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A Novel and Versatile Entry to Asymmetrically Substituted Pyrazines

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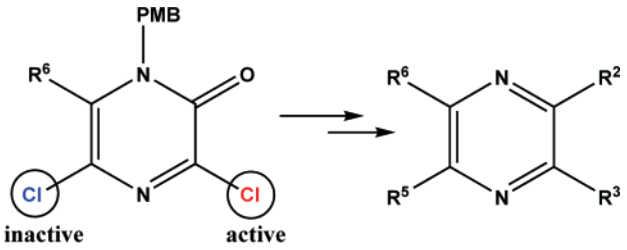

PMB = *p-methoxybenzyl*

A novel and convenient procedure for the synthesis of asymmetrically tri- and tetrasubstituted pyrazines starting from *para*-methoxybenzyl-protected 3,5-dichloro-2(1*H*)-pyrazinones was elaborated. The key step is the conversion of the intermediate *para*-methoxybenzyl-protected thiopyrazinone upon treatment with MeI/I_2, into a pyrazine, rendering the chlorine in the C5-position susceptible to substitution. This approach entails the orthogonal introduction of the four substituents of the pyrazine scaffold. The application of microwave irradiation during different steps of the sequence has been shown to be highly valuable for speeding up reactions.

Introduction

Substituted pyrazines represent the core structure of a number of important natural as well as man-made heterocyclic compounds. Tri- and tetrasubstituted pyrazines constitute flavor components in food[1] and are versatile synthetic intermediates.[2] Especially, pyrazines bearing a thioether moiety are known to possess a nice aroma.[1] Many substituted pyrazines possess important pharmacological activities such as antimutagenic[3] or vascular endothelial growth factor inhibitory activity[4] or as epithelial sodium channel blockers.[5] Despite their importance, only a limited number of synthetic methodologies are described for the generation of multisubstituted pyrazines.[6] The common methods for the preparation of alkylpyrazines through self-condensation of α-amino carbonyl compounds or via combination of α-diketones with vicinal diamines[7] are showing the lack of regioselectivity as a major impediment. Some modifications

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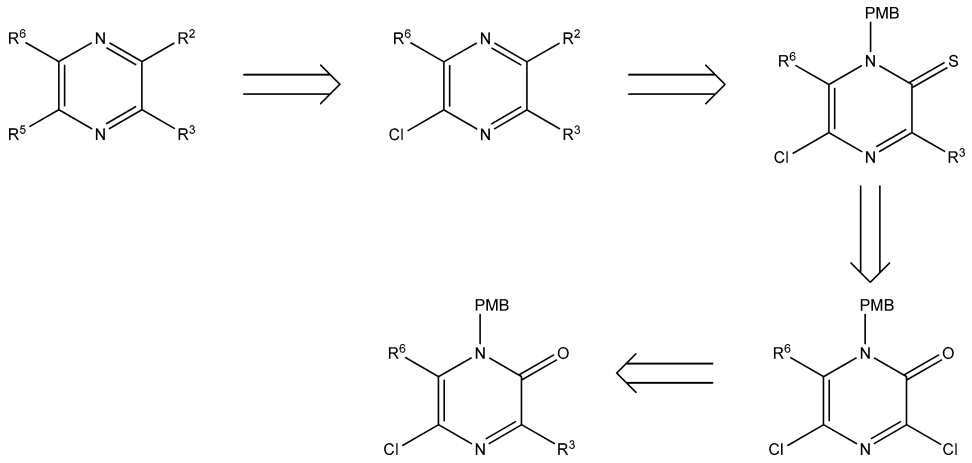
SCHEME 1. Retrosynthetic Analysis for the Generation of Asymmetrically Substituted Pyrazines



