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A General Route for the Synthesis of Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine Derivatives

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Summary. A facile synthesis of 8-substituted pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazines (**6a–i**) has been accomplished. The sequence involves the ring closure of a heterocyclic aminonitrile precursor (**3**) after reaction with (dichloromethylene)-dimethylammonium chloride.

Keywords. Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine derivatives; Thieno[2,3-*c*]pyridazine-6-carbonitrile; N,N-Dimethyldichloromethyleniminium chloride; Enaminonitrile.

Eine allgemeine Synthese von Pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazin-Derivaten

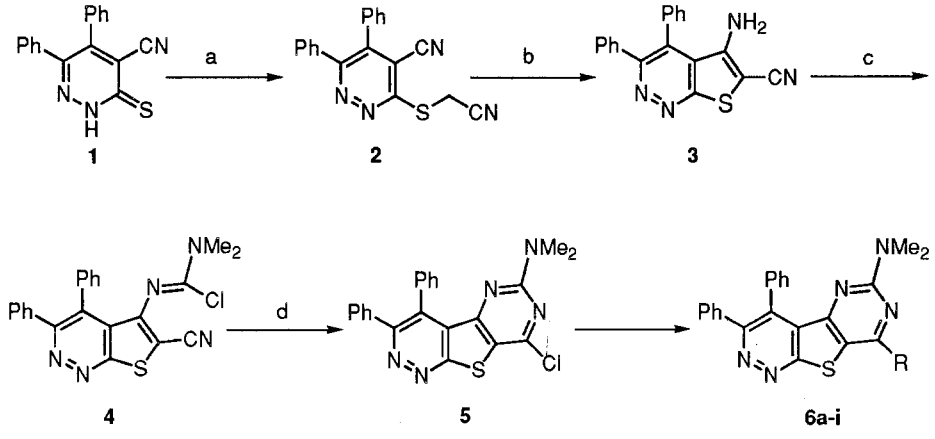
Zusammenfassung. Es wurde ein einfacher Syntheseweg für 8-substituierte Pyrimido[4′,5′:4,5]thieno-[2,3-*c*]pyridazine entwickelt. Die Reaktion verläuft über den Ringschluß eines heterocyclischen Aminonitrilvorläufers (**3**) nach Umsetzung mit Dichlormethylen-dimethylammoniumchlorid.

Introduction

The chemistry of phosgeniminium salts has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group [1]. The structural diversity and biological significance of fused pyrimidines have aroused much attention in the past few years owing to the wide range of biological activity of these compounds [2]. Many potential drugs have been modelled on them, particularly in cancer and virus research [3]. Syntheses of fused bi- and polycyclic compounds by annelation of a pyrimidine ring to an existing ring are numerous and were the subject of recent review [4]. Pyridazine derivatives and heterocyclic annelated pyridazines continue to attract great interest due to a wide variety of interesting biological activities observed [5]. Although pyridine-annelated sulfur-containing heterocycles have been studied extensively [6], comparatively little is known about aza-analogue systems in which an S-heterocycle is fused to a pyridazine nucleus. In this paper we describe a convenient one-pot procedure for new pyrimido[4′,5′:4.5]thieno[2,3-*c*]pyridazines in expectation of some biological activities as aza-isosters of pharmaceutically relevant pyridothienopyrimidines [7].

