Alkyl Heterocycles in Heterocyclic Synthesis (II): Novel Synthesis of Isoquinoline, Thiazolopyridine, and Thieno[2,3-*b*]pyridine Derivatives

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Received February 28, 2004

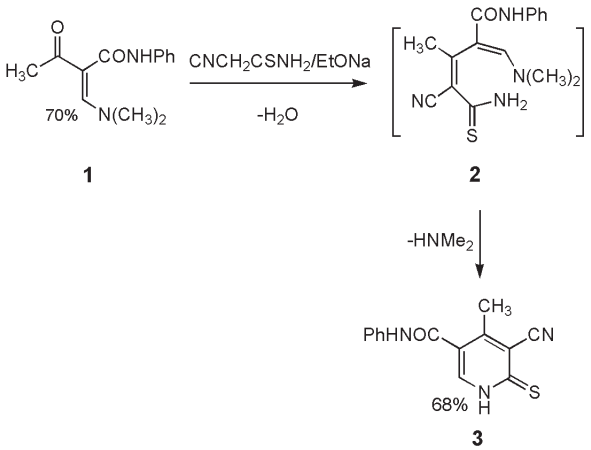
Treating 5-(4-phenylcarboxamido)-3-cyano-4-methylpyridin-2(1*H*)thione (**3**) with elemental sulfur yielded thienopyridine **4**. Compound **4** reacts with acrylonitrile to give isoquinoline **7**. Compound **7** was also, prepared from **3** and methylenemalononitrile. Reaction of **3** with dimethylacetylene dicarboxylate (DMAD) gave the pyridothiazole **9**. Also, **3** reacted with *N*,*N*-dimethylchloroacetamide (**10**) to afford compound **11** which further reacted with the reagents **12**, **13** and **14** providing the thieno[2,3-*b*]pyridine derivatives **15**, **16** and **17** respectively.

J. Heterocyclic Chem., **41**, 947 (2004).

Alkylheterocycles are versatile reagents and can be utilized in synthesis of polyfunctionally substituted benzo[*c*]-coumarine, benzo[*c*]pyrano[3,2-*c*]quinoline and pyridopyridazine derivatives [1-7]. These heterocycles are interesting as potential biodegradable agrochemicals [1-4,6], pharmaceuticals and intermediates for the preparation of dyes [6]. In the past decade, our research group was involved in a program to develop new synthetic routes to polyfunctionally substituted heteroarenes using methylazinylcarbonitriles as starting compounds [8,9].

In continuation to this interest, we report here the utility of 3-cyano-4-methylpyridin-2(1*H*)one derivative **3** as starting material to prepare polyfunctional substituted isoquinoline, pyridothiazole and thieno[2,3-*b*]pyridine derivatives. Thus, it has been found that 1-(*N*-*p*-chlorophenyl)-2-(*N*-dimethylaminomethino)-3-oxobutanamide [8] (**1**) was condensed with cyanothioacetamide in ethanol/sodium ethoxide to yield **3** (68%). The pyridine structure **3** is supported from its elemental composition and spectral data.

