



Catalyst-free regioselective synthesis of benzopyran-annulated thiopyrano[2,3-*b*]thiochromen-5-(4*H*)-one derivatives by domino-Knoevenagel-hetero-Diels–Alder reaction of terminal alkynes with 4-hydroxy dithiocoumarin in aqueous medium

K. C. Majumdar*, Abu Taher, Sudipta Ponra

Department of Chemistry, University of Kalyani, Kalyani 741 235, W.B, India

ARTICLE INFO

Article history:

Received 25 January 2010

Revised 15 February 2010

Accepted 20 February 2010

Available online 24 February 2010

Keywords:

Domino-Knoevenagel-hetero-Diels–Alder reaction

Unactivated alkynes

4-Hydroxy dithiocoumarin

Reaction in aqueous medium

ABSTRACT

The synthesis of novel pentacyclic benzopyran-annulated thiopyrano[2,3-*b*]thiochromen-5(4*H*)-ones has been described by domino-Knoevenagel-hetero-Diels–Alder reaction of 4-hydroxy dithiocoumarin and *O*-propargylated salicylaldehyde in aqueous medium and in the absence of any catalyst. The single step reaction is highly regioselective and provides polycyclic heterocycles in high yields.

© 2010 Elsevier Ltd. All rights reserved.

Coumarin derivatives are widely distributed in nature and show various biological activities such as anticoagulant, antifungal, insecticidal, anthelmintic, hypnotic, antioxidant, anticarcinogenic and HIV protease inhibition.¹ Thieno[2,3-*b*]benzothiopyran-4-one skeleton has been used as an intermediate for the synthesis of a series of anti-psychotic drugs.² Similarly, pharmacophores containing a chromone moiety show biological activity and many of them also have useful medicinal applications.³ These wide range of biological applications have stimulated considerable interest in evolving newer synthetic methods for the construction of polycyclic coumarin derivatives. There are several examples for the synthesis of thieno[2,3-*b*]thiochromen-4-one⁴ and thiopyrano[2,3-*b*]thiochromen-5(2*H*)-one^{4a,c,d,5} derivatives. In our laboratory we have synthesized coumarin- and pyrone-annulated [6,6]-fused benzopyranothiopyran derivatives using sequential Claisen rearrangement and tributyltin hydride-mediated radical cyclization, respectively.⁶ To our knowledge there is no report of the synthesis of thiochromone-annulated [6,6]-fused benzopyranothiopyran derivative. However, a thiochromone-annulated [6,5]-fused benzofurothiopyran has been reported.^{5b} We, therefore, became interested to synthesize thiochromone-annulated [6,6]-fused benzopyranothiopyran derivatives.

Recently, we have synthesized indole-annulated [6,6]-fused benzopyranothiopyran derivatives⁷ by domino-Knoevenagel-hetero-

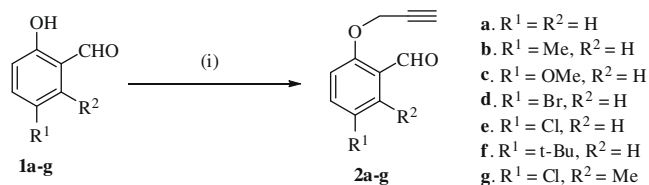
Diels–Alder reaction. A variety of heterocyclic compounds have been synthesized by domino-Knoevenagel-hetero-Diels–Alder reaction.⁸ Tietze extensively described the domino-Knoevenagel-hetero-Diels–Alder reaction of unsaturated aromatic and aliphatic aldehydes with several 1,3-dicarbonyl compounds for the synthesis of tetracycles with a pyran ring.⁹ There are several reports on the intramolecular domino-Knoevenagel-hetero-Diels–Alder reaction with alkenes¹⁰ but those with alkynes are rare. The reason may be the low reactivity of unactivated alkynes compared to the corresponding alkenes. Recently, Balalaie and co-workers examined a few hetero-Diels–Alder reaction with unactivated alkynes¹¹ using Cu^I-catalyst. But to our knowledge there are no reports of domino-Knoevenagel-hetero-Diels–Alder reaction with unactivated alkynes in the absence of any catalyst. Very recently, we have reported a catalyst free domino-Knoevenagel-hetero-Diels–Alder reaction of unactivated alkynes.¹² In order to expand the scope of this catalyst-free methodology, we focused our attention on the domino-Knoevenagel-hetero-Diels–Alder reaction of 4-hydroxy dithiocoumarin with unactivated terminal acetylenes. Herein, we report our results.