Results and Discussion

Heterocyclic α,β-enaminonitriles are versatile synthons for various cyclization reactions [8]. Recently, some new methods for the preparation of polyheterocyclic compounds containing the pyrimidine ring utilizing phosgeniminium chloride and heterocyclic β-enaminonitriles have been developed in our laboratory [9]. In continuation of our interest in the synthesis of compounds of the thieno[2,3-*c*] pyridazine type, we report a method for the preparation of substituted pyrimidothienopyridazine derivatives by reaction of a heterocyclic aminonitrile precursor and phosgeniminium chloride. The direct route into the title ring system proved to be the reaction of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbonitrile (**3**) with N,N-dimethyldichloromethyleniminium chloride. The starting material was prepared from the readily available 4-cyano-5,6-diphenylpyridazine-3(2*H*)-thione (**1**) [10]. The reaction of **1** with 2-chloroacetonitrile and subsequent base promoted intramolecular ring formation yielded the 5-aminothieno[2,3-*c*] pyridazine-6-carbonitrile **3** in 70% yield. The structure of compound **3** was determined from microanalyses and spectroscopic data. The mass spectrum showed the expected molecular ion peak, and the IR spectrum exhibited one strong absorption band at $\nu = 2200\,\mathrm{cm}^{-1}$ due to the cyano group. Formation of the desired aminonitrile compound **3** was also confirmed by ^{1}H NMR and decoupled ^{13}C NMR spectra. On treatment with (dichloromethylene)dimethylammonium chloride in refluxing 1,2-dichloroethane, **3** gave the amide halide intermediate **4** which underwent smooth cyclization to the corresponding fused pyrimidinethienopyridazine compound **5** by reaction with dry hydrogen chloride.

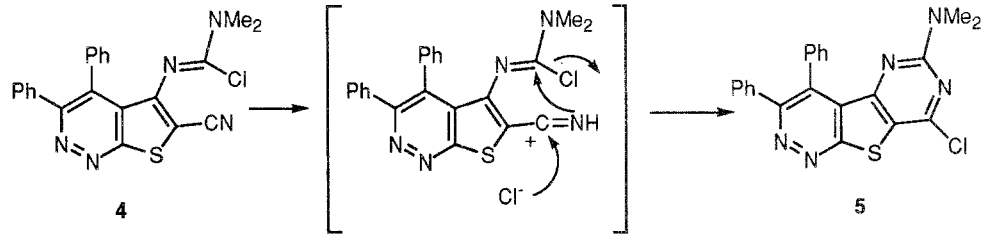


Reagents: a: $ClCH_2CN$, KI, K_2CO_3, acetone, room temperature, 1 h
b: piperidine, acetone/THF, reflux, 3 h
c: $Cl_2CN^+(Me)_2Cl^-$, 1,2-dichloroethane, reflux, 1 h
d: $HCl_{(g)}$, 1,2-dichloroethane

6	R	6	R
a	$NHNH_2$	e	*N*-(4-Acethylphenyl)piperazino
b	OEt	f	4-Methylpiperidino
c	Piperidino	g	4-Methylpiperazino
d	Morpholino	h	4-Thiomorpholino
		i	Thiophenyl

Scheme 1

Since the intermediate adduct **4** could be isolated the reaction can be assumed to proceed as follows [11]:



Scheme 2

Structural elucidation of compounds **4** and **5** was accomplished from their analytical and spectroscopic data. The mass spectra showed the expected molecular ion peak, and the IR spectrum of **4** exhibited a strong band at $\nu = 1650\,cm^{-1}$ due to the imino group. The most salient features of the ^1H NMR and ^{13}C NMR spectra are summarized under Experimental.

Treatment of the tricyclic 8-chloro-6-dimethylamino-3,4-diphenylpyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine (**5**) with various nucleophiles such as alkoxide ions, amines, and hydrazine led to normal halide displacement to the other 8-substituted derivatives **6a–i**. Compounds **6a–i** were characterized from their spectroscopic data.

This synthetic approach may be useful in view of the pharmacological interest in this class of compounds and shows that the reaction of aminocyanothienopyridazine **3** with N,N-dimethyldichloromethyleniminium chloride affords a new, general route to pyrimidothienopyridazines bearing various substituents at position 4 of the pyrimidine ring.

Experimental

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200 F instrument at room temperature. Mass spectra were measured at 70 eV using a VG-QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230–400 mesh) employed for medium-pressure chromatography (MPLC) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

3-Cyanomethylthio-4-cyano-5,6-diphenylpyridazine (**2**)

A mixture of **1** (0.45 g, 1.54 mmol), chloroacetonitrile (0.15 g, 1.54 mmol), potassium carbonate (0.23 g, 1.70 mmol), and a catalytic amount of KI in acetone (50 ml) was stirred at room temperature for 1 h. The insoluble solid was removed by filtration, washed with acetone, and combined filtrate and washings were evaporated. The residual solid was recrystallized from acetone to obtain 0.30 g (61% yield) of **2**. M.p.: 181–183 °C; $C_{19}H_{12}N_4S$ (328.39); calc.: C: 69.49, H: 3.68, N: 17.06; found: C: 69.37, H: 3.75, N: 16.93; ^1H NMR ($CDCl_3$): $\delta = 4.33$ (s, 2H, CH_2), 7.24–7.45 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$):

