

A novel synthesis of 2-acetyl-3-substituted-6-oxo-5-(arylmethylene)-1H-1,2,4-triazines

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Abstract: Mild treatment of 4-arylidene-2-methyloxazoline-5-ones and 4-arylidene-2-phenyloxazoline-5-ones with hydrazine hydrate gave corresponding cinnamhydrazides. These with excess acetic anhydride gave the title 1,2,4-triazines.

Introduction

A large number of uses were recorded in the literature for the 1,2,4-triazine ring system. Impressive results were obtained in their fuction as anti-bacterials,¹ antimalarials,² anti-inflammatory agents,³⁻⁶ antivirals,⁷⁻¹² antipsoriatics,¹³ antihypertensives,¹⁴ antiarthritics¹⁵ and coccidiostats.¹⁶⁻¹⁸ Other significant industrial attention was also paid to the triazines as pestisides, synthetic high polymers, chemical coatings, photographic fogging agent, dyes and intermediates in platic manufacture.

As a result of their demonstrated usefulness in many applications, and incontinuation of our interest in synthesizing various heterocyclic ring systems,¹⁹⁻²¹ we herein report a novel synthesis 1,2,4-triazines.

Discussion

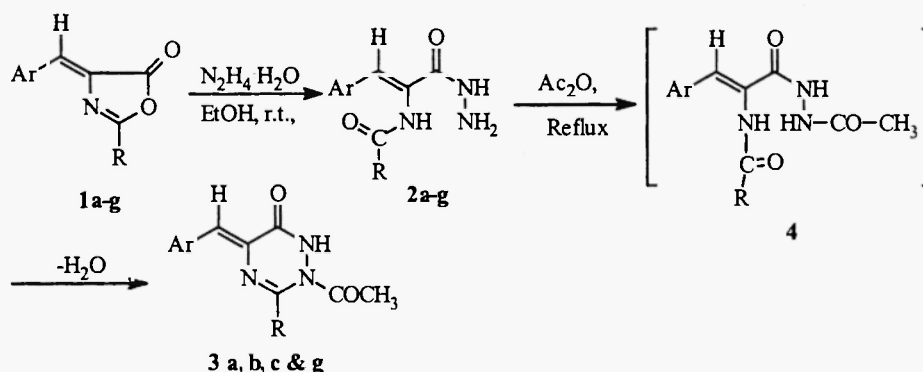
Treatment of 4-(4-fluorobenzylidene-2-methyloxazoline-5-one (**1a**) with hydrazine hydrate in ethanol at room temperature gave α -acetamido-4-fluorocinnamhydrazide (**2a**). Refluxion of (**2a**) with acetic anhydride gave light yellow crystalline compound m.p. 196°C (TLC single spot in ethylacetate). Mass spectrum of it revealed the molecular ion peak at m/z 261, corresponding to the molecular formula $C_{13}H_{12}N_3FO_2$. IR spectrum (KBr) indicates the presence of absorptions at 3294 cm^{-1} (NH) and 1720 cm^{-1} (δ -lactamic carbonyl). ^1H NMR (CDCl_3) revealed signals at δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, COCH_3), 7.1-8.3 (m, aromatic), 8.4 (br, 1H, NH, D_2O exchangeable). Based on the spectral data the strecture of the compound has been assigned as 2-acetyl-3-methyl-6-oxo-5-(4-fluorophenylmethylene)-1H-1,2,4-triaziene (**3a**).

The formation of the **3** can be best explained on the basis of attack of acetic anhydride on the primary amino group of **2** resulting in the unstable intermediate **4**. It readily undergoes dehydrative cyclization in the presence of acid

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to yield **3**.

Another interesting feature of the cyclization reaction **2** → **3**, is the influence of substituent group on the aromatic ring. Electron withdrawing groups on the aromatic ring of **2** facilitates to the desired 1,2,4-triazines **3a, b, c** & **g**. For electron releasing group like **2d** no compound was isolated. Starting material **1e, f** was recovered for the unsubstituted aromatic ring in **2e, f** (confirmed by ¹H NMR, IR and m.p.) (Scheme-1). Desired triazines **3e, f** were could not achieved even by using acetic anhydride in combination with AcOH, H₂SO₄ and PPA.



Scheme-1

1-3	R	Ar
a	CH ₃	4-FC ₆ H ₄
b	CH ₃	3-NO ₂ C ₆ H ₄
c	CH ₃	4-NO ₂ C ₆ H ₄
d	CH ₃	4-CH ₃ OC ₆ H ₄
e	CH ₃	C ₆ H ₅
f	C ₆ H ₅	C ₆ H ₅
g	C ₆ H ₅	4-FC ₆ H ₄

Experimental

Melting points were uncorrected and taken with sulphuric acid bath. IR spectra were recorded in KBr on a Perkin-Elmer 1650 spectro photo meter NMR spectra on a Bruker DRX-200 spectro meter with TMS as an internal standard and mass spectra on MS PE SCIEX API 3000 instruments.

General procedure - Cinnamhydrazides (**2**)

Oxazoline-5-ones (**1**, 0.03 mole) were mixed with a solution of hydrazine hydrate (100%) (0.06 mole) in ethanol 25 mL. The deep yellow colour of the oxazoline-5-one immediately changed to light yellow, which were filtered, washed and crystallised from methanol.

General Procedure - 1,2,4-Triazines (**3**)

Cinnamhydrazides (**2**, 3 g) were refluxed with 18 mL of Ac₂O for 1 h, excess of Ac₂O was distilled off and poured onto crushed ice. The solid thus separated was dried and chromatographed over a column of silica gel (80-120 mesh) using ethylacetate-hexane (85:15) as eluant to yield the corresponding 1,2,4-1*H*-triazines.

