THE FIRST RELIABLE, GENERAL SYNTHESIS OF THE 5-OXO DERIVATIVES OF 5,6-DIHYDRO-1,2,4-TRIAZOLO[4,3-c]-PYRIMIDINE AND THE RATES OF ISOMERIZATION OF THE [4,3-c] COMPOUNDS INTO THEIR [1,5-c] ISOMERS

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Abstract —— This paper describes a reliable synthesis of the 5-oxo derivatives (8) of 5,6-dihydro-1,2,4-triazolo[4,3-c]pyrimidine, by the reaction of 2-oxo-1,2-dihydropyrimidin-4-ylhydrazines (7) with the appropriate triethyl orthoesters in trifluoroacetic acid below 30 °C or by the oxidative cyclization of their aldehyde hydrazones (10) with 70% nitric acid in trifluoroacetic acid below 40 °C, and the rates of isomerization of the [4,3-c] compounds (8) into the [1,5-c] isomers (9).

Our recent papers1,2 have presented the synthesis of 9H-1,2,4-triazolo[3,4-i]purin-5(6H)-ones (1) and 7H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones (2) as a new class of potential xanthine oxidase inhibitors. The respective structures of the 1,2,4-triazole moiety of the tricyclic heterocycles were assigned as the [3,4-i] (1) and [4,3-c] (2) systems, rather than the [5,1-i] (3) and [1,5-c] (4) systems based on the isolation of only one side system and their stability in typical solvents. However, it has been asked whether compounds (1) and (2), assigned as above, are really stable. The possibility of mistaking the structures cannot be denied, since such tricyclic heterocycles arising from an oxo or thioxo group at the 5-position are easily rearranged into their isomers (3) and (4), since the Dimroth-like rearrangement of 1,2,4-triazolo[4,3-c]pyrimidines to the isomeric [1,5-c] series occurs in acid, alkali, and neutral media (thermally induced).3 Since [4,3-c] systems (5) with an oxo or thioxo group at the 5-position are rapidly rearranged into their [1,5-c] isomers (6), even in neutral solution at room temperature,4,5 it is difficult to isolate the compounds having [4,3-c] system (5) without isomerization. We could not verify whether tricyclic heterocycles (1) and (2) easily underwent the rearrangement reaction.1,2 Regrettably, it is also difficult to obtain a suitable crystal of these compounds for X-Ray
analysis. Therefore, in order to estimate the properties of such tricyclic systems, we examine here those of bicyclic systems (5), \textit{i.e.}, the 5-oxo derivatives (5) of the 5,6-dihydro-1,2,4-triazolo[4,3-c]pyrimidine system, which are included in tricyclic systems (1) and (2). No trustworthy synthesis of these 5-oxo and 5-thioxo derivatives (5) has been reported to date, because the compounds are too unstable in most solvents. Herein, we report the first reliable, general synthesis of the 5-oxo derivatives (5) of 5,6-dihydro-1,2,4-triazolo[4,3-c]pyrimidine and the rates of the Dimroth-like rearrangement from [4,3-c] compounds (5) into their [1,5-c] isomers (6) in neutral medium at room temperature.

In examining the reports on the synthesis of 1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones (5), we encountered some confusing reports.\textsuperscript{6–8} Subsequently, we confirmed that the [4,3-c] compounds (5) rapidly undergo rearrangement in the reaction solvents to afford the [1,2,4]triazolo[1,5-c]pyrimidin-5(6H)-ones (6).\textsuperscript{4} We succeeded in isolating pure [4,3-c] compounds (5) in trifluoroacetic acid (TFA) below 40 °C, as shown in Scheme 1.

Specifically, treatment of 4-hydrazinopyrimidin-2(1H)-one (7a)\textsuperscript{5} with the appropriate triethyl orthoesters (5 equiv.) in TFA at room temperature afforded the corresponding 1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones (8a, b) \textit{(route i)}.\textsuperscript{9} Similarly, the reaction of the 5- and 6-methyl derivatives (7b, c)\textsuperscript{10} with an appropriate triethyl orthoester gave the corresponding [4,3-c] derivatives (8d) (84%), (8e) (64%), (8f) (62%), and (8g) (61%). Furthermore, the cyclization of the hydrazones (10b, e, f, h, i), which were prepared by treatment of the hydrazino derivatives (7a–c) with appropriate aldehydes in methanol at room temperature in 70–90% yields \textit{(route ii)}, to the corresponding [4,3-c] compounds
(8b,e,f,h,i) was accomplished by oxidation using 70% nitric acid (ca. 1.2 equiv.) in TFA below 40 °C (route iii). For the reaction of 10c, the corresponding [4,3-c] compound (8c) was not obtained, but the [1,5-c] isomer (9c, 70%) was obtained. It was difficult to recrystallize the [4,3-c] compounds (8a,b,d–i) from any solvent, because they isomerized into the respective [1,5-c] isomers (9a,b,d–i) too rapidly in warmed solvent. The structures of all the new compounds (8) were verified by FAB-MS, IR, ¹H-NMR, and UV spectral data, which were consistent with the structures. Therefore, we clarified that the 5-oxo

