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FACILE SYNTHESIS OF 2-ANILINOPYRIMIDO [4,5-*e*][1,3,4]-THIADIAZINES

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Dedicated to Professor L. Overman on the occasion of his 65th birthday.

Abstract – One-pot synthesis of 2-anilino-pyrimido[4,5-*e*][1,3,4]thiadiazines through intermediates formed by reaction of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino) pyrimidine with arylisothiocyanates is reported.

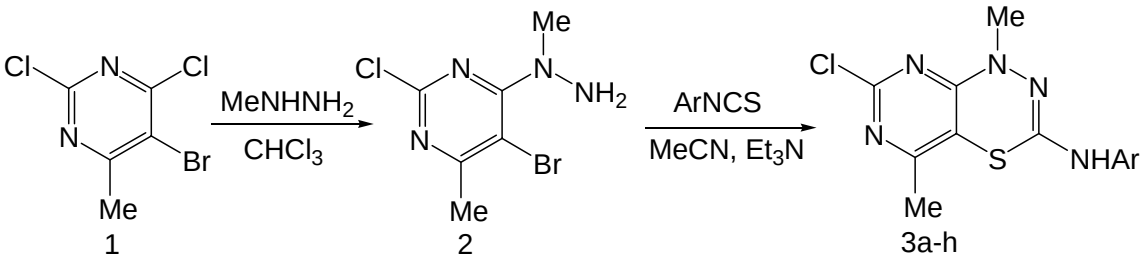
The distinct biological activities of pyrimido[4,5-*e*][1,3,4] thiadiazines prompted us to search for newer and more efficient synthetic methods for this class of heterocyclic compounds. Pyrimido[4,5-*e*][1,3,4] thiadiazines have the potential of being nucleoside analogues,[1,2] phosphodiesterase inhibitor[3] and diuretic, anti-inflammatory and hypotensive agents.[3,4]

The synthetic routes to these compounds are limited and only involve condensation of 2, 4-dichloro-5-nitro-6-methylpyrimidine with dithiazone,[5] the reaction of 6-hydrazinosubstituted uracils with isothiocyanates and *N*-bromosuccinimide,[4] heterocyclization of thiohydrazides with 4,5-dihalopyrimidines[6] and cyclocondensation of thiosemicarbazides with 5-bromobarbitoric acid.[7] Recently, we reported the synthesis of these compounds through the reaction of 5-bromo-2, 4-dichloro-6-methylpyrimidine with hydrazincarbodithioates.[8]

In pursuing our interest in the synthesis of this class of heterocycles, in this paper, we wish to report on the synthesis of new derivatives of 2-anilino-pyrimido[4,5-*e*][1,3,4]thiadiazines through intermediates formed by reaction of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine with various arylisothiocyanates.

5-Bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine **(2)** was prepared from the reaction of 5-bromo-2,4-dichloro-6-methyl pyrimidine **(1)** with methyl hydrazine according to the published

method.[8] The one-pot heterocyclization of compound **2** with various aromatic isothiocyanates in the presence of triethylamine in boiling acetonitrile under an atmosphere of nitrogen afforded the new derivatives of 2-anilino-pyrimido[4,5-*e*][1,3,4] thiadiazines **3a-h** as brownish needles (Scheme 1 & Table 1).



3a: Ar = C_6H_5, 3b: Ar = 4-Cl-C_6H_4, 3c: Ar = 3-Cl-C_6H_4, 3d: 4-Br-C_6H_4, 3e: 3-Br-C_6H_4, 3f: 2-Br-C_6H_4, 3g: 4-F-C_6H_4, 3h: 4-NO_2-C_6H_4

Scheme 1

The structures of these compounds were confirmed from their spectral and micro analytical data. For example, the ^{1}H NMR spectrum of compound **(3b)** did not show the signal at δ = 4.2 ppm belonging to NH_2 moiety of the precursor but instead showed a singlet for NH proton which was removed on deuteration. Furthermore, the spectrum showed an AB quartet peak at the aromatic region, confirming the presence of an aromatic ring and the occurrence of heterocyclization. The IR spectrum was also devoid of the stretching vibration bands at 3360 and 3280 cm^{-1} resembling the NH_2 moiety of the precursor but instead exhibited only one band at 3300 cm^{-1} for the NH moiety. The molecular ion peaks of compound **(3b)** was observed at 339(M) and 341 (M+2) corresponding to the molecular formula $C_{13}H_{11}Cl_2N_5S$.

In summary we have developed a simple one-pot synthesis of new 2-anilino-pyrimido[4,5-*e*][1,3,4]thiadiazines through intermediates formed by reaction of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino) pyrimidine with arylisothiocyanates. In comparison to other strategies which have been reported for the synthesis of various substituted pyrimido[4,5-*e*][1,3,4]thiadiazines in the literature, our strategy is very simple, very straightforward with short reaction times and with the potential to prepare several fused pyrimidothiadiazines.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are not corrected. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC l00 spectrometer. The mass spectra were obtained on a Varian Mat

Table 1. Physical, spectral and micro analytical data of pyrimido[4,3-*e*][1,3,4]thiadiazines **3a-h**
†The solvent for ^{1}H NMR is $CDCl_3$ and the chemical shifts are in ppm.

