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Highly Regioselective DABCO-Catalyzed Nucleophilic Aromatic Substitution (S_NAr) Reaction of Methyl 2,6-Dichloronicotinate with Phenols

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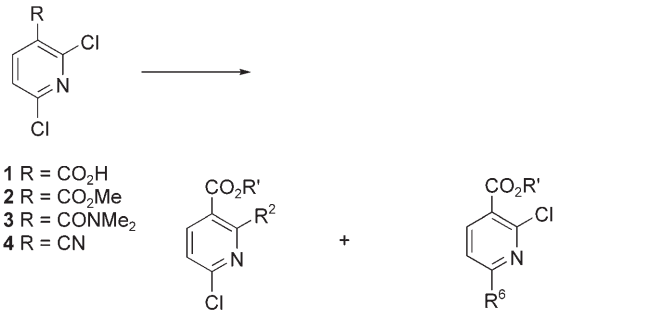
Abstract: Exclusive formation of 6-aryloxy ethers **9** from an S_NAr reaction of methyl 2,6-dichloronicotinate (**2**) with phenols **7** catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) in the presence of stoichiometric triethylamine is described. The reaction proceeds *via* the regioselective formation of an unprecedented DABCO-pyridine adduct **10a**.

Keywords: aromatic substitution; biaryl ether; DABCO catalysis; nucleophilic substitution; pyridines

Substituted pyridines often appear as important motifs in both biologically active compounds as well as pharmaceuticals.[1] Readily available 2,6-dichloronicotinic acid (**1**) and its derivatives **2**–**4** are useful starting materials for the preparation of unique building blocks in the synthesis of new drug candidates.[2] Selective substitution of one or two of the chloride atoms at the 2- and/or 6-position of these compounds, *via* a S_NAr reaction with different nucleophiles, continues to receive intense interest as a method to access the requisite substituted pyridines. For example, Kawato and Newkome reported the treatment of methyl 2,6-dichloronicotinate (**2**) with sodium ethoxide in xylene to give a mixture of monosubstituted **5b** (2-OEt isomer) and **6b** (6-OEt isomer) in favor of **5b**, the 2-OEt isomer.[3] Recently, Hirokawa, et al., reported a new S_NAr reaction of dichloronicotinic acid **1** with potassium methoxide (KOMe) in refluxing MeOH to produce **6a** (6-OMe isomer) as the major product in 66% overall yield after esterification.[4] This process was utilized in the preparation of a key intermediate for the synthesis of a potent serotonin 5-HT_3 and dopamine D_2 receptor antagonist. In addition, they also reported a highly selective S_NAr reaction of methyl 2,6-dichloronicotinate (**2**) with sodium 4-methylbenzenethiolate (*p*-MePhSNa) in DMF, providing the 6-isomer **6c** in both high yield and excellent selectivity (Scheme 1).[5] To our knowledge, the reaction of 2,6-dichloronicotinate derivatives with phenols has not been reported.

As part of an ongoing program to develop a practical synthesis for an investigational drug candidate, synthesis of the biaryl ether **9a** was required. In this paper, we report the discovery of an unprecedented DABCO-pyridine adduct **10a**, derived from the S_NAr reaction of methyl 2,6-dichloronicotinate (**2**) with DABCO and the successful development of a highly regioselective, DABCO-catalyzed S_NAr reaction of dichloronicotinate **2** with phenols **7** to provide 6-aryloxy ethers **9** in high yields.

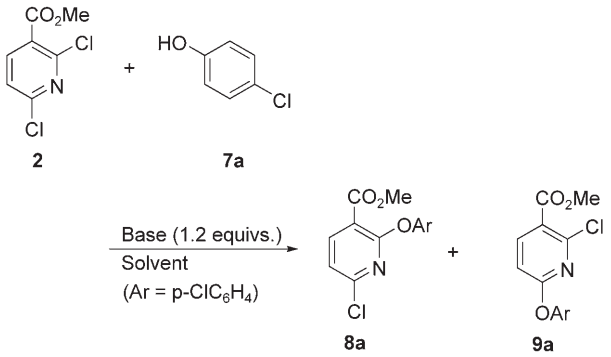
Initial examination of the S_NAr reaction between dichloronicotinate **2** and 4-chlorophenol (**7a**) revealed that slow addition of **7a** to a slurry of **2** and an excess of Cs_2CO_3 in DMF at room temperature, provided the products **8a**/**9a** (1:4) (Scheme 2).[6] Addition of water directly to the reaction mixture led to the crystallization of the crude products. Subsequent recrystallization from *i*-PrOH afforded pure **9a** in 60% overall yield from dichloronicotinate **2**.[7]



Scheme 1.

