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An Unequivocal Synthesis of Some Substituted 1,2,4-Triazolo[1,5—*a*]Pyrimidines

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An unequivocal synthesis of 5-chloro-7-methyl- (**8**) and 7-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**10**) from 2-amino-4-chloro-6-methylpyrimidine (**5**) through the corresponding amidine **6** and formamide oxime **7** was developed. It was unambigously shown by comparison of the chemical shifts and the magnitude of coupling constants that the compounds obtained by condensation of 3-amino-1,2,4-triazole (**12**) and ethyl acetoacetate (**13**) and some further transformations are isomeric 5-methyl substituted 1,2,4-triazolo[1,5—*a*]pyrimidines **1**, **9**, and **11**.

(Keywords: 1,2,4-Triazolo[1,5—a]pyrimidines; Cyclization with N—N bond formation; Structure determination by NMR)

Eine eindeutige Synthese einiger substituierter 1,2,4-Triazolo[1,5—a]pyrimidine

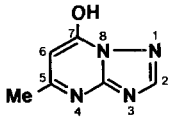
Es wurde ein eindeutiger Syntheseweg für 5-Chlor-7-methyl- (**8**) und 7-Methyl-1,2,4-triazolo[1,5—*a*]pyrimidin (**10**) ausgehend von 2-Amino-4-chlor-6-methylpyrimidin (**5**) über das entsprechende Amidin **6** und das Formamidoxim **7** entwickelt. Durch Vergleich von chemischen Verschiebungen und Kopplungskonstanten konnte eindeutig gezeigt werden, daß die Verbindungen, die bei der Kondensation von 3-Amino-1,2,4-triazol (**12**) and Ethylacetoacetat (**13**), sowie einige weitere Transformationsprodukte, isomere 5-Methyl-substituierte 1,2,4-Triazolo[1,5—*a*]pyrimidine sind (**1**, **9**, **11**).

Introduction

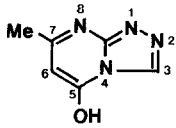
It has been reported that in the reaction of 3-amino-1,2,4-triazole with ethyl acetoacetate 7-hydroxy-5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**1**) is formed [1]. The same compound has been obtained also by cyclizing 2-hydrazino-4-hydroxy-6-methylpyrimidine with formic acid to which first an isomeric structure, 5-hydroxy-7-methyl-1,2,4-triazolo-

[4,3—*a*]pyrimidine (**2**), has been assigned [2], which later was corrected, since the compound **2** isomerizes into **1** under the reaction conditions [3]. The third isomer, 5-methyl-7-hydroxy-1,2,4-triazolo[4,3—*a*]pyrimidine (**3**) has been obtained from the corresponding 3-mercapto derivative [3]. Attempts to prepare the fourth isomer, 5-hydroxy-7-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**4**), have been unsuccessful [4] (Scheme 1). Furthermore, since many attempts to accomplish an unequivocal synthesis of any of these isomers have been unsuccessful, the structures of the isomers **1–3** are based mainly on the absorption spectra and on an assumption that the 1,2,4-triazolo[1,5—*a*]pyrimidine system is thermodynamically more stable than the isomeric 1,2,4-triazolo-[4,3—*a*]pyrimidine system [5].

Scheme 1



1



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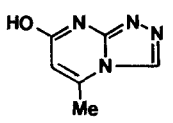

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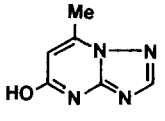