Entry	Yield (%)	Mp (ºC)	Spectral data†	Molecular formula	Found C% [calcd]	Found H% [calcd]	Found N% [calcd]	Found S% [calcd]
3a	55	219-220	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.2 (s, 3H, CH_3-N), 7.1-7.8 (m, 5H, ph), 12.7 (s, 1H, NH, D_2O exchangeable), IR: ν 3300, 3050, 1627, 1600, 1560, 1510 cm^{-1}, *m/z* 305 (M^+, 100%), 306 (15.6%), 307 (37.9%).	$C_{13}H_{12}ClN_5S$	51.10 [51.06]	3.84 [3.96]	22.75 [22.90]	10.30 [10.48]
3b	62	225-227	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.3 (s, 3H, CH_3-N), 7.2-7.5 (dd, *J*= 8 Hz, 4H, ph), 12.8 (s, 1H, NH, D_2O exchangeable), IR: ν 3300, 3005, 1660, 1595, 1560, 1495 cm^{-1}, *m/z* 339 (M^+, 100%), 340 (15.4%), 341 (68.9%).	$C_{13}H_{11}Cl_2N_5S$	45.55 [45.89]	3.23 [3.26]	20.51 [20.58]	9.29 [9.42]
3c	47	218-219	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.3 (s, 3H, CH_3-N), 7.0-7.7 (m, 4H, ph), 12.8 (s, 1H, NH, D_2O exchangeable), IR: ν 3310, 3015, 1645, 1610, 1585, 1490 cm^{-1}, *m/z* 339 (M^+, 100%), 340 (15.3%), 341 (70.0%).	$C_{13}H_{11}Cl_2N_5S$	45.70 [45.89]	3.20 [3.26]	20.46 [20.58]	9.36 [9.42]
3d	53	239-240	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.3 (s, 3H, CH_3-N), 7.3-7.6 (m, 4H, ph), 12.8 (s, 1H, NH, D_2O exchangeable), IR: ν 3320, 3005, 1655, 1598, 1560, 1498 cm^{-1}, *m/z* 383 (M^+, 74.0%), 385 (100%), 387 (28.0%).	$C_{13}H_{11}BrClN_5S$	40.37 [40.59]	2.79 [2.88]	18.01 [18.21]	8.10 [8.33]
3e	61	243	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.2 (s, 3H, CH_3-N), 7.1-7.8 (m, 4H, ph), 12.9 (s, 1H, NH, D_2O exchangeable), IR: ν 3320, 3053, 1645, 1590, 1578, 1538 cm^{-1}, *m/z* 383 (M^+, 72.3%), 385 (100%), 387 (27.6%).	$C_{13}H_{11}BrClN_5S$	40.42 [40.59]	2.82 [2.88]	18.15 [18.21]	8.25 [8.33]
3f	65	239	^{1}HNMR: δ 2.5(s, 3H, CH_3-pyrimidine), 4.2 (s, 3H, CH_3-N), 7.1-8.0 (m, 4H, ph), 12.7 (s, 1H, NH, D_2O exchangeable), IR: ν 3310, 3060, 1648, 1595, 1580, 1540 cm^{-1}, *m/z* 383 (M^+, 73.4%), 385 (100%), 387 (25.9%).	$C_{13}H_{11}BrClN_5S$	40.51 [40.59]	2.84 [2.88]	18.23 [18.21]	8.28 [8.33]
3g	43	250-251	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.2 (s, 3H, CH_3-N), 6.9-7.6 (m, 4H, ph), 12.7 (s, 1H, NH, D_2O exchangeable), IR: ν 3300, 3040, 1650, 1610, 1595, 1560, 1500 cm^{-1}, *m/z* 323 (M^+, 100%), 324 (15.4%), 325 (37.3%).	$C_{13}H_{11}ClFN_5S$	48.02 [48.23]	3.39 [3.42]	21.57 [21.63]	9.81 [9.90]
3h	48	268-269	^{1}HNMR: δ 2.5 (s, 3H, CH_3-pyrimidine), 4.2 (s, 3H, CH_3-N), 7.7-8.3 (dd, *J*= 10Hz, 4H, ph), 13.5 (s, 1H, NH, D_2O exchangeable), IR: ν 3340, 3050, 1635, 1585, 1520, 1490 cm^{-1}, *m/z* 350 (M^+, 100%), 351 (15.9%), 352 (37.8%).	$C_{13}H_{11}ClN_6O_2S$	44.47 [44.51]	3.03 [3.16]	23.87 [23.96]	8.99 [9.14]

CH-7 instrument at 70 eV. Elemental analysis was performed on a ThermoFinnigan Flash EA micro analyzer.

General procedure for preparation of pyrimido[4,3-*e*][1,3,4]thiadiazins **(3a-h)**:Compound **(2)** (0.25 g, 1 mmol) and appropriate arylisothiocyanates(1 mmol) in triethylamine (1.2 mmol) and acetonitrile(10 mL) were added to each other and refluxed for 2-3 h under the atmosphere of nitrogen.

The solvent was then removed in reduced pressure and the precipitate was recrystallized from EtOH. Their physical and spectral data of compound **3a-h** have been collected in Table1.

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