δ = 16.0 (CH_2), 111.9 (C-4), 112.5, 115.4 (CN), 128.3, 129.0, 129.2, 129.5, 129.7, 130.4, 132.2, 134.6 (C_6H_5), 141.8 (C-5), 157.0 (C-6), 158.0 (C-3) ppm; MS (DEI): *m/z* (%) = 328 (M^+, 46), 327 (94), 178 (13); IR (KBr): ν = 2220, 2240 (CN), 1570, 1530, 1470 cm^{-1}.

5-Amino-3,4-diphenylthieno[2,3-c]pyridazine-6-carbonitrile (**3**)

Method A:

A mixture of **2** (0.30 g, 0.91 mmol) and piperidine (0.08 g, 0.91 mmol) was refluxed in acetone/*THF* (1:1 v/v, 40 ml) for 5 h. The solvent was evaporated at reduced pressure. The solid was recrystallized from ethanol/acetone to obtain 0.21 g (70% yield) of **3**. M.p.: 208–210 °C; $C_{19}H_{12}N_4S$ (328.39); calc.: C: 69.49, H: 3.68, N: 17.06; found: C: 69.55; H: 3.97; N: 17.14; ^{1}H NMR ($CDCl_3$): δ = 4.46 (br s, 2H, NH_2), 7.24–7.52 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): δ = 82.8 (C-6), 113.9 (CN), 122.5 (C-4a), 127.9, 128.4, 129.0, 129.4, 129.7, 130.1, 132.1, 133.5 (C_6H_5), 135.7 (C-4), 148.2 (C-5), 155.6 (C-3), 162.2 (C-7a) ppm; MS (DEI): *m/z* (%) = 328 (M^+, 100), 310 (19), 298 (11); IR (KBr): ν = 3460, 3320 (NH), 2200 (CN), 1600, 1550, 1525 cm^{-1}.

Method B:

A mixture of **1** (0.45 g, 1.54 mmol), chloroacetamide (0.15 g, 1.54 mmol), potassium carbonate (0.21 g, 1.54 mmol), and a catalytic amount of KI in acetone (30 ml) was stirred at room temperature for 1 h. The insoluble solid was removed by filtration and washed with acetone and *THF* (25 ml). Piperidine (0.13 g, 1.54 mmol) was added to the combined filtrate and washings. The solution was refluxed for 5 h. The solvent was evaporated at reduced pressure and the solid was recrystallized from ethanol/acetone to give 0.34 g (67% yield) of **3**.

5-Chlorodimethylaminomethylenamino-6-cyano-3,4-diphenylthieno[2,3-c]pyridazine (**4**)

A solution of **3** (0.40 g, 1.2 mmol) and phosgene iminium salt (0.24 g, 1.5 mmol) in 1,2-dichloroethane (20 ml) was refluxed for 1 h. The solvent was removed under reduced pressure, and the resulting solid was recrystallized from acetone to give 0.3 g (60% yield) of **4**. M.p.: 229–231 °C; $C_{22}H_{16}N_5ClS$ (417.91); calc.: C: 63.23, H: 3.86, N: 16.76; found: C: 63.11, H: 3.69, N: 16.66; ^{1}H NMR ($CDCl_3$): δ = 2.73 (s, 6H, NMe_2), 7.08–7.36 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): δ = 39.7 (NMe_2), 99.2 (C-2), 113.4 (CN), 126.5 (C-4a), 127.2, 127.8, 127.9, 128.2, 129.9, 130.3, 133.4, 134.5 (C_6H_5), 136.1 (C-4), 140.4 (C-Cl), 150.5 (C-5), 156.2 (C-3), 162.0 (C-7a) ppm; MS (DEI): *m/z* (%) = 419 (M^+ + 2, 40), 417 (M^+, 100), 382 (62), 366 (16), 337 (10), 325 (39); IR (KBr): ν = 2220 (CN), 1650, 1540, 1440, 1320 cm^{-1}.

