Theses of Doctoral (PhD) Dissertation

PALLADIUM-CATALYZED INTER- AND INTRAMOLECULAR DIRECT ARYLATION REACTIONS OF O-HETERO CYCLES

Zoltán Sipos

Dissertation supervisor: dr. Krisztina Kónya

UNIVERSITY OF DEBRECEN
Doctoral School of Chemistry

1. Introduction and objectives

Transition metal-catalyzed cross-coupling reactions belong to the most commonly studied and most frequently applied transformations of organic syntheses. Traditional cross-coupling reactions require the use of preactivated organometallic compounds (Ar-M) and reaction partners that are bearing (pseudo)halide leaving groups (Ar’-X); therefore, these reactions might result in the formation of significant amounts of by-products (Scheme 1).

Scheme 1 Comparison of C-H bond functionalization and traditional cross-coupling reactions

On the other hand, in the case of carbon-hydrogen bond activation reactions a carbon-hydrogen bond is cleaved in one or both coupling partners. As a result, pathways with better atom efficiency can be developed that produce less by-products; moreover, prefunctionalization of the coupling partners is not or just partially necessary.

C-H Activation reactions – due to the strength of the carbon-hydrogen bond – often require high temperatures and long reaction times. Therefore, the application of microwave irradiation offers a beneficial alternative to facilitate the desired reactions; nevertheless, the number of known examples where this kind of heating is used to facilitate C-H bond activation reactions is relatively low.

Flavonoids and related compounds are prevalent structures in nature, particularly in the plant kingdom. They possess diverse biological activity: their antioxidant activity is excellent; nevertheless, derivatives showing antimicrobial, anti-cancer or even anti-inflammatory activities, among others, are also known. From a chemical point of view, the common structural moiety of the related compounds is the saturated or unsaturated oxygen containing benzo-fused heterocyclic ring.

Based on the above described details, our aim was to study the intra- and intermolecular C-H bond activation reactions of O-containing heterocycles in a microwave reactor.
Differently substituted polyhydroxy flavone derivatives were chosen as substrates of the intramolecular ring-closure reactions that were not available, thus we also had to carry out the syntheses of these compounds.

In the case of the intermolecular couplings, the bromo derivatives of O-heterocycles were selected in order to form new compounds bearing different 5-membered heteroarene moieties. The cross-coupling reactions of such haloflavonoids were thoroughly studied in our research group; however, their utilization in C-H bond activation reactions was unprecedented over the course of our previous studies.

2. Applied methods

Macro-, semi-micro- and micro-scale methods of the modern preparative organic chemistry were applied in the course of the experimental work. Microwave irradiation assisted ring-closure and heteroarylation reaction were carried out in a CEM Discover microwave synthesizer equipped with an autosampler. Reactions were monitored by thin-layer chromatography (TLC). The corresponding substrates, as well as the cyclized or the coupled products were purified by column chromatography and/ or crystallization. New compounds were characterized by classical analytical methods (melting point, elemental analysis) and their structures were elucidated by one and two-dimensional NMR measurements (1H NMR, 13C NMR, COSY, HSQC, HMBC), IR spectroscopy and mass spectrometry.

3. Results

3.1 A method was developed for the palladium-catalyzed direct intramolecular arylation of O-alkylated flavones in a microwave reactor. Studies were conducted to explain the observed regioselectivity.

During the design of our experimental work our aim was to accomplish intramolecular ring-closure reactions on different flavone derivatives. Therefore, a phenolic hydroxyl group of the appropriate molecules had to be converted to a 2-bromobenzyloxy group with 2-bromobenzyl bromide, then derivatives 63 and 71 could participate in the palladium-catalyzed ring-closure reactions to form the desired new six membered heterocyclic rings. As a result of this procedure, fused tetracyclic flavones 72 and 76 can be synthesized (Schemes 2 a and b).
Chrysin (61) was reacted with 2-bromobenzyl bromide to provide the appropriate product 63 in excellent yield, selectively bromobenzylated in the 7-position. Having tried several traditional or microwave irradiation assisted conditions, ring closure was accomplished by using Pd(OAc)$_2$ (10 mol%) as catalyst, PPh$_3$ (20 mol%) as ligand, K$_3$PO$_4$ (3.0 equiv) as base in a 1:1 mixture of N,N-dimethylformamide (DMF) and pivalic acid (PivOH) in a microwave reactor. Later it was proved that the use of a substoichiometric amount (30 mol%) of pivalic acid is sufficient to carry out the transformation. This experiment afforded regioisomers 72a and 72b as the products (Scheme 3).

