

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

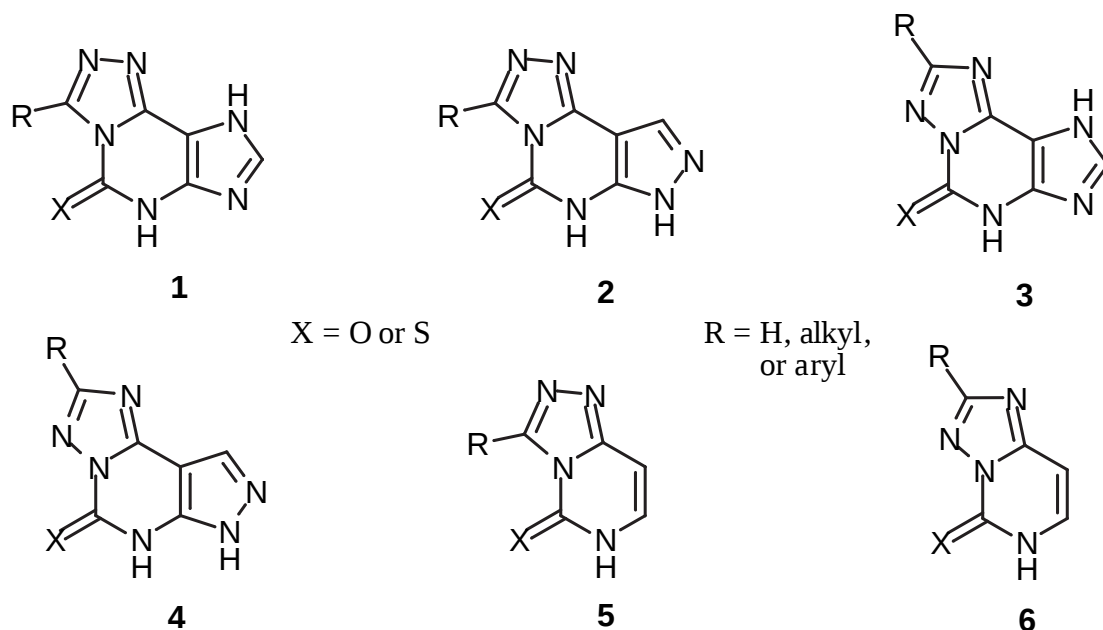
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Abstract — This paper describes a reliable synthesis of the 5-oxo derivatives (**8**) of 5,6-dihydro-1,2,4-triazolo[4,3-*c*]pyrimidine, by the reaction of 2-oxo-1,2-dihydropyrimidin-4-ylhydrazines (**7**) with the appropriate triethyl orthoesters in 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**).

