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Synthesis of Isoxazolo[3,4-*d*]pyrimidines from 6-Chloropyrimidine-5-carbaldehydes

by A. Kaminskas, M. Dailide and S. Tumkevicius

Department of Organic Chemistry, Faculty of Chemistry, Vilnius University, Naugarduko 24, 2006 Vilnius, Lithuania
E-mail: sigitas.tumkevicius@chf.vu.lt

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4-Dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes with sodium azide in dimethylformamide underwent ring closure reaction to form the corresponding isoxazolo[3,4-*d*]pyrimidines.

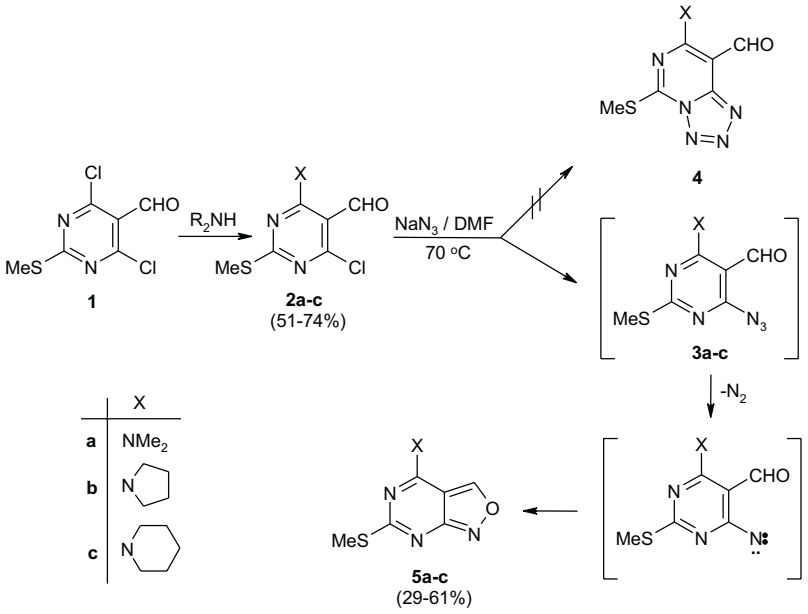
Key words: pyrimidine, isoxazolo[3,4-*d*]pyrimidine, azides, cyclization

Organic azides are versatile reagents for the synthesis of various nitrogen heterocyclic compounds. Heterocyclic azides (*e.g.* coumarins, quinolines, pyridines, pyrimidines and pyridazines) with aryl, carbonyl, nitro, carboxyl groups as *ortho* substituents under the thermal or photochemical conditions can undergo ring closure reactions with the formation of fused heterosystems [1–4]. Aryl and heteroaryl azides with suitable substituents are also employed for the synthesis of the corresponding phosphazenes, which in the following intramolecular aza-Wittig reaction with bifunctional reagents are capable to form nitrogen heterocycles [5,6]. Moreover, azines with the azide group attached at the *ortho* position to endocyclic nitrogen were shown to exist in the equilibrium with the corresponding tetrazoloazines [7–9]. In continuation of our ongoing search for new fused pyrimidine heterocycles of biological interest [10–13], we here wish to report our findings on a reaction of 4-dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes with sodium azide.

RESULTS AND DISCUSSION

The required compounds **2a–c** were obtained from the readily available 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde (**1**) [14]. The reaction of **1** with an excess of the selected secondary amines afforded the corresponding 4-dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes (**2a–c**). The structure of compounds **2a–c** was assigned on the basis of their spectral data. In the ^{1}H NMR spectra a set of signals of the dialkylamino group protons in the region of 1.69–3.58 ppm and a signal of the formyl group in the region of 10.17–10.27 ppm were observed. The IR spectra of compounds **2** showed the characteristic absorption of the formyl group at 1662–1666 cm^{-1}.

Scheme



The reported data on the synthesis of various heteroaryl azides allowed to expect that the reaction of 4-dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes (**2a–c**) and sodium azide will lead to the corresponding azides. The reaction of chloropyrimidines **2a–c** with sodium azide at different conditions was exemplified by the reaction of **2c**. It was found that at room temperature the reaction does not proceed. Performing of the reaction for 2 h at 40–50°C afforded an inseparable mixture of products. The ^{1}H NMR analysis of the obtained mixture showed that along with the initial chloropyrimidine **2c** there were two products in the mixture with the same set of signals for the protons of piperidino, methylthio and CH groups, respectively. The presence of the absorption band of the azide group at 2125 cm^{-1} in the IR spectrum of the mixture indicated on the formation of azidopyrimidine **3c**. Treatment of compounds **2a–c** with a four-fold excess of sodium azide in dimethylformamide at 70°C for a prolonged time did not afford the expected azides **3a–c** or tetrazolopyrimidines **4**. The isolated reaction products according to the results of ^{1}H NMR, IR spectra and elemental analyses appeared to be the corresponding isoxazolo[3,4-*d*]pyrimidines **5a–c**. The IR spectra of compounds **5a–c** did not show the characteristic absorption of the formyl and azido groups. In the ^{1}H NMR spectra a signal of the CH group was significantly upfield shifted in comparison with that of the corresponding carbaldehydes **2a–c** and was observed in the region of 8.90–8.99 ppm. All attempts to isolate the intermediate azide failed. It was a rather unexpected result because in most cases azides are rather stable to perform their conversions into the different valuable products. To the best of our knowledge, only 4-chloro-3-formyl-2-pyridones reacted with sodium azide at room temperature to give the corresponding isoxazolo[4,3-*c*]pyridines [3].