Scheme 1



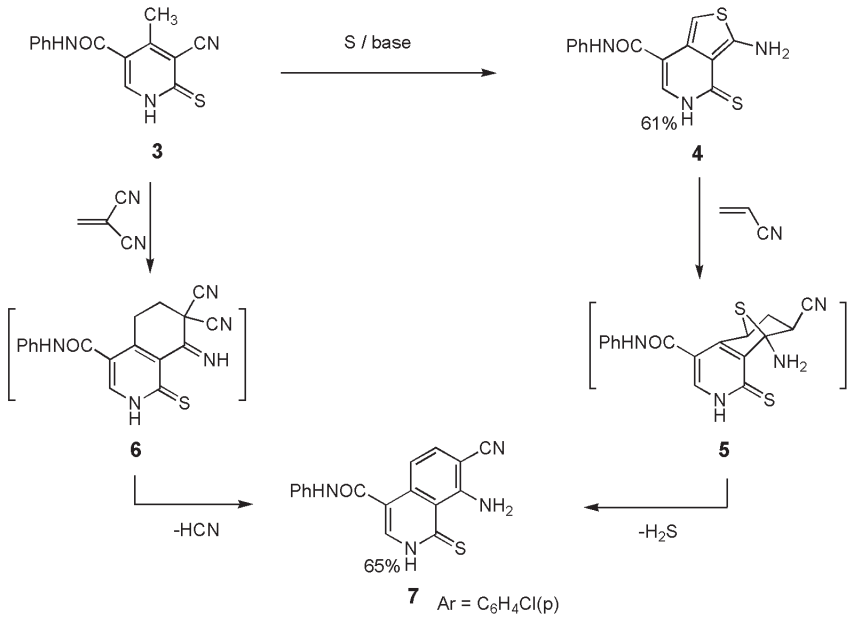
1 **2** **3**

Compound **3** reacted with elemental sulfur in ethanolic triethylamine solution to yield the thienopyridine **4** (61%). Compound **4** was found to be highly reactive toward activated double bond systems. Thus, the product of addition and hydrogen sulfide elimination was obtained upon reacting **4** with acrylonitrile in dioxane under reflux conditions with acetic acid catalyst. Structure **7** (65%) was assigned as a reaction product based on correct elemental composition and spectral data. Compound **7** was also synthesized *via* reacting **3** with methylenemalononitrile in ethanol containing a catalytic amount of piperidine (*cf.* Scheme **2**).

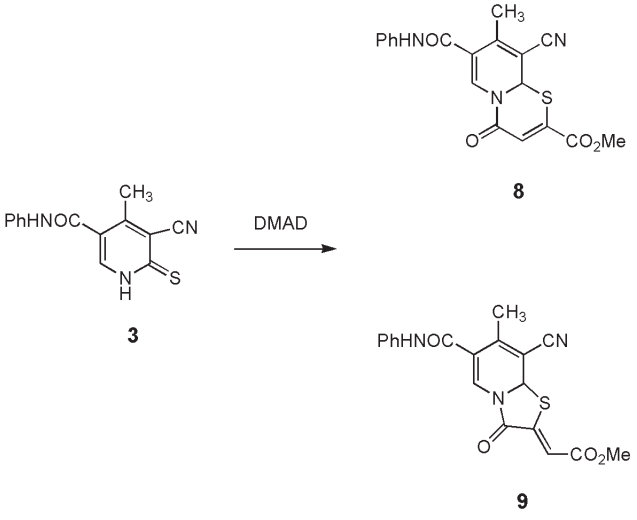
Reaction of 2(1*H*)-pyridinethiones with dimethylacetylene dicarboxylate (DMAD) is known to give thiazolo[3,2-*a*]pyridinium salts. At the same time, the reaction of 2(1*H*)-pyridinethiones with methyl propynoate results in acyclic condensation products [10,11]. By analogy with the reaction of malonothioamide and with the chemistry of the 5-mercaptoazoles [12], one can expect the formation of both pyridothiazine **8** and pyridothiazole of type **9** from the reaction of compound **3** with DMAD. It has been found that the reaction of pyridinethione **3** with DMAD in chloroform in the presence of triethyl amine selectively affords thiazolo[3,2-*a*]pyridine **9** in good yield. The structure assignment of the compound prepared follows from its NMR spectrum. The ^{1}H NMR spectrum of **9** shows a signal at 6.68 ppm. This is in accordance with the presence of an exocyclic double bond in the structure.

Thieno[2,3-*b*]pyridines are known for their anti-allergic activity in the passive coetaneous anaphylaxis [13,14] and as starting materials for tricyclic heterocycles. Thus, compound 3 was reacted with *N*,*N*-chloroacetamide (10) to give the target compound 11 in a one pot reaction *via* a carboxamidomethylthio derivative as intermediate (*cf.* Scheme 4).

Scheme 2



Scheme 3



Other ways for the synthesis of the title compounds were the aminolysis of compound 11 with morphline-4-caboxaldehyde (12) and dimethylformamide (13) as well as the reaction of compound 11 with 2,5-dimethoxytetrahydrofuran (14) to give the thieno[2,3-*b*]derivatives 15, 16 and 17 respectively (*cf*. Scheme 4).

In conclusion, this paper describes a novel one pot synthesis of isoquinoline, thiazolopyridine and thieno[2,3-*b*]pyridine derivatives using inexpensive and readily obtainable starting materials.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrophotomter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer with [$^2H_6$] DMSO as solvent and TMS as internal standard; chemical shifts are reported in ppm (δ). Mass spectra were measured on GC/MS INCOS XL Finnigan MAT. Microanalysis were performed on LECOCHNS-932

Reaction of **1** with Cyanothioacetamide: Formation of 5-(4-Phenylcarboxamido)-3-cyano-4-methylpyridin-2(1*H*)thione (**3**).

