Efficient Synthesis of Some New Spirochromens Containing Indoline Moiety

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ABSTRACT

2-Naphthol reacted with 3-dicyanomethylidine-1-ethyl-2-oxoindoline in absolute ethanol to afford 2-Amino-3-cyano-1'-ethylspiro{benzo[*f*]chromen-4,3'-indolin}-2'-one, which used as key intermediate to synthesis fused spiropolyheterocyclic derivatives of pyrimido- benzochromen and/or pyridobenzochromen nucleus incorporated indoline moiety.

Keywords :synthesis ,spiro ,spiroheterocycles ,benzochromen

INTRODUCTION

Nitriles were used as starting materials to prepare a variety of condensed pyrans[1-5] for their medicinal importance[6,7]. Pyrano derivatives have well known biological effect such as analgesic and anti-inflammatory activities[8]. Spiro derivatives have anticonvulsants, antibacterial and anticancer activities[9 10]. Spiroheterocycles were used as nitric oxide synthesis inhibitors[11]. Photochromism of indolinospirochromens containing condensed fragments in the indoline part of the molecule were achieved[12]. As continuation to our interest in this area[13-18] encouraged us to suggest the synthesis of some new spiropolyheterocycles of pyrans containing indoline moiety.

EXPERIMENTAL

The time required for completion of each reaction was monitored by TLC. All melting points are uncorrected and were measured on a Gallen Kamp apparatus. The IR spectra were recorded on a Shimadzu 470 IR spectrometer (KBr) ύ cm-1. The 1H and 13C-NMR spectra were measured on Varian EM-200 MHz spectrometer with TMS as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Mass spectra were determined on a Jeol-600 spectrometer. Column chromatography was performed with silica gel (230-400 mesh). Elemental analyses (C, H, N, and S) were performed on an elemental analysis system GmbH varioel V2.3, the results were found to be in good agreement with the calculated values.

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Synthesis of 2-Amino-3-cyano-1'-ethylspiro{benzo[*f*]chromen-4,3'-indolin}-2'-one (3).

A mixture of 3-dicyanomethylidine-1-ethyl-2-oxoindoline **2** (2.23 g, 10 mmol) and 2-naphthol **1** (10 mmol) in absolute ethanol (20 ml) and catalytic amount of morpholine (0.5 ml) was heated under reflux for 4 h. After cooling, the formed precipitate was collected by filtration, dried and recrystallized from ethanol/acetic acid mixture (5/1) to give brightness brown crystals yield 3.20 g (85%), mp 251-253 °C; IR (KBr): ύ = 3300-3150 (NH_2), 2200 (CN); 1705 (C=O) cm^{-1}; EI-MS: m/z (%) = 367 (M+, 3), 338 (21), 208 (100), 180 (87), 153 (85), 126 (98); ^{1}H-NMR *(DMSO-d_6)*: δ = 7.80-6.85 (m, 10H, arom. protons), 6.49 (s, 2H, NH_2, D_2O exchangeable), 3.40 (q, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

Synthesis of 4-Amino-1'-ethylspiro{pyrimido[4,5-*b*]benzo[*f*]chromen-5,3'-indolin}-2'-one (4).

A mixture of compound **3** (1.83 g, 5 mmol) and (10 ml) of formamide was heated under reflux for 4 h. The reaction mixture was allowed to cool and the product was collected, washed several times with cold water, dried and recrystallized from ethanol to give pale green crystals, yield 2.76 g (70%), mp 244-247 °C; IR (KBr): *ύ* = 3250-3100 (NH_2), 1705 (C=O), 1625 (C=N) cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): *δ* = 8.98 (s, 1H, CH), 8.00 (s, 2H, NH_2, D_2O-exchangeable), 7.79-6.95 (m, 10H, arom. protons), 3.30 (q, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

Synthesis of 4-Imino-1'-ethyl-2'-oxo-3-phenylspiro{pyrimido[4,5-*b*]benzo[*f*]chromen-5,3'-indolin}-2(1*H*)-thione (5).

