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Design and novel synthesis of aryl-heteroaryl-imidazole MAP kinase inhibitors

Markus R. Dobler

Syngenta Crop Protection AG, Lead Finding Chemistry, 4002 Basel, Switzerland

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Abstract—Inhibitors of the MAP kinase p38, potentially useful for the treatment of rheumatoid arthritis and inflammatory diseases, were found to exhibit antifungal activity. We have developed a new diversity-oriented strategy leading to concise and efficient syntheses of known and new members of this compound class. The strategy is based on carbon–carbon cross-coupling reactions using *N*-protected 4,5-diiodo-imidazoles as the starting templates.

Chronic inflammatory diseases such as rheumatoid arthritis and psoriasis affect millions of people. It is now clear that inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-α, play an important role in these diseases. The inhibition of the cytokine interactions have been recognized as rewarding targets for the development of tailor-made anti-inflammatory drugs.[1] Among the most promising small-molecular anti-cytokine agents are inhibitors of p38MAP kinase like SB 203580 (**1**).[2]

Recently it was found that these kinase inhibitors also act as powerful antifungal agents against phyto-pathogens.[3] In order to explore this interesting biological activity and to confirm it as a valid mode of action, we have established a novel diversity-oriented synthetic approach to this compound class (Fig. 1).

While numerous syntheses of substituted imidazoles are described in the literature, mostly based on a cyclization or condensation approaches,[4] little is known on the metallation and cross-coupling behavior of polyhalogenated imidazole templates.[5,6]

A potentially versatile and attractive route for the synthesis of polyfunctionalized imidazoles is via the sequential formation of imidazole anions and their reactions with electrophiles. However, this approach is complicated by the tendency of imidazole-4-yl and -5-yl anions to rapidly equilibrate to imidazole-2-yl anions.[7]

We planned to overcome this problem by applying a combination of metallation and metal–halogen exchange reactions in combination with metal-catalyzed cross-coupling reactions. The use of different *ortho*-directing or blocking *N*-protecting groups was investigated in order to broaden the scope of the methodology. Following the work of Lindell[5] and Benhida[6] we chose *N*-protected 4,5-diiodoimidazoles as the starting materials. Methyl, benzyl and dimethylsulfamoyl served as *N*-protecting groups.

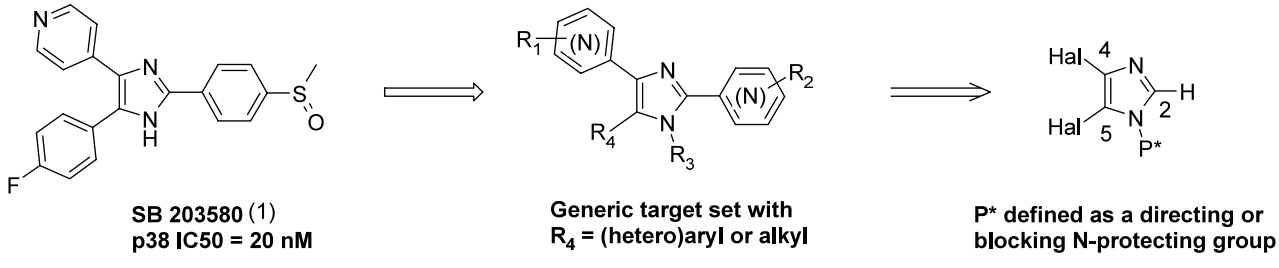

Figure 1. Lead structure **1** and retrosynthetic aspects.

E-mail: markus.dobler@syngenta.com

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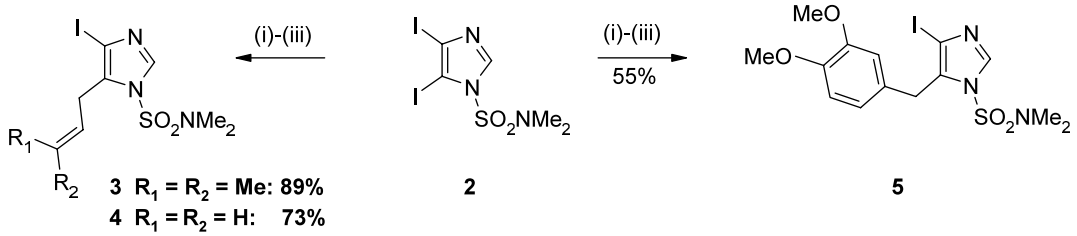
First we reinvestigated[5,6] the scope of the Grignard-type cross-coupling with our starting template **2** (Scheme 1). As expected the *ortho*-directing sulfamoyl *N*-protecting group greatly enhanced the stability of the in situ formed Mg-species. Sequential copper catalyzed cross-coupling of the Grignard intermediate following Knochel's protocol,[8] with a set of electrophiles, proceeded smoothly.

