Efficient Pallado-Catalyzed *C6*-(het)arylation of Imidazo[1,2-*b*][1,2,4,5]Tetrazines under Microwave Irradiations

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A versatile protocol for the preparation of a library of 5,6-(het)bisarylated imidazo[1,2-*b*][1,2,4,5]tetrazines is described. Target compounds were obtained in fairly good yields, starting from ethoxy-7-(4-methoxyphenyl)imidazo[1,2-*b*][1,2,4,5]tetrazine and a large panel of bromoaryl derivatives, using palladium catalysis under microwave irradiation. Compatibility with various chemical groups and heterocycles was proven. Steric and electronic effects do not have any effect on the efficiency of the reaction. Purifications were performed without any difficulties, and the structure of a final compound was proven by crystal X-ray diffraction studies.

Nitrogen-bridgehead heterocycles containing an imidazole ring are scaffolds which are widely used to design bioactive molecules. Indeed motifs such as imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines are interesting cores found in compounds showing a wide range of biological activities. Antiviral,[1] anti-ulcer,[2] antibacterial,[3] antifungal,[4] herbicidal,[5] and cyclin-dependent kinases (CDK) inhibitors[6] properties were, for example, often reported. Among these heterocycles, imidazo[1,2-*b*][1,2,4,5]tetrazines attracted, surprisingly, little attention: only a few reports on this core were published in the literature.[7] On the basis of the interests of our group in the synthesis of biologically active compounds, we thought that functionalized imidazo[1,2-*b*][1,2,4,5]tetrazines could be considered as aza-bioisosters of imidazo pyridines or pyrimidines. We thus envisioned the development of a new methodology giving access to a library containing such functionalized imidazo[1,2-*b*][1,2,4,5]tetrazines through a regioselective palladium-catalyzed (het)arylation as a key step.

We started our investigations with the synthesis of the model compounds **2** and **3**. Imidazo[1,2-*b*][1,2,4,5]tetrazine **2** was prepared by the reaction of amino-(1,2,3,4)-tetrazine **1**[8] with the corresponding 2-bromoacetophenone in 72% yield when the cyclization was run in the presence of a base (i.e., $NaHCO_3$) in boiling dioxane (Scheme 1). Compound **3** could also be directly prepared from aminotetrazine **1**, if the cyclization step is run in the presence of $NaHCO_3$, but using EtOH as solvent (Table 1, entry 1). In EtOH but without any base, the displacement of the 3,5-dimethylpyrazole moiety did not occur, and only **2** was isolated in 62% yield (entry 2). The same behavior was observed when reactions were run under microwave irradiations (entry 4−6). Unfortunately, even if the reaction time was considerably reduced, yields decreased drastically, mainly because of degradation. Classic thermal conditions were best suited for the synthesis of those precursors **2** and **3** from **1**. Noteworthy, the 3,5-dimethylpyrazole was easily displaced starting from **2** with sodium ethoxide to afford **3** in 89% yield by a S_NAr reaction.

The Pd(0)-mediated arylation of this *C*-6 unsubstituted imidazo[1,2-*b*][1,2,4,5]tetrazine was then evaluated (Scheme 2). Unfortunately, when a solution of **2** in dioxane was stirred, under microwave irradiations, with 1-bromo-4-methoxybenzene in the presence of a Cs_2CO_3 and $Pd(OAc)_2$/PPh_3, as catalytic system,[9] only degradation occurred. The sensitivity of the 3,5-dimethylpyrazole group in basic media could explain this disappointing result.

The Pd(0)-mediated arylation of **3**, using 1-bromo-4-fluorobenzene as coupling partner, was then tried under classic thermal conditions (Table 2, entry 1). The reaction afforded the desired *C*6-arylated imidazotetrazine **4**. Unexpectedly, the reaction was incomplete and gave an inseparable mixture of **3**, **4**, and **5**. Fortunately, complete conversion could be obtained in only 20 min using microwave irradiations (entry 2). In that case, the reaction still led to a separable mixture of **4** and **5**. Undoubtedly, this byproduct resulted from the insertion of Pd(0) into a C−P bond of triphenylphosphine. This reactivity is quite rare but has nevertheless already been published.[10] We thus thought that this side reaction could be avoided by the use of tricyclohexylphosphine. To our delight, this new ligand allowed us to isolate **4** as a single product in a very good yield of 87% (entry 3).[11]

To propose an eco-compatible alternative for the synthesis of **4**, we also envisioned its preparation through a copper(I)-phenanthroline catalytic system.[12] However the reaction

