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Synthesis of 2,3-disubstituted pyrazines and quinoxalines by Heck cross-coupling reactions of 2,3-dichloropyrazine and 2,3-dichloroquinoxaline. Influence of the temperature on the product distribution

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ABSTRACT

Heck cross-coupling reactions of 2,3-dichloropyrazine provide a convenient approach to 2,3-dialkenyl-, 2-alkenyl-3-alkyl-, and 2,3-dialkylpyrazines depending on the reaction conditions.

1. Introduction

Pyrazines and quinoxalines are of considerable pharmacological relevance and are present in various natural products. Examples include various simple alkyl-substituted pyrazine derivatives,[1] botryllazines A and B,[2] or 2,5-bis(3-indolylmethyl)pyrazine.[3] The quinoxaline echinoserine shows antibiotic activity.[4] Antimicrobial activity has been reported also for naturally occurring phenazines.[5] Biopterin[6] and pteridine[7] represent nucleobase-type natural products, which are also pharmacologically active (e.g., inhibition of tRNA-guanine transglycosylase). Other properties of pyrazines include anticoagulant activity[8] and promotion of the melamine synthesis.[9] The cephalostatins and ritterazines are prominent pyrazine natural products, which exhibit a strong cytotoxic and cancerostatic activity.[10]

2,3-Dichloropyrazine and 2,3-dichloroquinoxaline represent useful building blocks for the synthesis of substituted and annulated pyrazines and quinoxalines. Condensed heterocycles have been prepared by cyclization of 2,3-dichloropyrazine with 2-aminobenzenethiol,[11] 2-aminophenol,[12] 3-hydroxy-1*H*-pyridine-2-thione,[13] 3-amino-6-methoxy-1*H*-pyridine-2-thione,[14] 2-aminobenzeneselenol,[15] and pyrid-2-yl-acetonitrile.[16] Open-chained pyrazines have been prepared by reaction of 2,3-dichloropyrazine with 1 equiv of different enolates,[17] 2 equiv of thiols,[18] and DMAP.[19] Transition metal-catalyzed reactions of 2,3-dichloropyrazine have only scarcely been reported. 2,3-Diarylpyrazines and 2,3-di(alkynyl)pyrazines have been recently prepared by Suzuki[20] and Sonogashira reactions, respectively.[21] Herein, we report what are, to the best of our knowledge, the first Heck reactions of 2,3-dichloropyrazine and -quinoxaline.[22, 23] These reactions provide, depending on the reaction conditions, a convenient approach to 2,3-dialkenyl-, 2-alkenyl-3-alkyl-, and 2,3-dialkylpyrazines and their quinoxaline derivatives.

2. Results and discussion

The reaction of 2,3-dichloropyrazine (**1a**) with ethyl acrylate (**2a**), in the presence of $Pd(OAc)_2$ (5 mol %) and Xphos[24] (10 mol %), afforded the 2,3-dialkenylpyrazine **3a** in 83% yield (Scheme 1, Table 1). The employment of $Pd(PPh_3)_4$ was less successful in terms of yield. The best yields were obtained when 5 mol % of the catalyst, 10 mol % of the ligand, and a slight excess of the alkene (2.5 equiv) were employed and when the reaction mixture was stirred at 90 °C for 48 h. Partial hydrogenation was observed when the reaction

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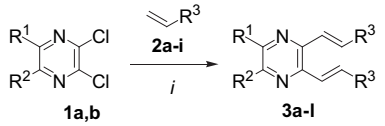
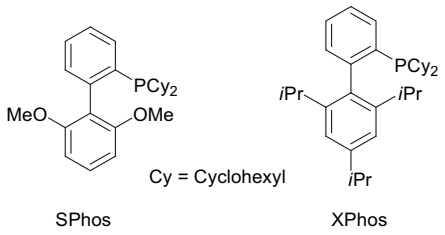
was carried out at higher temperature (vide infra). On the other hand, the yields also decreased when the temperature was decreased, due to lower conversion of the starting material.



Scheme 1. Synthesis of 2,3-di(alkenyl)pyrazines and quinoxalines **3a–l**. Conditions: *I*, **2a–I** (2.5 equiv), $Pd(OAc)_2$ (5 mol %), Xphos (for **3a**,**b**,**e–l**) or SPhos (for **3c**,**d**) (10 mol %, structures, see Scheme 2), NEt_3, DMF, 90 °C.



Scheme 2. Biaryl monophosphine ligands developed by Buchwald and co-workers (Ref. 24).

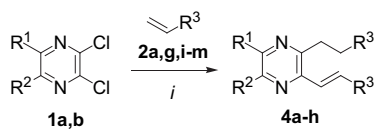
Table 1
Synthesis of **3a–l**

1	2	3	R^1	R^2	R^3	% (**3**)[a]	*T* [°C]
a	**a**	**a**	H	H	CO_2Et	83	90
a	**b**	**b**	H	H	Ph	82	90
a	**c**	**c**	H	H	4-$(MeO)C_6H_4$	78[b]	90
a	**d**	**d**	H	H	4-MeC_6H_4	82[b]	90
a	**e**	**e**	H	H	4-ClC_6H_4	66	90
a	**f**	**f**	H	H	4-(^{t}BuO)C_6H_4	64	90
b	**g**	**g**	–(CH=CH)$_2$–		CO_2Me	78	120
b	**h**	**h**	–(CH=CH)$_2$–		*c*Hex	67	120
b	**b**	**i**	–(CH=CH)$_2$–		Ph	72	120
b	**f**	**j**	–(CH=CH)$_2$–		4-(^{t}BuO)C_6H_4	67	120
b	**c**	**k**	–(CH=CH)$_2$–		4-$(MeO)C_6H_4$	83	120
b	**i**	**l**	–(CH=CH)$_2$–		4-^{t}BuC_6H_4	69	120

[a] Yield of isolated products.
[b] Sphos instead of Xphos was used.

