} mol/L), λ = 258.4 nm (1.729).

(*4E*)-*N*-(4-chlorophenyl)-5-substituted-2-diazo-3-oxopent-4-enoic acid amides 5a~j were prepared following the method

1.5 g of compound **4** was added to a solution of sodium hydroxide (0.8 g) in 10 mL water and 10 mL ethanol, then various arylaldehydes were dropped into the solution during continuous stirring at room temperature. The reaction mixture was stirred at room temperature for 8 h and acidified to pH = 7~8 with HCl (4 M), filtered and recrystalized from ethanol to give **5a~j**.

Compound **5b**. Uv ($CHCl_3$, c = 10^{-3} mol/L), λ = 280.4 nm (1.010), λ = 241.8 nm (0.957).

Compound **6**. Yield (methods A 56%, methods B 20%), mp 177-178 °C, IR υ_{max}: 3111 (Ar-H), 3027, 2916, (w, CH$_3$), 1670, 1688 (s, C=O), 1651, 1548, 1485 (s, Ar), 1216, 1070 (C-O-CH$_3$), 955, 830 (m, Ph-1,2H), 728 (C-Cl) cm^{-1}. ^{1}H NMR δ_H: 7.936-7.967 (d, 2H, *J* = 9.3 Hz, Ph-2,6H); 7.443-7.474 (d, 2H, *J* = 9.3 Hz, Ph-3,5H); 4.311 (s, 3H, CH$_3$O-), 2.609 (s, 3H, CH$_3$-) ppm. MS *m/z*: 251 ($M^{+\cdot}$, 21), 253 (M+2, 7), 236 (1), 194 (4), 141 (4), 139 (14), 113 (22), 111 (76), 84 (16), 75 (24), 69 (3), 63 (3), 55 (1), 50 (10), 43 (100), 42 (67). Uv ($CHCl_3$, c = 10^{-3} mol/L), λ = 324.6 nm (1.271), λ = 240.0 nm (0.510).

RESULTS AND DISCUSSION

The crystal structure of the title compound **5b** is shown in Fig. 1. In recent years the synthesis and characteristics of 5-amino-1-(4-chlorophenyl)-1,2,3-triazol-4-yl and 5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl derivatives have been investigated. These heterocyclic compounds contain a 1,2,3-triazole ring, and they are a series stable compounds.[20-23] In order to continue our earlier studies, we synthesized compounds **5a~j**.

We isolated the compound **4** that was an open ring product from 4-acetyl-1-(4-chlorophenyl)-5-hydroxy-1,2,3-triazole. We claim that the reaction mechanism is the following formation under the reaction conditions in Scheme II. It is in

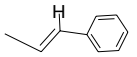
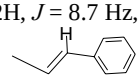
Table 1. Structures, yields and melting points of compounds **5a~j**

No	Ar	M.p. (°C)	Yield (%)
5a	phenyl	170-171	80
5b	3-chlorophenyl	159-160	87
5c	3,4-dimethoxyphenyl	169-170	50
5d	3,4-methylenedioxyphenyl	187-188	63
5e	4-methoxyphenyl	188-189	83
5f	2-furanyl	154-156	75
5g	4-*N,N*-dimethylaminophenyl	199-200	60
5h	4-hydroxyphenyl	190-192	62
5i	2-hydroxyphenyl	194-196	60
5j	4-hydroxy-3-methoxyphenyl	194-195	50

