SOLID-PHASE SYNTHESIS OF INDOLES FROM 2-NITROBENZENSULFONAMIDES VIA BASE-MEDIATED C-ARYLATION

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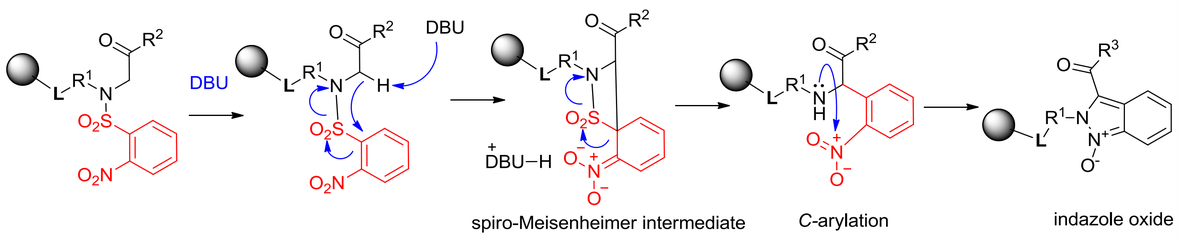
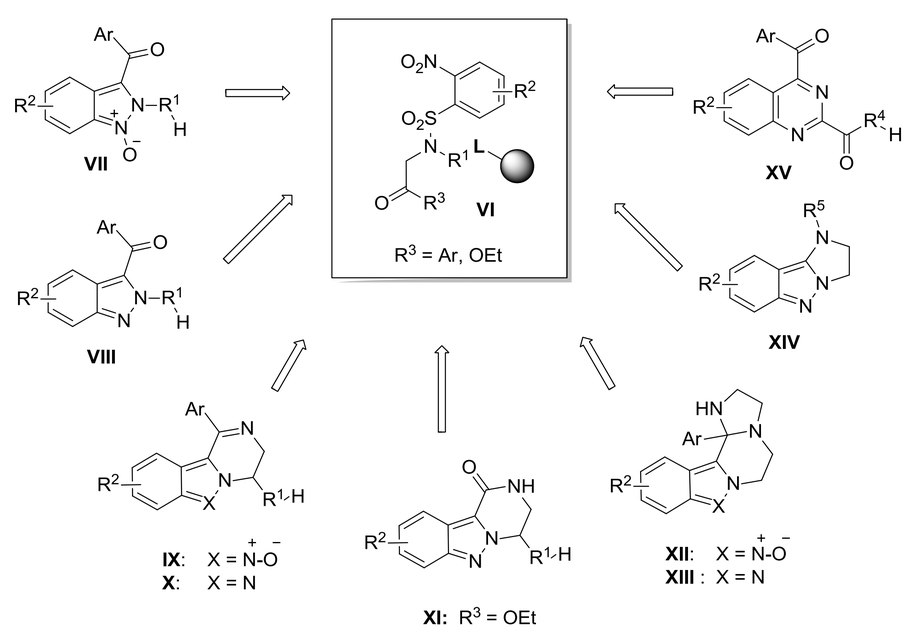
Introduction

2-Nitrobenzensulfonylchloride (2-Nos-Cl) and 4-nitrobenzensulfonylchloride (4-Nos-Cl) were introduced as effective protecting/activating group for regioselective *N*-monoalkylation of primary amines by Fukuyama et al.[1] Apart from that, 2-Nos can serve also as advantageous building block in the synthesis of heterocyclic compounds **I-V**:[2-6]

Our group observed an unprecedented difference in reactivity of 2- and 4-Nos derivatives. Whereas 4-Nos group was cleaved by treatment with conventional cleavage cocktail mercaptoethanol/DBU, 2-Nos derivatives underwent intramolecular *C*-arylation followed by *N-N* bond formation:[7]



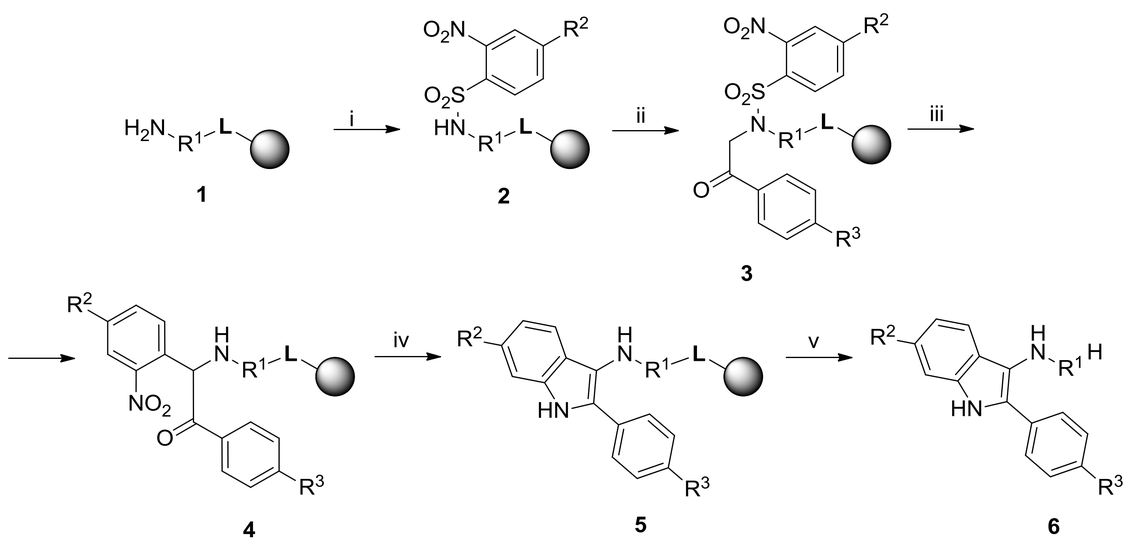
Consequent research led to the preparation of many heterocycles derived from indazole oxides (**VII, IX, XII**), indazoles (**VIII, X, XI, XIII, XIV**) and quinazolines (**XV**):[8-11]



