A Novel Practical Synthesis of *C*-2-Arylpurines

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Received: June 2, 2004; Accepted: August 30, 2004

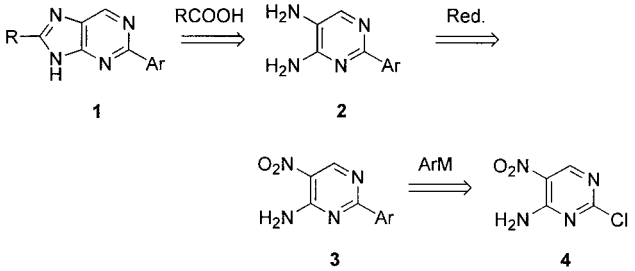
Abstract: Suzuki–Miyaura cross-coupling of halopurines with arylboronic acids would be one of the most efficient methods to synthesize *C*-2-arylpurines. However, as this approach implied some potential disadvantages, we needed to devise a more efficient process. Starting with 4-amino-2-chloro-5-nitropyrimidine, readily prepared from 5-nitrouracil, seemed to potentially obviate our concerns, and the applicability of the Suzuki–Miyaura coupling was examined in detail. Considerable competitive hydrolysis occurred simultaneously with the desired reaction under the aqueous conditions typically employed in the Suzuki–Miyaura protocol. Excellent yields were obtained with 1,1′-bis(di-*tert*-butylphosphino)ferrocene (=D-t-BPF) under anhydrous conditions. Tolerance of various arylboronic acids was also found. Subsequent reduction with H_2/Pd-C of one of the coupling adducts, 4-amino-5-nitro-2-phenylpyrimidine, gave the diamine, which was further condensed with activated acid derivatives to afford a wide variety of the 2-phenylpurine derivatives in excellent yields.

Keywords: P ligands; metallocenes; palladium; purine; pyrimidine; Suzuki–Miyaura cross-coupling

Introduction

In recent years, there has been interest in the synthesis of purine derivatives including nucleoside and nucleotide analogues due to the broad range of discovered biologically active compounds.[1] Purines bearing carbon substituents at the ring carbons have attracted much attention due to their potential biological activities. In particular, *C*-2-arylpurine derivatives are becoming especially important for drug discovery programs such as those towards anxiolytic agents[2] and interferon inducers,[3] potent/selective *c*-AMP phosphodiesterase inhibitors,[4] angiotensin II antagonists,[5], β-AST-IV inhibitors,[6] A_1 adenosine receptor antagonists,[7] or ADA (adenosine deaminase) inhibitors.[8] Despite their importance, synthetic efforts have not been sufficiently directed to the identification of synthetic pathways to provide ready access to these compounds.

There are relatively few methods available to produce *C*-2-arylpurine derivatives. Classical approaches for this involve ring construction by condensation of two components that needs the preparation of specific intermediates.[9] A simpler and more efficient approach would be the direct arylation of purine derivatives.[10–12] In recent research, the Pd-catalyzed cross-coupling of halopurines has been demonstrated to be among the most promising methods.[13,14] Of these methods, the Suzuki–Miyaura cross-coupling reaction[15] appears to be practically superior.[16,17] However, this approach implies some potential synthetic difficulties: (i) cross-coupling with chloropurine is not precedented and potentially requires specific conditions; (ii) less active aryl organometallics such as phenylboronic acids with electron-withdrawing groups are potentially hard to react; (iii) it is not readily applicable to analogues at C-8; (iv) in those cases where the R group is precious, the coupling reaction preferably should be implemented prior to introduction of R group. In this context, 4-amino-2-chloro-5-nitropyrimidine (**4**) is thought to be the most likely candidate for the introduction of an aryl group due to the presence of the nitro group. In addition, it potentially tolerates simple organometallics such as Grignard reagents. The nitro group acts not only as an activator but also as an amine equivalent. The putative diamine generally would react with a wide variety of carboxylic acids to afford the desired products in high yield (Scheme 1). In conjunction with development of our drug candidate, we required an efficient synthesis of 2-



Scheme 1.

 DOI: 10.1002/adsc.200404159

aryl-8-substituted purines, and this task also seemed to be quite challenging. Therefore, our efforts have been focused on the development of an efficient synthesis of 8-substituted analogues. Herein we report a novel and practical synthesis of 2-phenylpurines and 2-phenyl-8-substituted purines.

Results and Discussion

It has been reported that 4-amino-2-chloro-5-nitropyrimidine (**4**) was readily prepared from 5-nitrouracil.[18,19] We first tried reaction of **4** with simple aryl organometallics such as aryllithium, aryl-Grignard or milder arylzinc reagents. Unfortunately the reactions with these reagents were not successful, and resulted in only complex mixtures containing small amounts of the desired product and the side product reacted at the C-6 position even when excess amounts of organometallic reagents were used. Our attention was therefore focused on the transition metal-catalyzed cross-coupling reaction, and the Suzuki–Miyaura coupling was doubtlessly chosen since it has been proven to practically offer distinctive advantages over other approaches to date. In addition, this approach would allow us to eliminate the protection of the amino group due to its inert nucleophilic nature.

Synthesis of 4-Amino-5-nitro-2-(4-fluorophenyl)pyrimidine

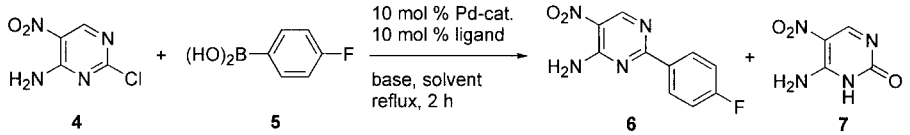
Suzuki–Miyaura Coupling under Aqueous Conditions

The typical Suzuki–Miyaura conditions we selected as a baseline reaction involved heating **4** and boronic acid with $Pd(PPh_3)_4$ or $Pd(OAc)_2$ in DME in the presence of aqueous Na_2CO_3.[15k] The relatively less reactive 4-fluorophenylboronic acid (**5**) was used as a coupling partner for the reaction. However, the reactions did not produce the desired product but rather gave the hydrolyzed product **7** predominantly under these conditions (Table 1, entries 1 and 2). Attempts to accelerate the desired reaction under aqueous condition met with failure (entries 3 and 4). When DPPF was used as the ligand, 43% of the desired product was obtained with 50% of pyrimidinone **7** (entry 5). Eventually, a variety of other palladium catalysts and ligands were screened for cross-coupling; however, the $Pd(OAc)_2$/DPPF system was proven to be the optimal among those examined. Solvents other than DME such as THF, DMF, DMSO, MeOH, EtOH, *i*-PrOH, toluene, CPME (cyclopentyl methyl ether) did not give any detectable amount of the desired product **6**. The optimal result was obtained by minimizing the amount of water (3 equivs.) giving 82% of the desired product **6** with 12% of the hydrolyzed product **7** (entry 6). $PdCl_2$(dppf) was also acceptable (entry 7). However, under anhydrous conditions (KF of DME is 13 ppm), the desired reaction did not proceed and almost all the starting material was recovered (entry 8). Since it would be difficult to eliminate the hydrolysis under aqueous condition, further investigation to accelerate the desired reaction *vs.* the hydrolysis was discontinued.

