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Studies on the Regioselective Nucleophilic Aromatic Substitution (S_NAr) Reaction of 2-Substituted 3,5-Dichloropyrazines

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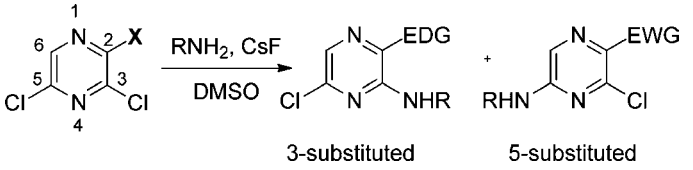
ABSTRACT

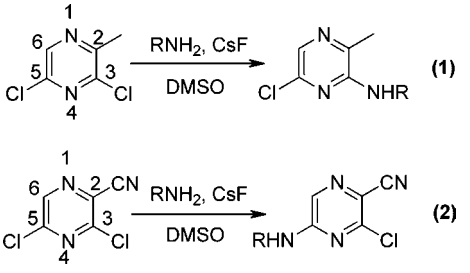


Differences in regioselectivity were observed during the S_NAr reaction of amines with unsymmetrical 3,5-dichloropyrazines. This study revealed that when the 2-position of the pyrazine was occupied with an electron-withdrawing group (EWG), nucleophilic attack occurred preferentially at the 5-position. When the 2-position was substituted with an electron-donating group (EDG), nucleophilic attack occurred preferentially at the 3-position. These results are reported along with a computational rationale for the experimental observations based on the Fukui index at the reacting centers.

Substituted pyrazines containing diverse functional groups are found in numerous naturally occurring compounds, many of which have important pharmacological activities.[1] The ability to install amines in a regioselective manner to an unsymmetrical pyrazine core was needed. Predicting this positional selectivity would be valuable in designing synthetic routes and would enable the SAR of a lead series. After making a small variety of 2-substituted 3,5-dichloropyrazines, a contrast in reactivity under standard S_NAr conditions using the same series of amines across different substrates was observed.

In the initial case (Scheme 1, eq 1), addition of an amine to 2-methyl-3,5-dichloropyrazine in DMSO with CsF gave regioselective substitution at the 3-position. A second reaction utilizing 3,5-dichloropyrazine-2-carbonitrile under identical conditions gave preferential substitution at the 5-position (Scheme 1, eq 2).[2] These intriguing results prompted an investigation into the regioselective S_NAr reaction of unsymmetrical pyrazines, and the exploitation

Scheme 1. First Attempts at Unsymmetrical Pyrazine Targets



† WuXi App Tec Co.

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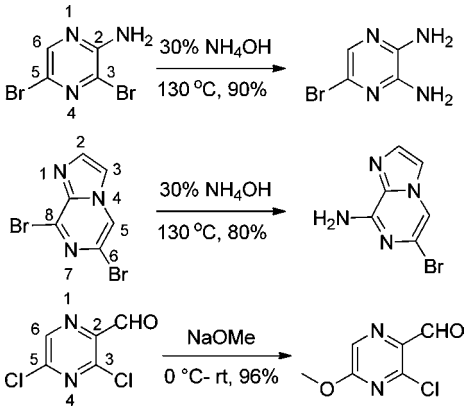
of a computational method to reliably predict this selectivity in subsequent reactions.

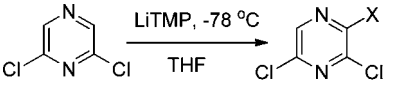
The first example of a regioslective S_NAr reaction with unsymmetrical pyrazines was reported by Camerino in 1960.[3] Nitrogen nucleophilies were added to 2-amino-3,5-dibromopyrazine, and attack occurred preferentially at the 3-position (Scheme 2). Numerous examples of this regioselective S_NAr reaction have been reported in the literature since.[4] Regiochemical selectivity was also reported with 6,8-dibromoimidazo[1,2-*a*]pyrazine where substitution at the 8-bromo position occurred preferentially over the 6-bromo position.[5] The opposite regioselectivity was observed during the reaction with 3,5-dichloropyrazine-2-carbaldehyde and sodium methoxide in which substitution occurred preferentially at the 5-position.[6]

