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DIAZOALKYLIDENEAMINE-1,2,3-TRIAZOLE RING- CHAIN TAUTOMERISM IN 1,2-TRIAZOLO[1,5-c] PYRIMIDINES

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Abstract
Triazolopyrimidines have been synthesized and the unknown diazoalkylidine amine ring-chain tautomerism demonstrated for this ring system. Acetamidine-hydrochloride reacted readily with diethylacetonedicarboxylate in ethanolic sodium ethoxide to give pyrimidinone (8). Treatment of the pyrimidinone with toluene-p-sulponyl azide in trimethylamine gave diazo-compound which cyclised readily when heated under reflux in dimethylsulphoxide for 24 hours to afford the expected 1,2,3-triazolo[1,5-c]pyrimidinone (11) in a good yield. Also described is the condensation of diethylacetonedicarboxylate with a triazole in acetic acid to give another product acetoxybenzyl pyrimidinone (17).

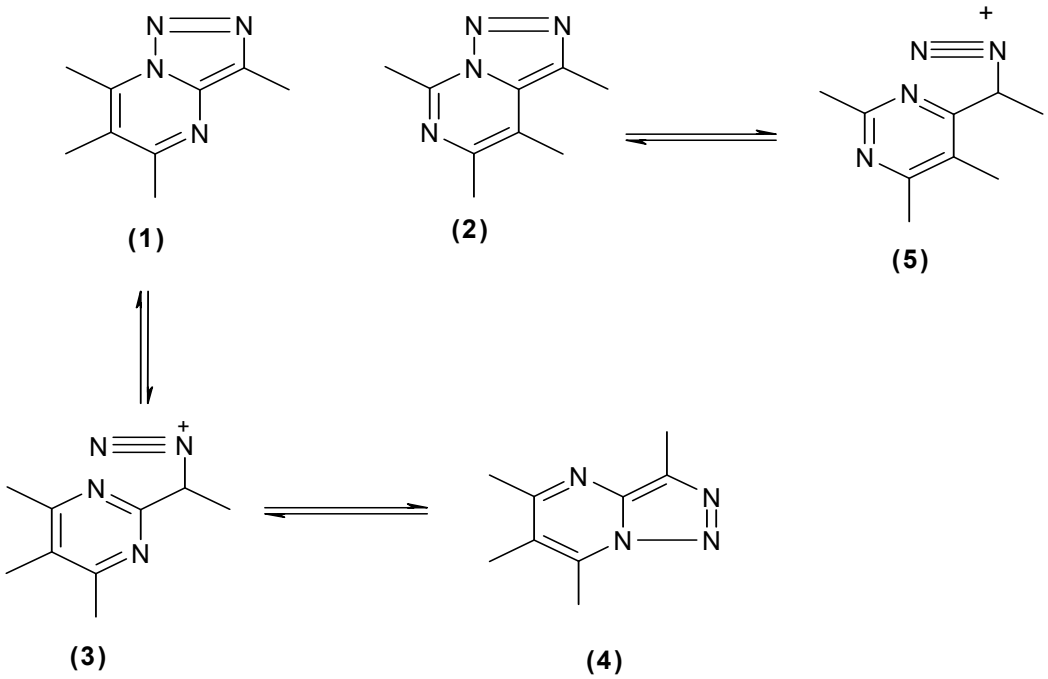
Key words: Triazolopyrimidines, Acetamidine HCl, toluene-p-sulponyl azide, ring-chain tautomerism

INTRODUCTION

Pyrimidine derivatives have diverse rang of significant biological and medicinal properties[1-8]. The 1,2,3-triazoles[9-11] on the other hand are important heterocycles which among other applications have been extensively used in medicine and agrochemicals. Recently, Dinakaran etal[12] reported that the fusion of pyrimidine moiety with different scaffolds gave rise to a class of hybrid heterocycles possessing improved activities.