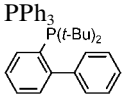
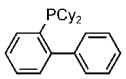
Suzuki–Miyaura Coupling under Anhydrous Conditions

We therefore turned our attention to the coupling reaction under anhydrous conditions. We attributed the fail-

Table 1. Suzuki–Miyaura coupling of **4** with **5** under aqueous conditions.

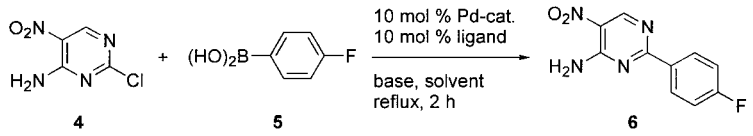


4 **5** **6** **7**

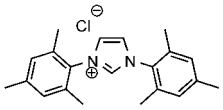
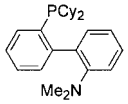
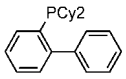
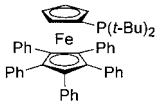
Entry	Pd Cat.	Ligand	Base	Solvent	Yield of **6**	Yield of **7**
1	$Pd(PPh_3)_4$	–	aq. Na_2CO_3	DME	ND	80%
2	$Pd(OAc)_2$	PPh_3	aq. Na_2CO_3	DME	~10%	65%
3	$Pd(OAc)_2$		aq. Na_2CO_3	DME	ND	80%
4	$Pd(OAc)_2$		aq. Na_2CO_3	DME	trace	73%
5	$Pd(OAc)_2$	DPPF	aq. Na_2CO_3	DME	43%	50%
6	$Pd(OAc)_2$	DPPF	anhyd. Na_2CO_3	DME[a]	82%	12%
7	$PdCl_2$(dppf)	none	anhyd. Na_2CO_3	DME[a]	65%	23%
8	$Pd(OAc)_2$	DPPF	anhyd. Na_2CO_3	DME[b]	trace	ND

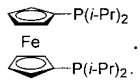
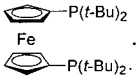
[a] With 3 equivs. of H_2O.
[b] KF = 13 ppm.

Table 2. Suzuki–Miyaura coupling of **4** with **5** under anhydrous conditions.



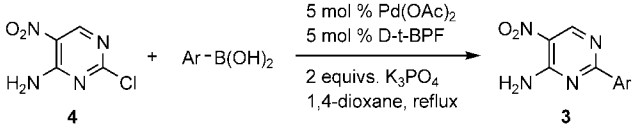
4 **5** **6**

Entry	Pd Cat.	Ligand	Base[a]	Solvent[b]	Yield
1	$Pd(OAc)_2$	DPPF	Na_2CO_3/TBAB	DME	trace
2	$Pd(OAc)_2$	DPPF	Et_3N	DME	ND
3	$Pd(OAc)_2$	DPPF	Cs_2CO_3	DME	ND
4	$Pd(OAc)_2$	BINAP	Cs_2CO_3	1,4-dioxane	ND
5	$Pd_2(dba)_3$		Cs_2CO_3	1,4-dioxane	ND
6	$Pd(OAc)_2$		K_3PO_4	1,4-dioxane	15%
7	$Pd(OAc)_2$		K_3PO_4	1,4-dioxane	trace
8	$Pd(OAc)_2$	P(*t*-Bu)$_3$	K_3PO_4	1,4-dioxane	trace
9	$Pd(OAc)_2$	DPPF	Na_2CO_3	1,4-dioxane	12%
10	$Pd(OAc)_2$	DPPF	K_2CO_3	1,4-dioxane	28%
11	$Pd(OAc)_2$	DPPF	K_3PO_4	1,4-dioxane	31%
12	$Pd(OAc)_2$	DPPE	K_3PO_4	1,4-dioxane	trace
13	$Pd(OAc)_2$	DPPP	K_3PO_4	1,4-dioxane	trace
14	$Pd(OAc)_2$	D-i-PrPF[c]	K_3PO_4	1,4-dioxane	76%
15	$Pd(OAc)_2$	D-t-BPF[d]	K_3PO_4	1,4-dioxane	93%
16	$Pd(OAc)_2$		K_3PO_4	1,4-dioxane	40%
17	$Pd(OAc)_2$	D-t-BPF[d]	K_2CO_3	1,4-dioxane	95%
18	$Pd(OAc)_2$	D-t-BPF[d]	K_2CO_3	2-MeTHF	95%

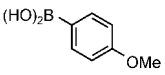
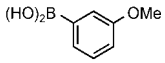
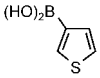
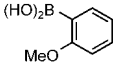
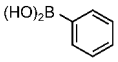
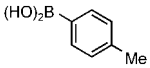
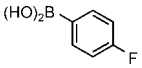
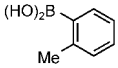
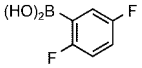
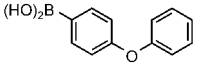
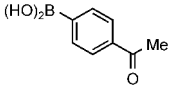
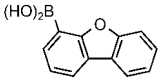
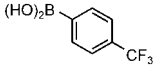
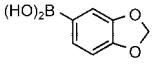
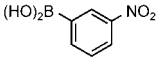
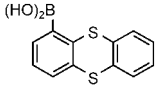
[a] Anhydrous inorganic base, dried organic base.
[b] KF < 50 ppm.
[c] D-i-PrPF:  .
[d] D-t-BPF:  .

ure to the insolubility of Na_2CO_3 in most of the organic solvents and so phase-transfer agents and amine bases were examined to promote the desired reaction. However, addition of tetrabutylammonium bromide (TBAB)[20] was not effective to enhance the rate of the coupling reaction (Table 2, entry 1). Triethylamine instead of Na_2CO_3 resulted in the addition of the diethylamino group (entry 2). The Hünig base, pyridine and Cs_2CO_3 (entry 3) did not give the desired product. The literature conditions[17d, e] did not give any product in good yield (entries 4–8). Solvent screening revealed that 1,4-dioxane was best with 12% yield (entry 9), and inorganic base[21] such as Na_2CO_3, K_2CO_3 and K_3PO_4 increased the yields in that order (entries 9–11). The bidentate phosphine, 1,2-bis(diphenylphosphino)-ethane (DPPE)[22] and 1,3-bis(diphenylphosphino)propane (DPPP)[23] were also inactive under anhydrous conditions (entries 12 and 13). In analogy with DPPF, the ferrocenyl phosphine ligand substituted with a bulky alkyl group, 1,1′-bis(diisopropylphosphino)ferrocene (D-i-PrPF)[24] improved the yield (entry 14). The more sterically hindered and electron-rich 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D-t-BPF)[25] was superior to all others tested. Even when 0.5 mol % $Pd(OAc)_2$ and 0.5 mol % D-t-BPF were employed, the reaction was completed in 93% yield within 16 h with no adduct of

Table 3. Synthesis of various arylated aminopyrimidines.



