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Catalytic and Stoichiometric Synthesis of Novel 3-Aminocarbonyl-, 3-Alkoxycarbonyl-, and 3-Amino-4-indolylmaleimides

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Novel nonsymmetrically substituted 4-indolylmaleimides have been synthesized via palladium-catalyzed alkoxy- and aminocarbonylation of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide (**1**) with alcohols and amines in the presence of carbon monoxide. The resulting carboxamide derivatives represent a new class of potentially bioactive compounds. In addition, the direct amination reaction of **1** proceeded smoothly in the absence of catalyst and gave the desired 3-amino-4-indolylmaleimides in good yields.

Introduction

Protein kinase C (PKC) represents an important family of serine/threonine kinases, which have been associated with numerous diseases such as cardiovascular illnesses, cancer, central nervous system disorders, Alzheimer, inflammation and autoimmune diseases, e.g. diabetes. Since PKCs are involved in signal transduction, gene expression, cell growth and cell differentiation,[1] they have been important targets for the development of new therapeutic agents. Hence, over the past few years there have been significant research activities towards selective inhibitors for PKC.[2]

In this respect, maleimides, especially symmetrical and nonsymmetrical (macrocyclic) 3,4-bis-indolylmaleimides have been found to be potent inhibitors of different protein kinases, especially PKC.[3] Among these products, naturally occurring arcyriarubins[4] and analogues thereof are useful intermediates in the synthesis of bioactive indolocarbazole alkaloids (Figure 1).[4,5]

Structurally related derivatives, in which one indole substituent is replaced by other (hetero)arenes, have been identified as strong kinase inhibitors as well.[3g,6] Notably, such 3-indolyl-4-(heteroaryl)maleimides show a wide spectra of further biological activities.[7]

Herein, we describe the synthesis of novel 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides through palladium-catalyzed alkoxy- and aminocarbonylation reactions of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide. To the best of our knowledge, such carbonylation reactions have not been studied, and the corresponding carb-

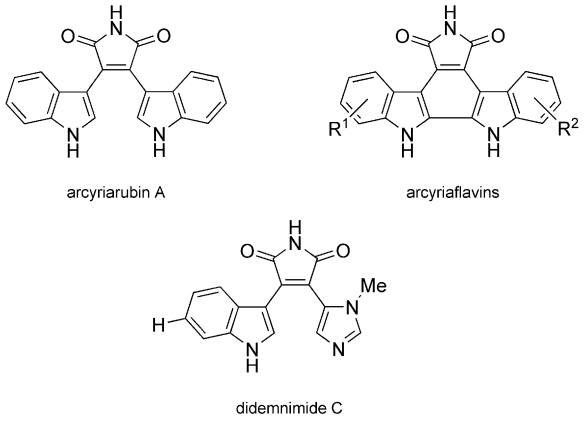

Figure 1. Biologically active compounds with an indolylmaleimide subunit.

oxamide derivatives are only mentioned in the patent literature.[8] Without the palladium catalyst, the corresponding 3-amino-4-indolylmaleimides are formed in good yield.

Results and Discussion

For some time, we have been engaged in transition-metal-catalyzed syntheses of indoles.[9] In addition, we are interested in the development of practical palladium catalysts and their application in different cross-coupling reactions of heteroaryl halides.[10,11] Recently, by combining these two areas, we presented an improved Pd-catalyzed synthesis of 3-aryl-4-indolylmaleimides[12] through the Suzuki coupling of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide.[13] The coupling of both aryl- and heteroaryl boronic acids proceeded smoothly with good to excellent yields by employing simple $Pd(OAc)_2/PPh_3$ or $Pd(OAc)_2$/di-1-ada-

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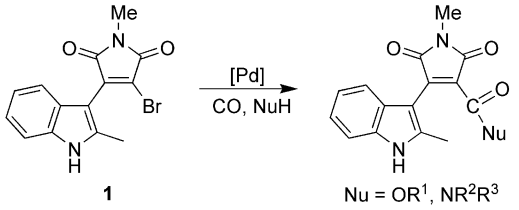
mantyl-*n*-butylphosphane (cata*CX*ium® A) as catalyst systems. Encouraged by these results and on the basis of our experiences in carbonylation chemistry,[14] we decided to investigate the carbonylation reactions of 3-bromo-4-indolylmaleimides.