Scheme 2. Examples of Regioselectivity in the Literature



This survey of the selective S_NAr reaction began with a series of pyrazines that featured both electron donating and electron withdrawing functionalities. Gram quantities of 2-substituted 3,5-dichloropyrazines were synthesized by metalation of commercially available 2,6-dichloropyrazine.[7] The symmetrical dichloropyrazine was deprotonated with lithium tetramethylpiperidide (LiTMP) at −78 °C and the anion was quenched with the appropriate electrophile (Scheme 3). Quenching the anion with methyliodide gave a 45% yield of 2-methyl-3,5-dichloropyrazine. Lower yields were obtained when iodine was used as the electrophile, giving a 27% yield of 3,5-dichloro-2-iodopyrazine. The methyl ester was synthesized using CO_2 to form the carboxylic acid which was converted directly to the methyl ester in 49% yield over the two steps.

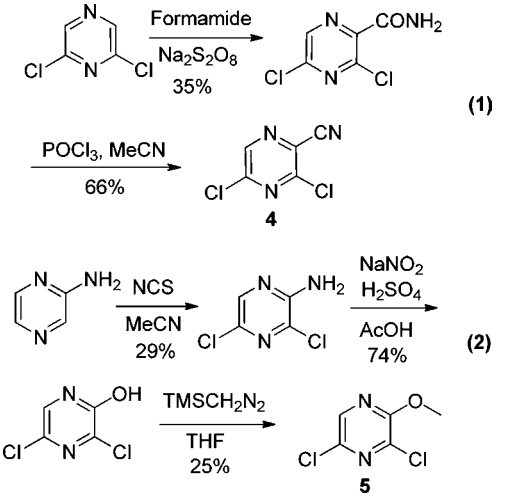
Scheme 3. Metalation of 2,6-Dichloropyrazine To Form Unsymmetrical Pyrazines



Product	X	E^+	%Y
1	CH_3	MeI	45%
2	I	I_2	27%
3	CO_2Me	CO_2/MeI	49%

Synthesis of the remaining starting materials is shown in Scheme 4. 2,6-Dichloropyrazine was converted to the carboamide in 35% yield using the Minisci reaction[8] followed by dehydration with $POCl_3$ to give 3,5-dichloropyrazine-2-carbonitrile (**4**) in 66% yield (Scheme 4, eq 1). 2-Methoxy-3,5-dichloropyrazine (**5**) was synthesized in three steps beginning with NCS-mediated chlorination of 2-aminopyrazine (Scheme 4, eq 2). Diazotization of the amino group and subsequent hydrolysis provided the phenol which was converted to the methyl ether in 5% yield over three steps.

Scheme 4. Synthesis of the Cyano- and Methoxydichloropyrazines



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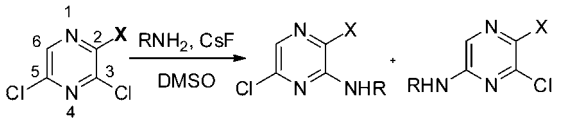
With the pyrazines in hand, we selected a series of amines with varying degrees of steric bulk and nucleophilicity to investigate the regioselective S_NAr reaction. The amines used for this study were isobutylamine, morpholine, benzylamine, diethylamine, and trifluoroethylamine. General S_NAr reaction conditions were used with a 1:1 stoichiometric ratio of pyrazine to amine, 3 equiv of CsF, and 0.3 M concentration in DMSO. Reactions were initially carried out at room temperature and monitored by LCMS after 2 h. If no desired product or minimal amount of product (< 10%) had been formed, the reactions were heated to 75 °C until all starting materials were consumed. For the pyrazines bearing electron-withdrawing substituents (CN, CO_2Me, I), reactions were usually complete within 2−5 h at room temperature, while heat was required for reactions with electron-donating functionalities (OMe, Me).

Table 1. Results of the S_NAr Reaction with Unsymmetrical Pyrazines



entry	X	RNH_2	product A (%)	product B (%)
1	CH_3	*i*-$BuNH_2$	**6A** (62)	**6B** (10[a])
2	CH_3	morpholine	**7A** (63)	**7B** (14)
3	CH_3	$BuNH_2$	**8A** (46)	**8B** (8[a])
4	CH_3	Et_2NH	**9A** (59)	–[b]
5	CH_3	$CF_3CH_2NH_2$	++	++
6	OCH_3	*i*-$BuNH_2$	**10A** (75)	–
7	OCH_3	morpholine	**11A** (82)	–
8	OCH_3	$BuNH_2$	**12A** (85)	–
9	OCH_3	Et_2NH	**13A** (46)	–
10	OCH_3	$CF_3CH_2NH_2$	**14A** (46)	–
11	CO_2Me	*i*-$BuNH_2$	**15A** (8)	**15B** (6)
12	CO_2Me	morpholine	**16A** (7)	**16B** (65)
13	CO_2Me	$BuNH_2$	**17A** (5)	**17B** (74)
14	CO_2Me	Et_2NH	**18A** (3)	**18B** (59)
15	CO_2Me	$CF_3CH_2NH_2$	**19A** (3)	**19B** (53)
16	CN	*i*-$BuNH_2$	–	**20B** (75)
17	CN	morpholine	**21A** (3)	**21B** (69)
18	CN	$BuNH_2$	**22A** (2)	**22B** (50)
19	CN	Et_2NH	–	**23B** (56)
20	CN	$CF_3CH_2NH_2$	–	**24B** (62)
21	I	*i*-$BuNH_2$	**25A** (60)	**25B** (20)
22	I	morpholine	**26A** (59)	**26B** (19)
23	I	$BuNH_2$	**27A** (54)	**27B** (21)
24	I	Et_2NH	**28A** (51)	**28B** (20)
25	I	$CF_3CH_2NH_2$	**29A** (42)	**29B** (11)

[a] Ratio determined by ^{1}HNMR. [b] – no product detected. ++ no product isolated.

All reactions were purified by silica gel column chromatography, and the regiochemistry of the products confirmed by NOE NMR experiments, or in some cases X-ray crystal structures.

The experiments revealed clear trends for selectivity of the unsymmetrical pyrazines shown in Table 1. In the examples shown, the nucleophilicity and steric bulk of the amine played a minimal role in the selectivity, while pyrazine substitution had a significant effect on regiochemical outcome of the reaction. When the 2-position was substituted with an electron-donating group, nucleophilic attack occurred preferentially at the 3-position. The methoxy group provided the greatest selectivity with none of the minor regioisomer being observed for any of the amines studies, whereas reactions with 2-methyl-3,5-dichloropyrazine typically gave 8−14% of the minor isomer. When the 2-position of the pyrazine was occupied with an electron-withdrawing group, nucleophilic attack occurred preferentially at the 5-position. The cyano and methyl ester functionalities gave similar selectivities in which 3−8% of the minor isomer was formed in most cases. Reactions with 3,5-dichloro-2-iodopyrazine were less selective and favored the 3-position despite the electron-withdrawing character usually associated with an iodine substituent. This may be explained by the increased electron density of the pyrazine ring through resonance effects of the iodo lone pair electrons.

With these results, we considered possible explanations for the observed selectivities and sought to identify a computational method for predicting positional selectivity of the reaction. Atomic charge distribution, solvent accessible surface area, sterics, the relief of *A* strain and Fukui function were considered as possible factors for the observed results. Calculated CM1A atomic charge[9] and solvent accessible surface area[10] values showed little differentiation between the C3 and C5 positions of the pyrazine as shown in Figure 1.

