Synthesis of a Solid-Phase Amino Imidazotriazine Library via Palladium Catalyzed Direct Arylation

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Heteroarenes, including imidazoles and triazines, are important structural units frequently found in natural products,[1] pharmaceuticals,[2] and agrochemicals.[3] The biological importance and structural variation of heterocyclic derivatives provide a significant synthetic challenge, particularly when concerned with efficiently synthesizing large numbers of discrete analogues. Modern combinatorial chemistry plays a key role in the search for lead structures displaying biological activity and represents a powerful methodology for the synthesis of compound libraries for biological evaluation.[4] Considering the frequent occurrence of heterocyclic frameworks in known pharmaceutical and agrochemical biologically active entities, they make an attractive target for diversification utilizing combinatorial synthetic approaches. Of particular importance to lead discovery is the incorporation of novel heterocyclic cores into library design and production. A good example is the imidazo[2,1-*f*]-[1,2,4]triazine core **1** (Figure 1), which represents a currently little known heterocylic system but which clearly has an interesting biological potential as illustrated by the adenosine deaminase inhibitor **5**,[5] the antiviral agent **6**,[6] the GABA agonist **7**,[7] and the tyrosine kinase inhibitor **8**.[8]

In the current work, we focused our attention on the use of the 7-amino-imidazo[2,1-*f*][1,2,4]triazine (**2**) (Figure 1) as an attractive core structure that we envisaged could be derivatized to give a protein kinase targeted library of general structure **3**.[9] For the production of the library, we planned to use a Heck-like direct arylation reaction to functionalize the *C*-3 position (Scheme 1). The direct arylation reaction of imidazotriazines[7] and of many other heterocyclic systems[10] has been previously reported but has, to the best of our knowledge, not been used to functionalize resin bound imidazole based heterocycles. This reaction has some advantages over traditional cross-coupling methods (e.g., Stille, Suzuki, and Negishi),[11] in that there is no need to synthesize heterocyclic halides or organometallic intermediates (B, Sn, Zn). In addition, undesired side reactions such as protodehalogenation and protodemetalation do not affect the purity of the final products, thus simplifying or even avoiding the need for postsynthesis purification. This paper discloses the synthesis and characterization of a sample solid-phase library of 20 compounds prepared using IRORI MicroKan technology.[12]

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Our synthesis program started from the amide **11** (Scheme 1), which we envisaged could be directly transformed into a resin-bound amine **12** by adaptating recently published solution-phase chemistry.[13] The starting heterocyclic amide **11** can be synthesized in three steps from the imidazole **9**[8] or in four steps from the triazine **10**[5,14] (Scheme 1).

Four simple alkyamines were chosen for the first diversity point R^1 (Figure 2). These amines were attached to a 2-(4-formyl-3-methoxyphenoxy)ethyl (FMPE) polystyrene resin by reductive amination to give resins **14** (contained in 20 MicroKans) (Scheme 2).[15] The substitution reaction to attach the heterocycle to the resin was carried out by treating the resins **14** and the heterocyclic amide **11** in DMF with DBU, followed by addition of PyBOP and heating to 60 °C for 66 h. Filtration and thorough washing of the MicroKans afforded the resin-bound intermediates **16**. Cleavage of trial MicroKans at this stage afforded good yields of products **4** which are also of interest as potential kinase inhibitors.

Five simple aryl bromides were chosen for the second diversity point R^2 (Figure 2). The key palladium catalyzed arylation coupling step to generate intermediate **17** on the solid phase (Scheme 2) was performed under a nitrogen-atmosphere with reagent grade solvents. No extensive drying or degassing protocols were necessary. A 5-fold excess of aryl halide and base was used to drive the reaction to completion. Since workup and purification involved a simple filtration, this did not cause any postsynthesis purification problems. Following arylation the products were cleaved from the resin using 50% TFA in CH_2Cl_2 to afford the products **3** listed in Table 1 and shown in Figure 3. The products were isolated in modest to good yield and in high purity demonstrating an advantage of this approach when compared to conventional coupling methodologies. The purities of the compounds were measured using ^{1}H NMR and both evaporative light scattering (ELS) and diode array detectors (DAD, 220 and 260 nm). There was a good overall agreement between compound purities determined by ^{1}H NMR, ELS, and UV at 260 nm. The ^{1}H NMR and mass spectra for all compounds were entirely in agreement with the assigned structures (see Supporting Information).

