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LETTERS TO THE EDITOR

3,5- and 3,6-Disubstituted 3,4-Dihydroquinazolines

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It has previously been shown that the reactions of *para*-substituted anilines with formaldehyde in the presence of hydrochloric [1–3] or oxalic acid [4] lead to the formation of 6(4')-substituted 3,4-dihydroquinazolines (11–38%). When replacing formaldehyde with another source of methylene group, metoxychloromethane, the reaction with arylamines afforded both 3,4-dihydroquinazolines (25%) and 1,2,3,4-tetrahydroquinazolines (48%) [5]. 3,4-Dihydroquinazolines (30–85%) can be prepared by reacting arylamines with formaldehyde in a ionic liquid (butylpyridinium 1-tetrafluoroborate) in the presence of 1-methyl-3-[2-(sulfooxy)ethyl]-1*H*-imidazol-3-ylium chloride as catalyst [6]. 1,3-Dioxolane is known to be used as a methylene group source in the synthesis of diarylmethane derivatives [7], which indicates the possibility of its use as a synthetic equivalent of formaldehyde or metoxychloromethane.

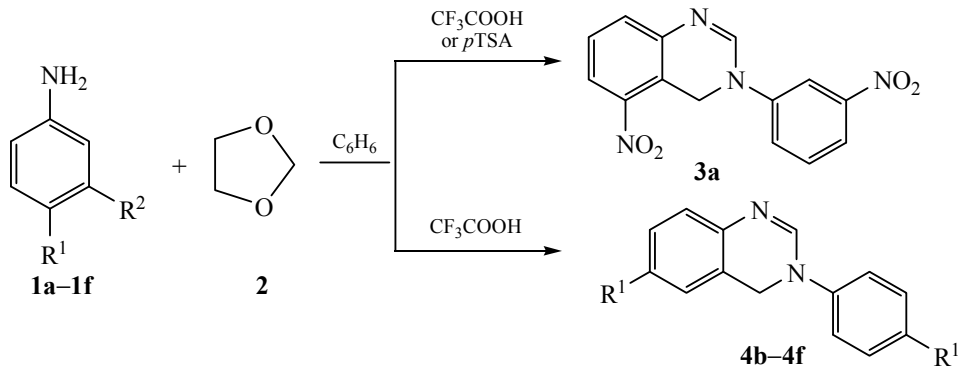
In this work we showed a possibility of using 1,3-dioxolane as a methylene group source in the synthesis of substituted 3,4-dihydroquinazolines based on *para*- and *meta*-substituted anilines.

The reactions of arylamines **1a**–**1f** with 1,3-dioxolane **2** proceeded in benzene in the presence of trifluoroacetic acid or *p*-toluenesulfonic acid (*p*TSA) at 80–85°C to form 3,4-dihydroquinazolines **3a** and **4b**–**4f** (Scheme 1).

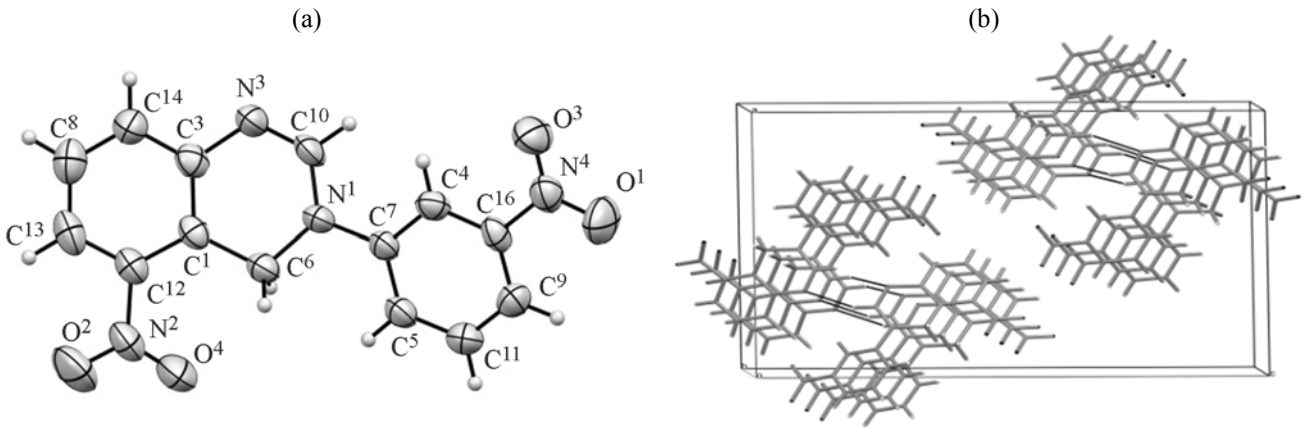
According to [7], in the case of *m*-nitroarylamine **1a** having a free *para*-position the formation of 4,4'-diamino-3,3'-dinitrodiphenylmethane would be expected as a result of diarylmethane derivatization.