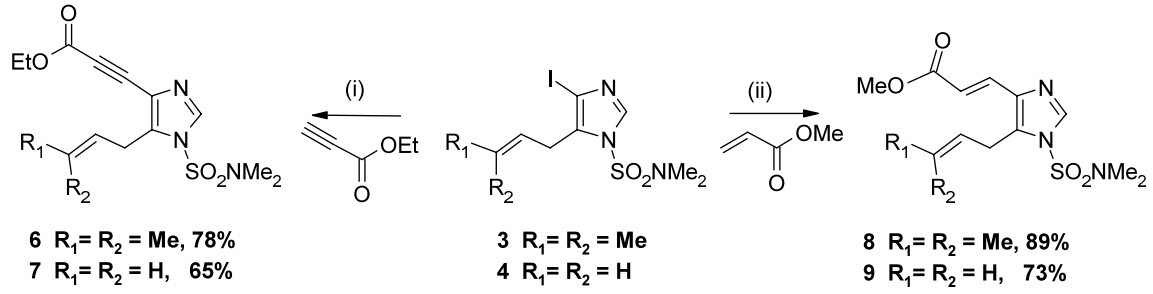
Subsequent Sonogashira- or Heck-type coupling worked equally well for a broad range of substrates and coupling partners. Representative examples are given in Scheme 2.

The diiodoimidazoles also served as versatile electrophilic coupling partners for the Suzuki cross-coupling reaction. The reactions with a wide range of commercially available boronic acids were investigated in close detail (Table 1).

The reactions proceeded with high initial regio-selectivity (C5≫C4) but in all cases subsequent bis-coupling was observed. However, a balance between the base and the base stability of the *N*-protecting group was found to be crucial for high overall yields. Especially the use of the sulfamoyl group led to certain limitations of the reaction conditions to choose from

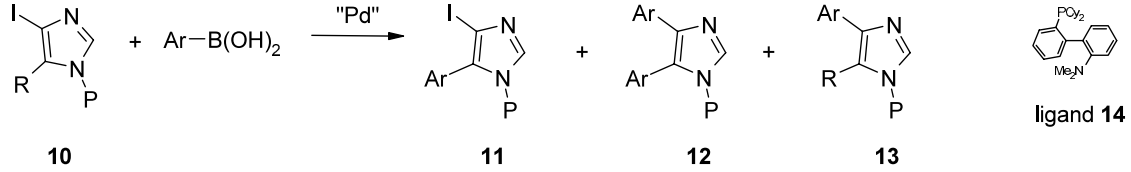


Scheme 1. *Reagents and conditions*: (i) EtMgBr, THF, –20°C, 30 min; (ii) CuCN·2LiCl, 15 min; (iii) electrophile, 0°C, 2 h.

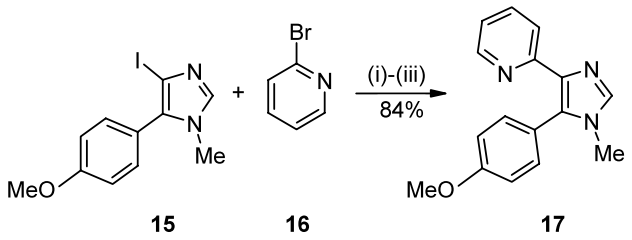


Scheme 2. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5%), CuI, K_2CO_3, PPh_3 (10%), DMF, 80°C, 16 h (syringe pump addition); (ii) $Pd(OAc)_2$ (5%), Et_3N, PPh_3 (10%), DMF, 80°C, 16 h.

Table 1. Selected Suzuki reactions, conditions and isolated yields



Entry	**R**	**P**	Ar-B(OH)$_2$	Conditions	**11** (%)	**12** (%)	**13** (%)
1	I	Bn	4-F-Ph (2 equiv.)	Na_2CO_3, EtOH, H_2O, DME, $Pd(PPh_3)_4$, 95°C, 8 h	27	53	–
2	I	Bn	4-F-Ph (4 equiv.)	Na_2CO_3, EtOH, H_2O, DME, $Pd(PPh_3)_4$, 95°C, 16 h	–	91	–
3	I	Bn	3,4-(MeO)$_2$-Ph (4 equiv.)	CsF, DMF, $Pd(OAc)_2$, dioxane, **14**, 80°C, 16 h	–	95	–
4	I	SO_2NMe_2	Ph (2 equiv.)	K_2CO_3, DMF, $Pd(PPh_3)_4$, 60°C, 12 h	16	24	–
5	I	Me	Ph (2 equiv.)	CsF, DMF, $Pd(OAc)_2$, dioxane, **14**, 80°C, 12 h	24	48	–
6	4-MeO	Me	4-F-Ph (2 equiv.)	CsF, DMF, $Pd(OAc)_2$, dioxane, **14**, 80°C, 12 h	–	–	79
7	Isoprenyl	Me	4-Pyridyl (2 equiv.)	CsF, DMF, $Pd(OAc)_2$, dioxane, **14**, 80°C, 12 h	–	–	65
8	4-MeS	Bn	3-MeO-Ph (2 equiv.)	CsF, DMF, $Pd(OAc)_2$, dioxane, **14**, 80°C, 12 h	–	–	77



