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Novel syntheses of 3-anilino-pyrazin-2(1*H*)-ones and 3-anilino-quinoxalin-2-(1*H*)-ones via microwave-mediated Smiles rearrangement

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Abstract

In this Letter, we report a novel approach to the preparation of 3-anilino-pyrazin-2(1*H*)-ones and 3-anilino-quinoxalin-2(1*H*)-ones from the corresponding 3-halo pyrazin-2-amines and 3-haloquinoxalin-2-amines, using a microwave-mediated Smiles rearrangement.

Amino-pyrazinones and amino-quinoxalinones are frequently encountered in the chemical literature as versatile scaffolds for medicinally relevant molecules (Fig. 1), such as anti-apoptotic protease inhibitors (**1**),[1] anti-diabetic glycogen phosphorylase inhibitors (**2**),[2] antithrombotics (**3**),[3] and antiviral HIV-reverse transcriptase inhibitors (**4**).[4] In this Letter, we disclose a novel and facile method to prepare 3-anilino-pyrazin-2(1*H*)-ones and

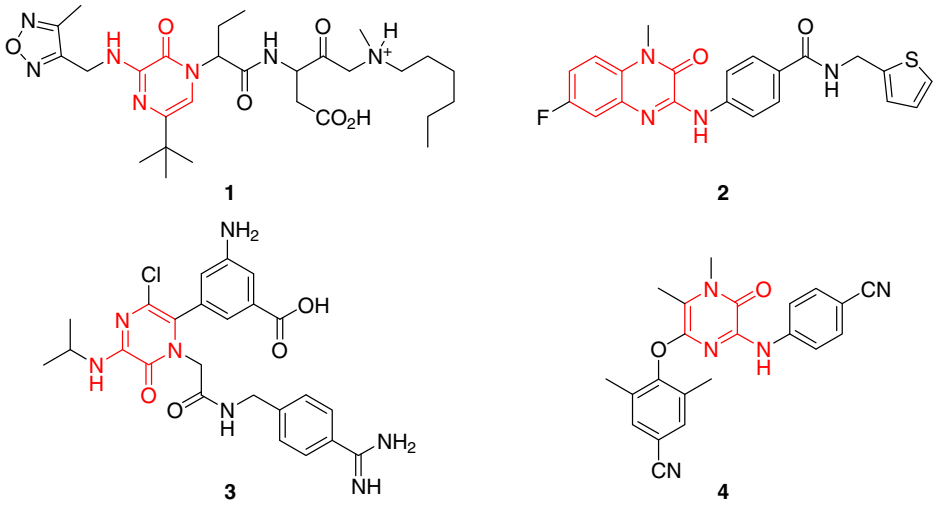

Fig. 1. Biologically active amino-pyrazinones and amino-quinoxalinones.

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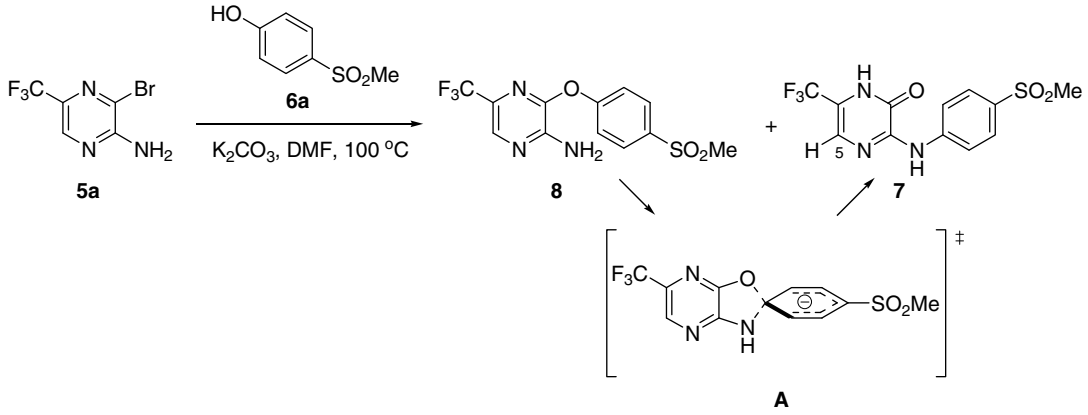
3-anilino-quinoxalin-2(1*H*)-ones, based on a microwave-mediated Smiles rearrangement.