of these strategies have surfaced as for example oxidative addition of amino alcohols to epoxides,[8] reaction of α-azido ketones with α-amino methoximes,[9] or treatment of α-nitro ketones with α-amino ketones using octyl viologen.[10] Although noteworthy in their own right, these methods often result in low yields and are insufficiently versatile for varying the substituent pattern. An interesting approach is the 1,4-addition of 1,2-diamines to 1,2-diaza-1,3-butadienes for the synthesis of tetrasubstituted pyrazines.[11] However, this procedure limits the substitution pattern at the C5-position to a methyl group. Another interesting report describes the treatment of a α-diazo-*β*-ketoester with an α-amino acid to produce tetrasubstituted pyrazines. However this method restricts the substitution pattern at the C6-position to an ester group.[12] The regioselective metalation of pyrazines is a useful alternative for the synthesis of multisubstituted pyrazines,[13] but this requires already the pyrazine scaffold as starting material and selective 2,3,5,6-substitution of pyrazines still remains a major and challenging problem. We will now report a novel and versatile methodology for the synthesis of asymmetrically substituted pyrazines.

We have previously explored the application of 3,5-dichloro-2(1*H*)-pyrazinones as attractive starting materials for the synthesis of different heterocyclic compounds.[14] We envisaged that the pyrazinone framework offers a unique gateway for the generation of asymmetrically tri- and tetrasubstituted pyrazines (Scheme 1). The substituent in the C6-position of the pyrazinone is determined by the aldehyde used during its construction,[15] while the substituent at the C3-position could be easily introduced via reaction of the imidoyl chloride moiety.[16]

Recently, Kappe and co-workers reported the arylation of thioamides and dihydropyrimidine thiones using a modified Liebeskind−Srogl protocol.[17] As we envisaged the application of this elegant protocol we planned to convert the pyrazinone into the corresponding pyrazine-thione followed by hydrolysis of the *p*-methoxybenzylether (PMB-ether). This should allow a Liebeskind−Srogl cross-coupling at the C2-position giving access to asymmetrically 2,3,6-trisubstituted pyrazines. Moreover pyrazine formation would render the hitherto unreactive chlorine in C5-position susceptible to transition metal-catalyzed substitution, paving the way for the synthesis of asymmetrically 2,3,5,6-tetrasubstituted pyrazines.

Results and Discussion

As a proof of concept the pyrazinones **1a,b** were subjected to the proposed procedure (Scheme 2). Both of the compounds were methoxylated at the C3-position using sodium hydride providing the required compounds **2a,b** in quantitative yield.[18] Treatment of **1a** with Me_4Sn under Stille conditions provided the methylated compound **2c** in 92% yield.[16] Compound **2a** was treated with 1 mol of Lawesson's reagent (LR) per mol of **2a** without any solvent, applying focused microwave irradiation at a ceiling temperature of 130 °C and 150 W maximum power, according to some literature protocols.[19] However, no product was formed even after 1 h of irradiation, and the majority of starting material remained unreacted. On the contrary, when toluene was added, keeping all other conditions unchanged, compound **3a** could be isolated in 56% yield along with

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SCHEME 2. Synthesis of the Thiopyazinones 3a−c