The time- and temperature-dependence of the reaction was scrutinized closely and the preferred product of the reaction was proved to be 5-hydroxy-2-phenyl-4H,8H-benzo[c]pyrano[2,3-f]chromen-4-one (72a). The best regioselectivity was achieved at 150 °C in 10 minutes; nevertheless, the reaction was complete with good regioselectivity at 120 °C using the same reaction time.
During the study of the time-dependence, it was observed that longer reaction times lead to lower regioselectivity (Table 1). This phenomenon was explained by the Wessely-Moser type rearrangement of 5,7,8-trisubstituted flavones that has a free hydroxyl group at position 5 to 5,6,7-trisubstituted derivatives; moreover, this hypothesis was also proven experimentally.

<p>| Table 1 Time-dependence of the ring-closure of 7-(2-bromobenzyl)chrysin (63) |
|---------------------------------|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>t (min)</th>
<th>72a (%)</th>
<th>72b (%)</th>
<th>Product ratios (72a:72b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>79</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>84</td>
<td>10</td>
<td>8.4</td>
</tr>
<tr>
<td>20</td>
<td>81</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>81</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>40</td>
<td>80</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>50</td>
<td>74</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>60</td>
<td>62</td>
<td>35</td>
<td>2</td>
</tr>
</tbody>
</table>

Based on the observations of the study of the intramolecular direct arylation of 7-(2-bromobenzyl)chrysin (63), we prepared some new derivatives 71 that contained a 2-bromobenzyl group at position 5 as shown in Scheme 2.

Scheme 4 Synthesis of the key intermediate 5-hydroxyflavones 69a-d

Reagents and conditions: i) Me$_2$SO$_4$ / K$_2$CO$_3$ / anhydr acetone; ii) 80% KOH / EtOH, rt; iii) I$_2$ (8 mol%) / DMSO / reflux; iv) AlCl$_3$ / anhydr MeCN /Δ
The diversely substituted 5-hydroxyflavones 69a-e that were required for the preparation of flavones 71a-e were either synthesized starting from floracetophenone (64) or in the case of quercetin by methylation (69e) (Scheme 4). Floracetophenone (64) was methylated by dimethyl sulfate; the obtained product 65 was reacted with benzaldehydes in Claisen-Schmidt condensations according to literature procedures to furnish the corresponding chalcones 67a-d in moderate to good yields. This was followed by an iodine-catalyzed ring-closure reaction to afford permethylated flavones 68a-d, which were then demethylated by AlCl₃ to give 5-hydroxyflavones 69a-d in moderate to good yields.

In order to synthesize apigenin derivative 69f an iodine-catalyzed ring-closure was followed by the reflux of perbenzylated 68f in a mixture of acetic acid and water (4:1) to cleave the benzyl protecting group in good yield selectively at position 5 (Scheme 5).

5-(2-Bromobenzyloxy) derivatives 71a-f were prepared from 69a-f in the presence of K₂CO₃ in DMF at room temperature by reacting with 2-bromobenzyl bromide (62) in good to excellent yields; the ring-closures were then carried out in a microwave reactor (Scheme 6).

