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CYCLOCONDENSATION OF 2-FLUORO-5-NITROBENZALDEHYDE WITH AMIDINES

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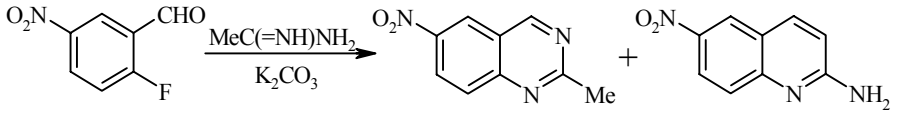
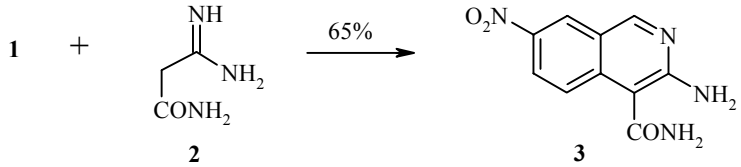
Keywords: amidines as N,N- and C,N-nucleophiles, 2-fluoro-5-nitrobenzaldehyde, cyclocondensation.

Kotsuki et al. [1] have recently reported the synthesis of 4-unsubstituted quinazolines by the cyclocondensation of *o*-fluorobenzaldehydes with amidines. Waring [2] and Mohamed [3] have reported that amidines containing α-hydrogen atoms may undergo cyclocondensation with esters of 3-oxocarboxylic acids and conjugated enols by acting not only as N,N-dinucleophiles but also as C,N-dinucleophiles. These findings have led us to study the reaction of 2-fluoro-5-nitrobenzaldehyde (**1**) with acetamidine under the same conditions as in the work of Kotsuki [1] and thoroughly separated the reaction mixture by column chromatography. The major reaction product, as expected, was 2-methyl-6-nitroquinazoline. Furthermore, isomeric 2-amino-6-nitroquinone formed in the nucleophilic attack of the amidine α-carbon atom on the benzaldehyde carbonyl group was obtained in trace amounts. Examples of cyclocondensation featuring unsubstituted acetamidine as a C,N-dinucleophile have not yet been reported.



1 58% 1.5%

When amidine **2**, containing an active methyl group, was introduced into the same reaction, 3-aminoisoquinoline **3** was the major cyclocondensation product.



2 **3**

Isoquinoline structure was assigned for **3** on the basis of the chemical shifts for 1-H and $C_{(1)}$ and the $^1J(C^1–H^1)$ coupling constant. These values are characteristic for a C–H fragment in the α-position to the nitrogen atom in azines [5].

2-Methyl-6-nitroquinazoline was isolated in 58% yield by chromatography on a silica gel column with 1:2 ether–hexane as the eluent; mp 152-154°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm, *J* (Hz): 2.84 (3H, s, CH_3); 8.05 (1H, d, *J* = 9, 8-H); 8.61 (1H, m, *J* = 9, 2-, 5-, 7-H); 9.12 (1H, d, *J* = 5-H); 9.78 (1H, s, 4-H). Found, %: C 57.21; H 3.72; N 22.10. $C_9H_7N_3O_2$. Calculated, %: C 57.14; H 3.73; N 22.21.

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2-Amino-6-nitroquinoline [14] was isolated in 1.5% yield by chromatography on a silica gel column with 3:1:1 ether–hexane–ethyl acetate as the eluent; mp 250°C (dec.). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 6.89 (1H, d, *J* = 9, 3-H); 7.23 (2H, NH_2); 7.50 (1H, d, *J* = 9, 8-H); 8.13 (1H, d, *J* = 9, 4-H); 8.22 (1H, m, *J* = 9, 2-, 5-, 7-H); 8.68 (1H, d, *J* = 2.5, 5-H).

3-Amino-7-nitroisoquinoline-4-carboxamide (3) was isolated in 65% yield by reprecipitation from DMF using 1:1 ether–ethanol; mp ~350°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 6.86 (2-H, 3-NH_2); 7.83 (2H, d, *J* = 9, 5-H); 7.85 (1H, CONH); 8.06 (1H, CONH); 8.24 (1H, m, *J* = 9, 2-, 5-, 6-H); 8.93 (1H, d, *J* = 2.5, 8-H); 9.19 (1H, s, 1-H). ^{13}C NMR spectrum, δ, ppm: 104.35 ($C_{(4)}$), 119.79 ($C_{(8a)}$), 123.83 ($C_{(6)}$), 126.14 ($C_{(8)}$), 137.41 ($C_{(4a)}$), 140.98 ($C_{(7)}$), 155.98 ($C_{(3)}$), 156.12 ($C_{(1)}$, $^1J_{(C–H)}$ = 181.5 Hz), 168.08 (CO). Found, %: C 51.66; H 3.52; N 24.19. $C_{10}H_8H_4O_3$. Calculated, %: C 51.73; H 3.47; N 24.13.

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