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Quinazoline addition to indole hydrazone derivatives in TFA as a facile synthesis of trifluoroacetylhydrazide quinazoline σ-adducts

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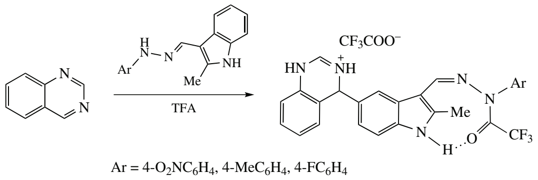
Addition of indole 3-carbaldehyde arylhydrazones to quinazoline in trifluoroacetic acid occurs at the C^5-atom of the indole moiety affording quinazoline σ-adducts with indole and trifluoroacetylhydrazide moieties.



Ar = 4-O$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$

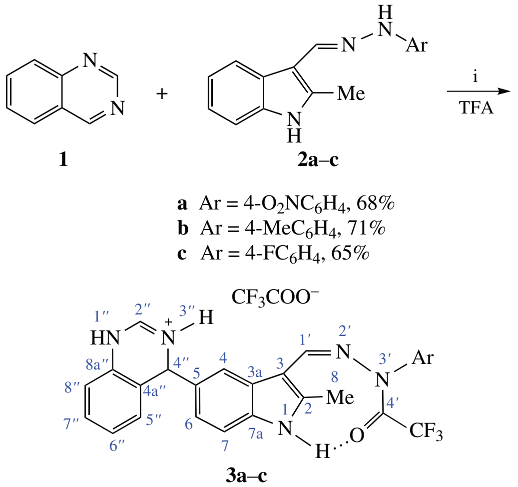
Keywords: quinazoline, indole-3-carbaldehyde, hydrazones, trifluoroacetylhydrazides, arylation, trifluoroacetic acid.

Quinazoline core is a common constituent of natural alkaloids.[1] Compounds that possess antimicrobial, antiallergic, hypotonic, antiviral, antitumor and radioprotective activities were identified among quinazoline derivatives.[2–4] Addition of C-nucleophiles to 3-methylquinazolinium iodide resulting in 4-substituted 3,4-dihydroquinazolines was reported.[5] Unsubstituted quinazoline **1** reacts with indole, 3-methyl-1-phenylpyrazol-5-one, 1,3-dimethylbarbituric acid and pyrogallol in the presence of an acid resulting in 4-σ-adducts.[6]

To create potential drugs of the quinazoline series, it is necessary to provide easy variation of pharmacophore moieties in their structure. This in turn allows one to tune the physicochemical properties like hydrophilicity or lipophilicity and thus affect bioavailability or activity.

In our search for synthetic approaches to biologically active quinazoline derivatives,[6] the most promising ones are so called atom-economy processes, which comply with the 'green chemistry' principles.[7] Reactions of this type include C,C-coupling under acidic catalysis conditions, which represent theoretically non-waste processes.[8] In this work, we used 2-methylindole-3-carbaldehyde arylhydrazones **2a–c** as nucleophiles (for their synthesis, see Online Supplementary Materials). In general, *E*-configuration of the C=N bond is thermodynamically favorable for phenylhydrazones, which has been confirmed by X-ray diffraction data.[9]

Heating of quinazoline **1** with hydrazono indoles **2a–c** in a trifluoroacetic acid afforded products **3a–c** (Scheme 1).



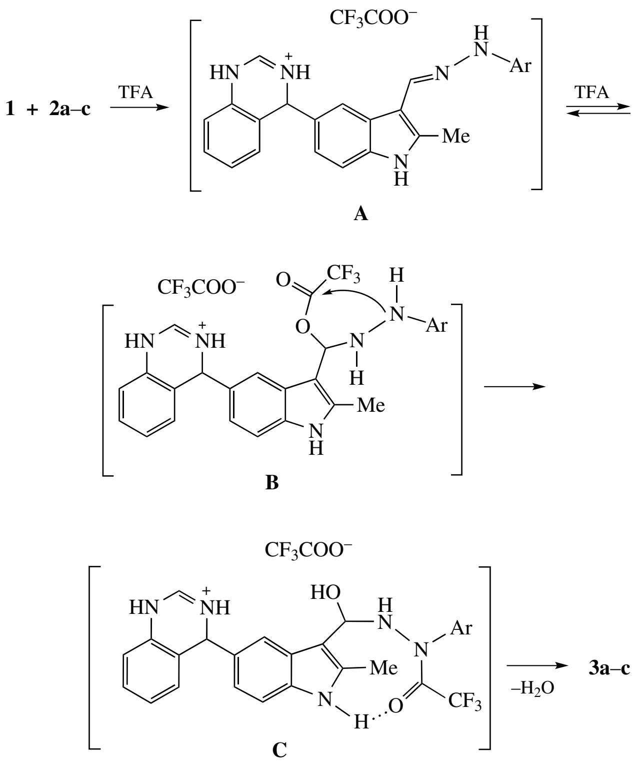
a Ar = 4-O$_2$NC$_6$H$_4$, 68%
b Ar = 4-MeC$_6$H$_4$, 71%
c Ar = 4-FC$_6$H$_4$, 65%

Scheme 1 *Reagents and conditions*: i, TFA, EtOH, reflux, 10 min.