8-Chloro-6-dimethylamino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**5**)

A stream of dry hydrogen chloride was passed through a mixture of **4** (0.20 g, 0.61 mmol) in 1,2-dichloroethane (15 ml) for 1 h. The reaction mixture was allowed to stand overnight at room temperature. The solid was filtered, washed with ethanol, and recrystallized from acetone to obtain 0.18 g (90% yield) of **5**. M.p.: 235–237 °C; $C_{22}H_{16}N_5ClS$ (417.91); calc.: C: 63.23, H: 3.86, N: 16.76; found: C: 63.13, H: 3.80, N: 16.63; ^{1}H NMR ($CDCl_3$): δ = 2.86 (br s, 6H, NMe_2), 7.21–7.44 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): δ = 37.0 (NMe_2), 118.3 (C-8a), 127.1 (C-4a), 127.8, 127.9, 128.2, 128.3, 130.1, 130.4, 133.2, 136.4 (C_6H_5), 136.5 (C-4), 155.5, 156.9 (C-3), 157.3, 160.4 (C-9a), 164.6 ppm; MS (DEI): *m/z* (%) = 419 (M^+ + 2, 39), 417 (M^+, 98), 402 (29), 388 (21), 283 (12), 209 (18); IR (KBr): ν = 1570, 1470, 1405 cm^{-1}.

8-Hydrazino-6-dimethylamino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6a**)

A solution of **5** (0.20 g, 0.48 mmol), NH_2NH_2 (0.03 g, 0.48 mmol) in EtOH/*THF* (20 ml, 2:3) was stirred at room temperature for 24 h. The resulting solid was filtered and washed with ethanol to obtain 0.18 g

(91% yield) of **6a**. M.p.: 220–222 °C; $C_{22}H_{19}N_7S$ (413.50); calc.: C: 63.90, H: 4.63, N: 23.71; found: C: 63.68, H: 4.45, N: 23.89; ^{1}H NMR ($CDCl_3$): $\delta = 2.78$ (s, 6H, NMe_2), 5.05 (s, 1H, NH, exchangeable with D_2O), 6.55 (s, 2H, NH_2, exchangeable with D_2O), 7.25–7.43 (m, 10H, C_6H_5) ppm; MS (FAB): m/z (%) = 414 ($(MH)^+$, 84), 412 (12), 400 (27), 399 (100), 383 (15); IR (KBr): $\nu = 3390$, 3360 (NH), 1610, 1560, 1440, 1400 cm^{-1}.

8-Ethoxy-6-dimethylamino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6b**)

5 (0.1 g, 0.24 mmol) was added to a solution of sodium ethoxide (0.01 g of sodium, 0.43 mmol) in ethanol (15 ml). The reaction was refluxed for 1.5 h. The solid was filtered and recrystallized from ethanol to obtain 0.08 g (75% yield) of **6b**. M.p.: 194–196 °C; $C_{24}H_{21}N_5OS$ (427.52); calc.: C: 67.43, H: 4.95, N: 16.38; found: C: 67.62, H: 5.08, N: 16.54; ^{1}H NMR ($CDCl_3$): $\delta = 1.49$ (t, 3H, $J = 7.1$ Hz, CH_3), 2.84 (s, 6H, NMe_2), 4.58 (q, 2H, $J = 7.1$ Hz, CH_2), 7.25–7.43 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.3$ (CH_3), 36.8 (NMe_2), 62.7 (OCH_2), 107.3 (C-8a), 127.3 (C-4a), 127.5, 127.8, 127.9, 128.0, 130.4, 130.5, 133.7, 135.6 (C_6H_5), 136.9 (C-4), 156.3, 156.4 (C-3), 160.8 (C-9a), 164.5, 165.8 ppm; MS (DEI): m/z (%) 427 (M^+, 100), 412 (9), 398 (50), 384 (17), 355 (12), 272 (10); IR (KBr): $\nu = 1585$, 1545, 1515, 1460 cm^{-1}.