4 **3**

Entry	Arylboronic acid	Product	Yield	Entry	Arylboronic acid	Product	Yield
1		**3a**	88%	10		**3j**	92%
2		**3b**	80%	11		**3k**	82%
3		**3c**	0%	12		**3l**	90%
4		**3d**	90%	13		**6**	92%
5		**3e**	87%	14		**3m**	84%
6		**3f**	76%	15		**3n**	75%
7		**3 g**	78%	16		**3o**	85%
8		**3 h**	86%	17		**3p**	85%
9		**3i**	72%				

self-condensation at the amino group (entry 15). The bulky monodentate ferrocenyldialkylphosphine ligand di-*tert*-butylphosphino pentaphenylferrocene, CTC-Q-PHOS[26] gave a much decreased the yield (entry 16). K_3PO_4 was switched to K_2CO_3 since K_2CO_3 was found to be less sensitive over fluctuation of the particle size (entry 17). Finally, the best yield was obtained with 2-MeTHF[27] which was preferred due to the carcinogenecity of 1,4-dioxane (entries 17 and 18). When the reaction was run using D-t-BPF under aqueous conditions, 20% of the hydrolyzed product **7** was obtained together with 72% of the desired product **6**.

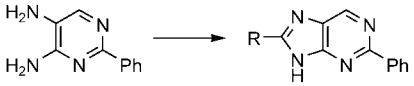
We next examined the tolerability of various arylboronic acids for our system under anhydrous conditions. The coupling of **4** with a wide variety of arylboronic acids is shown in Table 3. In our system, electron-rich arylboronic acids and/or more sterically hindered arylboronic acids reasonably resulted in good yields (entries 1, 2, 4–10). Exceptionally, the reaction with 2-methoxyphenylboronic acid did not occur (entry 3). This might be due to the tight coordination of both the oxygen in the aryl moiety and one of the nitrogens on the pyrimidine ring of the product to palladium, leading to termination of the catalytic cycle.[17d] Electronically neutral arylboronic acids were coupled with the substrate in high yields (entries 11 and 12). More importantly, even more electron-deficient boronic acids were well tolerated and gave fairly good yields (entries 13–17).

Finally, we examined synthesis of 2-phenylpurines possessing various substituents at the C-8 position. The Suzuki–Miyaura coupling adduct, 4-amino-5-nitro-2-phenylpyrimidines (**3l**), was readily reduced with Pd-C/H_2 to give corresponding 4,5-diamino-2-phenylpyrimidine (**8**)[28] in excellent yield. Diamine **8** was reacted with activated esters of carboxylic acids such as acid anhydrides, orthoformate, isothiocyanate, carbonyldiimidazole, xanthic acid to give a variety of 8-substituted 2-phenylpurines as depicted in Table 4. Orthoformate was reacted with **8** in toluene and DMF at 90 °C to afford the corresponding 2-phenylpurine (**9a**) in high yield (entry 1). 8-Phenyl- (**9b**),[29] 8-methyl- (**9c**),[19e] 8-phenylamino- (**9d**),[30] 8-hydroxy- (**9e**),[31] and 8-mercapto- (**9f**)[30] derivatives were easily prepared in good yields by the reported methods listed in Table 4 (entries 2–6).

Conclusion

We have developed a novel and efficient synthesis of 2-phenylpurine derivatives from 4-amino-2-chloro-5-ni-

Table 4. Synthesis of *C*-8 substituted purines from 4,5-diamino-2-phenylpyrimidine (**8**).



8 **9**

Entry	R	Conditions	Product	Yield
1	H	$(EtO)_3CH$, toluene/DMF, 90 °C	**9a**	92%
2	Ph	1) $(PhCO)_2$, pyridine, rt, 2) *t*-BuOK, IPA, 50 °C	**9b**	88%
3	Me	1) Ac_2O, pyridine, rt, 2) *t*-BuOK, IPA, 50 °C	**9c**	85%
4	PhNH	1) PhNCS, DMF, 2) MeI, DMF	**9d**	62%
5	OH	$(imidazolyl)_2CO$, THF, rt, 2 h	**9e**	82%
6	SH	$EtOCS_2K$, EtOH, reflux, 20 h	**9f**	87%

tropyrimidine (**4**) *via* the Suzuki–Miyaura reaction as key step. In general, the Suzuki–Miyaura reaction typically runs under aqueous conditions to generate a better reactivity than under anhydrous conditions. The reactive substrate **4**, which is readily hydrolyzed under aqueous conditions, was required for a break-through discovery under anhydrous conditions to obtain a satisfactory reactivity. Detailed studies allowed us to find specific conditions using D-t-BPF as ligand, which produced the desired product **6** in 95% yield even under anhydrous conditions without any protection of the amino group at C-2. Under the optimal conditions, the couplings with the electron-rich, sterically hindered, electronically neutral, and even in particular electron-deficient arylboronic acids proceeded in high yields. Hydrogenation of 4-amino-5-nitro-2-arylpyrimidines gave diamines, which were reacted with a variety of activated esters to afford the corresponding 2-phenyl-8-substituted purines in high yields. This novel approach would allow for the rapid construction of 2-phenyl- and 2-phenyl-8-substituted purines.

Experimental Section

$Pd(OAc)_2$ and D-t-BPF were purchased from Johnson Matthey. Anhydrous inorganic bases, K_3PO_4, K_2CO_3, Na_2CO_3 were purchased from Wako (40 ~ 70 μm particle size). Other reagents were purchased from either Tokyo Kasei, Wako, or Strem. All reagents were used as received. ^{1}H NMR confirmed that each boronic acid contained the boroxine (anhydrous boronic acid) to less than 30%. Organic solvents, purchased from Tokyo Kasei, were dried over 4 Å molecular sieves and degassed prior to use. CPME (cyclopentyl methyl ether) was purchased from ZEON Corporation. All reactions were performed under a dry nitrogen atmosphere in oven-dried glassware.

HPLC was performed on a Hitachi D-7000 instrument, with a YMC basic reverse-phase column. Thin-layer chromatography was performed on EM Science silica gel 60 plates with F-254 indicator (250 μm thickness). Visualization was accomplished by UV light or photomolybdic acid/ninhydrin solution. Column chromatography was performed with EM silica gel 60 (0.04 ~ 0.63 μm particle size). NMR data was acquired on a Bruker AV-500.