Initially, we prepared 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide (**1**) from commercially available 3,4-dibromomaleimide and 2-methylindole by applying lithium hexamethyldisilazane as base.[12] The desired compound **1** was obtained in excellent selectivity and yield (95%). Typically, all carbonylation experiments of **1** with different nucleophiles (Scheme 1) were carried out in a modified sixfold parallel autoclave with a reaction volume of 4 mL.

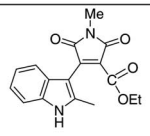
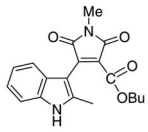
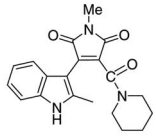
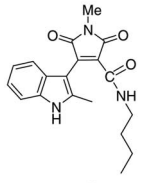
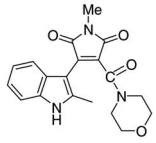
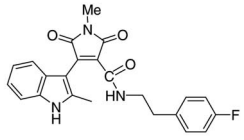
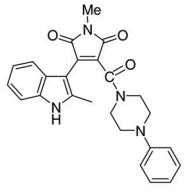


Scheme 1. Palladium-catalyzed carbonylation of **1** with alcohols or amines.

First, the alkoxycarbonylation of **1** in the presence of ethanol and *n*-butanol was investigated. More specifically, **1** reacted at 5 bar of carbon monoxide in the corresponding alcohol as solvent. By employing 0.5 mol-% $Pd(OAc)_2$ and a threefold excess of di-1-adamantyl-*n*-butylphosphane, the desired ethyl ester[15] **2** and butyl ester **3** were obtained in 25–29% isolated yields (Table 1, Entries 1 and 2).[16] Although the reaction proceeded with 100% conversion, 3-dimethylamino-1-methyl-4-(2-methyl-3-indolyl)maleimide and 1-methyl-3-(2-methyl-3-indolyl)maleimide were identified as main side products. Apparently, the primary side product was formed by nucleophilic exchange of the bromine atom as a result of the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) during the reaction. The latter by-product simply resulted from a reductive dehalogenation reaction of compound **1**, which also took place under these conditions. We then focused on the aminocarbonylation of **1**. This type of carbonylation reaction should be of wider interest because the resulting carboxamides offer an additional hydrogen-bonding motif.

All aminocarbonylation reactions were performed at two different carbon monoxide pressures (5 and 15 bar CO) and with different amine concentrations. The results for the optimized reaction conditions are shown in Table 1. Reaction of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide with 1 equiv. piperidine gave the best result at 15 bar of carbon monoxide [48% isolated yield of 1-methyl-4-(2-methyl-3-indolyl)maleimide-3-(piperidine)carboxamide **4**; Table 1, Entry 3]. NMR spectroscopy revealed a dynamic behaviour of the amide bond and the piperidine chair conformation. Again, we observed 100% conversion; however, the main side product was 1-methyl-4-(2-methyl-3-indolyl)-3-(1-piperidinyl)maleimide. Notably, this by-product was detected by gas chromatography even before carbonylation pro-

Table 1. Pd-catalyzed alkoxycarbonylation/aminocarbonylation of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide.[a]