6-Dimethylamino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazines (**6c–i**); *General procedure*

A solution of **5** (0.10 g, 0.24 mmol) and the appropriate amine or thiophenol (0.30 mmol) in ethanol/*THF* (10 ml, 1:4) was refluxed until the starting material had disappeared as checked by TLC. The solid was filtered off and recrystallized from ethanol/acetone.

6-Dimethylamino-3,4-diphenyl-8-piperidinopyridimo[4',5':4,5]thieno[2,3-c]pyridazine (**6c**): yield: 75%; m.p.: 214–216 °C; $C_{27}H_{26}N_6S$ (466.60); calc.: C: 69.50, H: 5.62, N: 18.01; found: C: 69.66, H: 5.78, N; 17.89; ^{1}H NMR ($CDCl_3$): $\delta = 1.73$ (s, 6H, CH_2), 2.76 (s, 6H, $NNMe_2$), 3.87 (s, 4H, NCH_2), 7.23–7.40 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.8$ (CH_2), 25.9 (CH_2), 36.5 (NMe_2), 47.6 (NCH_2), 105.3 (C-8a), 127.4, 127.6, 127.7, 127.9, 130.4, 130.5, 134.1, 135.4 (C_6H_5), 137.1 (C-4), 156.2, 156.4 (C-3), 158.9, 160.4 (C-9a), 163.9 ppm; MS (DEI): m/z (%) = 466 (M^+, 100), 498 (100), 451 (29), 437 (16), 423 (13), 383 (5), 283 (5), 233 (16); IR (KBr): $\nu = 2940$, 2860, 1560, 1515, 1440, 1390 cm^{-1}.

6-Dimethylamino-8-morphilino-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6d**): yield 76%; m.p.: 260–262 °C; $C_{26}H_{24}N_6OS$ (468.57); calc.: C: 66.65, H: 5.16, N: 17.93; found: C: 66.74, H: 5.23, N: 18.08; ^{1}H NMR ($CDCl_3$): $\delta = 2.77$ (s, 6H, NMe_2), 3.87 (br s, 8H, CH_2), 7.20–7.40 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 36.6$ (NMe_2), 46.6 (NCH_2), 66.6 (OCH_2), 105.1 (C-8a), 127.2 (C-4a), 127.5, 127.7, 128.0, 130.3, 130.5, 134.0, 135.6 (C_6H_5), 136.9 (C-4), 156.5, 156.6 (C-3), 159.3, 160.1 (C-9a), 163.8 ppm; MS (DEI): m/z (%) = 468 (M^+, 100), 453 (25), 410 (15), 366 (10), 283 (5), 234 (10); IR (KBr): $\nu = 1560$, 1555, 1510, 1440, 1390, 1250 cm^{-1}.

6-Dimethylamino-3,4-diphenyl-8-(4'-piperazinoacetophenone)pyrimido[4',5':4,5]thieno[2,3-c]-pyridazine (**6e**): yield: 53%; m.p.: 296–298 °C; $C_{34}H_{31}N_7OS$ (585.72); calc.: C: 69.72, H: 5.33, N: 16.74; found: C: 69.80, H: 5.15, N: 16.77; ^{1}H NMR ($CDCl_3$): $\delta = 2.55$ (s, 3H, $COCH_3$), 2.80 (s, 6H, NMe_2), 3.57 (t, 4H, $J = 4.9$ Hz, NCH_2), 4.11 (t, 4H, $J = 4.9$ Hz, NCH_2), 6.94, 7.93 (AA'XX' system, 4H, $J = 8.9$ Hz, C_6H_4), 7.26–7.41 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 26.2$ (CH_3), 36.6 (NMe_2), 45.6 (NCH_2), 46.9 (NCH_2), 105.1 (C-8a), 127.3 (C-4a), 113.3, 127.5, 127.8, 128.0, 130.3, 130.4, 133.9, 135.7 ($C_6H_5 + C_6H_4$), 136.8 (C-4), 153.6, 156.6 (C-3), 159.0, 160.1 (C-9a), 163.9, 196.5 (CO) ppm; MS (FAB): m/z (%) = 586 ($(MH)^+$, 100)), 420 (38), 418 (98), 415 (20), 288 (30); IR (KBr): $\nu = 1670$ (CO), 1600, 1565, 1520, 1440, 1380 cm^{-1}.