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**Scheme 5** Synthesis of 4',7-dibenzoyloxy-5-hydroxyflavone (69f)

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**Scheme 6** Synthesis of angular fused tetracyclic polyalkoxy flavones 76a-f
New fused tetracyclic flavones 76a-f were prepared by the conditions shown in Scheme 6. Longer reaction times (1-2 h) were required than in the case of chrysin derivative 63; however, full conversion was not always reached and the ring-closures were also accompanied by side-reactions (debenzylation, dehalogenation), hence further increasing the reaction times was detrimental to the product formation. Accordingly, the observed yields were moderate (12-55%). Apigenin derivative 71b furnished the desired product 76b in the best yield (55%) among these compounds; its benzylated analogue (71f) resulted in a lower yield, while 76d was obtained in the lowest yield. The decreased reactivity compared to the reaction of 63 might be explained by the increased steric hindrance, as well as the strong intramolecular hydrogen bond formed in the case of the 5-hydroxy derivatives, the formation of which might have been the driving force behind the debenzylation.

3.2 Conditions were developed to facilitate the coupling of O-heterocycles bearing a bromo leaving group in their A-rings with different O-, N- and S-heteroarenes. The occasional by-reactions were also studied thoroughly.

The other part of my research was to study the palladium-catalyzed coupling of bromoflavones 78 and 86 with various heteroarenes. The conditions for the reactions of 7-bromoflavone (78) and 1,2-dimethylimidazole (18a) or 1-methylindole (80) were optimized, respectively. As a result, new phosphine ligand-free conditions were developed to facilitate the microwave irradiation-assisted direct arylation reactions. We found that the coupling can be effectively carried out by using Pd(OAc)$_2$ (5 mol%) as catalyst, pivalic acid (30 mol%) and K$_2$CO$_3$ (1.5 equiv) as base; anhydr. DMF was used as solvent. The addition of PivOH was proved to be crucial as only lower conversions could be reached when it was omitted. Monocoupled products 79b and 79b’ and bis-coupled product 81 were all isolated in the reactions with 1-methylindole (80); the structures of these products were also confirmed (Scheme 7).

![Scheme 7](image.png)

**Scheme 7** The coupling reaction of 7-bromoflavone (78) with 1-methylindole (80)
7-Bromoflavone (78) and 6-bromoflavone (86), respectively, were successfully coupled with various five membered heteroarenes (Table 2) in moderate to good yields using the developed method (Scheme 8). Generally only a small excess of the heterocycles was used, however, the yields could be improved by the addition of a larger excess of heteroarenes in some cases. The heterocycle-bridged biflavones were also isolated occasionally.

**Scheme 8** Coupling of bromoflavones (78 and 86, respectively) with different heteroarenes

**Table 2** The heterocycles used as coupling partners

<table>
<thead>
<tr>
<th>Heteroarenes</th>
<th>Heteroarenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a, 18b, 18c, 18d, 18e, 18f and 18g</td>
<td>18f, 18g</td>
</tr>
<tr>
<td>18b 4-Phenyl-1-methylimidazole</td>
<td>16 Tiophene</td>
</tr>
<tr>
<td>18e Oxazole</td>
<td>26 Benzo[b]tiophene</td>
</tr>
</tbody>
</table>

The structures of the obtained products, as well as the coupling positions were confirmed by one and two dimensional NMR measurements. We found that in the case of the 1,3-azoles (18a, 18b, 18c, 18d, 18e, 18f and 18g) the coupling occurred at the 5-position of the heterocycles; in the case of 1-methyl-4-phenylimidazole (18d), the formation of the 2,5-diarylated derivative was also observed, however, the 2-arylated mono-coupling product was neither isolated nor detected by TLC. The position of the new carbon-carbon bond was usually adjacent to the heteroatom in the case of heteroarenes containing one such atom; moreover, in some cases the symmetrical heterocycle-bridged biflavones were also isolated. A few experiments involving 1-methylpyrazole (82) were carried out to demonstrate that by increasing the amount of the heterocycle the yields can be improved. Therefore, a few reactions where lower yields were achieved were repeated with 3.0 equiv of heteroarenes.