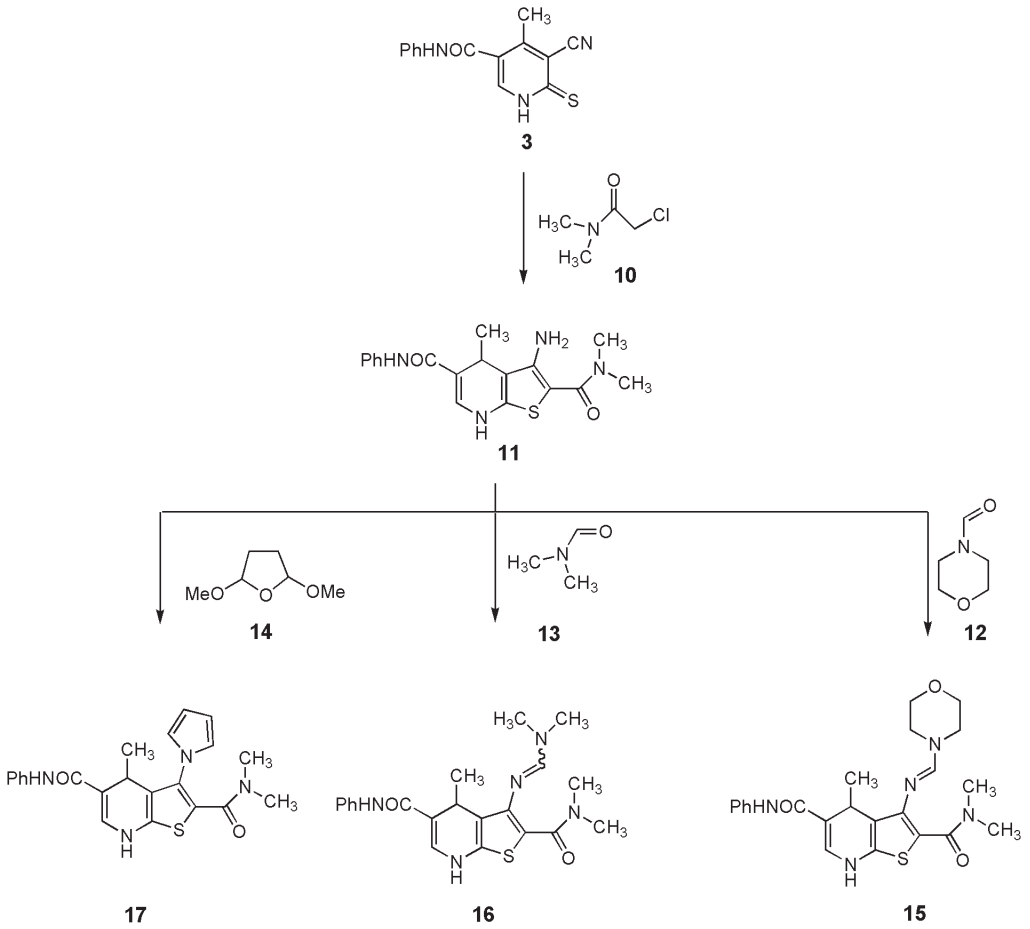
A mixture of compound **1** (2.32 g, 0.01 mol) and cyanothioacetamide (1.0 g, 0.01 mol) in ethanolic sodium ethoxide (30 mL) was refluxed for 30 min. The reaction mixture was poured into water and acidified with dil. HCl. The precipitate formed was collected by filtration and crystallized from ethanol to give compound **3**. Compound **3** was obtained as yellow crystals; mp 235 °C; yield 68 %; IR: ν_{max} 3322, 3200 (NH); 2220 (CN); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 1.71 (s, 3 H, CH_3); 7.00-7.64 (m, 5 H, arom-H); 8.2 (s, 1 H, CH); 9.2 (s, 1 H, NH); 14.2 (br s, 1H, NH); ^{13}C-NMR([$^2H_6$] DMSO): δ_C 185.8 (thioamide), 163.8 (CO-amide); 135.2, 128.7, 128.7, 124.1, 120.4, 120.4 (aromatic-carbons); 167.5, 143.1, 116.6, 107.8 (vinyl-carbons); 117.2 (CN); 12.00 (CH_3); MS (m/z) 269.

Anal. Calcd. For $C_{14}H_{11}N_3OS$ (269.32): C, 62.43; H, 4.12; N, 15.60. Found: C, 62.80; H, 4.16; N, 15.65.

3-Amino-4-(4-phenylcarboxamido)thienopyridine-2(1*H*)thione (**4**).

