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New routes for the synthesis of 3- and 5-substituted 2(1*H*)-pyrazinones

Rasha Azzam,[†] Wim De Borggraeve, Frans Compernolle[*] and Georges J. Hoornaert

Laboratorium voor Organische Synthese, K.U. Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

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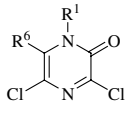
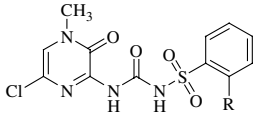
Abstract—Various 3-(hetero)aryl, 3-alkyl and 3-alkenyl-2(1*H*)-pyrazinones were prepared by applying the Suzuki and Heck reaction methodology to 3,5-dichloro-2(1*H*)-pyrazinones. Furthermore, following hydrogenolysis of the 5-chloro substituent and regioselective 5-bromination, this palladium-catalysed cross-coupling approach could be extended to the synthesis of the analogous 5-substituted 2(1*H*)-pyrazinones.

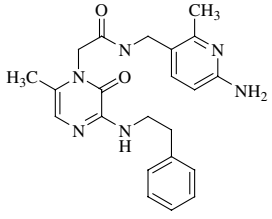
The 2(1*H*)-pyrazinone ring system can be utilised as a scaffold to introduce an assembly of pharmacophoric groups designed to fit the active site of a receptor or enzyme. Specifically, this scaffolding strategy has been applied for the construction of inhibitors of HIV reverse transcriptase.[1] Pyrazinones **1a** and **1b** are well-recognised ligands that bind to a new site on the $GABA_A$/chloride ionophore complex.[2] Pyrazinones **2** bearing various *ortho*-substituted phenylsulfonylurea groups at the C-3 position display selective herbicidal and growth-regulating properties.[3] On the other hand, 2(1*H*)-pyrazinones such as **3** that are substituted with alkyl amino groups at the C-3 position are useful inhibitors of thrombin and associated thrombotic occlusions.[4,5] Other 2(1*H*)-pyrazinones bearing substituted alkyl groups at N-1 and alkyl and phenyl groups at C-3 show an inhibitory action on platelet aggregation, vasodilating activity and/or inhibitory action on lipoperoxide generation.[6] Finally, polysubstituted pyrazinone derivatives such as **4** and **5** have been found useful in the treatment of various CRF (corticotrophin releasing factor)-related disorders,[7] and a variety of neurodegenerative and stress-related disorders.[8]



1a: R^1=Bn, R^6=2-chlorophenyl
1b: R^1=2-furylmethyl, R^6=Ph



2: R=$COOCH_3$, OC_2H_5, $SO_2N(CH_3)_2$



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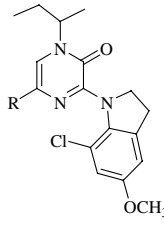
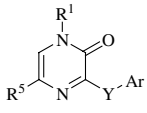


4: R=Cl, Br, H, alkyl



5: R^1=Et_2CH, $CH(CH_3OCH_2)_2$,
R^5= Cl, CN, Br, alkyl,
Y=NH, NEt, O, S,
Ar=phenyl, pyridyl, pyrimidinyl

Therefore, major interest centres around developing new routes for the introduction of more challenging substituents, for example, alkenyl and heteroaryl groups, at the reactive C-3 position and especially at the less accessible C-5 position of 2(1*H*)-pyrazinones. In this respect, Suzuki and Heck cross-coupling using organoboron reagents or vinyl compounds could offer an interesting route for introduction of a variety of (hetero)aryl and vinyl groups.

Keywords: 3- and 5-Substituted 2(1*H*)-pyrazinones; Heterocyclic compounds; Suzuki reaction; Heck reaction.
* Corresponding author. Tel.: +32-16-32-74-07; fax: +32-16-32-79-90; e-mail: frans.compernolle@chem.kuleuven.ac.be
† Present address: Department of Chemistry, Helwan University, Ain-Helwan, Cairo, Egypt, 11795.