Representative Procedure for the Suzuki–Miyaura Cross-Coupling Reaction

To a round-bottomed flask were added chloropyrimidine **4** (1.0 g), the boronic acid (1.5 equivs.), K_3PO_4 (2.0 equivs.), dry 1,4-dioxane (30 mL) or 2-MeTHF (30 mL). The mixture was degassed by three vacuum/N_2 cycles. Catalyst $Pd(OAc)_2$ (5 mol %) and D-t-BPF (5 mol %) were added and the mixture was degassed twice more. The mixture was heated to reflux (~ 100 °C) for 4 h and HPLC confirmed the completion of the reaction. The mixture was cooled to ambient temperature then the slurry was filtered to remove salts. The filter cake was washed with *i*-PrOAc. The filtrate was concentrated under vacuum to *ca.* 30 mL. To the solution were added *i*-PrOAc and 1 N aqueous NaOH to remove residual boronic acid. The organic layer was separated, washed with fresh 1 N aqueous NaOH and 20% aqueous NaCl successively, and evaporated to dryness. The product was purified by column chromatography on silica gel or crystallization using appropriate solvents (listed under individual compound headings, *vide infra*).

4-Amino-5-nitro-2-(4-methoxyphenyl)pyrimidine (3a): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.57. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.17 (s, 1H, pyrimidine-H), 8.69 (s, 1H, NH_2), 8.35 (d, J = 8.8 Hz, 2H, Ar-H), 8.29 (s, 1H, NH_2), 7.09 (d, J = 8.8 Hz, 2H, Ar-H), 3.86 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.62, 162.95, 156.66, 156.17, 131.16, 128.58, 125.18, 114.45, 55.81; HRMS: calcd. for $C_{11}H_{11}N_4O_3$ (M^+ + H): 247.0831; found: 247.0836.

4-Amino-5-nitro-2-(3-methoxyphenyl)pyrimidine (3b): crystallization from *i*-PrOAc/*n*-heptane, colorless crystals. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.21 (s, 1H, pyrimidine-H), 8.79 (bs, 1H, NH_2), 8.35 (bs, 1H, NH_2), 7.98 (d, J = 7.7 Hz, 1H, Ar-H), 7.92 (dd, J = 1.1, 1.2 Hz, 1H, Ar-H), 7.46 (dd, J = 7.7, 8.1 Hz, 1H, Ar-H), 7.17 (d, J = 8.1 Hz, 1H, Ar-H), 3.84 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.60, 159.84, 156.68, 156.18, 137.68, 130.14, 125.79, 121.57, 118.31, 113.94, 55.61; HRMS: calcd. for $C_{11}H_{11}N_4O_3$ (M^+ + H): 247.0831; found: 247.0841.

4-Amino-5-nitro-2-(4-methylphenyl)pyrimidine (3d): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.19 (s, 1H, pyrimidine-

H), 8.74 (s, 1H, NH_2), 8.32 (s, 1H, NH_2), 8.28 (d, $J=8.2$ Hz, 2H, Ar-H), 7.35 (d, $J=8.3$ Hz, 2H, Ar-H), 2.39 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.89, 156.69, 156.19, 142.61, 133.52, 129.67, 129.19, 125.52, 21.47; HRMS: calcd. for $C_{11}H_{11}N_4O_2$ ($M^+ + H$): 231.0882; found: 231.0881.

4-Amino-5-nitro-2-(2-methylphenyl)pyrimidine (3e): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.66. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.32 (s, 1H, pyrimidine-H), 7.85 (d, $J=8.0$ Hz, 1H, Ar-H), 7.84 (bs, 1H, NH_2), 7.39 (d, $J=7.5$ Hz, 1H, Ar-H), 7.31 (d, $J=8.0$ Hz, 1H, Ar-H), 7.29 (d, $J=7.5$ Hz, 1H, Ar-H), 6.43 (bs, 1H, NH_2), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.99, 156.66, 155.83, 138.48, 136.72, 132.05, 131.15, 131.04, 126.38, 125.65, 21.81; HRMS: calcd. for $C_{11}H_{11}N_4O_2$ ($M^+ + H$): 231.0882 found: 231.0877.

4-Amino-5-nitro-2-(4-phenoxyphenyl)pyrimidine (3f): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.61. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.19 (s, 1H, pyrimidine-H), 8.76 (s, 1H, NH_2), 8.39 (d, $J=6.9$ Hz, 2H, Ar-H), 8.33 (s, 1H, NH_2), 7.47 (d, $J=7.5$ Hz, 2H, Ar-H), 7.24 (d, $J=7.4$ Hz, 1H, Ar-H), 7.15 (d, $J=7.6$ Hz, 2H, Ar-H), 7.11 (d, $J=6.9$ Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.84, 160.46, 156.24, 155.77, 155.21, 130.92, 130.41, 130.21, 124.99, 124.45, 119.74, 117.45; HRMS: calcd. for $C_{16}H_{13}N_4O_3$ ($M^+ + H$): 309.0988; found: 309.1009.

4-Amino-5-nitro-2-(4-dibenzofuran)pyrimidine (3g): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.73. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.34 (s, 1H, pyrimidine-H), 8.88 (s, 1H, NH_2), 8.41 (s, 1H, NH_2), 8.39 (d, $J=7.5$ Hz, 1H, Ar-H), 8.31 (d, $J=7.7$ Hz, 1H, Ar-H), 8.23 (d, $J=7.7$ Hz, 1H, Ar-H), 7.78 (d, $J=8.0$ Hz, 1H, Ar-H), 7.59 (dd, $J=7.5$, 8.0 Hz, 1H, Ar-H), 7.57 (d, $J=7.7$ Hz, 1H, Ar-H), 7.46 (d, $J=7.5$ Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.31, 156.68, 156.09, 154.18, 129.49, 128.41, 125.75, 125.60, 124.83, 123.71, 123.34, 123.30, 122.32, 121.60, 112.19; HRMS: calcd. for $C_{16}H_{11}N_4O_3$ ($M^+ + H$): 307.0831; found: 307.0826.

4-Amino-5-nitro-2-[(3,4-methylenedioxy)phenyl]pyrimidine (3 h): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.68. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.16 (s, 1H, pyrimidine-H), 8.70 (s, 1H, NH_2), 8.30 (s, 1H, NH_2), 8.03 (dd, $J=1.6$, 8.3 Hz, 1H, Ar-H), 7.81 (d, $J=1.6$ Hz, 1H, Ar-H), 7.07 (d, $J=8.3$ Hz, 1H, Ar-H), 6.14 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.20, 156.59, 156.13, 151.17, 148.18, 130.38, 125.29, 124.86, 108.74, 108.48, 102.27; HRMS: calcd. for $C_{11}H_9N_4O_4$ ($M^+ + H$): 261.0624; found, 261.0640.

4-Amino-5-nitro-2-(1-thianthrene)pyrimidine (3i): Crystallization from *i*-PrOAc/*n*-heptane, yellow crystals, R_f (50% EtOAc in *n*-heptane) = 0.70. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.27 (s, 1H, pyrimidine-H), 8.96 (s, 1H, NH_2), 8.46 (s, 1H, NH_2), 7.88 (dd, $J=7.6$, 7.7 Hz, 1H, Ar-H), 7.75 (d, $J=7.8$ Hz, 1H, Ar-H), 7.58 (dd, $J=7.7$, 7.8 Hz, 1H, Ar-H), 7.46 (dd, $J=7.6$, 7.7 Hz, 2H, Ar-H), 7.34 (d, $J=7.6$ Hz, 1H, Ar-H), 7.29 (dd, $J=7.6$ Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.87, 156.19, 155.50, 138.38, 137.62, 135.98, 135.63, 134.41, 131.71, 130.03, 129.06, 128.93, 128.72, 128.49, 127.54, 125.62; HRMS: calcd. for $C_{16}H_{11}N_4O_2S_2$ ($M^+ + H$): 355.0323; found: 355.0303.