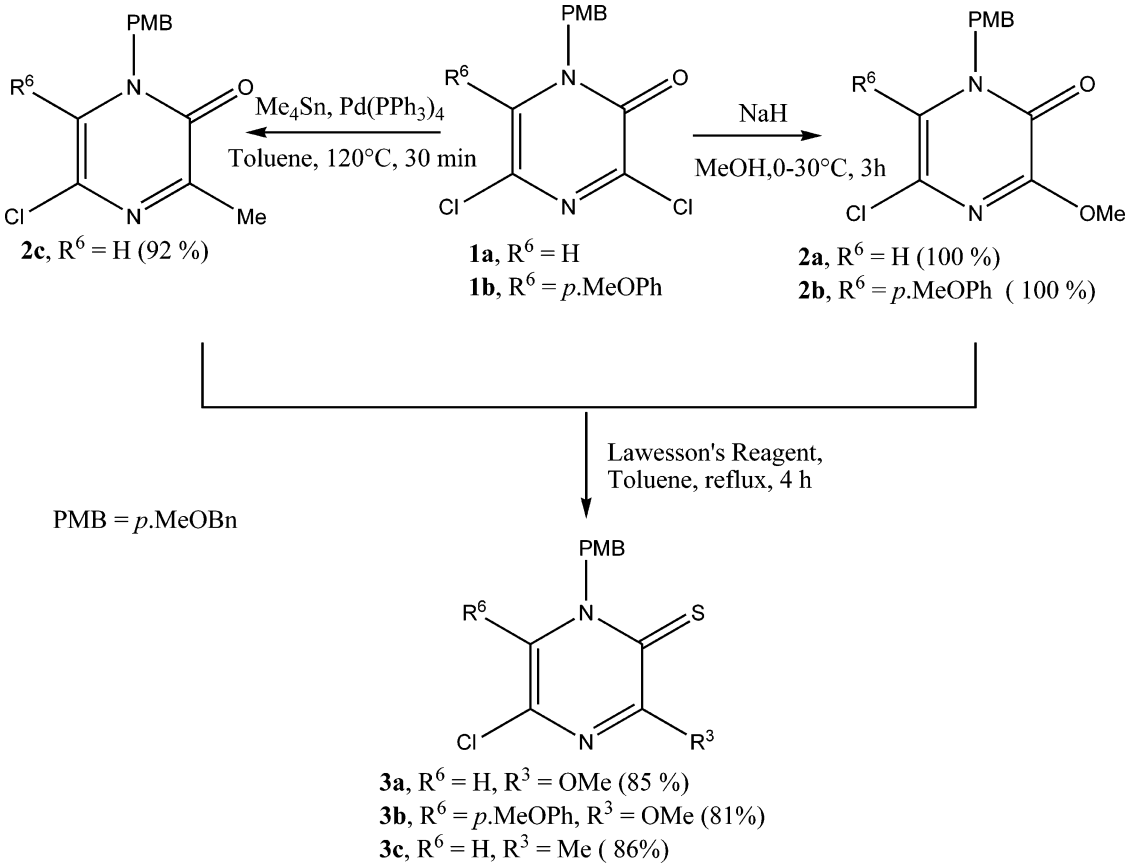
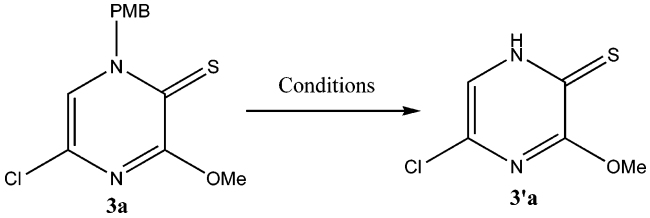


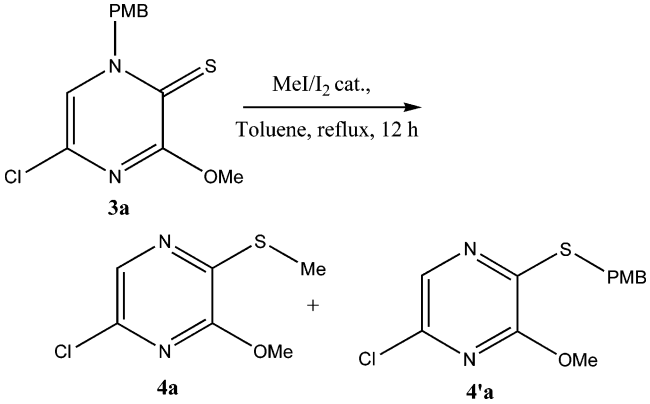
TABLE 1. Optimization Study for PMB Removal Group by the Action of Various Cleaving Agents[a]



entry	cleaving agent (equiv)	additive (equiv)	time (h)	method ΔT or MW	yield[b] (%)
1	TFA (10)	−	24	ΔT	10[c]
2	TFA (10)	−	0.5	MW	10[c]
3	TFA (10)	PMSA[d] (0.1)	24	ΔT	17[c]
4	TFA (10)	PMSA[d] (0.1)	0.5	MW	15[c]
5	TFA (10)	PMSA[d] (0.1)	1	MW	15[c]
6	TFA (10)	NaI (1.2)	24	ΔT	25[c]
7	TFA (10)	H_2O (excess)	24	ΔT	15[c]
8	TFA (10)	$HSiMe_3$ (1.5)	24	ΔT	17[c]
9	DDQ (2)	−	24	ΔT	0[e]
10	CAN (2)	−	10	ΔT	0[f]