\begin{align*}
8-10 & \quad R^1 \quad R^2 \quad R^3 \quad R^4 \\
\text{a} & \quad H \quad H \quad H \quad H \\
\text{b} & \quad H \quad H \quad H \quad Me \\
\text{c} & \quad H \quad H \quad H \quad Ph \\
\text{d} & \quad H \quad H \quad H \quad H \\
\text{e} & \quad Me \quad H \quad H \quad Me \\
\text{f} & \quad Me \quad H \quad H \quad Ph \\
\text{g} & \quad H \quad Me \quad H \quad H \\
\text{h} & \quad H \quad Me \quad H \quad Me \\
\text{i} & \quad H \quad Me \quad H \quad Ph \\
\text{j} & \quad H \quad H \quad Me \quad H \\
\text{k} & \quad H \quad H \quad Me \quad Me \\
\text{l} & \quad H \quad H \quad Me \quad Ph \\
\end{align*}

\textbf{Scheme 1} Reagents and conditions: i, R^4\text{C(OEt)}_3, TFA, rt–60 °C, 0.5–24 h; ii, R^4-CHO, MeOH, rt, 0.5 h; iii, 70% HNO\textsubscript{3}, TFA, rt–40 °C, 5–30 min; iv, EtOH or DMSO, rt; v, R^4\text{C(OEt)}_3, DMF, reflux, 0.5–1 h; vi, 70% HNO\textsubscript{3}, DMF, 100 °C, 1 h; vii, 0.1 N MeONa, MeOH, rt, 30 min; viii, MeI, EtONa, EtOH, reflux, 2 h.
derivatives (8) of such [4,3-c] ring systems were rapidly isomerized to their [1,5-c] isomers (9), even in neutral solvents, such as ethyl acetate, ethanol, DMSO, DMF, etc., at room temperature, while they were quite stable for several days in TFA or concentrated 36% HCl, but were gradually isomerized in glacial acetic acid within one day. Therefore, the [1,5-c] isomers (9a–i) were easily prepared by the rearrangement reaction of the [4,3-c] compounds (8a,b,d–i) in ethanol (100–200 parts) (route iv), by heating compounds (7a–c) with the appropriate orthoesters (5 equiv.) in DMF (ca. 50 parts) (route v), or by oxidative cyclization of the hydrazones (10b,c,e,f,h,i) with 70% HNO₃ (ca. 1.2 equiv.) in DMF (ca. 50 parts) at 100 °C (route vi).

Recently, there have been some noteworthy reports on the synthesis of 6-β-D-ribofuranosyl derivatives of the 5-oxo-[4,3-c] compound (8a) without isomerization.¹²⁻¹⁶ Therefore, we expected that the 6-substituted derivative of 8 might be stable in any solvent. In fact, we now conclude that the 6-alkyl derivatives (8j: 60%, mp 173–175 °C; 8k: 71%, mp 178–180 °C; 8l: 80%, mp 165–166 °C), prepared by the same method as used for 8a (route i), were quite stable. Consequently, the oxidation of the hydrazones (10k,l) with 70% HNO₃ in DMF at 100 °C gave the corresponding 3-substituted 6-methyl-1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones (8k,l) in 60–80% yields (route vi). When the compounds (8j-l, R³= Me) were treated with 0.1 N methanolic MeONa at room temperature, they were rearranged to the corresponding [1,5-c] isomers (9j–l) in 70–75% yields (route vii). The compounds (9j–l) were identical with those obtained by methylation of 9a–c with methyl iodide (4 equiv.) and sodium ethoxide (3 equiv.) in hot ethanol (50 parts) (route viii). Each isomer of the [4,3-c] (8) and [1,5-c] (9) compounds was distinguishable by UV and ¹H-NMR spectra. The UV spectrum of 8a in dry ethanol had a maximum at 257 nm, while that of 9a was at 264 nm. As a general rule, a bathochromic shift of the maximal absorption of 4–10 nm was observed in each UV spectrum for the [1,5-c] compounds (9) compared to the corresponding [4,3-c] isomers (8), except for the 3-phenyl derivatives (8f,i,l). In ¹H-NMR spectra of the [4,3-c] compounds (8a,d,g,j), the most prominent peak of each compound was observed as a singlet at δ 9.14–9.24 [(CD₃)₂SO], which appeared at the most downfield position, and was attributed to the proton at the 3-position. On the other hand, the peak in the [1,5-c] compounds (9a,d,g,j) was observed at δ ca. 0.8 upfield compared to that of the corresponding [4,3-c] isomers (8), i.e., at δ 8.33–8.42 as a singlet signal attributed to the proton at the 2-position.