Necessary precursors **2a–g** were prepared in high yields and purity by the reaction of substituted salicylaldehydes **1a–g** and propargyl bromide in the presence of anhydrous potassium carbonate in dry DMF at room temperature¹³ (Scheme 1).

A number of reactions including Diels–Alder reaction have been carried out in aqueous medium. Water is environment friendly, safe and easily available in nature.¹⁴ Therefore, we explored the

* Corresponding author. Tel.: +91 033 2582 7521; fax: +91 033 2582 8282.

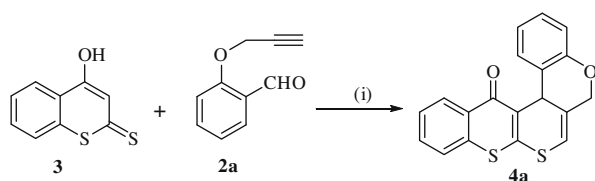
E-mail address: kcm_ku@yahoo.co.in (K.C. Majumdar).



Scheme 1. Reagents and conditions (i) propargyl bromide, anhydrous K_2CO_3 , DMF, rt.

use of water as a solvent for our proposed work. Accordingly, the domino-Knoevenagel-hetero-Diels–Alder reactions of 4-hydroxy dithiocoumarin **3** with **2a–g** were carried out in aqueous medium under refluxing condition. We have first chosen **2a** as a model substrate to optimize the reaction conditions (Scheme 2). The results are summarized in Table 1.

We have examined the influence of Lewis acid, base and solvents in the reaction. In our first attempt, when the reaction of **3** and **2a** was carried out in the absence of any Lewis acid in water under reflux conditions for 4 h the product **4a** was obtained in 80% yield (entry 1). When 20 mol % CuI was employed, the product was obtained in 58% yield after 4 h (entry 2). Increasing the amount of catalyst loading decreases the yield of the product (entry 3). The reason may be due to the coordination of soft sulfur atom¹⁵ with the d^{10} copper ions which prevents the hetero-Diels–Alder reaction and thereby decreasing the yield of the product. When the reaction was carried out in the presence of triethyl amine and CuI (20 mol %) in refluxing water for 4 h, the yield was increased to 65% (entry 4). A series of solvents (MeOH, CH_3CN , 1,4-dioxane, toluene) were investigated (entries 5–8). Among them water was found to be superior to others. Similar trend was also observed when $(NH_4)_2HPO_4$ was used as a base in place of triethyl amine (entries 9–12). Further variation of the catalyst, solvent and base proved that running the reaction in aqueous media without any catalyst provides the best results (Table 1). Using the optimized conditions, we have examined hetero-Diels–Alder reaction of **3** and several O-propargylated salicylaldehydes (**2b–g**). The results are listed in Table 2.



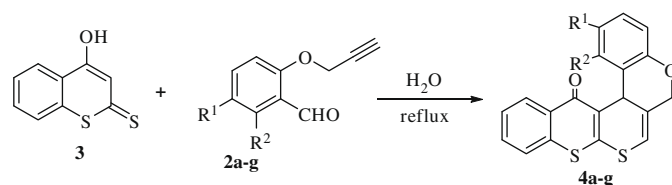
Scheme 2. Reagents and conditions (i) reflux in water.

Table 1
Influence of catalyst, solvent and base on the domino-Knoevenagel-hetero-Diels–Alder reaction^a of **3** and **2a**

Entry	Lewis acid (mol %)	Solvent	Base	Yield (%)
1	–	Water	–	80
2	CuI (20)	Water	–	58
3	CuI (30)	Water	–	49
4	CuI (20)	Water	NEt_3	65
5	CuI (20)	MeOH	NEt_3	35
6	CuI (20)	CH_3CN	NEt_3	32
7	CuI (20)	1,4-Dioxan	NEt_3	29
8	CuI (20)	Toluene	NEt_3	45
9	CuI (20)	Water	$(NH_4)_2HPO_4$	60
10	CuI (20)	MeOH	$(NH_4)_2HPO_4$	34
11	CuI (20)	CH_3CN	$(NH_4)_2HPO_4$	28
12	CuI (20)	1,4-Dioxan	$(NH_4)_2HPO_4$	23

^a All reactions were carried out for 4 h.