In the course of work on a medicinal chemistry program, we were interested in C(3)-phenoxy substituted 2-amino-5-trifluoromethylpyrazines such as **8** as novel chemical structures (Scheme 1). At the onset of this work, introduction of the C(3)-phenoxy group of **8** was envisioned to take place via S_NAr displacement of the corresponding aryl bromide. However, to our surprise, the reaction of bromide **5a** with phenol **6a** in the presence of a base gave rise to a small quantity of the desired adduct (**8**) along with an unexpected product, which based on spectral data was assigned as 3-anilino-pyrazine 2(1*H*)-one (**7**). Pyrazinone **7** is presumably generated by a Smiles rearrangement[5] of the desired product **8** via complex **A**. The facile equilibrium between the 2-hydroxypyrazine and pyrazin-2-one tautomers of **7** at ambient temperature complicated the structural assignment, because the C(5)–H of **7** appears as a very broad signal in the ^1H NMR spectrum in DMSO-d_6 solution.[6]

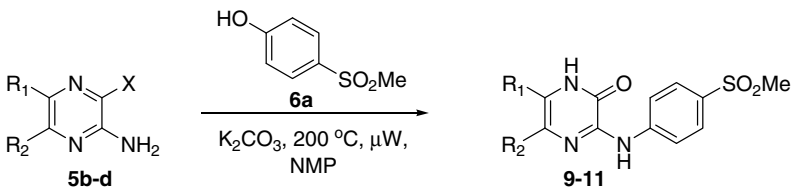
Encouraged by this result, we next examined the reactions of the readily available 3-halopyrazin-amines and 3-haloquinoxalin-amines with 4-methylsulfonylphenol (**6a**). Phenol **6a** was selected for the initial study due to the known rate acceleration effect of *ortho* or *para* electron-withdrawing groups on the Smiles rearrangement.[5] To greatly shorten the reaction time and thus make this transformation a more practical means to obtain 3-anilino-pyrazinones and 3-anilino-quinoxalinones, microwave-mediated conditions were chosen to replace the original thermal conditions. As summarized in Table 1, reactions proceeded smoothly with both aminoquinoxaline (**5b**) and aminopyrazine templates (**5c** and **5d**) to provide the rearrangement products in good yield and high purity after a simple work-up.[7] The structure of the rearrangement product **9** was confirmed by a single crystal X-ray analysis (Fig. 2).[8] As anticipated,[9] nucleophilic displacement took place exclusively at the 3-position of the 3,5-dihalo substituted 2-aminopyrazine templates (Table 1, entries 3 and 4). Subsequent rearrangement yielded 3-anilino-5-halo-pyrazin-2(1*H*)-ones containing multiple functional handles for medicinal chemistry exploration. Although reactions were originally run for 30 min, it was later found that 5–10 min was sufficient for reactions to go to completion (Table 1, entry 2).

To further explore the scope of this rearrangement, a set of substituted phenols possessing different electronic properties was identified to react with 2-amino-3-chloroquinox-



Scheme 1. Initial result.

Table 1
Reactions of halide **5** with 4-methylsulfonylphenol



Entry	Compound	R1, R2	X	Reaction *T* (min)	Product	Yield (%)
1	**5b**	CH=CH–CH=CH	Cl	30	**9**	86
2	**5b**	CH=CH–CH=CH	Cl	5	**9**	79
3	**5c**	Cl, H	Cl	30	**10**	76
4	**5d**	Br, H	Br	30	**11**	74

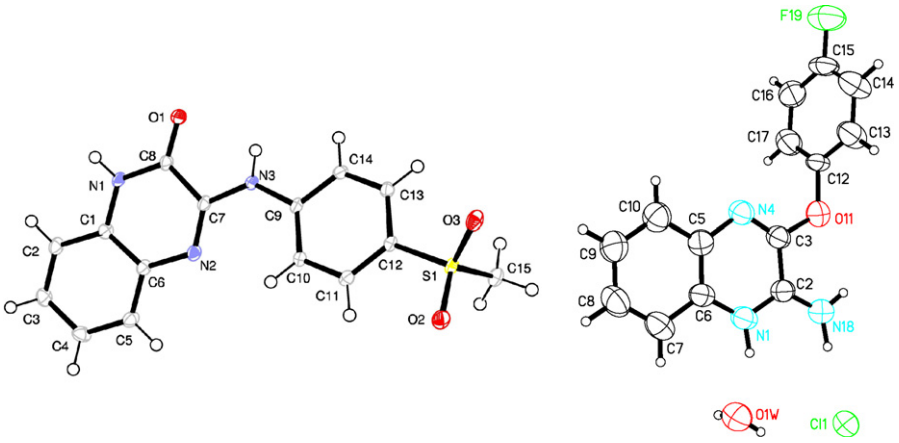
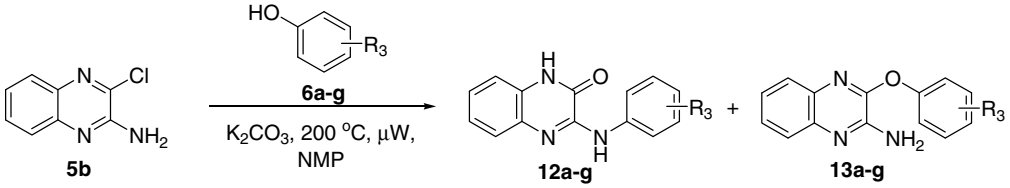


