Synthesis and Modification of 1-(1*H*-indazol-3-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one Derivatives

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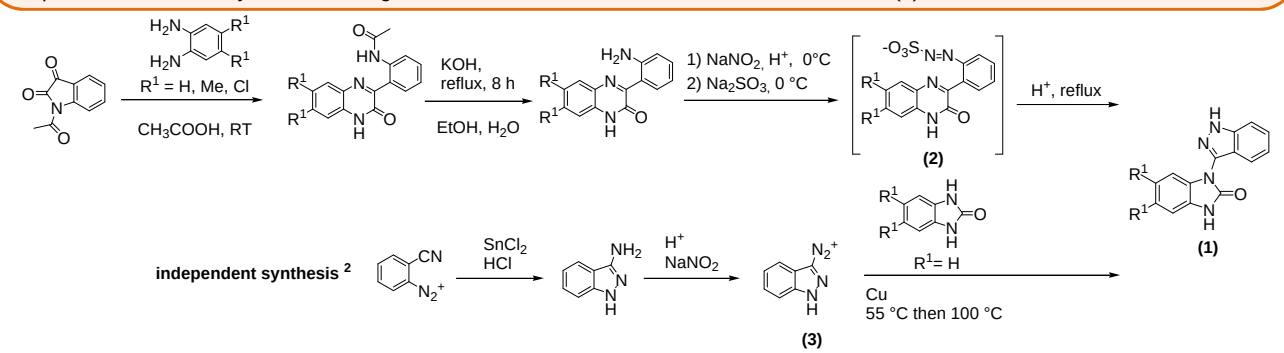
Introduction

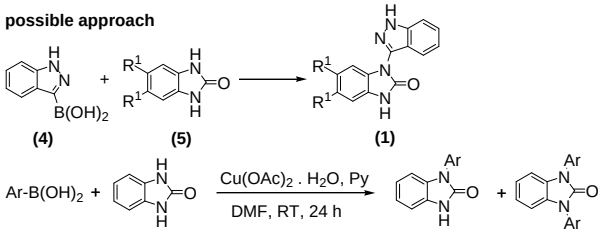
Synthesis and modification of heterocyclic compounds containing privileged structures is an important tool for drug discovery since the concept of privileged structures enables to find new lead drug candidates more efficiently. Combining two or more privileged heterocycles or their isosters might provide novel biologically active compounds.

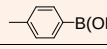
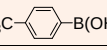
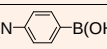
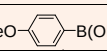
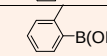
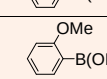
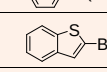
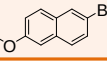
We report a serie of derivatives based on the 1-(1*H*-indazol-3-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one core (**1**) containing both benzimidazole and indazole moieties. This bisheterocyclic system was initially synthesized via unusual rearrangement starting from diazosulfonate (**2**). The structure of the resulting product was unequivocally determined by x-ray crystallography[1] and, subsequently, confirmed by the independent alternative synthesis utilizing Gatterman reaction from indazolediazonium chloride (**3**).[2]



Chan-Lam coupling approach

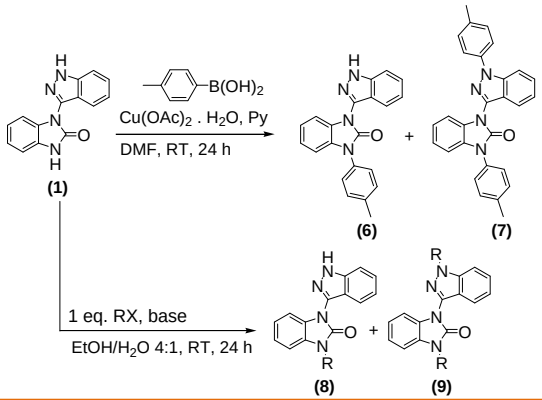
In order to find a more efficient methodology enabling to join benzimidazole and indazole heterocyclic systems, the Chan-Lam coupling reaction with indazole-3-boronic acid (**4**) and 1*H*-benzo[*d*]imidazol-2(3*H*)-one (**5**) and was chosen as a key step. Preliminary study using various boronic acids demonstrated the feasibility of this coupling reaction under mild reaction conditions.



No.	Ar-B(OH)$_2$	Monosunstituted Product (%)	Disubstituted Product (%)
1		45	28
2		58	22
3		54	4
4		33	8
5		48	31
6		27	0
7		40	14
8		62	0

Peripheral modifications – preliminary study

The synthesized bisheterocyclic system was subjected to peripheral modifications which were based on alkylations with benzyl bromide and methyl iodide and Chan-Lam coupling with tolylboronic acid. While Chan-Lam coupling yielded only the presented compounds (**6**) and (**7**), the alkylation reactions yielded mixture of mono and dialkylated compounds with the expected major products shown bellow (**8**,**9**).



Conclusion

We present a serie of new benzimidazolone derivatives synthesised either from 2-hydroxybenzimidazole or compound (**1**) by Chan-Lam coupling or by alkylations with alkyl halides. Both approaches yielded a mixture of mono and dialkylated products, therefore, further optimalization of reaction conditions will take place in near future.

Literature

1) Fryšová, I.; Travníček, Z.; Slouka, J.; Cankař, P., *Arkivoc* ***2011,*** *(ii), 127-136.*
2) Lyčka, A.; Fryšova, I.; Slouka, J., *Magnetic resonance in chemistry : MRC* ***2007,*** *45 (1), 46-50.*

Acknowledgement

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