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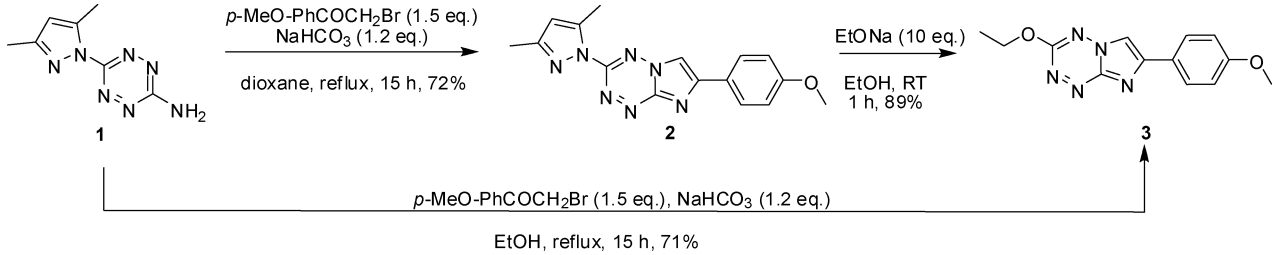
Scheme 1. Preparation of Compounds **2** and **3**



failed in our hands. The arylation of this imidazo[1,2-*b*][1,2,4,5]tetrazine skeleton thus proved to be efficient only when the reaction was Pd-catalyzed. All the spectral data were in concordance with the structure of compound **4**. In addition, isolation of a single crystal of **4** gave access to its X-ray structure analysis (Figure 1). It showed that the deviation of each atom in the different rings from the corresponding mean plane is within 0.008 Å. The dihedral angles between the 4-methoxyphenyl group and the imidazotetrazine core on the one hand, and between this core and the fluoro phenyl group on the other hand, are 0.58(2)° and 88.6(5)°, respectively. Except this fluoro phenyl group, all the other atoms are quasi planar (the root mean square (rms) deviation of fitted atoms is 0.02 Å) and parallel to the (1 0 1) plane. The Oak Ridge thermal ellipsoid plot (ORTEP) view presents the ethoxy chain in the major statistical occupancy (65%) for better clarity. At room temperature, the fluoro phenyl group shows a disordered little twist around the C(14)−C(17) axis which is not quantified.

To explore the scope and limitations of our methodology, we next envisioned to modify the nature of the bromobenzene derivative using our optimized conditions (Table 3).

Table 1. Preparation of Compounds **2** and **3**

entry	solvent	conditions	base	compound	yield
1	EtOH	reflux, 12 h	$NaHCO_3$	**3**	71%
3	EtOH	reflux, 12 h		**2**	62%
4	EtOH	MW,[a] 10 min	$NaHCO_3$	**3**	45%
5	dioxane	MW,[a] 10 min		**2**	52%
6	EtOH	MW,[a] 10 min		**2**	38%

[a] MW: microwave irradiation.

Bromobenzene derivatives bearing electron-withdrawing groups (F, NO_2, CN, Cl) gave the desired compounds in very good yields (Table 3, entries 1−5). The reaction of **3** with 1-bromo-4-chlorobenzene or 1-bromo-3,5-dichlorobenzene noteworthy afforded imidazotetrazines **6** and **7**, as single compounds, in 80% yield. No trace of the product resulting from the coupling reaction on the Cl moiety was detected, showing the complete chemoselectivity of this arylation.

The electronic nature of the bromobenzene derivative did not really have any influence on the yields, as bromobenzene and electron-enriched bromobenzenes still led to the desired compounds in very good yields (entries 6−11). Bromoaniline could also be employed (entry 12) but the reaction failed with bromo-phenols (entries 13−14). The phenate

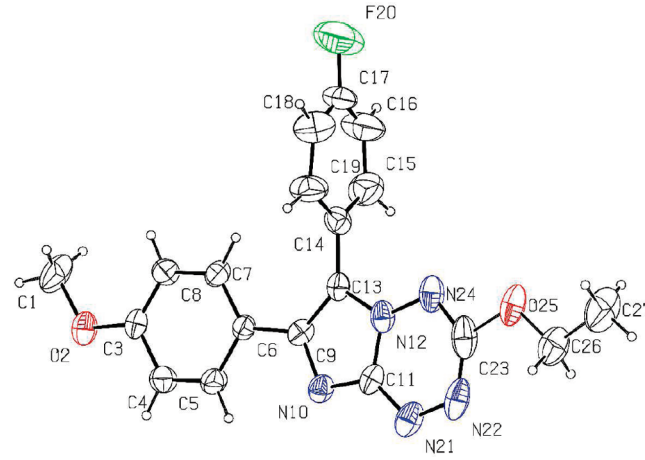


Figure 1. X-ray crystal structure of compound **4**.

