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A Simple and Efficient Method for the Synthesis of 2,3,5,6-Tetrachloro-4-iodopyridine, and its Reactivity Toward Hard and Soft Nucleophiles

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2,3,5,6-Tetrachloro-4-iodopyridine was successfully synthesized in one-step from the reaction of pentachloropyridine with sodium iodide using microwave irradiation and reflux condition. The reaction of *O*-, *N*- and *S*-centered nucleophiles with 2,3,5,6-tetrachloro-4-iodopyridine was studied in order to assess regiochemistry of aromatic nucleophilic substitution. Substitution occurs at the *para* position of 2,3,5,6-tetrachloro-4-iodopyridine by *S* centered nucleophiles, while *O*- and *N*-centered nucleophiles substitution occurs at the *ortho* position of pyridine ring based on the hard and soft interaction principles . IR, ^{1}H NMR and ^{13}C NMR spectroscopy confirmed the structures of all compounds.

Keywords: Pentachloropyridine, Tetrachloro-4-iodopyridine, Regiochemistry, Microwave, Heterocycle

INTRODUCTION

The chemistry of perhalogenated heteroaromatic compounds have been investigated for the synthetic applications [1-2]. Varieties of highly halogenated heterocyclic derivatives are commercially available, and indeed some are prepared on the industrial scale for biological applications and use as intermediates [3]. In the life science/industry discovery, strategies for the synthesis of novel families of poly substituted heterocyclic systems are increasingly gaining importance [4,6]. Also, these systems are useful building blocks for the synthesis of polyfunctional fluoropyridine derivatives [7,8].

The main reaction of perhalogenated heteraromatics is the replacement of halogen atoms with various nucleophiles [9-13]. Chambers *et al*. [14,15] suggested the 'hardness' and 'softness' explanations of nucleophiles to determine the position of attack in perfluorinated pyridine compounds bearing other substituents. They showed that the facility of reactivity of perfluorinated heteroaromatics into hard and soft nucleophiles is achieved by partial replacement of fluorine with bromine in pentafluoropyridine [14]. In our previous work, we showed that sodium enolates of ketones selectively react with pentafluoropyridine from the oxygen site of enolates. This selectivity was explained on the basis of hard-hard interaction principle [10].

Pentachloropyridine is one of the oldest and potent heterocyclic compounds used for preparation of the appropriate polyfunctional heterocyclic scaffolds for library synthesis in biological field [16]. Nucleophilic reactions of pentachloropyridine have been carried out with various nucleophiles [13,17-25]. The solvent and nucleophile steric hindrance affect the regiochemistry of the reactions. Large nucleophiles react in the less hindered 2-position of pyridine ring [19,25], whilst small nucleophiles are substituted at 4-position of pyridine ring [18,22,23].

In the previous work [26], we reported the synthesis of 4-phenylsulfonyl-2,3,5,6-tetrachloropyridine and its reaction with various nucleophiles. We showed that substitution with less steric hindrance nucleophiles occurs clearly at the *para* position of 4-phenylsulfonyl-2,3,5,6-tetrachloropyridine, while more steric hindrance

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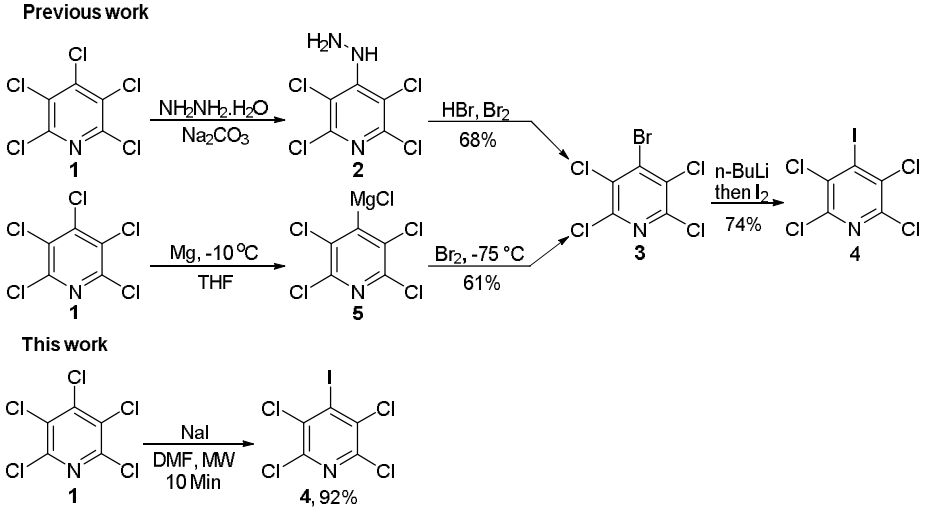