4-Amino-5-nitro-2-(1-naphthalene)pyrimidine (3j): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.25. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.41 (s, 1H, pyrimidine-H), 8.68 (d, $J=8.6$ Hz, 1H, Ar-H), 8.13 (dd, $J=1.0$, 7.2 Hz, 1H, Ar-H), 8.01 (d, $J=8.2$ Hz, 1H, Ar-H), 7.92 (d, $J=7.5$ Hz, Ar-H), 7.91 (s, 1H, NH_2), 7.59–7.52 (m, 3H, Ar-H), 6.37 (s, 1H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.14, 156.41, 155.66, 134.09, 134.04, 132.11, 130.80, 130.24, 128.73, 127.26, 126.21, 125.67, 125.45, 125.04; HRMS: calcd. for $C_{14}H_{11}N_4O_2$ ($M^+ + H$): 267.0882; found: 267.0876.

4-Amino-5-nitro-2-(3-thiophene)pyrimidine (3k): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.58. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.16 (s, 1H, pyrimidine-H), 8.74 (s, 1H, NH_2), 8.44 (dd, $J=1.1$, 3.0 Hz, 1H, thiophene-H), 8.31 (s, 1H, NH_2), 7.76 (dd, $J=1.0$, 5.0 Hz, 1H, thiophene-H), 7.68 (dd, $J=3.0$, 5.0 Hz, 1H, thiophene-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.55, 156.40, 155.89, 140.04, 131.36, 127.47, 127.31, 124.73; HRMS: calcd. for $C_8H_7N_4O_2S$ ($M^+ + H$): 223.0290; found: 223.0266.

4-Amino-5-nitro-2-phenylpyrimidine (3l): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.22 (s, 1H, pyrimidine-H), 8.79 (s, 1H, NH_2), 8.39 (dd, $J=7.2$, 8.7 Hz, 2H, Ar-H), 8.35 (s, 1H, NH_2), 7.62–7.54 (m, 3H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.86, 156.72, 156.22, 136.19, 132.40, 129.12, 129.04, 125.74; HRMS: calcd. for $C_{10}H_9N_4O_2$ ($M^+ + H$): 217.0725; found: 217.0744.

4-Amino-5-nitro-2-(4-fluorophenyl)pyrimidine (6): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.31 (s, 1H, pyrimidine-H), 8.47 (d, $J=8.9$ Hz, 1H, Ar-H), 8.46 (d, $J=8.9$ Hz, 1H, Ar-H), 7.93 (bs, 1H, NH_2), 7.18 (d, $J=8.7$ Hz, 1H, Ar-H), 7.16 (d, $J=8.7$ Hz, 1H, Ar-H), 6.10 (bs, 1H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.85, 156.68, 156.26, 131.70, 131.63, 125.69, 116.18, 116.00; HRMS: calcd. for $C_{10}H_8FN_4O_2$ ($M^+ + H$): 235.0631; found: 235.0631.

4-Amino-5-nitro-2-(2,5-difluorophenyl)pyrimidine (3 m): Crystallization from EtOAc/*n*-heptane, off-white solid, R_f (50% EtOAc in *n*-heptane) = 0.66. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.35 (s, 1H, pyrimidine-H), 7.94 (bs, 1H, NH_2), 7.87–7.83 (m, 1H, Ar-H), 7.22–7.14 (m, 2H, Ar-H), 6.22 (bs, 1H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.45, 155.78, 120.05, 119.97, 119.85, 119.78, 118.59, 118.50, 118.39, 118.30; HRMS: calcd. for $C_{10}H_7N_4O_2F_2$ ($M^+ + H$): 253.0537; found: 253.0520.

4-Amino-5-nitro-2-(4-acetylphenyl)pyrimidine (3n): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.77. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.25 (s, 1H, pyrimidine-H), 8.89 (bs, 1H, NH_2), 8.49 (d, $J=6.8$ Hz, 1H, Ar-H), 8.48 (d, $J=6.8$ Hz, 1H, Ar-H), 8.41 (bs, 1H, NH_2), 8.12 (d, $J=6.8$ Hz, 1H, Ar-H), 8.11 (d, $J=6.8$ Hz, 1H, Ar-H), 2.65 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.13, 164.90, 156.74, 156.27, 140.09, 139.39, 129.26, 128.86, 126.05, 27.34; HRMS: calcd. for $C_{12}H_{10}N_4O_3$ ($M^+ + H$): 259.0831; found: 259.0829.

4-Amino-5-nitro-2-(4-trifluoromethylphenyl)pyrimidine (3o): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals, R_f (50% EtOAc in *n*-heptane) = 0.73. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.25 (s, 1H, pyrimidine-H), 8.92 (s, 1H, NH_2), 8.55 (d, $J=8.2$ Hz, 2H, Ar-H), 8.43 (s, 1H, NH_2), 7.93 (d, $J=8.5$ Hz, 2H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.43, 156.75, 156.30, 139.98, 129.71, 126.21, 126.03,

126.00; HRMS: calcd. for $C_{11}H_8N_4O_2F_3$ ($M^+ + H$): 285.0599; found: 285.0600.

4-Amino-5-nitro-2-(3-nitrophenyl)pyrimidine (3p): Crystallization from *i*-PrOAc/*n*-heptane, colorless crystals. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.26 (s, 1H, pyrimidine-H), 9.11 (s, 1H, Ar-H), 8.99 (s, 1H, NH_2), 8.75 (d, J = 7.8 Hz, 1H, Ar-H), 8.46–8.42 (m, 2H, NH_2, Ar-H), 7.86 (d, J = 8.0 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.70, 156.76, 156.38, 148.57, 137.83, 134.96, 130.89, 126.69, 126.30, 123.37; HRMS: calcd. for $C_{10}H_8N_5O_4$ ($M^+ + H$): 262.0576; found: 262.0555.

