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Triazolo[4,5-*d*]pyrimidines. VIII.[1] Aryl Migration of 7-Aroyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines to 7-Aryl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines

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When mixtures of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**), aromatic aldehydes (**5**), and a catalytic amount of 1,3-dimethylbenzimidazolium iodide were refluxed in tetrahydrofuran (THF) in the presence of sodium hydride, 7-aroyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidines (**1**) were obtained in moderate yields. Although the yield was unsatisfactory, the reaction of **1** with sodium hydroxide in dimethyl sulfoxide (DMSO) resulted in aryl migration, followed by ready oxidative decarboxylation, giving 7-aryl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidines (**3**) by way of 7-aryl-6,7-dihydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylic acids (**2**). When the reaction mixture of **1** with sodium hydroxide was directly subjected to potassium ferricyanide oxidation, **1** was easily convertible to **3** in good yield.

Keywords——7-aroyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine; 7-aryl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylic acid; 7-aryl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine; nucleophilic aroylation; aryl migration; potassium ferricyanide oxidation

It was reported that, when a mixture of a 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (I) and sodium hydroxide in dimethyl sulfoxide (DMSO) is stirred for 1 h at room temperature, migration of the aryl group to the 4-position occurs, *i.e.*, the benzilic acid rearrangement, resulting in the formation of the corresponding 4-aryl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acid (II).[2] It was also reported that in the case of 4-aroylquinazolines (III), the reaction proceeds in two ways.[3] One is aryl migration leading to 4-aryl-3,4-dihydro-4-quinazolinecarboxylic acids (IV), and the other is fission of the C^4–CO bond to yield quinazoline (V) and aroic acids (VI).[3]

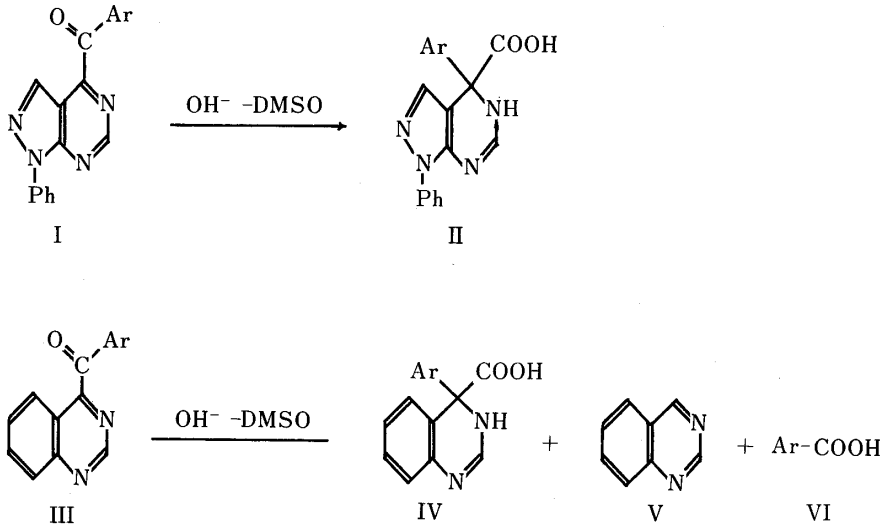
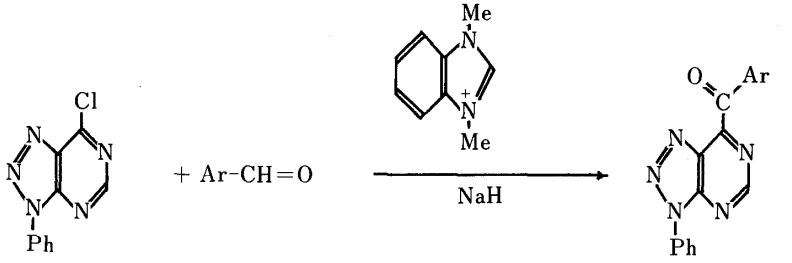


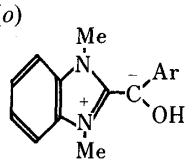
Chart 1

Since 7-aroyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**1**) are considered to be analogues of I or III, it was expected that a benzilic acid rearrangement of **1** to 7-aryl-6,7-dihydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylic acids (**2**) might proceed. Thus, we carried out the reaction of **1** with sodium hydroxide in DMSO, and found that migration of the aryl group to the 7-position, followed by ready oxidative decarboxylation, did take place, providing 7-aryl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3**). In the present paper we describe our detailed investigation of the aryl migration, as well as the preparation of **1** as suitable starting materials for **3**.