Table 1. The S_NAr reaction between dichloronicotinate **2** and phenol **7a** with various bases.

Entry	Base	Solvent	Temp.	Reaction Time [h]	Conversion	**8a** : **9a**
1	Cs_2CO_3	DMF	RT	4	100	1 : 4
2	Cs_2CO_3	THF	RT	16	~80	1 : 2
3	Cs_2CO_3	Toluene	RT	16	~50	1 : 2
4	Na_2CO_3	DMF	RT	16	~90	1 : 2
5	K_2CO_3	DMF	RT	16	100	1 : 3
6	LiOBu-*t*	DMF	RT to 60 °C	16	~80	1 : 2
7	NaOBu-*t*	DMF	RT	3	100	1 : 2
8	KOBu-*t*	DMF	−30 °C to RT	3	100	1 : 2
9	*i*-PrMgCl	DMF	0 °C to RT	16	0	–
10	NEt_3	DMF	RT	16	0	–
11	DBU	DMF	RT	8	100	1 : 3
12	DABCO	DMF	RT;	2	100	0 : 100



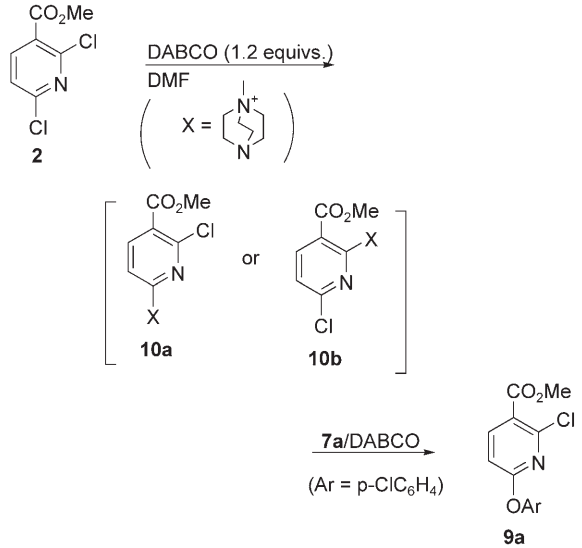
Scheme 2.

In attempting to improve the selectivity of the reaction, we screened solvents and bases. Less-polar solvents, such as THF and toluene (entries 2 and 3) resulted in lower selectivity for **9a** which was consistent with results reported in the literature.[5] Exploring the effect of different cations showed that substitution of Cs_2CO_3 with K_2CO_3, or Na_2CO_3 (entries 4 and 5), led to slower reactions without improving selectivity. In addition, *in situ* generation of the phenolic anion using *t*-BuOM (M = K, Na, or Li, entries 6–8) did not yield any improvement in the product ratio. The magnesium phenolate generated by pre-treatment of chlorophenol **7a** with isopropylmagnesium chloride, surprisingly, did not show any reaction (entry 9).

Substitution of inorganic bases with amine bases provided some interesting observations (Scheme 2). Use of triethylamine did not result in any conversion to products (entry 10), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided a similar ratio of products (1 : 3 ratio of **8a**/**9a**) compared with Cs_2CO_3. A break-through result was obtained when DABCO was added to a solution of dichloronicotinate **2** and chlorophenol **7a** in DMF. Under these conditions, we observed both consumption of the starting materials and exclusive formation of the desired aryl ether **9a** (entry 12).

