

Note

One pot synthesis of 3-acetoacetyl-5-oxo-5H-[1] benzopyrano [3,2-e]pyridin-2-one from triacetic acid lactone

Zeba N Siddiqui*, Gulrana Khuwaja & M Asad

*Department of Chemistry, Aligarh Muslim University,
Aligarh 202 002, India
E-mail: siddiqui_zeba@yahoo.co.in

Received 12 June 2006

The nucleophilic character of triacetic acid lactone has been exploited here in the Michael condensation reaction involving 2-amino-3-formylchromone as the starting material. The reaction, as visualized, afforded yellow crystalline product **4**. The compound has been characterized on the basis of spectral data and evaluated for antimicrobial activity.

Keywords: Triacetic acid lactone, 3-acetoacetyl-5-oxo-5H-[1] benzopyrano [3,2-e] pyridin-2-one, antimicrobial activity, green chemistry

IPC Code: Int. Cl.⁸ C07D

Triacetic acid lactone¹, TAL, is a polyketide as suggested by J N Collie² for polyketomethylene compounds $\text{CH}_3(\text{-CO-CH}_2-)_n$ and is involved in the biosynthesis of natural products. Recently it has been reported that type III polyketide synthases (PKS III) which are small homodimeric proteins catalyse the biosynthesis of aromatic polyketide in plants and bacteria^{3,4}. A number of type III PKS are present in plants other than chalcone synthase which is used for catalyzing naringenin chalcone, a precursor of flavonoids and isoflavonoids^{5,6}. This includes 2-pyrone synthase (PS) which gives TAL (4-hydroxy-6-methyl-2-pyrone). PS forms TAL by lactonization of a triketide intermediate⁷. TAL is, thus, precursor of a phytalexin in plant Gerbara hybrid^{8,9}. Polyketides, therefore, form a very large and diverse group of natural products having important physiological effects.

Besides these, compounds possessing varied pharmacological properties have also been synthesized from TAL. This includes a heterocyclic ketone which induces the production of thrombocytes, leukocytes, erythrocytes and is effective in cancer chemotherapy^{10,11}. Other derivatives of TAL are used as anticonvulsants and antiepileptics¹² whereas tricyclic and tetracyclic pyrones have been used as anticancer agents^{13,14}.

In view of diverse biological activities of com-

pounds from TAL, an easy and one-step synthesis of new polyketomethylene compound, 3-acetoacetyl-5-oxo-5H-[1] benzopyrano-[3,2-e] pyridin-2-one, involving TAL and 2-amino-3-formylchromone is reported. The compound obtained, is tested for antimicrobial activity. It is pertinent to mention that 2-amino-3-formylchromone is an interesting compound as it has been used for the synthesis of azaxanthones which possess antiallergic¹⁵⁻¹⁸ and bronchodilating activities^{19,20}.

