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Rapid metal free construction of 3-positioned 2-pyridyl substituent in indoles

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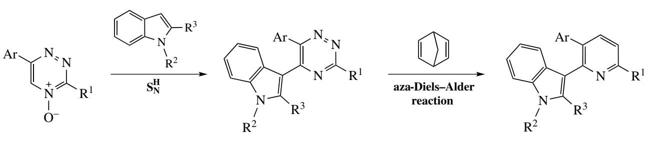
New access to substituted 2-(indol-3-yl)pyridines involves two stage protocol, namely, a reaction of deoxygenative nucleophilic substitution of hydrogen in 1,2,4-triazine-4-oxides under the action of indoles followed by aza-Diels–Alder reaction of thus obtained 5-indolyl-1,2,4-triazines with 2,5-norbornadiene in a pressure vessel. The reactions sequence provides good yields and is suitable for wide scope of substituted 1,2,4-triazines.



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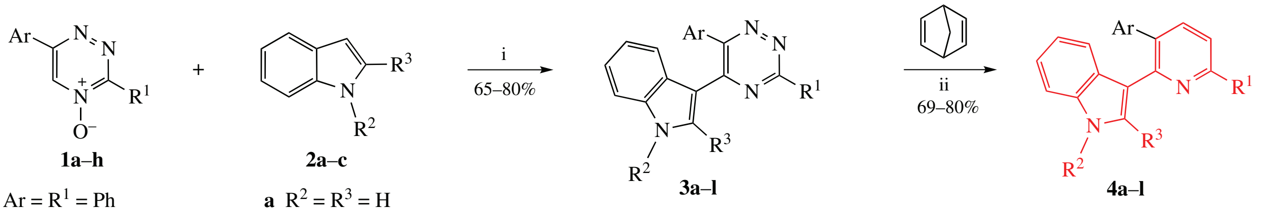
Indole fragment as a typical pharmacophore is met in a number of natural and synthetic compounds possesing cytotoxic,[1] antiviral, antimicrobial[2] and some other[3] activities. On the other hand, many bioactive compounds are represented in the pyridine series.[4] Compounds including fragments of both heterocycles, for example 2-(indol-3-yl)pyridines, are also bioactive,[5–7] in particular, exhibit anti-inflammatory, anti-infection and anti-androgenic properties.

Such compounds are commonly prepared by cross-coupling of 3-indolyl and 2-pyridyl components.[8–10] Also, a catalytic[11–15] and non-catalytic[16–18] construction of indole substituent at the position 2 of the pyridine core is documented. The corresponding pyridine *N*-oxides were used as the starting compounds when the final products were obtained *via* the deoxygenative nucleophilic substitution of hydrogen with the use of benzoyl chloride[19,20] or acetic anhydride[21] as O-acylating agents. In addition, the strategy of constructing a 2-pyridyl substituent at the position 3 of the indole core, including tandem reaction in unsubstituted indole[22] leading to pyridine incrementing at the indole system[23] was reported (for graphical depiction of the previous syntheses, see Online Supplementary Materials, Scheme S1).

The possibility of synthesizing pyridine derivatives *via* their 1,2,4-triazine precursors should also be mentioned[24] in the this aspect. Due to the higher electrophilicity of 1,2,4-triazines compared to pyridines, the possibilities of pre-functionalization of 1,2,4-triazines *via* the nucleophilic substitution of hydrogen seem topical.[25] Examples of using sequential S_N^H reactions, sometimes in combination with S_N^{ipso} reactions, and aza-Diels–Alder reactions to obtain a variety of multisubstituted (bi)-pyridines have been documented.[26] Here, we report a convenient synthetic approach to various 2-(indol-3-yl)pyridines using the convenient '1,2,4-triazine' method which does not require the use of any catalysts and expensive reagents.

Direct metal-free introduction of indole residues at the position 5 of 1,2,4-triazines[27] or their 4-oxides[28] has been described previously. This approach is quite interesting due to wide possibilities of varying substituents at the positions 3 and 6 of 1,2,4-triazines or their oxides. This method was herein used to obtain 1,2,4-triazin-6-yl-substituted indole precursors (Scheme 1).