[a] Reaction were run with **3a** (0.1 mmol) using various cleaving agents under conventional heating at reflux temperature or upon microwave irradiation (100 °C, 150 W). [b]Isolated yields. [c]Sluggish reaction yielding inseparable side products along with starting material. [d]PMSA = *p*-methane sulfonic acid. [e]Only starting material was recovered. [f]Starting material next to unidentified side products.

TABLE 2. Conditions for Concomitant PMB Cleavage and Thioether Formation[a]



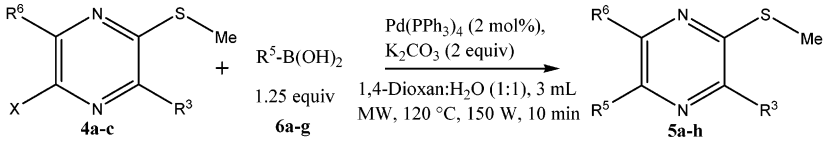
entry	cleaving agent (equiv)	catalyst (mol %)	time (h)	method (ΔT)	yield (%)[b] **4a** (**4′a**)
1	MeI (solvent)	I_2 (10)	12	ΔT	69 (20)
2	MeI (solvent)	I_2 (20)	12	ΔT	68 (20)
3	MeI[c] (10)	I_2 (10)	12	ΔT	71 (18)
4	MeI[c] (5)	I_2 (10)	12	ΔT	73 (20)
5	MeI[c] (5)	I_2 (10)	36	ΔT	64 (19)

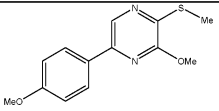
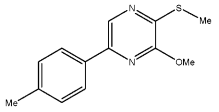
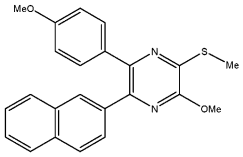
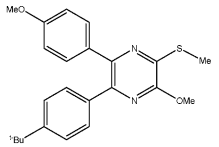
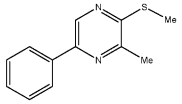
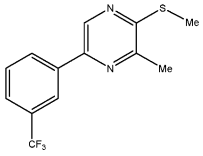
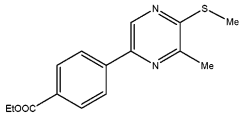
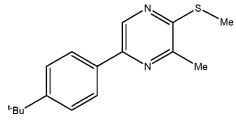
[a] Reactions were run with **3a** (0.1 mmol) and iodine (catalytic amount) in MeI (1.5 mL) under reflux for the stipulated period. [b]Isolated yields. [c]Reactions were run with **3a** (0.1 mmol) using MeI/I_2 in toluene (3 mL) under reflux conditions.

unreacted starting material. Interestingly, when switching to conventional reflux conditions in toluene, reaction of **2a** with LR provided 85% yield of the desired **3a** after 4 h of heating. Decreasing the amount of LR to 0.6 mol per mol starting material resulted in the same yield but with an increased reaction time to 15 h. Applying the same conditions compounds **3b,c** were obtained in excellent yields of 81% and 86%, respectively (Scheme 2).

During the next step, we encountered difficulties in finding suitable conditions for PMB-group removal. A number of

TABLE 3. Microwave-Assisted Suzuki−Miyaura Coupling of 5-Halo-2-(methylthio)-pyrazines[a]



entry	reactant	R^5	compd.	product	yield (%)[b]
1	**4a**	**4-MeO phenyl** **6a**	**5a**		92
2	**4a**	**4-Me phenyl** **6b**	**5b**		91
3	**4b**	**2-Naphthyl** **6c**	**5c**		94
4	**4b**	**4-^{t}Bu phenyl** **6d**	**5d**		87
5	**4c**	**Phenyl** **6e**	**5e**		82
6	**4c**	**3-CF_3 phenyl** **6f**	**5f**		68
7	**4c**	**4-COOEt phenyl** **6g**	**5g**		99
8	**4c**	**4-^{t}Bu phenyl** **6d**	**5h**		89

