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SYNTHESIS OF 2-AMINOPYRIDINIUM SALTS FROM 2-IMINOPYRIDINES AS A STARTING MATERIAL

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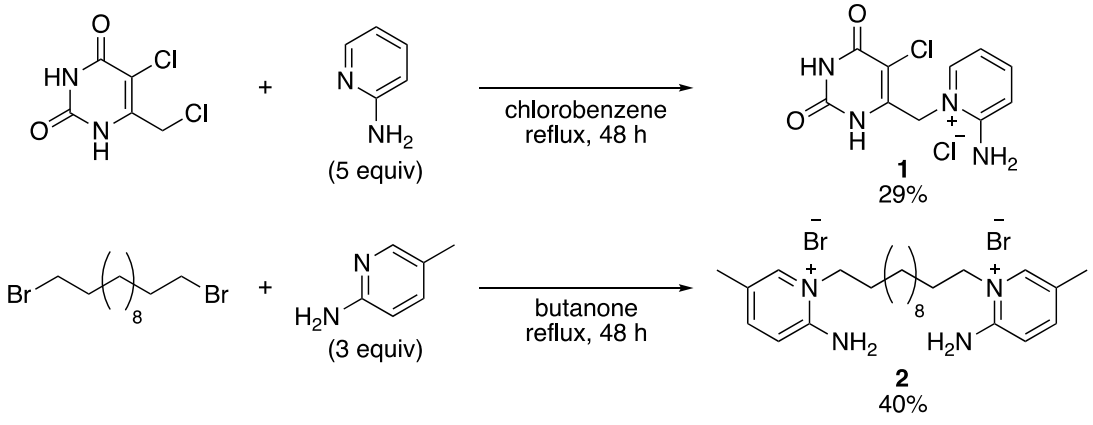
Abstract – Synthesis of multi-substituted 2-aminopyridinium salts is developed using 2-iminopyridines as a starting material. The reactions of multi-substituted 2-iminopyridines prepared by the conjugate addition of ethyl 2-cyanopropanoate to alkynyl imines with several acids proceeded smoothly to give multi-substituted 2-aminopyridinium salts in high yields.

Alkyl pyridinium salts are used as an antimicrobial agent and also developed as an ionic liquid. Cetylpyridinium chloride is one of the representative antimicrobial agents. On the other hand, the study of 2-aminopyridinium salts is rare compared to that of the corresponding pyridinium salts. Among them, there are 2-aminopyridinium salts (**1**), a thymidine phosphorylase inhibitor[1] and (**2**), a potent antimalarial agent.[2] Their 2-aminopyridinium salts are synthesized by the reaction of 2-aminopyridines with alkyl halides under the harsh reaction conditions (Scheme 1). Therefore, the synthetic methods for the multi-substituted 2-aminopyridinium salts under mild reaction conditions have been highly desired to investigate biological activities and functions.



Scheme 1. 2-Aminopyridinium salts having biological activities

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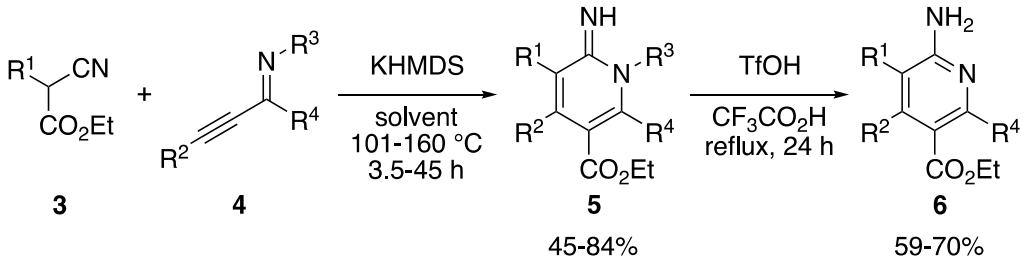
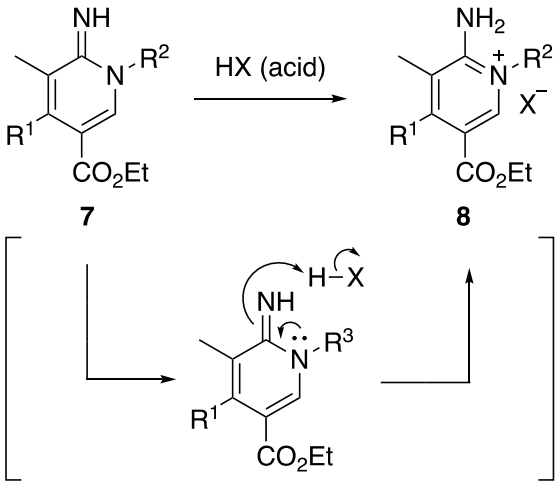
Dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday (Sotsuju).