However, 3-(*m*-nitrophenyl)-5-nitro-3,4-dihydroquinazoline **3a** was isolated as the reaction product, apparently due to the steric hindrances caused by the presence of nitro moiety in the *meta*-position. The

Scheme 1.



R^1 = H, R^2 = NO_2 (**a**), R^1 = NO_2, R^2 = H (**b**), R^1 = Br, R^2 = H (**c**), R^1 = $COOCH_3$, R^2 = H (**d**), R^1 = $COOC_2H_5$, R^2 = H (**e**), R^1 = $COOC_4H_9$, R^2 = H (**f**).



(a) Crystal structure and (b) molecular packing of compound **3a**.

structure compound **3a** was confirmed by X-ray diffraction (XRD) method (see figure).

In conclusion, the proposed non-catalytic method of synthesizing 3,5- and and 3,6-disubstituted dihydroquinazolines involving 1,3-dioxolane as a synthetic equivalent of formaldehyde allows to reduce the reaction time and to increase the yield of the target products.

3-(*m*-Nitrophenyl)-5-nitro-3,4-dihydroqunazoline (3a). *a*. A mixture of 4.14 g (30 mmol) of *m*-nitroaniline **1a**, 8 mL of benzene, 4.44 g (60 mmol) of 1,3-dioxolane **2**, and 8 mL of trifluoroacetic acid was heated for 1.5 h at 80–85°C. After cooling the mixture was diluted with water. The precipitate was separated, washed twice with water, neutralized with 10% NH_4OH solution to pH 8, and dried. Yield 2.3 g (52%), yellow crystals, mp 198–200°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.35 s (2H, CH_2), 7.35–7.69 m ($5H_{Ar}$), 7.93 d (1H, C^6H, J = 8.4 Hz), 8.09–8.12 m (2H, $C^{4'}H$, CH=N). Mass spectrum, m/z (I_{rel}, %): 298 (10.36) $[M]^+$.

b. A mixture of 1.38 g (10 mmol) of *m*-nitroaniline **1a**, 1 mL of benzene, 1.1 g (15 mmol) of 1,3-dioxolane **2,** and 2 g of *p*-toluenesulfonic acid was heated for 1.5 h at 80–85°C. After cooling the mixture was diluted with water. The precipitate was separated, washed twice with water, neutralized with 10% NH_4OH solution to pH 8, and dried. Yield 0.4 g (27%).

Compounds **4b**–**4f** were prepared similarly by the method *a*.

3-(*p*-Nitrophenyl)-6-nitro-3,4-dihydroquinazoline (4b). Yield 0.87 g (58%), mp 227–229°C (benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.16 s (2H, CH_2), 7.26 d (1H, C^8H, J = 6.3 Hz), 7.59 d (2H, $C^{2',6'}H$, J = 6.9 Hz), 8.07–8.10 m (3H, $C^{5,7}H$, CH=N), 8.32 d (2H, $C^{3',5'}H$, J = 6.6 Hz). Mass spectrum, m/z: 299.0776 $[M + H]^+$.

