SEVERAL APPROACHES TO CYANIDE ION-CATALYZED SYNTHESIS OF 4-AROYL-1-PHENYL-1*H*-PYRAZOLO[3,4-*d*]PYRIMIDINES

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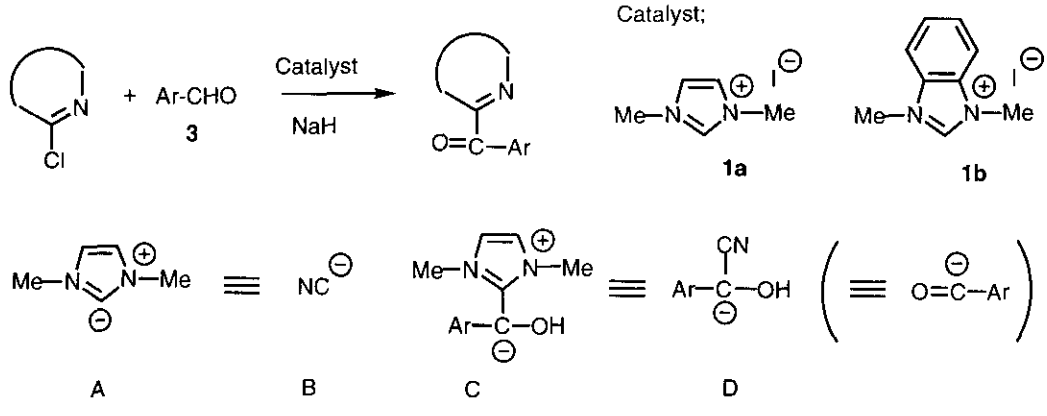
Abstract — 4-Aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**5**) were formed in low yields by reaction of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**4**) with arenecarbaldehydes (**3**) in the presence of potassium cyanide. Similar reaction of 4-tosyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**9**) with **3** gave the ketones (**5**) in higher yields (60–74%). In the presence of catalytic amounts of both sodium *p*-toluenesulfinate (**10**) and potassium cyanide, the reaction of **4** with **3** gave the ketones (**5**) in good yields.

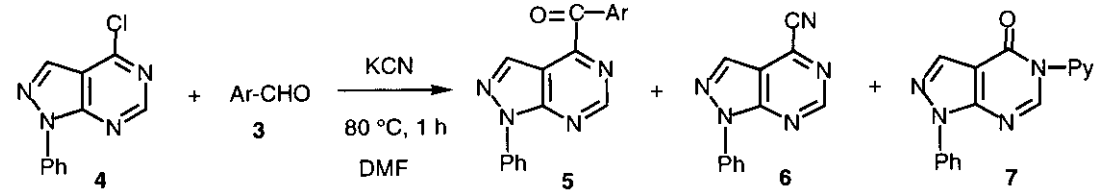
In the preceding papers, we have shown that aroylheteroarenes, such as aroylquinazolines and aroylpyrazolopyrimidines, can be easily synthesized by nucleophilic aroylation using arenecarbaldehydes.[1] Azolium salts, the 1,3-dimethylimidazolium salt (**1a**) and the 1,3-dimethylbenzimidazolium iodide (**1b**), are effective catalysts in this aroylation. We have further shown that this aroylation proceeds through the formation

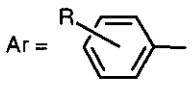


Scheme 1

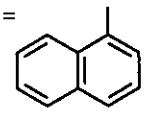
of the key intermediate (C).[1,2] Based on the chemical similarity between azolium ylide (A) and cyanide ion (B),[3] the intermediate (C) can be regarded as an equivalent of mandelonitrile anion (D).[4] In the benzoin condensation, catalysis by cyanide ion and azolium ylide involves the formation of the corresponding key intermediates (C and D).[2,4] We therefore speculated that cyanide ion might be employed instead of azolium ylide as a catalyst for the nucleophilic aroylation. In this paper, we wish to describe the results of several approaches to the synthesis of 4-aroylpyrazolopyrimidines catalyzed by cyanide ion.

