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

T.V. Maruthikumar and P. Hanumantha Rao*

Department of Chemistry, Osmania University, Hyderabad-500 007, India
E-mail : tvmarutikumar@hotmail.com

Abstract: Mild treatment of 4-arylidene-2-methyloxazoline-5-ones and 4-arylidene-2-phenyloxazoline-5-ones with hydrazine hydrate gave corresponding cinnamhydrzides. 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] antiarthritics[15] 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 platsic 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

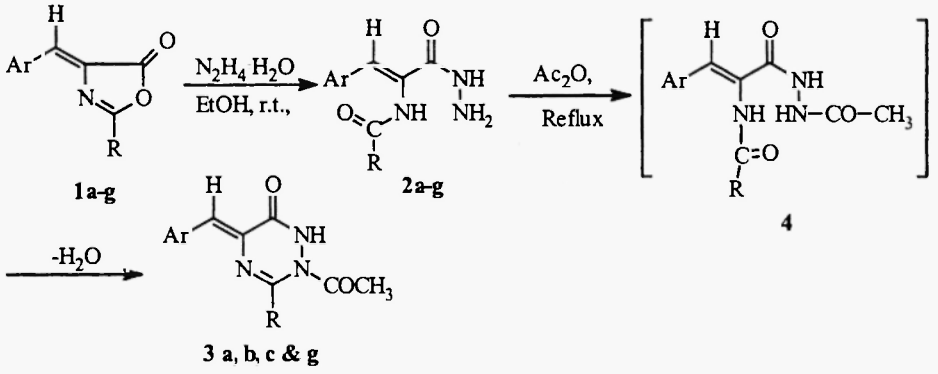
Treatment of 4-(4-fluorobenzylidene-2-methyloxazoline-5-one (**1a**) with hydrazine hydrate in ethanol at room temperature gave α-acetamido-4-flurocinnamhydrazide (**2a**). Refluxion of (**2a**) with acetic anhydride gave light yellow crystalline compound m.p. 196°C (TLC single spot in ethylacetate). 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)-1*H*-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

* To whom correspondence should be addressed
(Previous name was P. Hanumanthu)

to yield **3**.

Another interesting feature of the cyclization reaction **2** → **3**, is the influence of substituent group on the aromatic ring. Electron with drawing 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 ^{1}H NMR, IR and m.p.) (Scheme-1). Desired triazines **3e, f** were could not achieved even by using acetic anhydride in combination with AcOH, H_2SO_4 and PPA.



Scheme-1

1-3	R	Ar
a	CH_3	4-FC_6H_4
b	CH_3	3-$NO_2C_6H_4$
c	CH_3	4-$NO_2C_6H_4$
d	CH_3	4-$CH_3OC_6H_4$
e	CH_3	C_6H_5
f	C_6H_5	C_6H_5
g	C_6H_5	4-FC_6H_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 Brucker 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-Trazines (3)

Cinnamhydrazides (**2**, 3 g) were refluxed with 18 mL of Ac_2O for 1 h, excess of Ac_2O 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} (NH_2), 3003 (-NH); ^{1}H NMR (DMSO-d_6) : δ 1.9 (s, 3H, $COCH_3$), 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.0 (s, 1H, CH-Ar), 7.2-7.7 (m, 4H, aromatic), 9.3 (br, 1H, NH, D_2O

exchangeable), 9.4 (br, 1H, NH, D_2O exchangeable).

2b : M.P. : 123-126°C; Yield : 85%; I.R (KBr) : 3150, 3300 cm^{-1} (NH_2), 3000 (-NH); ^1H NMR (DMSO-d_6) : δ 2.0 (s, 3H, $COCH_3$), 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.7 (m, 4H, aromatic), 9.2 (br, 1H, NH, D_2O exchangeable), 9.3 (br, 1H, NH, D_2O exchangeable).

2c : M.P. : 179°C; Yield : 88%; I.R (KBr) : 3125, 3310 cm^{-1} (-NH_2), 3000 (-NH); ^1H NMR (DMSO-d_6) : δ 2.0 (s, 3H, $COCH_3$), 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.8 (m, 4H, aromatic), 9.2 (br, 1H, NH, D_2O exchangeable), 9.3 (br, 1H, NH, D_2O exchangeable).

2d : M.P. : 99-102°C; Yield : 85%; I.R (KBr) : 3220, 3315 cm^{-1} (-NH_2), 3000 (-NH); ^1H NMR (DMSO-d_6) : δ 1.9 (s, 3H, $COCH_3$), 3.8 (s, 3H, OCH_3), 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.1 (s, 1H, CH-Ar), 7.1-8.0 (m, 4H, aromatic), 9.4 (br, 1H, NH, D_2O exchangeable), 9.5 (br, 1H, NH, D_2O exchangeable).

