[4+2] Cycloaddition reaction : Synthesis of 7,9-diaryl-1,3,5-trimethyl-2,4,8-trioxohexahydro-9H-pyrimido[2,1-g]purine derivatives

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Abstract : [4+2] Cycloaddition reaction between 8-arylidineaminocaffeine and aryl ketene or chloro keten generated *in situ* from aryl acetyl chloride or chloro acetyl chloride and triethylamine) formed 7,9-diaryl-1,3,5-trimethyl-2,4,8-trioxohexahydro-9H-pyrimido[2,1-g]purine in dioxane solvent is described.

Keywords : Cycloaddition, purines, heterocycles.

The purines are important class of heterocyclic nitrogen compounds and a large number of purine derivatives are found to be biologically active. Purines with a fused heterocyclic ring system are more interesting. An unusual class of compounds in which a carbohydrate moiety is fused to a purine ring in the 8,9-position has been reported. These tricyclic purine are reported¹ to be antiviral agents. A number of fused purine ring derivatives are reported to be adenosine receptor antagonists², antitumor agents³, antiviral⁴, potent PDE inhibitors⁵. It has been reported⁶ that tricyclic [2,1-f]theophylline possess sedative and analgesic activity, have long-lasting hypothermic effect and possess anticonvulsant properties. Purine derivatives such as theophylline, theobromine and caffeine are widely distributed in nature and have biological activities⁷. Therefore, it was assumed that it might be interesting to utilise caffeine for the syntheses of some possible pharmacologically active purines fused nitrogen heterocycles.

Results and discussion

In this paper a [4+2] cycloaddition reaction of 8-arylidineaminocaffeine with ketenes is disclosed. It is reported that phenylacetyl chloride in presence of triethylamine generally gives an azetidinones⁸ ring system. However, in our case the reaction of 8-arylidineaminocaffeine with ketene generated *in situ* from phenylacetyl chloride or chloroacetyl chloride in presence of triethylamine gives 7,9-diaryl-1,3,5-trimethyl-2,4,8-trioxohexahydro-9H-pyrimido[2,1-g]purine in good yield (Table 1). In this system, a part of the heterocyclic moiety (caffeine part) is incorporated

with the Schiff base comprises a heterodine system and attributes as 4 π component in Diels-Alder reactions. [4+2] Cycloaddition reaction were carried out by dropwise addition of a solution of phenylacetyl chloride or chloroacetyl chloride in dry 1,4-dioxane to a cool, stirred solution of 8-arylidineaminocaffeine in dry 1,4-dioxane and triethylamine for a period of 30 min. After the complete addition of acid chloride, the reaction mixture was stirred for a further period of 8 to 10 h more at 80 °C (Scheme 1).

Scheme 1

The structure of the compound 3 were assigned on the basis of elemental analysis and spectroscopic (IR, ¹H NMR and mass) data. The IR spectra (KBr) of the compound 3a showed an absorption band at 1708 cm⁻¹ due to the (C=O) group (6 membered C=O) at C-8 position of pyrimido pu-

Table 1. Physical data of 7,9-diaryl-1,3,5-trimethyl-2,4,8-trioxohexahydro-9H-pyrimido[2,1-g]purine (3a-g)

Compd	R ₁	R ₂	Yield (%)	M p (°C)
3a	H	Ph	75	288
3b	4-OCH ₃	Ph	78	295
3c	2-OCH ₃	Ph	70	300
3d	4-NO ₂	Ph	82	310
3e	4-Cl	Ph	80	290
3f	4-OCH ₃	Cl	70	265
3g	H	Cl	72	255

Table 2. Analytical and spectroscopic data for compound 3(a-g)