The starting materials (**1**) were prepared by the following nucleophilic aroylation[5] of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**).[4] Thus, when mixtures of **4**, aromatic aldehydes (**5**), and a catalytic amount of 1,3-dimethylbenzimidazolium iodide[6] were refluxed in tetrahydrofuran (THF) for 30 min in the presence of sodium hydride, the desired compounds (**1**) were obtained in moderate yields, as shown in Chart 2.



4	5	Ar	1	yield (%)
	5a	C_6H_5	**1a**	56
	5b	C_6H_4–Cl (*p*)	**1b**	63
	5c	C_6H_4–Cl (*o*)	**1c**	60
	5d	C_6H_4–OMe (*p*)	**1d**	78
	5e	C_6H_4–OMe (*o*)	**1e**	33
	5f	C_6H_4–Me (*p*)	**1f**	49
	5g	C_6H_4–Me (*o*)	**1g**	41



A

Chart 2

The aroylation may well occur by the initial formation of an activated aldehyde (A), similar to the intermediate observed in the benzoin condensation catalyzed by certain imidazolium compounds[6] and thiazolium salts,[7,8] followed by substitution with **4** to provide **1** with elimination of the benzimidazolium ion.

The structures of **1a**—**g** were supported by their elemental analyses, and confirmed by analyses of their infrared absorption (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra, as shown in Table I.

When a mixture of 7-(*p*-methoxybenzoyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**1d**) and sodium hydroxide in DMSO was stirred for 5 min at room temperature, 6,7-dihydro-7-(*p*-methoxyphenyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylic acid (**2d**) and 7-(*p*-methoxyphenyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**3d**) were obtained in 59 and 6% yields.

The structure of **2d** was suggested by the elemental analysis, and confirmed by analyses of the IR and ^{1}H-NMR spectral data, as described in the experimental section.

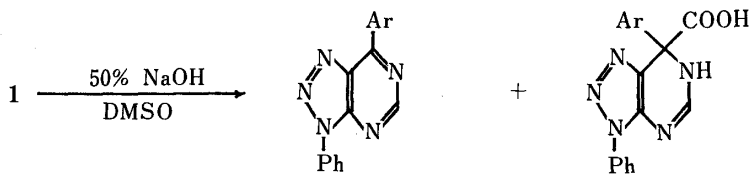
However, in the cases of the benzoyl (**1a**) and *p*-chlorobenzoyl derivatives (**1b**), the

TABLE I. Melting Points, Elemental Analyses, and Spectral Data for **1** and **3**

No.	mp (°C)	Formula	Analysis (%) Calcd (Found)			IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm		
			C	H	N	C=O	C^5-H (s)	Aromatic H (m)	OMe or Me (s)
1a	141[a,e]	$C_{17}H_{11}N_5O$	67.76 (67.70)	3.68 3.51	23.25 23.08)	1680	9.14	7.14—8.13 (10H)	
1b	169[b,f]	$C_{17}H_{10}ClN_5O$	60.81 (60.45	3.00 2.89	20.86 20.99)	1690	9.20	7.13—8.19 (9H)	
1c	163[c,f]	$C_{17}H_{10}ClN_5O$	60.81 (60.59	3.00 3.01	20.86 20.70)	1690	9.20	7.15—8.25 (9H)	
1d	172[a,f]	$C_{18}H_{13}N_5O_2$	65.25 (65.25	3.96 3.85	21.14 21.24)	1640	9.22	6.81—8.22 (9H)	3.81
1e	144[a,f]	$C_{18}H_{13}N_5O_2$	65.25 (64.96	3.96 3.96	21.14 21.11)	1675	9.13	6.75—8.24 (9H)	3.35
1f	135[a,f]	$C_{18}H_{13}N_5O$	68.56 (68.29	4.16 4.20	22.21 22.30)	1680	9.19	7.01—8.18 (9H)	2.40
1g	139[a,f]	$C_{18}H_{13}N_5O$	68.56 (68.77	4.16 4.19	22.21 21.93)	1680	9.17	7.05—8.20 (9H)	2.62
3b	203[d,e]	$C_{16}H_{10}ClN_5$	62.45 (62.39	3.27 3.25	22.76 22.86)		9.08	7.40—8.90 (9H)	
3c	101[d,e]	$C_{16}H_{10}ClN_5$	62.45 (62.66	3.27 3.23	22.76 22.79)		9.16	7.02—8.22 (9H)	
3d	181[d,e]	$C_{17}H_{13}N_5O$	67.31 (67.25	4.32 4.28	23.09 23.03)		9.02	6.93—8.26 (9H)	3.87
3e	140[d,e]	$C_{17}H_{13}N_5O$	67.31 (67.52	4.32 4.30	23.09 23.05)		9.16	7.00—8.26 (9H)	3.88
3f	154[d,e]	$C_{17}H_{13}N_5$	71.06 (71.22	4.56 4.53	24.38 24.13)		8.99	7.14—8.78 (9H)	2.40
3g	117[d,e]	$C_{17}H_{13}N_5$	71.06 (70.97	4.56 4.41	24.38 24.35)		9.17	7.16—8.28 (9H)	2.54