[a] Reactions were run on a 0.3 mmol scale of **4a**−**c**, boronic acid (1.25 equiv), $Pd(PPh_3)_4$ (2 mol %), K_2CO_3 (2 equiv) in 1,4-dioxan/H_2O (1:1) (3 mL); the mixture was irradiated in a sealed tube at a ceiling temperature of 120 °C and 150 W maximum power for 10 min. [b]Isolated yields are reported (single runs).

reported protocols for the removal of the PMB group were tried.[20] For example, experiments involving **3a** were performed applying trifluoroacetic acid (TFA) as a cleaving agent, but the desired compound **3′**a was formed in disappointingly low yields along with a mixture of inseparable side products (Table 1, entries 1−8). The use of microwave irradiation did not result in higher yields (Table 1, entries 2, 4 and 5). Switching to alternative cleaving agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or cerium ammonium nitrate (CAN)

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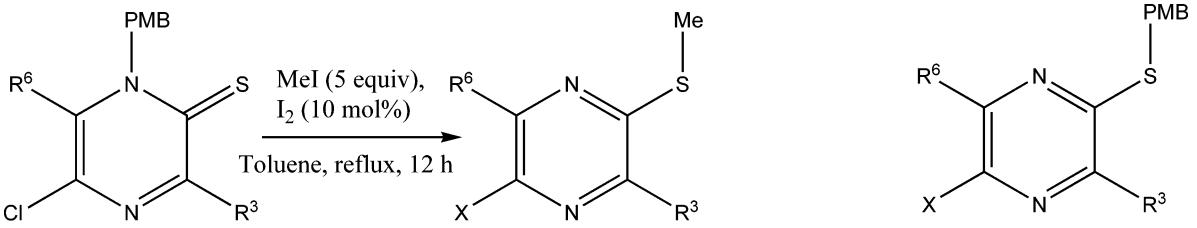
SCHEME 3. Preparation of Thioethers 4a−c along with Side Products 4′a−c



3a, R^6 = H, R^3 = OMe
3b, R^6 = *p*.MeOPh, R^3 = OMe
3c, R^6 = H, R^3 = Me
PMB = *p*.MeOBn

4a, R^6 = H, R^3 = OMe, X = Cl (73 %)
4b, R^6 = *p*.MeOPh, R^3 = OMe, X = Cl (71 %)
4c, R^6 = H, R^3 = Me, X = I (67 %)

4'a = 20 %
4'b= 22 %
4'c= 19 %

did not bring any amelioration. With DDQ no reaction took place (Table 1, entry 9), whereas with CAN the starting material disappeared within 15 min resulting in the formation of an inseparable mixture of products (Table 1, entry 10). Apparently the deprotected pyrazine−thione is rather unstable and undergoes rapid decomposition once formed.

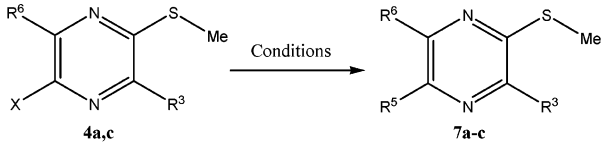
According to the literature thioamides could be activated toward hydrolysis upon alkylation.[21] However, refluxing a solution of compound **3a** in MeI only resulted in salt formation. Gratifyingly we found that upon reflux of a mixture of compound **3a**, a catalytic amount of I_2 (10 mol %), and an excess of MeI for 12 h, the desired thioether **4a** was obtained in 69% yield however along with 20% of the C2 *p*-methoxybenzyl thioether **4′a** as the main side compound (Table 2, entry 1). Although no further enhancement of product yield or reduction of side product could be achieved by altering the reaction conditions (Table 2), the amount of MeI could be significantly lowered to 5 equiv when toluene was used as the solvent (Table 2, entry 4).

This optimized protocol was applied for the conversion of **3b,c** into **4b,c** (Scheme 3). While **3b** produced the expected product **4b**, reaction of **3c** resulted in the formation of the corresponding iodo substituted compound **4c** at C5-position**.** Most probably the presence of a methoxy group at the C3-position of **3a,b** renders the chlorine in the C5-position less sensitive for nucleophilic displacement by iodide. In both cases the undesired *p*-methoxybenzyl ethers **4′b,c** were formed in small amounts of 22% and 19%, respectively.

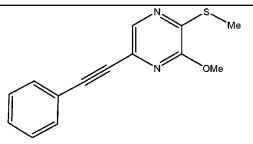
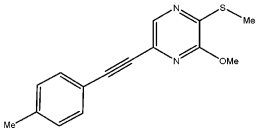
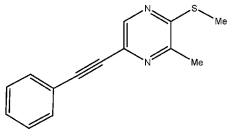
To the best of our knowledge, there is no literature precedent about the conversion of a PMB-protected thioamide into a methyl imidithioate applying a MeI/I_2 mixture.

In the generated pyrazines the chlorine becomes susceptible for transition metal-catalyzed reactions. First we evaluated the Suzuki−Miyaura cross-coupling.[22] The reactions were performed on substrates **4a−c** using 1.25 equiv of boronic acids **6a−g** and 2 mol % $Pd(PPh_3)_4$ as the catalyst in 3 mL of dioxane/H_2O (1:1). The mixture was irradiated at a ceiling temperature of 120 °C and a maximum power of 150 W for 10 min, providing excellent yields ranging from 68 to 99% (Table 3). Next we investigated the Sonogoshira cross-coupling[23] for the substrates **4a,c**. Reactions were performed under focused microwave irradiation at 90 °C (50 W), for 20 min, using 1 mol % $Pd(PPh_3)_2Cl_2$ in DMF/TEA (1:1) and 1.2 equiv of the appropriate acetylene. The products were isolated in good yields of 69% to 81% (Table 4). Finally, amination was evaluated applying Buchwald−Hartwig conditions.[24] A mixture of compound **4a** (0.3 mmol), morpholine (1.25 equiv), NaO^{t}Bu (1.5 equiv), tetrabutyl ammonium bromide (TBAB) (1.2 equiv), and

TABLE 4. Microwave-Assisted Sonogashira Reaction of 5-Halo-2-(methylthio)-pyrazines[a]



4a,c **7a-c**

entry	reactant	compd.	product	yield (%)[b]
1	**4a**	**7a**		69
2	**4a**	**7b**		74
3	**4c**	**7c**		81[c]

[a] Reactions were run on a 0.31 mmol scale of **4a−c**, acetylene (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (5 mol %), TBAB (1.2 equiv) in 3 mL of DMF/TEA (1:1); the mixture was irradiated in a sealed tube at a ceiling temperature of 90 °C and 50 W maximum power for 20 min. [b]Isolated yields are reported (single runs). [c]The reaction was run without addition of TBAB. TBAB = tetrabutyl ammonium bromide.

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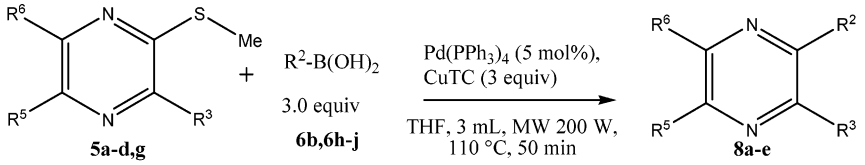
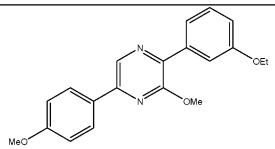
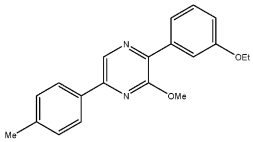
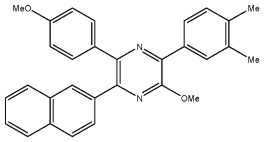
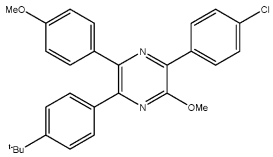
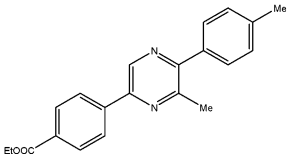
TABLE 5. Microwave-Assisted Liebeskind−Srogl Coupling of 2-(Methylthio)-pyrazines[a]



