Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 243–246

Unusual conversion of substituted-3-formylchromones to 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones: a facile and efficient route to novel 1,2,4-dithiazoles

Tilak Raj,[a] M. P. S. Ishar,[a,*] Vivek Gupta,[b] Ajay Pal Singh Pannu,[c] Priyanka Kanwal[b] and Gurpinder Singh[a]

[a]*Bio-Organic and Photochemistry Laboratory, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, Punjab, India*
[b]*P.G. Department of Physics, University of Jammu, Jammu Tawi 180 006, India*
[c]*Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, Punjab, India*

Received 24 September 2007; revised 7 November 2007; accepted 14 November 2007
Available online 19 November 2007

Abstract—Substituted 3-formylchromones react with 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene (**4**) or thio-benzamide (**7**) by heating their toluene solution in a sealed tube to give novel substituted 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones (**6a**–**e**) in high yields.

Biologically active heterocycles continue to provide stimulus for organic synthesis, leading to the development of new strategies, reactions and reagents. It has been observed that heterocycles containing both nitrogen and sulfur are important components of many biologically active molecules.[1] Cycloadditions involving thio-azadienes represent a straightforward and efficient approach to N- and S-containing six-membered heterocycles;[2] the latter are essential constituents of numerous pharmaceutically active molecules,[3,4] including antibacterials such as cephalosporins.

The chromone moiety forms the nucleus of a class of natural products called flavanoids and is also part of pharmacophores of various biologically active molecules,[5] including anticancer agents such as psorospermin and pluramycin A.[6,7] Some other recent examples include hetero- and carbo-annulated chromone derivatives which are useful antiplatelet,[8] antifungal[9] and anticancer agents.[10] The involvement of the C2–C3 π-bond of 3-formylchromone as a 2π component in cycloadditions is well known.[11] For instance, we have reported[12] the addition of an all carbon 1,3-dipole to 3-formylchromones **1** leading, after deformylation of the initially formed cycloadduct, to cyclopentannulated chromones **2** (Scheme 1).

Therefore, it was decided to utilize the hetero-Diels–Alder cycloaddition of 1-thia-3-azadiene with 6,7-subsituted-3-formylchromones to synthesize chromanothiazines. Thus, reactions were performed by reacting substituted 3-formylchromones **3** with 2-phenyl-4-dimethylamino-1-thia-3-azabuta-1,3-diene (**4**) in a sealed tube for 7 h to obtain chromanothiazines **5** (Scheme 2).

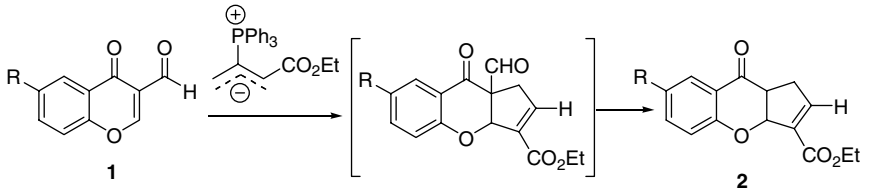
However, to our surprise, the reaction afforded novel 3-(5-phenyl-3*H*-[1,2,4]dithiazol-3-yl)chromen-4-ones **6** in good yields (Scheme 2, Table 1).

All the products **6a**–**e** were characterized by spectroscopic (^{1}H and ^{13}C NMR, IR and mass) and microanalytical data.[13] Subsequently the structure of **6a** was confirmed by X-ray crystallography (Fig. 1).[14]