2e : M.P. : 174°C; Yield : 84%; I.R (KBr) : 3228.6, 3163 cm^{-1} (NH_2), 3020.3 cm^{-1} (NH); ^{1}HNMR (DMSO-d_6) δ : 1.9 (s, 3H, $COCH_3$), 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.0 (s,1H, CH-Ar), 7.32-8.3 (m, 5H, Aromatic), 9.4 (br, 1H, NH, D_2O exchangeable), 9.5 (br, 1H, NH, D_2O exchangeable).

2f : M.P. : 174-176°C; Yield : 75%; I.R (KBr) : 3200, 3150 cm^{-1} (-NH_2), 3000 (-NH); ^1H NMR (DMSO-d_6) : δ 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.1 (s, 1H, CH-Ar), 7.2-7.7 (m, 10H, aromatic), 9.4 (br, 1H, NH, D_2O exchangeable), 9.8 (1H, NH, D_2O exchangeable).

2g : M.P. : 165-167°C; Yield : 80%; I.R (KBr) : 3200, 3150 cm^{-1} (-NH_2), 3020 (-NH); ^1H NMR (DMSO-d_6) : δ 4.3 (br, 2H, NH_2, D_2O exchangeable), 7.0 (s, 1H, CH-Ar), 7.1-7.7 (m, 9H, aromatic), 9.4 (1H, NH, D_2O exchangeable), 9.8 (1H, NH, D_2O exchangeable).

3a : M.P. : 196-197°C; Yield : 60%; I.R (KBr) : 3294 cm^{-1} (-NH), 1720 (CO); ^1H NMR ($CDCl_3$) : 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); MS : m/z 261; Anal. calcd. for $C_{13}H_{12}N_3FO_2$: 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 ($CDCl_3$) : δ 2.3 (s, 3H, CH_3), 2.5 (s, 3H, $COCH_3$), 7.0-8.2 (m, aromatic), 8.5 (br, 1H, NH, D_2O exchangeable); MS : m/z 288. Anal. calcd. for $C_{13}H_{12}N_4O_4$: 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 ($CDCl_3$) : δ 2.3 (s, 3H, CH_3), 2.5 (s, 3H, $COCH_3$), 7.0-8.2 (m, aromatic), 8.5 (br, 1H, NH, D_2O exchangeable); MS : m/z 288; Anal. calcd. for $C_{13}H_{12}N_4O_4$: 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 ($CDCl_3$) : δ 2.5 (s, 3H, $COCH_3$), 7.0-8.5 (m, aromatic), 9.5 (br, 1H, NH, D_2O exchangeable); M.S : m/z 323; Anal. calcd. for $C_{18}H_{14}N_3FO_2$: C, 66.87; H, 4.33; N, 13.00; Found C, 66.75; H, 4.22; N, 12.8%.

Acknowledgement : One of the author (T.V.M.K) is thankful to the Head, Department of Chemistry Osmania University for providing lab facilities.

References

1. German Patent 2,353,129.

2. L. March, G. Bajue, J. Lee, K. Wasti and M. Jouillie, M. J. Med. Chem. 19, 845 (1976).

3. U.S. Patent 4,018,923.

4. G. Bennett, R. Mason, L. Alden and J. Jr. Roach, J. Med. Chem. 21, 623 (1978).

5. U.S. Patent 4,021,553.

6. M. O'Rourke, S. Jr. Lang and E. Cohen, J. Med. Chem. 20, 723 (1977).

7. Russian Patent 518,194.

8. U.S. Patent 3,980,774.

9. U.S. Patent 4,032, 659.

10. CA 1977, 87, 62810.

11. U.S. Patent 4,027,039.

12. E. Decleraeq and A. Haly, J. Med. Chem. **22**, 510 (1979).

13. F. Perlic, J. Elis and M. Kublikova, Eur. J. Clim. Pharmacol. **6**, 141 (1973).

14. W. Heilman, R. Heilman, J. Scozzie, R. Wayner, J. Gullo and Z. Ariyan, J. Med. Chem. **22**, 671 (1979).

15. R. Sofia, L. Danielson and H. Vassar, Pharmacol. Res. Commun. **11**, 179 (1979).

16. U.S. Patent 4,053,602.

17. B. Mylari, M. Miller, H. Jr. Howes, S. Figdor, J. Lynch and R. Koch, J. Med. Chem. **20**, 475 (1977).

18. A. Kluge, J. Caroon, S. Unger and J. Ryley, J. Med. Chem. **21**, 529 (1978).

19. A. Naraharibabu, V.N.S. Ramesh Babu, P. Hanumanthu, Synth. Commun. **27**, 1487 (1997).

20. A. Naraharibabu, V.N.S. Ramesh Babu, P. Hanumanthu, Synth. Commun., **28**, 4439 (1998).

21. A. Naraharibabu, V.N.S. Ramesh Babu, P. Hanumanthu, Synth. Commun., **29**, 665 (1999).

Received on September 28, 2002