Scheme 1. Methods for the synthesis of 2

nucleophiles give mostly a mixture of *ortho*- and *para*-substituted products. The regiochemistry of this reaction was explained based on the steric hindrance principles.

Mack *et al.* [27] reported synthesis of 2,3,5,6-tetrachloro-4-iodopyridine in three and two steps from pentachloropyridine (Scheme 1). In this paper, we report efficient one-step synthesis of tetrachloro-4-iodopyridine using microwave irradiation in high yield highlighting our initial investigations that demonstrate region-controlled nucleophilic substitution of 2 with *N*-, *S*- and *O*-centered nucleophile nucleophiles.

EXPERIMENTAL

All solvents and starting materials were obtained commercially (Merck). The solvents were dried using the procedures recommended in the literature and distilled before use. Ethos Advanced Microwave Digestion System, Milestone, was used for the synthesis of compounds. ^{1}H NMR spectra were recorded at 500 and 300 MHz. ^{13}C NMR spectra were recorded at 125 and 75 MHz. TLC analysis was performed on silica gel TLC plates (Merck).

Synthesis of 2,3,5,6-Tetrachloro-4-iodopyridine

Method a. A suspension of pentachloropyridine (1 mmol, 0.251 g) in 3 ml of DMF was treated with sodium iodide (4.5 mmol, 0.674 g) and refluxed for 1.5 h. The reaction mixture was poured into water (10 ml), filtered and dried. Recrystallization with EtOH gave 2,3,5,6-tetrachloro-4-iodopyridine 2 (88% yield) as white crystals; m.p.: 198-200 °C (lite.[27] 200-202 °C).

Method b. A solution of pentachloropyridine (1 mmol, 0.251 g), sodium iodide (2 mmol 0.300 g) and DMF (3 ml) was irradiated with microwave at 600 w in 140 °C for 10 min. The reaction mixture was poured into water (10 ml), filtered and dried. The recrystallization of precipitate with EtOH resulted in 2 in 92% yield.

Typical Procedure for Reaction between 2,3,5,6-Tetrachloro-4-iodopyridine and Various Nucleophiles

Method a. 2,3,5,6-Tetrachloro-4-iodopyridine (1 mmol,0.343 g) was added to a solution of nucleophile (1 mmol) and K_2CO_3 (except for 7a and 7e) in 5 ml of CH_3CN or EtOH (for 7a). The mixture was refluxed. The reaction mixture was poured into water (10 ml) and extracted with $CHCl_3$ (3 × 8 ml), then dried with $MgSO_4$. Removal of the solvent in vacuum and purification of the residue by silica gel column chromatography with ethyl acetate: n-Hexane (5:1) afforded the desired product.

Method b. A mixture of 2,3,5,6-tetrachloro-4-iodo-pyridine (1 mmol, 0.343 g), Nucleophile (1 mmol), K_2CO_3 (except for 7a and 7e) and DMF (3 ml) or EtOH (3 ml, for 7a) was irradiated with microwave at 600 w in 80 °C for

indicated time in Table 2. The reaction mixture was poured into water (10 ml) and extracted with $CHCl_3$ (3 × 8 ml), then dried with $MgSO_4$. Removal of the solvent in vacuum and purification of the residue by silica gel column chromatography with ethyl acetate: n-Hexane (5:1) afforded the desired product.

