



Convenient one-step Synthesis of Substituted Pyrano[2,3-c]isoquinoline (2-amino-4*H*-chromenes) via three Component Reaction between Alkyl isocyanides and Dialkyl Acetylenedicarboxylate in the presence of 3-Hydroxyisoquinoline

Bitra Mohtat^{1,*}, Shahla Salmani¹, Amineh Aminian¹, Hoorieh Djahaniani²

1.Chemistry Department, Karaj Branch, Islamic Azad University, Karaj, Iran

*Corresponding author: b_mohtat@yahoo.com

2.Chemistry Department, East Tehtan Branch, Islamic Azad University, Tehran, Iran

ABSTRACT

The reactive intermediate generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylate are trapped by 3-hydroxyisoquinoline to produce highly functionalized 4*H*-chromenes in 83-92% yields.

Keywords

4*H*-chromenes; alkyl isocyanides; acetylenic ester; 3-hydroxyisoquinoline.

Academic Discipline And Sub-Disciplines

Chemistry, organic

SUBJECT CLASSIFICATION

Organic, synthesis

TYPE (METHOD/APPROACH)

Experimental

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Chemistry

Vol. 6, No. 1

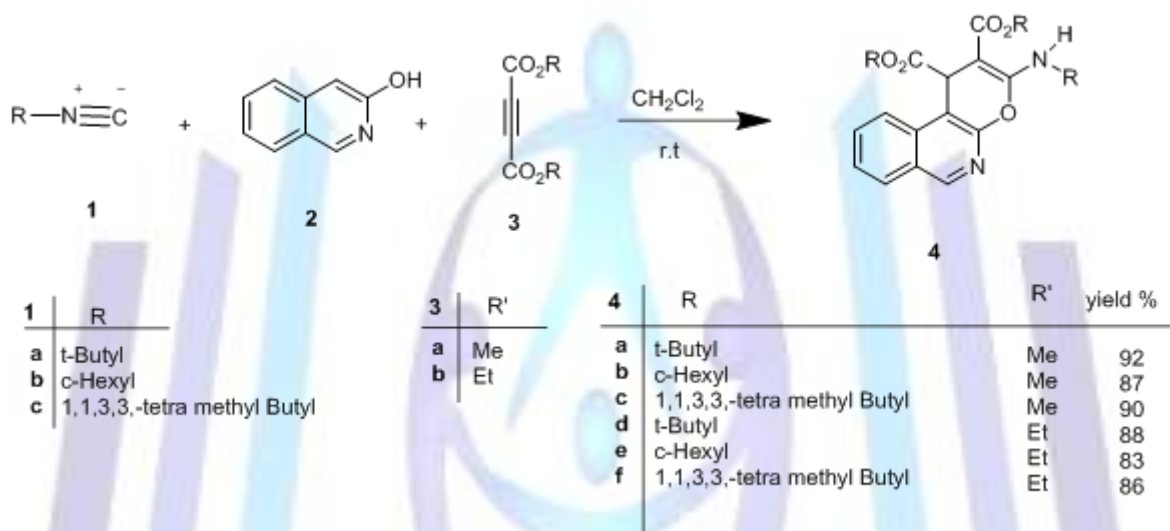
editor@cirworld.com

www.cirworld.com, member.cirworld.com

Introduction

2-Amino-4*H*-chromenes are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmolytic-, diuretic-, anticoagulant-, antibacterial- and antianaphylactic activities [1]. In addition substituted 2-amino-4*H*-benzochromenes can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [2]. The current interest in 2-amino-4*H*-chromenes arises from their application in the treatment of human inflammatory TNF α -mediated diseases, such as rheumatoid and psoriatic arthritis and in cancer therapy [1, 3].

Because of their importance in pharmaceuticals, their syntheses have attracted considerable attention and some methods have been reported for their synthesis [4-11]. Recently, we have described a convenient method for preparation of 2-amino-4*H*-chromene derivatives, by three component reaction of 6-hydroxyquinoline or 7-hydroxycoumarin, dialkyl acetylenedicarboxylates and alkyl isocyanide [12, 13]. Here we extend this methodology using 3-hydroxyisoquinoline. Thus, the reaction of alkyl isocyanides **1** and dialkyl acetylene dicarboxylates **2** in the presence of 3-hydroxyisoquinoline **3** leads to 2-amino-4*H*-chromenes (Scheme 1).