Table 2. IR spectral data for compounds **5a-j**

No	IR (cm^{-1}) (KBr disc)
5a	3237 (b, -N-H), 3188, 3112 (Ar-H), 3060, 3029 (w, CH_3), 2122 (s, diazo), 1671, 1642 (s, C=O, -CONH-), 1580, 1545, 1488 (s, Ar), 977, 821 (m, Ph-1,2H), 836, 756 (m), 687 (C-Cl).
5b	3224 (b, -N-H), 3179, 3110 (Ar-H), 3060, 2938 (w, CH_3), 2120 (s, diazo), 1668, 1641 (s, C=O, -CONH-), 1576, 1543, 1490 (s, Ar), 975, 830 (m, Ph-1,2H), 925, 789, 789 (m, 3-chlorophyl 1H or 3H), 738, 692 (C-Cl).
5c	3234 (b, -N-H), 3183, 3116 (Ar-H), 3067, 2936 (w, CH_3), 2116 (s, diazo), 1676, 1634 (s, C=O, -CONH-), 1571, 1542, 1508 (s, Ar), 1266, 1242, 1019 (s, Ar-O-CH_3), 966, 831 (m, Ph-1,2H), 801, 717 (m), 736 (C-Cl).
5d	3225 (b, -N-H), 3180, 3108 (Ar-H), 3058, 2978, 2904 (w, CH_3), 2117 (s, diazo), 1670, 1635 (s, C=O, -CONH-), 1569, 1542, 1488 (s, Ar), 1253, 1238, 1037, 1018 (s, Ar-O-CH_3), 973, 833 (m, Ph-1,2H), 805, 718 (m), 739 (C-Cl).
5e	3225 (b, -N-H), 3177, 3108 (Ar-H), 3061, 2939 (w, CH_3), 2116 (s, diazo), 1672, 1633 (s, C=O, -CONH-), 1605, 1569, 1541, 1511 (s, Ar), 1265, 1237, 1023 (s, Ar-O-CH_3), 982, 823 (m, Ph-1,2H), 714 (C-Cl).
5f	3234 (b, -N-H), 3182, 3110 (Ar-H), 3063, 2904 (w, CH_3), 2123 (s, diazo), 1672, 1637 (s, C=O, -CONH-), 1572, 1542, 1490 (s, Ar), 1267, 1243, 1011 (s, Furanyl), 966, 821 (m, Ph-1,2H), 754 (m), 731 (C-Cl).
5g	3226 (b, -N-H), 3175, 3108 (Ar-H), 3063, 2896, 2821 (w, CH_3), 2118 (s, diazo), 1670, 1612 (s, C=O, -CONH-), 1524, 1435 (s, Ar), 1240, 1171, 1023, 1001 (s, Ar-N-CH_3), 974, 836, 804 (m, Ph-1,2H), 741(C-Cl).
5h	3393 (ms, b, -OH and -N-H), 2922 (w, CH_3), 2114 (m, diazo), 1607 (s, b, C=O, -CONH-), 1493 (s, Ar), 1254, 1070 (s, Ar-OH), 966, 836 (m, Ph-1,2H), 718 (C-Cl).
5i	3386 (ms, b, -OH and -N-H), 2919 (w, CH_3), 2126 (m, diazo), 1604 (s, b, C=O, -CONH-), 1494 (s, Ar), 1239, 1069 (s, Ar-OH), 966, 814, 754 (m, Ph-1,2H), 718 (C-Cl).
5j	3402 (ms, b, -OH and -N-H), 2923 (w, CH_3), 2121 (m, diazo), 1603 (s, b, C=O, -CONH-), 1509, 1424 (s, Ar), 1273, 1239, 1070 (s, Ar-O-CH_3, Ar-OH), 966, 818 (m, Ph-1,2H), 708 (C-Cl).