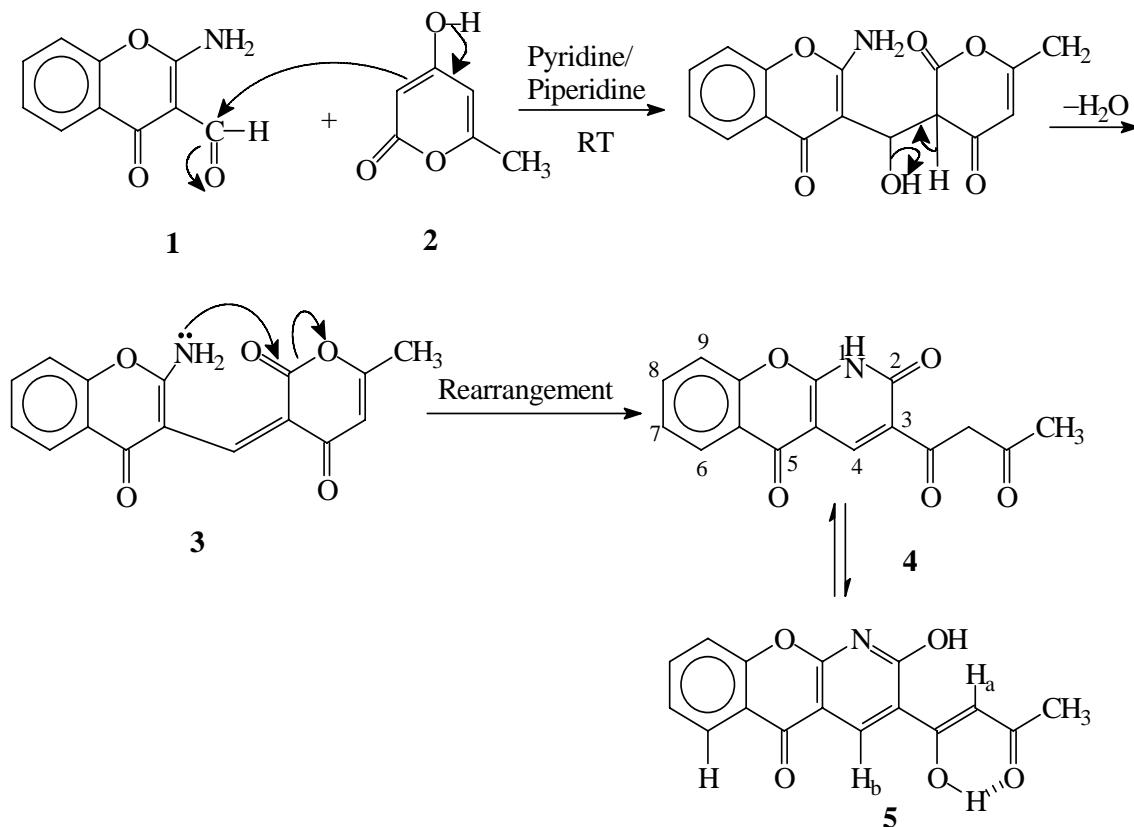
Results and Discussion

Due to the presence of C=C bond at position 3, TAL, **2** exhibits nucleophilic properties similar to 4-hydroxycoumarin. Thus, Michael addition and aldol condensation occur readily to give interesting polyketomethylenes²¹⁻²³.

In a series of papers Spanish workers have discussed at length that enol lactones react with salicycaldehyde to form products through intramolecular translactonization^{24,25}. In an attempt to synthesize 3-formyl derivative of **2**, which was need in the context of another project, the reaction mixture, however, afforded the rearranged product through intramolecular translactonization²⁶.

The intramolecular translactonization takes place by opening up of the lactone ring by nucleophilic attack of hydroxyl group of salicylaldehyde. Since amino group shows better nucleophilic property than hydroxyl group, the intramolecular translactonization will occur much easily to afford the rearranged product. A similar type of rearrangement is, thus, possible in the reaction carried out by treatment of 2-amino-3-formylchromone **1** with **2** to give **4**. A positive ferric chloride test further supported that this actually has happened (**Scheme I**).

The IR spectrum showed strong bands at 1647 with shoulders at 1652 and 1642 cm^{-1} for chromone, lactam and chelated carbonyl groups. In the ¹H NMR spectrum methyl singlet was clearly discernible at δ 2.28. A sharp singlet at δ 7.09 was assigned to H_a proton. The presence of chromone ring was established by *ortho* coupled doublet of C₆ proton at δ 8.2 (*J* = 9 Hz). The most deshielded olefinic proton in the compound H_b appeared as a sharp singlet at δ 8.86.



Scheme I

Two broad singlets which appeared at δ 16.5 and 13.5 (D_2O exchangeable) indicated the presence of two OH groups in the compound. Thus, **4**, also exists in tautomeric form **5**. The structure **4** of the compound was supported by its mass spectrum which showed M^+ at 297. The other relevant peaks were obtained as shown in **Scheme II**.

Transformation of **4** to other heterocyclic compounds is in progress.

The compound **4** showed moderate antibacterial activity against two types of organism (*Bacillus subtilis* and *Staphylococcus aureus*). However, the compound was not active against gram-negative bacteria. Similarly, the compound demonstrated fair activity against *Candida albicans* and filamentous fungi (*Helminthosporum oryzae*, *Macrophomina phaseolina*) as compared to antifungal drug nystatin (**Table I**).

