Tetrahedron Letters 53 (2012) 5034–5037

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of some tetrazole fused pyrido[2,3-*c*]coumarin derivatives from a one-pot three-component reaction via intramolecular 1,3-dipolar cycloaddition reaction of azide to nitriles

Pallabi Borah, P. Seetham Naidu, Pulak J. Bhuyan *

Medicinal Chemistry Division, CSIR-North East Institute of Science Technology, Jorhat 785006, Assam, India

ARTICLE INFO

Article history:
Received 11 June 2012
Revised 11 July 2012
Accepted 13 July 2012
Available online 20 July 2012

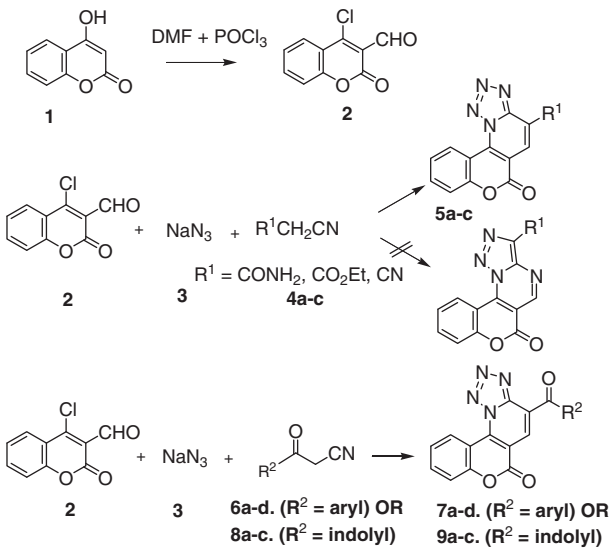
Keywords:
Pyrido[2,3-*c*]coumarin
Tetrazole
Multi-component reactions (MCRs)
Azides
Nitriles

ABSTRACT

Some novel tetrazole fused pyrido[2,3-*c*]coumarin derivatives **5/7/9** were synthesized from a one-pot three-component reaction of 4-chloro-3-formylcoumarins **2**, sodium azide **3,** and alkyl/aryl acetonitriles **4/6/8**.

Coumarins are an important class of compounds obtained from both nature and synthetic origin that possess diverse pharmaceutical and biological activities, often depending on the substituent they bear in the parent benzopyran moiety.[1] As for instance, benzopyranone-pyridine or piperidines interact with DNA,[2] for energy transfer in photophysical processes,[3] to act as potential platelet activating factor antagonists,[4] to be depressant or hypotensive activators[5] and potent antipsychotic agents.[6] Some of their representatives exhibit antibacterial,[7] antitumor,[8] anticholinergic,[9] and antimicrobial[10] activities. Pyridine annelated coumarins also show antiallergic, anticoagulant, antidiabetic, and analgesic properties.[11] Similarly, imidazolo–coumarins act as CNS depressant, mammalian cancer growth inhibitor, and also as phosphor-diesterase VII inhibitors for the treatment of immunity associated diseases.[12] Notably, most of these bioactive compounds are fused 3,4-heterocyclic coumarin derivatives. Therefore, considerable efforts have been made toward the synthetic manipulation of coumarins to find more useful compounds. As a result of this effort a number of annelated coumarin derivatives have been obtained with diverse biological activities.[13]

Tetrazoles are an important class of compounds which have been the subject of intensive research and applied investigations.[14] Tetrazoles are regarded as biologically equivalent to the carboxylic acid group.[15] Both carboxylic acid and tetrazoles act as ligand binding functionality for CYP450-derived oxidative metabolic processes, and tetrazoles have the advantage over carboxylic acids in terms of escaping most bio-transformations by Phase-II reaction pathways.[16] 1*H*- and 2*H*-tetrazoles are frequently employed in