In conclusion, the present investigation showed that the reaction of 4-dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes with sodium azide proceeds *via* the corresponding azides with subsequent thermal generation of nitrene and following ring closure to form isoxazolo[3,4-*d*]pyrimidines.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ^{1}H NMR spectra were recorded on a Tesla BS 587A spectrometer (80 MHz) using tetramethylsilane as internal standard. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light. All reagents and solvents were purchased from Aldrich. Microanalyses were performed by the Microanalysis Laboratory of the Departament of Organic Chemistry of Vilnius University.

4-Dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes (2a–c). *Typical procedure.* To a mixture of compound **1** (2 g, 8.97 mmol) in methanol (20 ml) the corresponding dialkylamine (17.9 mmol) was added dropwise at room temperature (in case of the synthesis of **2b** 8.97 mmol of pyrrolidine and 8.97 mmol of triethylamine were used). The reaction mixture was stirred at room temperature until compound **1** disappeared from TLC plate. The precipitate was filtered off, the filtrate was concentrated to 1/3 of the initial volume and diluted with water. The solid was filtered off, combined with the earlier obtained, washed with water and recrystallized from 2-propanol to give compounds **2a–c**.

6-Chloro-4-dimethylamino-2-methylthiopyrimidine-5-carbaldehyde (2a). The reaction time – 2 h. Yield 51%, m.p. 110–113°C. IR: 1662 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): 2.54 (3H, s, SCH_3), 3.14 (6H, s, NCH_3), 10.25 (1H, s, CHO). Anal. Calcd. for $C_8H_{10}ClN_3OS$: C, 41.5; H, 4.35; N, 18.1. Found: C, 41.6; H, 4.7; N, 18.2.

6-Chloro-4-pyrrolidino-2-methylthiopyrimidine-5-carbaldehyde (2b). The reaction time – 11 h. Yield 64%, m.p. 143–144°C. IR: 1666 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): 1.89–2.15 (4H, m, CH_2), 2.52 (3H, s, SCH_3), 3.25–3.73 (4H, m, NCH_2), 10.27 (1H, s, CHO). Anal. Calcd. for $C_{10}H_{12}ClN_3OS$: C, 46.6; H, 4.7; N, 16.3. Found: C, 47.0; H, 4.8; N, 16.4.

6-Chloro-4-piperidino-2-methylthiopyrimidine-5-carbaldehyde (2c). The reaction time – 1 h. Yield 74%, m.p. 129–131°C. IR: 1663 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): 1.51–1.85 (6H, m, CH_2), 2.50 (3H, s, SCH_3), 3.4–3.72 (4H, m, NCH_2), 10.17 (1H, s, CHO). Anal. Calcd. for $C_{11}H_{14}ClN_3OS$: C, 48.6; H, 5.2; N, 15.5. Found: C, 49.0; H, 5.4; N, 15.5.

4-Dialkylamino-6-methylthioisoxazolo[3,4-*d*]pyrimidines (5a-c). *Typical procedure.* A mixture of the corresponding compound **2a–c** (2.21 mmol), sodium azide (0.575 g, 8.84 mmol) and dry DMF (10 ml) was heated at 65–70°C and monitored by TLC. When chloropyrimidines disappeared, the reaction mixture was poured to water, the precipitate was filtered off and recrystallized from benzene to give compounds **5a–c**.

4-Dimethylamino-6-methylthioisoxazolo[3,4-*d*]pyrimidine (5a). The reaction time – 17 h. Yield 61%, m.p. 235–238°C (dec.). ^{1}H NMR ($CDCl_3$): 2.59 (3H, s, SCH_3), 3.40 (6H, s, NCH_3), 8.95 (1H, s, CH). Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.7; H, 4.8; N, 26.65. Found: C, 45.9; H, 4.8; N, 26.8.

6-Methylthio-4-pyrrolidinoisoxazolo[3,4-*d*]pyrimidine (5b). The reaction time – 38 h. Yield 29%, m.p. 202–204°C. ^{1}H NMR (CD_2Cl_2): 1.82–2.33 (4H, m, CH_2), 2.54 (3H, s, SCH_3), 3.55–3.89 (4H, m, NCH_2), 8.90 (1H, s, CH). Anal. Calcd. for $C_{10}H_{12}N_4OS$: C, 50.8; H, 5.1; N, 23.7. Found: C, 50.4; H, 4.8; N, 23.9.

6-Methylthio-4-piperidinoisoxazolo[3,4-*d*]pyrimidine (5c). The reaction time – 8 h. Yield 57%, m.p. 179–182°C. ^{1}H NMR ($CDCl_3$): 1.53–1.89 (6H, m, CH_2), 2.56 (3H, s, SCH_3), 3.63–4.04 (4H, m, NCH_2), 8.99 (1H, s, CH). Anal. Calcd. for $C_{11}H_{14}N_4OS$: C, 52.8; H, 5.6; N, 22.4. Found: C, 53.05; H, 5.8; N, 22.1.

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