4,5-Diamino-2-phenylpyrimidine hydrochloride (8)

A solution of 4-amino-5-nitro-2-phenylpyrimidine **3 l** (1.0 g) in DME (15 mL) was charged into a 100-mL reactor with a mechanical stirrer, thermocouple, and N_2/H_2 inlet. The addition funnel was charged with the 10% palladium-on-carbon catalyst (100 mg, 50% wet). The batch was hydrogenated at 40 °C under H_2 atmosphere (0.1 ~ 0.15 MPa) for 5 h with vigorous stirring. The reaction time is measured by looking for the disappearance of the respective starting materials as judged by HPLC. The catalyst was filtered off and then washed with DME (20 mL). The filtrate and washings were combined, and concentrated under vacuum to *ca.* 20 mL. The DME solution was treated with activated charcoal (Shirasagi P, 100 g) for 2 h at ambient temperature. The charcoal was filtered off and the filter cake was washed with DME (10 mL). The filtrate and washings were concentrated under vacuum to *ca.* 20 mL and checked residual water. If the residual water level was > 0.2%, to the DME solution was added fresh DME (20 mL) then concentrated under vacuum to *ca.* 10 mL and fresh DME (10 mL) added. After reducing the water level (< 0.2%), the DME solution (*ca.* 20 mL) was diluted with MeOH (2.0 mL). To the solution was added 4 N HCl (2.6 mL, in EtOAc) dropwise over 0.5 h at ambient temperature, then agitated for 1 h at ambient temperature. The resulting slurry was filtered and the filter cake was washed with DME (20 mL), then dried overnight at 40 °C under vacuum to give 4,5-diamino-2-phenyl)pyrimidine hydrochloride as a white solid; yield: 873 mg (85%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.81 (bs, 2H, NH_2), 8.43 (bs, 2H, NH_2), 8.20 (s, 1H, pyrimidine-H), 8.19–8.18 (m, 2H, Ar-H), 7.62–7.56 (m, 4H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.31, 147.77, 131.98, 131.25, 129.33, 127.83, 127.48, 120.45; HRMS: calcd. for $C_{10}H_{11}ClFN_4$ ($M^+ + H$): 241.0553; found: 241.0611.

Preparation of 8-Substituted-2-phenylpurines from 4,5-Diamino-2-phenylpyrimidine

2-Phenylpurine (9a): To a suspension of 4,5-diamino-2-phenylpyrimidine hydrochloride (223 mg, 1 mmol) in toluene/DMF (2:1, 3.0 mL) was added ethyl orthoformate (0.25 mL, 1.5 mmol) at ambient temperature. The solution was stirred for 13 h at 90 °C, at which time HPLC analysis showed complete disappearance of the starting material. The resulting slurry was concentrated under reduced pressure to remove the solvent. The residue was diluted with EtOAc, and crystallized by addition of *n*-heptane to afford the title compound as a white sold; yield: 873 mg (85%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.53 (bs, 1H, NH), 9.22 (s, 1H, pyrimidine-H), 8.61 (bs, 1H, purine-8H), 8.46 (d, J = 8.4 Hz, 1H, Ar-H), 8.46 (d, J = 8.0 Hz, 1H, Ar-H), 7.55–7.49 (m, 3H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.57, 157.99, 136.78, 136.28, 130.29, 128.96, 127.95, 122.36; HRMS: calcd. for $C_{11}H_9N_4$ ($M^+ + H$): 197.0827; found: 197.0828.

2,8-Diphenylpurine (9b)

4,5-Diamino-2-phenylpyrimidine hydrochloride (223 mg, 1 mmol) was treated with benzoic acid anhydride (250 mg, 1.1 mmol) in pyridine (2.2 mL) and THF (4.0 mL). The suspension was stirred for 15 h at ambient temperature, at which time HPLC analysis showed complete disappearance of the starting material. The solvent was evaporated under vacuum to dryness. The resulting amide was converted to benzimidazole by treatment with KO-*t*-Bu (337 mg, 3.0 mmol) in isopropyl alcohol (2.2 mL) at 50 °C for 15 h. The solvent was evaporated under vacuum to dryness, the residue was diluted with ethyl acetate and washed with H_2O. The organic layer was separated and evaporated under vacuum to dryness and crude product was chromatographed on silica gel to afford the title compound as a white solid; yield: 240 mg (88% diamine). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.20 (s, 1H, pyrimidine-H), 8.48 (d, J = 8.5 Hz, 1H, Ar-H), 8.48 (d, J = 8.1 Hz, 1H, Ar-H), 8.30 (d, J = 7.9 Hz, 1H, Ar-H), 8.30 (d, J = 7.3 Hz, 1H, Ar-H), 7.64–7.59 (m, 3H, Ar-H), 7.56–7.46 (m, 3H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.84, 138.50, 131.60, 130.24, 129.50, 128.98, 127.88, 127.53; HRMS: calcd. for $C_{17}H_{13}N_4$ ($M^+ + H$): 273.1140; found: 273.1118.

2-Phenyl-8-methylpurine (9c)

4,5-Diamino-2-phenylpyrimidine hydrochloride (223 mg, 1.0 mmol) was treated with acetic anhydride (0.1 mL, 1.1 mmol) in pyridine (2.2 mL). The suspension was stirred for 15 h at ambient temperature, at which time HPLC analysis showed complete disappearance of the starting material. The solvent was evaporated under vacuum to dryness. The resulting amide was converted to benzimidazole by treatment with *t*-BuOK (337 mg, 3.0 mmol) in isopropyl alcohol (2.2 mL) at 50 °C for 15 h. The solvent was evaporated under vacuum to dryness, the residue was diluted with ethyl acetate and washed with H_2O. The organic layer was separated and evaporated under vacuum to dryness and the crude product was chromatographed on silica gel to afford the title compound as a white solid; yield: 178 mg (85% from diamine). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.96 (s, 1H, pyrimidine-H), 8.42 (d, J = 7.2 Hz, 2H, Ar-H), 7.51–7.43 (m, 3H, Ar-H), 2.57 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.28, 156.62, 143.49, 138.97, 129.76, 128.81, 127.72, 16.07; HRMS: calcd. for $C_{12}H_{11}N_4$ ($M^+ + H$): 211.0984; found: 211.1008.

8-Aminophenyl-2-phenylpurine (9d)

Benzyl isothiocyanate (230 mg, 1.7 mmol) was mixed with 4,5-diamino-2-phenylpyrimidine hydrochloride (223 mg, 1.0 mmol) in dimethylformamide (4.5 mL) containing triethylamine (0.5 mL). The suspension was stirred for 2 h at ambient temperature, by which time a reddish solution was obtained.

The solution was added to toluene, and the precipitate was allowed to settle at 0∼5 °C for 2 h then collected by filtration, rinsed with toluene, and resuspended in H_2O. The tan precipitate which formed on cooling was collected by filtration and dried under vacuum to afford 257 mg (80% yield) of the corresponding thiourea. The thiourea was dissolved in dimethylformamide (5.0 mL) and treated with CH_3I (0.5 mL, 8 mmol) for 1 h at ambient temperature, at which time HPLC analysis showed complete disappearance of thiourea. The solvent was evaporated under vacuum, the residue was triturated with $CHCl_3$ to yield the methylisothiuronium salt. The solution of isothiuronium salt in dimethylformamide was converted to the corresponding benzimidazole by heating for 3 h at 90 °C. Conversion appeared nearly quantitative by HPLC, and recovery was 177 mg (62% yield from diamine) as white solid after the column purification (EtOAc/*n*-heptane = 1:2). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.54 (bs, 1H, NH), 8.97 (s, 1H, pyrimidine-H), 8.42–8.40 (m, 3H, Ar-H), 8.34–8.32 (m, 1H, Ar-H), 7.53–7.45 (m, 6H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.60, 157.34, 152.73, 137.29, 135.04, 129.99, 129.67, 128.52, 128.47, 127.32, 127.22, 123.51, 13.39; HRMS: calcd. for $C_{17}H_{14}N_5$ ($M^+ + H$): 288.1249; found: 288.1271.