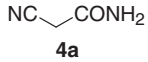
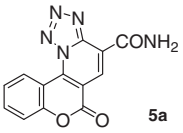
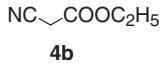
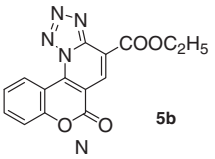
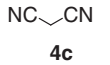
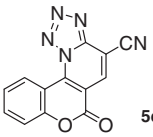
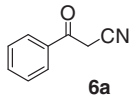
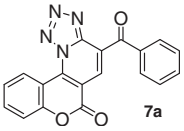
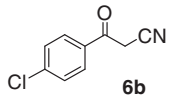
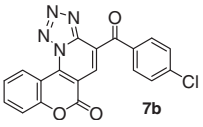
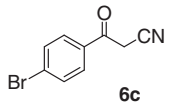
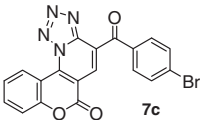
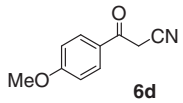
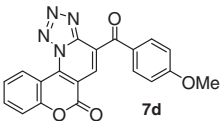
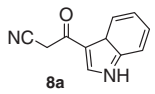
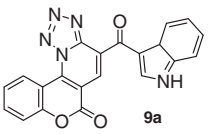
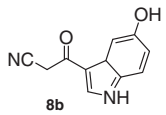
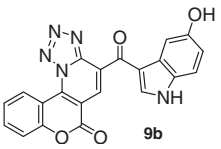
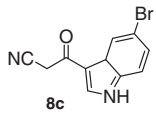
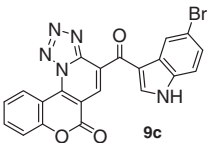


Scheme 1.

* Corresponding author. Tel.: +91 376 2370121; fax: +91 376 2370011.
E-mail address: pulak_jyoti@yahoo.com (P.J. Bhuyan).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.060

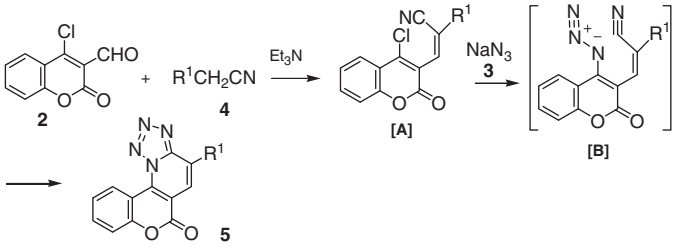
Table 1
Synthesis of tetrazolo[4′,5′:1,6]pyrido[2,3-*c*]coumarin derivatives **5/7/9**

Entry	Substrate	Product	Reaction time (h)	Yield (%)
1	 **4a**	 **5a**	3	82
2	 **4b**	 **5b**	3	83
3	 **4c**	 **5c**	3	78
4	 **6a**	 **7a**	4.5	80
5	 **6b**	 **7b**	3.5	83
6	 **6c**	 **7c**	3.5	85
7	 **6d**	 **7d**	5	75
8	 **8a**	 **9a**	5	78
9	 **8b**	 **9b**	4	81
10	 **8c**	 **9c**	4	86

the lead optimization of ethical drug candidates to enhance the oral bioavailability. Several successful examples of this strategy are present in the sartane drug family, which is used to treat hypertension.[17]

The attack of cyanide-stabilized carbanions on azide functions leading to 1,2,3-triazole is a well established conversion in organic synthesis.[18] In an extensive study, the carbanion derived from diethylacetonedicarboxylate has also been employed in this reaction process, and the triazoles resulting from the reaction undergo base catalyzed intramolecular condensation at the ortho substituent to give well functionalized triazolo[1,5-*a*]quinolines.[19]

As part of our continued interest on the synthesis of diverse heterocyclic compounds of biological significance,[20] recently we reported the synthesis of some novel isoxazole and pyrazole fused pyrido[2,3-*c*]coumarins via an intramolecular 1,3-dipolar cycloaddition reaction involving nitrone, nitrile oxide, and nitrile imine as 1,3-dipole.[21] There are many other recent examples of the application of 1,3-dipolar cycloaddition reaction in the synthesis of complex heterocyclic compounds of biological importance.[22] In the present paper, we report the synthesis of some novel tetrazole fused pyrido[2,3-*c*]coumarin derivatives **5/7/9** from a one-pot three-component reaction of 4-chloro-3-formylcoumarins **2**, sodium azide **3**,



Scheme 2.

and alkyl/aryl acetonitriles **4/6/8**, and by exploring intramolecular 1,3-dipolar cycloaddition reaction of azide to nitriles (Scheme 1).

