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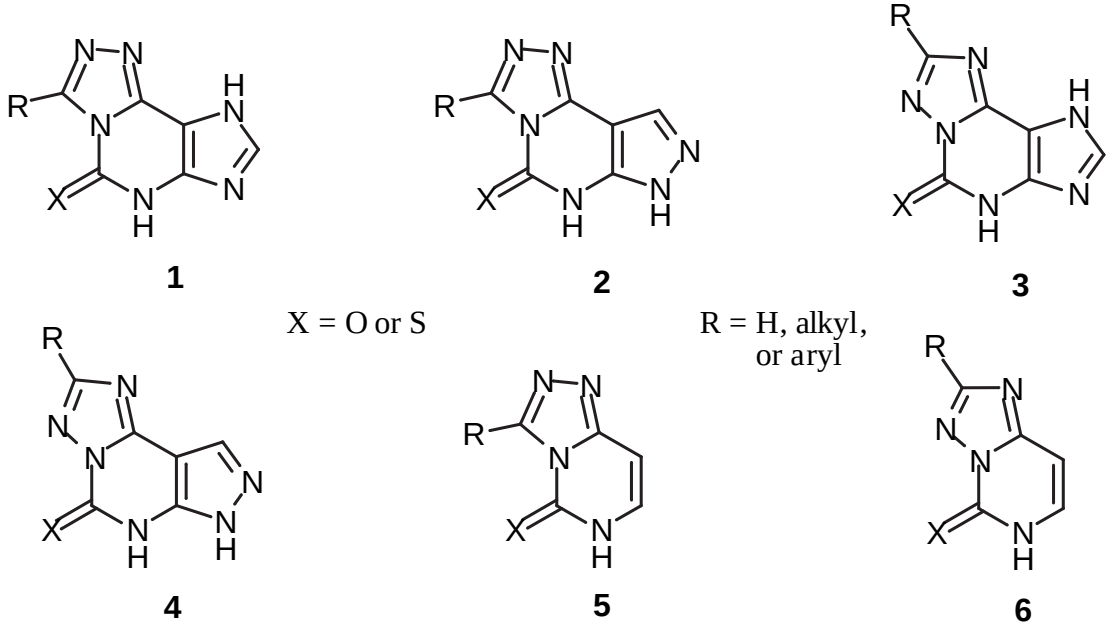
Abstract ----- This paper describes a reliable synthesis of the 5-oxo derivatives (**8**) of 5,6-dihydro-1,2,4-triazolo[4,3-*c*]pyrimidine, by the reaction of 2-oxo-1,2-dihydropyrimidin-4-ylhydrazines (**7**) with the appropriate triethyl orthoesters in trifluoroacetic acid below 30 ℃ or by the oxidative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