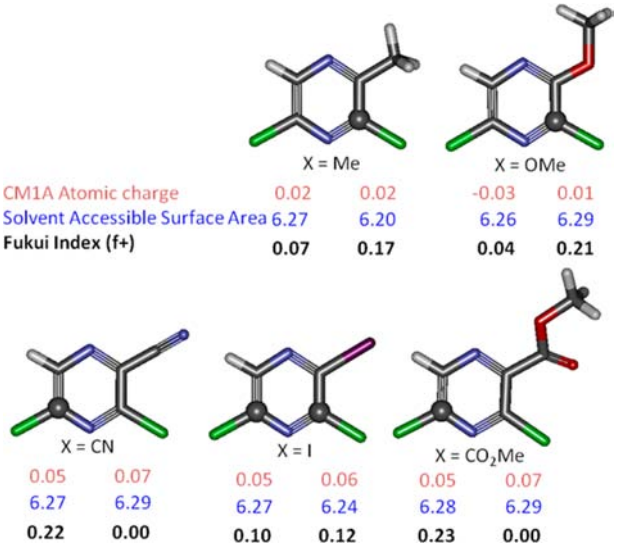


Figure 1. Calculated atom-based Fukui indices.

Given the *A*-values are ranked CH_3 (1.7) > CO_2CH_3 (1.27) > OCH_3 (0.6) > I (0.43) > CN (0.17), this would

(9) CM1A atomic charge: The input molecules were first minimized using OPLS2005 FF with water as solvent in MacroModel and then further geometry optimized at the AM1 level. The CM1A (AM1+CM1) atomic charges were calculated using the AMSOL program.

predict that methyl and ester substituents would provide greater selectivity at the 3-position over methoxy, iodo, and cyano, and as such, *A* strain values did not correlate with the observed experimental trends. On the other hand, Fukui indices did show differentiation between the C3 and C5 positions of the 3,5-dichloropyrazines and correlated well with the observed experimental trends (Figure 1). The Fukui function[11] is a computational model that has been used to predict regioselectivity in organic reactions involving nucleophiles and electrophiles such as dipole addition reactions[12] and Michael reactions.[13] The Fukui function represents the changes in the molecular electron density upon addition or removal of charge. For a given reference atom in a series of related molecules, one can rank them according to the values of a particular Fukui index for that atom. High positive values (f+) indicate reactivity toward nucleophilic attack while high negative values (f−) indicate reactivity toward electrophilic attack. Atom-based Fukui indices were calculated for the five unsymmetrical pyrazines in Figure 1 using Jaguar from Schrodinger[14] and were in good agreement with the observed experimental regioselectivites. The preferred site of reactivity is rendered as a solid gray ball. The calculated Fukui indices (f+) agree with our experimental results where the larger (f+) is the preferred site for nucleophilic attack. In addition, there is little differentiation between the calculated C3 and C5 values (f+) for the iodo pyrazine, which correlates well with our observations that iodo pyrazines showed reduced selectivities in the S_NAr reaction.

In conclusion, we have shown that the addition of nitrogen nucleophilies to unsymmetrical 3,5-dichloropyrazine is both regioselective and occurs in modest chemical yields. Clear trends exist in which electron withdrawing groups direct substitution to the 5-chloro position of the pyrazine while electron donating groups direct substitution to the 3-chloro position. In addition, calculated Fukui indices for the unsymmetrical 3,5-dichloropyrazines correlate well with experimental regioselectivities and can be used to reliably predict the preferred site of reactivity.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(10) (a) Solvent-accessible surface area: The input molecules were first minimized using OPLS2005 FF with water as solvent in MacroModel with probe radius 1.4 Å and the rest of the parameters as default from MSMS: (b) Sanner, M. F.; Spehner, J. C.; Olson, A. J. *Biopolymers* **1996**, *38*, 305–320.

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(14) The Fukui index is calculated in the following way: The input molecules were first minimized using OPLS2005 FF with water as solvent in MacroModel. The minimized conformations were then geometry optimized using B3LYP/6-31G** basis set. The Fukui indices were then calculated based on the optimized geometry at the same level. All QM calculations were performed using Jaguar from Schrodinger.