The electron-deficient aryl halide **15**{*1*} reacted as a very efficient electrophile in the arylation reaction affording products **3**{*1,1*}, **3**{*2,1*}, **3**{*3,1*}, and **3**{*4,1*} in excellent purity >97% as determined by ^{1}H NMR (Table 1, entries 1, 6, 11, 16). The deactivated aryl halides **15**{*2*} and **15**{*4*} also gave the products in excellent purity >95% (Table 1). The direct arylation reaction also proved highly successful with the relatively sterically hindered substrate **15**{*3*}, affording **3**{*1,3*}, **3**{*2,3*}, **3**{*3,3*}, **3**{*4,3*} (Table 1, entries 3, 8, 13, 18) although some nonarylated product could be detected after cleavage (<5%). Utilization of the relatively more electron rich aryl halide **15**{*5*} afforded the products with the lowest average purity in the test subset, although even here the purity was mostly good, laying at around 90%

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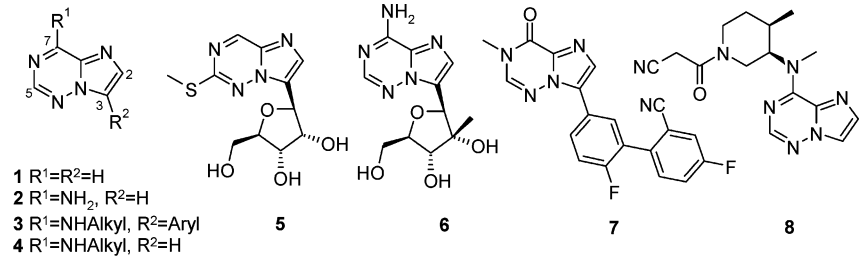
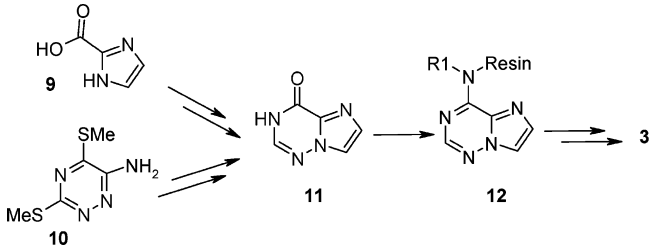


Figure 1. Biologically interesting imidazotriazines.

Scheme 1. Synthesis of Intermediate **11** and Potential Elaboration to Target Compounds



with the exception of entry 10. Here too, the main impurity after cleavage was the nonarylated product.

In summary, a 20-membered test library of 3-aryl-7-amino-imidazo[2,1-*f*][1,2,4]triazines **3** has been synthesized on the solid phase utilizing a palladium catalyzed direct arylation reaction. The products were obtained in modest to good yields and high purity. The strategy provides an efficient way to access 3-arylated-7-amino-imidazo[2,1-*f*][1,2,4]triazine analogues which are of interest to the pharmaceutical and agrochemical industries. The methodology proved to be robust enough to enable the subsequent production of a >350 member solid-phase combinatorial library.[16] It is of particular interest to note that attempts to perform the direct arylation reaction on substrates **4** as a normal solution-phase reaction failed, leading only to the recovery of unreacted starting material, presumably because of interference by the free NH group.[17] Thus, in this case the solid phase polymer is not only acting as an aid to efficient parallel synthesis but also as an NH-protecting group.