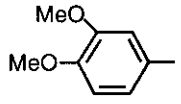
As shown in Scheme 2, in the presence of potassium cyanide, the treatment of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**4**)[6] with arenecarbaldehydes (**3**) having various substituents, including fluoro, chloro, bromo, methyl, and methoxy groups, in DMF resulted in the formation of the corresponding 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (method A).[1a,5] However, the yields were low because of the formation of by-products, *i. e.*, 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**6**)[7] and 1,5-dihydro-5-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-phenypyrazolo[3,4-*d*]pyrimidin-4-one (**7**). The chloro compound (**4**) was presumably hydrolyzed to 1,5-dihydro-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one by contaminating H_2O, and further reaction furnished **7**. Thus, it is clear that the cyanide ion does behave as a catalyst in the nucleophilic aroylation, but the catalytic activity is low in comparison with the activity of





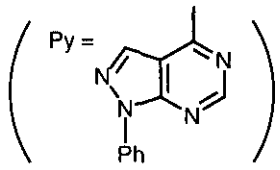
a : R = *o*-F, **b**: R = *p*-F, **c**: R = *p*-Cl, **d**: R = *p*-Br,
e: R = H, **f**: R = *o*-Me, **g**: R = *m*-Me, **h**: R = *p*-Me,
i: R = *o*-OMe, **j**: R = *m*-OMe, **k**: R = *p*-OMe,
l: R = *p*-CN, **m**: R = *p*-NO_2, **n**: R = *p*-N(Me)$_2$

o: Ar = 

p: Ar = 

q: Ar = 

r: Ar = 

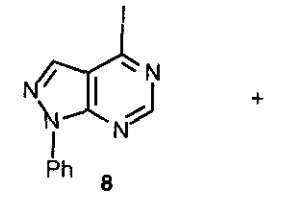


Aldehyde	Products; Yield (%) Ketone (**5**)	**5**	**6** (**7**)
3a	**5a**	22	10 (6)
3b	**5b**	33	5 (23)
3c	**5c**	21	8 (9)
3d	**5d**	29	12 (11)
3e	**5e**	25	8 (13)
3f	**5f**	29	16 (6)
3g	**5g**	18	22 (18)
3h	**5h**	24	12 (13)
3i	**5i**	24	– (32)
3j	**5j**	29	– (21)
3k	**5k**	35	2 (31)
3l	**5l**	2	10 (22)
3m	**5m**	–	12 (47)
3n	**5n**	–	51 (12)
3o	**5o**	55	– (–)
3p	**5p**	14	24 (7)
3q	**5q**	41	– (8)
3r	**5r**	30	3 (15)

Scheme 2

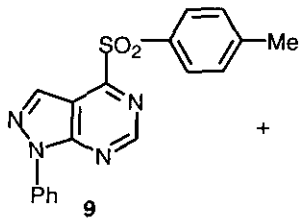
azolium ylide.

In an attempt to improve the cyanide ion–catalyzed aroylation, we used pyrazolopyrimidine having an iodo or a tosyl group at the 4-position as the leaving group. The aroylation results with iodopyrazolopyrimidine (**8**) were little different from those with **4**. We have previously shown that the tosyl group is a more effective leaving group than the chloro group,[8] and 4-tosylpyrazolopyrimidine (**9**) reacted with arenecarbaldehydes (**3**) in the



+ Ar-CHO (**3**) —KCN, 80 °C, 1 h, DMF→ **5**

Aldehyde	Ketone (**5**) Yield (%)	
3e	**5e**	26
3k	**5k**	46

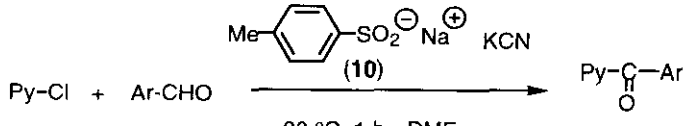


+ Ar-CHO (**3**) —KCN, 80 °C, 1 h, DMF→ **5**

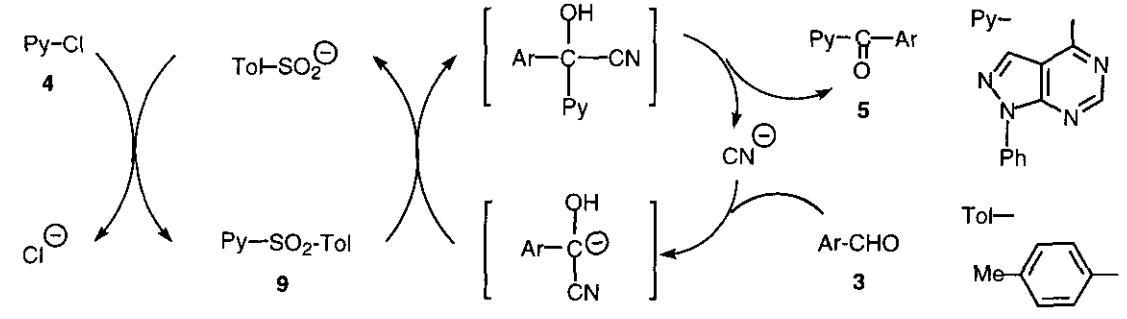
Aldehyde	Ketone (**5**) Yield (%)	
3b	**5b**	62
3e	**5e**	74
3k	**5k**	60