8-Hydroxy-2-phenylpurine (9e)

A stirred mixture of 4,5-diamino-2-phenylpyrimidine hydrochloride (223 mg, 1.0 mmol) and (imidazolyl)$_2$CO (243 mg, 1.5 mmol) in THF (2.2 mL) was agitated for 2 h at ambient temperature. The solid was collected by filtration. The residual solid was washed with THF and dried under vacuum to afford the desired compound as hydrochloride salt; yield: 204 mg (82%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.91 (bs, 1H, NH), 11.19 (bs, 1H, NH), 8.66 (s, 1H, pyrimidine-H), 8.29 (d, J = 6.1 Hz, 1H, Ar-H), 7.49–7.43 (m, 4H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.28, 154.37, 151.70, 138.22, 132.98, 129.94, 128.84, 127.32, 121.99, 120.36; HRMS: calcd. for $C_{11}H_9N_4O$ ($M^+ + H$): 223.0290; found: 213.0784.

8-Mercapto-2-phenylpurine (9f)

A stirred mixture of 4,5-diamino-2-phenylpyrimidine (223 mg, 1.0 mmol) and *O*-potassium *O*-ethyldithiocarbonate (260 mg, 1.8 mmol) in EtOH (4.5 mL) was refluxed for overnight and then concentrated under reduced pressure. The yellow solid residue was dissolved in water and filtered. The filtrate was acidified with acetic acid and the resulting yellow solid was collected, washed with H_2O and dried under vacuum to afford the title compound; yield: 198 mg (87%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.34–8.32 (m, 2H, Ar-H), 8.26 (s, 1H, pyrimidine-H), 7.46–7.37 (m, 4H, Ar-H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.27, 139.49, 133.08, 129.10, 128.58, 127.32, 126.67; HRMS: calcd. for $C_{11}H_9N_4S$ ($M^+ + H$): 229.0548; found: 229.0550.

Acknowledgements

We would like to thank Dr. Shinji Kato for sample of 4-amino-2-chloro-5-nitropyrimidine and helpful discussion. We thank Mr. Moriaki Ishikawa for HRMS analysis.

References and Notes

[1] a) H. Haning, U. Niewöhner, T. Schenke, M. Es-Sayed, G, Schmidt, T. Lampe, E. Bischoff, *Bioorg. Med. Chem. Lett.* **2002**, *12,* 865–868; b) J. C. Morales, E. T. Kool, *J. Am. Chem. Soc.* **1999**, *121*, 2323–2324; c) E. T. Kool, J. C. Morales, K. M. Guckian, *Angew. Chem. Int. Ed.* **2000**, *39*, 990–1009; d) J. C. Morales, E. T. Kool, *J. Am. Chem. Soc.* **2000**, *122*, 1001–1007; e) C. L. Chepanoske, C. R. Langelier, N. H. Chmiel, S. S. David, *Org. Lett.* **2000**, *2*, 1341–1344; f) E. D. Clercq, *J. Med. Chem.* **19 86**, *29*, 1561–1569; g) C. G. Wong, R. B. Jr. Meyer, *J. Med. Chem.* **1984**, *27*, 429–432; h) A. K. Bakkestuen, L. L. Gundersen, G. Langli, F. Liu, J. M. J. Nolsøe, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1207–1210.

[2] A. Murata, K. Masumoto, M. Kondo, K. Furukawa, M. Oka, *Japanese Patents* JP 2002167387, JP 2001048882 A2, JP 20010220.

[3] K. Hirota, K. Kazaoka, I. Niimoto, H. Kumihara, H. Sajiki, Y. Isobe, H. Takaku, M. Tobe, H. Ogita, T. Ogino, S. Ichii, A. Kurimoto, H. Kawakami, *J. Med. Chem.* **2002**, 45, 5419–5422.

[4] J.-J. Bourguignon, L. Désaubry, P. Raboisson, C.-G. Wermuth, C. Lugnier, *J. Med. Chem.* **1997**, *40*, 1768–1770.

[5] Y. Maki, Y. Fujioka, S. Oohara, C. Kin, *Japanese Patent* JP 08165292 A2, JP 19960625, **1996**.

[6] E. Chapman, S. Ding, P. G. Schultz, C-H. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 14524–14525.

[7] A. M. Bianucci, G. Biagi, A. Coi, I. Giorgi, L. Oreste, F. Pacchini, V. Scartoni, A. Lucacchini, B. Costa, *Drug Dev. Res.* **2001**, *54*, 52–65.

[8] a) G. Biagi, I. Giorgi, O. Livi, F. Pacchini, P. Rum, V. Scartoni, B. Costa, M. R. Mazzoni, L. Giusti, *Farmaco* **2002**, *57.* 221–233; b) G. Bojack, C. G. Earnshaw, R. Klein, S. D. Lindell, C. Lowinski, R. Preuss, *Org. Lett.* **2001**, *3*, 839–842; c) T. Yamada, *Japanese Patent* JP 07118288 A2 19950509, **1995**; d) G. Biagi, I. Giorgi, L. Oreste, S. Valerio, *Farmaco* **1992**, *47*, 537–550.

[9] a) T. J. J. Muller, R. Braun, M. Ansorge, *Org. Lett.* **2000**, *2*, 1967–1970; b) E. C. Taylor, O. Vogl, C. C. Cheng, *J. Am. Chem. Soc.* **1959**, *81*, 2442–2448; c) R. M. Dodson, J. K. Seyler, *J. Org. Chem.* **1951**, *16*, 461–465; d) B. L. Booth, A. M. Dias, M. F. Proença, M. E. A. Zaki, *J. Org. Chem.* **2001**, *66*, 8436–8441; e) R. B. Jr. Meyer, D. A. Shuman, R. K. Robins, *J. Am. Chem. Soc.* **1974**, *9 6*, 4962–4966.

[10] a) V. Nair, D. A. Young, R. Jr. DeSilvia, *J. Org. Chem.* **19 87**, *52*, 1344–1347; b) V. Nair, D. A. Young, *J. Org. Chem.* **1984**, *49*, 4340–4344; c) V. Nair, S. G. Richardson, R. E. Coffman, *J. Org. Chem.* **1982**. *47*, 4520–4524.

[11] A. Matsuda, K. Satoh, H. Tanaka, T. Miyasaka, *Synthesis* **1984**, 963–965.

[12] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429–4438; b) N. M. Simkovsky, M. Ermann, S. M. Roberts, D. M. Parry, A. D. Baxter, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1847–1849.