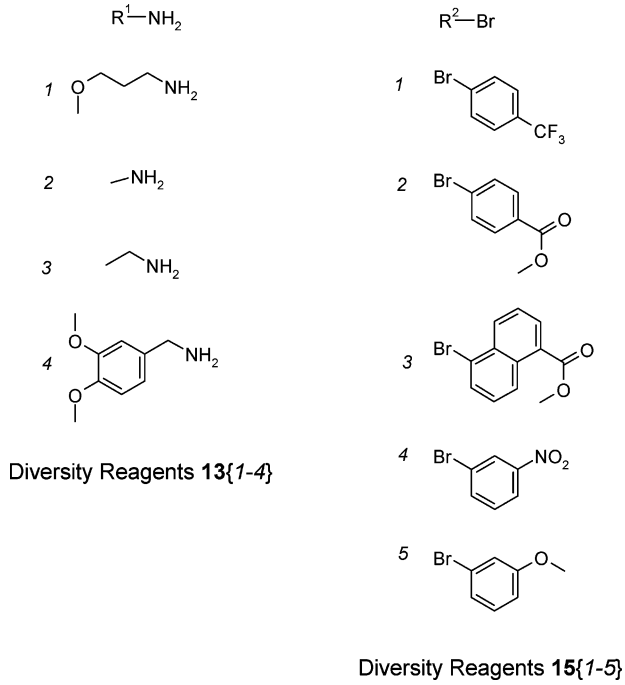
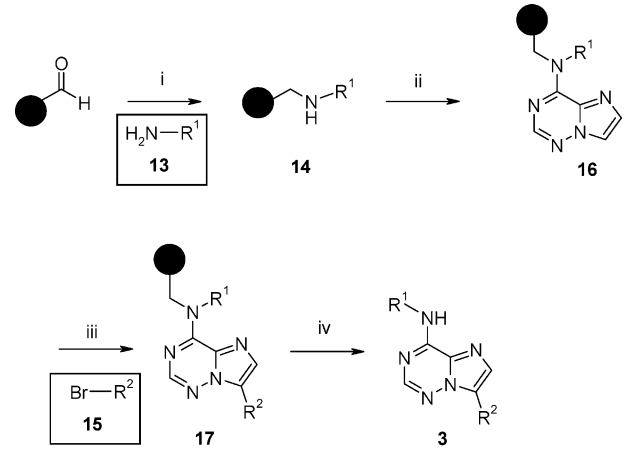


Figure 2. Diversity reagents **13**{*1*−*4*} and **15**{*1*−*5*}.

Scheme 2. Combinatorial Synthesis of Target Compounds[a]



[a] Reagents and Conditions: (i) (a) R^1NH_2, TMOF, (b) $NaBH_4$, MeOH, 24 h; (ii) DBU, **11**, PyBOP, DMF; (iii) $Pd(OAc)_2$, KOAc, PPh_3, R^2Br, DMAc; (iv) TFA/DCM 1:1.

Table 1. Results of Library Synthesis According to Scheme *2*

			purity[b]				mass[c]	
entry	product	isolated yield	NMR	ELS	DAD 260 nm	DAD 220 nm	MW expected	MW found
1	**3**{*1,1*}	66%	>97%	100%	77%	0%[a]	352.1	352.2
2	**3**{*1,2*}	24%	>97%	100%	67%	0%[a]	342.2	342.2
3	**3**{*1,3*}	91%	95%	99%	91%	87%	392.4	392.3
4	**3**{*1,4*}	54%	>97%	100%	76%	0%[a]	329.1	329.4
5	**3**{*1,5*}	86%	90%	94%	62%	55%	314.2	314.2
6	**3**{*2,1*}	61%	>97%	100%	91%	61%	294.1	294.1
7	**3**{*2,2*}	33%	95%	100%	96%	43%	284.1	284.2
8	**3**{*2,3*}	53%	95%	98%	91%	88%	334.4.	334.2
9	**3**{*2,4*}	16%	95%	100%	100%	0%[a]	271.1	271.2
10	**3**{*2,5*}	69%	70%	100%	90%	97%	256.1	256.2
11	**3**{*3,1*}	46%	>97%	100%	93%	0%[a]	308.1	308.1
12	**3**{*3,2*}	53%	96%	100%	80%	50%	298.1	298.3
13	**3**{*3,3*}	76%	95%	100%	91%	85%	348.4	348.2
14	**3**{*3,4*}	41%	>97%	100%	85%	44%	285.1	285.2
15	**3**{*3,5*}	78%	90%	100%	77%	70%	270.1	270.2
16	**3**{*4,1*}	47%	>97%	99%	95%	86%	430.1	430.3
17	**3**{*4,2*}	72%	95%	100%	88%	82%	402.4	420.3
18	**3**{*4,3*}	47%	95%	89%	87%	66%	470.5	470.4
19	**3**{*4,4*}	74%	97%	92%	96%	62%	407.1	407.3
20	**3**{4,5}	65%	91%	81%	82%	65%	392.2	392.3
	average	58%	94%	98%	86%	52%		

[a] No signal was detected. [b] Purity refers to product analyzed after cleavage using ^1H NMR, ELS, or UV (220 and 260 nm). [c] Measured by ESI-MS and hence reported weights are for MH^+.