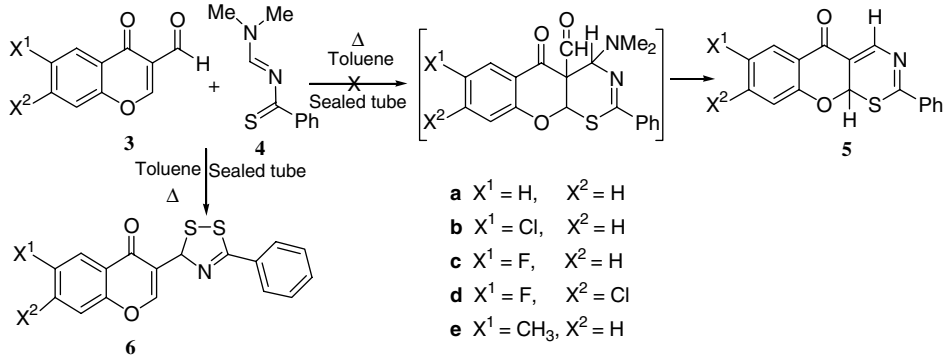
Mechanistically, the above transformation may involve two plausible steps **I** and **II** (Scheme 3). The first step involves thionation of chromone, which can occur either by reaction with thio-azadiene or with thio-benzamide;

Keywords: Dithiazoles; 3-Formylchromones; Thio-azadiene; Thio-benzamide.
* Corresponding author. Tel.: +91 183 2258802 09x3321; fax: +91 183 2258820; e-mail: mpsishar@yahoo.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.081



Scheme 1.



Scheme 2.

Table 1. Reaction yields (%) of products **6**

Entry	Chromone	Product	% Yield[a]	% Yield[b]
1	**3a**	**6a**	45	70
2	**3b**	**6b**	43	73
3	**3c**	**6c**	45	72
4	**3d**	**6d**	46	73
5	**3e**	**6e**	42	74

[a] Reaction yield with 1 M equiv of thio-azadiene **4**.
[b] Reaction yield with 2 M equiv of thio-azadiene **4**.

thio-benzamide may be generated by the hydrolysis of thio-azadiene in the presence of a small amount of moisture and further hydrolysis can occur due to in situ generated water. The second step most likely involves the reaction of 3-thioformylchromone with another molecule of thio-benzamide followed by the oxidative cyclization of **C**; oxidative cyclization of related intermediates **C** to 1,2,4-dithiazoles is precedented in the literature.[15] HPLC analysis of the crude reaction mixture showed the presence of *N*,*N*-dimethylformamide and benzonitrile in the reaction mixture, thereby, supporting the proposed mechanistic rationale. A perusal of the literature revealed that the reaction of thiobenzamide with an aldehyde generates a 6*H*-1,3,5-oxathiazine, which on heating with excess sulfur undergoes a retro-cycloaddition generating thio-azadienes in situ; the later are converted to 1,2,4-dithiazoles on reaction with sulfur.[16] However, in the present case, 1,3-thio-azadienes were synthesized[17] and reacted with 3-formylchromones, no additional sulfur was added.

Further, to substantiate the mechanistic proposals the reactions of various substituted 3-formylchromones **3a–e** were carried out with 1 or 2 equiv of thio-benzamide under identical conditions, leading to the isolation of the same dithiazoles **6a–e** (Scheme 4, Table 2).

Though, the full mechanistic details of the transformation are yet to be confirmed, the reaction provides an