We discovered and proved by means of spectroscopy, as well as experimentally that homo-coupling also occurs during the reactions to a varying degree, which decreased the yields of the desired products. During these experiments, in the case of 7-bromoflavone (78)
7,7”-biflavone (93), while in the case of 6-bromoflavone (86) 6,6”-biflavone was the major product of the reaction, respectively. The obtained yields could be compared with the corresponding values from the literature. As a consequence, the developed reaction conditions facilitate a simple way to synthesize symmetrical biflavones (Scheme 9).

Scheme 9 Synthesis of symmetrical biflavones 93 and 94 by Pd-catalysis

By comparing the reactivity of 7-bromoflavone (78) and 6-bromoflavone (86), except for a few cases, 86 afforded similar or even better yields than 78. A competitiveness experiment was carried out between 78 and 86 using 1,2-dimethylimidazole (18a) as the coupling partner and the ratio of the formed products 79a and 87a was found to be 1.7:1 based on the 1H NMR spectrum. Considering the fact that the by-reactions such as dehalogenation and homocoupling were detrimental to the overall isolated yields in the case of both substrates, we assumed that the oxidative addition of palladium to the carbon-halide bond occurs faster in the case of 7-bromoflavone, which might have a higher chance to be followed by the additional by-reactions and the homocoupling.

The application of the developed conditions was expanded to additional O-containing heterocycles, such as 7-bromochromone (96), 7-bromocoumarin (95) as well as 6-bromoaurone (97). These substrates were successfully coupled with a few selected heterocycles: 1,2-dimethylimidazole (18a), 1-methylindole (80), oxazole (18e), thiazole (18f) and 4-methylthiazole (18g) in low to moderate yields. The lowest yields were achieved in the case of the reactions with oxazole (18e), while the highest yields of the desired products 98-100 were isolated in the reactions that involved 1,2-dimethylimidazole (18a). When 18a was combined with 6-bromoaurone (97), the E- and Z-isomers of 100a were separated and (Z)-100a was found to be the major product.

No product was isolated in the case of 7-bromoflavanone, only the rupture of the flavanone ring was observed.
Scheme 10 Heteroarylation of 7-bromochromone (96), 7-bromocoumarin (95) and 6-bromoaurone (97)

3.3 A method was elaborated for the C-2 regioselective coupling of 1,3-azoles with O-heterocycles. The optimized conditions were studied through the coupling of a number of O-heterocycles and heteroarenes.

Based on our previous experiences, microwave irradiation assisted phosphine ligandless conditions were developed to facilitate the C-2 selective coupling of 1,3-azoles. Optimization reactions were carried out between 1-methylimidazole (18b) and 7-bromoflavone (78) (Scheme 11).

Scheme 11 C-2 selective coupling of 1-methylimidazole (18b) with 7-bromoflavone (78)

The best results were achieved when 5 mol% Pd(OAc)$_2$ and 1.0 equiv of CuI was used at 140 °C for 1 h in a microwave reactor. We demonstrated that the use of CuI is inevitable in order to reach high yields and good regioselectivity.

These conditions were also applied to additional O-heterocycles and 1,3-azoles (Scheme 12). 7-Bromoflavone (78) and 7-bromochromone (96) showed similar reactivity, reactions with 6-bromoflavone (86) and 7-bromocoumarin (95) provided the desired products in lower yields. No difference was found in the yields when 102 bearing a 4’-methoxyphenyl group was used instead of 78; however, a significantly lower yield was experienced when 7-benzyloxy-6-bromoflavone (103) was used instead of 86. We observed that in the case of 6-
and 7-bromoflavone (86 and 78) the reactions with oxazole (18e) resulted in very low yields, respectively; nevertheless, better yields could be achieved by increasing the amount of copper(I) iodide. The regioselectivity of the reactions was excellent under these conditions.

Scheme 12 Coupling of O-heterocycles (78, 86, 96, 95, 102 and 103) with 1,3-azoles

The same reactions were also done with derivatives that had a saturated heterocyclic ring. 7-Bromochromanone (104) and 6-bromochromanone (105) were successfully coupled with 1,3-azoles (Scheme 13) to afford the desired chromanones 111 and 112 in moderate to good yields.