There are just two possible bridged fused ring systems derivable by the fusion of pyrimidine ring with a 1,2,3-triazole. These are the 1,2,3-triazolo[1,5-a]pyrimidine ring system **(1)** which is known[13] and the yet unknown 1,2,3-triazolo[1,5-c]pyrimidine **(2).** The 1,2,3-triazolo[1,5-a]pyrimidine ring system is of interest because it exhibits the diazoalkylideneamine-1,2,3-triazole tautomerism **[(1) and (3)]**[14]**.** Consequently, it is of interest to investigate the possible existence of analogous ring-chain tautomerism **[(2) and (5)]** in triazolo[1,5-c]pyrimidines.

Also the demonstration of diazoalkylideneamine 1,2,3-triazole tautomerism in **[(2) and (5)]** would not be complicated by the concomitant Dimroth rearrangement **[(1), (3) and (4)]** exhibited by triazolo[1,5-a]pyrimidines.



EXPERIMENTAL

Solvents and reagents were purchased from Sigma-Aldrich and were used without further purification. Melting points were determined using Scott scientific melting point apparatus and are uncorrected. Infrared spectra data were obtained on FTIR-8400S and absorption were in wave number (cm^{-1}). Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) were determined on Variant 200MHz NMR instrument. Chemical shifts are reported on the δ-ppm scale. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quartet and multiplet respectively. The mass spectra were measured at 800kv on an A.E.I. M.S 902 instrument. Elemental analysis were obtained using Heraeus CHN-O rapid analyzer.

5-Aminotriazole (15) was prepared as described by Vevers[19]

6-Ethoxycarbonylemethylene-2-methylpyrimidin-4(3H)-one (8)

A solution of diethylacetonedicarboxylate (7) (0.81 g, 0.004 mol) and acetamidine hydrochloride (0.38 g, 0.004 mol) in absolute ethanol 20 ml was refluxed with a solution of sodium (0.23 g, 0.01 g atom) in absolute ethanol 10 ml for 1 h. the solid left after evaporation was dissolved in water, extracted with chloroform which on evaporation left oil. The oil was treated with ether to give colourless pyrimidinone (8) (0.37 g, 47%), m.p. 133^{o} (from benzene), ν_{max}. 1730 and 1690cm-1 (CO), ^{1}H-NMR ($CDCl_3$) δ: 6.30 (CH, s, CH), 4.20 (2H, 9, J 7Hz, CH_2), 3.55 (2H, s, CH_2), 2.55 (3H, s, CH_2) and 1.28 (3H, J 7Hz, CH_3).

Anal. Calcd. For $C_9H_{12}N_2O_3$: C, 55.00; H, 6.10; N, 14.30; M^+ 196

Found: C, 54.80; H, 6.00; N, 14.30; M^+ 196

6-(2-Diazoethoxycarbonylemethylene)-2-methylpyrimidine-4(H)-one (9)

A solution of the pyrimidinone ester (8) (1.57 g, 0.008 mol) in absolute ethanol 85 ml was cooled to 0^{o} (ice-salt bath), stirred and treated in one portion with triethylamine (3.20 g, 0.32 mol). This mixture was then treated drop wise with stirring, with a solution of toluene-p-sulponyl azide (3.15 g, 0.016 mol.) in absolute ethanol 25 ml and stirred in melting ice for 2 h. The mixture on evaporation left oily solid treated with ethanol-ether to give the diazo ester **(9)** as yellow needle (1.11 g) m.p. 211^{o}. i.r. (ethanol) ν_{max}; cm-^{1} 2150 (-N_2^+), 1700 and 1660 (CO). [$CDCl_3$] δ: 6.14 (1H, s, pyrimidine H), 4.10 (2H, q, J 7Hz, CH_2), 2.28 (3H, s, CH_3), 1.22 (3H, t, J 7Hz, CH_3); mass spectrum m/z (relative intensity %): 39(10), 46(5), 116(6), 121(25), 148(16), 265(25), 194(100), 22[M^+, 12] and 223(1).