a) Pale yellow needles. *b*) Pale yellow powder. *c*) Yellow powder. *d*) Colorless needles. *e*) Recrystn. from benzene–petr. ether. *f*) Recrystn. from MeOH.

corresponding carboxylic acids (**2a**, **b**) were not isolated, and 7-phenyl- (**3a**)[9] and 7-(*p*-chlorophenyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3b**) were obtained in 24 and 45% yields, respectively. It is assumed that the first step in the reaction is the formation of the carboxylic acids (**2**), which could not be isolated due to their high susceptibility to decarboxylation. Subsequent oxidation of **2** presumably yields **3**. In fact, the carboxylic acid (**2d**) was easily convertible to **3d** in good yield by potassium ferricyanide oxidation or by recrystallization from methanol.



	Ar	3	yield (%)	2	yield (%)
1a	C_6H_5	**3a**	24	**2a**	—
1b	C_6H_4–Cl (*p*)	**3b**	45	**2b**	—
1d	C_6H_4–OMe (*p*)	**3d**	6	**2d**	59

Chart 3

When the reaction mixture obtained after stirring **1** with sodium hydroxide in DMSO was directly subjected to potassium ferricyanide oxidation, the compounds (**1**) were converted into the corresponding 7-aryl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3**) in good yields, as shown in Chart 4.

1 —(1) NaOH–DMSO; (2) $K_3Fe(CN)_6$)→ **3**

	Ar		yield (%)
1a	C_6H_5	**3a**	95
1b	C_6H_4–Cl (*p*)	**3b**	93
1c	C_6H_4–Cl (*o*)	**3c**	90
1d	C_6H_4–OMe (*p*)	**3d**	66
1e	C_6H_4–OMe (*o*)	**3e**	86
1f	C_6H_4–Me (*p*)	**3f**	77
1g	C_6H_4–Me (*o*)	**3g**	49

Chart 4

Based on the results obtained by the above one-step preparation method for **3**, it appears that the yield of **3** may reflect the yield of the carboxylic acid (**2**).

Compound **3a** showed undepressed melting point on admixture with an authentic sample[9] prepared by Grignard reaction of 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**6**)[10] with phenylmagnesium bromide, followed by potassium ferricyanide oxidation. The structures of **3b**—**g** were supported by their elemental analyses, and confirmed by analysis of the ^{1}H-NMR spectral data, as shown in Table I.

It was reported that the mechanism of the aryl migration of I to II is a type of benzilic acid rearrangement.[2] A similar mechanism could also be applicable to the aryl migration of **1** to **2**, as shown in Chart 5.