Scheme 2. Arylation of Compound **2**

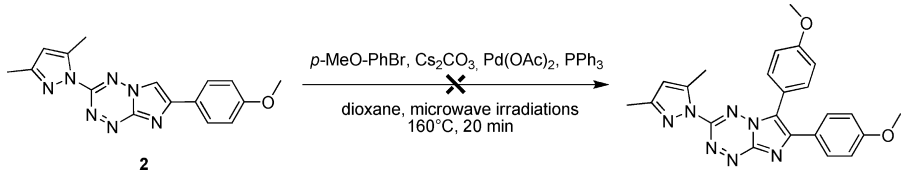
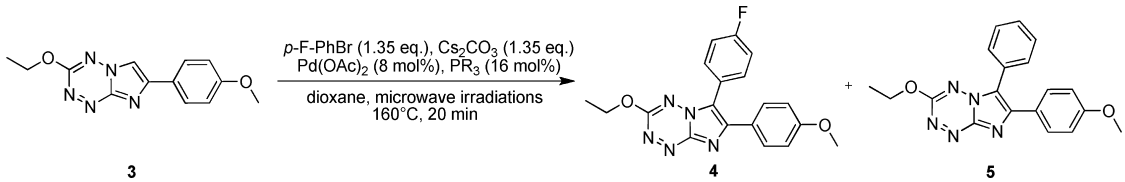


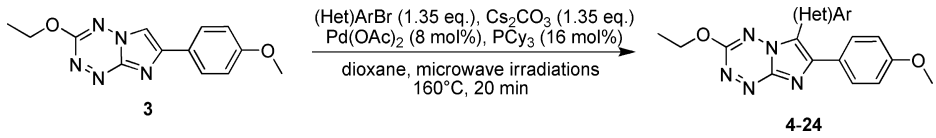
Table 2. Preparation of Compound **4**

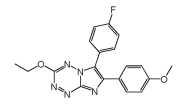
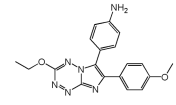
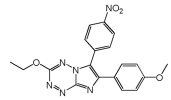
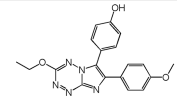
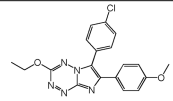
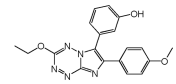
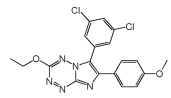
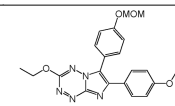
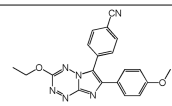
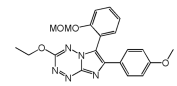
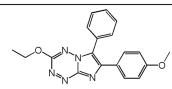
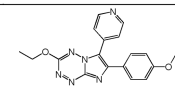
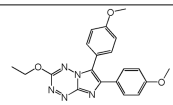
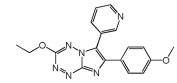
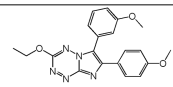
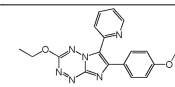
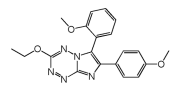
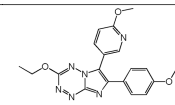
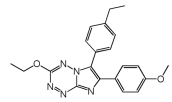
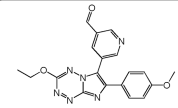
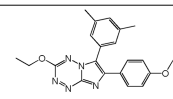


entry	phosphine	heating system	conversion	ratio **4/5**	yield of **4**[b]
1	PPh_3	reflux, 12 h	82%	60/40	41%
2	PPh_3	MW,[a] 20 min	100%	60/40	45%
3	PCy_3	MW,[a] 20 min	100%	100/0	87%

[a] MW: microwave irradiation. [b] Yields were determined by ^1H NMR.