We have already developed new efficient synthetic methods for a variety of nitrogen-containing heterocycles using the conjugate additions of several carbon nucleophiles to α,β-alkynyl imines.[3,4] Among them, we have reported the synthesis of multi-substituted 2-iminopyridines (**5**) by the conjugate addition of ethyl 2-cyanoacetate derivatives (**4**) to alkynyl imines (**3**) and the subsequent transformation of 2-iminopyridines (**5**) into 2-aminopyridines (**6**) by deprotection of the substituent on the nitrogen under strong acidic conditions (Scheme 2).[5]



Scheme 2. Synthesis of multi-substituted 2-iminopyridine and 2-aminopyridine

We envisioned the synthesis of 2-aminopyridinium salts (**8**) from 2-iminopyridines (**7**) without deprotection by using the mild reaction conditions. Herein, we report an easy and highly efficient synthetic method of 2-aminopyridinium salts (**8**) using the reaction of 2-iminopyridines (**7**) with several acids (Scheme 3).

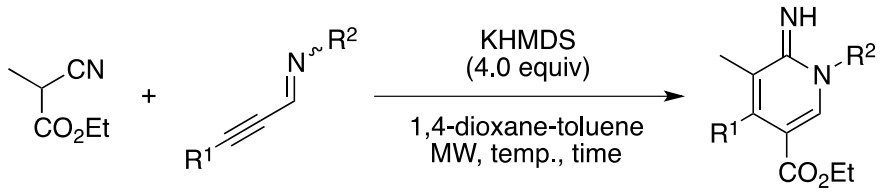


Scheme 3. Synthesis of 2-aminopyridinium salts

First, we examined reducing reaction time under microwave irradiation conditions to synthesize several 2-aminopyridines efficiently.[6,7] Table 1 summarizes the results.[8] When the conjugate addition of ethyl 2-cyanopropanoate (**9**) to alkynyl imine (**10a**) was carried out under microwave irradiation in 1,4-dioxane-toluene at 160 °C for 0.5 h, the desired 2-iminopyridine (**7a**) was obtained in 80% yield (entry 1). While the reaction of alkynyl imine (**10b**) gave the 2-iminopyridine (**7b**) in slightly lower 57%

yield, the reaction of the alkynyl imine (**10c**) having an electron-withdrawing *p*-chlorophenyl group afforded the 2-iminopyridine (**7c**) in higher 68% yield compared to that under batch conditions (entries 2 and 3). The reaction of the alkynyl imine (**10d**) having an electron-withdrawing *p*-bromophenyl group also gave the 2-iminopyridine (**7d**) in 61% yield (entry 4). The use of alkynyl imine (**10e**) having a 2-thienyl group afforded the 2-iminopyridine (**7e**) in high yield (entry 5). Regarding the reaction of *N*-aliphatic alkynyl imine, microwave irradiation conditions were found to be effective. The reaction of *N*-pentyl alkynyl imine (**10f**) yielded only a trace amount of 2-iminopyridine (**7f**) probably due to instability of (**10f**) under basic conditions for a long reaction time. On the other hand, when the reaction of (**10f**) was carried out under microwave irradiation conditions at 160 °C for 1.0 h, the desired 2-iminopyridine (**7f**) was obtained in 38% yield (entry 6). When the reaction of (**10f**) was carried out at 180 °C for 1.0 h, the yield of (**7f**) improved to 45% (entry 7). The reactions of other *N*-aliphatic alkynyl imines (**10g**) and (**10h**) afforded the 2-iminopyridines (**7g**) and (**7h**) in 48% and 35% yields, respectively (entries 8 and 9).