4-Hydroxy coumarin **1** was taken as starting material in our reaction strategy which on treatment with Vilsmeier reagent ($DMF + POCl_3$) afforded the key intermediate 4-chloro-3-formyl coumarin **2** (Scheme 1).[23] In a simple experimental procedure,[24] treatment of 4-chloro-3-formyl coumarin **2**, sodium azide **3**, and cyanoacetamide **4a** for 3 h at 50–60 °C in the presence of catalytic amounts of triethylamine using dimethylformamide as solvent afforded after work-up tetrazolo[4′,5′:1,6]pyrido[2,3-*c*]coumarin derivative **5a** in excellent yields. The structure of the compound was ascertained from the spectroscopic data and elemental analysis. Although there was a possibility of the formation of triazolo fused pyrimido[4,5-*c*]coumarin derivative, we obtained exclusively the tetrazole fused coumarin derivative **5a**. The generality of the reaction was established by synthesizing a series of compounds **5a–c, 7a–d**, and **9a–c** by utilizing **2** and **3** with **4/6/8** and characterizing them (Table 1). The compounds **6** and **8** were prepared following the standard reaction protocol.[25]

The formation of the products from the three-component reactions was confirmed by performing the reactions stepwise (Scheme 2). First, intermediate [**A**] was prepared from the condensation of compound **2** with **4** in the presence of catalytic amounts of triethylamine at room temperature using ethanol as solvent.[26] Then the intermediate [**A**] was reacted with sodium azide **3** at 50–60 °C using DMF as solvent which afforded compound **5**.[27] The intermediate [**B**] could not be isolated in all the cases. Similarly, compounds **7** and **9** were synthesized by performing the reactions stepwise.

It was observed that malononitrile **4c** and ethyl-cyanoacetate **4b** are more reactive than cyano-acetamide **4a**. However, product **5a** could be isolated much more easily than the others. Although, compounds **6** and **8** bearing a variety of either electron donating or electron withdrawing functional groups at the benzene ring were efficient for the three-component reaction, those bearing electron-withdrawing groups were found more reactive and thus products were obtained in high yields and in shorter reaction time than the others.

In summary, we have reported the synthesis of some novel tetrazole fused pyrido[2,3-*c*]coumarin derivatives from a one-pot three component reaction via intramolecular 1,3-dipolar cycloaddition reaction of azide to nitriles. The work-up procedure of the reaction is simple; products were isolated simply by filtration and purified by chromatography. This reaction which can be further utilized for the synthesis of many other heterocyclic compounds of biological importance is a valuable addition to the chemistry of coumarins in particular and heterocyclic compounds as a whole. Further study of the reaction is in progress.

Acknowledgement

The authors thank the DST, New Delhi, for financial support and P.S.N. thanks UGC, New Delhi for Junior Research Fellowship.