Table 2
Domino-Knoevenagel-hetero-Diels–Alder reaction of **3** and **2a–g**^a in aqueous medium

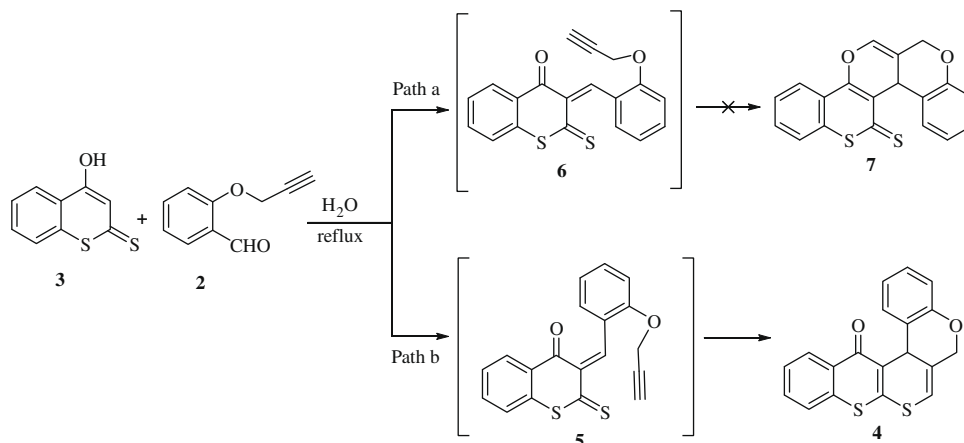


Entry	Aromatic aldehyde (2)	Product (4a–g)	Yield ^b
1			80
2			75
3			76
4			79
5			77
6			72
7			69

^a All the reactions were carried out in refluxing aqueous medium for 4 h.

^b Isolated yields.

Reaction of **3** with 1 equiv of **2b** in refluxing aqueous medium gave the product **4b** in 75% yield (entry 2). When the same reaction was carried out with **2c** and **2d**, the desired products **4c** and **4d** were obtained in 76% and 79% yields, respectively (entries 3 and 4). The product **4e** was obtained in 77% yield when the reaction was carried out with **2e** (entry 5). Similar treatment of **2f** and **2g** separately with **3** under the same reaction conditions afforded the product **4f** and **4g** in 72% and 69% yields, respectively (entries 6 and 7). The structures of the products were determined from their elemental analyses and



Scheme 3. Probable mechanism of domino-Knoevenagel-hetero-Diels-Alder reaction.

spectroscopic data. The characteristic peaks for **4a–g** in the ^1H NMR spectra are an AB quartet for the $-\text{OCH}_2$ protons between $\delta = 4.62$ and 4.94 ppm followed closely by a singlet for the $\text{SCH}=\text{C}$ proton at $\delta = 5.99$ – 6.57 ppm. The corresponding carbon signal for the OCH_2 , $\text{SCH}=\text{C}$ and $\text{C}=\text{O}$ groups of compound **4a** in the ^{13}C spectra appear at 69.7 , 109.4 , 177.1 ppm, respectively.¹⁶

It is remarkable that the domino-Knoevenagel-hetero-Diels-Alder reaction of unactivated alkynes occurs without the help of a Lewis acid/ catalyst. In this particular case, the reactivity may perhaps be explained by considering the presence of soft sulfur atom in the diene moiety of the substrates. The sulfur atom may offer itself a reactive centre and is more polarizable than the other heteroatoms. Moreover, there are empty d-orbitals in the sulfur atom having a matching symmetry with that of the π -orbitals of the acetylene moiety for interaction.¹²

A probable mechanism for the domino-Knoevenagel-hetero-Diels-Alder reaction is depicted in Scheme 3. The first step is the Knoevenagel condensation between 4-hydroxy dithiocoumarin **3** and O-propargylated salicylaldehyde **2** to give an alkene intermediate, which has not been isolated. The alkene heterodiene intermediate may arrange in two different ways (intermediates **5** and **6**), one of which may undergo hetero-Diels-Alder reaction to give two different hetero-Diels-Alder products (products **4** and **7**) that is, through 'path a' or 'path b'. Here only products **4** were isolated which shows that the reaction proceeds via 'path b' and it may be attributed to the presence of the sulfur atom. High polarizability and softness of sulfur atom make the HOMO-LUMO energy gap smaller when thiocarbonyl group of thioester acts as heterodiene than that of the carbonyl group of α,β -unsaturated ketone system and thus the reaction proceeds via 'path b' to give the products **4**.