Table 1. Synthesis of 2-iminopyridines under microwave conditions

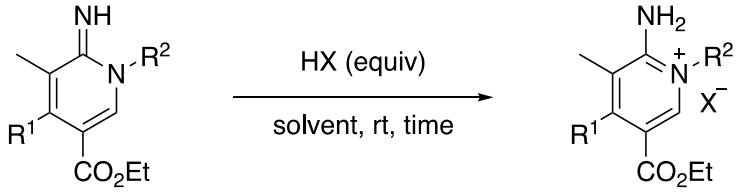


9 (5.0 equiv) **10** **7**

entry	**10**	R^1	R^2	temp. (°C)	time (h)	**7**	yield (%)
1	**10a**	Ph	PMP[a]	160	0.5	**7a**	80 (81)[b,c]
2	**10b**	Ph	MPM[d]	160	0.5	**7b**	57 (70)[b,e]
3	**10c**	Ph	*p*-ClC_6H_4	160	0.5	**7c**	68 (22)[b,f]
4	**10d**	Ph	*p*-BrC_6H_4	160	0.5	**7d**	61 (30)[b,g]
5	**10e**	2-thienyl	PMP[a]	160	0.5	**7e**	85 (75)[b,h]
6	**10f**	Ph	pentyl	160	1.0	**7f**	38 (trace)[b,i]
7	**10f**	Ph	pentyl	180	1.0	**7f**	45
8	**10g**	Ph	octyl	180	1.0	**7g**	48
9	**10h**	Ph	dodecyl	180	1.0	**7h**	35

[a]PMP = *p*-methoxyphenyl. [b]Yields under the batch conditions in parenthesis. [c]In 1,4-dioxane-toluene under reflux for 25 h. [d]MPM = *p*-methoxyphenylmethyl. [e]In $(MeOCH_2CH_2)_2O$-toluene at 160 °C for 20 h. [f]In 1,4-dioxane-toluene under reflux for 17.5 h. [g]In 1,4-dioxane-toluene under reflux for 36 h. [h]In 1,4-dioxane-toluene under reflux for 38 h. [i]In $(MeOCH_2CH_2)_2O$-toluene at 160 °C for 3 h.

Table 2. Synthesis of 2-iminopyridium salts



7 **8**

entry	**7**	R^1	R^2	X	equiv	solvent	time (min)	**8**	yield (%)
1[a]	**7a**	Ph	PMP	Cl	excess	MeOH	55	**8a**	98
2	**7a**	Ph	PMP	Br	excess	AcOH	30	**8b**	99
3[b]	**7a**	Ph	PMP	I	excess	MeOH	1	**8c**	90
4	**7a**	Ph	PMP	CF_3CO_2	13	CH_2Cl_2	80	**8d**	94
5	**7a**	Ph	PMP	CF_3SO_3	2.0	CH_2Cl_2	80	**8e**	quant
6	**7a**	Ph	PMP	*p*-$MeC_6H_4SO_3$	1.2	CH_2Cl_2	30	**8f**	96
7[a]	**7b**	Ph	MPM	Cl	excess	MeOH	30	**8g**	quant
8[a]	**7c**	Ph	*p*-ClC_6H_4	Cl	excess	MeOH	30	**8h**	quant
9	**7d**	Ph	*p*-BrC_6H_4	*p*-$MeC_6H_4SO_3$	1.0	CH_2Cl_2	30	**8i**	98
10	**7e**	2-thienyl	PMP	*p*-$MeC_6H_4SO_3$	2.0	CH_2Cl_2	1	**8j**	quant
11[a]	**7f**	Ph	pentyl	Cl	excess	MeOH	30	**8k**	97
12	**7f**	Ph	pentyl	*p*-$MeC_6H_4SO_3$	1.0	CH_2Cl_2	1	**8l**	quant
13	**7g**	Ph	octyl	*p*-$MeC_6H_4SO_3$	1.0	CH_2Cl_2	1	**8m**	quant
14	**7h**	Ph	dodecyl	*p*-$MeC_6H_4SO_3$	1.0	CH_2Cl_2	30	**8n**	quant

[a]Hydrogen chloride was in situ prepared from acetyl chloride with methanol. [b]Hydrogen iodide was in situ prepared from trimethylsilyl iodide with methanol.

With several *N*-substituted-2-iminopyridines (**7**), we examined the synthesis of a variety of 2-aminopyridinium salts (**8**). Table 2 summarizes the results. First, the reactions of *N*-PMP-2-iminopyridine (**7a**) with hydrogen halides as an inorganic acid were carried out at room temperature. The desired 2-aminopyridinium salts (**8a-c**) were obtained in high yields (entries 1-3). The reaction of (**7a**) with organic acids such as trifluoroacetic, trifluoromethanesulfonic, and acids proceeded smoothly to give the 2-aminopyridinium salts (**8d-f**) in high yields (entries 4-6). The reaction of 2-iminopyridines (**7b**) and (**7c**) with hydrogen chloride also worked well to afford the 2-aminopyridinium salts (**8g**) and (**8h**) in quantitative yields (entries 7 and 8). The reaction of 2-iminopyridine (**7d**) having a 4-bromophenyl group with *p*-toluenesulfonic acid also gave the 2-aminopyridinium salts (**8i**) in 98% yield (entry 9).[9] The reaction of 2-iminopyridine (**7e**) having a

2-thienyl group with *p*-toluenesulfonic acid proceeded rapidly to yield the 2-aminopyridinium salts (**8j**) quantitatively (entry 10). The reaction of *N*-pentyl-2-iminopyridine (**7f**) with hydrogen chloride gave the 2-aminopyridinium salt (**8k**) in high yield (entry 11). When the reactions of *N*-aliphatic 2-iminopyridines (**7f-h**) with *p*-toluenesulfonic acid were carried out, the desired 2-aminopyridinium salts (**8l-n**) were obtained in quantitative yields (entries 12-14).

