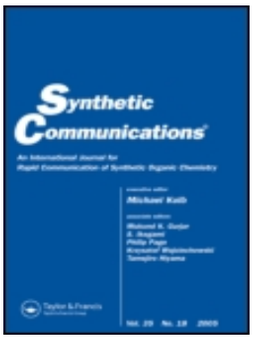


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: www.tandfonline.com/journals/lsyc20

Synthesis of 3-(2-(4-Chlorophenylimino)-3-(4-chlorophenyl)-2,3-dihydrothiazol-4-yl)-2 h-Chromen-2-one via Multicomponent Approach

Raj Kumar Ramagiri & Rajeswar Rao Vedula

To cite this article: Raj Kumar Ramagiri & Rajeswar Rao Vedula (2014) Synthesis of 3-(2-(4-Chlorophenylimino)-3-(4-chlorophenyl)-2,3-dihydrothiazol-4-yl)-2 h-Chromen-2-one via Multicomponent Approach, Synthetic Communications, 44:9, 1301-1306, DOI: 10.1080/00397911.2013.854915

To link to this article: https://doi.org/10.1080/00397911.2013.854915

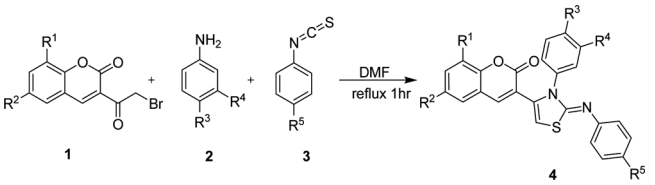
Synthetic Communications®, 44: 1301–1306, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.854915

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF 3-(2-(4-CHLOROPHENYLIMINO)-3-(4-CHLOROPHENYL)-2,3-DIHYDROTHIAZOL-4-YL)-2H-CHROMEN-2-ONE VIA MULTICOMPONENT APPROACH

Raj Kumar Ramagiri and Rajeswar Rao Vedula
Department of Chemistry, National Institute of Technology, Warangal, India



Abstract *A simple and highly efficient one-pot, three-component synthesis of 3-(2-(4-chlorophenylimino)-3-(4-chlorophenyl)-2,3-dihydrothiazol-4-yl)-2H-chromen-2-ones has been reported by the reaction of 3-(2-bromoacetyl)-2H-chromen-2-one, primary amines, and phenyl isothiocyanates in presence of dimethylformamide as a solvent. The structures of newly synthesized compounds were confirmed by their analytical and spectral data.*

Keywords Coumarin; isothiocyanate; multicomponent reaction; phenyl; primary amines; thiazol-2-imine

INTRODUCTION

In multicomponent reactions (MCRs) more than two components are assembled into the product in a one-step reaction. The advantages of MCRs are atom economy, simplicity, and time-saving features. These are useful for the synthesis of biologically active compounds such as drugs and agrochemicals, and diversity is achieved easily by varying the components.[1–3]

Coumarin (benzopyran-2-one) derivatives have found various medicinal applications as antibacterial,[4,5] antifungal,[6,7] herbicidal,[8] antitumoral,[9] cytotoxic,[10] and anti-HIV agents.[11,12] The compounds containing the coumarin motif are widely used as additives in food and cosmetic products and known as luminescent materials.[13] They also act as anticoagulants,[14] free radical scavengers,[15] antioxidant,[16] lipoxygenase,[17] and cyclooxygenase inhibitors.[18]

Received July 19, 2013.
Address correspondence to Rajeswar Rao Vedula, Department of Chemistry, National Institute of Technology, Warangal 506004, AP, India. E-mail: vrajesw@yahoo.com

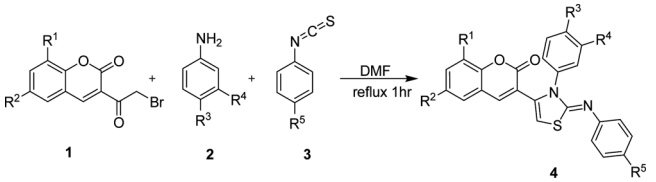
Heterocyclic systems having nitrogen and sulfur are very interesting because of their physicochemical properties with relevance to the design of new drugs. In particular the thiazoline ring system has attracted considerable attention because of its presence in several drug molecules with different biological activities such as antifungal,[19] anti-inflammatory,[20] anti-HIV,[21] analgesic, kinase inhibition,[22] and melanin-reducing activity.[23] These are also applied in agriculture as acricides, insecticides, and plant-growth regulators.

Our current studies are focused on the development of new routes for the synthesis of thiazol-2-imine incorporating coumarin moieties.