Anal. Calcd. For $C_2H_{11}N_4O_3$: C, 48.40; H, 4.90; N, 25.10; M^+, 223

Found: C, 48.60; H, 5.00; N, 25.00; M^+, 223

6-(2-Acetoxyethoxycarbonylmethylene)-2-methylpyrimidin-4(3H)-one (10)

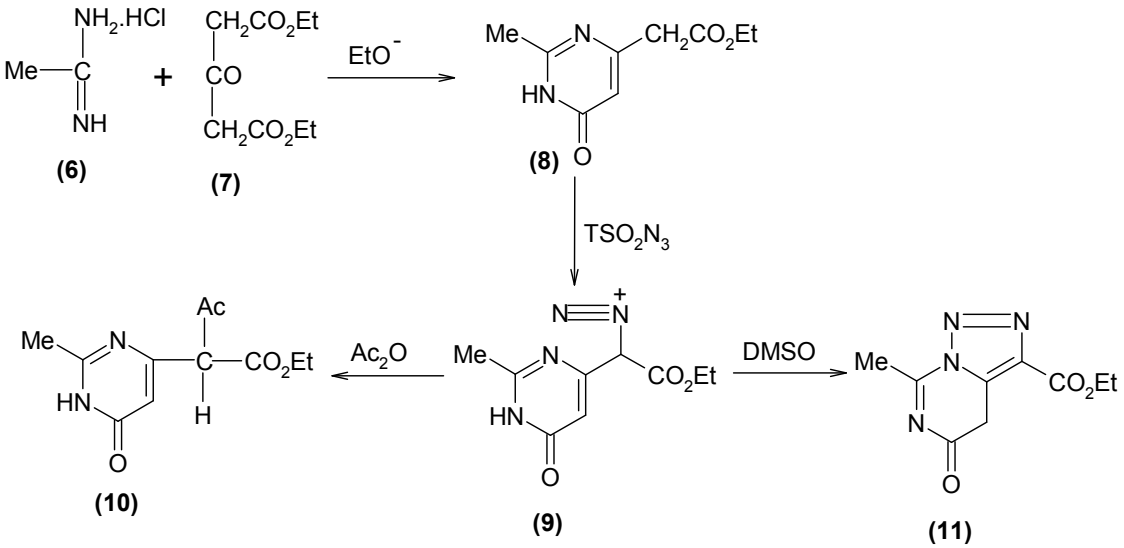
The diazoester (9) (0.44 g, 0.002 mol) was heated under reflux in glacial acetic acid (15.00 ml) for 17 h. the dark solution on evaporation left a dark oil whose trituration with ether gave the colourless acetoxy derivative (10) (0.27,g) m.p 121^{o} (benzene-light petroleum), $v_{max.}$ cm-^{1}: 1750 and 1620 (CO); [$(CD_3)_2SO$] δ: 6.34 (1H, s, CH), 5.68 (1H, s. CH), 4.14 (1H, 7Hz, CH_3); mass spectrum m/z (relative intensity); 433(2), 79(80), 1074(100), 122(45), 150(26), 166(70), 195(72), 238(M^+, 72), 239(0.5).
Anal. Calcd. For $C_{11}H_{14}N_2O_4$: C, 55.40; H, 5.80; N, 11.70, M^+ 238
Found: C, 55.50; H, 5.6; N, 11.8; M^+, 238.