Compd.	Molecular formula (M ⁺)	Found (required) %			IR $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr)	¹ H NMR δ_{H} (CDCl ₃ + DMSO- <i>d</i> ₆)
		C	H	N		
3a	C ₂₃ H ₂₁ N ₅ O ₃ (415)	66.45 (66.50)	5.02 (5.06)	16.82 (16.86)	1708, 1690, 1640, 1605	3.22 (3H, s, N ₁ -CH ₃), 3.40 (3H, s, N ₃ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.35 (3H, s, N ₅ -CH ₃), 7.50–7.90 (10H, m, Ar-H)
3b	C ₂₄ H ₂₃ N ₅ O ₄ (445)	64.74 (64.72)	5.19 (5.17)	15.70 (15.73)	1700, 1690, 1640, 1605	3.02 (3H, s, OCH ₃), 3.22 (3H, s, N ₁ -CH ₃), 3.40 (3H, s, N ₅ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.50 (3H, s, N ₅ -CH ₃), 7.60–7.90 (9H, m, Ar-H)
3c	C ₂₄ H ₂₃ N ₅ O ₄ (445)	64.71 (64.72)	5.19 (5.17)	15.68 (15.73)	1710, 1690, 1640, 1610	3.10 (3H, s, OCH ₃), 3.25 (3H, s, N ₁ -CH ₃), 3.38 (3H, s, N ₅ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.40 (3H, s, N ₅ -CH ₃), 7.50–7.80 (9H, m, Ar-H)
3d	C ₂₃ H ₂₀ N ₆ O ₅ (460)	60.04 (60.00)	4.27 (4.34)	18.24 (18.26)	1710, 1695, 1652, 1610	3.21 (3H, s, N ₃ -CH ₃), 3.38 (3H, s, N ₃ -CH ₃), 3.55 (3H, s, N ₅ -CH ₃), 3.60 (1H, s, C-7), 3.81 (1H, s, C-9), 6.62–7.50 (9H, m, Ar-H)
3e	C ₂₃ H ₂₀ N ₅ O ₃ Cl (449)	61.46 (61.47)	4.42 (4.45)	14.58 (15.59)	1715, 1690, 1650, 1605	3.19 (3H, s, N ₃ -CH ₃), 3.38 (3H, s, N ₅ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.43 (3H, s, N ₅ -CH ₃), 7.30–8.10 (9H, m, Ar-H)
3f	C ₁₈ H ₁₈ N ₅ O ₄ Cl (403)	53.56 (53.59)	4.40 (4.46)	17.29 (17.37)	1710, 1695, 1640, 1610	3.02 (3H, s, OCH ₃), 3.28 (3H, s, N ₁ -CH ₃), 3.35 (3H, s, N ₅ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.45 (1H, s, N ₅ -CH ₃), 7.00–7.50 (4H, m, Ar-H)
3g	C ₁₇ H ₁₆ N ₅ O ₃ Cl (373)	54.65 (54.69)	4.25 (4.29)	18.70 (18.72)	1705, 1690, 1640, 1605	3.28 (3H, s, N ₁ -CH ₃), 3.35 (3H, s, N ₅ -CH ₃), 3.42 (1H, s), 3.45 (1H, s), 4.45 (1H, s, N ₅ -CH ₃), 7.00–7.50 (5H, m, Ar-H)

rine ring system, which clearly rules out the formation of β -lactum ring⁸. The ¹H NMR spectra of the compound 3a showed a singlet at δ 3.42 ppm and δ 3.45 ppm due to two isolated protons at C-9 and C-7 positions, 3.22 (3H, s, N₁-CH₃), 3.40 (3H, s, N₃-CH₃), 4.35 (3H, s, N₇-CH₃), 7.50–7.90 (10H, m, Ar-H). The mass spectra showed a molecular ion peak at 415 (M⁺, 100%). Similarly, other compounds 3(b-g) were prepared (Table 2).

Experimental

M.p.s were determined on a Buchi apparatus. Mass spectra were recorded with a LC-MS Bruker (Model esquire 3000) mass spectrophotometer. IR spectra were recorded on a Perkin-Elmer system-2000 FT IR spectrometer and ¹H NMR spectra were recorded on a Varian T-60/90 MHz spectrometer. Commercially available caffeine was used after recrystallization. 8-Nitro caffeine, 8-amino caffeine were prepared following literature procedure⁹.

Preparation of 7,9-diaryl-1,3,5-trimethyl-2,4,8-trioxo-hexahydro-9H-pyrimido[2,1-g]purine (3a) :

To a solution of 8-benzylideneaminocaffeine 1a 0.297 g (0.001 mol) in dry 1,4-dioxane (25 ml) was added triethylamine (0.5 ml). To this solution phenylacetyl chloride 0.154 g (0.001 mol) 2a in dry 1,4-dioxane (5 ml) was added dropwise at 0 °C with stirring for 30 min. The reaction mixture was brought to room temperature and stirring was continued for a further period of 6 h at 80 °C. The reaction mixture was cool to room temperature and poured into ice (100 g), extracted with chloroform (2 × 40 ml) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, the residue was recrystallized to gave 3a, yield 75%, m.p. 288 °C. IR (KBr, cm⁻¹) 1708, 1690, 1640 (C=O), 1605 (C=N), *m/z* 415 (M⁺, 100%), 118 (PhCH=C=O), 91 (PhCH/PhCH₂); δ_{H} 3.42 (1H, s, C-7), 3.45 (1H, s, C-9), 7.50–7.90 (10H, m, Ar-H). Similarly other compounds 3(b-g) were prepared. Physical and spectroscopic data of the compounds 3(a-g) are given in Tables 1 and 2.

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