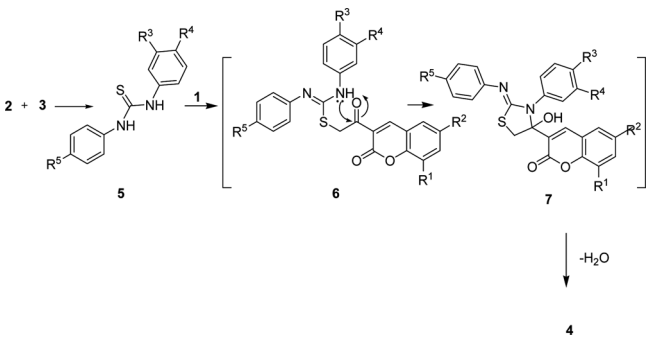
RESULTS AND DISCUSSION

Reaction of 3-(2-bromoacetyl)-2*H*-chromen-2-one **1,** primary amines **2** with different phenyl isothiocyanates **3** in presences of dimethylformamide **(**DMF) gave thiazole-2-imine **4** in good yields (Table 1). All the synthesized compounds are new and not reported in the literature (Scheme 1).

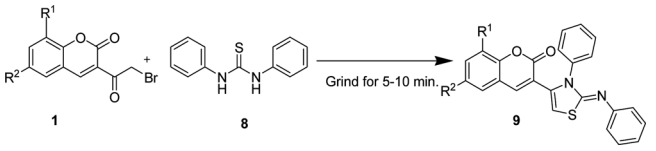
The mechanism for the formation of these products is discussed in Scheme 2. In this procedure we have modified the known Hantzsch method for thiazole synthesis involving the reaction of phenyl isothiocyanates, primary amines, and 3-(2-bromoacetyl)-2*H*-chromen-2-one compounds. In the literature[24] the synthesis of 3-(4-phenyl thiazoline-2-anil)-2*H*-1-benzopyran-2-ones **9** by the condensation of 3-(2-bromoacetyl)-2*H*-chromen-2-ones **1** with symmetrical thiourea such as diphenylthiourea **8** (Scheme 3) has been reported. As the scope for the synthesis of these compounds is rather limited, we tried to develop the present one-pot multicomponent synthesis of the title compounds. This procedures may find extensive applications in the synthesis of a wide variety of substituted thiazolines. This procedure is



Scheme 1. Three component one pot synthesis of thiazole-2-imines.



Scheme 2. Mechanism for the formation of **4**.



Scheme 3. Literature method.

Table 1. Synthesis of compounds **4** and their corresponding yields

Product 4	R^1	R^2	R^3	R^4	R^5	Yield (%)
a	H	H	Cl	H	Cl	69
b	H	H	OCH_3	H	Cl	79
c	H	H	Cl	H	CH_3	64
d	H	H	OCH_3	H	H	62
e	H	H	H	NO_2	Cl	68
f	H	H	H	NO_2	H	63
g	H	H	CH_3	H	CH_3	74
h	H	Cl	Cl	H	Cl	78
i	5,6-benzo		Cl	H	Cl	76

also novel compared to existing literature procedure. The structures of compounds **4a–i** were confirmed by their infrared (IR), ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4a** in dimethylsulfoxide (DMSO) showed thiazole proton as a singlet at 6.92 and C_4 proton of coumarin appeared at 8.30 δ ppm. In the ^{13}C NMR spectrum of **4a** the imino and carbonyl carbons resonate at 157.7 and 158.8 δ ppm respectively. The mass spectrum of **4a** exhibited the $[M+H]^+$ peak at *m/z* 465. The reaction is presumed to start with interaction of primary amine with phenyl isothiocyanate to give unsymmetrical thiourea **5**. Then **5** reacts with 3-(2-bromoacetyl)-2*H*-chromen-2-one to form intermediate **6**, which cyclizes to result in **7**. On loss of a water molecule this gives the end product **4**.

CONCLUSIONS

This article reports an efficient, one-pot, three-component method for the synthesis of 3-(2-(4-chlorophenylimino)-3-(4-chlorophenyl)-2,3-dihydrothiazol-4-yl)-2*H*-chromen-2-ones from the reaction of 3-(2-bromoacetyl)-2*H*-chromen-2-ones in good yields. The experimental conditions are simple and inexpensive and have easy workup and clean reaction profiles. This multicomponent approach may be useful in the synthesis of derivatives of medicinal importance.