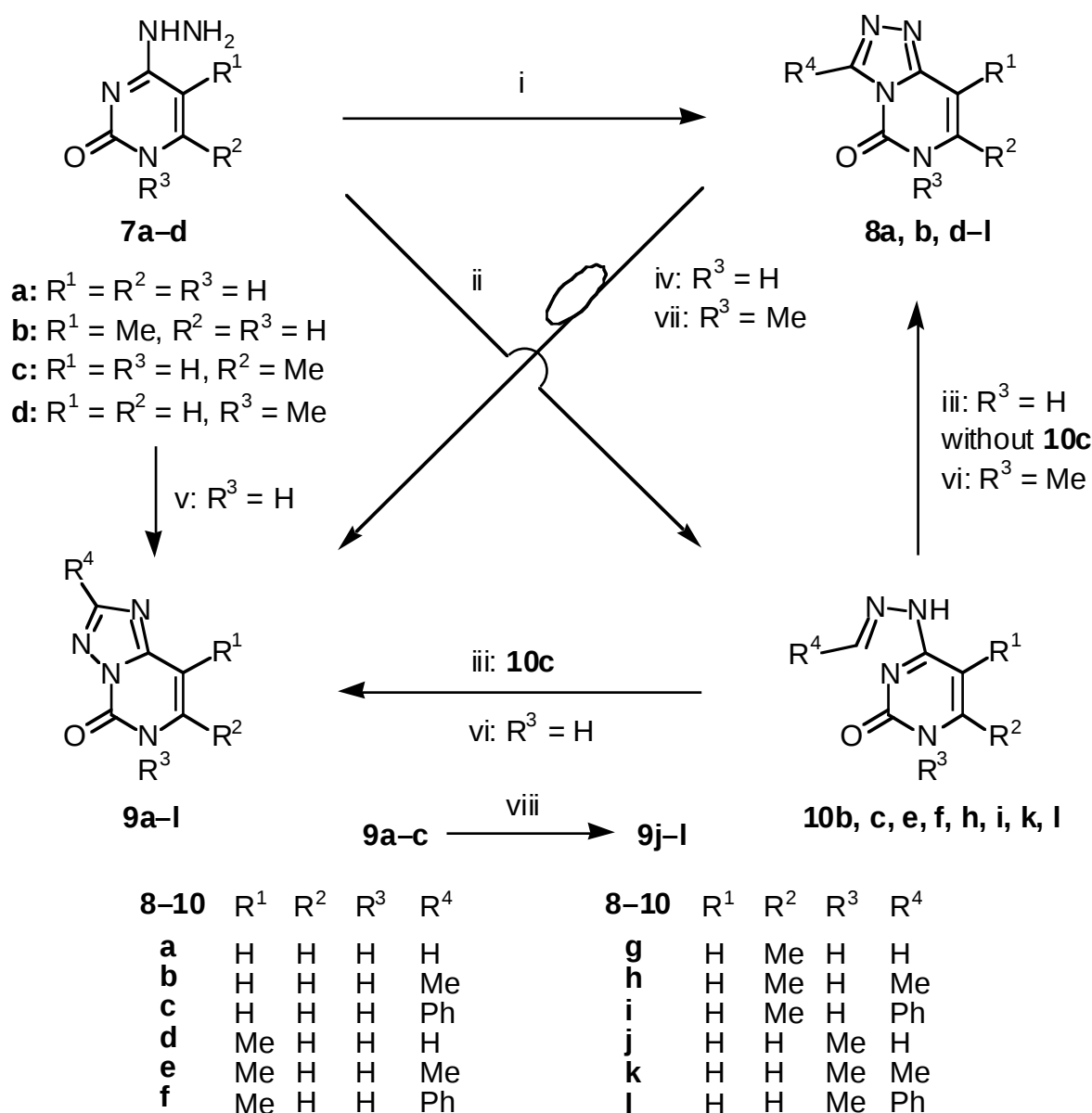
Our recent papers^{1,2} have presented the synthesis of 9*H*-1,2,4-triazolo[3,4-*i*]purin-5(6*H*)-ones (**1**) and 7*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**2**) as a new class of potential xanthine oxidase inhibitors. The respective structures of the 1,2,4-triazole moiety 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), *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(6*H*)-ones (5), we encountered some confusing reports.^{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(6*H*)-ones (6).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(1*H*)-one (7a)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(6*H*)-ones (8a,b) (*route i*).⁹ Similarly, the reaction of the 5- and 6-methyl derivatives (7b,c)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 (*route ii*), to the corresponding [4,3-*c*] compounds



Scheme 1 Reagents and conditions: i, $R^4C(OEt)_3$, TFA, rt–60 °C, 0.5–24 h; ii, R^4-CHO , MeOH, rt, 0.5 h; iii, 70% HNO_3 , TFA, rt–40 °C, 5–30 min; iv, EtOH or DMSO, rt; v, $R^4C(OEt)_3$, DMF, reflux, 0.5–1 h; vi, 70% HNO_3 , DMF, 100 °C, 1 h; vii, 0.1 N MeONa, MeOH, rt, 30 min; viii, MeI, EtONa, EtOH, reflux, 2 h.