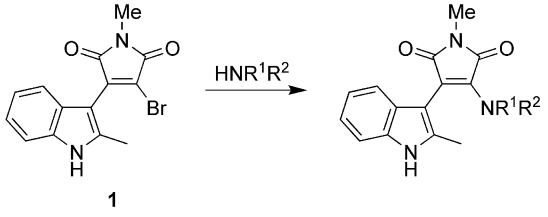
Entry	Product	p_{CO} [bar]	T [°C]	Isolated yield [%]
1[b]	 **2**	5	90	25
2[b]	 **3**	5	115	29
3[c,d]	 **4**	15	115	48
4[c,e,f]	 **5**	5	115	32
5[g]	 **6**	15	100	32
6[g]	 **7**	15	100	60
7[g]	 **8**	15	100	70

[a] Reaction conditions: 3-Bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide (0.25 mmol), $Pd(OAc)_2$ (0.5 mol-%), di-1-adamantyl-*n*-butylphosphane (1.5 mol-%), solvent (2 mL), base, 16 h. [b] Reaction performed in the corresponding alcohol, TMEDA (0.75 equiv.) as base. [c] Toluene as solvent, TMEDA (0.75 equiv.) as base. [d] Addition of piperidine (1 equiv.). [e] Addition of *n*-butylamine (4 equiv.). [f] *N*,1-Dibutyl-4-(2-methyl-3-indolyl)maleimide-3-carboxamide was obtained as a side product (10% yield). [g] Addition of the corresponding amine (2 equiv.), dioxane as solvent, NEt_3 (0.75 equiv.) as base.

ceeded. Clearly, catalytic aminocarbonylation competed with nucleophilic substitution by the corresponding amine under these reaction conditions.

By applying *n*-butylamine, the catalytic carbonylation proceeded best at lower CO pressures (5 bar). After column chromatography, *N*-butyl-1-methyl-4-(2-methyl-3-indolyl)-maleimide-3-carboxamide (**5**) was obtained in 32% yield (Table 1, Entry 4). Surprisingly, we also isolated the corresponding *N*,1-dibutyl-4-(2-methyl-3-indolyl)maleimide-3-carboxamide in 10% yield. In addition, a significant amount of 3-butylamino-1-methyl-4-(2-methyl-3-indolyl)-maleimide was formed, which resulted from the noncatalytic amination reaction. Carbonylation of **1** at 15 bar CO in the presence of morpholine, 4-fluorophenylethylamine and *N*-phenylpiperazine occurred with high conversion (>95%) and gave the respective amides **6**–**8** in 32%, 60% and 70% yield, respectively (Table 1, Entries 5–7). In each case, minor amounts (<10%) of the corresponding amination products were formed as well.

Because of the competing amination, we decided to investigate this reaction for the selective synthesis of 3-amino-4-indolylmaleimides in more detail (Scheme 2). Sergheraert et al. reported that PKC selectivity is promoted by the addition of amine substituents on the maleimide ring.[17] Thus, various polyamine–linked-,[17,18] alkylamino-,[19] arylalkylamino-,[20] anilinoindolylmaleimides,[21] indolylimidazolylmaleimides[6a,22] (e.g. didemnimides) and indolopyrrolemaleimides[7a,7d,7f,23] have been synthesized. Moreover, transformation of 3-bromo-4-indolylmaleimides to the corresponding amines have been described.[15a,17–19,20b] Interestingly, there is one known example of a Pd-catalyzed cross-coupling of an analogue bromide with aniline.[24]

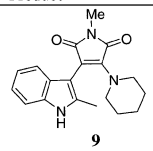
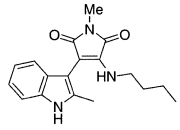
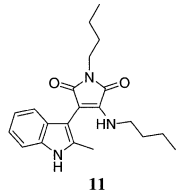
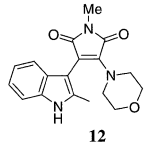
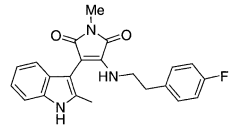
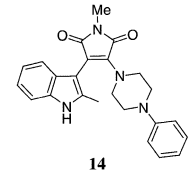
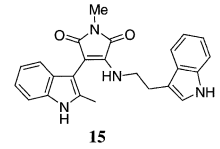
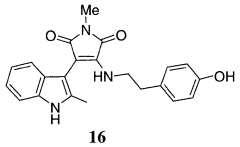


Scheme 2. Amination of the model substrate **1**.