entry	reactant	R^2	compd.	product	yield (%)[b]
1	**5a**	**3-EtO phenyl** **6h**	**8a**		82
2	**5b**	**3-EtO phenyl** **6h**	**8b**		91
3	**5c**	**3,4-diMe phenyl** **6i**	**8c**		94
4	**5d**	**4-Cl phenyl** **6j**	**8d**		89
5	**5g**	**4-Me phenyl** **6b**	**8e**		78

[a] Reactions were run on a 0.2 mmol scale of **5a−d,g**, boronic acid (3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), CuTC (3 equiv) in THF (3 mL); the mixture was irradiated in a sealed tube at a ceiling temperature of 110 °C and 200 W maximum power for 50 min. [b]Isolated yields are reported (single runs). CuTC = copper thiophene-2-carboxylate.

3 mol % of $Pd(OAc)_2$/(±)-BINAP (1/1.1) as the catalytic system in 1,4-dioxane (3 mL) was irradiated for 25 min at a ceiling temperature of 130 °C and a maximum power of 300 W. The desired aminated compound 4-(6-methoxy-5-methylsulfanyl-pyrazin-2-yl)-morpholine (**7d**) was isolated in 62% yield along with some starting material.

We were eager to know if the thiomethylether group at the C2-position of the newly generated pyrazines should be sensitive to Liebeskind−Srogl conditions[25] (Table 5). A THF solution of compounds **5a−d,g** was reacted with various boronic acids **6a−d**, in the presence of $Pd(PPh_3)_4$ (5 mol %) and Copper thiophene-2-carboxylate (CuTC) (3.0 equiv) as the catalytic system, applying a ceiling temperature of 110 °C at 200 W maximum power for 50 min. To our satisfaction, the reactions proceeded smoothly delivering the compounds in excellent yields ranging from 78% to 94%.

(25) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

The conformation of asymmetrically substituted pyrazine **8c**, which was crystallized from dichloromethane/heptane (1:1), was unambiguously confirmed by X-ray crystallography.[26]

Conclusion

In conclusion we have developed an orthogonal procedure for the generation of asymmetrically tri- and tetrasubstituted pyrazines starting from 3,5-dichloro-2(1*H*)-pyrazinones protected with a *p*-methoxybenzylether at their N1-position. The key step of this sequence is a mild, one-step iodine-catalyzed methylation with concomitant aromatization of the generated thiopyrazinone. The 5-chloro substituent, inactive in the pyrazinone, becomes sensitive to substitution in the pyrazine, paving

(26) CCDC − **666941** contains the structure and supplementary crystallographic data for the structure **8c**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.

the way for further derivatization via Suzuki, Sonogoshira, and Buchwald−Hartwig coupling reactions. The thioether moiety of these tri- and tetrasubstituted pyrazines was finally successfully subjected to Liebeskind−Srogl coupling conditions to yield unique asymmetrically substituted pyrazines, which are difficult to obtain via other methodologies. The application of microwave irradiation during different steps of the sequence has been shown to be highly valuable for speeding up reactions.

Experimental Section

A Typical Procedure for the Suzuki Coupling To Generate Compound 5a−h. In a 10 mL microwave vial the following were successively dissolved in dioxane/H_2O (1:1, 3 mL): halopyrazine **4a**−**c** (0.3 mmol), boronic acid **6a**−**g** (0.36 mmol, 1.2 equiv), Pd(PPh_3)$_4$ (8 mg, 2 mol %), and K_2CO_3 (84 mg, 2 equiv). The reaction tube was sealed and irradiated at a ceiling temperature of 120 °C using 150 W maximum power for 10 min. After the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to preparative HPLC column chromatography. All the compounds were purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water/acetonitrile/HCOOH) and 0:100:0.01 (water/acetonitrile/HCOOH) for 20 min, with the UV detector set at λ = 215 and 254 nm to afford compounds **5a**−**h**.