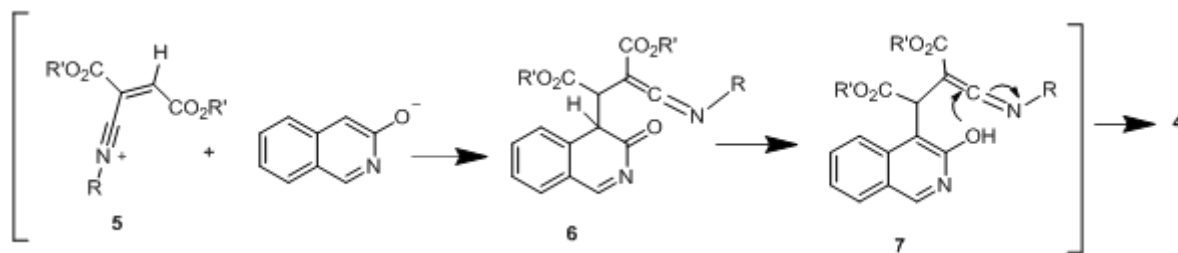


Scheme 1 Typical procedure for synthesis of compounds **4**

Results and Discussion

The reaction of dimethyl acetylenedicarboxylate (DMAD) with tert-butyl isocyanide in the presence of 3-hydroxyisoquinoline proceeded spontaneously at room temperature in dichloromethane, and produced dimethyl 3-(tert-butylamino)-1*H*-pyrano[2,3-*c*]isoquinoline-1,2-dicarboxylate (**4a**) (Scheme 1). The structure of **4a** was determined on the basis of its elemental analyses, mass spectrum (MS), ¹H and ¹³C NMR and IR spectroscopic data. The ¹H NMR spectrum of **4a** exhibited four singlets identified as tert-butyl (δ = 1.55), methoxy (δ = 3.60 and 3.79) and methine (δ = 5.35), quinolinol moiety appeared at (δ = 7.51-8.90) ppm. The NH proton resonance at δ = 8.82 disappeared after addition of D₂O to the CDCl₃ solution of **4a**. The proton decoupled ¹³C NMR spectrum of **4a** showed 18 distinct resonances in agreement with the proposed structure. The presence of oxo and amino groups at one end of the double bond leads to polarization of the olefinic system. The α -carbon atom of this polarized system appears at δ = 173.0, while the β -carbon at δ = 71.8 ppm. Similar chemical shifts have been observed for the polarized carbon-carbon double bonds in 2-alkylamino-4*H*-benzo[*h*]chromene derivatives [4]. The carbonyl groups of **4a** appear at δ = 162.3 and 169.5 ppm.

A possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [14, 15] it is reasonable to assume that compounds **4** result from nucleophilic addition of alkyl isocyanides to the acetylenic system and subsequent protonation of the 1:1 adduct by the OH-acid. Then, the positively charged ion **5** is attacked by the anion of the OH-acid to form ketenimine **6**. Such an addition product may tautomerize into **7** and then cyclize, under the reaction conditions employed, to produce **4**. Similar mechanistic scheme can be considered for formation of compounds **4b-4f** (Scheme 2).



Scheme 2A possible mechanism for preparation of 4

Conclusion

In conclusion, we have found an efficient synthetic method for the preparation of some pyrano[2,3-*c*]isoquinoline (4*H*-chromenes). The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ¹H and ¹³C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with CDCl₃ as solvent at 300.1 and 75.5 MHz, respectively. Alkyl isocyanides, dialkyl acetylenedicarboxylates and 3-hydroxyisoquinoline were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure for pyrano[2,3-*c*]isoquinolines 4a-f

To a magnetically stirred solution of 3-hydroxyisoquinoline (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in 10 mL CH₂Cl₂ was added dropwise at -10 °C over 10 min alkyl isocyanide (2 mmol). The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the residue was purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F254) 20×20 cm plates using n-hexane-AcOEt (1:1) as eluent.