The structure of compounds **3a–c** was confirmed using high resolution mass spectrometry as well as ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, including two-dimensional 2D ^{1}H–^{13}C gHMBC/gHSQC and 2D ^{1}H–^{15}N gHMBC correlation experiments. Addition of hydrazono indoles **2a–c** to the quinazoline core occurs at 5-position of the indole moiety. This is confirmed by the presence of characteristic cross peaks from coupling of the C^{7a} atom with the broadened H^4 proton signal and the H^6 doublet in 2D ^{1}H–^{13}C HMBC spectrum of compound **3a** as an example. If alternative addition at 6-position had occurred, coupling with a doublet of the H^4 hydrogen atom would be observed for the C^{7a} carbon. The ^{1}H NMR spectra of compounds **3a–c** also contain characteristic singlets for H$^{4''}$ protons at 6.25–6.26 ppm, the corresponding sp^3 hybridized quinazoline C$^{4''}$ atom resonates at 54.14–54.61 ppm in the ^{13}C NMR spectrum. The signals of H$^{5'}$ and H$^{6'}$ protons of the aryl substituent appear as two-proton doublets and are determined from correlation with nitrogen atoms in the 2D ^{1}H–^{15}N gHMBC spectrum.

The acylation of reaction intermediate **A** (Scheme 2) with trifluoroacetic acid occurs at the N$^{3'}$ atom, this is confirmed by a significant downfield shift of the N$^{3'}$ nitrogen signal in the ^{15}N NMR spectra. In hydrazone **2a**, the chemical shift for the corresponding nitrogen atom is 155.43 ppm, compared to 215.5 ppm for the acylation product **3a**. Moreover, the ^{1}H NMR spectrum of adduct **3a** retains the signals of NH-protons for indole and quinazoline moieties. Hence, this is the hydrazine part of the molecule that undergoes acylation.

Note, that the 2D ^{1}H–^{13}C gHMBC spectra of acylation products **3a–c** contain intense cross peaks between the characteristic quartet of C$^{4'}$ carbon in the trifluoroacetyl group, in particular, at 155.4 ppm for compound **3a** ($^2J_{C–F}$ = 36.7 Hz), and the broadened signal of N^{1}H proton (see Figure 1).



Scheme 2

The $^{2h}J_{\mathrm{C(4')-H(1)}}$ = 3.2 Hz value resulting from the stable intramolecular hydrogen bond NH···O=C was determined from the ^{13}C spectrum without proton decoupling. The presence of an intramolecular hydrogen bond suggests that in DMSO-d_6 compounds **3a–c** have C=N bond in *Z* configuration.

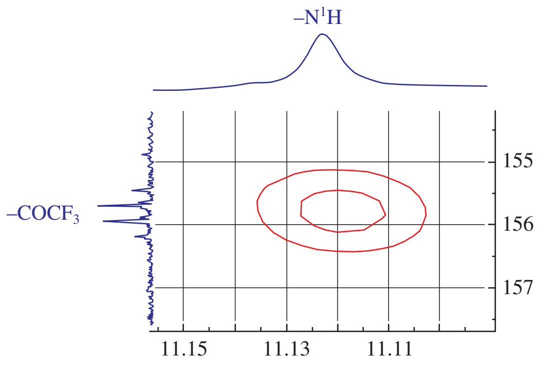


Figure 1 Part of the NMR 2D ^{1}H–^{13}C HMBC spectrum for compound **3a**.

The formation of trifluoroacetyl adducts **3a–c** probably occurs through addition of hydrazono indoles **2a–c** to quinazoline **1** affording intermediate **A**. Further, acylation begins with the addition of trifluoroacetic acid to the C=N bond (intermediate **B**), followed by intramolecular rearrangement resulting in *N*-acetyl intermediate **C**. Its subsequent dehydration affords compounds **3a–c** containing a pseudocycle with a hydrogen bond between the carbonyl of trifluoroacetyl group and the NH group of indole core (Scheme 2).

In summary, to the best of our knowledge, the addition of benzene part of indoles to quinazolines has not been documented previously. In our case, unusual acylation of the hydrazone NH-group with trifluoroacetic acid occurs with reversal of the *E*-configuration of the hydrazone C=N double bond to the *Z* one in acyl 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.2020.03.032.

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