2-Ethoxy-3,5,6-trichloro-4-iodopyridine (7a). Yield: 40% method a, 42% method b; white solid; m.p.: 101-103 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ = 4.33 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 1.33 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_2). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 155.7 (Ar-C), 141.4 (Ar-C), 126.3 (Ar-C), 122.9 (Ar-C), 120.8 (Ar-C), 64.5 (CH_2), 14.2 (CH_3).

4-(3,5,6-Trichloro-4-iodopyridin-2-yl)morpholine (7b). K_2CO_3 (1.5 mmol, 0.207 g); Yield: 50% method a, 53% method b; white solid; m.p: 127-130 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.69 (m, 4H, CH_2), 3.24 (m, 4H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.2 (Ar-C), 142.0 (Ar-C), 126.7 (Ar-C), 126.1 (Ar-C), 121.8 (Ar-C), 65.8 (CH_2), 49.2 (CH_2).

2-(Benzyloxy)-3,5,6-trichloro-4-iodopyridine (7c). K_2CO_3 (1.5 mmol, 0.207 g); Yield: 40% method a, 45% method b; pale yellow solid; m.p.: 188-190 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.48 (d, 2H, $^3J_{HH}$ = 6.9 Hz, Ar-H), 7.41 (t, 2H, $^3J_{HH}$ = 7.0 Hz, Ar-H), 7.36 (t, 1H, $^3J_{HH}$ = 7.2 Hz, Ar-H), 5.38 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.7 (py-C), 140.9 (py-C), 137.4 (Ar-C), 135.7 (py-C), 128.5 (Ar-CH), 127.1 (py-C), 127.5 (Ar-CH), 127 (Ar-CH), 64.9 (CH_2) ppm.

2-((Perchloropyridin-4-yl)thio)aniline (7d). K_2CO_3 (3 mmol, 0.415 g); Yield: 45% method a, 45% method b; oily product; IR (KBr): ν_{max} = 3385, 3360 (NH_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (d, 1H, J = 8.0 Hz, Ar-H), 7.19 (d, 1H, J = 7.8 Hz, Ar-H), 6.70-6.74 (m, 2H, Ar-H), 4.22 (bs, 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.4 (py-C), 148.2 (py-C), 146.5 (Ar-C), 144.6 (Ar-C), 135.8 (Ar-CH), 132.4 (py-C), 131.2 (Ar-CH), 119.1 (Ar-CH), 115.8 (Ar-CH) ppm.

2,3,5,6-Tetrachloro-4-thiocyanatopyridine (7e). Yield: 70% method a, 75% method b; brown solid; m.p.: 127-128 °C (lite. [28] 125 °C). IR (KBr): ν_{max} = 2074 (CN) cm^{-1}.

4-(Benzylthio)-2,3,5,6-tetrachloropyridine (7f). K_2CO_3 (1.5 mmol, 0.207 g); Yield: 44% method a, 50% method b; yellow solid; m.p.: 67-69 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.25-7.36 (m, 5H, Ar-H), 3.63 (s, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 144.4 (py-C), 140.2 (py-C), 137.4 (Ar-C), 135.7 (py-C), 129.4 (Ar-CH), 128.5 (Ar-CH), 127.4 (Ar-CH), 43.4 (CH_2).

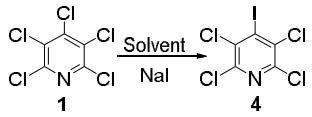
2-((Perchloropyridin-4-yl) thio) pyrimidine-4,6-diamine (7g). K_2CO_3 (3 mmol, 0.415 g); Yield: 50% method a, 55% method b; pale yellow solid; m.p.: 245 °C (dec.); IR (KBr): ν_{max} = 3361, 3345 (NH_2) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.19 (bs, 4H, NH_2), 5.15 (s, 1H, pyrimidine-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.2 (pyrimidine-CH), 164.2 (pyrimidine-CH), 146.1 (py-C), 145.4 (py-C), 135.5 (py-C), 79.4 (pyrimidine-CH).