Table 3. Synthesis of Compounds **4**−**24**



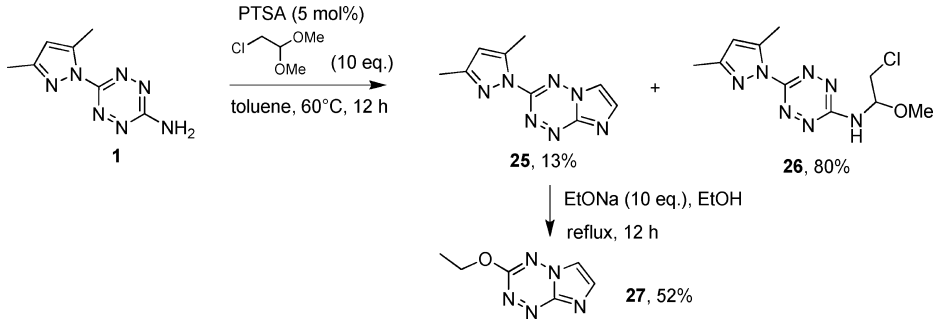
Entry	Product	Structure	Yields	Entry	Product	Structure	Yields
1	**4**		87%	12	**15**		75%
2	**5**		82%	13	**16**		ND[a]
3	**6**		80%	14	**17**		ND[a]
4	**7**		80%	15	**18**		88%
5	**8**		78%	16	**19**		76%
6	**9**		76%	17	**20**		92%[b]
7	**10**		84%	18	**21**		94%
8	**11**		72%	19	**22**		ND[a]
9	**12**		86%	20	**23**		87%
10	**13**		85%	21	**24**		82%
11	**14**		88%				

[a] ND: Not Detected. [b] 4-iodopyridine was used as starting material.

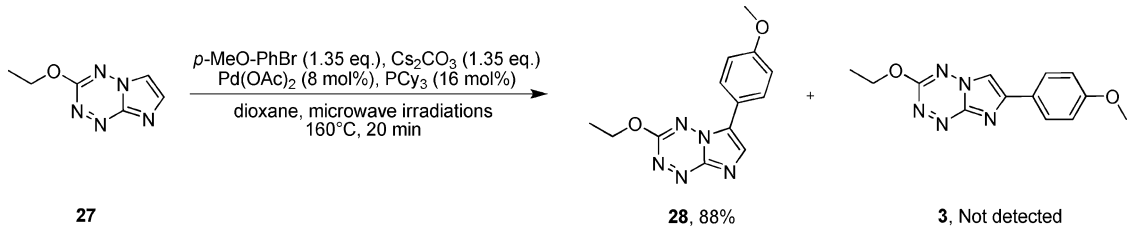
formation during the reaction thus seems detrimental to its efficiency. Fortunately, the reactivity could be fully restored using MOM-protected bromo-phenols (entries 15−16). The displacement of the substituent to the *C*-2 position did not affect the yields (entries 9, 16), demonstrating that sterically hindered bromobenzenes could be employed without any loss of reactivity.

To prove the efficiency of the CH arylation in heteroaromatic series, we then focused our study on the pyridine skeleton. Bromo-pyridines generally gave good results (entries 17,18), except 2-bromopyridine (entry 19). In that case, starting material was fully recovered. Complexation of palladium with the pyridinic nitrogen atom could inactivate the catalytic cycle. For the synthesis of **20**, the use of 4-iodopyridine, instead of 4-bromopyridine, was needed to obtain full conversion. Electron-enriched or deactivated pyridines could also be employed, affording interesting compounds such as **23** and **24** (entries 20−21).

Scheme 3. Preparation of Compound **27**



Scheme 4. Arylation of Compound **27**



To complete our investigations, the arylation of the *C*-6 and *C*-7 unsubstituted imidazotetrazine **27** was tested. This compound was synthesized through the reaction of **1** with chloroacetaldehyde using acidic conditions (Scheme 3).[13] Unfortunately, the intermediate **25** was isolated in only 13% yield. The major compound of this reaction appeared to be tetrazine **26** (80%), which results from the hemiacetal formation by the amino group instead of the commonly accepted nucleophilic substitution of the chlorine atom (*N*-2 or *N*-4 of the tetrazine). All attempts to avoid this side-reaction failed in our hands (basic or acidic media). Nevertheless, in the presence of EtONa, the displacement of the 3,5-dimethylpyrazole of **25** spontaneously occurred, and **27** was isolated in 52% yield.

When **27** was irradiated with 1-bromo-4-methoxybenzene using the described conditions, only the product of *C*-6 arylation **28** was isolated in 88% yield. No trace of **3**, which would result from the *C*-7 arylation, was observed, showing the complete regioselectivity of this very interesting *C*-6 arylation (Scheme 4).

In conclusion, we have shown in this article that *C*-6 functionalized imidazo[1,2-*b*][1,2,4,5]tetrazines could be efficiently synthesized using our regioselective palladium-catalyzed arylation. Good to excellent yields were obtained with a wide range of bromobenzene derivatives, with no noticeable effect of the electronic nature of their substituents. This new methodology should be suitable for the design of more complex heterocyclic structures, such as bioactive derivatives containing an imidazo[1,2-*b*][1,2,4,5]tetrazine core.

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Supporting Information Available. Experimental procedures, spectral data of compounds **1**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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