Table 3. ^{1}H NMR spectral data for compounds

No	^{1}H NMR ($CDCl_3$-*d*) δ (ppm), *J* (Hz)
5a	10.669 (b, 1H, NH), 7.836-7.887 (d, 1H, *J* = 15 Hz,  = -H), 7.576-7.617 (m, 4H, Ar-H), 7.437-7.457 (m, 3H, Ar2-H), 7.293-7.322 (d, 2H, *J* = 8.7 Hz, Ar1-H), 5.503-5.544 (d, 1H, *J* = 15 Hz,  = -H), 300 MHz.
5b	10.576 (b, 1H, NH), 7.719-7.769 (d, 1H, *J* = 15 Hz, = -H), 7.287-7.549 (m, 8H, Ar-H), 6.837-6.888 (d, 1H, *J* = 15 Hz, = -H).
5c	10.721 (b, 1H, NH), 7.676-7.847 (d, 1H, *J* = 15 Hz, = -H), 7.568-7.612 (d, 2H, *J* = 9 Hz, Ar1-H), 7.201-7.323 (m, 3H, Ar-H), 7.069 (s, 1H, Ar2-H), 6.889-6.930 (d, 1H, *J* = 9 Hz, Ar2-H), 6.727-6.802 (d, 1H, *J* = 15 Hz, = -H), 3.945 (s, 6H, -OCH_3) 200 MHz.
5d	10.706 (b, 1H, NH), 7.739-7.790 (d, 1H, *J* = 15 Hz, = -H), 7.569-7.598 (d, 2H, *J* = 8.7 Hz, Ar1-H), 7.285-7.314 (d, 2H, *J* = 8.7 Hz, Ar1-H), 7.085-7.097 (d, 2H, Ar2-H), 6.847-6.874 (d, 1H, *J* = 8.1 Hz, Ar2-H), 6.705-6.755 (d, 1H, *J* = 15 Hz, = -H), 6.050 (s, 2H, -OCH_2O-H) 300 MHz.
5e	10.733 (b, 1H, NH), 7.788-7.862 (d, 1H, *J* = 15 Hz, = -H), 7.546-7.712 (q, 4H, Ar-H) 7.280-7.325 (d, 2H, *J* = 9 Hz, Ar1-H), 6.929-6.972 (d, 2H, *J* = 8.6 Hz, Ar2-H), 6.753-6.828 (d, 1H, *J* = 15Hz, = -H), 3.872 (s, 3H, -OCH_3) 300 MHz.
5f	10.681 (b, 1H, NH), 7.561-7.611 (d, 1H, *J* = 15 Hz, = -H), 7.551-7.572 (m, 3H, Ar-H), 7.281-7.310 (m, 2H, Ar-H), 6.783-6.831 (d, 1H, *J* = 15 Hz, = -H), 6.783-6.794 (m, 1H, Ar2-H), 6.536-6.554 (m, 1H, Ar2-H).
5g	10.823 (b, 1H, NH), 7.785-7.836 (d, 1H, *J* = 15.3 Hz, = -H), 7.502-7.605 (q, 4H, Ar-H), 7.281-7.310 (d, 2H, *J* = 8.7 Hz, Ar1-H), 6.767-6.794 (d, 2H, *J* = 8.1 Hz, Ar2-H), 6.685-6.736 (d, 1H, *J* = 15.3 Hz, = -H), 3.078 (s, 6H, -NCH_3) 300 MHz.
5h	10.831 (b, 1H, NH), 7.719-7.771 (d, 1H, *J* = 15.6 Hz, = -H), 7.711-7.740 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.371-7.400 (d, 2H, *J* = 8.7 Hz, Ar1-H), 7.337-7.371 (d, 2H, *J* = 9 Hz, Ar2-H), 7.228-7.263 (d, 2H, *J* = 9 Hz, Ar2-H), 6.939-6.977 (d, 1H, *J* = 15.3 Hz, = -H), 3.011 (b, -OH), 300 MHz (CD_3COCD_3).
5i	10.851 (b, 1H, NH), 8.133-8.183 (d, 1H, *J* = 15 Hz, = -H), 7.721-7.750 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.405-7.455 (d, 1H, *J* = 15 Hz, = -H), 7.373-7.402 (d, 2H, *J* = 8.7 Hz, Ar1-H), 7.276-7.351 (m, 2H, Ar2-H), 7.001-7.028 (d, 1H, *J* = 9 Hz, Ar2-H), 6.885-6.935 (t, 1H, Ar2-H), 2.975 (b, -OH) 300 MHz CD_3COCD_3.
5j	10.925 (b, 1H, NH), 7.755-7.805 (d, 1H, *J* = 15 Hz, = -H), 7.707-7.736 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.457 (s, 1H, Ar2-H), 7.370-7.399 (d, 2H, *J* = 8.7 Hz, Ar1-H), 7.290-7.318 (d, 2H, *J* = 8.4 Hz, Ar2-H), 7.161-7.210 (d, 1H, *J* = 15 Hz, = -H), 6.890-6.918 (d, 1H, *J* = 8.4 Hz, Ar2-H), 3.896 (s, 3H, Ar-O-CH_3), 2.966 (b, -OH) 300 MHz CD_3COCD_3.

agreement with the reaction mechanism reported by Maier.[27] Although the reaction mechanism was described, title compounds were reported as 1,2,3-triazole ring derivatives[26,28] or as steadier structures.[29] We know that the steadiness of the structure has something to do with the medium.