A mixture of compound **3** (1.83 g, 5 mmol) and phenyl isothiocyanate (0.68 g, 5 mmol) in dry pyridine (15 ml) was heated under reflux for 12 h, and allowed to cool. The reaction mixture was poured into ice/water mixture, whereby a solid product was obtained, filtered off, washed several times with water, dried and recrystallized from DMF to give brown crystals, yield 1.43 g (57%), mp >300 °C; IR (KBr): *ύ* = 3150 (NH), 3100 (NH), 1700 (C=O), 1620 (C=N), 1240 (C=S) cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): *δ* = 9.76 (s, 1H, NH), 8.27 (s, 1H, NH), 7.85-6.43 (m, 15H, arom. protons); 3.35 (q, 2H, CH_2), 1.13 (t, 3H, CH_3) ppm.

Synthesis of 1'-Ethylspiro{pyrimido[4,5-*b*]benzo[*f*]chromen-5,3'-indoline}-2',4(3*H*)-dione (6).

A mixture of compound **3** (1.83 g, 5 mmol) and formic acid (10 ml) was heated under reflux for 4 h, after cooling the reaction mixture was poured into an ice/water, and the formed solid product was filtered off, dried, and recrystallized from ethanol to give pale yellow crystals, yield 1.18 g (60%), mp 273-276 °C; IR (KBr): *ύ* = 3320 (NH), 1710 (C=O), 1700 (C=O), 1635 (C=N) cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): *δ* = 10.09 (s, 1H, NH), 8.78 (s, 1H, CH*pyrimidine*), 7.80-6.86 (m, 10H, arom. protons), 3.34 (q, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

Synthesis of 4-Amino-3-cyano-1'-ethylspiro{pyrido[2,3-*b*]benzo[*f*]chromen-5,3'-indoline}-2(1*H*),2'-dione (7).

A mixture of compound **3** (1.83 g, 5 mmol) and ethyl cyanoacetate (0.57 g, 5 mmol) was heated under reflux for 2 h. The formed solid product was collected and recrystallized from dioxane to give scarlet red crystals, yield 1.30 g (60%), mp 269-171 °C; IR (KBr): *ύ* = 3350-3250 (NH_2), 3100 (NH), 2200 (CN), 1708 (C=O), 1700 (C=O), 1625 (C=N) cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): *δ* = 9.85 (s, 1H, NH), 7.86-6.88 (m, 10H, arom. protons), 5.39 (s, 2H, NH_2), 3.33 (q, 2H, CH_2), 1.11 (t, 3H, CH_3) ppm.

Synthesis of 2-Amino-3-(4,5-dihydro-1*H*-imidazol-2-yl)-1'-ethylspiro{benzo[*f*]chromen-4,3'-indolin} -2'-one (8).

A mixture of compound **3** (1.83 g, 5 mmol), ethylenediamine (0.36 g, 6 mmol) and *p*-toluenesulfonic acid monohydrate (1.33 g, 7 mmol) was heated under reflux at 200 °C for 12 h. The reaction mixture was made alkaline with a saturated aqueous solution of sodium carbonate and the formed precipitate was purified by silica-gel column chromatography using acetone-ethyl acetate (2:1) as eluent (R_f= 0.68), and recrystallized from ethanol to give orange crystals, yield 1.02 g (50%), mp 235-237 °C; IR (KBr): ύ = 3250-3200 (NH_2), 3130 (NH), 1705 (C=O), 1640 (C=N) cm^{-1}; ^{1}H-NMR (*$CDCl_3$*): δ = 7.97 (s, 1H, NH), 7.82-6.80 (m, 10H, arom. protons), 5.88 (s, 2H, NH_2), 4.35 (t, 2H, CH_2), 3.78 (t, 2H, CH_2), 3.36 (q, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

Synthesis of 1'-Ethylspiro{imidazolino[1',2':1,6]pyrimido[4,5-*b*]benzo[*f*]chromen-14,3'-indolin}-2'-one (9).

A mixture of compound **8** (0.41 g, 1 mmol), triethyl orthoformate (10 ml) and glacial acetic acid (1 cm^3) was heated under reflux for 5 h. The formed solid precipitate was collected by filtration, dried, and recrystallized from ethanol to give brownish-yellow crystals, yield 0.19 g (45%), mp 247-249 °C; IR (KBr): ύ = 1705 (C=O), 1640 (C=N), 1620 (C=N) cm^{-1}; ^{1}H-NMR (*$CDCl_3$*): δ = 8.06-6.76 (m, 11H, arom. protons), 4.34 (t, 2H, CH_2); 3.76 (t, 2H, CH_2), 3.33 (q, 2H, CH_2), 1.12 (t, 3H, CH_3) ppm.

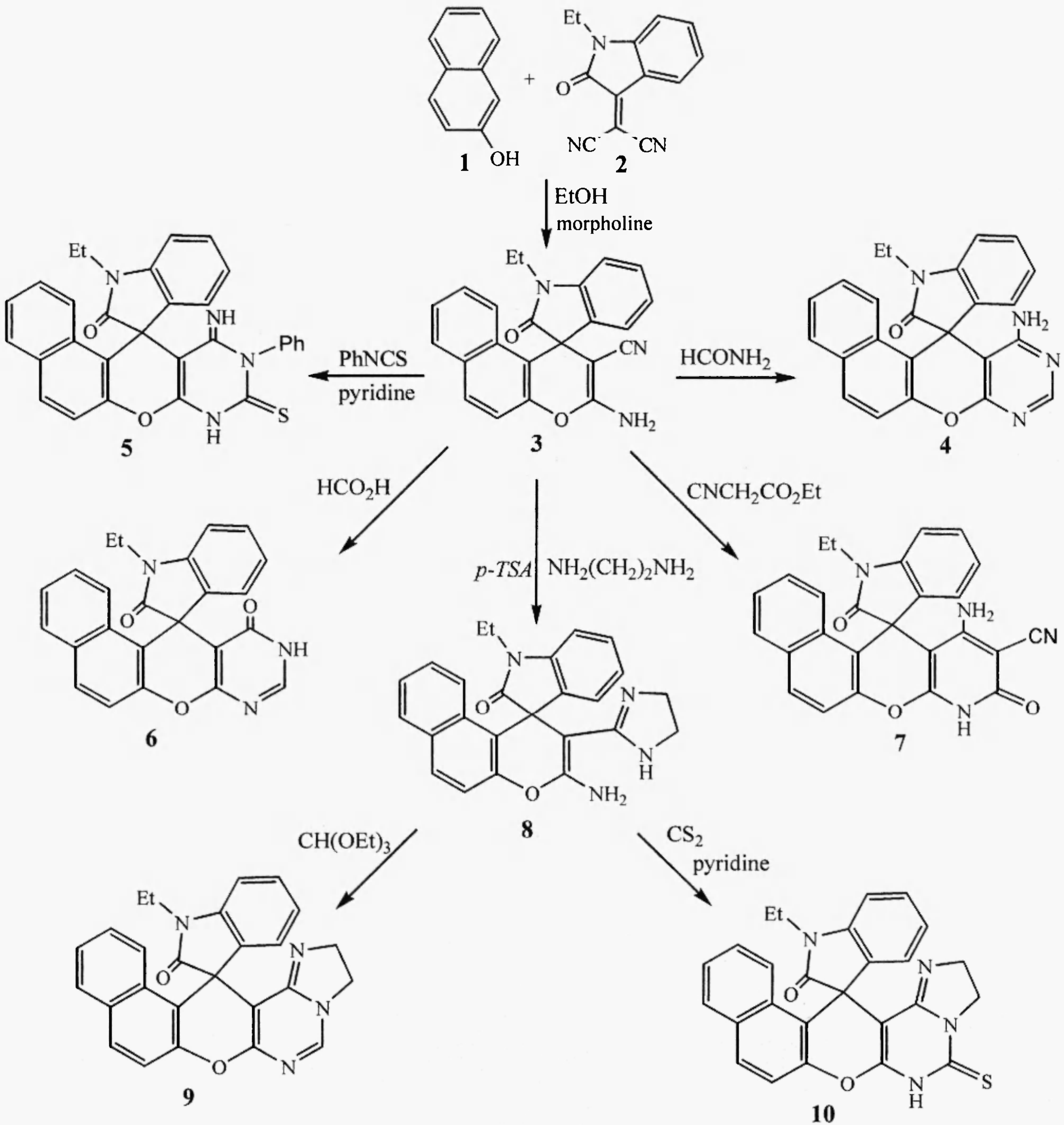
Synthesis of 1'-Ethyl-2'-oxospiro{imidazolino[1',2':1,6]pyrimido[4,5-*b*]benzo[*f*] chromen-14,3'-indolin}-5(6*H*)-thione (10).

A mixture of compound **8** (0.41 g, 1 mmol) and carbon disulfide (2 ml) in dry pyridine (10 ml) was heated on water bath for 20 h, then the reaction mixture was left to cool. The formed solid precipitate was filtered off, washed with water, dried, and recrystallized from DMF to give brown crystals, yield 0.19 g (42%), mp >300 °C; IR (KBr): ύ = 3200 (NH), 1705 (C=O), 1640 (C=N), 1420 (C=S) cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): δ = 10.50 (s, 1H, NH); 8.01-6.69 (m, 10H, arom. protons); 4.33 (t, 2H, CH_2), 3.75 (t, 2H, CH_2), 3.37 (q, 2H, CH_2), 1.14 (t, 3H, CH_3) ppm.

RESULTS AND DISCUSSION

2-Amino-3-cyano-1'-ethylspiro{benzo[*f*]chromen-4,3'-indolin}-2'-one **3** was afforded by the reaction of 1-ethyl-3-dicyanomethylidine-2-oxoindoline **2** with 2-naphthol **1** in absolute ethanol and catalytic amount of morpholine via a type of Michael addition followed by intramolecular cyclization. Compound **3** was subjected to further reactions with formamide, phenyl isothiocyanate, formic acid, ethyl cyanoacetate, erthylene diamine to give fused spiroheterocyclic systems incorporate pyrimidine and/or pyridine nucleus in addition to benzochromen and indoline moieties **4-8** respectively. Also, cyclization of **8** with triethyl orthoformate and/or carbon disulfide gave the corresponding spiro compounds 9 and/or **10** respectively (**Scheme 1**).

The structures of all synthesized compounds 3-10 were established from their elemental analyses (**Table 1**) and spectral data.


1
OH
2
Et
N
O
NC
CN
EtOH
morpholine
3
Et
N
O
CN
O
NH2
PhNCS
pyridine
5
NH
N
Ph
N
H
S
HCONH2
4
NH2
N
N
HCO2H
6
O
NH
N
CNCH2CO2Et
7
NH2
CN
N
H
O
p-TSA
NH2(CH2)2NH2
8
N
N
H
NH2
CH(OEt)3
9
N
N
N
CS2
pyridine
10
N
N
N
H
S

Scheme 1

Table 1
The Elemental Analyses for the new synthesized compounds **(3-10)**

Compound No.	**Elemental Analyses (C, H, N, S, and halogen) %**				
3	Calcd.	**C**; 75.19	**H**; 4.66	**N**; 11.44	
	Found	**C**; 75.08	**H**; 4.57	**N**; 11.34	
4	Calcd.	**C**; 73.08	**H**; 4.60	**N**; 14.20	
	Found	**C**; 73.00	**H**; 4.42	**N**; 14.11	
5	Calcd.	**C**; 71.69	**H**; 4.41	**N**; 11.15	**S**; 6.38
	Found	**C**; 71.58	**H**; 4.38	**N**; 11.14	**S**; 6.32
6	Calcd.	**C**; 72.90	**H**; 4.33	**N**; 10.63	
	Found	**C**; 72.85	**H**; 4.21	**N**; 10.57	
7	Calcd.	**C**; 71.88	**H**; 4.18	**N**; 12.90	
	Found	**C**; 71.73	**H**; 4.06	**N**; 12.85	
8	Calcd.	**C**; 73.15	**H**; 5.40	**N**; 13.65	
	Found	**C**; 73.02	**H**; 5.28	**N**; 13.56	
9	Calcd.	**C**; 74.27	**H**; 4.79	**N**; 13.33	
	Found	**C**; 74.12	**H**; 4.59	**N**; 13.20	
10	Calcd.	**C**; 69.01	**H**; 4.45	**N**; 12.38	**S**; 7.09
	Found	**C**; 68.89	**H**; 4.20	**N**; 12.21	**S**; 6.96

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