Here we report further expansion of *C*-arylation chemistry of basic labile advanced intermediates (**VI**), that can be converted into another class of heterocycles – indoles.

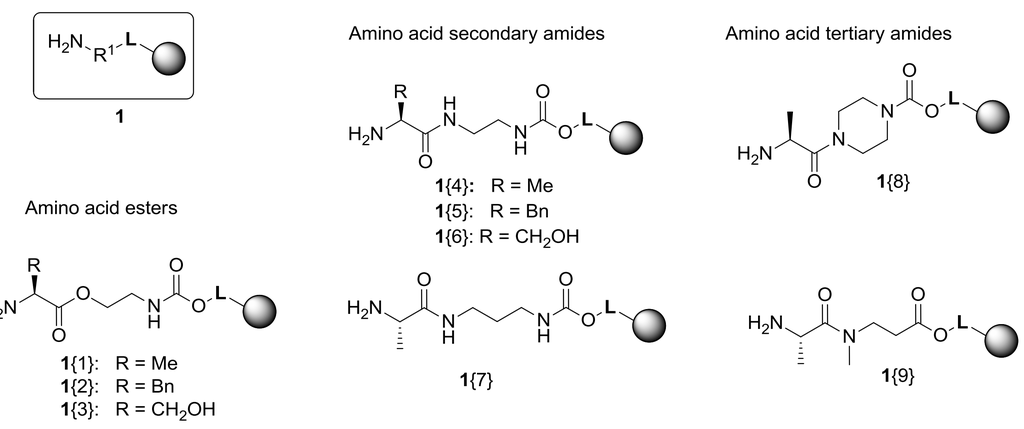
Synthesis

Reaction scheme of polymer-supported synthesis of 2,3-disubstituted indoles **6**.[a]

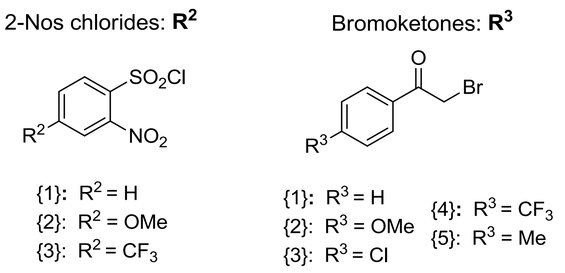


[a]Reagents and conditions: (i) 2-Nos-Cl, 2,6-lutidine, DCM, rt, overnight; (ii) α-bromoketone, DIEA, DMF, rt, overnight; (iii) base (TEA or DABCO), DMF, rt, 1h – overnight; (iv) $Na_2S_2O_4$, K_2CO_3, TBAHS, H_2O/DCM (1:1), rt, 1h or overnight, (v) TFA/DCM (1:1), rt, 1h or TFA/TES/DCM (5:1:4), rt, 1h.

Immobilization of bifunctional amines *via* a spacer (L = Wang linker) on solid support:



Structures of building blocks: 2-Nos chlorides and bromoketones:



R[1] effect: We prepared model compounds derived from amino acids attached via esters, secondary amides, and tertiary amides. A common feature of compounds with an ester linkers **3**{1,R^2,R^3} and **3**{2,R^2,R^3} was the need to use a base for *C*-arylation. In contrast, the secondary amide linker including compounds **3**{4,R^2,R^3}, **3**{5,R^2,R^3}, **3**{7,R^2,R^3} already contained 40 – 80% of the *C*-arylated structure (**4**) after reaction with α-bromoketone.

Effect of R^2 and R^3: The synthesis was compatible with both electron withdrawing and electron donating substituents present on either aromatic ring. Electron withdrawing groups accelerated *C*-arylation, but also subsequent unwanted cyclization to indazole oxides. Electron donating group (OCH_3) increased the stability of sulfonamides and rearrangement leading to *C*-aryl action required several days.

Conclusion

To conclude, we developed an efficient synthetic route for solid-phase synthesis of 2-aryl-3-alkylamino-1*H*-indoles from acyclic precursors, 2-nitro-*N*-(2-oxo-2-arylethyl)benzenesulfonamides. We optimized base-mediated *C*-arylation, reduction time and cleavage. In addition to indoles, other heterocycles including morpholines, indazole oxides and indazoles were obtained by modification of reaction conditions and combination of building blocks.

References

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