RESULTS AND DISCUSSION

Initially, we focused on a new method for one-step synthesis of tetrachloro-4-iodopyridine with high yield in a very short reaction time. To this purpose, we optimized the reaction conditions for the synthesis of tetrachloro-4-iodopyridine 4 using pentachloropyridine 1 and sodium iodide as a model reaction (Table 1). In the first instance, the effect of solvent on the yield of the product was evaluated. Among various solvents tested, DMF yielded the best results at room temperature and reflux conditions (Table 1, entry 5, 6), whereas CH_3CN, THF and acetone gave the products in low yields (Table 1, entry 2-4). The reaction gave trace yield in ethanol at room temperature (Table 1, entry 1). Next, we investigated the effect of mole ratio of reactants on the synthesis of tetrachloro-4-iodopyridine at reflux condition. We found that the yield improved when the reaction of pentachloropyridine 1 with sodium iodide was carried out in mole ratio of 1:4.5, respectively (Table 1, entry 7). In order to improve yield, the reaction was carried out under ultrasonic and microwave conditions. Surprisingly, the results showed about 90% saving in time, hence saving in consumption of chemical materials (Table 1, entry 8, 9). The optimum reaction condition for the synthesis of tetrachloro-4-iodopyridine 4 was found to be: pentachloropyridine (1 equiv.), sodium iodide (2 equiv.), and use microwave irradiation with DMF as the solvent.

After synthesis of tetrachloro-4-iodopyridine, it is interesting to know which atoms (Cl or I) of pyridine ring are replaced by nucleophile in the substitution reaction. To

Table 1. Optimization of Reaction Condition for the Formation of 2



1 4

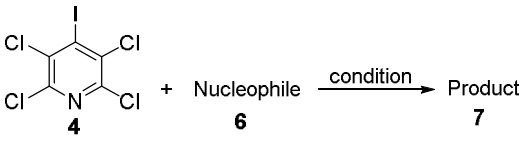
Entry	Solvent	Condition	Molar ratio (1:NaI)	Time	Yield (%)
1	Ethanol	r.t	1:1	5 h	30
2	Acetone	r.t	1:1	5 h	trace
3	CH_3CN	r.t	1:1	5 h	40
4	THF	r.t	1:1	5 h	20
5	DMF	r.t	1:1	5 h	70
6	DMF	Reflux	1:1	3	80
7	DMF	Reflux	1:4.5	1.5 h	88
8	DNF	MW	1:2	10 min	92
9	DMF	Ultrasonic	1:4	30 min	90

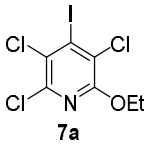
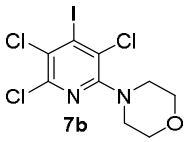
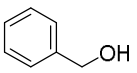
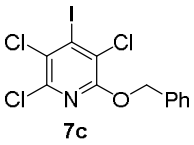
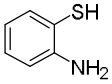
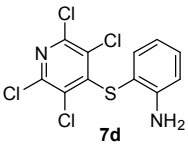
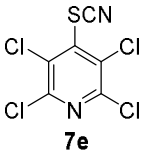
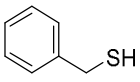
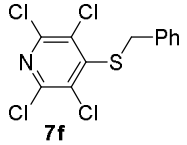
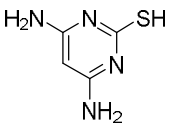
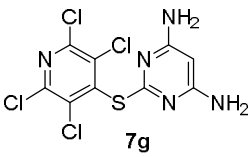
this end, annelation processes involving reaction between tetrachloro-4-iodopyridine and *O*-, *N*- and *S*-centered nucleophiles were studied. Tetrachloro-4-iodopyridine 4 and sodium ethoxide in ethanol gave trichloro-6-ethoxy-4-iodopyridine 7a (Table 2, entry 1) after purification using column chromatography eluted by ethyl acetate/*n*-hexane. Five resonances by ^{13}C NMR indicate displacement of chlorine atom attached to the *ortho* position of the pyridine ring. Chemical shifts of pyridine carbons were located at δ = 120.8, 122.9, 126.3, 141.4 and 155.7 ppm. In addition, carbons of methyl and methylene of ethoxy group were located at δ = 14.2 and 64.5 ppm, respectively. ^1H NMR spectrum of compound 7a showed a triplet peak at δ = 1.33 for CH_3 and a quartet peak at δ = 4.33 ppm for CH_2 group. Similarly, the reaction of morpholine and benzyl alcohol with 4 produced 7b and 7c, respectively, arising by substitution at the *ortho* position of the pyridine ring.