6-Dimethylamino-8-(4-methylpiperidino)-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6f**): yield: 78%; m.p.: 204–206 °C; $C_{28}H_{28}N_6S$ (480.63); calc.: C: 69.97, H: 5.87, N: 17.48; found: C: 69.87, H: 5.92, N: 17.54; ^{1}H NMR ($CDCl_3$): $\delta = 0.98$ (d, 3H, $J = 6.07$ Hz, CH_3), 1.20–1.39 (m, 2H, CH_2), 1.67–1.81 (m, 3H, CH + CH_2), 2.76 (br s, 6H, NMe_2), 3.07 (t, 2H, $J = 12.4$ Hz, NCH_2), 4.66 (d, 2H, $J = 18.4$ Hz, NCH_2), 7.21–7.40 (m, 10H, C_6H_5) ppm; ^{13} NMR ($CDCl_3$): $\delta = 21.8$ (CH_3), 31.4 (CH), 34.1 (CH_2), 36.6 (NMe_2), 46.9 (NCH_2), 105.3 (C-8a), 127.4, 127.6, 127.7, 127.9, 130.4, 130.5, 134.1, 135.5 (C_6H_5), 137.0 (C-4), 156.2, 156.4 (C-3), 158.8, 160.3 (C-9a), 163.9 ppm; MS (DEI): m/z (%) = 480 (M^+, 47), 465 (14), 411 (8), 283 (11), 240 (13); IR (KBr): $\nu = 2950$, 1550, 1510, 1440, 1410, 1375 cm^{-1}.

6-Dimethylamino-8-(4-methylpiperazino)-3,4-diphenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6g**): yield: 72%; m.p.: 230–232 °C; $C_{27}H_{27}N_7S$ (481.62); calc.: C: 67.33, H: 5.65, N: 20.36; found: C: 67.28, H: 5.82, N: 20.40; ^{1}H NMR ($CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 2.56 (t, 4H, $J = 4.9$ Hz, NCH_2), 2.76 (br s, 6H, NMe_2), 3.92 (t, 4H, $J = 4.9$ Hz, NCH_2), 7.20–7.40 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 36.6$ (NMe_2), 46.0 (CH_3), 46.1 (NCH_2), 54.8 (NCH_2), 105.1 (C-8a), 127.3 (C-4a), 127.4, 127.6, 127.7, 127.9, 130.3, 130.4, 134.0, 135.5 (C_6H_5), 136.9 (C-4), 156.5 (C-3), 159.0, 160.2 (C-9a), 163.8 ppm; MS (DEI): m/z (%) = 481 (M^+, 12), 411 (66), 409 (15), 398 (22); IR (KBr): $\nu = 1560$, 1510, 1440, 1410, 1370 cm^{-1}.

6-Dimethylamino-3,4-diphenyl-8-thiomorpholinopyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6h**): yield: 73%; m.p.: 259–261 °C; $C_{26}H_{24}N_6S_2$ (484.63); calc.: C: 64.44, H: 4.99, N: 17.34; found: C: 64.54, H: 4.78, N: 17.45; ^{1}H NMR ($CDCl_3$): $\delta = 2.75$–2.80 (m, 4H, SCH_2), 2.77 (s, 6H, NMe_2), 4.20–4.25 (m, 4H, NCH_2), 7.22–7.40 (m, 10H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 26.8$ (SCH_2), 36.6 (NMe_2), 49.3 (NCH_2), 105.1 (C-8a), 127.3 (C-4a), 127.5, 127.8, 128.0, 130.3, 130.5, 134.0, 135.6 (C_6H_5), 136.9 (C-4), 156.6 (C-3), 156.7, 158.6, 160.2 (C-9a), 163.7 ppm; MS (DEI): m/z (%) = 484 (M^+, 88), 411 (100), 382 (8), 366 (10), 242 (14); IR (KBr): $\nu = 1550$, 1520, 1440, 1410, 1390, 1360 cm^{-1}.