A solution of compound **3** (2.69 g, 0.01 mol) in DMF (10 mL) was treated with elemental sulfur (0.32 g, 0.01 mol) and piperidine (0.2 mL). The reaction mixture was refluxed for 4 h, then poured into water, the solid product, so formed, was collected by filtration and crystallized from ethanol-DMF. Compound **4** was

Scheme 4



obtained as brown crystals; mp 275 °C; yield 61%; IR: ν_{max} 3400, 3280 (NH_2 and NH); 1680 (CO); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 6.4 (s, 1 H, thiophene-H); 7.00-8.3 (7 H, arom-H and NH_2); 8.18 (s, 1 H, CH); 9.24 (s, 1 H, NH); 12.4 (br s, 1 H, NH). ^{13}C-NMR ([$^2H_6$] DMSO): δ_C 195.1 (thioamide), 163.8 (CO); 138.2, 120.4, 128.7, 124.1, 128.7, 120.4 (aromatic-carbons); 122.1, 133.3, 142.0, 138.2 (thiophene-carbons); 117.5 (vinyl-carbon); MS (m/z) 301.

Anal. Calcd. for $C_{14}H_{10}N_3OS_2$ (301.39): C, 55.79; H, 3.68; N, 13.94. Found: C, 55.40; H, 4.10; N, 13.82.

Preparation of 3-Amino-7-(phenylcarboxamido)-4-cyanoisoquinoline-2(1*H*)thione (**7**).

Method A.

A mixture of compound **4** (3.01 g, 0.01 mol) and (0.65 g, 0.01 mol) of acrylonitrile in dioxane (30 mL) was heated under reflux for 6 hours. The reaction mixture was cooled and the solvent evaporated *in vacuo* to give a solid product that was collected by filtration and recrystallized from ethanol/DMF.

Method B.

In a 100 ml flask, a solution of compound **3** (2.69g, 0.01 mol) in pyridine (30 mL) was treated with methylenemalononitrile (0.01 mol). The reaction mixture was refluxed for 4-6 h, left to cool to rt, poured into ice-cold water, and neutralized with HCl (10 %). The solid product was collected by filtration and crystallized from ethanol. Compound **7** was obtained as brown crystals; mp 300 °C; yield 65 %; IR: ν_{max} 3448, 3290 (NH_2 and NH); 2221 (CN) and 1660 (CO); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 6.16 (s, 1 H, CH); 6.8-7.1 (m, 6 H, arom-H and NH_2), 7.33(d, 1H, CH), 7.46(d, 1H, CH), 8.34 (s, 1 H, CH); 9.40 (br s, 1 H, NH); 12.21 (br s, 1H, NH); ^{13}C-NMR ([$^2H_6$] DMSO): δ_C 195.5 (thioamide), 164.2(CO-amide), 148.9, 136.3, 136.2, 135.1, 129.4, 129.1, 129.1, 121.8, 121.8, 118.5, 117.0, 98.4 (aromatic-carbons), 126.1, 117.4 (vinyl-carbons), 116.2 (nitrile-carbon); MS (m/z) 320.37.

Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.37): C, 63.73; H, 3.78; N, 17.49 %. Found: C, 63.70; H, 3.42; N, 17.42

Reaction of Compound **3** with DMAD: Formation of Methyl (8-Cyano-7-methyl-3-oxo-6-phenylcarbamoyl-8a*H*-thiazolo[3,2-*a*]-pyridine-2-ylidine)acetate (**9**).

The acetylenecarboxylic ester (0.0015 mol) was added to a suspension of compound **3** (2.69 g, 0.001 mol) in chloroform with triethylamine (0.001 mol). The reaction mixture was stirred at room temperature for 1-3 h until, according to TLC, all the starting material had disappeared. On cooling, a precipitate was formed, which was collected by filtration and crystallized from methanol

to afford compound **9** as yellow crystals, mp> 300 °C; yield 50 %; IR: ν_{max} 3448 (NH); 2221 (CN), 1710 (CO-ester) and 1660 (CO-amide); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 2.30 (s, 3 H, CH_3); 3.81 (s, 3 H, OCH_3), 4.76 (s, 1H, CH), 6.68 (s, 1H, $C_{(5)}H$), 7.25-7.60 (m, 5 H, arom. H), 8.2 (s, 1H, CH), 9.40 (br s, 1 H, NH); ^{13}C-NMR ([$^2H_6$] DMSO): δ_C 166.2(CO), 138.2, 128.7, 128.7, 124.1, 120.4, 120.4 (aromatic-carbons), 143.1, 113.7 (vinyl-carbons), 52.3 (OCH_3), 11.6 (CH_3), 119.2 (CN); MS (m/z) 381.