Supporting Information Available. Experimental procedures and ^1H NMR for all compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

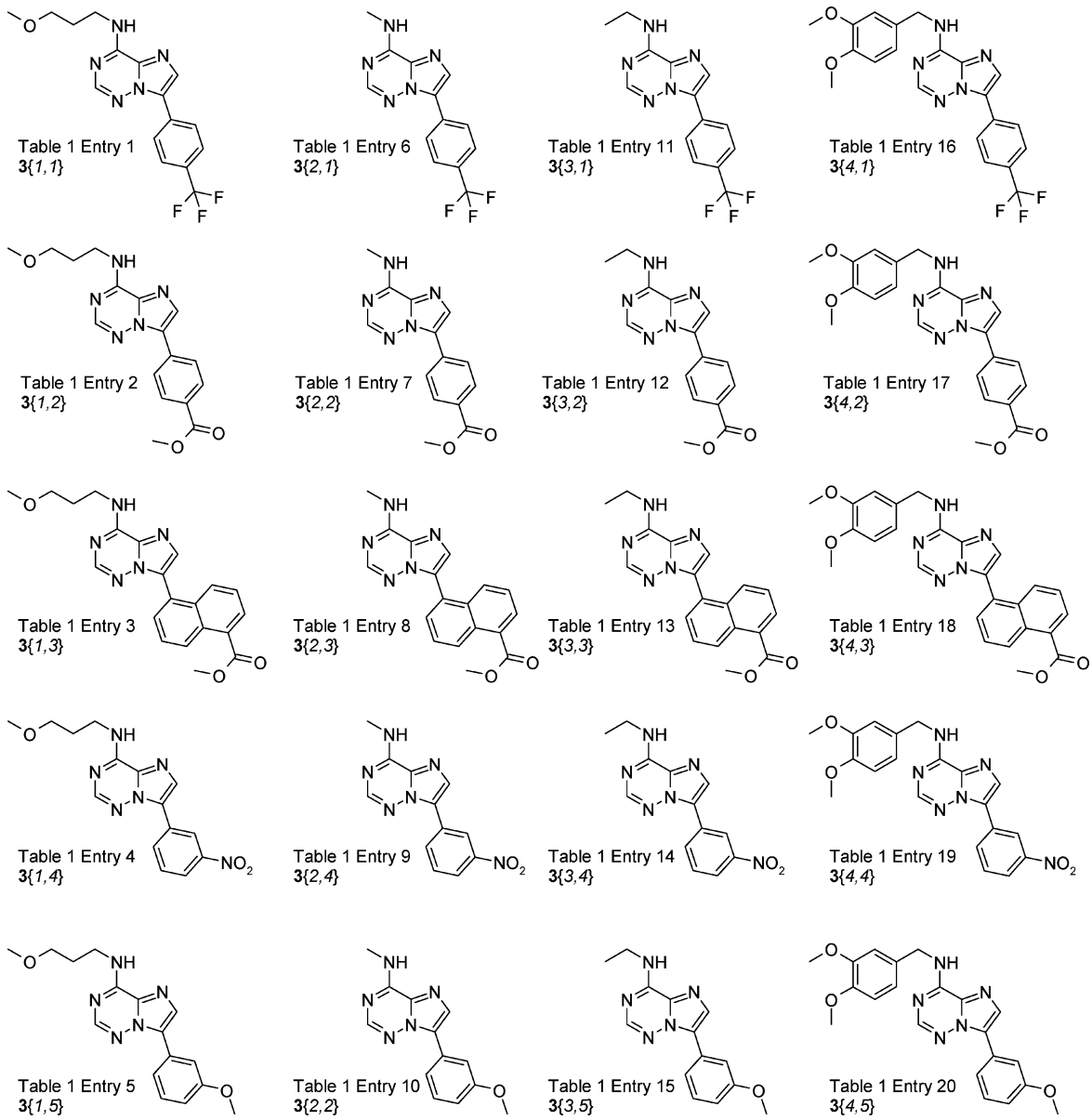


Figure 3. Library of 3-aryl-7-amino-imidazo[1,2-*f*][1,2,4]triazines.

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(17) In support of this proposal, it is noted that when the free NH_2 group of compound **2** is replaced by a morpholino group; then the palladium catalysed direct arylation reaction proceeds smoothly with aryl bromide **15**{*1*} to give the expected product in 62% yield after chromatography. Maechling, S.; Lindell; S. D. Unpublished results.

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