[13] a) V. Nair, G. A. Turner, S. D. Chamberlain, *J. Am. Chem. Soc.* **1987**, *109*, 7223–7224; b) V. Nair, G. A. Turn-

er, S. D. Buenger, S. D. Chamberlain, *J. Org. Chem.* **1988**, *53*, 3051–3057; c) L. L. Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øversa, F. Rise, *Tetrahedron* **1994**, *50*, 9 743–9756; d) L. L. Gundersen, *Tetrahedron Lett.* **1994**, *35*, 3155–3158; e) G. Langli, L. L. Gundersen, F. Rise, *Tetrahedron* **1996**, *52*, 5625–5638; f) V. Nair, G. S. Buenger, *J. Am. Chem. Soc.* **1989**, *111*, 8502–8504; g) V. Nair, D. F. Purdy, T. B. Sells, *J. Chem. Soc. Chem. Commun.* **1989**, 878–879; h) V. Nair, D. F. Purdy, *Tetrahedron* **199 1**, *47*, 365–382.

[14] a) K. Hirota, Y. Kitade, Y. Kanbe, Y. Maki, *J. Org. Chem.* **1992**, *57*, 5268–5270; b) A. Holy, J. Günter, H. Dvořáková, M. Masojídková, G. Andrei, R. Snoeck, J. Balzarini, E. De Clercq, *J. Med. Chem.* **1999**, *42*, 2064–2086; c) M. Česnek, M. Hocek, A. Holý, *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357–1373; d) M. Hocek, A. Holý, H. Dvořáková, *Collect. Czech. Chem. Commun.* **2002**, *67*, 325–335; e) H. Dvořáková, D. Dvořák, A. Holý, *Tetrahedron Lett.* **1996**, *37*, 1285–1288; f) H. Dvořáková, D. Dvořák, A. Holý, *Collect. Czech. Chem. Commun.* **1998**, *63*, 2065–2074; g) M. Hocek, H. Dvořáková, *J. Org. Chem.* **2003**, *68*, 5773–5776.

[15] a) A. Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178–184; b) A. Suzuki, *Pure Appl. Chem.* **1994**, *66*, 213–222; c) A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749–1758; d) A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419–422; e) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; f) V. Sniekus, *Chem. Rev.* **1990**, *90*, 879–933; g) D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859–1885; h) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; i) N. Miyaura; A. Suzuki, *Chem. Commun.* **1979**, *19*, 866–867; j) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440; k) N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513–519; l) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; m) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.

[16] a) M. Havelková, D. Dvořák, M. Hocek, *Synthesis* **2001**, 1704–1710; b) M. Havelková, M. Hocek, M. Česnek, D. Dvořák, *Synlett* **1999**, 1145–1147; c) M. Hocek, A. Holý, I. Votruba, H. Dvořáková, *Collect. Czech. Chem. Commun.* **2000**, *65*, 1683–1697; d) M. Hocek, A. Holý, I. Votruba, H. Dvořáková, *Collect. Czech. Chem. Commun.* **2001**, *66*, 483–499.

[17] a) L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875–1916; b) M. Hocek, *Eur. J. Org. Chem.* **2003**, 245–254; c) M. K. Lakshman, *J. Organomet. Chem.* **2002**, *653*, 234–251; d) M. K. Lakshman, J. H. Hilmer, J. Q. Martin, J. C. Keeler, Y. Q. V. Dinh, F. N. Ngassa, L. M. Russon, *J. Am. Chem. Soc.* **2001**, *123*, 7779–7787; e) S. Ding, N. S. Gray, Q. Ding, P. G. Schultz, *Tetrahedron Lett.* **2001**, *42*, 8751–8755; f) E. C. Western, J. R. Daft, E. M. Johnson, II, P. M. Gannett, K. H. Shaughnessy, *J. Org. Chem.* **2003**, *68*, 6767–6774.

[18] N. Whittaker, T. S. G. Jones, *J. Chem. Soc.* **1951**, 1565–1570.

[19] a) K. Ohno, W. Ishida, K. Kamata, K. Oda, M. Machida, *Heterocycles* **2003**, *59*, 317–322; b) N. B. Ambati, V. N. S. R. Babu, V. Anand, P. Hanumanthu, *Synthetic Commun.* **1999**, *29*, 289–294; c) D. H. Swenson, K. El-Bayoumy, G.-H. Shuie, S. S. Hecht, E. Fiala, F. F. Kadlubar, J. P. Freeman, *Chem. Res. Toxicol.* **1993**, *6*, 480–485; d) J. Valdez, R. Cedillo, A. Hernández-Campos, L. Yépez, F. Hernández-Luis, G. Navarrete-Vázquez, A. Tapia, R. Cortés, M. Hernández, R. Castillo, *Bioorg. & Med. Chem. Lett.* **2002**, *12*, 2221–2224; e) B. Singh, G. Y. Lesher, *Synthesis* **1991**, *3*, 211–213.

[20] a) D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170–7173; b) N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 5660–5667.

[21] The reaction rate strongly depends on the particle size of inorganic base (40 ~ 70 μm).

[22] D. J. Ager, M. B. East, A. Eisenstadt, S. A. Laneman, *Chem. Commun.* **1997**, *24*, 2359–2360.

[23] W. Shen, *Tetrahedron Lett.* **1997**, *38*, 5575–5578.

[24] J. H. L. Ong, C. Nataro, J. A. Golen, A. L. Rheingold, *Organometallics* **2003**, *22*, 5027–5032.

[25] a) W. R. Cullen, T. J. Kim, F. W. B. Einstein, T. Jones, *Organometallics* **1983**, *2*, 714–719; b) I. R. Butler, W. R. Cullen, T. J. Kim, S. J. Rettig, J. Trotter, *Organometallics* **1985**, *4*, 972–980; c) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370; d) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478; e) S. V. Gagnier, R. C. Larock, *J. Org. Chem.* **2000**, *65*, 1525–1529.

[26] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.

[27] THF (86% yield), dimethoxyethane (86% yield), diethoxyethane (88% yield), toluene (78% yield) were also acceptable solvents.

[28] J. Clark, P. N. T. Murdoch, D. L. Roberts, *J. Chem. Soc. C: Org.* **1969**, 1408–1412.

[29] C. L. Duc, C. Charlon, P. DeMenge, C. A. DeLord, *Farmaco, Edizione Scientifica* **1978**, *33*, 516–521.

[30] a) D. H. Swenson, K. El-Bayoumy, G-.H. Shuie, S. S. Hecht, E. Fiala, F. F. Kadlubar, J. P. Freeman, *Chem. Res. Toxicol.* **1993**, *6*, 480–485; b) J. Garin, E. Melendez, F. L. Merchan, T. Tejero, *Synthesis* **1985**, 867–870.

[31] G. Levin, A. Kalmus, F. Bergmann, *J. Org. Chem.* **1960**, *25*, 1752–1754.