3-Methoxy-5-(4-methoxyphenyl)-2-(methylthio)pyrazine (5a): 92% yield. white crystalline solid. Mp 95−97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.92 (d, J = 9.9 Hz, 2H), 6.97 (d, J = 9.9 Hz, 2H), 4.09 (s, 3H), 3.85 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 155.8, 143.8, 143.6, 131.6, 129.0, 127.6, 114.3, 55.5, 53.8, 12.1. HR-MS (EI): $C_{13}H_{14}N_2O_2S$ calcd 262.0776, found 262.0772.

Sonogashira Coupling Reaction on 4a, 4c. A Typical Procedure. In a 10 mL microwave vial the following were successively dissolved in DMF/Et_3N (1:1, 3 mL): compound **4a**, **4c** (0.31 mmol), acetylene (0.37 mmol, 1.2 equiv), Pd(PPh_3)Cl_2 (5 mg, 2 mol %), TBAB (1.2 equiv), and CuI (3 mg, 5 mol %). The reaction tube was sealed and irradiated in a microwave at a ceiling temperature of 90 °C using 50 W maximum power for 20 min. After the reaction mixture was cooled with an air flow for 15 min, it was extracted with dichloromethane (2 × 150 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to preparative HPLC column chromatography. All the compounds were purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water/acetonitrile/HCOOH) and 0:100:0.01 (water/acetonitrile/HCOOH) for 20 min, with the UV detector set at λ = 215 and 254 nm to afford compounds **7a**−**c**.

3-Methoxy-2-(methylthio)-5-(2-phenylethynyl)pyrazine (7a): 69% yield. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.60−7.57 (m, 2H), 7.39−7.37 (m, 3H), 4.07 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 147.0, 139.1, 131.9, 129.6, 129.1, 128.5, 122.2, 116.5, 91.5, 86.3, 54.4, 12.1. HR-MS (EI): $C_{14}H_{12}N_2OS$ calcd 256.0670, found 256.0675.

A Typical Procedure for the Leibeskind−Srogl Coupling To Generate Compound 8a−e. In a 10 mL microwave vial the following were successively added: compound **5a**−**d**, **5g** (0.2 mmol), THF (3 mL), boronic acid **6a**−**d** (0.6 mmol, 3.0 equiv), Pd(PPh_3)$_4$ (11 mg, 5 mol %), and CuTC (76 mg, 2 equiv). The reaction tube was sealed and irradiated at a ceiling temperature of 110 °C using 200 W maximum power for 50 min. After the reaction mixture was cooled with an air flow for 15 min, it was extracted with dichloromethane (2 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to preparative HPLC column chromatography. The compound was purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water/acetonitrile/HCOOH) and 0:100:0.01 (water/acetonitrile/HCOOH) for 25 min, with the UV detector set at λ = 215 and 254 nm to afford compound **8a**−**e**.

2-(3-Ethoxyphenyl)-3-methoxy-5-(4-methoxyphenyl)pyrazine (8a): 82% yield. White crystalline solid. Mp 102−104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.04 (d, J = 9.5 Hz, 2H), 7.71−7.67 (m, 2H), 7. 39−7.34 (t, J = 8.7 Hz, 1H), 7.01 (d, J = 9.9 Hz, 2H), 6.97−6.93 (dd, 1H), 4.15−4.08 (m, 2H), 4.12 (s, 3H), 3.86 (s, 3H), 1.46−1.41 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 158.9, 157.1, 147.3, 139.9, 137.3, 132.1, 129.2, 128.7, 128.1 (× 2C), 121.5, 115.5, 114.9, 114.4 (× 2C), 63.6, 55.5, 53.5, 14.9. HR-MS (EI): $C_{20}H_{20}N_2O_3$ calcd 336.1474, found 336.1470.

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Supporting Information Available: Detailed experimental description and spectral data (NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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