*Dimethyl 3-(tert-butylamino)-1H-pyrano[2,3-*c*]isoquinoline-1,2-dicarboxylate (4a)*

Was obtained in 0.68 g (92%) yield as a yellow powder; mp 87-91 °C (dec); IR ν 3430, 1744, 1660, 1631, 1413, 1261, 1097 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.55 (s, 9H), 3.60 (s, 3H), 3.79 (s, 3H), 5.35 (s, 1H), 7.51-7.54 (m, 2H), 8.09 (d, 1H, *J* = 9.1 Hz), 8.70 (d, 1H, *J* = 8.3 Hz), 8.82 (br s, 1H), 8.88 (d, 1H, *J* = 4.2 Hz); ¹³C NMR (75.5 MHz, CDCl₃): δ 30.5, 38.7, 51.9, 52.9, 53.1, 71.8, 123.1, 126.1, 127.4, 128.2, 131.5, 132.4, 135.8, 137.5, 151.3, 162.3, 169.5, 173.0. Anal. calcd for C₂₀H₂₂N₂O₅: C, 64.85; H, 5.99; N, 7.56; Found: C, 64.80; H, 6.07; N, 7.54.

*Dimethyl 3-(cyclohexylamino)-1H-pyrano[2,3-*c*]isoquinoline-1,2-dicarboxylate (4b)*

Was obtained in 0.69 g (87%) yield as a yellow powder; mp 102-105 °C (dec); IR ν 3444 (NH), 1727 (C=O), 1644 (C=O), 1436, 1258, 1095 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.28-2.10 (m, 5H), 3.60 (s, 3H), 3.78 (s, 3H), 3.95 (m, 1H), 5.33 (s, 1H), 7.49-7.55 (m, 2H), 8.11 (d, 1H, *J* = 9.2 Hz), 8.63 (br s, 1H), 8.72 (d, 1H, *J* = 8.6 Hz), 8.9 (d, 1H, *J* = 4.2 Hz); ¹³C NMR (75.5 MHz, CDCl₃): δ 23.8, 24.5, 25.3, 32.4, 33.8, 38.3, 52.0, 52.6, 67.9, 72.6, 123.1, 126.1, 127.0, 128.9, 130.6, 135.5, 138.2, 140.6, 152.5, 164.5, 170.3, 171.5. Anal. calcd for C₂₂H₂₄N₂O₅: C, 66.65; H, 6.10; N, 7.07; Found: C, 66.62; H, 6.10; N, 7.15.

*Dimethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-pyrano[2,3-*c*]isoquinoline-1,2-dicarboxylate (4c)*

Was obtained in 0.77 g (90%) yield as a yellow powder; mp 118-122 °C (dec); IR ν 3371, 1732, 1694, 1626, 1463, 1254, 1097 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.02 (s, 9H), 1.56 (s, 3H), 1.58 (s, 3H), 1.85 (d, 1H, *J* = 14.9 Hz), 1.92 (d, 1H, *J* = 14.9 Hz), 3.56 (s, 3H), 3.77 (s, 3H), 5.34 (s, 1H), 7.50-7.54 (m, 2H), 8.10 (d, 1H, *J* = 9.1 Hz), 8.71 (d, 1H, *J* = 8.6 Hz), 8.88 (br s, 1H), 8.90 (d, 1H, *J* = 4.1 Hz); ¹³C NMR (75.5 MHz, CDCl₃): δ 31.3, 31.4, 31.6, 31.7, 32.3, 51.6, 52.9, 55.8, 56.3, 76.0, 124.5, 126.1, 127.7, 128.1, 131.8, 135.8, 138.2, 139.0, 152.8, 162.2, 170.5, 173.0. Anal. calcd for C₂₄H₃₀N₂O₅: C, 67.59; H, 7.09; N, 6.57; Found: C, 67.62; H, 6.95; N, 6.51.