Fig. 2. ORTEP plots of **9** and **13f**.

aline **5b**. As illustrated in Table 2, rearrangement reactions took place readily with phenols containing a range of electron-withdrawing groups at the *ortho*- or *para*-positions (entries 1–4). In this case, typical reaction times were less than 10 min. Under identical reaction conditions, more electron-rich phenols, such as *para*-fluoro substituted, *para*-chloro substituted, and unsubstituted phenols, predominantly gave rise to normal S_NAr products (entries 5–7, $T = 10$ min).[10] However, products **13e–g** could be converted to the rearrangement products **12e–g** in reasonable yield upon isolation and prolonged reaction times (Table 3).[11]

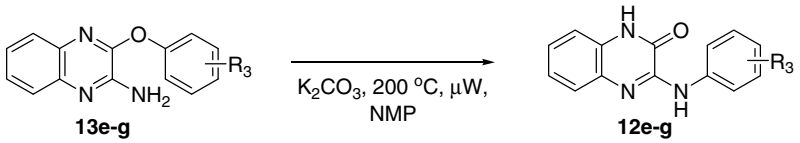
In summary, we have developed a novel approach to provide access to 3-anilino-pyrazin-2(1*H*)-ones and 3-anilino-quinoxalin-2(1*H*)-ones from the corresponding 3-halopyrazin-2-amines and 3-haloquinoxalin-2-amines,

Table 2
Reactions of halide **5b** with substituted phenols (ND: Not detected by ^{1}H NMR)



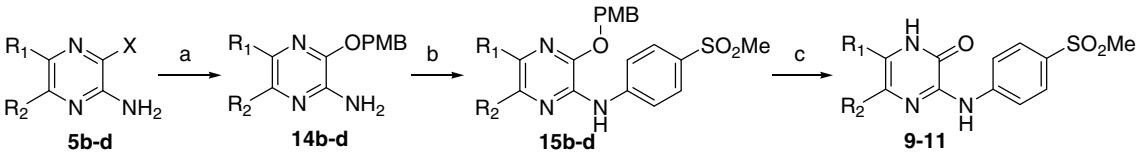
Entry	Compound	R3	Reaction T (min)	**12a–g** % yield	**13a–g** % yield
1	**6a**	*p*-SO_2Me	5	79	Trace
2	**6b**	*o*-SO_2Me	10	75	ND
3	**6c**	*p*-CN	10	77	ND
4	**6d**	*p*-Ac	10	79	ND
5	**6e**	*p*-Cl	10	Trace	76
6	**6f**	*p*-F	10	ND	63
7	**6g**	*p*-H	10	ND	37

Table 3
Smiles rearrangement



Entry	Compound	Reaction T (min)	**12e–g** % yield
1	**13e**	30	90
2	**13f**	90	58
3	**13g**	90	53

based on a microwave-mediated Smiles rearrangement. A selection of readily available 3-halopyrazin-2-amines and 3-haloquinoxalin-amines, and phenols with a range of electronic properties and substitution patterns can be employed successfully in this rearrangement reaction. To the best of our knowledge, this constitutes the first published account of a Smiles rearrangement of amino-aryloxy substituted pyrazines and quinoxalines.



(a) PMBOH, t-BuOK, dioxane, Δ; (b) NaH, 4-fluorophenyl methyl sulfone, DMF, 80 °C; (c) Et_3SiH, TFA, CH_2Cl_2.