In conclusion, we have developed a mild, efficient and catalyst-free protocol for the synthesis of benzopyran-annulated thiopyranthiochromen-5(4H)-ones by domino-Knoevenagel-hetero-Diels-Alder reaction of unactivated terminal alkynes. The advantage of the reaction is that water is used as a reaction media which is benign, environment friendly and easily available in nature. One interesting feature of this single step reaction is that C–C and C–S bond formation occurs without the help of any catalyst and base.

Acknowledgments

We thank CSIR (New Delhi) and DST (New Delhi) for financial assistance. Two of us (A.T. and S.P.) are grateful to CSIR (New Delhi) for a Senior and a Junior Research Fellowship. We also thank the DST

(New Delhi) for providing Bruker NMR Spectrometer (400 MHz) and Perkin-Elmer CHN Analyzer under its FIST programme.

References and notes

- (a) Ellis, G. P.; Lockhart, I. M.; Meeder-Nycz, D.; Schweizer, E. E. In *Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; John Wiley and Sons, 1997; (b) Feuer, G. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; North-Holland Publishing Co.: New York, 1974; (c) Kostova, I. *Curr. Med. Chem. Anti-Cancer Agents* **2005**, *5*, 29; (d) Wenkert, E.; Buckwalter, B. L. *J. Am. Chem. Soc.* **1972**, *94*, 4367; (e) Deana, A. A. *J. Med. Chem.* **1983**, *26*, 580.
- (a) Vink, P. *Neth. Appl.* **6**, 411, 477 (Cl, Co7d), April 9, **1965**, Swiss Appl. Oct. 8, **1963** and July 29, **1964**; 7pp; *Chem. Abstr.* **1965**, *63*, 13265.; (b) El-Subbagh, H. I.; El-Emam, A. A.; El-Ashmawy, M. B.; Shehata, I. A. *Arch. Pharm. Res.* **1990**, *13*, 24, and references cited therein.
- (a) Korkina, G. L.; Afanas'ev, I. B. In Sies, H., Ed.; *Adv. Pharmacol.* **1997**, *38*, 151.; (b) Buslig, B. S. In *Flavonoids in Living Systems: Advances in Experimental Medicine and Biology*; Manthey, J. A., Ed.; Plenum: New York, 1998; Vol. 439, (c) Negwer, M. *Organic Chemical Drugs and their Synonyms*, 7th ed.; Akademie: Stuttgart, 1994; (d) Groundwater, P. W.; Solomon, K. R. H.; Drewe, J. A.; Munawar, M. A. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: Amsterdam, 1996; Vol. 33, p 233.
- (a) Majumdar, K. C.; Khan, A. T.; Saha, S. *Synlett* **1991**, 595; (b) Majumdar, K. C.; Bandyopadhyay, A.; Ghosh, S. K. *Synth. Commun.* **2004**, *34*, 2159; (c) Majumdar, K. C.; Bandyopadhyay, A. *Monatsh. für Chem.* **2004**, *135*, 581; (d) Majumdar, K. C.; Saha, S.; Khan, A. T. *Indian J. Chem.* **1994**, *33B*, 216.
- (a) Majumdar, K. C.; Khan, A. T.; Saha, S. *Synth. Commun.* **1992**, *22*, 901; (b) Majumdar, K. C.; Bandyopadhyay, A.; Biswas, A. *Tetrahedron* **2003**, *59*, 5289.
- (a) Majumdar, K. C.; Muhuri, S. *Synthesis* **2006**, 2725; (b) Majumdar, K. C.; Kundu, U. K.; Ghosh, S. K. *Org. Lett.* **2002**, *4*, 2629.
- Majumdar, K. C.; Taher, A.; Ray, K. *Tetrahedron Lett.* **2009**, *50*, 3889.
- (a) Yadav, J. S.; Reddy, B. V. S.; Sadashiv, K.; Padmavani, B. *Adv. Synth. Catal.* **2004**, *346*, 607; (b) Yamanaka, M.; Nishida, A.; Nakagana, M. *Org. Lett.* **2000**, *2*, 159; (c) Deligny, M.; Carreaux, F.; Toupet, L.; Carboni, B. *Adv. Synth. Catal.* **2003**, *345*, 1215; (d) Berkessel, A.; Erturk, E.; Laporte, C. *Adv. Synth. Catal.* **2006**, *348*, 223; (e) Baudelle, R.; Melnyk, P.; Deprez, B.; Tartar, A. *Tetrahedron* **1998**, *54*, 4125.
- (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH, 2006; (c) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967; (d) Tietze, L. F.; Ott, C.; Gerke, K.; Buback, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1485.
- (a) Ramesh, E.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 1812; (b) Lee, Y. R.; Xia, L. *Tetrahedron Lett.* **2008**, *49*, 3283; (c) Jimenez-Alonso, S.; Chavez, H.; Estevez-Braun, A.; Ravelo, A. G.; Feresin, G.; Tapia, A. *Tetrahedron* **2008**, *64*, 8938; (d) Jimenez-Alonso, S.; Estevez-Braun, A.; Ravelo, A. G.; Zarate, R.; Lopez, M. *Tetrahedron* **2007**, *63*, 3066; (e) Manikandan, S.; Raghunathan, R. *Tetrahedron* **2002**, *58*, 8957; (f) Yadav, J. S.; Reddy, B. V. S.; Narsimhaswamy, D.; Lakshmi, P. N.; Narsimulu, K.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3493; (g) Lee, Y. R.; Kim, Y. M.; Kim, S. H. *Tetrahedron* **2009**, *65*, 101.
- (a) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. *Synlett* **2009**, 55; (b) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. *ARKIVOC* **2009**, ix, 114; (c) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Rominger, F.; Gross, J. H. *Tetrahedron Lett.* **2008**, *49*, 6965; (d) Khoshkholgh, M. J.; Balalaie, S.; Gleiter, R.; Rominger, F. *Tetrahedron Lett.* **2008**, *49*, 10924; (e) Khoshkholgh, M. J.; Lotfi, M.; Balalaie, S.; Rominger, F. *Tetrahedron* **2009**, *65*, 4228.
- Majumdar, K. C.; Taher, A.; Ponra, S. *Tetrahedron Lett.* **2010**, *51*, 147.
- Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2004**, *45*, 1567.