Scheme 3

presence of potassium cyanide to give the ketones (**5**) in higher yields (Scheme 3). We therefore decided to try sodium *p*-toluenesulfinate (**10**) as a catalyst. We have already reported that sodium *p*-toluenesulfinate (**10**) can be employed as an effective catalyst for preparing heteroarenecarbonitriles.[9] In the presence of catalytic amounts of both sodium *p*-toluenesulfinate (**10**) and potassium cyanide, a mixture of chloropyrazolopyrimidine



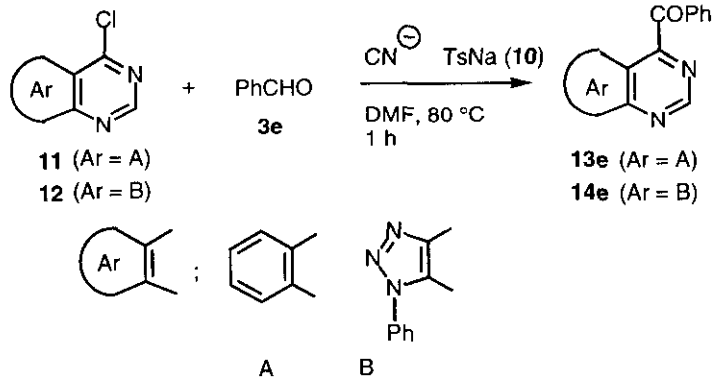
Aldehyde	Ketone (**5**) Yield (%)	
3b	**5b**	65
3c	**5c**	63
3e	**5e**	72
3k	**5k**	65



Scheme 4

(**4**) and benzaldehyde (**3e**) afforded benzoylpyrazolopyrimidine (**5e**) in 72% yield (method B). A similar catalytic effect of sodium *p*-toluenesulfinate (**10**) was observed in the reactions with **3b**, **3c** and **3k**. Namely, in the cases of **3b**, **3c**, and **3k**, the aroylpyrazolopyrimidines (**5b**, **5c**, and **5k**) were formed in moderate to good yields. This aroylation may proceed through the formation of the tosylpyrazolopyrimidine (**9**) as shown in Scheme 4.

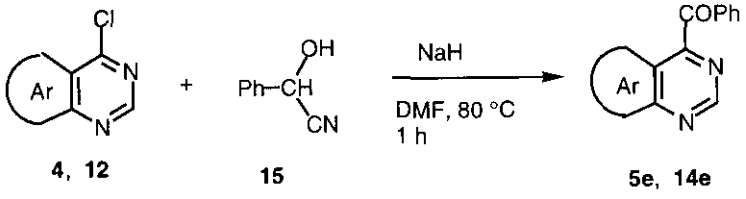
Thus, we have established an effective procedure (method B) by utilization of the catalytic action of sodium *p*-toluenesulfinate (**10**) together with potassium cyanide. This method is also applicable to other aroylheteroarenes. 4-Benzoylquinazoline (**13e**) and 7-benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**14e**) were synthesized by this method in good yields (Scheme 5).



Compd	Ketone Yield (%)	
11	**13e**	73
12	**14e**	77

Scheme 5

Reported results indicate that the aroylation catalyzed by cyanide ion proceeds through the formation of the mandelonitrile anion (D). [1,4] However, when we examined the aroylation of chloropyrazolopyrimidine (**4**) or chlorotriazolopyrimidine (**12**) with mandelonitrile (**15**), the yields were low, being similar to those obtained with cyanide ion alone. It is assumed that this is due to the low nucleophilic activity of the mandelonitrile anion (D) (Scheme 6).



Compd	Ketone Yield (%)	
4	**5e**	22
12	**14e**	18

Scheme 6

In conclusion, based on our idea that the chemical behavior of cyanide ion is similar to that of azolium ylide, we have shown that cyanide ion can catalyze the formation of aroylpyrazolopyrimidines, like azolium ylide.

Synthesis of 4-aroylpyrazolopyrimidines (**5**) with potassium cyanide alone as a catalyst afforded low yields (method A), but we developed a modified method using both sodium *p*-toluenesulfinate (**10**) and potassium cyanide, as catalysts (method B), and obtained the aroylated products in moderate to good yields.

EXPERIMENTAL

All melting points were measured without correction. The structures of the products obtained in this paper were supported by comparison of spectral data and melting points with those of authentic samples.