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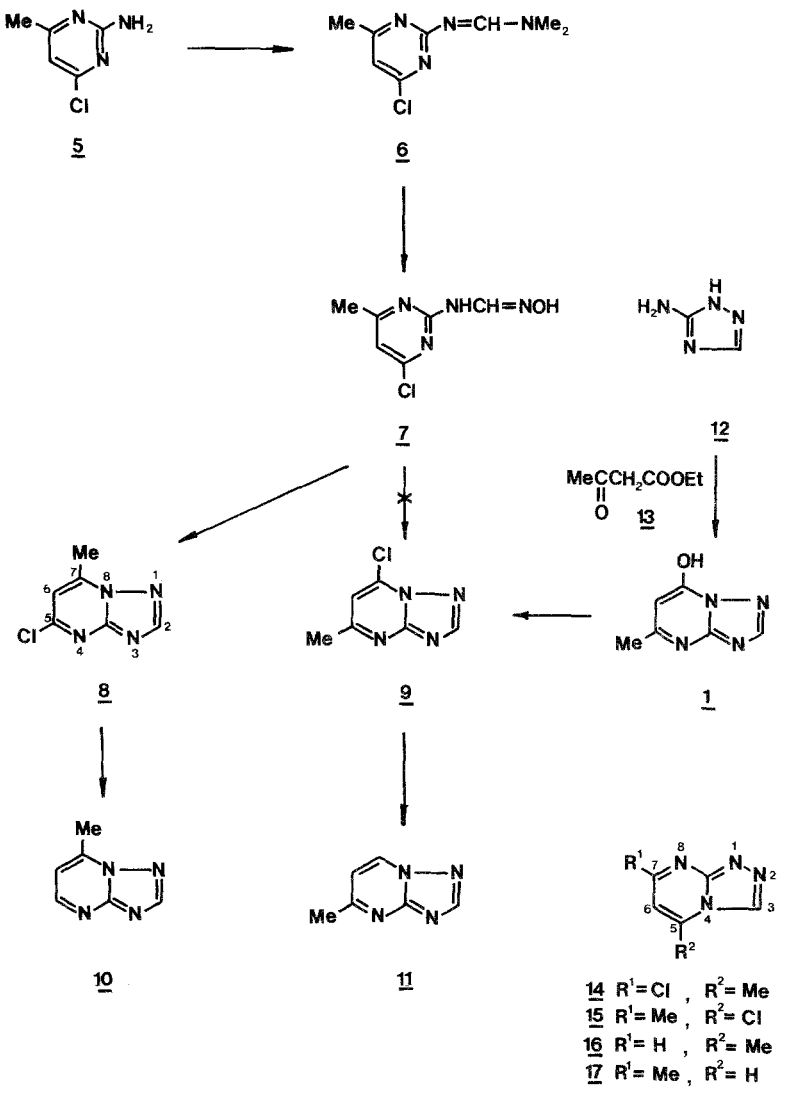
Results and Discussion

Several years ago a general unequivocal method for the preparation of 1,2,4-triazolo[1,5—*x*]azines from the corresponding N-heteroarylformamide oxime has been developed in our laboratory and successfully applied to the preparation of many systems [6–10]. In the pyrimidine series it has been applied, however, only to unsubstituted 2-aminopyrimidine and symmetrically disubstituted derivatives [6].

In this communication we report on the synthesis of 5-chloro-7-methyl- and 5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine [10]. 2-Amino-6-chloro-4-methylpyrimidine (**5**) was converted with N,N-dimethylformamide dimethyl acetal (*DMFDMA*) into 2-(N,N-dimethylaminomethyleneamino)-6-chloro-4-methylpyrimidine (**6**) fol-

lowed by treatment with hydroxylamine hydrochloride to give 2-hydroxyiminomethyleneamino-6-chloro-4-methylpyrimidine (**7**). Cyclodehydration of **7** with polyphosphoric acid (*PPA*) could give either 5-chloro-7-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**8**) or the isomeric 7-chloro-5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**9**) (Scheme 2).

Scheme 2



Its ^{1}H NMR spectrum shows one doublet at $\delta = 2.70$ ppm for a methyl group, a singlet at $\delta = 8.10$ ppm for H_2, and a quartet a $\delta = 6.65$ ppm for H_7. On the basis of the chemical shift for H_2, which falls in the region characteristic for the corresponding proton in other 1,2,4-triazolo[1,5—*x*]azines [6], a rearrangement into the isomeric compounds **14** or **15** can be excluded. Namely, H_3 in isomeric 1,2,4-triazolo[4,3—*a*]pyrimidines **14** and **15** would have been expected at δ below 8.7 ppm [11]. Furthermore, a long range coupling constant between methyl group and the adjacent proton ($J_{Me,H_7} = 0.5$ Hz) is in favor of the structure **8**.