2-(α-Acetoxybenzyl)-6-ethoxycarbonylmethylenepyrimidin-4(3H)-one (17)
A mixture of the amino-triazole (15) (0.64 g, 0.004 mol) and diethylacetonedicarboxylate (0.8 g, 0.004 mol) was refluxed in glacial acetic acid (10 ml) for 3 h. the solution was evaporated under reduced pressure to give an oil which on treatment with ethanol-ether gave the pyrimidinone (17) as a colourless solid (0.36 g) m.p. 158^{o} (water-ethanol) v_{max} 3160w (NH), 1755 and 1750 cm-1 (CO); [$(CD_3)_2SO$] δ: 7.37 (5H, S, Ar-H), 6.20 (1H, s, pyrimidine-H), 6.14 (1H, s, CHOAc), 4.00 (2H, q, J Hz, CH_2), 3.50 (2H, s, CH_2), 2.09 (3H, s, $OCOCH_3$) and 1.10 (3H, t, J Hz, CH_3); mass spectrum m/z (relative intensity): 28(4), 35(6), 91(100), 180(72), 271(25), 330(M^+ 26) and 331
Anal. Calcd. For $C_{17}H_{18}N_2O_5$: C, 61.80; H, 5.50; N, 8.50; M^+, 330
Found: C, 61.60; H, 5.50; N, 8.50; M^+, 330

6(2-Diazoethoxycarbonylmethylene)-2(α-hydroxybenzyl)pyrimidin-4-(2H)-one (18)
A solution of the pyrimidinone (17) (0.66 g, 0.002 mol) in absolute ethanol 75 ml was cooled to 0^{o} (ice-salt bath), stirred, treated in one portion with triethylamine (0.8 g, 0.008 mol) and then drop wise with toluene-p-sulphonyl azide (0.8 g, 0.004 mol) in absolute ethanol 5.0 ml. the mixture was suspended in 2 M sodium hydroxide. The alkaline solution was evaporated to give (18) as shiny yellow crystals (0.20 g) m.p. 200^{o} (ethanol-light petroleum); v_{max} cm-^{1}; 3360 br, 3130 w (NH), 2130 (-N_2^+) and 1785, 1760 (CO); [$(CD_3)_2SO$] δ: 7.44 (5H, m, Ar-H), 6.55 (1H, s, pyrimidine-H), 6.30 (1H, s, CHOH), 4.20 (2H, q, J 7Hz, CH_2) and 1.22 (3H, t, J 7Hz, CH_3); mass spectrum m/z (relative intensity): 28(10), 91(100), 122(7), 150(26), 178(70), 269(25), 286(14), 314 (M^+, 26) and 315.
Anal. Calcd. For $C_{15}H_{14}N_4O_4$: C, 57.20; H, 4.50; N, 17.80; M^+, 314
Found: C, 56.80; H, 4.59; N, 17.50; M^+, 314

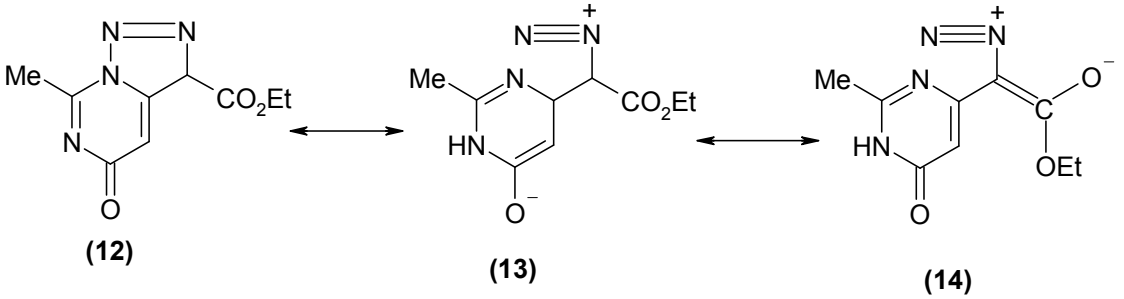
7-Benzyl-3-ethoxycarbonyl1,2,3-triazolo[1,5-c]pyrimidin-5-ol (19)
The diazo-ester (18) (1.2 g, 0.0038 mol) was heated under reflux in dimethylformamide 50 ml for 24 h. the solvent was evaporated under reduced pressure to give an oil which on treatment with ether gave the colourless triazole[1,5-c]pyrimidinol (19) (0.8 g) m.p. 214^{o} (ether); v_{max}; cm-^{1}: 3400 br (OH), 1725 (CO), [$(CD_3)_2SO$] δ: 7.35 (5H, s, Ar-H), 6.40 (1H, s, pyrimidine-H), 4.80 (2H, s, CH_2), 4.20 (2H, q, J 7Hz, CH_2), 1.15 (3H, t, J 7Hz, CH_3), -9.00 (1H, s, OH); mass spectrum m/z (relative intensity): 28(2), 73(21), 105(100), 196(32), 269(1), 270(32), 298[M^+, (16)], 299(0.5).
Anal. Calcd. For $C_{15}H_{14}N_4O_3$: C, 60.40, H, 4.70, N, 18.80; M^+, 298
Found: C, 66.50, H, 4.60, N, 18.70; M^+, 298.