Starting 1,2,4-triazine 4-oxides **1a–h** were obtained as previously described.[29,30] As a result of deoxygenative nucleophilic hydrogen substitution,[28] 5-(3-indolyl)-1,2,4-triazines **3a–l** were prepared in up to 80% yields. To further access the target 2-(indol-3-yl)pyridines **4**, we intended to employ the aza-



1a–h

a Ar = R^1 = Ph
b Ar = R^1 = 4-FC_6H_4
c Ar = 4-$MeOC_6H_4$, R^1 = Me
d Ar = 4-ClC_6H_4, R^1 = Ph
e Ar = 4-FC_6H_4, R^1 = 2-furyl
f Ar = 4-MeC_6H_4, R^1 = 2-thienyl
g Ar = 4-MeC_6H_4, R^1 = Et
h Ar = 4-MeC_6H_4, R^1 = Me

2a–c

a R^2 = R^3 = H
b R^2 = H, R^3 = Me
c R^2 = Me, R^3 = H

3a–l, **4a–l**

a Ar = R^1 = Ph, R^2 = R^3 = H
b Ar = R^1 = 4-FC_6H_4, R^2 = R^3 = H
c Ar = 4-$MeOC_6H_4$, R^1 = Me, R^2 = R^3 = H
d Ar = 4-ClC_6H_4, R^1 = Ph, R^2 = H, R^3 = Me
e Ar = 4-$MeOC_6H_4$, R^1 = R^3 = Me, R^2 = H
f Ar = R^1 = 4-FC_6H_4, R^2 = H, R^3 = Me
g Ar = 4-MeC_6H_4, R^1 = 2-furyl, R^2 = H, R^3 = Me
h Ar = 4-MeC_6H_4, R^1 = 2-thienyl, R^2 = H, R^3 = Me
i Ar = 4-$MeOC_6H_4$, R^1 = R^2 = Me, R^3 = H
j Ar = 4-MeC_6H_4, R^1 = Et, R^2 = Me, R^3 = H
k Ar = 4-MeC_6H_4, R^1 = R^2 = Me, R^3 = H
l Ar = R^1 = 4-FC_6H_4, R^2 = Me, R^3 = H

Scheme 1 *Reagents and conditions*: i, PhC(O)Cl, CH_2Cl_2, 20 °C, 2 h; ii, 1,2-dichlorobenzene, 215 °C, 20 h.

Diels–Alder reaction of triazines **3** with 2,5-norbornadiene as a dienophile.[31] However, the application of typical conditions to these reactants, namely, boiling in *o*-xylene or 1,2-dichlorobenzene, provided low (5–10%) conversions even under the prolonged (72 h) processing. Luckily, carrying the reaction in a pressure vessel (which was previously implemented for 1,2,4-triazines with electron-donating substituents[32]) at 215 °C for 20 h followed by flash chromatography afforded the desired pyridines **4a–l** in yields up to 79%. In this case, no influence of the nature of the reactant substituents on the reaction outcome was observed.

The structure of the obtained products **4** was confirmed based on the data of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Thus, two characteristic doublets for protons of newly formed pyridine ring are observed in the ^{1}H NMR spectra. Also, the signals for protons of the substituents at the positions 3 and 6 of the former 1,2,4-triazine ring, as well as signals for protons of the indole fragments are presented. In most cases, a noticeable upfield shift for the signals of all the protons is observed upon the conversion of 1,2,4-triazines **3** into pyridines **4**. In particular, for the signal of proton of the indole NH group, a shift from 11.41–12.44 to 10.8–11.05 ppm can be noted.

In summary, we have reported herein a convenient metal-free synthesis of 2-(indol-3-yl)pyridines, which are of interest as promising biologically active candidates. Reaction sequence proceeds *via* the transformation of 1,2,4-triazine precursors, in the absence of expensive catalysts or reagents. The approach allows one to vary in a wide range a nature of substituents in the heterocyclic core of the target products (such as at the positions 3 and 6 of pyridine, as well as in the indolyl moiety) by using previously described convenient methods on the stage of the synthesis of starting 1,2,4-triazine-4-oxides and their derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.007.

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