References and notes

1. (a) Murray, R. D. H.; Mendez, J.; Brown, R. A. *The Natural Coumarins*; John Wiley Sons: New York, 1982; (b) Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813.
2. Guillo, L. A.; Beylot, B.; Vigny, P.; Spassky, A. *Photochem. Photobiol.* **1996**, *64*, 349.
3. Bangar. Raju, B.; Eliasson, B. J. *Photochem. Photobiol.* **1998**, *116*, 135.
4. Guinn, D. E.; Summers, J. B.; Heyman, H. R.; Conway, R. G.; Rhein, D. A.; Albert, D. H.; Magoc, T.; Carter, G. W. *J. Med. Chem.* **1992**, *35*, 2055.
5. Pars, H. G.; Granchelli, F. E.; Razdan, R. K.; Keller, J. K.; Teiger, D. G.; Rosenberg, F. J.; Hris, L. S. *J. Med. Chem.* **1976**, *19*, 445.
6. (a) Mach, U. R.; Hackling, A. E.; Perachon, S.; Ferry, S.; Wermuth, C. G.; Schwartz, J.-C.; Sokoloff, P.; Stark, H. *Chem. Bio. Chem.* **2004**, *5*, 508; (b) Unangst, P. C.; Capiris, T.; Connor, D. T.; Heffner, T. G.; MacKenzie, R. G.; Miller, S. R.; Pugsley, T. A.; Wise, L. D. *J. Med. Chem.* **1997**, *40*, 2688; (c) Zhang, M.-R.; Haradahira, T.; Maeda, J.; Okauchi, T.; Kawabe, K.; Kida, T.; Obayashi, S.; Suzuki, K.; Suhara, T. *Nucl. Med. Biol.* **2002**, *29*, 469.
7. *Coumarins: Biology, Applications and Mode of Action;* O'Kennedy, R., Thornes, R. D., Eds.; Wiley: Chichester, 1997.
8. Raev, L. D.; Voinova, E.; Ivanov, I. C.; Popov, D. *Pharmazie* **1990**, *45*, 696.
9. Connor, D. T.; Unangst, P. C.; Schwender, C. F.; Sorenson, R. J.; Carethers, M. E.; Puchalski, C.; Brown, R. E.; Finkel, M. P. *J. Med. Chem.* **1989**, *32*, 683.
10. Khan, I. A.; Kulkarni, M. V.; Gopal, M.; Shahabuddin, M. S.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584.
11. (a) Ukawa, K.; Ishiguro, T.; Wada, Y.; Nohara, A. *Heterocycles* **1931**, *1986*, 24; (b) Heber, D. *Arch. Pharm.* **1987**, *320*, 402; (c) Heber, D.; Berghaus, T. *J. Heterocyclic Chem.* **1994**, *31*, 1353.
12. (a) Savel'ev, V. L.; Pryanishnikova, N. T.; Zagorevskii, V. A.; Chernyakova, I. V.; Artamonova, O. S.; Shavyrina, V. V.; Malysheva, L. I. *Khim. Farm. Zh.* **1983**, *17*, 697; (b) Trkovnik, M.; Kalaj, V.; Kitan, D. *Org. Prep. Proced. Int.* **1987**, *19*, 450; (c) Eggenweiler, M.; Rochus, J.; Wolf, M.; Gassen, M.; Poeschke, O.; *Merck Patent Gmbh, Germany*, PCT Int. Appl. 2001.
13. (a) Beccalli, E. M.; Contini, A.; Trimarco, P. *Eur. J. Org. Chem.* **2003**, 3976; (b) Beccalli, E. M.; Contini, A.; Trimarco, P. *Tetrahedron Lett.* **2004**, *45*, 3447; (c) Gautam, D. R.; Protopappas, J.; Fylaktakidou, C. K.; Litinus, K. E.; Nicolaides, D. N.; Tsoleridis, C. A. *Tetrahedron Lett.* **2009**, *50*, 448.
14. Zubarev, V. Y.; Ostrovskii, V. A. *Chem. Het. Comp.* **2000**, *36*, 759.
15. Bulter, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 791.
16. Herr, J. R. *Bioorg. Med. Chem.* **2002**, *10*, 3379. and the references cited therein.
17. (a) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M *J. Med. Chem.* **1996**, *39*, 625; (b) Schmidt, B.; Scieffer, B. *J. Med. Chem.* **2003**, *46*, 2261; (c) Schmidt, B.; Drexler, H.; Scieffer, B. *Am. J. Cardiovasc. Drugs* **2004**, *4*, 361.
18. (a) Tennant, G. *J. Chem. Soc. C* **1966**, 2290; (b) Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Per. Trans* **1974**, *I*, 534; (c) Westerlurd, C. *J. Heterocycl. Chem.* **1980**, *17*, 1765; (d) Lauria, A.; Patella, C.; Diana, P.; Barraja, P.; Montalbano, A.; Cirrincione, G.; Dattallo, G.; Almerico, A. M. *Tetrahedron Lett.* **2006**, *47*, 2187.
19. Smalley, R. K.; Teguiche, M. *Synthesis* **1990**, 654.
20. (a) Baruah, B.; Bhuyan, P. J. *Tetrahedron* **2009**, *65*, 7099; (b) Deb, M. L.; Majumder, S.; Baruah, B.; Bhuyan, P. J. *Synthesis* **2010**, 929; (c) Majumder, S.; Bhuyan, P. J. *Tetrahedron Lett.* **2012**, *53*, 137; (d) Naidu, P. S.; Bhuyan, P. J. *Tetrahedron Lett.* **2012**, *53*, 426; (e) Majumder, S.; Bhuyan, P. J. *Tetrahedron Lett.* **2012**, *53*, 762.
21. Majumder, S.; Bora, P.; Bhuyan, P. J. *Mol. Diver.* **2012**, *16*, 279.
22. (a) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Pellegrino, S. *Tetrahedron* **2008**, *64*, 8182; (b) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Khansaa, M.; Rigamonti, M. *Eur. J. Org. Chem.* **2010**, 1694; (c) Butkovic, K.; Marinic, Z.; Molcanov, K.; Kojic-Prodic, B.; Sindler-Kulyk, M. *Beil. J. Org. Chem.* **2011**, 1663; (d) Yonekwa, M.; Koyama, Y.; Kuwata, S.; Takata, T. *Org. Lett.* **2012**, *14*, 1164.
23. Andrieux, J.; Battioni, J.-P.; Giraud, M.; Molho, D. *Bull. Soc. Chem. Fr.* **1973**, *6*, 2093.
24. **Representative procedure for the synthesis of tetrazolo[4′,5′:1,6]pyrido[2,3-*c*]coumarins 5/7/9:**
4-Chloro-3-formyl coumarin **2** (1 mmol, 208 mg), sodium azide **3** (1.25 mmol, 80 mg) and cyanoacetamide **4a** (1.5 mmol, 126 mg) were taken in a round bottom flask. To this were added DMF (5 ml) and one drop of triethylamine. The reaction mixture was stirred with a magnetic stirrer at 50–60 °C for 3 h. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and then poured into water (10 mL) with stirring. A brown coloured solid product appears. The mixture was kept in a refrigerator for 3 h. The solid product was filtered and purified by column chromatography using petroleum ether and ethyl acetate (7:3) as eluent. The structure of the compound was ascertained as **5a** from the spectroscopic data and elemental analysis. Yield = 0.203 g (72.24%). Compound **5a**: Light brown solid: Mp 228–229 °C. IR (KBr) ν_{max} = 3419, 2945, 1719, 1702 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 6.21 (s, 1H), 7.10 (m, 2H), 7.21 (d, 1H), 7.49 (d, 1H), 7.70 (brs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.88, 117.22, 118.85, 124.71, 125.19, 125.57, 125.95, 135.82, 147.78, 148.70, 153.20, 158.33, 161.85. MS (*m*/*z*) 281.2 [M^+]. Anal. calcd for $C_{13}H_7N_5O_3$: C, 55.52; H, 2.49; N, 24.91%. Found: C, 55.43; H, 2.58; N, 24.83%. Similarly compounds **5b–c/7a–d/9a–c** were synthesized and characterized.
25. (a) Slatt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760; (b) Nowwill, R. N.; Patel, T. J.; Beasley, D. L.; Alvarez, J. A.; Jackso, E., III; Hizer, T.; Ghiviriga, I.; Mateer, S. C.; Feske, B. D. *Tetrahedron Lett.* **2011**, *52*, 2440.