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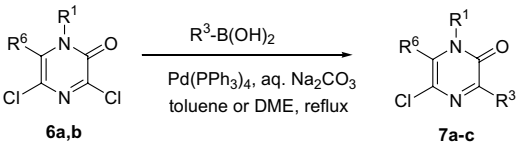
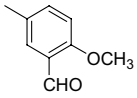
Table 1. Suzuki-coupling of (hetero)arylboronic acid at C-3 of 2(1*H*)-pyrazinones **6a**,**b** to form 3-(hetero)aryl-5-chloro-2(1*H*)-pyrazinones **7a**–**c**



6a,b **7a-c**

	R^1	R^3	R^6	Solvent	Yield (%)
7a	Ph	Ph	CH_3	Toluene	92
7b	Bn		Ph	Toluene	65
7c	Bn		Ph	Toluene	70

We studied the cross-coupling reaction of (hetero)arylboronic acids with 3,5-dichloro-2(1*H*)-pyrazinones with the intention of introducing groups different from those obtained previously by using organotin reagents.[9] As seen before for the Stille reaction, the initial oxidative addition occurs preferentially at the more reactive C-3 position (Table 1). We chose coupling conditions that were optimised previously for the Suzuki coupling of π-deficient heteroaryl chlorides.[10,11] The best results were obtained using tetrakis(triphenylphosphine)palladium(0) as a catalyst, aqueous Na_2CO_3 as base and toluene as solvent. Thus reaction of pyrazinones **6a**[12] and **6b**[13] with 1.2 equiv of (hetero)arylboronic acids and 3 mol% of $Pd(PPh_3)_4$ in toluene under reflux overnight produced 3-aryl-2(1*H*)-pyrazinones **7a**,**b** and the corresponding 3-thienyl product **7c** in good yields. After completion of the reaction and usual workup, the mixture was subjected to column chromatography to remove Ph_3PO.

We also investigated the cross-coupling reaction of 3,5-dichloro-2(1*H*)-pyrazinone **6b** and some alkyl-9-BBN derivatives (Table 2).[14–16] The latter were prepared in situ by adding 9-BBN in THF to a THF solution of some representative alkenes under an argon atmosphere. The mixture was stirred for 6 h at room temperature, and 2(1*H*)-pyrazinone, $Pd(dppf)Cl_2$ and aq NaOH were added. After reaction at room temperature overnight, complete conversion into 3-substituted products **8a**,**b** was observed.

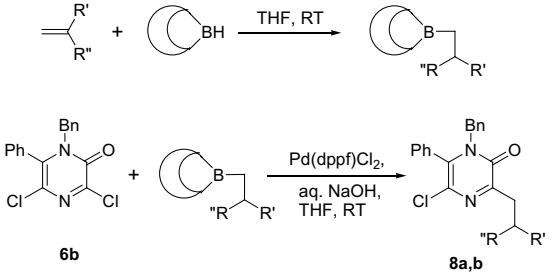
From the results displayed, it appears that primary alkyl-9-BBN reagents having either a single (phenyl) or double (cyclohexyl branching) substitution at the β-position of the alkyl group attached to boron, all react well with 3,5-dichloro-2(1*H*)-pyrazinone **6b** to give the corresponding products **8a**,**b** in good yields. However, no coupling was observed for the reaction of **6b** with the secondary cyclopentyl-9-BBN reagent prepared from cyclopentene.

Applying the Heck reaction to 3,5-dichloro-2(1*H*)-pyrazinones provides a direct method for preparing the corresponding 3-alkenyl derivatives. Thus reaction of **6b** with various alkenes afforded 3-alkenyl products **9a**–**d** in good yield (Table 3). The best conditions consisted of using 3 mol% of $Pd(OAc)_2$, 7 mol% of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C. Less satisfactory results or no conversion at all were observed when replacing DMF with acetonitrile.

To avoid evaporation and/or oxidation of volatile vinylic starting materials, the reaction was carried out under argon in a capped heavy-walled glass tube heated in an oil bath. Both styrene and methyl acrylate reacted in the expected way to produce **9a** and **9b** in 80% and 75% yields, respectively. A lower yield was observed for the reaction of **6b** with cyclohexene. The reaction of **6b** with ethyl vinyl ether afforded an unstable enol ether product **9c**, which was isolated in 87% yield by flash column chromatography. The (*E*)-configuration of the double bond was established by the magnitude of the coupling constant between the two vinylic protons in **9a**,**b** (16 Hz) and in the enol ether product **9c** (12 Hz).