The fact that DABCO (pK_a 2.97 and 8.82) is less basic than triethylamine (pK_a 10.75),[8] which alone was not effective in producing any products, led us to think that the unique nucleophility of DABCO might be responsible for the dramatic improvement in selectivity.[9] When DABCO (1.2 equivs.) was directly mixed with dichloronicotinate **2** in DMF-d_7, NMR analysis clearly showed the formation of a new product (Scheme 3). The product was identified as the DABCO-pyridine adduct **10a**. Interestingly, none of the isomeric DABCO-pyridine adduct **10b** was detected. Although DABCO adducts of purine, pyrimidine, and 2,4-dinitrobenzene have been reported previously, the formation of the DABCO-pyridine adducts from 2,6-dichloronicotinate derivatives is to the best of our knowledge unprecedented.[10,11,12]

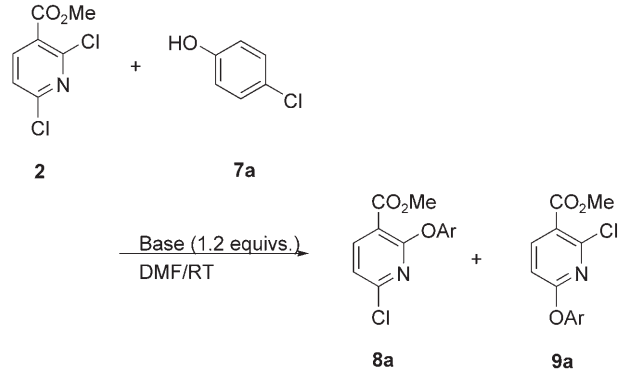
In contrast to the parent dichloronicotinate **2**, the resulting adduct **10a** is much more reactive and readily undergoes the sequential S_NAr reaction with chlorophenol **7a** to give the desired product **9a**.



Scheme 3.

Table 2. The S_NAr reaction of **2** and **7a** using different amine-bases.

Entry	Base	Product(s)	Comments
1	$Me_3N \cdot HCl$	**9a**	1.5 equivs. NEt_3 added
2	quinuclidine	**9a**	
3	3-quinuclidinol	**9a**	
4	TMEDA	**9a**	Low conversion
5	DMAP	**8a**/**9a**	~1:1 ratio



Scheme 4.

Additional experiments carried out using amine bases similar to DABCO, such as trimethylamine,[13] quinuclidine,[11] 3-quinuclidinol and *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA), all provided the desired biaryl ether **9a** exclusively, although a slower reaction with TMEDA was observed (Scheme 4, entries 1–4). It is interesting to note that when 4-dimethylaminopyridine (DMAP) was used, no selectivity was observed (entry 5).[14]

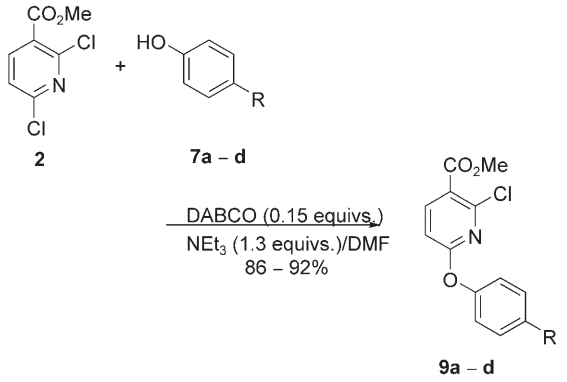
After gaining an understanding of the function of DABCO during *this two-stage S_NAr reaction sequence*, a catalytic DABCO reaction was investigated.[15] In order to regenerate the catalyst (DABCO) from the resulting unreactive HCl salt (DABCO·HCl), a stoichiometric amount of stronger base was required. Triethylamine was an ideal choice since it is more basic than DABCO and not effective alone in promoting the reaction of dichloronicotinate **2** and chlorophenol **7a**. Indeed when catalytic DABCO (0.15 equivs.) and stoichiometric triethylamine (1.3 equivs.) were used, the reaction of dichloronicotinate **2** with chlorophenol **7a** (1.0 equiv.) was complete within 5 h at room temperature and provided the desired biaryl ether **9a** in an excellent 92% yield (Scheme 5). Furthermore, the reaction was extended successfully to other phenols **7b**–**d**, to provide the 6-aryloxy ethers **9b**–**d**, exclusively in high yield (entries 2–4).