RESULTS AND DISCUSSION
Acetamidine-hydrochloride (6) reacted readily with diethylacetonedicarboxylate (7) in ethanolic sodium ethoxide to give the pyrimidinone (8) containing an ethoxycarbonylmethylene group at C4. The spectral properties of (8) are consistent with the assigned structure. Thus its infrared spectrum showed NH and carbonyl absorptions characteristic of a cyclic amide structure. Also its ^{1}H-NMR spectrum contained a one proton singlet at δ 6.30 due to (H-5), a two proton singlet at δ 3.55 due to the methylene group and a three proton singlet at δ 2.45 attributed the methyl group.
The pyrimidinone (8) reacted with toluene-p-sulponyl azide in trimethylamine, in the diazo-transfer reaction[15], to give an excellent yield of the diazo-compound (9) whose structure was assigned on the basis of its n.m.r., mass spectrum and combustion analysis. Particularly, its mass spectrum showed a parent ion at m/z 222 and a fragment at m/e 194 (M^+-28) due to the loss of nitrogen. The structure of this diazomethylpyrimidinone (9) was firmly established by its conversion in hot solution of acetic anhydride into acetoxy-compound (10) whose i.r., n.m.r., mass spectrum and elemental analysis were consistent with the assigned structure. This formation of the acetoxy-compound (10) is typical of the diazo-alkyl species[3] scheme 1.