In Table 2, the results for the direct amination are summarized. Reaction of **1** with 1 equiv. piperidine in the absence of carbon monoxide took place already at room temperature and yielded 50% of 1-methyl-4-(2-methyl-3-indolyl)-3-(1-piperidinyl)maleimide (**9**).[25] Noteworthy, the reaction proceeded similarly without any palladium catalyst. Thus, all following amination experiments were carried out in the absence of any catalyst.

By using twice the amount of TMEDA (1.5 equiv.) and piperidine as solvent, the yield of amine **9** increased to 91% (Table 2, Entry 1). When *n*-butylamine was employed as solvent, we obtained 79% of 1-butyl-3-butylamino-4-(2-methyl-3-indolyl)maleimide (**11**) as the main product (Table 2, Entry 3) and 17% of 3-butylamino-1-methyl-4-(2-methyl-3-indolyl)maleimide (**10**). However, in dioxane as solvent (4 equiv. *n*-butylamine), product **10** was isolated in

Table 2. Amination of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide.[a]

Entry	Product	Isolated yield [%]
1[b]	 **9**	91
2[c]	 **10**	71
3[b]	 **11**	79
4[d]	 **12**	88
5[e]	 **13**	69
6[e]	 **14**	75
7[f]	 **15**	70
8[f]	 **16**	89

[a] Reaction conditions: 3-Bromo-1-methyl-4-(2-methyl-3-indolyl)-maleimide (1 mmol). [b] Corresponding amine (10 mL), TMEDA (1.5 equiv.), room temperature, overnight. [c] *n*-Butylamine (4 equiv.), dioxane (10 mL), TMEDA (0.75 equiv.), 50 °C, overnight. [d] Morpholine (4 equiv.), dioxane (10 mL), TMEDA (1.5 equiv.), 100 °C, overnight. [e] Corresponding amine (4 equiv.), dioxane (10 mL), NEt_3 (1 equiv.), 100 °C, overnight. [f] Corresponding amine (4 equiv.), dioxane (10 mL), NEt_3 (2 equiv.), 100 °C, overnight.

good selectivity and yield (71%, Table 2, Entry 2). By increasing the temperature, 1-methyl-4-(2-methyl-3-indolyl)-3-(4-morpholinyl)maleimide (**12**) was maintained in high yield (88%, Table 2, Entry 4). Similarly, 3-amino-4-indolylmaleimides **13** and **14** were isolated in 69% and 75% yield, when NEt_3 was applied as base (Table 2, Entries 5 and 6). Finally, 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide was treated with tryptamine and tyramine in the presence of 2 equiv. NEt_3 to give the corresponding 3-amino-4-indolylmaleimides **15** and **16** in 70% and 89% yield, respectively (Table 2, Entries 7 and 8). All isolated products are bright-coloured crystalline compounds.

Conclusions

In summary, we have demonstrated that 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide can successfully be carbonylated with alcohols or amines in the presence of $Pd(OAc)_2$/di-1-adamantyl-*n*-butylphosphane (cata*CX*ium® A). The resulting 3-alkoxycarbonyl-4-indolylmaleimides and 3-aminocarbonyl-4-indolylmaleimides were obtained in 25–70% yields. Stoichiometric amination of 3-bromo-1-methyl-4-(2-methyl-3-indolyl)maleimide was carried out to synthesize several novel 3-amino-4-indolylmaleimides in good yields. Biological tests of the isolated compounds are currently in progress.

Supporting Information (see footnote on the first page of this article): Experimental procedure and detailed spectroscopic data for all new compounds are presented.

Acknowledgments

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