Reaction of 4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (4) with Arenecarbaldehyde (3) in the Presence of Potassium Cyanide (Method A); General Procedure. Potassium cyanide (KCN, 293 mg, 4.5 mmol) was added to a solution of chloropyrazolopyrimidine (**4**, 692 mg, 3.0 mmol) and an arenecarbaldehyde (**3**, 4.5 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was dissolved in a small portion of benzene, and the insoluble material was collected by filtration, affording 1,5-dihydro-5-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one (**7**). The filtrate was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The first fraction eluted with benzene gave 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**6**). The fraction eluted with $CHCl_3$ gave 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5**).

1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**6**): Colorless needles (benzene), mp 190–190.5 °C (lit.,[7] 190–190.5 °C).

1,5-Dihydro-5-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one (**7**): Colorless powder (MeOH), mp 284–285 °C. *Anal.* Calcd for $C_{22}H_{14}N_8O$: C, 65.02; H, 3.47; N, 27.57. Found: C, 64.86; H, 3.51; N, 27.47. IR (KBr) cm^{-1}: 1730 (CO). The compound (**7**) could be synthesized as following; Sodium hydride (60% in oil, 100 mg, 2.5 mmol) was added to a solution of 1,5-dihydro-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one (424 mg, 2.0 mmol) and chloropyrazolopyrimidine (**4**, 461 mg, 2.0 mmol) in DMF (20 mL), and the mixture was stirred at rt for 2 h. The reaction mixture was poured into H_2O, and separated crystalline was collected, washed with MeOH then $CHCl_3$ and dried to give **7** in 79% yield (638 mg) as colorless powder. The structures of 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**5**) obtained were confirmed by comparison of the spectral data and melting points with those of authentic samples.[1a] The results are summarized in Scheme 1.

Synthesis of 4-Iodo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (8). Hydroiodic acid (57%, 0.5 mL, *ca.*

2.2 mmol) was added to a mixture of 4-chloropyrazolopyrimidine (**4**, 692 mg, 3.0 mmol) and NaI (900 mg, 6.0 mmol) in 2-butanone (30 mL), and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated, poured into H_2O, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on Al_2O_3 with $CHCl_3$. The fraction gave 4-iodo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8**) in 95% yield (918 mg). Colorless scales (petroleum benzin), mp 159–161 °C. *Anal.* Calcd for $C_{11}H_7N_4I$: C, 41.02; H, 2.19; N, 17.39. Found: C, 40.76; H, 2.22; N, 17.47. ^{1}H-NMR ($CDCl_3$) δ: 8.58 (1H, s, C^6–H), 7.94 (1H, s, C^3–H), 8.21–7.90 (2H, m, Ph), 7.60–7.14 (3H, m, Ph).

Reaction of 4-Iodo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (8) with Arenecarbaldehyde (3) in the Presence of Potassium Cyanide; General Procedure. Potassium cyanide (293 mg, 4.5 mmol) was added to a solution of 4-iodopyrazolopyrimidine (**8**, 966 mg, 3.0 mmol) and an arenecarbaldehyde (**3**, 4.5 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4 , and concentrated. The residue was dissolved in a small portion of benzene, and the insoluble material was collected by filtration, affording 1,5-dihydro-5-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**7**). The filtrate was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5**).
In the case of the aroylation with **3e**, a 22% yield (131 mg) of **7** was obtained. In the case of the aroylation with **5k**, the yield of **7** was 22% (136 mg). These results are shown in Scheme 3.

Reaction of 4-Tosyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (9) with Arenecarbaldehyde (3) in the Presence of Potassium Cyanide; General Procedure. Potassium cyanide (293 mg, 4.5 mmol) was added to a solution of 4-tosylpyrazolopyrimidine (**9**, 1146 mg, 3.0 mmol) and an arenecarbaldehyde (**3**, 4.5 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5**). These results are shown in Scheme 3.

Reaction of 4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (4) with Arenecarbaldehyde (3) in the Presence of Potassium Cyanide and Sodium *p*-Toluenesulfinate (Method B); General Procedure. Potassium cyanide (293 mg, 4.5 mmol) was added to a solution of chloropyrazolopyrimidine (**4**, 692 mg, 3.0 mmol), an arenecarbaldehyde (**3**, 4.5 mmol), and sodium *p*-toluenesulfinate (**10**, 178 mg, 1.0 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and

extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5**). These results are shown in Scheme 4.

Synthesis of 4-Benzoylquinazoline (Method B). Potassium cyanide (293 mg, 4.5 mmol) was added to a solution of 4-chloroquinazoline (**8**, 494 mg, 3.0 mmol), benzaldehyde (**3e**, 477 mg, 4.5 mmol) and sodium *p*-toluenesulfinate (**10**, 178 mg, 1.0 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-benzoylquinazoline (**13e**) in 73% yield (513 mg). Colorless needles (MeOH), mp 98–99 °C (lit.,[5] 97–98 °C).

