Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 85–87

A one-pot synthesis of an annelated [*a*]aza-thieno[3,2-*g*]-naphthalenone through ring transformation followed by photocyclization☆

Ramendra Pratap,[a] Ashoke Sharon,[b] Prakas R. Maulik[b] and Vishnu Ji Ram[a,b,*]

[a]*Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Division of Molecular and Structural Biology, Central Drug Research Institute, Lucknow 226 001, India*

Received 28 July 2004; revised 27 October 2004; accepted 5 November 2004

Abstract—A concise synthesis of 4-aryl-10-oxo-1,2,3,10-tetrahydro-9-thia-1,3a-diazadicyclopenta[*a*,*g*]naphthalene-6-carbonitriles **5a**–**f** and 5-aryl-11-oxo-1,3,4,11-tetrahydro-2*H*-10-thia-1,4a-diaza-cyclopenta[*b*]phenanthrene-7-carbonitriles **5g**–**i** has been delineated through ring transformations of the 2*H*-pyran-2-one **1**, followed by photocyclization of product **4**.

Heterocyclic compounds are widely distributed in nature and occupy a prominent place in medicinal chemistry as pharmaceuticals and drug intermediates. They play a significant role in the metabolism of all living cells and many are in clinical use for the treatment of various diseases. The therapeutic importance of heterocycles has generated much interest in the synthesis of new classes of heterocyclic systems in order to explore their biodynamic properties.

Annelated [*a*]aza-thieno[3,2-*g*]naphthalenones have not been reported. The construction of such compounds **5** having three different heterocycles, thiophene, isoquinoline and imidazole or pyrimidine in a specific manner is a challenging task. We conceived a scheme in which **5** could be made through reaction of 2*H*-pyran-2-one **1** with α-oxoketene cyclic aminals **2**, obtained[1] from the reaction of α-oxoketene dithioacetal with 1,2- and 1,3-diaminoalkanes, followed by photocyclization.

The 2*H*-pyran-2-one **1** has been used for nucleophile induced ring transformation reactions for the synthesis of various arenes and heteroarenes.[2] The synthetic potential of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1** led us to use it as a precursor for the synthesis of 4-aryl-10-oxo-1,2,3,10-tetrahydro-9-thia-1,3a-diazadicyclopenta[*a*,*g*]naphthalene-6-carbonitriles **5a**–**f** and 5-aryl-11-oxo-1,3,4,11-tetrahydro-2*H*-10-thia-1,4a-diaza-cyclopenta[*b*]phenanthrene-7-carbonitriles **5g**–**i**. In principle two ring transformed products, either **3** or **4**, could result from the reaction of **1** and α-oxoketene cyclic aminals **2**, depending upon the initial participation of either the secondary amino group or carbon as a nucleophile (Scheme 1). The formation of ring transformed product **3** initiated by a carbanion was ruled out on the basis of a single crystal X-ray diffraction study of photocyclized product **5**, which could only have been obtained from the ring transformed product **4**. Photoirradiation of a solution of **4a**,**d** or **4h** in chloroform with a 200 W electric bulb provided cyclized products **5a**,**d** or **5h**, respectively. The ring transformation and photocyclization could be carried out directly in a single step by irradiating a mixture of 2*H*-pyran-2-one **1**, α-oxoketene cyclic aminal **2** and NaH in dry THF with stirring for 15 h.

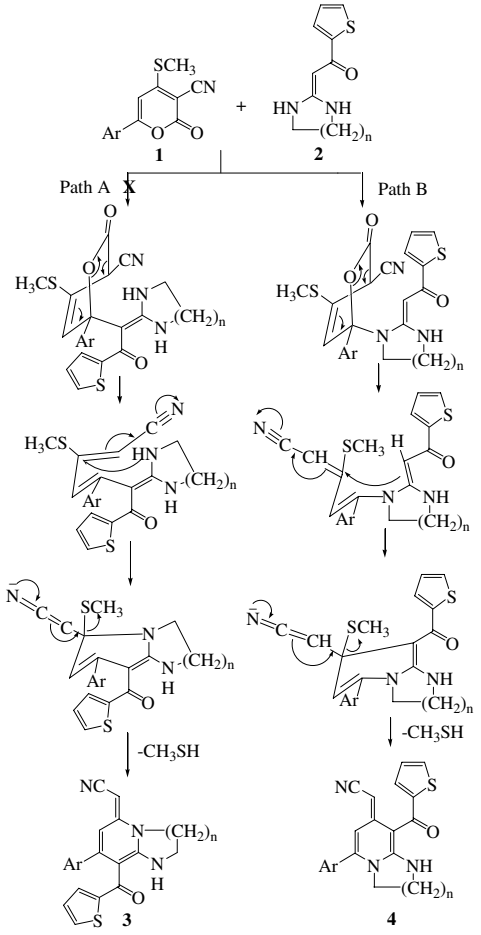
The removal of solvent under reduced pressure followed by work-up led to **5**, in moderate yield, identical in all respect to the product isolated through irradiation of the ring transformed product **4**. Since the intermediate **4** is highly sensitive to light, the isolation and purification through Si gel column chromatography were carried out in the dark.