Scheme 3. *Reagents and conditions*: (i) EtMgBr, THF, −20°C; (ii) $ZnCl_2$, −20°C to rt, 1 h; (iii) $Pd(OAc)_2$, **14**, reflux, 6 h.

and often resulted in moderate to low reaction yields (entry 4).

Both electron deficient and electron rich boronic acids were found to react with the diiodoimidazole under the highlighted conditions.

Exploration of Negishi-type cross-couplings completed our investigation. The imidazol-4-yl-zinc reagent was generated by treating **15** with Grignard reagent followed by the addition of $ZnCl_2$.[8] The Negishi reaction with 2-iodopyridine led to the desired arylpyridylimidazole (Scheme 3).

Metallation followed by $ZnCl_2$ addition was suitable for preparing the imidazoyl-2-zinc coupling partners in situ.[9] An example is given in Scheme 4. The organozinc reagent was cross-coupled with 2-iodopyridine to give the desired bisarylpyridylimidazole. The use of 2-iodopyridine gave a higher coupling yield than 2-bromopyridine. Final deprotection was achieved by hydrogenation.

In summary, we have developed a concise and efficient synthesis methodology leading to a structurally diverse array of aryl-heteroaryl-imidazoles.[10]

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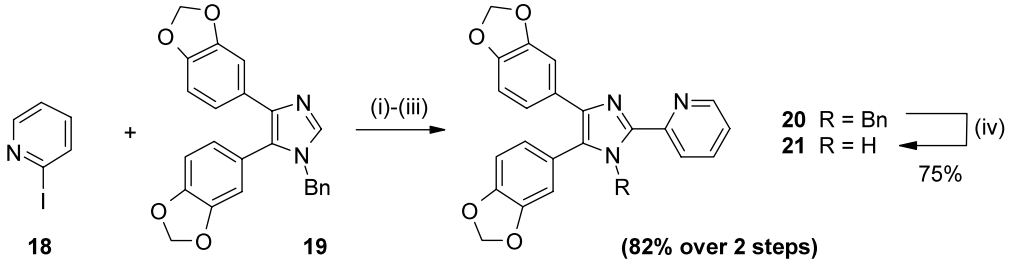
10. All new compounds were completely characterized and gave satisfactory spectral and analytical data. Selected data: Compound **10** (P = Bn, R = I) ^{1}H NMR δ: 7.53 (s, 1H); 7.24–7.19 (m, 3H); 7.08–7.02 (m, 2H); 5.02 (s, 2H); ES-MS m/z 411 (M^{+1}); mp: 87–89°C (diethyl ether). Compound **19** ^{1}H NMR δ: 7.60 (s, 1H); 7.31–7.28 (m, 3H); 7.06 (dd, 1H); 7.03–6.95 (m, 3H); 6.81 (d, 1H); 6.71–6.61 (m, 3H); 6.05 (s, 2H); 5.92 (s, 2H); 4.94 (s, 2H); ES-MS m/z 399 (M^{+1}). Compound **20** ^{1}H NMR δ: 8.29 (d, 1H); 8.12 (d, 1H); 7.54 (dd, 1H); 7.02–6.88 (m, 6H); 6.68–6.59 (m, 3H); 6.57–6.42 (m, 3H); 5.80 (s, 2H); 5.82 (s, 2H); 5.53 (s, 2H); ES-MS m/z 476 (M^{+1}). Compound **21** ^{1}H NMR δ: 8.43 (t, 1H); 7.81 (t, 1H); 7.22 (dd, 1H); 7.05–6.98 (m, 4H); 6.70 (d, 2H); 5.89 (s, 4H); ES-MS m/z 386 (M^{+1}).



Scheme 4. *Reagents and conditions*: (i) *t*BuLi, THF, −78°C; (ii) $ZnCl_2$, −78°C to rt, 1 h; (iii) $Pd(OAc)_2$, **14**, reflux, 4 h; (iv) cyclohexadiene, Pd/C, reflux, 72 h.