Synthesis of 7-Benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (Method B). Potassium cyanide (293 mg, 4.5 mmol) was added to a solution of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**9**, 695 mg, 3.0 mmol), benzaldehyde (**3e**, 477 mg, 4.5 mmol) and sodium *p*-toluenesulfinate (**10**, 178 mg, 1.0 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 7-benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**14e**) in 77% yield (695 mg). Pale yellow needles (benzene–petroleum benzin), mp 145–145.5 °C (lit.,[11] 141 °C).

Reaction of 4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (4) with Mandelonitrile (15) in the Presence of NaH. Sodium hydride (60% in oil, 100 mg, 2.5 mmol) was added to a solution of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**4**, 460 mg, 2.0 mmol) and mandelonitrile (**15**, 266 mg, 2.0 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-benzoyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5e**) in 22% yield (132 mg). The structure was confirmed by comparison of the spectral data and the melting point with those of authentic sample.[1a]

Reaction of 7-Chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (12) with Mandelonitrile (15) in the Presence of NaH. Sodium hydride (60% in oil, 100 mg, 2.5 mmol) was added to a solution of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**12**, 462 mg, 2.0 mmol) and mandelonitrile (**15**, 266 mg, 2.0 mmol) in DMF (20 mL), and the mixture was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-

H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 7-benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**14e**) in 18% yield (108 mg). The structure was confirmed by comparison of the spectral data and the melting point with those of authentic sample.[11]

REFERENCES

1. (*a*) A. Miyashita, H. Matsuda, C. Iijima, and T. Higashino, *Chem. Pharm. Bull.*, 1990, **38**, 1147; (*b*) A. Miyashita, H. Matsuda, C. Iijima, and T. Higashino, *Chem. Pharm. Bull.*, 1992, **40**, 43; (*c*) A. Miyashita, H. Matsuda, and T. Higashino, *Chem. Pharm. Bull.*, 1992, **40**, 2627; (*d*) A. Miyashita, H. Matsuda, Y. Suzuki, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*, 1994, **42**, 2017; (*e*) A. Miyashita, H. Matsuda, Y. Suzuki, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*,1994, **42**, 2633.
2. (*a*) A. Miyashita, Y. Suzuki, M. Kobayashi, N. Kuriyama, and T. Higashino, *Heterocycles*, 1996, **43**, 509; (*b*) A. Miyashita, A. Kurachi, Y. Matsuoka, N. Tanabe, Y. Suzuki, K. Iwamoto, and T. Higashino *Heterocycles*, 1997, **44**, 417.
3. (*a*) A. Miyashita, Y. Matsuoka, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*, 1994, **42**, 1960; (*b*) A. Miyashita, Y. Suzuki, Y. Okumura, and T. Higashino, *Chem. Pharm. Bull.*, 1996, **44**, 252.
4. (*a*) A. Lapworth, *J. Chem. Soc.*, 1903, **83**, 995 ; (*b*) T. Ugai, T. Tanaka, and S. Dokawa, *Yakugaku Zasshi*, 1943, **63**, 296; (*c*) W. S. Ide and J. S. Buck, *Org. React.*, 1948, **4**, 269; (*d*) R. Breslow, *Chem. Ind.* (London), **1957**, 893; (*e*) R. Breslow and Macnelis, *J. Am. Chem. Soc.*,1959, **81**, 3080; (*f*) J. P. Kuebrich, R. L. Schowen, M. Wang, and M. E. Lupes, *J. Am. Chem. Soc.*, 1971, **93**, 1214.
5. T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.*, 1974, **22**, 2493.
6. C. C. Cheng and R. K. Robins, *J. Org. Chem.*, 1958, **23**, 191.
7. E. Hayashi, T. Higashino, and S. Suzuki, *Yakugaku Zasshi*, 1978, **98**, 89.
8. E. Hayashi, N. Shimada, and A. Miyashita, *Yakugaku Zasshi*, 1976, **96**, 1370.
9. A. Miyashita, Y. Suzuki, K. Ohta, and T. Higashino, *Heterocycles*, 1994, **39**, 345.
10. (*a*) G. Simchen and H. Kobler, *Synthesis*, **1975**, 605; (*b*) J. Casstells and E. Dunach, *Chem. Lett.*, **1984**, 1859.
11. T. Higashino, M. Takemoto, A. Miyashita, and E. Hayashi, *Chem. Pharm. Bull.*, 1985, **33**, 1395.

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