14. (a) Grieco, P. A. *Organic Synthesis in Water*; Blacky Academic & Professional Publishers: London, 1998. p. 82; (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (d) Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*; Wiley and Sons: New York, 2007.
15. Dai, J.; Munakata, M.; Wu, L.-P.; Sowa, T.-K.; Suenaga, Y. *Inorg. Chim. Acta* **1997**, *258*, 65.
16. An equi-molar mixture of 4-hydroxy dithiocoumarin **3** and O-propargyl salicylaldehyde **2a** was refluxed in water for 4 h. After completion of the reaction as monitored by TLC the reaction mixture was cooled and diluted with water (50 mL). This was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine and dried over anhydrous Na₂SO₄. The solvent was distilled off. The crude product was purified by column chromatography over silica gel (60–120 mesh) using petroleum ether–ethyl acetate mixture (85:15) as eluent to give compound **4a**. Yield: 80%, colourless solid; mp 212–214 °C; IR(KBr): ν_{max} = 746, 1144, 1603, 2923 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ_{H} = 4.65 (d, *J* = 12.0 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 5.45 (s, 1H), 6.04 (s, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.50–7.65 (m, 3H), 8.51 (d, *J* = 7.8 Hz, 1H) ppm. ¹³C NMR (100 MHz): 35.8, 72.8, 109.4, 117.0, 120.8, 121.6, 125.1, 127.1, 127.6, 127.8, 129.6, 130.4, 130.6, 131.7, 135.7, 146.1, 154.1, 177.0 ppm. HRMS: *m/z* calcd for C₁₉H₁₂O₂S₂ [M+H]⁺: 337.0352; found: 337.0391.