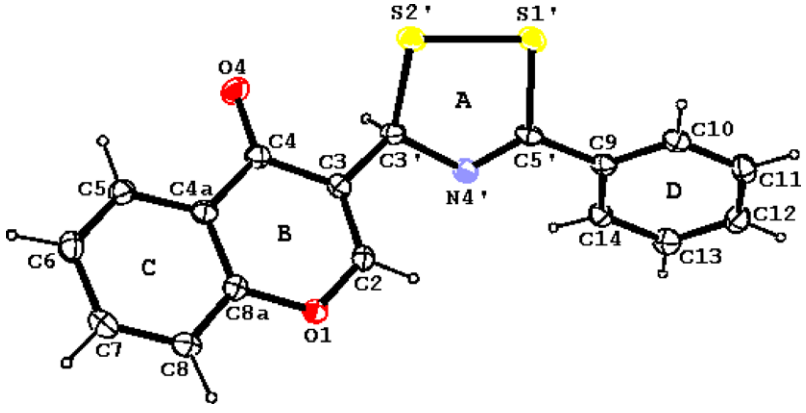
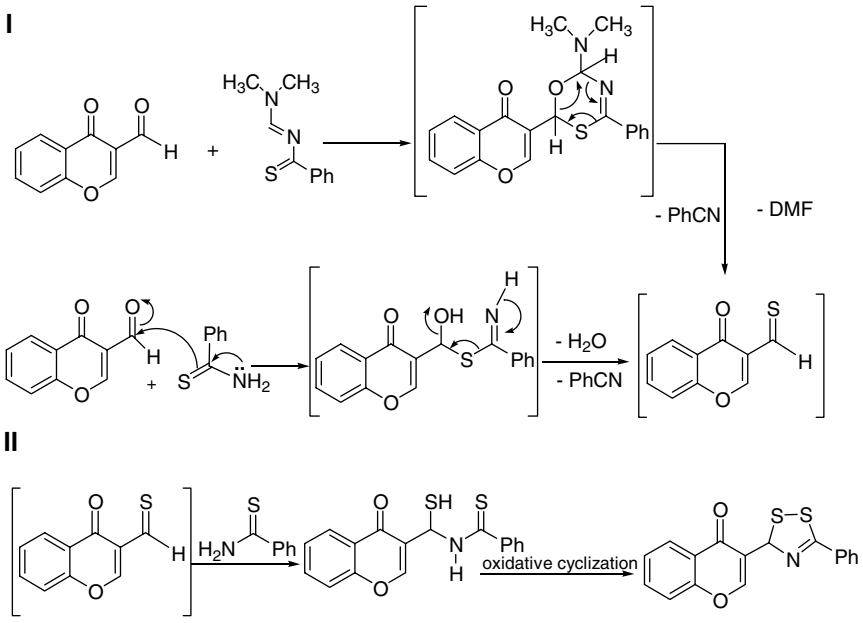
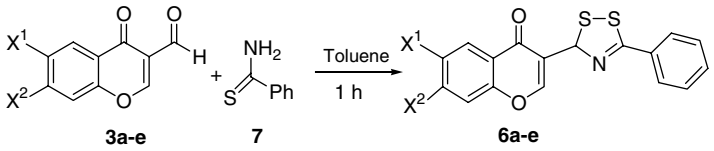


Figure 1. ORTEP view of **6a**.



Scheme 3.



Scheme 4.

Table 2. Reaction yields (%) of products 6

Entry	Chromone	Product	% Yield[a]	% Yield[b]
1	**3a**	**6a**	50	76
2	**3b**	**6b**	53	73
3	**3c**	**6c**	56	72
4	**3d**	**6d**	52	73
5	**3e**	**6e**	54	74

[a] Reaction yield with 1 M equiv of thio-benzamide **7**.
[b] Reaction yield with 2 M equiv of thio-benzamide **7**.

easy access to novel 1,2,4-dithiazoles. Molecules containing the dithiazole moiety are known to display biological activities such as antifungal[18]and antibacterial.[19] It is pertinent to mention here that a perusal of the literature revealed only a few approaches for the synthesis of 1,2,4-dithiazoles.[15,16,20] The failure of the cycloaddition of the thio-azadiene to the C2–C3 π-bond of 3-formylchromone requires further investigation.

Acknowledgement

Use of 300 MHz NMR facilities provided by the Department of Science and Technology, Government of India, at the Chemistry Department, Guru Nanak Dev University, Amritsar, is gratefully acknowledged.

Supplementary data

General experimental procedures, ^{1}H and ^{13}C NMR spectra of compounds **6a**–**e** and X-ray crystallography data of compound **6a** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.081.