In order to differentiate between structures **8** and **9** a catalytic dehalogenation was carried out to give a compound which shows in ^{1}H-NMR a doublet at $\delta = 2.72$ ppm for a methyl group, a singlet at $\delta = 8.05$ for H_2, a quartet of a doublet at $\delta = 6.60$ ppm, and a doublet at $\delta = 8.25$ ppm for H_5. The magnitude of the coupling constant, $J_{H_5,H_6} = 4.5$ Hz, is in agreement with the corresponding coupling constants in other azolopyrimidines with a bridgehead nitrogen atom [12] supported also by a long range coupling constant, $J_{Me,H_6} = 0.5$ Hz. This means also that, since the chemical shift for H_2 is the same as in the chloro derivative **8**, we can exclude a skeleton rearrangement during the dehalogenation. All this evidence is in agreement with 7-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**10**) and not with the isomeric 5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**11**). Consequently, cyclization of the formamide oxime derivative **7** is taking place to the ring nitrogen close to the methyl group to give the compound **8**. Therefore the isomeric structure **9** can be excluded.

On the other hand, the isomeric compound **11** was obtained in the following way: 3-Amino-1,2,4-triazole (**12**) was treated with ethyl acetoacetate in essentially the same way as reported earlier [1] to give 7-hydroxy-5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**1**), subsequently converted with phosphorus oxychloride into 7-chloro-5-methyl-1,2,4-triazolo[1,5—*a*]pyrimidine (**9**) and consequently dehalogenated to give **11** as its hydrochloride (Scheme 2).

The structure of the latter was confirmed by the ^{1}H NMR spectrum, which shows two singlets at $\delta = 8.90$ ppm for H_2 shifted downfield in comparison with the chloro derivative, due to the protonation taking place in the 5-membered 1,2,4-triazole part of the bicyclic system [13] and two doublets at $\delta = 7.60$ ppm for H_6 and at $\delta = 9.20$ ppm for H_7 with the coupling constant, $J_{H_6,H_7} = 7.5$ Hz. The magnitude of this coupling constant is in agreement with the corresponding coupling constants in other azolopyrimidines with a bridgehead nitrogen atom [11, 12]. The absence of the long range coupling constant between the methyl group and the adjacent proton suggests that the methyl group is attached at position 5. Furthermore, the chemical shifts for H_2 at $\delta = 7.92$ ppm in the compound **9** and for H_2 at $\delta = 8.90$ ppm in the compound **11** make it possible to assign the structures of **9** and **11** unambigously and indicate consequently that the original assignement of the compound **1** obtained from 3-amino-1,2,4-triazole and ethyl acetoacetate [1] has been correct.

The formation of isomeric structure **16** and **17**, belonging to the isomeric 1,2,4-triazolo[4,3—*a*]pyrimidine systems, obtained by treatment of the compound **1** with phosphorus oxychloride are excluded, since H_3 would appear invariably below 8.7 ppm.

Acknowledgement

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Experimental

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H NMR spectra were recorded on a Jeol C 60 HL spectrometer (*TMS* as internal standard, δ-values in ppm), mass spectra on a Hitachi-Perkin-Elmer RMU-6L mass spectrometer. Elemental analyses (C, H, N) were obtained with a Perkin-Elmer Analyser 240 °C.

4-Chloro-2-(N,N-dimethylaminomethyleneamino)-6-methylpyrimidine (**6**)

A mixture of 1 g **5** and 2 ml of N,N-dimethylformamide dimethyl acetal (*DMFDMA*) was heated under reflux for 2 h. The volatile components were evaporated *in vacuo* to give 0.3 g (22%) of the product as oily residue. MS (*m/e*): 143 (M^+). NMR ($CDCl_3$): 2.42 (s, *Me*), 3.20 (s, N*Me*$_2$), 6.80 (s, H_5), 8.78 (s, N CH).

This compound was without further purification used for the preparation of **7**.

4-Chloro-2-hydroxyiminomethyleneamino-6-methylpyrimidine (**7**)

To a suspension of 2.4 g **6** in 24 ml of methanol 1.18 g of hydroxylamine hydrochloride was added and the mixture was left at room temperature for 3 h. The precipitate was collected by filtration and washed with cold water to give 2.1 g (93%) of **7**, m.p. 166–168 °C (from *DMF*). MS (*m/e*): 186 (M^+). NMR (*DMSO-*d_6): 2.20 (s, *Me*), 6.44 (s, H_5), 7.20 (s, CH N), 8.0 (br, s, NH), 9.2 (br, s, OH).