Acknowledgments

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5. For a review on Smiles rearrangement, see: (a) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99–215. For more recent literature examples, see: (b) Xiang, J.; Zheng, L.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765–767; (c) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019–4021.
6. The C(5)–H signal became sharper when running the ^{1}H NMR at elevated temperature. Structure of similar Smiles rearrangement products **9**, **10**, and **11** was confirmed through preparation via an independent chemical route: Reaction of appropriate starting material **5b–d** with *p*-methoxybenzylalcohol (PMB-OH) in the presence of potassium *tert*-butoxide in hot dioxane gave the 2-PMB ethers **14b–d**. Deprotonation of these amines with sodium hydride followed by an addition to 4-fluorophenyl methyl sulfone in DMF at 80 °C yielded the corresponding 3-(4-methylsulfonylphenylamino) compounds **15b–d**. Removal of the PMB protecting group with TES/TFA in dichloromethane yielded the equivalent products **9**, **10**, and **11**.
7. *Representative procedure*: A 2–5 mL microwave vial equipped with a stir-bar was charged with 2-amino-3-chloroquinoxaline (**5b**) (180 mg, 1.0 mmol), 4-methylsulfonylphenol (**6a**) (207 mg, 1.2 mmol) and potassium carbonate (691 mg, 5.0 mmol). 1-Methyl-2-pyrrolidinone (NMP, 3.5 mL) was added, and the vessel was subsequently sealed and heated to 200 °C in the microwave reactor (Biotage Initiator) for 30 min. The reaction mixture was cooled to rt, diluted with 20 mL of water, and acidified to pH 2 with 1 N HCl. The resulting precipitate was collected via a medium-pore frit funnel, and washed sequentially with water (20 mL) and MeOH (2 mL). The residue was dried in vacuo to give 3-(4-(methylsulfonyl)phenylamino)quinoxalin-2(*1H*)-one (**9**) as a yellow solid (270 mg, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 9.91 (s, 1H), 8.42 (d, 2H, $J = 8.9$), 7.86 (d, 2H, $J = 8.9$), 7.56 (d, 1H, $J = 7.5$), 7.21–7.30 (m, 3H), 3.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.03, 147.85, 144.86, 134.26, 132.36, 129.57, 128.54, 126.53, 126.41, 124.27, 120.10, 115.83, 44.57. IR (neat) 3293, 1680, 1599, 1574, 1554, 1539, 1287, 1135, 1088, 795, 772, 752, 716, 606, 579, 535 cm^{-1}. HRMS: Calcd for $C_{15}H_{14}N_3O_3S$ (MH^+): 316.0750, found: 316.0747.
8. The data collection for **9** was carried out at the University of California—San Diego X-ray facility using direct methods (SIR-97) and refined with SHELXL-97: $C_{15}H_{13}N_3O_3S$; Fw = 315.34; yellow needle, monoclinic; space group *C*2/*c*; unit cell dimensions: $a = 22.8162(10)$ Å, $\alpha = 90°$; $b = 5.4818(3)$ Å, $\beta = 101.342(2)°$; $c = 22.7237(10)$ Å, $\gamma = 90°$; volume = 2786.6(2) Å^3; $Z = 8$; $D_{calcd} = 1.503$ Mg/m^3; absorption coefficient = 2.227 mm^{-1}; $F(000) = 1312$; GOF on $F^2 = 1.132$; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0407$, $wR_2 = 0.1154$; $R_1 = 0.0463$, $wR_2 = 0.1188$ for all data.
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10. Normal S_NAr products were isolated as HCl salts with unexpected low aqueous solubility. Salt formation was confirmed by ^{1}H NMR of the corresponding *p*-TsOH salt of **13f**. Structural assignment of normal S_NAr products was confirmed by a single crystal X-ray structure of compound **13f**. The data for **13f** were collected on a Bruker APEX diffractometer at Pfizer Groton Laboratories, and all crystallographic calculations were facilitated by the SHELXTL system: $C_{14}H_{11}N_3OF^+Cl^-\cdot H_2O$; Fw = 309.72; triclinic; space group $P\bar{1}$; unit cell dimensions: $a = 5.3954(2)$ Å, $\alpha = 81.067(2)°$; $b = 8.8496(2)$ Å, $\beta = 88.690(2)°$; $c = 15.1200(5)$ Å, $\gamma = 87.780(2)°$; volume = 712.54(4) Å^3; $Z = 2$; $D_{calcd} = 1.444$ Mg/m^3; absorption coefficient = 2.563 mm^{-1}; $F(000) = 320$; GOF on $F^2 = 1.027$; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0448$, $wR_2 = 0.1289$.
11. Isolation of the normal S_NAr product of the less reactive 4-fluorophenol followed by subsequent re-subjection of it to prolonged heating provided better yield than the one-pot procedure. Reaction of the corresponding normal S_NAr product of the more electron-rich 4-methoxyphenol failed to give any desired rearrangement product, even at higher temperature ($T = 250$ °C) and prolonged reaction time.