The UV spectrum of a freshly prepared (0.01 mM) solution of **4** in chloroform showed two absorption bands at 305 and 235 nm, which completely disappeared after irradiation for 2 h, with the appearance of two new

☆CDRI Communication No. 6625.

* Corresponding author. Tel.: +91 522 2212411 4381; fax: +91 522 2623405/2623938; e-mail: vjiram@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.037



4/5	Ar	n	Yield (%) 4	5
a	C_6H_5	1	77	35
b	4-ClC_6H_4	1	-	41
c	4-BrC_6H_4	1	-	54
d	4-$CH_3OC_6H_4$	1	80	51
e	4-$CH_3C_6H_4$	1	-	39
f	2-theinyl	1	-	55
g	4-BrC_6H_4	2	-	48
h	4-$CH_3C_6H_4$	2	85	52
i	1-naphthyl	2	-	44

Scheme 1. Proposed mechanism for the formation of **5**.

absorption maxima at 410 and 281 nm. The presence of an electron withdrawing substituent in the 2*H*-pyran-2-one **1** at position-3 facilitates the ring transformation reactions by increasing the electrophilicity of C6, making it vulnerable to nucleophilic attack. 6-Aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** can be considered as a cyclic ketene hemithioacetal, prone to nucleophilic attack. Excitation of the ketone in **4** leads to hydrogen atom abstraction from the N–H and redistribution of the radicals leads to a conjugated 6-π electron enol system. This then undergoes electrocyclization followed by tautomerization and oxidation. Thus, this reaction possibly proceeds through a photochemically allowed conrotatory cyclization[3] followed by aerial oxidation of a dihydro-intermediate to yield **5**.

A plausible initial step in the mechanism of this reaction is nucleophilic attack at C6 of the pyran ring by the secondary amino group with ring opening followed by decarboxylation and recyclization, involving the vinylic

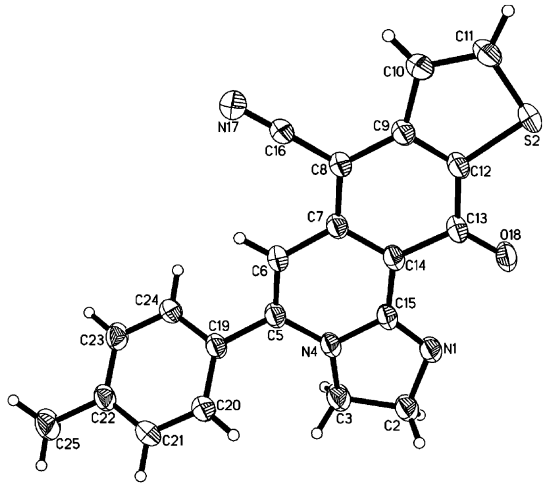


Figure 1. ORTEP diagram of **5e** showing the X-ray molecular structure at the 30% probability level.

carbon and *S*-methyl bearing carbon liberating methyl mercaptan to yield **4** (Scheme 1). The stereoselectivity in the formation of **4** is possibly due to either strong intramolecular hydrogen bonding between the NH and C=O functionalities or steric hindrance, which plays a crucial role in restricting the rotation of the aroyl group thereby leading to *E*-geometry. The intermediates **4** were isolated and characterized spectroscopically as (*E*)-2-(8-thienoyl-5-aryl-2,3-dihydro-1*H*-imidazo[1,2-*a*]-pyridine-2-ylidene)acetonitrile (**4**, $n = 1$) and (*E*)-2-(9-thienoyl-6-aryl-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrimidin-8-ylidene)acetonitrile (**4**, $n = 2$). The structure of the isolated photocyclized products **5** was confirmed spectroscopically[4] and that of **5e** by a single crystal X-ray diffraction analysis (Fig. 1).[5] The X-ray structure revealed that two molecules are present in one asymmetric unit of the crystal structure.

Our methodology provides a one-pot synthesis of a new class of heterocycles using readily available precursors and reagents under very mild conditions without the use of any catalyst. This procedure opens a new avenue for the one-pot synthesis of various new types of heterocycles.

