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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

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ABTRACT

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

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

Academic Discipline And Sub-Disciplines

Chemistry, organic

SUBJECT CLASSIFICATION

Organic, synthesis

TYPE (METHOD/APPROACH)

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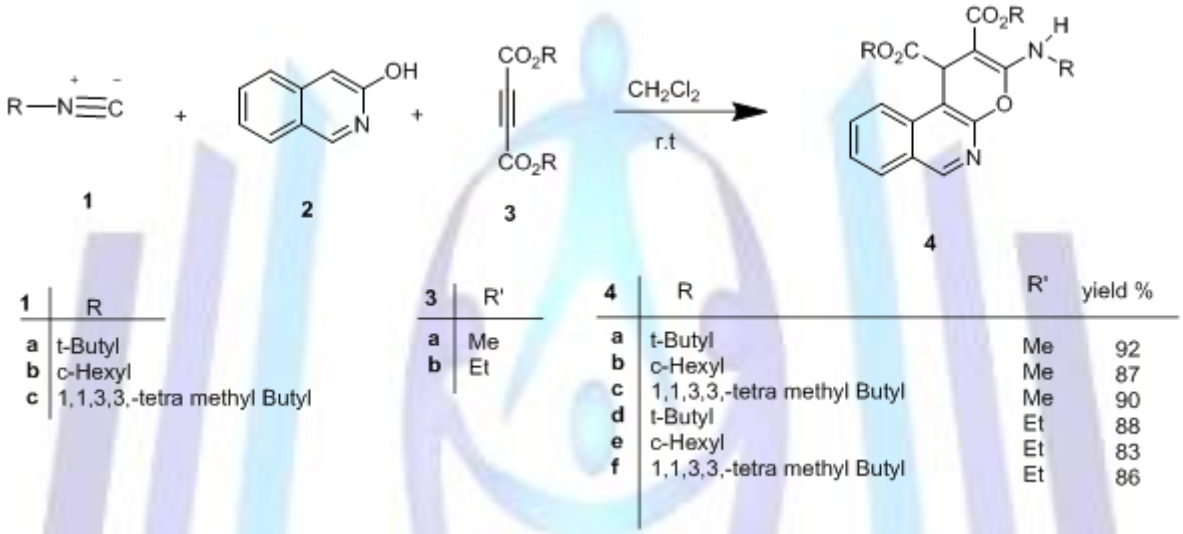
Introduction

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 spasmolitic-, diuretic-, anticoagulant-, antibacterial- and antianaphylactic activities [1]. In addition substituted 2-amino-4*H*-benzochromenescan be used as cognitive enhancers for the treatmentof neurodegenerative diseases, including Alzheimer'sdisease, amyotrophic lateral sclerosis, Huntington's disease,Parkinson's disease, AIDS associated dementia andDown's syndrome as well as for the treatment of schizophreniaand myoclonus [2]. The current interest in 2-amino-4*H*-chromenes arises from their application in the treatment of human inflammatory TNFa-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 and some methods have been reported for their synthesis [4-11]. Recently, we have described a convenient method forpreparation of 2-amino-4*H*-chromene derivatives, by threecomponentreaction of 6-hydroxyquinoline or 7-hydroxycoumarine, 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).



1	R
a	t-Butyl
b	c-Hexyl
c	1,1,3,3,-tetra methyl Butyl

3	R'
a	Me
b	Et

4	R	R'	yield %
a	t-Butyl	Me	92
b	c-Hexyl	Me	87
c	1,1,3,3,-tetra methyl Butyl	Me	90
d	t-Butyl	Et	88
e	c-Hexyl	Et	83
f	1,1,3,3,-tetra methyl Butyl	Et	86

Scheme 1Typical 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)-1H-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), ^{1}H and ^{13}C NMR and IR spectroscopic data. The ^{1}H 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 D_2O to the $CDCl_3$ solution of **4a**. The protondecoupled ^{13}C 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 apears at δ =173.0, while and 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).

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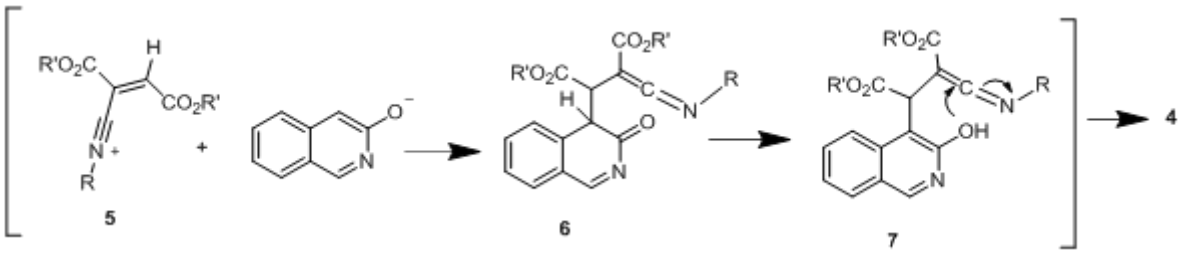

Scheme 2A possible mechanism for preparation of 4

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. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ 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-hydroxyquinoline (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in 10 mL CH_2Cl_2 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 v3430, 1744, 1660, 1631, 1413, 1261, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *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); ^{13}C NMR (75.5 MHz, $CDCl_3$): *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 $C_{20}H_{22}N_2O_5$: 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 v 3444 (NH), 1727 (C=O), 1644 (C=O), 1436, 1258, 1095 cm^{-1},^{1}H NMR (300 MHz, $CDCl_3$): *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 (brs, 1H), 8.72 (d, 1H, *J* = 8.6 Hz), 8.9 (d, 1H, *J* = 4.2 Hz);^{13}C NMR (75.5 MHz, $CDCl_3$): *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 $C_{22}H_{24}N_2O_5$: 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 v 3371, 1732, 1694, 1626, 1463, 1254, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *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); ^{13}C NMR (75.5 MHz, $CDCl_3$): *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 $C_{24}H_{30}N_2O_5$: 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 v 3390 (NH), 1730 (C=O), 1668 (C=O), 1506, 1366, 1217, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *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); ^{13}C NMR (75.5 MHz, $CDCl_3$): *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 v 3254 (NH), 1729 (C=O), 1671 (C=O), 1593, 1443, 1224, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ1.12 (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 v 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.

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