References and notes

1. Marchand, A.-H.; Collet, S.; Guingant, A.; Pradere, J.-P.; Toupet, L. *Tetrahedron* **2004**, *60*, 1827–1839.
2. (a) Pradere, J. P.; Quiniou, H. *Ann. Chim.* **1973**, *63*, 563–573; (b) Pradere, J. P.; N'Guessan, Y. T.; Quiniou, H.; Tonnard, F. *Tetrahedron* **1975**, *31*, 3059–3064; (c) Meslin, J. C.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1979**, *116*, 347–349.
3. Bakavoli, M.; Nikapour, M.; Rahimizadeh, M.; Saberi, M. R.; Sadeghian, H. *Bioorg. Med. Chem.* **2007**, *15*, 2120–2126.
4. (a) Charrier, J. D.; Landreau, C.; Deniaud, D.; Reliquet, F.; Reliquet, A.; Meslin, J. C. *Tetrahedron* **2001**, *57*, 4195–4202; (b) Benedini, F.; Bertolini, G.; Ferrario, F.; Guindani, R.; Sala, A. *J. Heterocycl. Chem.* **1994**, *31*, 1589–1592.
5. (a) Hurley, L. H. *Nat. Rev. Cancer* **2001**, *3*, 188–200; (b) Hurley, L. H. *Biochem. Soc. Trans.* **2001**, *29*, 692–696; (c) Kupchan, S. M.; Streelmann, D. R.; Sneden, A. T. *J. Nat. Prod.* **1980**, *43*, 296–301; (d) Hansen, M. R.; Hurley, L. H. *Acc. Chem. Res.* **1996**, *5*, 249–258; (e) Bocian, W.;

Kawechi, R.; Bednarek, E.; Sitkowski, J.; Ulkowska, A.; Kozerski, L. *New J. Chem.* **2006**, *30*, 467–472; (f) Mukherjee, A. K.; Basu, S.; Sarkar, N.; Ghosh, A. C. *Curr. Med. Chem.* **2001**, *8*, 1467–1486; (g) Shi, Y.-Q.; Fukai, T.; Sakagami, H.; Chang, W.-J.; Yang, P.-Q.; Wang, F.-P.; Nomura, T. *J. Nat. Prod.* **2001**, *64*, 181–188.