In conclusion, a highly regioselective, DABCO-catalyzed S_NAr reaction of methyl 2,6-dichloronicotinate (**2**) with phenols **7a**–**d** in the presence of triethylamine has been developed to afford, exclusively, the 6-substituted products **9a**–**d** in high yields. We have also demonstrated that the reaction proceeds through the regioselective generation of an unprecedented DABCO-pyridine adduct **10a**. Additional studies of the DABCO-catalyzed S_NAr reaction of 2,6-dichloronicotinic acid (**1**) or its derivatives (**3** and **4**) are in progress and the results will be reported in due course.

Experimental Section

Formation of DABCO-Pyridine Adduct (10a)

To a solution of methyl dichloronicotinate **2** (5.2 g, 25.2 mmol) in THF (50 mL) at 5 °C was added solid DABCO (3.3 g, 29.4 mmol) to provide a clear solution. The reaction mixture was stirred at 5 °C for 0.5 h to produce a white slurry. The slurry was warmed to room temperature and stirred for 16 h. After HPLC showed no remaining **2**, the slurry was diluted with THF (25 mL) to aid the filtration. The resulting slurry was filtered to give DABCO-pyridine adduct **10a** as a white solid; yield: 8.0 g (quantitative); mp 165 °C (dec.); ^{1}H NMR (400 MHz, DMF-d_7): $\delta = 3.43$ (br t, $J = 7.4$ Hz, 6H), 4.01 (s,



Scheme 5.

Table 3. DABCO-catalyzed S_NAr reaction of dichloronicotinate **2** with phenols **7a**–**d**.

Entry	Phenol (R)	6-Aryloxy Ethers	Reaction Time [h]	Yield [%]
1	**7a** (Cl)	**9a**	5	92
2	**7b** (H)	**9b**	10	86
3	**7c** (OMe)	**9c**	8	91
4	**7d** (NO_2)	**9d**	4	88

3H), 4.29 (br t, $J=7.4$ Hz, 6H), 8.73 (d, $J=8.4$ Hz, 1H), 8.86 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMF-d_7): $\delta=45.7$, 53.3, 54.8, 117.7, 129.4, 145.2, 147.0, 157.1, 163.9; HR-MS: calcd. for $C_{13}H_{17}ClN_3O_2^+$ (M−Cl): 282.1004; found: 282.1004.

Synthesis of Biaryl Ether 9a by the DABCO-Catalyzed S_NAr Reaction

To a solution of 19.6 g of dichloronicotinate **2** (95.0 mmol) in DMF (80 mL) was added a solution of 4-chlorophenol (**7a**; 12.2 g, 95.0 mmol, 36.6 mL of DMF) at 22 °C, followed by addition of triethylamine (17.3 mL, 124.0 mmol) at 22–24 °C over 15 min. To the resulting solution was added solid DABCO (1.6 g, 14.2 mmol) in one portion (a temperature increase by ~3 °C was observed, a water bath was used to maintain the reaction temperature). The reaction mixture was stirred at 22 °C for 4–5 h and monitored by HPLC (the solution turned into a light slurry and the completion of the reaction was determined by the disappearance of chlorophenol **7a**). To the resulting light slurry was added acetic acid (2.72 mL, 47.5 mmol) and 2-propanol (57.5 mL). Water (30 mL) was added over 0.5 h maintaining the internal temperature at 22–25 °C (during the addition of water, the slurry turned into a clear solution, and eventually a slurry of **9a** was formed providing a good seed-bed). After stirring at 22 °C for 0.5 h, the remaining water (86 mL) was added over 0.5 h. After the slurry had been stirred at 22 °C for 2 h, it was filtered. The product was washed with mixed solvents (60 mL of IPA/H_2O = 1/1). The isolated solid was dried in the vacuum-oven at 50 °C for 8 h to provide a white cotton-like solid **9a**; yield: 24.6 g (89%);[16] mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.92$ (s, 3H), 6.85 (d, $J=8.5$ Hz, 1H), 7.11 (d, $J=8.9$ Hz, 2H), 7.38 (d, $J=8.9$ Hz, 2H), 8.22 (d, $J=8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=52.6$, 109.2, 120.7, 122.6, 129,8, 130.8, 143.9, 149.3, 151.3, 163.5, 164.4.

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[16] The product loss to the mother liquor was at ~3%; the retention time (R_t) obtained by HPLC was identical to the authentic **9a** provided by Dr. Guo Q. Shi from our Laboratories.