2a M.P. 179-180°C; Yield 75%; I.R (KBr) : 3217, 3323 cm⁻¹ (NH₂), 3003 (-NH); ¹H NMR (DMSO-d₆) : δ 1.9 (s, 3H, COCH₃), 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.0 (s, 1H, CH-Ar), 7.2-7.7 (m, 4H, aromatic), 9.3 (br, 1H, NH, D₂O

exchangeable), 9.4 (br, 1H, NH, D₂O exchangeable).

2b : M.P. : 123-126°C; Yield : 85%; I.R (KBr) : 3150, 3300 cm⁻¹ (NH₂), 3000 (-NH); ¹H NMR (DMSO-d₆) : δ 2.0 (s, 3H, COCH₃), 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.7 (m, 4H, aromatic), 9.2 (br, 1H, NH, D₂O exchangeable), 9.3 (br, 1H, NH, D₂O exchangeable).

2c : M.P. : 179°C; Yield : 88%; I.R (KBr) : 3125, 3310 cm⁻¹ (-NH₂), 3000 (-NH); ¹H NMR (DMSO-d₆) : δ 2.0 (s, 3H, COCH₃), 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.8 (m, 4H, aromatic), 9.2 (br, 1H, NH, D₂O exchangeable), 9.3 (br, 1H, NH, D₂O exchangeable).

2d : M.P. : 99-102°C; Yield : 85%; I.R (KBr) : 3220, 3315 cm⁻¹ (-NH₂), 3000 (-NH); ¹H NMR (DMSO-d₆) : δ 1.9 (s, 3H, COCH₃), 3.8 (s, 3H, OCH₃), 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.1 (s, 1H, CH-Ar), 7.1-8.0 (m, 4H, aromatic), 9.4 (br, 1H, NH, D₂O exchangeable), 9.5 (br, 1H, NH, D₂O exchangeable).

2e : M.P. : 174°C; Yield : 84%; I.R (KBr) : 3228.6, 3163 cm⁻¹ (NH₂), 3020.3 cm⁻¹ (NH); ¹H NMR (DMSO-d₆) : δ 1.9 (s, 3H, COCH₃), 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.0 (s, 1H, CH-Ar), 7.32-8.3 (m, 5H, Aromatic), 9.4 (br, 1H, NH, D₂O exchangeable), 9.5 (br, 1H, NH, D₂O exchangeable).

2f : M.P. : 174-176°C; Yield : 75%; I.R (KBr) : 3200, 3150 cm⁻¹ (-NH₂), 3000 (-NH); ¹H NMR (DMSO-d₆) : δ 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.7 (m, 10H, aromatic), 9.4 (br, 1H, NH, D₂O exchangeable), 9.8 (1H, NH, D₂O exchangeable).

2g : M.P. : 165-167°C; Yield : 80%; I.R (KBr) : 3200, 3150 cm⁻¹ (-NH₂), 3020 (-NH); ¹H NMR (DMSO-d₆) : δ 4.3 (br, 2H, NH₂, D₂O exchangeable), 7.0 (s, 1H, CH-Ar), 7.1-7.7 (m, 9H, aromatic), 9.4 (1H, NH, D₂O exchangeable), 9.8 (1H, NH, D₂O exchangeable).

3a : M.P. : 196-197°C; Yield : 60%; I.R (KBr) : 3294 cm⁻¹ (-NH), 1720 (CO); ¹H NMR (CDCl₃) : δ 2.2 (s, 3H, CH₃), 2.4 (s, 3H, COCH₃), 7.1-8.3 (m, aromatic), 8.4 (br, 1H, NH, D₂O exchangeable); MS : m/z 261; Anal. calcd. for C₁₃H₁₂N₃FO₂ : C, 59.77; H, 4.59; N, 16.09; Found C, 59.6; H, 4.42; N, 15.9%.

3b : M.P. : 194-195°C; Yield : 55%; I.R (KBr) : 3300 cm⁻¹ (-NH), 1720 cm⁻¹ (CO); ¹H NMR (CDCl₃) : δ 2.3 (s, 3H, CH₃), 2.5 (s, 3H, COCH₃), 7.0-8.2 (m, aromatic), 8.5 (br, 1H, NH, D₂O exchangeable); MS : m/z 288. Anal. calcd. for C₁₃H₁₂N₄O₄ : C, 54.16; H, 4.16; N, 19.44; Found C, 54.0; H, 4.05; N, 19.3%.

3c : M.P. : 248-250°C (decomp.); Yield : 60%; I.R (KBr) : 3310 cm⁻¹ (-NH), 1745 cm⁻¹ (CO); ¹H NMR (CDCl₃) : δ 2.3 (s, 3H, CH₃), 2.5 (s, 3H, COCH₃), 7.0-8.2 (m, aromatic), 8.5 (br, 1H, NH, D₂O exchangeable); MS : m/z 288; Anal. calcd. for C₁₃H₁₂N₄O₄ : C, 54.16; H, 4.16; N, 19.44; Found C, 53.96; H, 4.00; N, 12.80%.

3g : M.P. : 165-197°C (decomp.); Yield : 63%; I.R (KBr) : 3265 cm⁻¹ (-NH), 1735 cm⁻¹ (CO); ¹H NMR (CDCl₃) : δ 2.5 (s, 3H, COCH₃), 7.0-8.5 (m, aromatic), 9.5 (br, 1H, NH, D₂O exchangeable); M.S : m/z 323; Anal. calcd. for C₁₈H₁₄N₃FO₂ : C, 66.87; H, 4.33; N, 13.00; Found C, 66.75; H, 4.22; N, 12.8%.

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