26. Representative procedure for the synthesis of intermediate [A]: To a solution of 4-chloro-3-formylcoumarin **2** (2 mmol, 416 mg) and cyanoacetamide **4a** (2.5 mmol, 210 mg) in ethanol (8 mL) was added one drop of piperidine and the reaction mixture was allowed to stir at rt for 30 min. The solution was cooled in a refrigerator for 3 h. The yellow solid which appeared in the reaction mixture was filtered and washed with ethanol and dried. Yield 430 mg (79%). mp 200–202 °C. The structure of the compound was ascertained as 2-(4-chloro-2-oxo-2*H*-chromeno-3-yl)-2cyano-acrylamide from the spectroscopic data. IR (KBr) ν_{max} = 3410, 2889, 2200, 1715, 1698 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 6.62 (s, 1H), 7.39 (m, 2H), 7.60 (m, 1H), 7.89 (m, 1H).

27. Representative procedure for the reaction of intermediate [A] with sodium azide 3: To a solution of 2-(4-chloro-2-oxo-2*H*-chromeno-3-yl)-2cyano-acrylamide [**A**] (274.5 mg, 1 mmol) and NaN_3 (80 mg, 1.25 mmol) in DMF (10 mL) added catalytic amounts of triethylamine and the reaction mixture was stirred for four hours at 50–60 °C. The solution was cooled to rt and then poured into water under continuous stirring. A brown colored solid which appeared was filtered and purified by preparative TLC using 7:3 petroleum ether and ethyl acetate as eluent. Yield = 190 mg (67.6 %). Mp 228–229 °C. The compound was comparable in all respects with **5a** obtained from the three-component reaction.