Conclusion

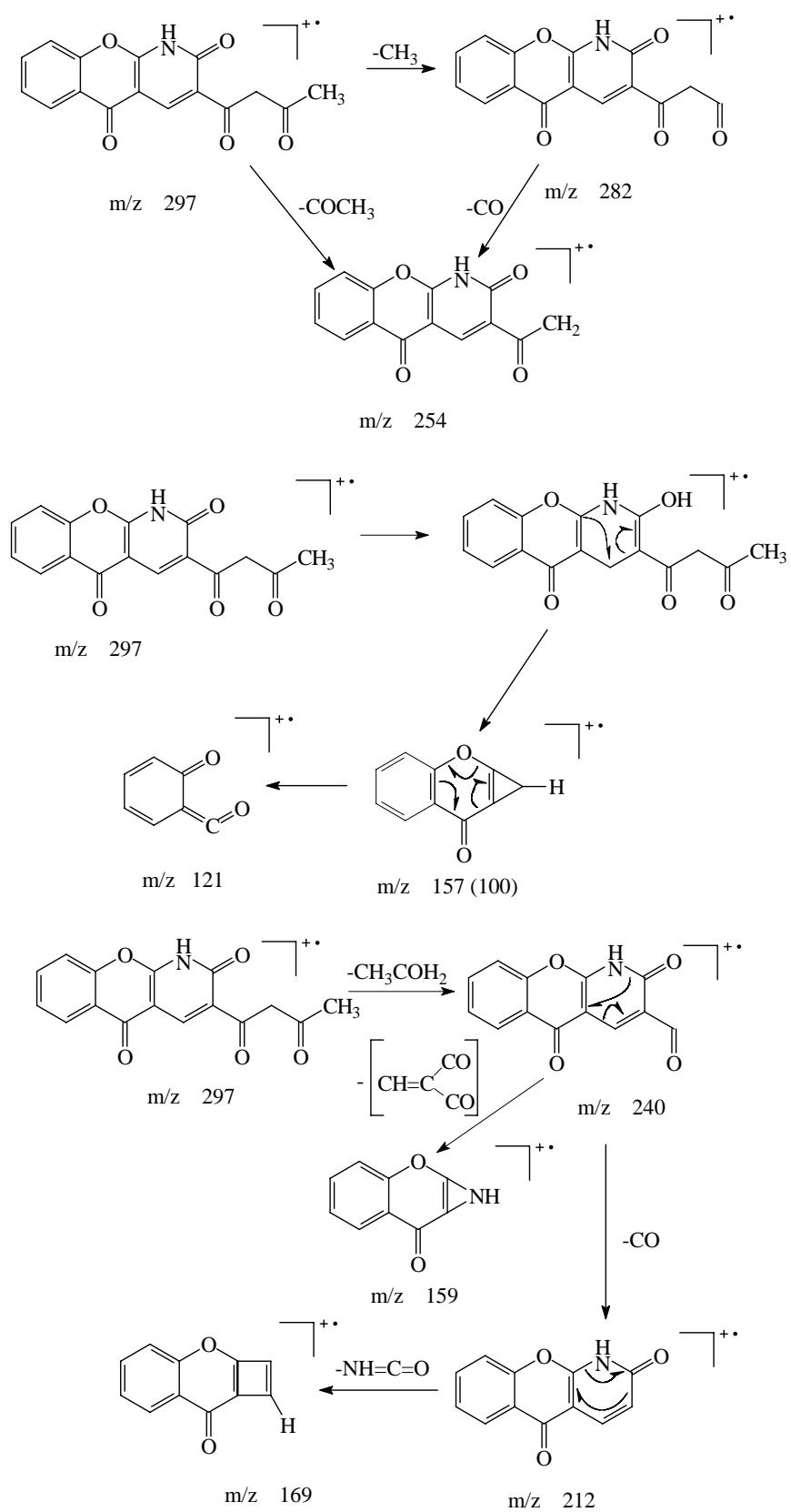
Hagen *et al.* have synthesized similar compounds with herbicidal activities using more drastic condi-

tions²⁷. Thus, we have provided a sustainable energy saving method for the synthesis of 3-substituted pyrano[2,1-f]quinolin-2-one at room temperature in quantitative yield.

The compound has shown moderate activity against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and good activity against fungi. The activity was determined on the basis of size of growth inhibition zone which was found 10 and 9 mm for the test bacteria and 10-12 mm against test fungi.

Experimental Section

The melting points were taken in open capillary tube and are uncorrected. IR spectrum of the compounds was recorded on a Perkin-Elmer R XI spectrometer, 1H NMR spectrum on a Bruker DRX-300 MHz spectrometer with TMS as internal solvent and mass spectrum on a Jeol SX-102 (FAB). The purity of the compound was checked by TLC on glass plates coded with silica gel G (Merck-Germany) using benzene-ethyl acetate as mobile phase and visualized by iodine vapors.



Scheme II

Table I – Antimicrobial activity of **4**

S. No.	Bacteria	Test microorganisms	Zone of inhibition size in mm	Antibiotic control chloramphenicol
1	G+	<i>Bacillus subtilis</i>	10	38
2		<i>Staphylococcus aureus</i>	09	33
3		<i>Salmonella typhi</i>	-	16
4	G-	<i>Pseudomonas aeruginosa</i>	-	26
5		<i>Escherichia coli</i>	-	30
6		<i>Salmonella typhimurium</i>	-	35
7.	Yeast	<i>Candida albicans</i>	12	-
8.		<i>Fusarium chlamydosporum</i>	-	19
9.		<i>Aspergillus niger</i>	-	18
10.	Filamentous fungi	<i>Fusarium solani</i>	-	18
11.		<i>Helminthosporum oryzae</i>	10	16
12.		<i>Macrophomina phaseolina</i>	10	21

- No activity detected.

Culture media and inoculum

Nutrient (N) and Sabouraud Dextrose (SD) (Hi-Media Pvt. Ltd., Mumbai, India) were used to culture the test bacteria and fungi respectively. The microbial cultures (test bacteria and *Candida albicans*) were grown at 37°C for 18 hr and then appropriately diluted with sterile 0.8% saline solution to obtain a cell suspension of 10⁵ CFU/mL. Similarly an inoculum of viable spore/mycelial fragments (10⁵ CFU/mL) was prepared from filamentous fungi²⁸.

Antimicrobial assays

Antimicrobial activity of the compounds was assayed by the disc diffusion method²⁹ with little modification. Briefly 0.1 mL of diluted inoculum (10⁵ CFU/mL) of test organism was spread on nutrient agar/Sabouraud dextrose agar plates. Sterile paper disc impregnated with 50 µg of compounds and a disc without compound was used as a negative control. The plates were incubated for 18 hr at 37°C for test bacteria and *Candida albicans*. The fungi plates were incubated for 5-6 days at 28°C. The antimicrobial activity was evaluated by measuring the zone of growth inhibition around disc of test organism. Antibiotics chloramphenicol (30 µg/disc) and nystatin (100 units/disc) (Hi-Media Pvt Ltd, Mumbai, India) were used as positive controls.

Synthesis of 3-acetoacetyl-5-oxo-5H-[1]benzopyrano[3,2-e] pyridin-2-one 4

2-Amino-3-formylchromone **1** (1 g, 5.29 mmole)

was dissolved in pyridine (30 mL) containing piperidine (0.899 mL, 10.5 mmoles) and triacetic acid lactone **2** (0.999 g, 7.936 mmoles) added to it. The reaction mixture was kept at room temperature for 7 days. The product **4**, crystallised out as cannery yellow solid was filtered, washed with cold water and dried. The mother liquor was poured in to ice-cold water and acidified with HCl. The solid, which precipitated out was filtered, washed with water, dried and recrystallised from chloroform-methanol. Yield 1.3 g, 82%; m.p. 180°C. IR (KBr): 3443, 3752, 1652, 1647, 1642 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.28 (s, CH₃), 7.09 (s, H_a), 8.2(d, *J* = 9 Hz), 8.85 (s, H_b), 14.0 (s, -OH, D₂O exchangeable), 16.3 (s, -OH, D₂O exchangeable); MS: m/z 297 (M⁺ 62%), 282(6), 254(11), 240(4), 212(3), 169(4), 159(16), 157(100), 141(6), 121(6).

Acknowledgement

Financial Assistance by UGC, New Delhi, is gratefully acknowledged. The authors thanks are due to SAIF, CDRI, Lucknow for spectral data and Dr. Iqbal Ahmad, Mr. Farrukh Aqil, Department of Agricultural Microbiology, Aligarh Muslim University, Aligarh for biological screening.

References

- 1 Butt M A & Elvidge J A, *J Chem Soc*, **1963**, 4483.
- 2 Bentley R, *J Chem Education*, **76**(1), **1999**, 41.
- 3 Moore B S & Hopke J N, *Chem Biochem*, **2**, **2001**, 35.
- 4 Schröder J, *Trends Plant Sci*, **2**, **1997**, 373.
- 5 Funai N, Ohnishi Y, Ebizuka Y & Horinouchi S, *Biochem J*, **367**, **2002**, 781.