Proton magnetic resonance spectroscopy proved invaluable in determining whether 1,2,4-triazolo[4,3-
c]pyrimidines (8) or the isomeric [1,2,4]triazolo[1,5-c]pyrimidines (9) resulted from a given reaction. The susceptibilities of the [4,3-c] compounds (8) to rearrangement into their [1,5-c] isomers (9) were found by measuring the time for half the [4,3-c] compounds (8) to disappear under standardized conditions at 22 °C in (CD$_3$)$_2$SO, as shown in Figure 1. The rate (t$_{1/2}$) of rearrangement of the parent compound (8a) was 102 min. The addition of a substituent at the 3-position (R$^4$) of the parent compound (8a) produced an appreciable increase in the rate of the rearrangement, i.e., the t$_{1/2}$ of 8b was 17 min. The rearrangement was too rapid to isolate the 3-phenyl [4,3-c] compound (8c). However, the introduction of a methyl substituent at the 8- or 7-position (R$^1$ or R$^2$) of 8a decreased the rate by a factor of about two, i.e., the t$_{1/2}$ of 8d and 8g was 234 and 216 min, respectively. Therefore, the 8-methyl (8f) and 7-methyl (8i) derivatives of 3-phenyl-1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-one (8c) were isolated, i.e., the t$_{1/2}$ of 8f and 8g was 46 and 33 min, respectively.

![Figure 1 Rearrangement rates of the [4,3-c] compounds (8) into the [1,5-c] isomers 9 in (CD$_3$)$_2$SO (30 mM) at 20 °C obtained by the ratio of the both integral values of the optional protons in $^1$H-NMR spectra. The t$_{1/2}$ were obtained by plots of log [Ia / (Ia + Ib)] against time (min), where Ia and Ib are the integral values of the [4,3-c] compound 8 and the [1,5-c] isomer 9, respectively. The t$_{1/2}$ (min): 8a (102), 8b (17), 8d (234), 8f (46), 8g (216), 8h (55), 8i (33).]

Thus, this is the first reliable, general synthesis of the 5-oxo derivatives (8) of 5,6-dihydro-1,2,4-
triazolo[4,3-c]pyrimidine. Further synthetic and kinetic rearrangement investigations of the 5-thioxo and 5-amino derivatives of 5,6-dihydro-1,2,4-triazolo[4,3-c]pyrimidine (5) and also of 9H-1,2,4-triazolo[3,4-i]purin-5(6H)-ones (1) and 7H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidin-5(6H)-ones (2) are in progress, and will be reported in detail shortly.

REFERENCES AND NOTES

9. Typical procedure: A solution of 7a (0.2 g, 1.59 mmol) with triethyl orthoformate (1.17 g, 7.89 mmol) in TFA (3 mL) was stirred at room temperature for 1 h. After the reaction was complete, the solution was concentrated to dryness below 25 °C in vacuo and treated with ether to afford the crystals (8a, 0.19 g, 88%, mp >300 °C), which were collected by filtration and carefully washed in 0.5% aq. potassium hydrogen carbonate. Other derivative (8b) (mp >300 °C) was prepared in only 3% yield in a similar manner to 8a, but 8c was not obtained.
11. Typical procedure: A solution of 4-ethylidenehydrazinopyrimidin-2(1H)-one (10b, 0.1 g, 0.66 mmol) with 70% nitric acid (0.07 mL, 0.77 mmol) in TFA (3 mL) was stirred at room temperature for 30 min. After the reaction was complete, the same work-up as noted above gave the crystals of the [4,3-c] compound (8b) in 71% yield. Other derivatives 8e (81%, mp >300 °C), 8f (65%, mp 279–281 °C, decom), 8h (91%, mp >227 °C, decom), and 8i (71%, mp >300 °C) were prepared by the same method as used for 8b. Only one plausible synthesis of 8b was reported by Hayatsu et al. in 1978.12 However, the compound (8b) isolated was not chemically characterized and easily isomerized to 9a in heating water. The mps of 8d and 8g were 252–253 and >260 °C, respectively.