Acknowledgements

V. J. Ram and R. Pratap thank ICMR for financial support. A. Sharon thanks CSIR, New Delhi, India for providing a Senior Research Fellowship. The authors thank SAIF, CDRI, Lucknow for providing spectroscopic and analytical data.

References and notes

1. (a) Li, Z.-J.; Yang, Q.; Chen, X.-M.; Huang, Z.-T. *Synthesis* **1999**, 231–233; (b) Huang, Z.-T.; Liu, Z.-R. *Chem. Ber.* **1989**, *122*, 95–100.
2. (a) Ram, V. J.; Srivastava, P.; Goel, A. *Tetrahedron* **2003**, *59*, 7141–7146; (b) Sharon, A.; Maulik, P. R.; Vithana, C.;

Ohashi, Y.; Ram, V. J. *Eur. J. Org. Chem.* **2004**, 886–893; (c) Ram, V. J.; Goel, A. *Tetrahedron Lett.* **1996**, *37*, 93–96; (d) Saxena, A. S.; Goel, A.; Ram, V. J. *Synlett* **2002**, 1491–1492.

3. Cuppen, Th. J. H. M.; Laarhoven, W. H. *J. Am. Chem. Soc.* **1972**, *94*, 5914–5915.
4. Typical procedure for **4**: A mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1** (1 mmol), α-oxoketene cyclic aminal **2** (1 mmol) and NaH (1.5 mmol) in dry THF was stirred for 15 h at room temperature in the dark then poured onto ice water. The aqueous solution was neutralized with 10% HCl and the precipitate obtained was filtered, washed with water, dried and finally purified by Si gel column chromatography using 4% methanol in chloroform as eluent. The entire process was carried out in the dark to prevent photochemical cyclization. Compound **4a**: Yield 77%; mp >250 °C; IR (KBr): ν = 1639 (CO), 2167 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.71–3.89 (m, 4H, $2NCH_2$), 4.19 (s, 1H, CH), 6.38 (s, 1H, ArH), 7.02–7.06 (m, 1H, ArH), 7.45–7.49 (m, 5H, ArH), 7.54 (d, J = 4.7 Hz, 1H, ArH), 7.80 (d, J = 3.4 Hz, 1H, ArH); FAB (MS) 346 (M^++1). Typical procedure **A** for **5**: A stirred solution of **4** (0.05 mmol) in chloroform was irradiated for 16 h using a 200 W electric bulb. The solution was evaporated and the residue obtained was treated with a small quantity of methanol and filtered. The crude product was finally purified by column chromatography using 5% methanol in chloroform as eluent. Typical procedure **B** for **5**: A mixture of 2*H*-pyran-2-one **1** (1 mmol), α-oxoketene cyclic aminal **2** (1 mmol) and NaH (1.5 mmol) in dry THF was stirred for 15 h at ambient temperature under light irradiation. The reaction mixture was then poured onto ice-water and neutralized with 10% HCl and the precipitate obtained was filtered, washed with water, dried and finally purified by Si gel column chromatography using 5% methanol in chloroform as eluent. Compound **5a**: Yield 35%; mp: >250 °C; IR (KBr): ν = 1628 (CO), 2191 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, CD_3OD): δ = 4.10–4.26 (m, 4H, $2NCH_2$), 6.93 (s, 1H, ArH), 7.4 (d, J = 5.24 Hz, 1H, ArH), 7.49–7.57 (m, 5H, ArH), 7.78 (d, J = 5.3 Hz, 1H, ArH); FAB (MS) 344 (M^++1). Compound **5g**: Yield 48%; mp: >250 °C; IR (KBr): ν = 1648 (CO), 2198 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, CD_3OD): δ = 2.07–2.13 (m, 2H, CH_2), 3.61 (t, J = 5.8 Hz, 2H, NCH_2), 3.8 (t, J = 6.0 Hz, 2H, NCH_2), 6.86 (s, 1H, ArH), 7.31 (d, J = 8.3 Hz, 2H, ArH), 7.43 (d, J = 5.24 Hz, 1H, ArH), 7.66 (d, J = 8.30 Hz, 2H, ArH), 7.72 (d, J = 5.3 Hz, 1H, ArH); FAB (MS) 437 (M^++1).
5. Crystal data of **5e**: $C_{21}H_{14}N_3OS$, M = 356.41, triclinic, space group P-1, a = 10.032(1), b = 11.608(1), c = 15.694(1) Å, α = 70.28(1), β = 85.03(1), γ = 84.03(1)°, V = 1708.5(3) $Å^3$, T = 293 K, Z = 4, μ = 0.41 mm^{-1}, $R1$ = 0.0390 for 4507 Fo > 4sig(Fo) and 0.0560 for all 5902 data. CCDC No. 245953 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U. K; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997].