In contrast to the easy addition–elimination reaction of the 3-imidoyl chloride function, analogous substitution at the C-5-chloro position of 3,5-dichloro-2(1*H*)-pyrazinones appears difficult. Substitution of this group has

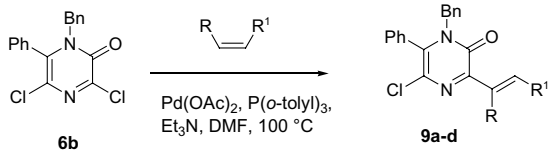
Table 2. Pd-catalysed cross-coupling of alkyl-9-BBN derivatives at the C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-alkyl-5-chloro-2(1*H*)-pyrazinones **8a**,**b**



6b **8a,b**

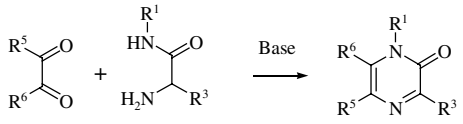
	R′	R″	Yield (%)
8a	H	Ph	60
8b	$-CH_2(CH_2)_3CH_2-$		80

Table 3. Heck reaction at the C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-vinyl-5-chloro-2(1*H*)-pyrazinones **9a**–**d**



6b **9a-d**

	R	R^1	AcCN yield (%)	DMF yield (%)
9a	H	Ph	60	80
9b	H	CO_2CH_3	50	75
9c	H	OC_2H_5	—	87
9d	$-CH_2(CH_2)_2CH_2-$		—	50



Scheme 1. Synthesis of 5-alkyl and 5-aryl-2(1*H*)-pyrazinones.

been achieved only in an indirect way via isomerisation of 6-alkyl- or 6-benzyl-5-chloro-3-methoxy-2(1*H*)-pyrazinones to form the tautomeric 6-alkylidene/benzylidene-5-chloro-3,6-dihydropyrazin-2(1*H*)-ones having a reactive 5-imidoyl chloride group: subsequent reaction with organotin reagents or amines then produced the corresponding 5-alkyl/aryl or 5-amino-6-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones, respectively.[17]

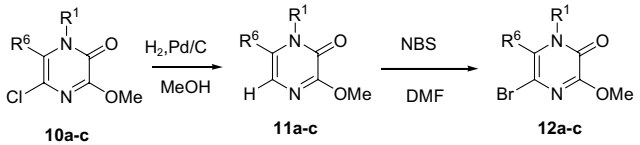
2(1*H*)-Pyrazinones bearing a 5-alkyl substituent (and their 5-H analogues) can also be obtained directly by base-catalysed condensation of 1,2-dicarbonyl compounds with various α-amino N-substituted carboxamide derivatives (Scheme 1).[18] However, this reaction is useful only for equal substituents R^5 and R^6, since a mixture of regioisomeric pyrazinones is produced when R^5 and R^6 are different.

The easy access to 3-substituted 5-chloropyrazinones prompted us to apply the Suzuki-coupling methodology firstly to these compounds. However, using $Pd(PPh_3)_4$ catalyst and aq Na_2CO_3 in either toluene or DME at reflux failed to produce the corresponding 5-aryl-2(1*H*)-pyrazinones. Other conditions involving the use of $Pd_2(dba)_3$, combined with P(*t*-Bu)$_3$ and CsF or KF in THF or dioxane, that is, the conditions used for the synthesis of biaryl compounds starting from an aryl chloride,[19] were also unsuccessful. Therefore we turned our attention to the corresponding 5-bromo-2(1*H*)-pyrazinones to introduce the desired 5-aryl/alkyl substituents.

To our knowledge, the synthesis of 3-substituted 5-bromo-2(1*H*)-pyrazinones possessing various substituents at the N-1 position has not yet been reported. However, 3,6-disubstituted 5-halo-2-pyrazinols have been prepared by halogenation at the C-5 position of the corresponding 2-pyrazinols.[20] Accordingly, we examined the analogous C-5 bromination of 1-Bn and 1-Ph substituted pyrazinones **11a–c**. Following hydrogenolysis of **10a–c**, effected by using a 10% Pd/C catalyst in methanol,[21] the resulting 5-dechlorinated compounds **11a–c** were subjected to treatment with *N*-bromosuccinimide in DMF (Table 4). Bromination with NBS proceeded at room temperature in the dark and was complete within 1 h. Bromine was introduced selectively at the C-5 position, even when $R^6 = H$. Presumably electrophilic attack at C-5 is facilitated by delocalisation of the lone pair on N-1.