EXPERIMENTAL

All the reagents and solvents were pure, purchased from commercial sources, and used without further purification unless otherwise stated. 3-(2-Bromo-acetyl)-2*H*-chromen-2-ones were prepared by the literature procedure.[25] Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. CHN analysis was carried out by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer

chromatography (TLC) plates (E. Merck, Mumbai, India). IR spectra were recorded on a thermo Nicolet Nexus 670 Q8 instrument (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane (TMS) as the standard. Mass spectra (EI-MS) were determined on a Perkin-Elmer spectrometer (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for 4

A mixture of 3-(2-bromoacetyl)-2*H*-chromen-2-one **1** (1 mmol), primary amine **2** (1 mmol), and phenyl isothiocyanate **3** (1 mmol) were taken in DMF (10 ml) and refluxed for 1 h. After completion of the reaction, the resulting mixture was cooled, filtered, and recrystallized from ethanol.

3-(2-(4-Chlorophenylimino)-3-(4-chlorophenyl)-2,3-dihydrothiazol-4-yl)-2H-chromen-2-one (4a)

A mixture of 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol), 4-chloro aniline (1 mmol), and 4-chlorophenyl isothiocyanate (1 mmol) were taken in DMF (10 ml) and refluxed for 1 h. After completion of the reaction, the resulting mixture was cooled, filtered, and recrystallized from ethanol. Color: white solid, mp: 298–300 °C, yield: 69%; IR (KBr) cm^{-1}: 1718 (lactone C=O), 1636 (C=N), 1599 (C=C); ^{1}H NMR (400 MHZ, DMSO-*d*6): δ 6.92 (1H, s, =CH), 7.11 (2H, d, *J* = 8 Hz, ArH), 7.36–7.49 (8H, m, ArH), 7.64–7.68 (1H, m, ArH), 7.77 (1H, d, *J* = 8 Hz, ArH), 8.30 (1H, s, C-4 of coumarin) ppm, ^{13}C NMR (DMSO-*d*6): δ 101.6, 116.2,118.3, 118.6, 122.8, 124.9, 126.8, 128.7, 129, 129.4 130.2, 132.2, 132.8, 133.6, 135.9, 145, 149.9, 153.3, 157.7, 158.8 ppm; ESI-MS: *m*/*z* (%); 465 $[M+H]^+$. Anal. calcd for $C_{24}H_{14}Cl_2N_2O_2S$: C, 61.94; H, 3.03; N, 6.02. Found: C, 61.90; H, 3.12; N, 6.12.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Basso, A.; Banfi, L.; Riva, R.; Guanti, G. A novel highly selective chiral auxiliary for the asymmetric synthesis of L- and D-α-amino acid derivatives via a multicomponent Ugi reaction. *J. Org. Chem.* **2005**, *70*, 575–579; (b) Ramon, D. J.; Yus, M. Asymmetric multicomponent reactions (AMCRs). *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.
2. Zhu, J.; Bienyame, H. *Multi-component Reactions* Wiley- VCH: Weinheim, 2005.
3. Domling, A.; Ugi, I. Multi-component reactions with isocyanides. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
4. Mulwad, V. V.; Pawar, R. B. Synthesis of some antibacterial compounds from 4-hydroxy coumarin. *Indian J. Chem*. **2003**, *42B*, 2091–2096.
5. Sharma, P.; Pritmani, S. Synthesis, characterization, and antimicrobial studies of some novel 3-aryl-azo-7-hydroxy-4-methyl coumarins. *Indian J. Chem*. **1999**, *38B*, 1139–1142.
6. Rajanarendar, E.; Karunakar, D.; Srinivas, M. Synthesis and biological activity of isoxazolyl thiazoles, isoxazolylthiazolyl chromen-2-ones, isoxazolyl thiazinanes, and isoxazolyl thiazolidinones. *Indian J. Chem*. **2004**, *43B*, 643–648.

7. Anklekar, K. Y.; Lakkannavar, C. D.; Kulkarni, G. M.; Kulkarni, M. V. Synthesis, spectral studies, and biological evaluation of some new 4-substituted coumarins. *Indian J. Chem.* **2003**, *42B*, 1548–1550.
8. Purohit, N. V. Synthesis and studies on biological activities of some substituted 2-benzo pyran-1H-one, 1H-2-oxo-benzopyran-3-carboxylic acids and 2-benzofuran-1(H)-one, *Indian J. Chem*. **2001**, *40B*, 222–227.
9. Nawrot, M. J.; Nawrot, E.; Graczyk, J. *In vivo* antitumor, in vitro antibacterial activity, and alkylating properties of phasphorohydrazine derivatives of coumarin and chromone. *Eur. J. Med. Chem.* **2006**, *41*, 1301–1309.
10. Kostova, I. Synthetic and natural coumarins as cytotoxic agents. *Curr. Med. Chem. Anti Canc. Agents.* **2005**, *5*, 29–46.
11. Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Hughes, S. H.; John, H. C.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. The calanoids, a novel HIV inhibitory class of coumarin derivatives from the tropical rain forest tree, *Calophyllum lanigerum. J. Med. Chem*. **1993**, *36*, 1110–1110.
12. Sandhya, B.; Vinod, M.; Lolitha, P.; Aswini, T.; Shravani, A. Synthesis, characterization, and pharmacological activities of coumarin derivatives. *Int. J. Pharm. Sci.***2011**, *1*, 17–25.
13. Bullock, S. J.; Felton, C. E.; Fennessy, R. V.; Harding, L. P.; Andrews, M.; Pope, S. J. A.; Rice, C. R.; Riis-Johannessen, T. Coumarin-based luminescent ligand that forms helicates with dicationic metal ions. *Dalton Trans.* **2009**, *47*, 10570–10573.
14. Ghazaryan, A.; Khatchadouria, A.; Karagyozyan, M.; Kachatryan, A.; Sekoyan, E.; Bdoyan, H.; Melkumyan, H.; Karageuzyan, K. Peculiarities of the anticoagulant properties for the newly synthesized preparations of coumarin-related compounds. *Cardiovasc. Hematol. Disord. Drug Targets.* **2007**, *7*, 170–173.
15. Kancheva, V. D.; Boranova, P. V.; Nechev, J. T.; Manolov, I. I. Structure–activity relationships of new 4-hydroxy bis-coumarins as radical scavengers and chain-breaking antioxidants. *Biochimie* **2010**, *92,* 1138–1146.
16. Morabito, G.; Domenico, T.; Singh Brajendra, K.; Prasad Ashok, K.; Parmar Virinder, S.; Clara Naccari, F. M.; Saija, A.; Cristani, M.; Firuzio, O.; Saso, L. Antioxidant properties of 4-methyl coumarins in in vitro cell-free systems. *Bio chimie* **2010**, *92*, 1101–1107.
17. Grimm, E.; Brideau, C., Chauret, N.; Chan, C.; Delorme, D.; Ducharme, Y.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Joucelyne, G.; Hamel, P.; Denis, R.; Breau, C. S.; Philip, T.; Girard, Y.; Guay, J. Substituted coumarins as potent 5-lipoxygenase inhibitors. *Bio org. Med. Chem. Lett.* **2006**, *16*, 2528–2531.
18. Resch, M.; Steigel, A.; Chen, Z.-L.; Bauer, R. 5-Lipoxygenase and cyclooxygenase inhibitory active compounds from *Atractylodes lance*. *J. Nat. Prod.* **1998**, *61,* 347–350.
19. Liu, H.-L.; Li, Z.; Anthonsen, T. Synthesis and fungicidal activity of 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and their 5-arylidene derivatives. *Molecules* **2000**, *5*, 1055–1061.
20. Sham, M. S.; Amrender, D. D.; Jaiveer, S.; Guptha, P. P. Synthesis and anti-inflammatory activity evaluation of some sulfonamides, amidines, and thiazoline derivatives. *Indian J. Chem*. **2010**, *49B*, 1076–1082.
21. Aamer, S.; Najim, A.; Chrisopher, P. In-vitro anti-HIV activity of new thiazol-2-ylidine substituted benzamide analogues. *Pharm. Chem*. **2012**, *4*(1), 106–115.
22. Sondhi, S. M.; Singh, N.; Lahoti, A. M.; Kiran, B.; Ashok, K.; Lozach, O.; Meijer, L. Synthesis of acridinyl-thiazolino derivatives and their evaluation for anti-inflammatory, analgesic, and kinase inhibition activities. *Bio-org. Med. Chem*. **2005**, *13*, 4291–4299.
23. Kim, D. S.; Jeong, Y. M.; Park, I. K.; Hahn, H. G.; Lee, H. K.; Kwon, S. B.; Jeong, J. H.; Yang, S. J.; Sohn, U. D.; Park, K. C. A new 2-imino-1,3-thiazoline derivative, KHG 22394, inhibits melanin synthesis in mouse B16 melanoma cells. *Biol. Pharm. Bull.* **2007**, *30*, 180–183.

24. Vijaykumar, P.; Vinod Reddy, R.; Rajeswar Rao, V. Synthesis of 3-(2-allylamino-4-thia zolyl)-2*H*-1-benzopyran-2-ones and 3-(4-phenylthiazoline-2-anil)-2*H*-1-benzopyran-2-ones in solid state. *Indian J. Chem*. **2003**, *42*, 1738–1741.
25. Rajeswar Rao, V.; Padmanabha Rao, T. V. Studies of thiazolyl, imidazolyl-2H-1-benzo pyran-2-ones. *Indian J. Chem*. **1986**, *25B*, 413–415.