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EFFICIENT ROUTE TO SUBSTITUTED 2-AMINOQUINOLINE

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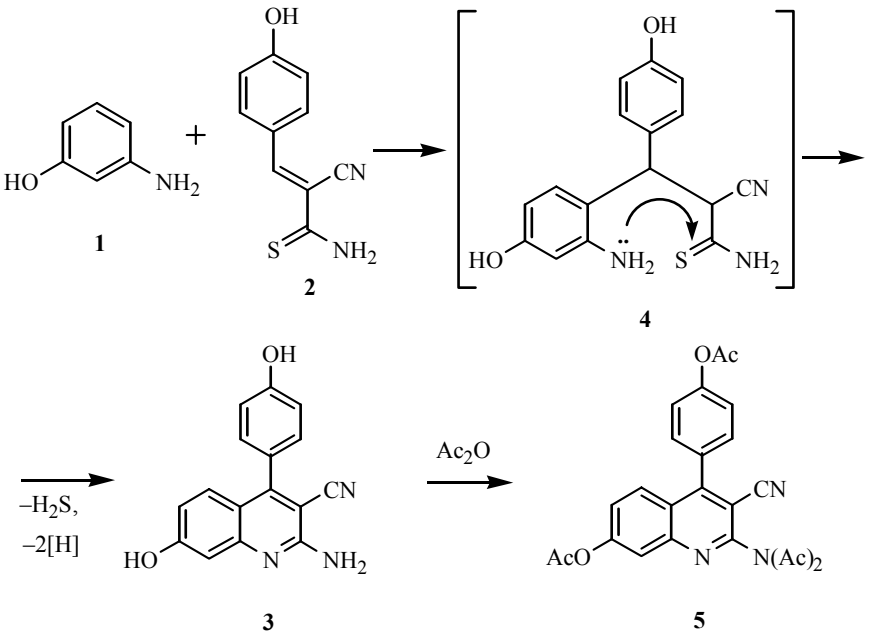
1,3-Aminophenol undergoes a Michael addition to 4-hydroxyphenylmethylene malononitrile followed by intramolecular cyclization to form substituted 2,7-diamino-4H-benzo[*b*]pyran [1]. We observed that reacting 4-hydroxyphenylmethylene cyanothioacetamide (**2**) with 1,3-aminophenol **1** in ethanol in the presence of morpholine leads to formation of 2-amino-3-cyano-7-hydroxy-4-(4-hydroxyphenyl)quinoline (**3**). Thus 1,3-aminophenol **1** does not initially add to activated alkene **2** at the 6 position, which would lead to the corresponding pyran, but rather to position 4 with formation of the Michael adduct **4**. The latter, when treated with morpholine, even at room temperature undergoes intramolecular cyclization to form substituted 2-aminoquinoline **3**. Refluxing it in acetic anhydride allows us to obtain the corresponding tetraacyl derivative **5**, which is promising for drug discovery [2].



The ^{1}H NMR spectra were taken on a Bruker DR-500 (500 MHz) in DMSO-d_6.

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2-Amino-3-cyano-7-hydroxy-4-(4-hydroxyphenyl)quinoline (3). Yield 76%; mp 198-200°C (EtOH). IR spectrum (vaseline oil), ν, cm^{-1}: 3304, 3420, 3495 (NH_2, OH); 2218 (C≡N); 1673 (δNH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 11.32 and 10.11 (1H each, both br. s, 2OH); 8.21 (2H, br. s, NH_2); 7.34 (3H, m, H_{arom}); 7.06 (1H, s, H-8); 6.98 (3H, m, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 278 $[M+1]^+$ (27), 277 $[M]^+$ (100), 260 (12), 249 (25). Found, %: C 69.14; H 3.82; N 15.36. $C_{16}H_{11}N_3O_2$. Calculated, %: C 69.31; H 4.00; N 15.15.

7-Acetoxy-3-cyano-2-diacetylamino-4-(4-acetoxyphenyl)quinoline (5). Yield 70%; mp 168°C (AcOH). IR spectrum (vaseline oil), ν, cm^{-1}: 2216 (C≡N); 1694 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.95 (1H, s, H-8); 7.88 (1H, d, *J* = 9.30, H-6); 7.70 (2H, d, *J* = 7.74, H-3 and H-5 Ar); 7.68 (1H, d, *J* = 9.30, H-5); 7.48 (2H, d, *J* = 7.74, H-2 and H-6 Ar); 2.35 (12H, s, $4CH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 445 $[M]^+$ (6), 403 (29), 388 (25), 361 (32), 346 (41), 319 (40), 304 (42), 277 (43), 43 $[Ac]^+$ (100). Found, %: C 64.61; H 4.12; N 9.50. $C_{24}H_{19}N_3O_6$. Calculated, %: C 64.72; H 4.30; N 9.43.

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