- 6 Suh D Y, Fukuma K, Kagami J, Yamazaki Y, Shibuya M, Ebizuka Y & Sankawa U, *Biochem J*, 350, **2000**, 229.
- 7 Schröder J, *Nat Struct Biol*, 6, **1999**, 714.
- 8 Eckermann C, Schröder G, Eckermann S, Strack D, Schmidt J, Schneider B & Schröder J, *Phytochemistry*, 62, **2003**, 271.
- 9 Abe I, Oguro S, Utsumi Y, Sano Y & Noguchi H, *J Am Chem Soc*, 127, **2005**, 12709.
- 10 Tsuyoshi M, Hideki K, Kiyoshi O, Katsuyuki M & Yasumato Adachi, *Jap Pat Appl* 97/262, 032, **1997**, 37; *Chem Abstr*, 130, **1999**, 267345z.
- 11 Yuji S, Hideki K, Tsuyoshi M, Kiyoshi O & Satoko T, *Jap Pat Appl* 97/262, 033, **1997**, 64; *Chem Abstr*, 130, **1999**, 281990n.
- 12 Shyamsunder C & Hermann H, *Ger Pat, Appl* 19, 750, 623, **1997**, 12; *Chem Abstr*, 130, **1999**, 338018h.
- 13 Hua D H & Perchellet J P, *USA Pat, Appl* 813, 514, **1997**, 44; *Chem Abstr*, 131, **1999**, 243259u.
- 14 Hua D H & Perchellet J P, *USA Pat, Appl* 902/ 053, **1997**, 96; *Chem Abstr*, 129, **1998**, 245135h.
- 15 Akira N, Hirosoda S & Kiyoshi U, *Jap Pat Appl* 85/11, 686 **1985**, 14; *Chem Abstr*, 104, **1986**, 186390w.
- 16 Akira N, Hirosoda S & Kiyoshi U, *Jap Pat Appl* 85/11, 687, **1985**, 9; *Chem Abstr*, 104, **1986**, 207250t.
- 17 Akira N, Toshihiro I, Kiyoshi U, Hirosoda S, Yoshitaka M & Yosuhi S, *J Med Chem*, 28(5), **1985**, 559.
- 18 Akira N, Toshihiro I & Kiyoshi U, *Jap Pat Appl* 77/115, 817, **1977**, 25; *Chem Abstr*, 92, **1980**, 76518v.
- 19 Akira N, Hirosoda S & Kiyoshi U, *Jap Pat Appl* 77/25, 654, **1977**, 12; *Chem Abstr*, 94, **1981**, 192310m.
- 20 Akira N, Hirosoda S & Kiyoshi U, *Jap Pat Appl* 77/25, 654, **1977**, 58; *Chem Abstr*, 89, **1978**, 215391b.
- 21 Kota K, Hiratu Y & Yamamura S, *J Chem Soc (c)*, **1969**, 1997.
- 22 Tan S F & Tjia T H, *J Chem Soc, Perkin Trans 1*, **1975**, 2405.
- 23 Tan S F & Tjia T H, *J Chem Soc Perkin Trans 1*, **1976**, 2137.
- 24 March P D, Manas M M & Roca J N, *J Heterocyclic Chem*, 21, **1984**, 1371.
- 25 Cervello J, Gil M, March P D, Marquest J, Manas M M, Roca J L & Ferrando F S, *Tetrahedron*, 43(10), **1987**, 2381.
- 26 Rehman M, Uddin R, Siddiqui Z S, Zaman A, Rahman A & Chaudhry M I, *Indian J Chem*, 33B, **1994**, 1023.
- 27 Helmut H, Gerhard N, Gerhard W & Andreas L, *Ger Pat Appl. DE* 4, 039, 272 (Cl. C070491/052), **1990**; 22, *Chem Abstr*, 117, **1992**, 171416d.
- 28 Aqil F & Ahmad I, *World J Microbiol Biotechnol*, 19, **2003**, 653.
- 29 Bauer A W, Kirby W M M, Sherries J C & Turch M, *Am J Clin Path*, 45, **1966**, 494.