With these successful and clean reactions in hand, we then proceeded to investigate other nucleophiles (Table 2, entry 4–7). Reaction of 2-aminothiophenol with 4 in the presence of potassium carbonate at CH_3CN resulted in 2-((perchloropyridin-4-yl)thio)aniline 7d arising displacement of iodine atom attached to the *para* position of the pyridine ring by nucleophilic attack of the thiol group over the amino group. In ^{13}C NMR spectrum of compound 7d, pyridine ring carbons were located at δ = 148.4, 148.2 and 132.4 ppm and aromatic carbons were located at δ = 146.5, 144.6, 135.8, 131.2, 119.1 and 115.8 ppm. ^1H NMR analysis of 7d showed two doublet peaks at δ = 7.28 and 7.19 ppm and a multiple peak in the range of at δ = 6.70-6.74 ppm for aromatic hydrogens, and a broad singlet peak at δ = 4.22 ppm for NH_2. Thiocyanate anion reacted with 4 from more nucleophilic S site with a preference for nucleophilic attack at the 4-position of pyridine ring that produced 2,3,5,6-tetrachloro-4-thiocyanatopyridine 7e [28]. Similarly, the reaction of benzyl mercaptan and 4,6-diaminopyrimidine-2-thiol with 4 led to 7f and 7g, respectively, arising from the substitution of the *para* position of the pyridine ring by thiol group.

The regiochemistry of the aromatic nucleophilic substitution in pentachloropyridine was described based on the steric hindrance of nucleophile so that large nucleophiles

Table 2. Reaction of Tetrachloro-4-iodopyridine with Various Nucleophiles



Entry	Nucleophile	Product	Reflux		Microwave	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	NaOEt	 **7a**	24	40	20	42
2		 **7b**	30	50	25	53
3		 **7c**	16	40	30	45
4		 **7d**	28	45	20	45
5	KSCN	 **7e**	28	70	15	75
6		 **7f**	12	44	30	50
7		 **7g**	10	50	30	55

were substituted at the 2- position of pyridine ring, whilst small nucleophiles were substituted at 4-position of pyridine ring [18,19,22,23,25]. The regiochemistry of the aromatic nucleophilic substitution in tetrachloro-4-iodopyridine 4 provided some surprise. Harder nucleophiles *e.g.* sodium ethoxide, morpholine and benzyl alcohol caused exclusive displacement of chlorine at the 2-position (Table 2, entries 1-3). However, softer nucleophiles, *e.g.* 2-Aminothiophenol, thiocyanate, benzyl mercaptan and 4,6-diaminopyrimidine-2-thiol made exclusive displacement of iodine at the 4-position (Table 2, entries 4-7) .These results suggest that the regiochemistry of nucleophilic attack for system 4 is, in general, based on the hard and soft interaction principles. The hard nucleophiles were preferred to attack the hard C-Cl bond, and soft nucleophiles were preferred to attack the soft C-I bond.

Postulated mechanism for these reactions followed from simple bimolecular addition-elimination mechanism via meisenheimer intermediate [13]. In conclusion, we demonstrated the one-step synthesis of 2,3,5,6-tetrachloro-4-iodopyridine using microwave irradiation in high yield. We also showed that 2,3,5,6-tetrachloro-4-iodopyridine reacts with nucleophiles at both *ortho* and *para* positions to ring nitrogen. *O*- and *N*-centered nucleophiles were substituted at the *ortho* position to the ring nitrogen. In contrast, *S*-centered nucleophiles gave para-substituted products. These results were explained based on the hard and soft interaction principles.

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