*Diethyl 3-(tert-butylamino)-1H-pyrano[2,3-*c*]isoquinoline-1,2-dicarboxylate (4d)*

Was obtained in 0.70 g (88%) yield as a yellow powder; mp 95-99 °C (dec); IR ν 3390 (NH), 1730 (C=O), 1668 (C=O), 1506, 1366, 1217, 1070 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.12 (t, 3H, *J* = 7.1 Hz), 1.32 (t, 3H, *J* = 7.1 Hz), 1.52 (s, 9H), 4.03 (m, 2H), 4.23 (m, 2H), 5.29 (s, 1H), 7.42-7.51 (m, 2H), 8.03 (d, 1H, *J* = 9.1 Hz), 8.71 (d, 1H, *J* = 8.4 Hz), 8.82 (br s, 1H), 8.88 (d, 1H, *J* = 4.2 Hz); ¹³C NMR (75.5 MHz, CDCl₃): δ 13.9, 14.7, 30.4, 38.8, 53.0, 59.9, 61.2, 72.1, 123.3, 126.5,



127.5, 128.6, 131.3, 132.7, 135.7, 137.3, 151.5, 162.6, 169.8, 173.2. Anal. calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03; Found: C, 66.33; H, 6.60; N, 6.98.

Diethyl 3-(cyclohexylamino)-1H-pyrano[2,3-c]isoquinoline-1,2-dicarboxylate (4e)

Was obtained in 0.70 g (83%) yield as a yellow powder; mp 107-110 °C (dec); IR ν 3254 (NH), 1729 (C=O), 1671 (C=O), 1593, 1443, 1224, 1095 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, 3H, $J = 7.1$ Hz), 1.33 (t, 3H, $J = 7.1$ Hz), 1.28-2.09 (m, 5H), 3.90 (m, 1H), 4.05 (m, 2H), 4.25 (m, 2H), 5.30 (s, 1H), 7.46-7.53 (m, 2H), 8.08 (d, 1H, $J = 9.1$ Hz) 8.68 (br s, 1H), 8.75 (d, 1H, $J = 8.5$ Hz), 8.87 (d, 1H, $J = 4.0$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0, 14.5, 24.5, 25.3, 32.4, 33.3, 33.7, 38.3, 49.9, 59.4, 61.1, 72.2, 122.9, 126.1, 126.8, 128.5, 130.4, 135.7, 138.6, 140.1, 152.5, 164.3, 169.7, 171.1. Anal. calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60; Found: C, 67.91; H, 6.69; N, 6.62.

Diethyl 3-(2,4,4-trimethylpentan-2-ylamino)-1H-pyrano[2,3-c]isoquinoline-1,2-dicarboxylate (4f)

Was obtained in 0.78 g (86%) yield as a Yellow powder; mp 135-140 °C (dec); IR ν 3404, 1751, 1696, 1614, 1477, 1252, 1029 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.11 (t, 3H, $J = 7.1$ Hz), 1.33 (t, 3H, $J = 7.1$ Hz), 1.55 (s, 3H), 1.57 (s, 3H), 1.68 (d, 1H, $J = 14.6$ Hz), 1.75 (d, 1H, $J = 14.6$ Hz), 4.04 (m, 2H), 4.23 (m, 2H), 5.34 (s, 1H), 7.44-7.53 (m, 2H), 8.08 (d, 1H, $J = 9.1$ Hz), 8.75 (d, 1H, $J = 8.4$ Hz), 8.84 (br s, 1H), 8.90 (d, 1H, $J = 4.2$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9, 14.4, 31.1, 31.4, 31.6, 31.7, 35.3, 53.2, 54.6, 60.3, 61.6, 73.9, 123.8, 126.4, 127.4, 128.5, 131.7, 136.2, 137.7, 139.3, 152.6, 162.9, 170.0, 172.3. Anal. calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16; Found: C, 68.73; H, 7.52; N, 6.14.