3-(*p*-Bromophenyl)-6-bromo-3,4-dihydroqunazoline (4c). Yield 0.62 g (57%), mp 199–201°C (benzene) (mp 195–200°C [5]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.90 s (2H, CH_2), 6.98 d (2H, $C^{2',6'}H$, J = 8.4 Hz), 7.25–7.37 m (4H, Ar-H), 7.60 d (2H, $C^{5,7}H$, J = 8.8 Hz), 7.67 s (1H, CH=N). Mass spectrum, m/z: 366.9267 $[M + H]^+$.

3-(*p*-Carbomethoxyphenyl)-6-carbomethoxy-3,4-dihydroquinazoline (4d). Yield 1.53 g (47%), mp 242–245°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.90 s (3H, $NC_6H_4COO\underline{CH_3}$), 3.92 s (3H, $COO\underline{CH_3}$), 4.99 s (2H, CH_2), 7.19–7.23 m (3H, $C^{2',6'}H$, C^8H), 7.35 s (1H, C^5H), 7.74 s (1H, CH=N), 7.93 d (1H, C^7H, J = 7.8 Hz), 8.12 d (2H, $C^{3',5'}H$, J = 8.4 Hz). Mass spectrum, m/z: 325.1185 $[M + H]^+$.

3-(*p*-Carboethoxyphenyl)-6-carboethoxy-3,4-dihydroquinazoline (4e). Yield 0.21 g (36%), mp 190°C (benzene) (mp 185–188°C [5]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 t (6H, CH_3), 4.35 q (4H, OCH_2), 5.11 s (2H, CH_2), 7.10–7.22 m (2H, $C^{5,8}H$), 7.50–7.53 d (2H, $C^{2',6'}H$, J = 8.4 Hz) 7.80 s (1H, CH=N), 7.86 d (1H, C^7H, J = 6.6 Hz), 8.04–8.07 d (2H, $C^{3',5'}H$, J = 8.4 Hz). Mass spectrum, m/z: 353.1498 $[M + H]^+$.

3-(*p*-Butoxycarbonylphenyl)-6-butoxycarbonyl-3,4-dihydroquinazoline (4f). Yield 0.45 g (45%), mp 140°C (dichloromethane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98 t (6H, CH_3), 1.41–1.54 m (4H, CH_2), 1.70–1.80 m (4H, CH_2), 4.28–4.35 m (4H, OCH_2), 4.99 s (2H, CH_2), 7.19–7.26 m (3H, $C^{2',6'}H$, C^8H), 7.74 s (1H,

CH=N), 7.93 d (2H, $C^{5,7}H$, J = 7.5 Hz), 8.12 d (2H, $C^{3',5'}H$). Mass spectrum, m/z: 409.2120 $[M + H]^+$.

^1H NMR spectra were obtained on a Mercury 300 instrument (300 MHz), internal reference HMDS. Mass spectra were recorded on a high resolution mass spectrometer maXis Impact HD Bruker Daltonik GmbH.

X-Ray diffraction experiment for compound 3a. The parameters of the unit cell and the intensity of the reflections were measured at 295(2) K on a Xcalibur R diffractometer. The extinction was accounted for empirically by multiscan method using SCALE3 ABSPACK algorithm [9]. The structure was solved by the direct method and refined by full-matrix least-squares method using SHELX2013 software package [10]. The structure was refined by using a data file with reflections intensities of HKLF 5 format as a twin with two components. The final refinement parameters: R_1 = 0.0659, wR_2 = 0.1671 [for 2092 reflections with $I > 2\sigma(I)$], R_1 = 0.1642, wR_2 = 0.1911 (for all 5849 independent reflections), S 0.785, the ratio of twinning components 0.505(2) : 0.495(2) . Crystals of compound **3a** are monoclinic, $C_{14}H_{10}N_4O_4$, space group $P21/n$, the unit cell parameters: a = 14.909(6), b = 3.8772(11), c = 22.142(7) Å, β = 91.78(3)°, V = 1279.3(7) $Å^3$, d_{calc} = 1.549 g cm^{-3}, μ = 0.117 mm^{-1}, Z = 4, λ(MoK_α) = 0.71073 Å.

Crystallographic data were deposited in the Cambridge Crystallographic Data Centre (CCDC 1,481,780).

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