(**8b,e,f,h,i**) was accomplished by oxidation using 70% nitric acid (ca. 1.2 equiv.) in TFA below 40 °C (route iii).¹¹ 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

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(6*H*)-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 (CD₃)₂SO, 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 (R⁴) 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 (R¹ or R²) 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(6*H*)-one (**8c**) were isolated, *i.e.*, the $t_{1/2}$ of **8f** and **8g** was 46 and 33 min, respectively.

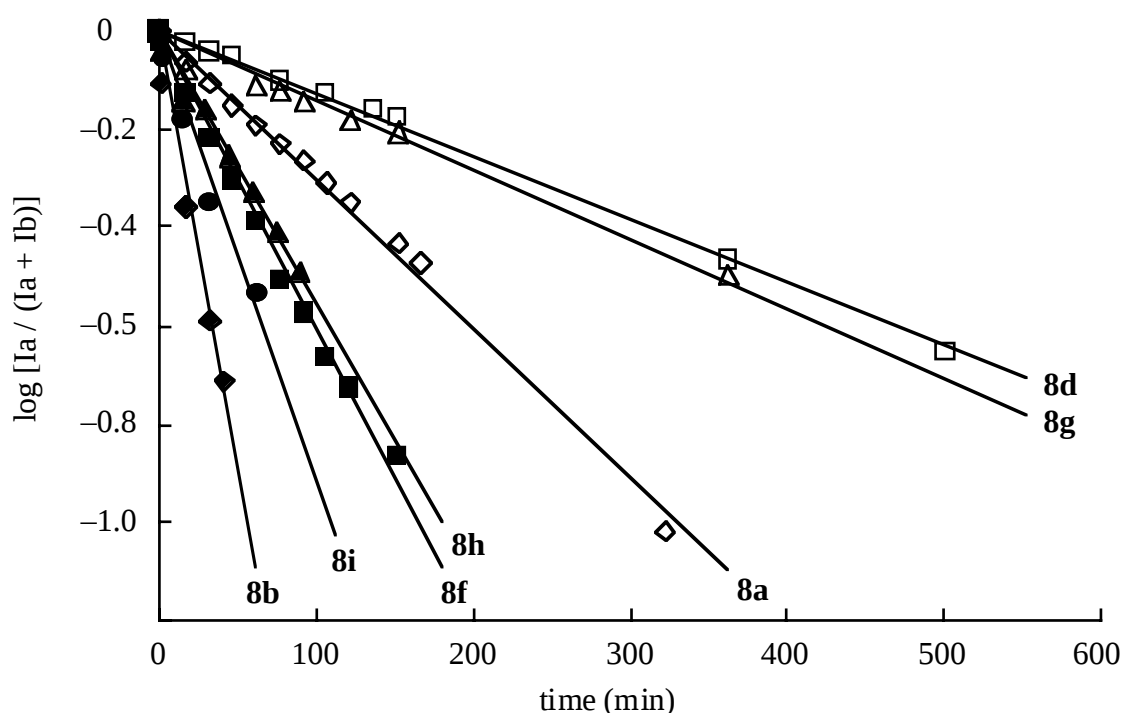


Figure 1 Rearrangement rates of the [4,3-c] compounds (**8**) into the [1,5-c] isomers **9** in (CD₃)₂SO (30 mM) at 20 °C obtained by the ratio of the both integral values of the optional protons in ¹H-NMR spectra. The $t_{1/2}$ were obtained by plots of $\log [Ia / (Ia + Ib)]$ against time (min), where 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 9*H*-1,2,4-triazolo[3,4-*i*]purin-5(6*H*)-ones (**1**) and 7*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**2**) are in progress, and will be reported in detail shortly.

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11. *Typical procedure*: A solution of 4-ethylidenehydrazinopyrimidin-2(1*H*)-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, decomp), **8h** (91%, mp >227 °C, decomp), 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.
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