The position of the 5-Br substituent was verified by ^{1}H-coupled ^{13}C NMR analysis of **12a**. In this ^{1}H-coupled spectrum, the methylene C-atom of the *N*-benzyl group appears as a triplet of quartets (tq) with $^1J = 284.8$ Hz and $^3J = 3.2$ Hz: these are due to coupling with two

Table 4. 5-Bromination of 2(1*H*)-pyrazinones



10a-c **11a-c** **12a-c**

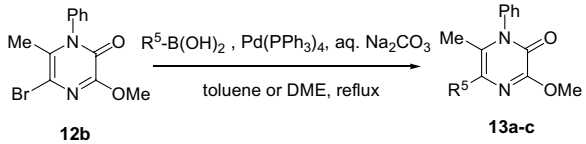
Starting compound	Product **12**	R^1	R^6	Yield (%)
11a	**12a**	Bn	H	75
11b	**12b**	Ph	CH_3	73
11c	**12c**	Bn	Ph	82

attached protons (^1J) and to coupling with two *ortho*-protons of the phenyl ring plus the 6-H atom on the 2(1*H*)-pyrazinone ring (^3J). For the carbonyl carbon atom (C-2) a doublet of triplets (dt) coupling pattern was observed with $^3J = 5$ and 3 Hz, which can be related to the coupling of C-2 with H-6 and the methylene protons of the *N*-benzyl group. The carbon atom C-5 attached to the Br-atom appears as a doublet (d, $^2J = 2.5$ Hz) at δ 78.7 ppm, due to coupling with H-6. Carbon C-6 in turn is detected as a doublet of triplets (dt) with $^1J = 189$ Hz and $^3J = 4.6$ Hz, due to coupling with H-6 and the methylene protons of the *N*-benzyl group.

In a preliminary study concerning the application of the 5-bromo-2(1*H*)-pyrazinones in palladium-catalysed coupling reactions, we examined the cross-coupling of **12b** with some representative boronic acids and alkenes. Suzuki coupling (Table 5) of **12b** with phenylboronic acid and 3-thienylboronic acid was carried out using aq Na_2CO_3 and $Pd(PPh_3)_4$ and went to completion after heating in toluene or DME at reflux for 18 h. The yields of these coupling procedures were 94% and 55%. Similar cross-coupling of **12b** with (*E*)-2-phenylethenyl-boronic acid in DME afforded compound **13c** in 95% yield.

The Heck reaction of 5-bromo-2(1*H*)-pyrazinone **12c** with styrene, methyl acrylate and cyclohexene was carried out in a similar manner to that described above for 3-chloro-2(1*H*)-pyrazinones. Thus treatment of **12c** with

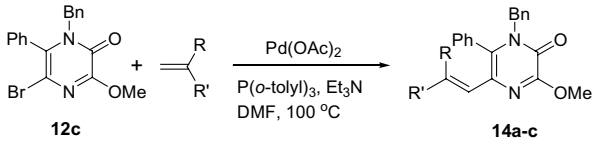
Table 5. Suzuki cross-coupling reaction of (hetero)aryl- and 1-alkenylboronic acid with 5-bromo-2(1*H*)-pyrazinone **12b**



12b **13a-c**

Product	R^5	Yield (%)
13a	Ph	94
13b		55
13c		95

Table 6. Heck-coupling of 5-bromopyrazinone **12c** with alkenes



	R	R′	Yield (%)
14a	H	Ph	71
14b	H	CO_2CH_3	66
14c	$-CH_2(CH_2)_3CH_2-$		60

3 mol% of $Pd(OAc)_2$, 7 mol% of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C was found to be the most effective for conversion into the corresponding 5-substituted alkenyl-2(1*H*)-pyrazinones **14a**–**c** (Table 6).

Obviously, 5-boronic acid or 5-boronate ester derivatives of 3-substituted 2(1*H*)-pyrazinones would be very useful as a common intermediate in reverse cross-coupling reactions with various hetero(aryl) and alkenyl halides. Therefore cross-coupling of 5-bromo-2(1*H*)-pyrazinones **12b** and tetra(alkoxo)diborons was attempted using conditions that were previously optimised for preparing pinacol arylboronates, that is, 1.1 equiv of bis(pinacolato)diboron, 3 mol% of $Pd(dba)_2$, 3.3 mol% of P(*t*-Bu)$_3$ and 3 equiv of KOAc in dioxane at 80 °C.[22] However, this procedure failed when applied to 5-bromo-2(1*H*)-pyrazinone **12b**, and only starting material was recovered from the reaction mixture.

Conclusion

Palladium-catalysed Suzuki and Heck reactions of 3-chloro- and 5-bromo-2(1*H*)-pyrazinones were used successfully to introduce (hetero)aryl, alkenyl and alkyl groups at both C-3 and C-5. The required 5-bromopyrazinone precursors were prepared via dechlorination followed by electrophilic substitution at C-5. In future work, this approach will be extended to include palladium-catalysed cross-coupling reactions of other pyrazinones, for example, 5-iodo-2(1*H*)-pyrazinones, and more extensive boronate or alkene reaction partners.

Acknowledgements

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