Anal. Calcd. For $C_{19}H_{15}N_3O_4S$ (381.41): C, 59.83; H, 3.96; N, 11.02 %. Found: C, 60.00; H, 3.91; N, 11.12.

Reaction of Compound **3** with *N*,*N*-Dimethylchloroacetamide: Formation of Compound **11**.

To a solution of compound **3** (2.65 g, 0.01 mol) in methanol (30 ml) containing sodium methoxide was added 0.01 mol of compound **10**. The mixture was heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice-cold water. The solid product deposited was collected by filtration and crystallized from ethanol to afford compound **11** as yellow crystals, mp 220 °C; yield 60 %; IR: ν_{max} 3448, 3330 (NH_2, NH); 1700, 1680 (CO-amide); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 2.30 (s, 3 H, CH_3); 3.51 (s, 6 H, 2 N-CH_3), 7.00-7.50 (m, 5 H, arom. H), 8.19 (s, 1H, CH), 9.30 (br s, 1 H, NH); MS (m/z) 356.44.

Anal. Calcd. for $C_{18}H_{20}N_4O_2S$ (356.44): C, 60.65; H, 5.66; N, 15.72 %. Found: C, 60.50; H, 5.61; N, 15.62.

General Procedure for the Reaction of Compound **11** with Compounds **12**, **13** and **14**: Formation of Compounds **15**, **16** and **17**.

To a solution of compound **11** (3.56 g, 0.01 mol) in $POCl_3$ (15 ml) was added 0.01 mol of, as appropriate, reagents **12**, **13** and **14**. The reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into ice-cold water and then neutralized with ammonia solution. The precipitate formed was collected by filtration and crystallized from the proper solvent.

4-Methyl-3-[morphlino-4-ylmethylene)-amino]-4,7-dihydrothieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide-5-phenylamide (**15**).

Compound **15** was obtained as yellow crystals from EtOH/DMF, mp 280 °C; yield 65 %; IR: $\nu_{max:}$ 3548 (NH); 1700, 1685 (CO-amide); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 2.22 (s, 3 H, CH_3); 3.41 (s, 6 H, 2 NCH_3), 7.00-7.50 (m, 5 H, arom. H), 8.20 (s, 1H, CH), 9.32 (br s, 1 H, NH); MS (m/z) 453.

Anal. Calcd. For C_{23} $H_{27}N_5O_3S$ (453.56): C, 60.91; H, 6.00; N, 15.44 %. Found: C, 60.83; H, 5.98; N, 15.42.

3-(Dimethylaminomethyleneamino)-4-methyl-4,7-dihydrothieno[2,3-*b*]pyridine-2,5-dicarboxy-2-dimethylamide-5-phenylamide (**16**).

Compound **16** was obtained as brown crystals from dioxan, mp 275 °C; yield 63 %; IR: ν_{max} 3548 (NH); 1700, 1685 (CO-amide); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 2.22 (s, 3 H, CH_3); 3.41 (s, 6 H, 2 NCH_3), 7.00-7.50 (m, 5 H, arom. H), 8.20 (s, 1H, CH), 9.32 (br s, 1 H, NH); (m/z) 411.

Anal. Calcd. for $C_{21}H_{25}N_5O_2S$ (411.52); C, 61.29; H, 6.12; N, 17.02 %. Found: C, 61.23; H, 6.00; N, 17.12.

4-Methyl-3-pyrrol-1-yl-4,7-dihydrothieno[2,3-b]pyridine-2,5-dicarboxylicacid-2-dimethylamide-5-phenylamide (**17**).

Compound **17** was obtained as yellow crystals from EtOH/DMF, mp > 300 °C; yield 60 %; IR: $\nu_{max:}$ 3548 (NH); 1700, 1685 (CO-amide); ^{1}H-NMR ([$^2H_6$] DMSO): δ_H 2.22 (s, 3 H, CH_3); 3.41 (s, 6 H, 2 N-CH_3), 7.00-7.50 (m, 5 H, arom. H), 8.20 (s, 1H, CH), 9.32 (br s, 1 H, NH); MS (m/z) 406.

Anal. Calcd. for $C_{22}H_{22}N_4O_2S$ (406.50): C, 65.00; H, 5.46; N, 13.78 %. Found: C, 65.13; H, 5.33; N, 13.72.

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