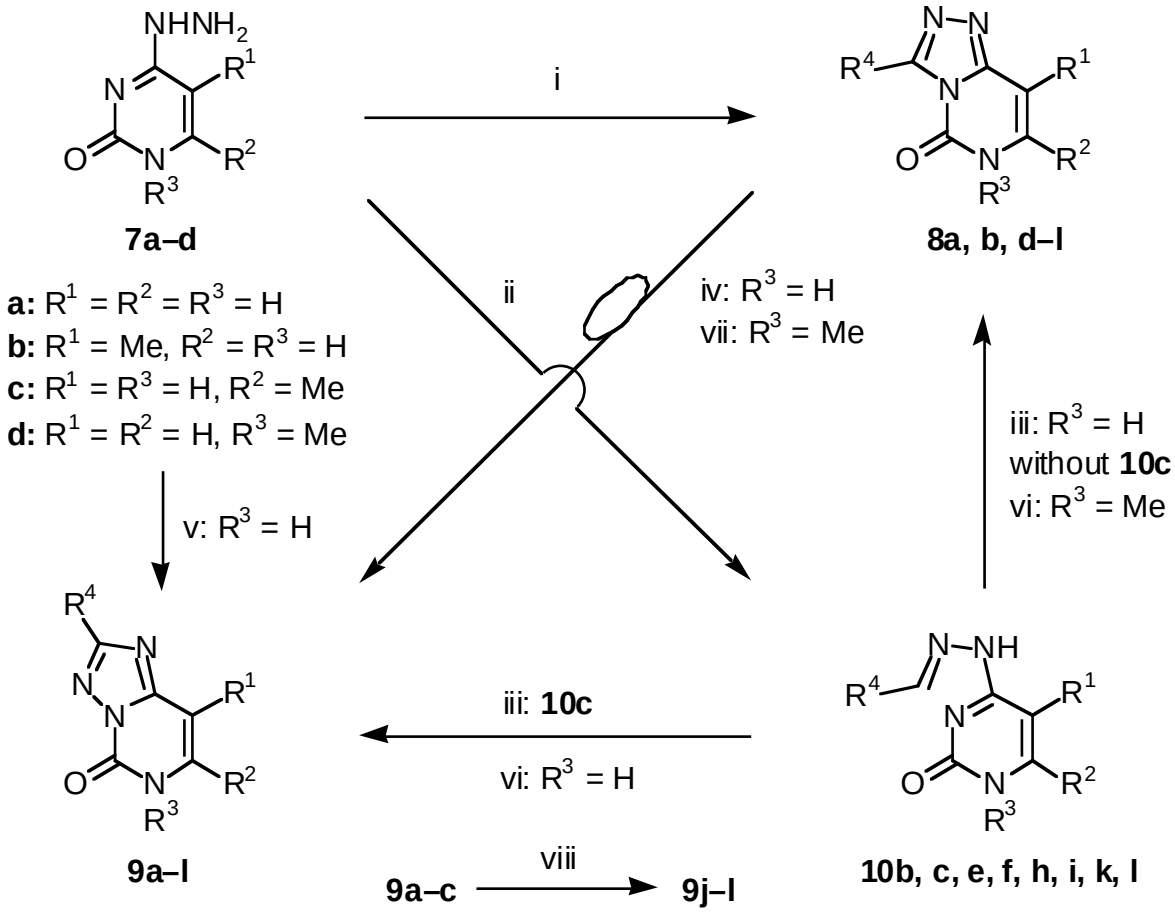


1 **2** **3**

4 **5** **6**

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 ℃, 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



a: $R^1 = R^2 = R^3 = H$
b: $R^1 = Me$, $R^2 = R^3 = H$
c: $R^1 = R^3 = H$, $R^2 = Me$
d: $R^1 = R^2 = H$, $R^3 = Me$

8–10	R^1	R^2	R^3	R^4	8–10	R^1	R^2	R^3	R^4
a	H	H	H	H	**g**	H	Me	H	H
b	H	H	H	Me	**h**	H	Me	H	Me
c	H	H	H	Ph	**i**	H	Me	H	Ph
d	Me	H	H	H	**j**	H	H	Me	H
e	Me	H	H	Me	**k**	H	H	Me	Me
f	Me	H	H	Ph	**l**	H	H	Me	Ph

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 ℃ (*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, ^{1}H-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% HNO_3 (*ca.* 1.2 equiv.) in DMF (*ca.* 50 parts) at 100 ℃ (*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 ℃; **8k**: 71%, mp 178–180 ℃; **8l**: 80%, mp 165–166 ℃), prepared by the same method as used for **8a** (*route* i), were quite stable. Consequently, the oxidation of the hydrazones (**10k,l**) with 70% HNO_3 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**, R^3= 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 ^{1}H-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 ^{1}H-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 [$(CD_3)_2SO$], 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 $(CD_3)_2SO$, 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 (R^4) of the parent compound (**8a**) produced anappreciable 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(6*H*)-one (**8c**) were isolated, *i.e.*, the $t_{1/2}$ of **8f** and **8g** was 46 and 33 min, respectively.

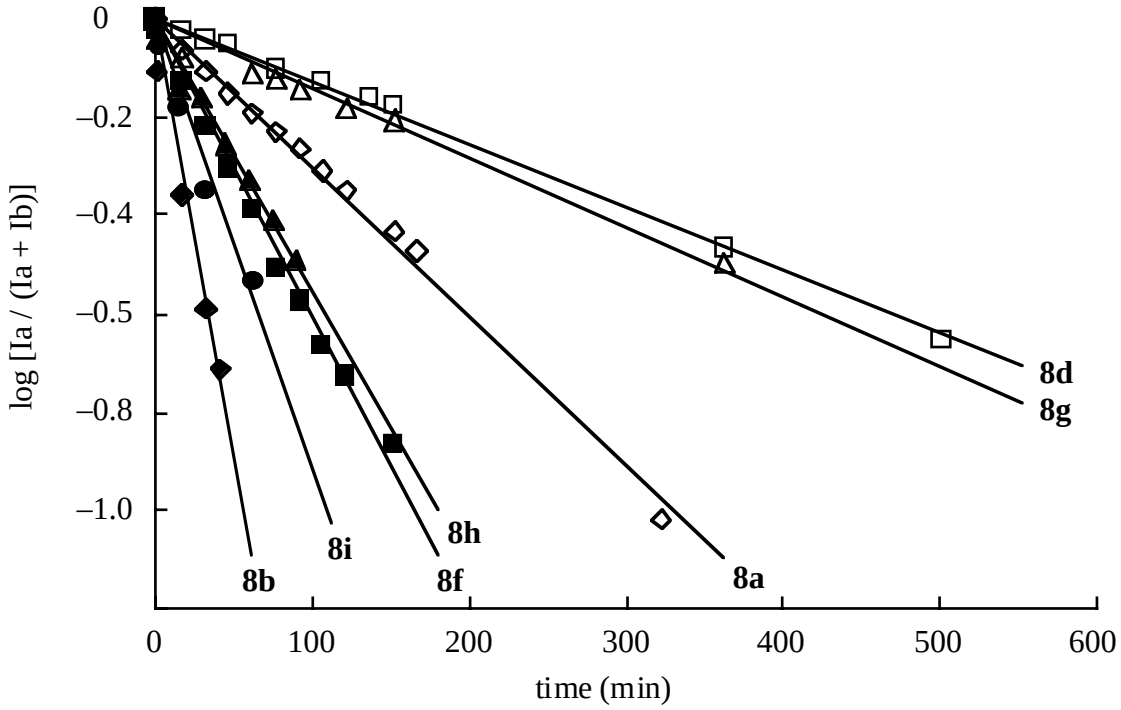


Figure 1 Rearrangement rates of the [4,3-*c*] compounds (**8**) into the [1,5-*c*] isomers **9** in $(CD_3)_2SO$ (30 mM) at 20 °C obtained by the ratio of the both integral values of the optional protons in ^{1}H-NMR spectra. The $t_{1/2}$ were obtained by plots of log [Ia / (Ia + Ib)] against time (min), 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 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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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.
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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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