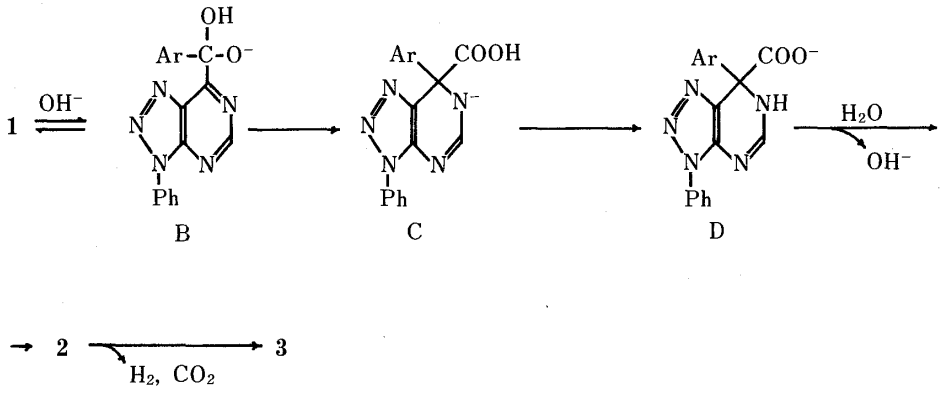


Chart 5

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco IRA-1 grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24 high-resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet and m = multiplet.

Preparation of 7-Aroyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (1)——A mixture of 1 mmol of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**), 1.5 mmol of an aromatic aldehyde (**5**), and 0.2 mmol of 1,3-dimethylbenzimidazolium iodide in the presence of 100 mg of 50% NaH (in oil) in 5 ml of THF was refluxed for 30 min. The reaction mixture was poured into an excess of ice-H_2O, neutralized with AcOH, and extracted with

$CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave **1**, which was purified by recrystallization from the appropriate solvent shown in Table I. The yields are shown in Chart 2, and the melting points, elemental analysis, and spectral data in Table I.

Reaction of 1d with NaOH——A mixture of 1 mmol (331 mg) of **1d** and 1 ml of 50% NaOH in 10 ml of DMSO was stirred for 5 min. The reaction mixture was poured into an excess of ice-H_2O, neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 10% NaOH. The $CHCl_3$ layer was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave **3d**, which was recrystallized from petr. ether–benzene to give colorless needles, mp 181 °C, in 6% yield (18 mg). The spectral and elemental analysis data are shown in Table I.

The NaOH layer was neutralized with AcOH to separate **2d**, mp 105 °C, as a colorless powder in 59% yield (211 mg). *Anal.* Calcd for $C_{18}H_{15}N_5O_3 \cdot 1/2H_2O$: C, 60.33; H, 4.50; N, 19.54. Found: C, 59.94; H, 4.14; N, 20.01. IR ν_{max}^{KBr} cm^{-1}: 2800—3600 (NH and OH), 1700 (C=O). ^{1}H-NMR (DMSO-d_6): 7.00—8.47 (13H, m, aromatic H, OH, and NH), 3.88 (3H, s, OCH_3).

Reaction of 1a with NaOH——Compound **3a**, mp 128 °C, was obtained in 24% yield (33 mg) from the reaction of 0.5 mmol (150 mg) of **1a** with 0.5 ml of 50% NaOH in 10 ml of DMSO in essentially the same manner as described for the reaction of **1d** with NaOH.

A mixture melting point test of **3a** with an authentic sample[9] prepared by another route showed no depression.

Reaction of 1b with NaOH——Compound **3b**, mp 203 °C from benzene–petr. ether, was obtained in 45% yield (69 mg) from the reaction of 0.5 mmol (168 mg) of **1b** with 0.5 ml of 50% NaOH in 10 ml of DMSO in essentially the same manner as described for the reaction of **1d** with NaOH. The spectral and elemental analysis data are shown in Table I.

Oxidation of 2d with $K_3Fe(CN)_6$——A mixture of 0.42 mmol (150 mg) of **2d**, 1.6 g of $K_3Fe(CN)_6$, and 1 ml of 33% KOH in 10 ml of H_2O was vigorously shaken for 30 min. The reaction mixture was extracted with benzene. The benzene extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave **3d** in 61% yield (78 mg).

Reaction of 1 with NaOH Being Added with $K_3Fe(CN)_6$——A mixture of 0.5 mmol of **1** and 0.5 ml of 50% NaOH in 5 ml of DMSO was stirred for 5 min. A solution of 1.6 g of $K_3Fe(CN)_6$ and 1 ml of 33% KOH dissolved in 15 ml of H_2O was added to the above reaction mixture, and the whole was vigorously shaken for 30 min. The reaction mixture was extracted with benzene. The benzene extract was dried over Na_2SO_4, and passed through a column of Al_2O_3 to remove impurities. Recrystallization from petr. ether–benzene afforded **3** in good yield, as shown in Chart 4. The melting points, elemental analyses and spectral data are shown in Table I.

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References and Notes

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