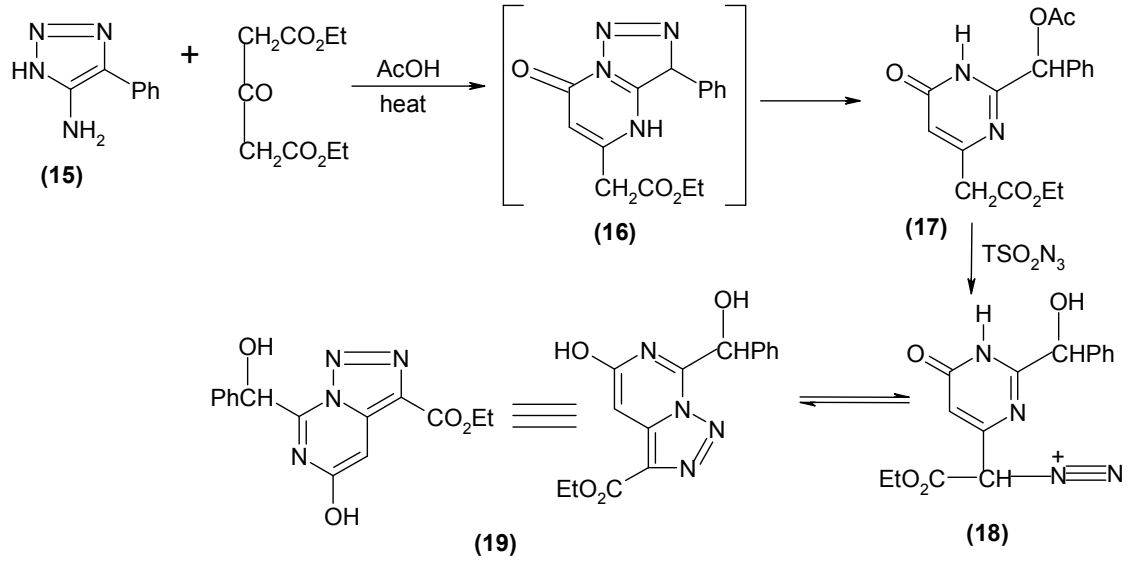
Scheme 1

Compound (10) was remarkably stable. Thus it was unaffected by attempted pyrolysis in refluxing toluene or xylene and it failed to undergo cycloaddition with either diethyl fumarate or dimethylacelenediacarboxylate. This stability of compound (10) may be due to the enhanced delocalization as shown in scheme 2.



Scheme 2

The diazonium compound (9) cyclised readily when heated under reflux in dimethylsulphoxide for 24 hours to afford the expected 1,2,3-triazolo[1,5-c] pyrimidinone (11) in a good yield. The structure (11) assigned to this triazolo[1,5-c]pyrimidinone was based on its spectral characteristics. Thus the i.r. spectrum of (11) contained NH absorption at 3400cm-[1]. Its ^{1}H-NMR spectrum showed a methyl at (C-7), a methylene group at (C-4) and an intact ethyl group. The combustion analysis of (11) was also in agreement with $C_9H_{10}N_4O_3$ while its mass spectrum showed M^+ of 222 and m/z 194(M^+-N_2) due to the loss of molecular nitrogen. The triazole (15) condensed with diethylacetonedicarboxylate in acetic acid to give a product whose properties are consistent with acetoxybenzyl pyrimidinone (17) scheme 3.



Scheme3

The i.r. spectrum of (17) in addition to a band due to the NH group, contained a high CO band at 1755cm-[1] attributed to the acetoxy group, and ester absorption at 1725cm-[1]. Also its [1]H-NMR spectrum showed a one proton single at δ 6.20 due to H (5), a proton singlet at δ 6.12.due to benzylic proton, a two proton signal at δ 3.42 due to methlene group and a three proton singlet δ 2.09 due to the acetoxy group in structure (17). The formation of this product (17) is readily explained by the formation of the expected triazolopyrimidinone (19) and its in situ acid-catalyzed triazole scission to the acetoxybenzylpyrimidinone (17)[16,17,18]. The structure of (17) was further established by its reaction at 0°C with toluene-p-sulphonyl azide in trimethylamine to give the diazo-compound (18) with concomitant hydrolysis of the acetoxy-group to the corresponding alcohol. The i.r. spectrum of (18) in addition to N and carbonyl absorption showed a diazo band at 2130cm-[1]. Its [1]H-NMR spectrum contained one proton singlet at δ 6.55 due to NH (5) and benzylic hydrogen respectively while the absorption due to the acetoxy group in the precursor (17) has disappeared. When the diazo compound (18) was heated under reflux with dimethyl formamide of a long period it cyclised to the expected triazo[1,5-c]pyrimideimine (19). The structure assigned to (19) was based on its spectral properties. Thus its i.r. spectrum showed a broad band at 3400cm-1 due to C (5) hydroxyl group and an intact ester group. The $_1$H-NMR spectrum showed a proton singlet at δ9.0 due to the acidic proton, one proton singlet at δ 6.50 due to the benzylic hydrogen and a two proton singlet at δ 4.75 due to the benzyl protons. Its combustion analysis is also correct for $C_{15}H_{14}N_4O_3$.

CONCLUSION

The various steps for the synthesis of the new expected 1,2,3-triazolo[1,5-c]pyrimidinone and its derivatives are described. All the intermediates and derivatives were characterized by spectral studies and elemental analysis.

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