Scheme 13 Reactions of chromanones (104, 105) with 1,3-azoles

To exploit the complementary selectivity of the developed direct arylation methods, compound 78c was coupled with 4-bromoanizole (1a) and 1-bromo-4-fluorobenzene (1b) to afford 113a and 113b; moreover, 101a was transformed to 2,5-diarylazole 114 by coupling with 1a (Scheme 14). This way we could demonstrate that the developed methods complement each other in the synthesis of new, diversely substituted heterocycles.
3.4 The fluorescent properties of a few synthesized products were examined.

Based on TLC studies we found that some of our heteroaryl flavones exhibited fluorescence when irradiated by UV light at a wavelength of 365 nm.

**Scheme 15** Fluorescent emission spectra of a few products coupled with indole and imidazole

In the case of a few selected compounds, the UV-VIS spectra were recorded at different concentrations and the absorption maxima and the molar absorption coefficients ($\varepsilon$) were determined. The corresponding compounds were then irradiated at 350 nm and the fluorescent emission spectra were also recorded (for example, see Scheme 15) at the appropriate concentrations. The emission maxima and quantum yields ($\Phi_F$) of these compounds were also determined using quinine sulfate as reference.

The observed quantum yield of coumarin derivative 98a ($\Phi_F = 0.439$) stood out among the measured values, the other quantum yields were significantly lower than this one. We also discovered that among the flavones coupled with 1-methylindole (80) (79b, 79b', 87b and 87b') those showed better photophysical properties in which the coupling occurred at the C-3 position of the indole ring, possibly due to the more favourable conjugated system formed during the excitation.
4. Possible applications of the results

Over the course of my research, I was studying direct arylation reactions, a highly atom efficient type of the palladium-catalyzed coupling reactions. By utilizing this type of reactivity, a high number of novel O-heterocycles were synthesized in intra- and intermolecular direct arylation reactions. The application of microwave irradiation technique to facilitate the reactions resulted in shorter reactions times and excellent conversions; moreover, the couplings usually provided the desired products in good selectivity. When compared to the results from the literature, we can assess that the yields of these reactions are not superior; however, the versatility of these methods, as well as the applied shorter reaction times suggest that our methodology can be a valuable asset of organic synthesis.

The aim of this work was mainly to prepare novel flavone derivatives and related compounds with only a few known examples in the literature as part of the basic research. According to literature analogies, the prepared derivatives may be potentially biologically active; however, no studies have been done to explore this so far. Recently, as a result of an in silico screening by Eli Lilly and Company, 30 of our compounds were chosen for biological studies, these studies are in progress at the moment. Moreover, several of our products showed fluorescent emission, which may provide an additional level to the application of these new derivatives.

In conclusion, as a result of our research a highly efficient synthetic methodology was developed by pairing direct arylation reactions and microwave irradiation techniques that can be used to carry out library syntheses, as well as late-stage functionalization of heterocyclic compounds.
List of publications

Publications related to the dissertation


Lectures related to the dissertation


5. Sipos Zoltán, Kónya Krisztina: *Flavonoidok mikrohullámú aktiválás segítette C-H funkcionalizálási reakcióinak vizsgálata*


Posters related to the dissertation


List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

   *Synlett.* 29 (18), 2412-2416, 2018. ISSN: 0936-5214.
   DOI: http://dx.doi.org/10.1055/s-0037-1611012
   IF: 2.369 (2017)

   *Synthesis.* 50 (08), 1610-1620, 2018. ISSN: 0039-7881.
   DOI: http://dx.doi.org/10.1055/s-0036-1591773
   IF: 2.722 (2017)
Foreign language abstracts (1)

   Szélpál Szilárd, Magyar Kémikusok Egyesülete, Budapest, 59-60, 2014. ISBN:
   9789639970526

Total IF of journals (all publications): 5,091
Total IF of journals (publications related to the dissertation): 5,091

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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