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NaH-Mediated One-Pot Cyclocondensation of 6-Nitroquinoline with Aromatic Hydrazones To Form [1.2.4]Triazino[6,5-*f*]quinolines and/or Pyrazolo[3,4-*f*]quinolines

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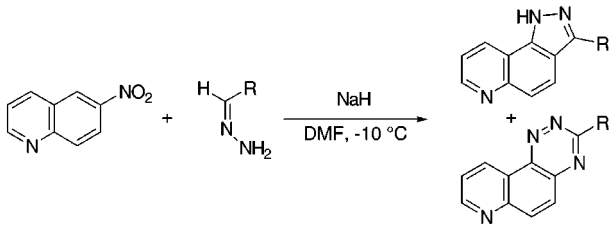
ABSTRACT



6-Nitroquinoline undergoes direct cyclocondensation with aromatic hydrazones in the presence of sodium hydride in DMF at −10 °C, giving the corresponding 3-aryl-1(3)*H*-pyrazolo[3,4-*f*]quinolines and/or 3-aryl[1.2.4]triazino[6,5-*f*]quinolines in low to moderate yield. The mode of cyclocondensation is considerably dependent on the electronic nature of ring substituent of hydrazones, an electron-donating substituent favoring the formation of the latter heterocycles.

Condensed polyazaarenes are important ring systems present in a variety of natural products, pharmaceuticals, and agrochemicals.[1] A large number of methods for preparation have been proposed to date, but many of them require multistep procedures starting from inconvenient materials.[2] In the course of our continued study on the nucleophilic displacement of hydrogen in nitroarenes,[3] we have observed that 6-nitroquinoline (**1**) undergoes cyclocondensation with benzophenone hydrazone (**2a**) in the presence of sodium hydride, leading in a straightforward manner to the [1.2.4]-triazino[6,5-*f*]quinoline framework (Scheme 1). Thus, 6-nitroquinoline (**1**; 0.300 g, 1.72 mmol), **2a** (0.396 g, 2.02 mmol), and sodium hydride (0.285 g) were stirred in DMF (15 mL) at −10 °C for 12 h. The reaction mixture was diluted with water (100 mL), and the organic phase was extracted with EtOAc (3 × 50 mL). The combined extracts were evaporated and chromatographed on silica gel using a mixture of EtOAc and hexane as the eluent to give 3,3-diphenyl-2,3-dihydro-[1.2.4]triazino[6,5-*f*]quinoline-4-oxide (**3**), which was recrystallized from ethanol in 43% isolated yield. The structure of **3** was assigned on the basis of spectral data and elemental analysis.[4] Weaker bases such as potassium *tert*-butoxide and

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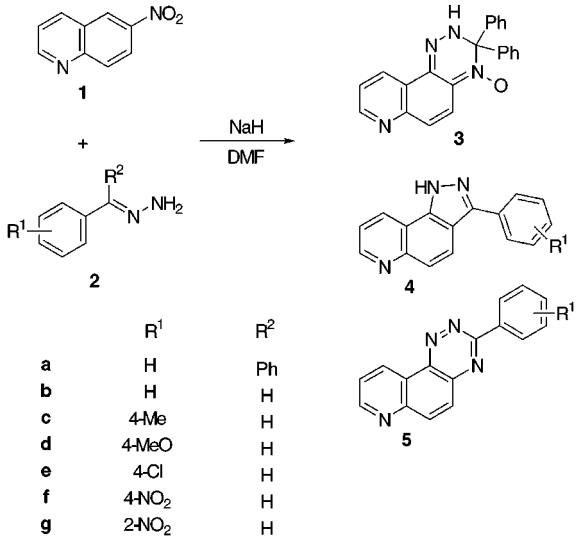
Scheme 1



	R^1	R^2
a	H	Ph
b	H	H
c	4-Me	H
d	4-MeO	H
e	4-Cl	H
f	4-NO_2	H
g	2-NO_2	H

lithium hydride were without effect. Considerable amounts of undefined polar byproducts accompanied the reaction, but they were readily removed by chromatography on silica gel. Elevated temperature facilitated the reaction but led to a diminished yield. Use of *N*-methyl-2-pyrrolidinone (NMP) as the solvent gave similar results. This observation encouraged us to examine the potential of hydrazones as an ambident nucleophile to construct the less common polyaazarene frameworks, since a nitroarene−hydrazone cyclocondensation of this type has not previously been reported. When the reaction was similarly carried out using benzaldehyde hydrazone (**2b**: R^1, R^2 = H), rather surprisingly, two different modes of cyclocondesation took place in parallel, giving 3-phenyl-1(3)*H*-pyrazolo[3,4-*f*]quinoline (**4b**) and 3-phenyl[1.2.4]triazino[6,5-*f*]quinoline (**5b**) in 22 and 19% yields, respectively.