6. (a) Kim, M. Y.; Na, Y.; Vankayalapati, H.; Gleason-Guzman, M.; Hurley, L. H. *J. Med. Chem.* **2003**, *46*, 2958–2972; (b) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559–592.
7. (a) Cassady, J. M.; Baird, W. M.; Chang, C. J. *J. Nat. Prod.* **1990**, *53*, 23–41; (b) Kupchan, S. M.; Streelman, D. R.; Sneden, A. T. *J. Nat. Prod.* **1980**, *43*, 296–301.
8. (a) Morris, J.; Wishka, D. G.; Lin, A. H.; Humphrey, W. R.; Wiltse, A. L.; Gammil, R. B.; Judge, T. M.; Bisaha, S. L.; Olds, N. L.; Jacob, C. S.; Bergh, C. L.; Cudahy, M. M.; Williams, D. J.; Nishizawa, E. E.; Thomas, E. W.; Gorman, R. R.; Benjamin, C. W.; Shebuski, R. J. *J. Med. Chem.* **1993**, *36*, 2026–2032; (b) Mazzei, M.; Balbi, A.; Roma, G.; Di Braccio, M.; Leoncini, G.; Buzzi, E.; Maresca, M. *Eur. J. Med. Chem.* **1988**, *23*, 237–242; (c) Mazzei, M.; Sottofattori, E.; Di Braccio, M.; Balbi, A.; Leoncini, G.; Buzzi, E.; Maresca, M. *Eur. J. Med. Chem.* **1990**, *25*, 617–622; (d) Leoncini, G.; Maresca, M.; Colao, C.; Buzzi, E.; Mazzei, M. *Cell Biochem. Funct.* **1991**, *9*, 79–85.
9. (a) Wang, H.-J.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **1995**, *36*, 5847–5850; (b) Fujimoto, H.; Ingaki, M.; Satoh, Y.; Yoshida, E.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1090–1092; (c) Graham, J. G.; Zhang, H.; Pendland, S. L.; Santalsiero, B. D.; Mesecar, A. D.; Cabieres, F.; Farnsworth, N. R. *J. Nat. Prod.* **2004**, *67*, 225–227.
10. Ishar, M. P. S.; Singh, G.; Singh, S.; Sreenivasan, K. K.; Singh, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1366–1370.
11. (a) Ghosh, C. K.; Ghosh, C. *Indian J. Chem., Sect. B* **1997**, *36*, 968–980; (b) Ghosh, C. K. *Heterocycles* **2004**, *63*, 2875–2898; (c) Lee, Y.-G.; Iwasaki, H.; Ohkata, K.; Akiba, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1319–1320; (d) Ghosh, C. K.; Sahana, S.; Patra, A. *Tetrahedron* **1993**, *49*, 4127–4134; (e) Ghosh, C. K.; Sahana, S. *Indian J. Chem., Sect. B* **1992**, *31*, 346–348; (f) Cremins, P. J.; Saenchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075–3082.
12. Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023–2025.
13. *General procedure for the synthesis of dithiazoles*: The reactions were carried out by reacting substituted 3-formylchromone (500 mg, 2.8 mmol) with thio-azadiene (1142 mg, 5.6 mmol) or thio-benzamide (767 mg, 5.6 mmol) in a sealed tube using toluene (5 mL) as the solvent at a temperature of 120 °C. The heating duration was standardized by monitoring the progress of the reaction by TLC. After the completion of the reaction, the tube was allowed to cool and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography over silica 60–120 mesh (Loba Cheme 20 g packed in hexane) and eluted with 1% EtOAc in hexane. The purified products were characterized by various spectroscopic techniques (UV, IR, ^{1}H and ^{13}C NMR, mass) and by elemental analysis. *3-(5-Phenyl-3H-[1,2,4]dithiazol-3-yl)chromen-4-one* (**6a**): Yield: 76%; Light orange crystalline solid, mp 184–186 °C (chloroform/hexane, 1:1); UV (MeOH): 380, 367, 298, 248 nm; IR (KBr): ν_{max} 1645, 1510, 1245, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$ (dd, 1H, $J = 7.9$ and 1.8 Hz, ArH), 7.98–7.94 (m, 2H, ArH), 7.76 (d, 1H, $J = 1.2$ Hz, C_2H), 7.68 (ddd, 1H, $J = 8.4$, 7.2 and 1.8 Hz, ArH), 7.57–7.32 (m, 6H, 5-ArH and $C_{5'}$H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.8$ (C_4), 170.4 ($C_{3'}$), 156.5 (q), 152.6 (C_2), 133.9 (q), 132.4 (C_7), 131.8 (CH), 129.3 (C_5), 128.9 (CH), 126.2 (CH), 125.4 (q), 123.8 (C_6), 122.9 (C_8), 118.2 (C_3), 83.0 ($C_{5'}$); MS (ESI): m/z 348 (M+Na$^+$); Anal. Calcd for $C_{17}H_{11}NO_2S_2$: C, 62.75; H, 3.41; N, 4.30. Found: C, 62.63; H, 3.34; N, 4.18.
14. The data for **6a** has been submitted to The Cambridge Crystallographic Data Centre (CCDC No. 286229).
15. Shimada, K.; Aikawa, K.; Fujita, T.; Sato, M.; Goto, K.; Aoyagi, S.; Takikawa, Y.; Kabuto, C. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 511–525.
16. Rafiqul, I. M.; Shimada, K.; Aoyagi, S.; Fujisawa, Y.; Takikawa, Y. *Tetrahedron Lett.* **2004**, *45*, 6187–6190.
17. Meslin, J. C.; Quiniou, H. *Tetrahedron* **1975**, *31*, 3055–3058.
18. Niewiadomy, A.; Kulak, E. K.; Lukaszuk, C.; Matysiak, J.; Kostecka, M. *Rocz. Akad. Med. Bialymst.* **2005**, *50*, 31–35.
19. Cottenceau, G.; Besson, T.; Gautier, V.; Rees, C. W.; Pons, A.-M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 529–532.
20. MacDonald, J. W.; McKinnon, D. M. *Can. J. Chem.* **1967**, *45*, 1225–1229.