In order to confirm the reaction mechanism, compound **6** was prepared independently by the follow route of synthesis in Scheme III.

It is identified as a diazo compound showing strong IR absorption at 2125 cm^{-1} of **4** and 2114~2126 cm^{-1} of **5a~j**, as a dicarbonyl compound showing strong IR absorption at 1670, 1638 cm^{-1} of **4** and 1603~1676 cm^{-1} of **5a~j**, as a diazo com-

Table 4. MS spectral data for compounds **5a-j**

No	M^+	*m/z* (%)
5a	325 (18)	327 (M+2, 6%), 269 (2), 240 (5.6), 216 (4), 206 (10), 193 (5), 178 (3), 171 (17), 160 (6), 154 (3), 144 (15), 138 (6), 131 (66), 127 (28), 120 (38), 115 (100), 111 (15), 103 (37), 91 (20), 77 (40), 75 (25), 63 (22), 51 (25).
5b	359 (15)	361 (M+2, 10.2%), 278 (0.4), 276 (0.8), 274 (1.9), 233 (3), 207 (3), 205 (9), 195 (2.5), 193 (7), 182 (2), 180 (7), 178 (16), 167 (20), 165 (52), 151 (21), 149 (52), 131 (21), 127 (47), 125 (24), 115 (54), 111 (50), 91 (16), 77 (18), 69 (70), 57 (93), 43 (100).
5c	385 (15)	383 (M+2, 3.5%), 357 (3), 326 (3), 322 (2), 300 (3), 278 (2), 263 (3), 230 (100), 215 (10), 204 (47), 203 (32), 191 (54), 187 (28), 175 (40), 161 (33), 138 (7), 131 (36), 126 (23), 118 (23), 111 (21), 89 (38), 77 (37), 63 (40), 51 (27), 43 (31).
5d	369 (29)	371 (M+2, 12%), 286 (1.2), 284 (5), 248 (2), 215 (56), 214 (73), 204 (3), 188 (89), 186 (52), 185 (23), 175 (43), 164 (9), 159 (69), 145 (44), 135 (41), 127 (64), 117 (31), 111 (40), 102 (78), 91 (38), 89 (87), 77 (48), 75 (90), 63 (93), 51 (50), 43 (100).
5e	355 (11)	357 (M+2, 3%), 270 (1), 201 (15), 184 (2), 174 (19), 161 (35), 156 (15), 145 (42), 139 (18), 131 (22), 127 (19), 118 (11), 115 (11), 111 (23), 107 (19), 102 (32), 99 (16), 91 (26), 89 (21), 77 (37), 63 (30), 51 (24), 44 (100), 43 (48).
5f	315 (50)	317 (M+2, 17%), 260 (6), 258 (17), 252 (13), 237 (4), 230 (10), 202 (3), 193 (5), 178 (4), 167 (8), 161 (12), 154 (5), 150 (7), 138 (12), 134 (24), 126 (26), 121 (100), 111 (28), 105 (56), 99 (27), 94 (26), 78 (82), 65 (71), 51 (55), 43 (25), 39 (50).
5g	368 (15)	370 (M+2, 4%), 342 (5), 340 (4), 312 (1), 283 (3), 237 (2), 214 (10), 213 (14), 204 (1), 188 (8), 186 (35), 185 (52), 174 (36), 158 (100), 144 (22), 131 (15), 127 (21), 121 (5), 115 (41), 111 (19), 102 (12), 99 (16), 91 (14), 77 (17), 75 (19), 63 (19), 57 (37), 43 (42).
5h	341 (FAB)	342, 316, 307, 279, 237, 233, 214, 165, 157, 154, 147, 138, 136, 121, 120, 118, 115, 111, 107, 105, 91, 89, 84, 79, 77, 59.
5i	341 (FAB)	342, 307, 289, 284, 282, 256, 233, 214, 196, 179, 175, 171, 166, 152, 145, 144, 137, 127, 116, 115, 111.
5j	371 (FAB)	372, 307, 289, 279, 273, 232, 214, 165, 157, 155, 154, 147, 136, 135, 134, 121, 120, 118, 115, 111, 107, 105, 91, 89, 87, 84, 79, 77, 59, 56279.