The mode of cyclocondensation was found to depend considerably on the electronic nature of ring substituent of aromatic hydrazones **2**. The electron-donating methyl and methoxy groups favor ring closure with a neighboring nitro group to afford the [1.2.4]triazino[6,5-*f*]quinoline ring system **5**, while the electron-withdrawing nitro group tends to result in the removal of the nitro group to produce the pyrazolo-[3,4-*f*]quinoline ring system **4**. With the inductively positive but mesomerically negative 4-chlorine substituent, both types of polyazaarenes (**4** and **5**) are formed in parallel, the latter ring system predominanting over the former (Table 1). These two products were readily separated by chromatography on silica gel using a mixture of hexane and EtOAc as the solvent. The product yields could not be improved by the use of other combinations of base and solvent or by prolonged reaction time.

(4) Mp 136−137 °C. ^{1}H NMR ($CDCl_3$) δ 3.72 (br, 1H), 7.20−7.55 (m, 12H), 7.66 (d, 1H, J = 10.0), 8.32 (dd, 1H, J = 1.8, 8.1), 8.62 (dd, 1H, J = 1.8, 4.7). MS *m*/*z* (CI) 339 (5.4), 307 (100), 182 (31). IR (KBr) 3484 (br), 3183, 2923, 1447, 1235, 1084, 691. Anal. Calcd for $C_{22}H_{16}N_4O\cdot{}^1/_2$-EtOH: C, 73.58; H, 5.10; N, 14.92. Found: C, 73.58; H, 5.02, N, 14.63.

Table 1. Reaction of 6-Nitroquinoline **1** with Hydrazones **2a−g**

Hydrazone	Time (h)	Yield (%)[a]	
		4	**5**
2a	12	-	-[b]
2b	4	22	19
2c	4	-	28
2d	4	trace	24
2e	4	6	27
2f	3	50	-
2g	4	-[c]	-

[a] Isolated yield. [b] Compound **3a** was obtained in 43 % yield. [c] No expected products were obtained; the substrate was recovered in 25 % yield.

Although the mechanism for the formation of **4** and **5** is not clear at present, a possible reaction sequence is depicted in Scheme 2. In the initial step, the terminal nitrogen of the hydrazone anion attaches to the 5-position of 6-nitroquinoline **1** to form a Meisenheimer intermediate (**6**),[5,6] which can undergo intramolecular cyclization via two different pathways, i.e., via the nucleophilic addition of the hydrazone carbon atom either to the ring carbon at 6-position (pathway a) or to the nitrogen atom of the neighboring nitroso group in **7** (pathway b). According to Scheme 2, the formation of compounds **3** and **5** is straightforward, but the formation of compound **4** is somewhat tricky to explain. We tentatively assume the liberation of dinitrogen oxide which, however, is not yet confirmed by gas analysis. The electron-withdrawing nitro group in anion **6** would facilitate the proton transfer from the N−H bond, resulting in the formation of pyrazoloquinoline **4**, whereas the electron-donating methyl and methoxy groups would increase the electronic density of the hydrazone unit, working favorably for the proton removal from the ring to lead to triazinoquinoline **5**. In any event, the mechanism for the formation of compounds **3**−**5** remains to be clarified. As expected, the crowded benzophenone hydrazone **2a** preferred ring closure with the nitro nitrogen atom, forming six-membered condensed ring system **3** as the sole product.

When 8-nitroquinoline was allowed to react with aromatic hydrazones under similar conditions, pyrazolo[3,4-*h*]quinoline derivatives were obtained at best in yields up to 20%. Unsatisfactory results may be attributed to the electronic repulsion between the oxygen atom of the nitro group and the unshared electrons of the ring nitrogen atom, which would work adversely toward the attachment of a hydrazone nucleophile at the 7-position of 8-nitroquinoline.[5]

Unfortunately, aliphatic hydrazones cannot be used for the present purpose. This is not unexpected, however, in view of supposedly low stability of the resulting anionic hydrazone intermediate. The study is in progress and the details will be reported elsewhere.