In conclusion, we have developed the efficient synthetic methods for 2-aminopyridinium salts. The present 2-aminopyridinium salts synthesis is an attractive method because multi-functionalized 2-iminopyridines as a starting material are readily available using a conjugate addition reaction of ethyl 2-cyanopropanoate to alkynyl imines, and the reactions of them with several acids proceed rapidly under mild reaction conditions to give the 2-aminopyridinium salts in high yields. Furthermore, another characteristic feature is that *N*-aryl-2-aminopyridinium salts can be synthesized because it is impossible to synthesize them using S_N2 reaction of a 2-aminopyridine with an aryl halide.

ACKNOWLEDGEMENTS

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8. Typical procedure (Table 1, entry 4): KHMDS (1.6 mL, 0.50 M in toluene, 0.80 mmol) was added to a 1,4-dioxane (1.4 mL) solution of ethyl 2-cyanopropanoate (**9**) (127 mg, 1.0 mmol) in a microwave reactor vial including a magnetic stirring bar at room temperature. Alkynyl imine (**10d**) (56.8 mg, 0.2 mmol) in 1,4-dioxane (2.0 mL) was added to the mixture. The vial was placed in the microwave reactor, and irradiated at 160 °C for 0.5 h. The mixture was cooled to room temperature and then poured into a saturated aqueous $NaHCO_3$ solution (40 mL) to quench the reaction. The mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (ammonia solution in CH_2Cl_2/MeOH = 9:1) to give 2-iminopyridine (**7d**) as a brown solid (50.0 mg, 61%). Mp 139-142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.65-7.74 (m, 2H), 7.30-7.45 (m, 5H), 7.10-7.18 (m, 2H), 5.83 (brs, 1H), 3.92 (q, *J* = 7.3 Hz, 2H), 1.85 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.9, 159.0, 143.7, 140.6, 140.3, 139.1, 133.3, 128.9, 127.9, 127.7, 127.2, 125.5, 123.1, 109.0, 60.3, 15.5, 13.6. IR (neat) 3310, 3089, 3053, 2994, 2957, 2903, 1702, 1634, 1597, 1563, 1487, 1412, 1364, 1346, 1288, 1219, 1181, 1134, 1032, 1007, 795, 775, 707 cm^{-1}. HRMS (EI): Calculated for $C_{21}H_{19}BrN_2O_2$ $(M)^+$ 410.0630, found 410.0610.
9. Synthesis of aminopyridinium salt (**8i**) (Table 2, entry 9): CH_2Cl_2 (2.0 mL) was added to a mixture of 2-iminopyridine (**7d**) (39.6 mg, 0.096 mmol) and *p*-toluenesulfonic acid monohydrate (18.3 mg, 0.096 mmol) in a 30 mL two-neck round-bottom flask at room temperature. The reaction mixture was stirred at room temperature for 0.5 h, transferred into a 50 mL round-bottom flask, and then

concentrated in vacuo. The aminopyridinium salt (**8i**) was obtained as a light brown solid without further purification (55.1 mg, 98%). Mp 162-164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (s, 1H), 7.68-7.74 (m, 2H), 7.59-7.65 (m, 2H), 7.40-7.50 (m, 5H), 7.07-7.14 (m, 4H), 5.80 (brs, 2H), 3.96 (q, *J* = 7.3 Hz, 2H), 2.31 (s, 3H), 2.06 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.3, 155.5, 151.7, 142.9, 139.2, 136.7, 136.6, 134.4, 128.5, 128.3, 128.2, 128.1, 127.3, 125.9, 125.7, 124.3, 116.6, 61.5, 21.2, 15.3, 13.4. IR (KBr) 3309, 3089, 3057, 2991, 2902, 1702, 1635, 1561, 1485, 1396, 1364, 1344, 1290, 1218, 1182, 1134, 1035, 1012, 795, 774, 707 cm^{-1}. HRMS (DART, positive): Calculated for $C_{21}H_{20}BrN_2O_2^+$ $(M)^+$ 411.0703, found 411.0720. HRMS (DART, negative): Calculated for $C_7H_7O_3S^-$ $(M)^-$ 171.0121, found 171.0110.