REFERENCES

- [1] Elinson, M. N., Dorofeev, A. S., Miloserdov, F. M., Ilovaisky, A. I., Feducovich, S. K., Belyakov, P. A. and Nikishin, G. I. Catalysis of salicylaldehydes and two different C-H acids with electricity: First example of an efficient multicomponent approach to the design of functionalized medicinally privileged 2-amino-4H-chromene scaffold. *Adv. Synth. Catal.* 350, (2008) 591-601.
- [2] Konkoy, C. S., Fisk, D. B., Cai, S. X., Lan, N. C. and Keana, J. F.W. PCT Int. Appl. WO 0075123, 2000; *Chem. Abstr.* 134, (2001) 29313a.
- [3] Kemnitzer, W., Drewe, J., Jiang, S., Zhang, H., Zhao, J., Crogan-Grundy, C., Xu, L., Lamothe, S., Gourdeau, H., Denis, R., Tseng, B., Kasibhatla, S. and Cai, S. X. Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 3. Structure-activity relationships of fused rings at the 7,8-positions. *J. Med. Chem.* 50, (2007) 2858-2864.
- [4] Yavari, I., Djahaniani, H. and Nasiri, F. Reaction between alkyl isocyanides and dimethyl acetylenedicarboxylate in the presence of polyhydroxybenzenes. Synthesis of 4H-chromene derivatives. *Tetrahedron* 59, (2003) 9409-9412.
- [5] Yavari, I., Anary-Abbasinejad, M., Alizadeh, A. and Hossaini, Z. A simple and efficient approach to the synthesis of highly functionalized fused benzochromenes. *Tetrahedron* 59, (2003) 1289-1292.
- [6] Yavari, I., Djahaniani, H. and Nasiri, F. Synthesis of coumarines and 4H-chromenes through the reaction of tert-butyl isocyanide and dialkyl acetylenedicarboxylates in presence of 2-hydroxybenzaldehydes. *Synthesis* (2004) 679-682.
- [7] Yavari, I., Djahaniani, H. and Nasiri, F. Synthesis of highly functionalised 1H-furo [3, 4-b]chromenes. *Mendeleev Commun.* (2004) 214-216.
- [8] Teimouri, M. B., Bazhrang, R., Eslamimanesh, V. and Nouri, A. Reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of strong CH-acids: one-pot synthesis of highly functionalized annulated 4H-pyrans. *Tetrahedron* 62, (2006) 3016-3020.
- [9] Yavari, I., Hossaini, Z. and Sabbaghan, M. Synthesis and dynamic NMR study of functionalized 1-(3-Furyl)-1H-indole-2,3-diones. *Monatsh. Chem.* 138, (2007) 107-110.
- [10] Eshghi, H., Zohuri, G. H., Sandaroos, R. and Damavandi, S. Synthesis of novel benzo[f] chromene compounds catalyzed by ionic liquid Heterocycl. *Commun.* 18, (2012) 67-70.
- [11] Osyanin, V. A., Osipov, D. V. and Klimochkin, Y. N. Convenient one-step synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles and 5-unsubstituted 5H-chromeno[2,3-b]pyridine-3-carbonitriles from quaternary ammonium salts. *Tetrahedron*, 68, (2012) 5612-5618.
- [12] Mohtat, B., Djahaniani, H., Yavari, I., Dehbalaei, M.G. and Jam, S.A. Synthesis of 4H-chromene derivatives by reaction between alkyl isocyanides and dialkyl acetylenedicarboxylate in the presence of 6-hydroxyquinoline. *Chin. Chem. Lett.* 22, (2011) 771-773.
- [13] Mohtat, B., Farsijani, S., Razaghi, M. and Djahaniani, H. Reaction between 7-hydroxy coumarin, alkyl isocyanides and dialkyl Acetylenedicarboxylate: Synthesis of 4H-chromenes and 1-azabuta-1,3-dienes. *J. Mex. Chem. Soc.* 57, (2013) 92-95
- [14] Ugi, I. From isocyanides via four-component condensations to antibiotic syntheses. *Angew. Chem. Int. Ed. Engl.* 21, (1982) 810-819.



[15] Marcaccini, S. and Torroba, T. The use of isocyanidse in heterocyclic synthesis. Org. Prep. Proced. Int. 25, (1993) 141-208

Author's biography with Photo



Dr. Bita Mohtat is associate professor in the department of chemistry , Karaj Branch, Islamic Azad University, Karaj, Iran