6-Dimethylamino-3,4-diphenyl-8-thiophenylpyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**6i**): yield: 82%; m.p.: 226–228 °C; $C_{28}H_{21}N_5S_2$ (491.63); calc.: C: 68.41, H: 4.30, N: 14.24; found: C: 68.57, H: 4.48, N: 14.33; ^{1}H NMR ($CDCl_3$): $\delta = 2.63$ (s, 6H, NMe_2), 7.27–7.67 (m, 15H, C_6H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 36.4$ (NMe_2), 116.7 (C-8a), 127.2 (C-4a), 127.0, 127.6, 127.8, 128.0, 128.1, 129.0, 129.6, 130.3, 130.4, 133.5, 135.8, 136.1 (C_6H_5), 136.6 (C-4), 154.9, 156.6 (C-3), 159.7, 164.5, 164.6 ppm; MS (DEI): m/z (%) = 491 (M^+, 3), 77 (100); IR (KBr): $\nu = 1565$, 1480, 1440, 1400 cm^{-1}.

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References

[1] (a) Janousek Z, Viehe HG (1976) Chemistry of Dichloromethyleniminium salts. In: Böhme H, Viehe HG (eds) Advances in Organic Chemistry, vol 9, Part 1. Wiley, New York, p 343 (b) Viehe HG, Janousek Z (1973) Angew Chem Int Ed **12**: 806 (c) Viehe HG (1977) Chem Ind 386 (d) Kukhar VP, Pasternak VI (1974) Synthesis 563 (e) Kodel B (1994) J Heterocycl Chem **31**: 845 (f) Guillot N, Viehe HG, Tinault B, Clerq JP (1990) Tetrahedron **46**: 3897 (g) Liebscher J (1988) Z Chem **28**: 291

[2] Brown DJ (1983) Pyrimidines and their Benzo Derivatives. In: Boulton AJ, McKillop A (eds) Katritzky and Rees Comprehensive Heterocyclic Chemistry, vol 3. Pergamon Press, Oxford, p 57

[3] (a) De Clercq E (1986) J Med Chem **29**: 1561 (b) Baba M, Pauwels R, Herwig P, De Clercq E, Demistev J, Vaudepulfe M (1987) Biochem Biophys Res Communs **142**: 128 (c) Heilderberg C, Arafield FJ (1963) Cancer Res **23**: 1226 (d) De Clercq E (1986) Anticancer Res **6**: 549 (e) Kelley JL, Linn JA, Selway JWT (1989) J Med Chem **32**: 218

[4] Albert A (1982) Adv Heterocycl Chem **32**: 1

[5] (a) Heinisch G, Kopelent H (1990) In: Ellis GP and West GB (eds) Progress in Medicinal Chemistry, vol 27. Elsevier, Amsterdam, p 1 (b) Heinisch G, Kopelent H (1992) In: Ellis GP and West GB (eds) Progress in Medicinal Chemistry, vol 29. Elsevier, Amsterdam, p 141

[6] Ellis GP (1991) Synthesis of Fused Heterocycles. In: Taylor EC (ed) The Chemistry of Heterocyclic Compounds, vol 47. Wiley, New York

[7] Cheng CC (1989) In: Ellis GP, West GB (eds) Progress in Medicinal Chemistry, vol 25. Elsevier Amsterdam, p 35 and references therein

[8] (a)Wamhoff H (1985) Adv Heterocycl Chem **38**: 300 (b) Elnadgi MH, Motaleb RMA, Mustafa M, Zayed MF, Kamel EM (1987) J Heterocycl Chem **24**: 1677 (c) Zayed SE, Abou Elmaged EI, Metwally SA, Elnadgi MH (1991) Collect Czech Chem Commun **56**: 2175 and references therein (d) Charvát T, Potácek M, Marek J (1995) Monatsh Chem **126**: 333

[9] (a) Peinador C, Veiga MC, Ojea V, Quintela JM (1994) Heterocycles **38**: 2065 (b) Quintela JM, Peinador C, Moreira MJ (1995) Tetrahedron **51**: 5901

[10] Deeb A, Said SA, Hamed MM, Yasin F (1990) J Chin Chem Soc **37**: 287

[11] Kokel B, Menichi G, Hobar-Habart M (1984) Tetrahedron Lett 1557

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