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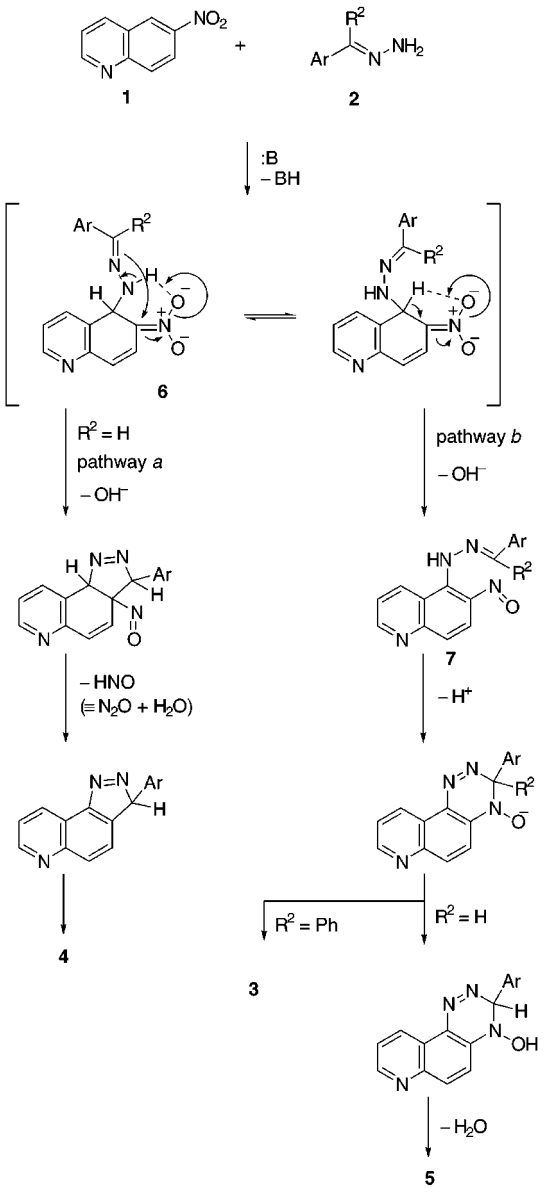
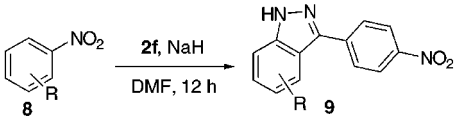
Scheme 2



To make clear the scope of this interesting reaction, the present methodology was extended to monocyclic nitroarenes. As expected from the substituent effect of the aromatic hydrazone side, substituted benzopyrazoles (**9**) were obtained from monocyclic nitroarenes such as 4-chloronitrobenzene and 1,3- and 1,4-dinitrobenzenes, though the results in terms of the yield were not so satisfactory (Table 2). Thus, by the reaction of 1,3-dinitrobenzene (**8**: R = 3-NO_2) with 4-nitrobenzaldehyde hydrazone (**2f**: R^1 = 4-NO_2, R^2 = H), the cyclocondensation occurred by replacement of one of the nitro group, giving 5-nitro-3-(4-nitrophenyl)benzopyrazole as the sole product in 37% yield. A similar reaction of 4-chloronitrobenzene (**8**: R = 4-Cl) led to 6-chloro-3-(4-nitrophenyl)benzopyrazole **9** (R = 6-Cl) in 35% yield, where the chlorine atom remained intact despite its presence at the activated position of substrate **8**. Excess sodium hydride was found to work adversely. In contrast, when 4-methylbenzaldehyde hydrazone (**2c**: R^1 = 4-Me, R^2 = H) was employed as a nucleophile, the preferential displacement of the chlorine atom took place and no cyclocondensation product could be obtained.

Table 2. Reaction of Monocyclic Nitroarenes with **2f**



R	Temp (°C)	Yield (%)[a]
3-NO_2	-10	37
4-Cl	r.t.	21(35)[b]
4-NO_2	r.t.	36

[a] Isolated yield. [b] Starting material was recovered in 40 % yield. Numeral in parenthesis refers to conversion yield.

In summary, we have developed a convenient straightforward method for the construction of the [1.2.4]triazino[6,5-*f*]quinoline and pyrazolo[3,4-*f*]quinoline frameworks which involves the direct cyclocondensation of 6-nitroquinoline with aromatic hydrazones in the presence of sodium hydride. It may represent a potentially useful route to otherwise laboriously accessible pyrazolo- and [1.2.4]triazolo-condensed azaarene ring systems. The method can be carried out under mild conditions using readily accessible or commercially available inexpensive materials. The yields of the products are moderate, but this disadvantage would be compensated by ease of manipulation, economy, a single pot procedure, and mild conditions.

Supporting Information Available: Supporting Information Available: Experimental details for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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