$C_6H_7ClN_4O$ (186.60). Calcd. C 38.61 H 3.75 N 30.03.
Found. C 38.51 H 3.95 N 30.29.

5-Chloro-7-methyl-1,2,4-triazolo[1,5—a]pyrimidine (**8**)

A mixture of 0.6 g **7** and 9 g of *PPA* was heated at 95 °C for 30 min. The mixture was, after cooling, diluted with 20 ml of water and neutralized with solid sodium hydrogen carbonate. The solution was extracted with chloroform (5 times, 15 ml each time) and the combined extracts were dried with anhydrous sodium sulphate. After evaporation of chloroform 62 mg (11%) of **8** were obtained, m.p. 125–127 °C (from a mixture of chloroform and petroleum ether). MS (*m/e*): 168 (M^+). NMR ($CDCl_3$): 2.70 (s, *Me*), 6.65 (q, H_6), 8.10 (s, H_2), $J_{5\text{-}Me,H_6} = 0.5$ Hz.

$C_6H_5ClN_4$ (168.59). Calcd. C 42.75 H 2.99 N 33.23.
Found. C 42.80 H 3.02 N 33.20.

7-Methyl-1,2,4-triazolo[1,5—a]pyrimidine (**10**)

To a solution of 239 mg **8** in 10 ml of methanol a suspension of 23 mg of Pd/C (5%) in 15 ml of methanol was added and the mixture was hydrogenated at normal pressure for 12 h. The mixture was filtered and the filtrate evaporated *in vacuo* to

give 170 mg (90%) of **10**, m.p. 128–130 °C (subl. 70 °C, 1 Torr). MS (*m/e*): 134 (M^+). NMR ($CDCl_3$): 2.72 (s, *Me*), 6.60 (qd, H_6), 8.05 (s, H_2), 8.25 (d, H_5), $J_{H_5,H_6} = 4.5$ Hz, $J_{7\text{-}Me,H_6} = 0.5$ Hz.

$C_6H_6N_4$ (134.13). Calcd. C 53.72 H 4.51 N 41.77.
Found. C 53.54 H 4.77 N 41.54.

7-Hydroxy-5-methyl-1,2,4-triazolo[1,5—a]pyrimidine (**1**)

This compound was prepared in essentially the same as described in Ref. [1] in 61% yield, m.p. 224–226 °C, Ref. [14] m.p. 227–229 °C. NMR (*DMSO-d_6*): 2.20 (s, *Me*), 7.00 (s, H_6), 7.65 (s, H_2).

7-Chloro-5-methyl-1,2,4-triazolo[1,5—a]pyrimidine (**9**)

This compound was prepared from **1** and phosphorus oxychloride in essentially the same way as described in Ref. [14] in 60% yield, m.p. 144–147 °C (from a mixture of chloroform and petroleum ether), Ref. [14] m.p. 151–153 °C. MS (*m/e*): 168 (M^+). NMR ($CDCl_3$): 2.53 (s, *Me*), 6.63 (s, H_6), 7.92 (s, H_2).

5-Methyl-1,2,4-triazolo[1,5—a]pyrimidine (**11**)

A mixture of 200 mg **9** and 20 mg of Pd/C (5%) in 10 ml of ethanol was hydrogenated at normal pressure for 12 h. The mixture was filtered and the filtrate evaporated *in vacuo* to give 54 mg (34%) of **11** in the form of its hydrochloride, m.p. 223–225 °C. MS (*m/e*): 134 (M^+-HCl). NMR (CD_3OD): 2.80 (s, *Me*), 7.60 (d, H_6), 8.90 (s, H_2), 9.20 (d, H_7), $J_{H_6,H_7} = 7.5$ Hz.

$C_6H_6N_4 \times HCl$ (170.59). Calcd. C 42.24 H 4.14 N 32.84.
Found. C 42.38 H 4.16 N 32.61.

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