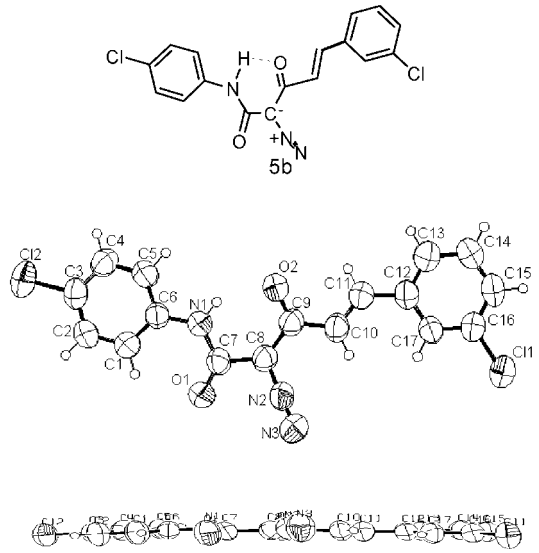
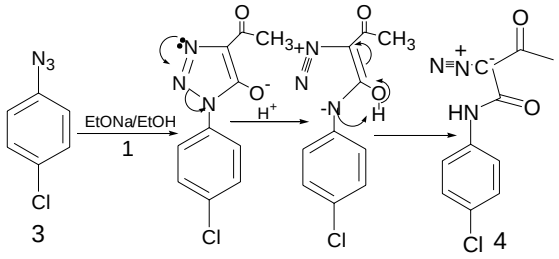
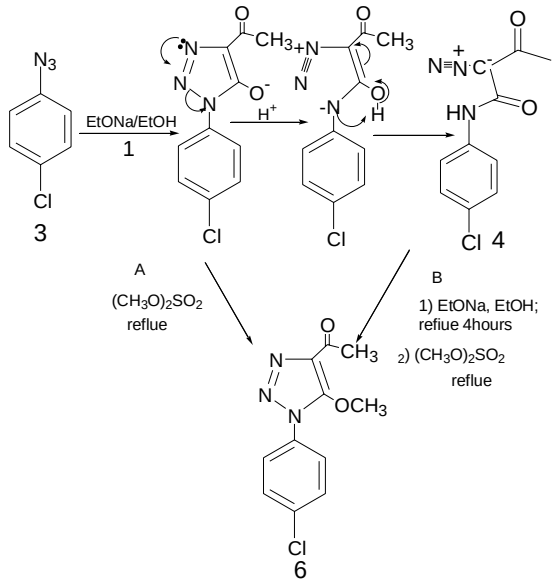


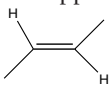
Fig. 1. ORTEP drawing of the title compound **5b** showing the atom numbering scheme.

Scheme II



Scheme III



pound showing -CONH- ^{1}H NMR peak at 10.216 ppm of **4** and 10.576~10.925 ppm of **5a~j** and showing  ^{1}H NMR dual peak 7.919~8.183 ppm, 5.053~7.445 ppm, J = 15~15.3 Hz of **5a~j** there is not 1,2,3-triazole ring system in molecule structure of compounds.[27] The bond lengths of N2-N3 1.116(6) Å in compound **5** aren't in agreement with the values reported for 1,2,3-triazole ring. The bond length is shorter than N=N (N1-N2 1.361(5) Å, N2-N3 1.295(5) Å).

The ring system and all atoms are planar in intermolecular, there is the conjugate of the pi-pi. It is shown in Fig. 1 and Fig. 2.

There are the strong interactions of hydrogen bond on the molecular stacking [N1-H1A 0.90 H1A⋯⋯O2 1.95 N1-H1A⋯⋯O2 2.697(5) Å N1-H1A⋯⋯O2 139.7(°)] but weak intermolecular interaction of the pi-pi.

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