The $Pd(OAc)_2$-catalyzed reaction of **1a** with styrenes **2b–f**, in the presence of Xphos or SPhos[24], gave the 2,3-dialkenylpyrazines **3b–f** in 64–83% yields. The reaction of 2,3-dichloroquinoxaline (**1b**) with **2b**,**c**,**f**,**–l** afforded the 2,3-dialkenylquinoxalines **3g–l** in 67–83% yields. The synthesis of the quinoxaline derivatives had to be carried out at 120 instead of 90 °C to obtain good yields.

The $Pd(OAc)_2$-catalyzed reaction of 2,3-dichloropyrazine (**1a**) with acrylates **2a**,**g**,**i–m** (2.5 equiv), carried out at 110 rather than 90 °C, afforded the 2-alkenyl-2-alkylpyrazines **4a–g** in 69–83% yield (Scheme 3, Table 2). The formation of products **4a–g** can be explained by partial reduction of the in situ formed 2,3-dialkenylpyrazines. The reaction of 2,3-dichloroquinoxaline (**1b**) with *tert*-butyl acrylate (**2k**), carried out at 130, gave 2-alkenyl-2-alkylquinoxaline **4h**. The formation of products **4a–h** might be explained by protodemetalation or reduction.[25]



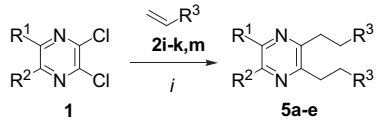
Scheme 3. Synthesis of 2-alkenyl-3-alkylpyrazines and -quinoxalines **4a–h**. Conditions: *I*,: **2a**,**g**,**i–m** (2.5 equiv), $Pd(OAc)_2$ (5 mol %), Xphos (10 mol %), NEt_3, DMF, 110 °C, 48 h (for **4a–g**), 24 h (for **4h**).

Table 2
Synthesis of **4a–h**

1	2	4	R^1	R^2	R^3	% (**4**)[a]	*T* [°C]
a	**g**	**a**	H	H	CO_2Me	78	110
a	**a**	**b**	H	H	CO_2Et	71	110
a	**i**	**c**	H	H	CO_2nBu	74	110
a	**j**	**d**	H	H	$CO_2{}^t$Bu	75	110
a	**k**	**e**	H	H	$CO_2{}^t$Bu	83	110
a	**l**	**f**	H	H	CO_2nHex	79	110
a	**m**	**g**	H	H	CO_2R[b]	69	110
b	**k**	**h**	–(CH=CH)$_2$–		$CO_2{}^t$Bu	75	130

[a] Yield of isolated products.
[b] R=$CH_2CH(Et)(CH_2)_3CH_3$.

The $Pd(OAc)_2$-catalyzed reaction of **1a** with 2.5 equiv of acrylates **2i–k**,**m**, carried out at 140 °C, afforded the 2,3-dialkylpyrazines **5a–c** in good yield (Scheme 4, Table 3). The formation of products **5a–c** can be explained by complete reduction, due to the high temperatures. The reaction of **1b** with **2m** and **2k**, carried out at 150 °C, afforded the 2,3-dialkylquinoxalines **5d** and **5e**, respectively. The formation of products **5a–e** can be again explained by protodemetalation or reduction.



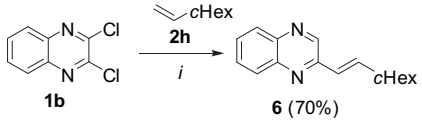
Scheme 4. Synthesis of 2,3-dialkylpyrazines and -quinoxalines **5a–e**. Conditions: *I*: **2i–k**,**m** (2.5 equiv), $Pd(OAc)_2$ (5 mol %), Xphos (10 mol %), NEt_3, DMF, 140 °C, 48 h (for **5a–c**), 24 h (for **5d**, **e**).

Table 3
Synthesis of **5a–e**

1	2	5	R^1	R^2	R^3	% (**5**)[a]	*T* [°C]
a	**i**	**a**	H	H	CO_2nBu	69	140
a	**j**	**b**	H	H	CO_2iBu	76	140
a	**k**	**c**	H	H	$CO_2{}^t$Bu	70	140
b	**m**	**d**	–(CH=CH)$_2$–		CO_2R[b]	69	150
b	**k**	**e**	–(CH=CH)$_2$–		$CO_2{}^t$Bu	77	150

[a] Yield of isolated products.
[b] R=$CH_2CH(Et)(CH_2)_3CH_3$.

The $Pd(OAc)_2$-catalyzed reaction of **1b** with 1.25 rather than 2.5 equiv of **2h**, carried out at 120 °C, afforded the 2-alkenylquinoxaline **6** in 70% yield (Scheme 5). The formation of product **6** can be explained by partial reduction of the in situ formed 2-bromo-3-alkenylquinoxaline.



Scheme 5. Conditions: *I*, Pd $(OAc)_2$ (5 mol %), **Xphos** (10 mol %), 2 h (1.25 equiv) NEt_3, DMF, 120 °C, 48 h.

In conclusion, we have reported the synthesis of 2,3-dialkenyl-, 2-alkenyl-3-alkyl-, and 2,3-dialkylpyrazines and their quinoxaline derivatives based on Heck cross-coupling reactions of 2,3-dichloropyrazine and -quinoxaline. An increase of the reaction temperature results in partial or complete hydrogenation of the double bond.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR