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A straightforward synthesis of some fused aza-arenes *via* nucleophilic displacement of a ring hydrogen atom in nitroarenes by aromatic hydrazone anions

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6-Nitroquinoline **6** undergoes direct cyclocondensation with aromatic aldehyde hydrazones **9** in the presence of sodium hydride in DMF at low temperature, giving the corresponding 3-aryl-1*H*-pyrazolo[3,4-*f*]quinolines **10** and/or 3-aryl[1,2,4]triazino[6,5-*f*]quinolines **11** in low to moderate yield. With aromatic keto hydrazones **7**, 3,3-disubstituted 2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline-4-oxides **8** are obtained in moderate to good yield. The mode of cyclocondensation is considerably dependent on the electronic nature of a ring substituent of the aromatic hydrazones; electron-donating substituents favor the formation of **11**, while electron-withdrawing substituents work favorably for the formation of **10**. Monocyclic nitroarenes **15** react similarly with 4-nitrobenzaldehyde hydrazone **9a** to give another type of cyclocondensation product, 3-aryl-1*H*-indazoles **16**, in moderate yield. In contrast, nucleophilic substitution of a ring hydrogen atom takes place with 4-methylbenzaldehyde hydrazone **9f** to yield *N*-arylated hydrazone **22b**, which, however, fails to cyclize to **16** under the conditions employed. The reaction has been suggested to proceed through the initial attack of a hydrazone anion on the position adjacent to the nitro group, followed by migration of an *ipso* hydrogen atom to the nitro group in the Meisenheimer intermediate **18**. The resulting N^2-arylated hydrazone anion would undergo ring closure *via* either addition to the nitroso group or displacement of this moiety, eventually leading to the fused aza-arenes **8**, **10/11**, **13** or **16**.

Introduction

Fused [1,2,4]triazines are important as the basic framework for a variety of pharmaceuticals and agrochemicals. Representative examples are shown in Chart 1, where 3-aminobenzo[1,2,4]-triazine 1,4-dioxide **1** (SR4233) received considerable attention as a new class of anti-tumor agent owing to its selective toxicity toward hypoxic cells both *in vitro* and *in vivo*.[1,2] The mechanism of DNA cleavage by this type of compound is of biochemical and pharmaceutical interest.[3] 7-Chloro-3-aminobenzo[1,2,4]-triazine 1-oxide **2** is long known for its activity as antimalarial,[4] while 3-dimethylamino-4*H*-[1,2,4]triazino[5,6-*b*]indazole **3** exhibits a herbicidal effect.[5] 6,8-Dimethylpyrimido[5,4-*e*][1,2,4]-triazine-5,7(6*H*,8*H*)-dione (fervenulin) **4** is a broad-spectrum antibiotic isolated from natural source.[6] 3-Methoxy-2-methyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **5** is a red pigment of a unique chromophore produced by a microorganism.[7] Although a few methods are available in the literature for the construction of this type of polycondensed aza-arenes, most of them involve a multi-step procedure starting from inconvenient materials.[8]

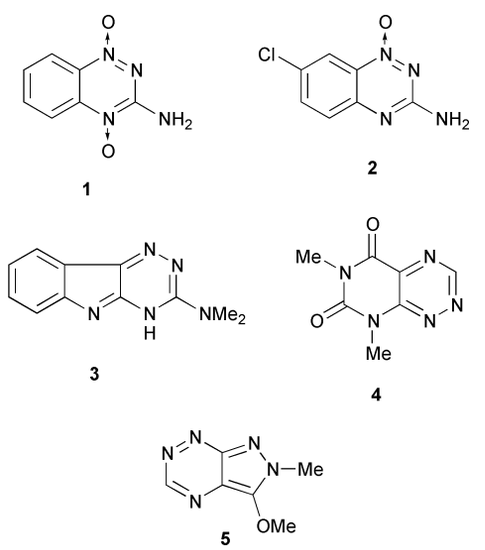

Chart 1

We have recently reported that a strong base such as sodium hydride can promote the displacement of a ring hydrogen atom of nitroarenes by nucleophiles, providing a straightforward route to a variety of functionalized arenes. Typical examples are shown in Scheme 1, taking 6-nitroquinoline **6** as the common substrate.[9–14] As part of our ongoing programme, we have extended this new type of aromatic nucleophilic substitution to the single-step construction of the pyrazolo[3,4-*f*]quinoline and [1,2,4]triazino[6,5-*f*]quinoline structures **10** and **11**.

Results and discussion

Reaction of 6-nitroquinoline with aromatic hydrazone anions

When 6-nitroquinoline **6** was treated with benzophenone hydrazone **7a** in the presence of sodium hydride (NaH) in *N,N*-dimethylformamide (DMF) at low temperature, a new type of cyclocondensation took place to produce 3,3-diphenyl-2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline 4-oxide **8a** in a moderate yield (Scheme 2). Best results were obtained when nitroarene **6** and hydrazone **7a** were treated in a 1 : 1 molar ratio in the presence of 4 equiv. of NaH (Table 1, Entry 6). Considerable amounts of undefined polar by-products accompanied the reaction, but they were easily removed by simple filtration over a thin bed of silica gel. Elevated temperature promoted side reactions and resulted in a diminished yield of **8a**. When a weaker base such as ^{t}BuOK or LiH was used, compound **8a** could not be obtained. The use of *N*-methylpyrrolidin-2-one

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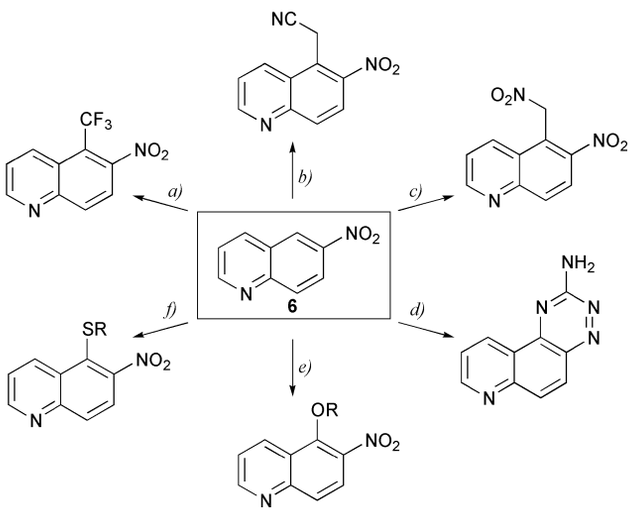
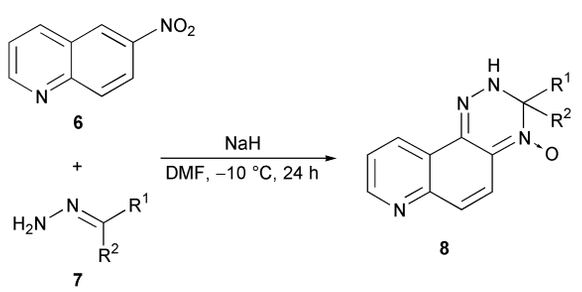
Table 1 Reaction of 6-nitroquinoline **6** with benzophenone hydrazone **7a**[a]

Entry	**7a** (equiv)	NaH (equiv)	Temp. (°C)	Solvent	Yields of **8a** (%)[b]
1	1	4	rt	DMF	17
2[c]	1	4	rt	DMF	3
3	1	4	−25	DMF	32[d]
4	1	8	−25	DMF	38[e]
5	2	4	−25	DMF	35[f]
6	1	4	−10	DMF	61 (59)[g]
7	2	4	−10	DMF	60 (53)[g]
8	1	4	−10	NMP	14
9	2	4	−10	NMP	15
10	1	4	−10	THF	35

[a] All reactions were carried out in a given solvent (15 mL) for 24 h, unless otherwise stated. [b] HPLC yield. [c] To a DMF solution (5 mL) of **6** was added dropwise a solution of **7a** in the same solvent (10 mL) during 5 h. [d] Substrate **6** was recovered in 13, 3 and 2% yield, respectively. [e] Substrate **6** was recovered in 13, 3 and 2% yield, respectively. [f] Substrate **6** was recovered in 13, 3 and 2% yield, respectively. [g] Numeral in parenthesis refers to isolated yield.



Scheme 1 *Reagents and conditions: a)* Me_3SiCF_3, KF, DMF;[9] *b)* MeCN, NaOEt, DMF;[10] *c)* $MeNO_2$, Bu^{t}OLi, DMF;[11] *d)* Guanidine, Bu^{t}OK, THF;[12] *e)* KOR, THF;[13] *f)* RSH, NaH, THF.[14]



a R^1=R^2=Ph
b R^1=R^2=4-MeC_6H_4
c R^1=Me; R^2=Ph
d R^1=Me; R^2=4-MeC_6H_4
e R^1=Me; R^2=4-BrC_6H_4

Scheme 2

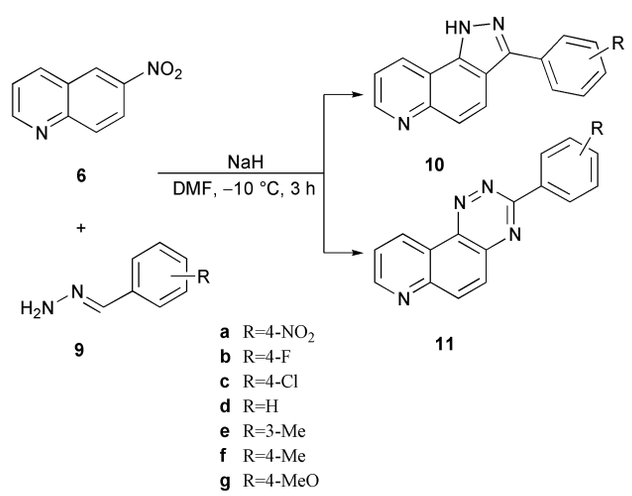
(NMP) or tetrahydrofuran (THF) as the solvent gave less satisfactory results (Table 1, Entries 8–10). To our knowledge, this type of cyclocondensation between nitroarenes and hydrazones has not previously been reported. Therefore, the use of the hydrazone anion as an ambident *C*,*N*-nucleophile may provide an attractive new tool for the single-step construction of multifunctionalized aza-arene structures.

6-Nitroquinoline **6** reacted with benzaldehyde hydrazones **9a**–**g** under similar conditions to afford 3-aryl-1*H*-pyrazolo[3,4-*f*]quinolines **10** and/or 3-aryl [1,2,4]triazino[6,5-*f*]quinolines **11** (Scheme 3). The results are listed in Table 2. The mode of cyclocondensation was found to depend considerably on the

Table 2 Reaction of 6-nitroquinoline **6** with benzaldehyde hydrazones **9a**–**g**

	Yield (%)[a]	
Hydrazone	**10**	**11**
9a	50	—
9b	trace[b]	19
9c	6	27
9d	—	24
9e	—	16
9f	—	28
9g	—	24

[a] Isolated yield. [b] Detected by NMR.



a R=4-NO_2
b R=4-F
c R=4-Cl
d R=H
e R=3-Me
f R=4-Me
g R=4-MeO

Scheme 3

electronic nature of a ring substituent on the aromatic hydrazones **9**. Electron-donating groups such as methyl and methoxy favored the ring closure with a nitrogen atom of the nitro group of **6** to afford the [1,2,4]triazino[6,5-*f*]quinoline ring system **11d**–**g**, while the electron-withdrawing nitro group led to the ring closure involving replacement of the nitro group of **6**, producing the pyrazolo[3,4-*f*]quinoline ring system **10a**. With the inductively positive to electron-withdrawing but mesomerically negative to electron-donating 4-chlorine substituent, both types of cyclocondensation took place in parallel to yield aza-arenes **10c** and **11c**, the latter predominating in amount over the former (Table 2). With the fluorine substituent, however, compound **11b** was much preferred. The reason is not clear. Both types of product were readily separated by chromatography on silica gel using a mixture of hexane and EtOAc as the eluting solvent. Unfortunately, all attempts to improve the product yield have failed; a different combination of base and solvent as

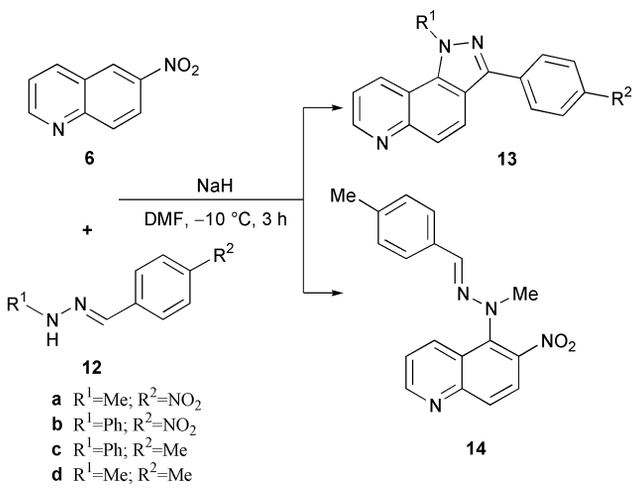
Table 3 Reaction of 6-nitroquinoline **6** with hydrazones **12a–d**

Hydrazone	Yield (%)[a] **13**	**14**
12a	26	—
12b	13	—
12c	35	—
12d	—	13

[a] Isolated yield.

well as a prolonged reaction time proved to be fruitless. Since benzaldehyde hydrazones were partly lost as the corresponding azines under the conditions employed, this may also have caused the diminished yield.

When compound **6** was treated with hydrazones **12a–d** bearing a substituent on the terminal nitrogen atom, different results ensued (Scheme 4; Table 3). When a nitro group was



Scheme 4

present on the aromatic ring of the hydrazone, the cyclization involving the replacement of the nitro group of **6** took place to give pyrazolo[3,4-*f*]quinolines **13a**,**b**. In contrast, when the corresponding substituent is a methyl group, compound **6** simply underwent nucleophilic displacement of a ring hydrogen atom at 5-position by the hydrazone anion to yield *N*-arylated hydrazone **14**. Interestingly, when a phenyl group was present on the terminal nitrogen atom of the hydrazone, ring closure took place again *via* the replacement of the nitro group to afford the corresponding 3-arylpyrazolo[3,4-*f*]quinoline **13b**,**c**, irrespective of the electronic nature of the ring substituent groups on the hydrazone.

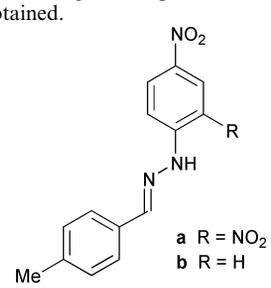
Reaction of monocyclic nitroarenes with aromatic hydrazones

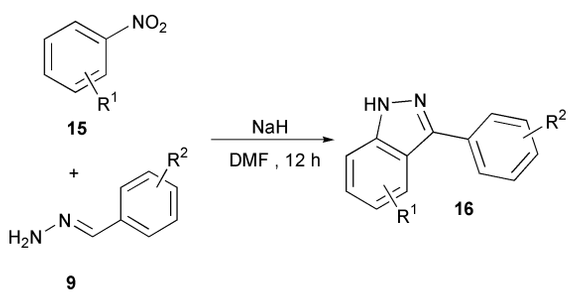
When substituted nitrobenzenes **15** were similarly treated with aromatic hydrazones **9**, a different type of cyclocondensation took place to produce 3-arylindazoles **16**, though the yield of the products was not satisfactory (Scheme 5; Table 4). Thus, 1,3-dinitrobenzene **15a** underwent cyclocondensation with 4-nitrobenzaldehyde hydrazone **9a** *via* the replacement of the nitro group of **15a**, giving 5-nitro-3-(4-nitrophenyl)indazole **16a** as the sole product in 37% isolated yield. A similar reaction of 4-chloronitrobenzene **15b** led to 6-chloro-3-(4-nitrophenyl)-indazole **16b** in 21% isolated yield. Interestingly enough, the chlorine atom remained intact despite of its presence at the most activated position of the substrate. In contrast, when 4-methylbenzaldehyde hydrazone **9f** was employed as the nucleophile, preferential displacement of the chlorine atom took place and no cyclocondensation product was obtained. A similar attempt to cyclocondense 1,3-dinitrobenzene **15a** with hydrazone **9f** resulted in the displacement of a ring hydrogen atom at the 4-position by the hydrazone anion, giving the *N*^{2}-(2,4-dinitrophenyl) derivative **22a** of the original hydrazone as the main product.

Table 4 Reaction of monocyclic nitroarenes **15** with hydrazones **9**

Nitroarene	Hydrazone	Temp.(°C)	Yield of **16** (%)[a]
15a R^1 = 3-NO_2	**9a**	−10	37
15b R^1 = 4-Cl	**9a**	rt	21 (35)[b,c]
15c R^1 = 4-NO_2	**9a**	rt	36
15a R^1 = 3-NO_2	**9f**	rt	—[d]
15b R^1 = 4-Cl	**9f**	−10	—[e]
15c R^1 = 4-NO_2	**9f**	−10	—[f]

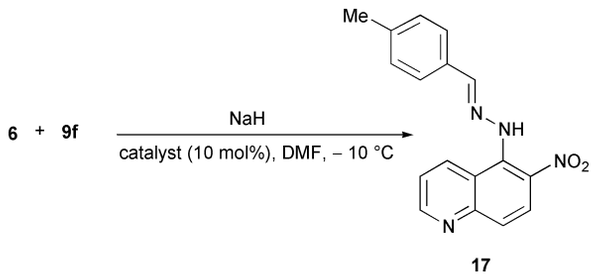
[a] Isolated yield. [b] Starting material was recovered in (40%). [c] Numeral in parenthesis refers to conversion. [d] *N*^{2}-(2, 4-dinitrophenyl)hydrazone **22a** was obtained. [e] Dehalogenation product was obtained. [f] Denitration product was obtained.





Scheme 5

Copper salts are known to catalyze the addition of *O*-methylhydroxylamine to nitroarenes. Thus, Seko *et al.* carried out the reaction of nitroarenes with *O*-alkylhydroxylamines in the presence of some copper catalyst and obtained the corresponding nitroanilines in high yield.[15] In the hope of similar catalysis, nitroarene **6** was treated with the anion of **9f** in the presence of several metal salts such as CuCl, $CuCl_2$ or $ZnCl_2$. To our disappointment, however, only nucleophilic displacement of a hydrogen atom took place at the 5 position of **6**, giving *N*-nitroaryl derivative **17** of the original hydrazone as the sole main product (Scheme 6). Little or no cyclocondensation



Scheme 6

product was obtained under these conditions (Table 5). All attempts to cyclize **17** with sodium hydride in DMF failed, thus ruling out the possible role of this hydrazone as an intermediate to the triazino[6,5-*f*]quinoline **11f**.

Table 5 Reaction of 6-nitroquinoline **6** with hydrazone **9f** in the presence of metal salt

Metal salt	Time (*t*/h)	Yield (%)[a] **11f**	**17**
CuCl	3	trace[b]	14
$CuCl_2$	3	3	6
$ZnCl_2$	6	—	12
$PdCl_2$	3	—	—[c]

[a] Isolated yield. [b] Detected by NMR. [c] A tarry material was obtained.

Table 6 The reaction of 6-nitroquinoline **6** with hydrazones **7a**–**e**

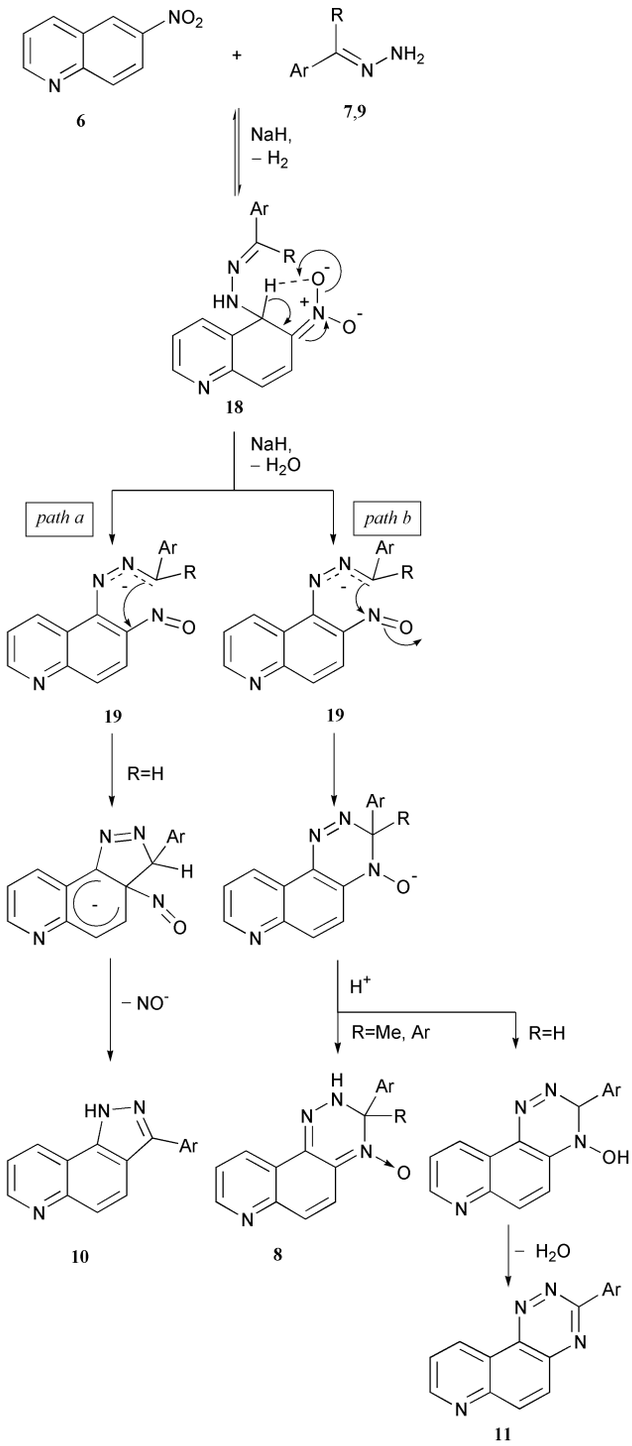
Hydrazone	R	Ar	Yield of **8** (%)[a,b]
7a	C_6H_5	C_6H_5	59
7b	4-MeC_6H_4	4-MeC_6H_4	48 (51)
7c	Me	C_6H_5	61 (68)
7d	Me	4-MeC_6H_4	63 (70)
7e	Me	4-BrC_6H_4	63 (68)

[a] Isolated yield. [b] Numeral in parenthesis refers to conversion.

Possible reaction mechanism

Although the mechanism for the formation of compounds **10** and **11** is not clear at present, a possible reaction sequence is outlined in Scheme 7. In the initial stage, the hydrazone anion attacks the 5-position of 6-nitroquinoline **6** to form a Meisenheimer intermediate **18**.[16,17] This intermediate anion undergoes the nitro–*aci*-nitro isomerization followed by dehydration to form the anion **19**,[18] which then would cyclize *via* two competing pathways depending on the electronic nature of the ring substituent group of the original chemical aromatic hydrazone. When the substituent is electron-withdrawing, such as nitro, the hydrazone anion is stabilized and undergoes an ordinary addition–elimination sequence to displace the NO moiety (path a).[19] On the other hand, electron-releasing substituent groups such as methyl and methoxy destabilize the anion by increasing the electron density at the anionic center, which will be readily trapped by the nearby nitroso group to form the triazino-[6,5-*f*]quinoline structure **8** or **11** (path b). The reduction of the nitro group to a nitroso group has often been observed in the strong-base-assisted nucleophilic aromatic substitution of nitroarenes.[20,21] Due to steric bulkiness, the hydrazone anion generated from keto hydrazones **7** undergoes exclusive ring closure with the nitroso group. Thus, the reaction of **6** and **7** under similar conditions produces triazino[6,5-*f*]quinoline oxides **8** in good yield (Table 6).

The formation of 3-arylated indazoles **16** is somewhat tricky to explain. We depict a possible route from **15b** to **16b** in Scheme 8. Nitroarene **15b** reacts with a benzaldehyde hydrazone anion to form a Meisenheimer intermediate **20** *via* the kinetically controlled addition of the anion to a position adjacent to the nitro group in **15b**. The electron-withdrawing nitro group of **9a** would facilitate the generation and attack of the hydrazone anion, resulting in the formation of the indazole **16b** *via* the displacement of the nitro group (path c). On the other hand, the electron-donating methyl group in **9f** does not stabilize the hydrazone anion and consequently the Meisenheimer intermediate **21** is reluctant to cyclize and eventually leads to N^2-arylated hydrazone **22b** (path d).



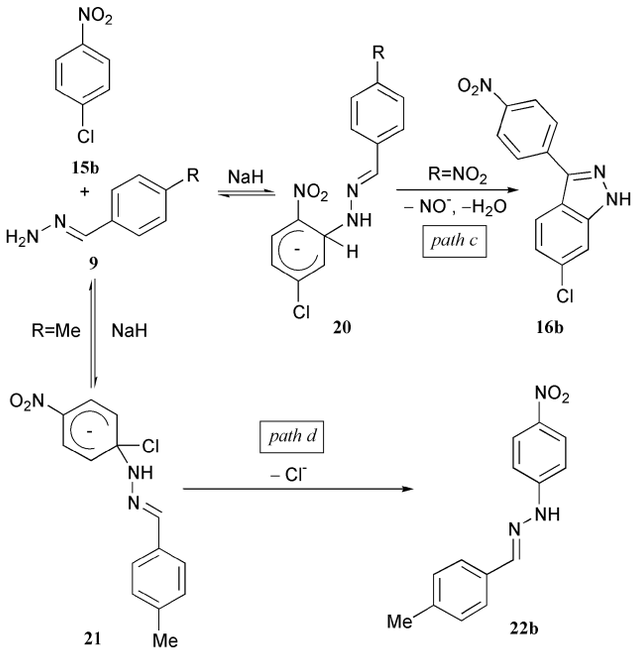
Scheme 7

Conclusions

We have developed a new, straightforward method for the construction of the [1,2,4]triazino[6,5-*f*]quinoline, pyrazolo[3,4-*f*]-quinoline, and indazole frameworks, which is based on the direct cyclocondensation of nitroarenes with aromatic hydrazones in the presence of sodium hydride. It 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 for by readily accessible starting materials, simple manipulation, economy, a one-pot procedure, and mild conditions.

Experimental

Melting points were determined on a Yanaco MP S3 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and/or DMSO-d_6 on a JEOL JNM-A400 NMR spectrometer using tetramethylsilane as internal reference, unless otherwise mentioned. *J*-values are given in Hz. IR measure-



Scheme 8

ments were made on a JEOL FTIR-5300 spectrophotometer for KBr pellets and only prominent peaks in the region 2000–700 cm^{-1} were recorded. CI mass spectra were determined at 70 eV on a Shimadzu GCMS-QP5000 mass spectrometer using isobutane as ionizing gas. All reagents excepting hydrazones were reagent-grade commercial products and used as received. DMF was distilled from CaH_2 prior to use. Progress of the reaction was monitored by thin-layer chromatography (TLC) on a glass plate coated with silica gel 60 F_{254} (Merck). Preparative chromatography was performed on a column packed with Merck Silica Gel (230–400 mesh), using a mixture of EtOAc and hexane as the eluent. Gradient HPLC was carried out on a Shimadzu LC-10 apparatus using a mixture of methanol and water. Microanalyses were performed at Advanced Instrumentation Center, Ehime University. [1,2,4]Triazino[6,5-*f*]-quinolines **8** and **11** and pyrazolo[3,4-*f*]quinolines **10** are poorly soluble in common organic solvents and were recrystallized from EtOH–dichloromethane or pyridine. With some compounds, small amounts of solvent were strongly retained in crystals and could not be removed even after drying under vacuum.

Synthesis of 3,3-disubstituted 2,3-dihydro[1,2,4]triazino[6,5-*f*]-quinoline 4-oxides 8a–e. Typical procedure

A mixture of 6-nitroquinoline **6** (0.30 g, 1.7 mmol), NaH (0.29 g, 7.0 mmol) and DMF (15 mL) was cooled to −10 °C and benzophenone hydrazone **7a** (0.40 g, 2.0 mmol) was added in one portion. The resulting dark red solution was stirred at this temperature for 24 h and then diluted with water (50 mL). The organic phase was collected with EtOAc (50 mL × 3), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel using a mixture of EtOAc and hexane (1 : 3 to 1 : 1) to give the [1,2,4]triazino[6,5-*f*]quinoline-4-oxide **8a** as an orange-colored solid (0.35 g, 59%), which was recrystallized from ethanol to give crystalline **8a** as an ethanol solvate.

3,3-Diphenyl-2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline 4-oxide 8a. Mp 136–137 °C; δ_H (DMSO-d_6) 7.27 (d, 1H, J = 10.0), 7.32–7.34 (m, 3H), 7.37 (dd, 1H, J = 4.6, 8.1), 7.40–7.56 (m, 8H), 8.26 (dd, 1H, J = 1.7, 4.6), 8.26 (dd, 1H, J = 1.7, 8.1), 10.45 (s, 1H); δ_C (DMSO-d_6) 86.1, 120.1, 123.1, 126.0, 128.1 (4C), 128.4 (4C), 129.2 (2C), 129.6, 130.9, 132.5, 132.7, 136.4 (2C), 147.8, 149.9; *m*/*z* (CI) 339 (5.4%), 307 (M^+ − 45, 100), 182 (31); ν_{max} (KBr)/cm^{-1} 3484br, 3183, 2923, 1447, 1235, 1084, 691 (Found: C, 73.58; H, 5.02; N, 14.63. $C_{22}H_{16}N_4O$·1/2EtOH requires C, 73.58; H, 5.10; N, 14.92%.)

3,3-Bis-(4-methylphenyl)-2,3-dihydro[1,2,4]triazino[6,5-*f*]-quinoline 4-oxide 8b. Mp 135–137 °C; δ_H ($CDCl_3$) 2.35 (s, 6H), 7.17 (d, 4H, J = 7.8), 7.22 (dd, 1H, J = 4.6, 8.1), 7.24–7.31 (m, 6H), 7.63 (d, 1H, J = 10.0), 8.30 (d, 1H, J = 4.6), 8.60 (d, 1H, J = 8.1); δ_C ($CDCl_3$) 21.2, 21.7, 23.7, 116.7, 120.8, 122.0, 122.6, 127.9 (2C), 128.6 (4C), 129.0 (4C), 132.7 (2C), 140.0, 141.1, 148.5, 150.0, 150.7; *m*/*z* (EI) 349 (5%), 334 (M^+ − 46, 68), 319 (95), 159 (100); ν_{max} (KBr)/cm^{-1} 3491 br(NH), 1512, 1445, 1373, 1227, 1179, 1074, 1059, 1032, 856, 801, 762, 681, 550 (Found: C, 75.74; H, 5.36; N, 14.63. $C_{24}H_{20}N_4O$ requires C, 75.77; H, 5.30; N, 14.73%).

3-Methyl-3-phenyl-2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline 4-oxide 8c. Mp 121–123 °C; δ_H (DMSO-d_6) 1.90 (s, 3H), 7.22–7.37 (m, 7H), 7.53 (d, 1H, J = 10.0), 8.24 (d, 1H, J = 7.6), 8.59 (d, 1H, J = 4.4), 10.49 (s, 1H); δ_C ($CDCl_3$) 23.9, 80.8, 120.4, 122.5, 125.0 (2C), 126.4, 128.5 (2C), 128.9, 130.4, 130.8, 132.6, 135.2, 138.1, 148.7, 149.8; *m*/*z* (CI) 245 (M^+ − 45, 100%), 246 (36), 244 (14), 120 (6) ν_{max} (KBr)/cm^{-1} 3187 br(NH), 1466, 1445, 1400, 1368, 1254, 1084, 997, 826, 764, 702 (Found: C, 70.14; H, 4.90; N, 19.25. $C_{17}H_{14}N_4O$ requires C, 70.33; H, 4.86; N, 19.30%).

3-Methyl-3-(4-methylphenyl)-2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline 4-oxide 8d. Mp 123–125 °C; δ_H (DMSO-d_6) 1.87 (s, 3H), 2.18 (s, 3H), 7.09 (d, 2H, J = 8.0), 7.20–7.30 (m, 3H), 7.35 (dd, 1H, J = 4.8, 7.6), 7.51 (d, 1H, J = 10.0), 8.23 (d, 1H, J = 7.6), 8.59 (d, 1H, J = 4.8), 10.44 (s, 1H); δ_C ($CDCl_3$) 20.9, 23.8, 80.7, 120.4, 122.5, 125.0 (2C), 126.4, 129.1 (2C), 130.3, 130.6, 132.7, 135.0, 135.1, 138.8, 148.8, 149.8; *m*/*z* (CI) 259 (M^+ − 45, 100%), 258 (18), 216 (5), 160 (17); ν_{max} (KBr)/cm^{-1} 3264 br(NH), 1512, 1465, 1445, 1370, 1246, 1208, 1082, 812, 687, 592, 473 (Found: C, 70.82; H, 5.59; N, 18.05. $C_{18}H_{16}N_4O$ requires C, 71.04; H, 5.30; N, 18.41%).

3-(4-Bromophenyl)-3-methyl-2,3-dihydro[1,2,4]triazino[6,5-*f*]quinoline 4-oxide 8e. Mp 133–134 °C; δ_H (DMSO-d_6) 1.89 (s, 3H), 7.25 (d, 1H, J = 10.0), 7.28 (d, 2H, J = 6.8), 7.37 (dd, 1H, J = 4.8, 7.6), 7.50–7.53 (m, 3H), 8.24 (d, 1H, J = 7.6), 8.61 (d, 1H, J = 4.8), 10.51 (s, 1H); δ_C ($CDCl_3$) 9.7, 117.1, 122.9 (2C), 126.4, 126.8, 128.5, 128.6, 129.1, 129.3, 131.8, 132.0, 133.3 (2C), 137.2, 143.7, 151.0; *m*/*z* (CI) 325 (M^+ − 44, 100%), 324 (M^+ − 45, 37), 323 (M^+ − 46, 73); ν_{max} (KBr)/cm^{-1} 3192 (NH), 1514, 1466, 1399, 1368, 1254, 1084, 1009, 826, 806 (Found: C, 54.87; H, 3.64; N, 14.91. $C_{17}H_{13}BrN_4O$ requires C, 55.30; H, 3.55; N, 15.17%).

Synthesis of 3-aryl-1*H*-pyrazolo[3,4-*f*]quinolines 10a–c/13a–c and 3-aryl[1,2,4]triazino[6,5-*f*]quinolines 11b–g. Typical procedure

A suspension of NaH (0.29 g, 7.0 mmol) in DMF (15 mL) was cooled to −10 °C and 6-nitroquinoline **6** (0.30 g, 1.7 mmol) followed by 4-chlorobenzaldehyde hydrazone **9c** (0.31 g, 2.0 mmol) were added. The resulting dark red solution was stirred at this temperature for 24 h and then diluted with water (50 mL). The aqueous phase was extracted with EtOAc (50 mL × 3) and the combined extracts were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using a mixture of EtOAc and hexane (1 : 3 to 1 : 1) to elute 3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*f*]quinoline **10c** (0.028 g, 6%) and 3-(4-chlorophenyl)[1,2,4]triazino[6,5-*f*]quinoline **11c** (0.13 g, 27%) in that order.

Other 3-aryl-1*H*-pyrazolo[3,4-*f*]quinolines **10/13** and 3-aryl-[1,2,4]triazino[6,5-*f*]quinolines were obtained similarly.

3-(4-Nitrophenyl)-1*H*-pyrazolo[3,4-*f*]quinoline 10a. Mp 281–282 °C; δ_H (DMSO-d_6) 7.51 (dd, 1H, J = 4.0), 7.96–7.99 (m, 2H), 8.04 (d, 2H, J = 8.0), 8.39–8.44 (m, 3H), 8.83 (d, 1H, J = 4.4), 14.03 (s, 1H); δ_C (DMSO-d_6) 113.8, 115.2, 121.8, 122.0, 123.9 (2C), 129.5, 129.8, 130.4 (2C), 139.3, 141.4, 144.8, 145.8, 147.3, 147.9; *m*/*z* (CI) 290 (M^+ + 1, 100%), 244 (39), 190 (51); ν_{max} (KBr)/cm^{-1} 3110 br(NH), 1601, 1545, 1516, 1350, 968, 855, 808 (Found: C, 65.82; H, 3.76; N, 18.94. $C_{16}H_{10}N_4O_2$ requires C, 66.20; H, 3.47; N, 19.30%).

3-(4-Fluorophenyl)-1*H*-pyrazolo[3,4-*f*]quinoline 10b. δ_H (CDCl$_3$) 7.06 (d, 1H, J = 9.6), 7.10 (d, 2H, J = 9.2), 7.41 (dd, 1H, J = 4.2, 9.2), 7.46 (d, 1H, J = 9.6), 7.66 (d, 2H, J = 9.2), 8.32 (d, 1H, J = 9.2), 8.93 (d, 1H, J = 4.2), 12.48 (s, 1H). This compound was difficult to obtain in a form completely free from **11b**.

3-(4-Chlorophenyl)-1*H*-pyrazolo[3,4-*f*]quinoline 10c. Mp 262–263 °C; δ_H (DMSO-d_6) 7.48–7.53 (m, 3H), 7.60–7.67 (m, 3H), 8.03 (d, 1H, J = 9.2), 8.99 (d, 1H, J = 4.3), 9.15 (d, 1H, J = 8.8), 11.66 (s, 1H); *m*/*z* (CI) 281 (M^+ + 2, 12%), 279 (M^+, 59), 277 (85), 140 (100). This compound was difficult to obtain in a form completely free from **11c**.

1-Methyl-3-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*f*]quinoline 13a. Mp 291–293 °C; δ_H (CDCl$_3$) 4.26 (s, 3H), 7.39 (dd, 1H, J = 4.0, 8.0), 7.78 (d, 1H, J = 9.2), 7.97 (d, 2H, J = 8.8), 8.08 (d, 1H, J = 9.2), 8.43 (m, 3H), 8.88 (d, 1H, J = 4.0); δ_C (CDCl$_3$) 36.18, 108.9, 113.5, 121.7, 124.1 (2C), 130.2 (2C), 130.4, 135.2, 139.3, 141.3, 144.2, 146.2, 147.9, 148.2, 148.3; *m*/*z* (EI) 304 (M^+, 100%), 303 (12), 257 (16), 243 (17), 231 (8), 214 (14), 203 (8); ν_{max} (KBr)/cm^{-1} 1599, 1514, 1346, 1146, 1105, 972, 808 (Found: C, 67.23; H, 4.04; N, 18.14. $C_{17}H_{12}N_4O_2$ requires C, 67.10; H, 3.97; N, 18.41%).

3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*f*]quinoline 13b. Mp 213–214 °C; δ_H (CDCl$_3$) 7.42 (dd, 1H, J = 4.4, 8.8), 7.51 (t, 1H, J = 7.4), 7.63 (t, 2H, J = 7.4), 7.79 (d, 2H, J = 7.6), 8.01–8.12 (m, 4H), 8.40–8.47 (m, 3H), 8.91, (d, 1H, J = 4.4); δ_C (CDCl$_3$) 114.7, 116.6, 121.8, 122.7, 124.01 (2C), 124.03 (2C), 128.2, 129.7 (2C), 130.3, 130.5 (2C), 130.9, 138.5, 139.0, 140.9, 146.1, 146.5, 148.1, 148.6; *m*/*z* (EI) 366 (M^+, 100%), 365 (11), 319 (29), 159 (32); ν_{max} (KBr)/cm^{-1} 1599, 1522, 1348, 1136, 968, 856 810, 756, 694; (Found: C, 71.74; H, 4.05; N, 15.05. $C_{22}H_{14}N_4O_2$ requires C, 72.12; H, 3.85; N, 15.29%).

3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*f*]quinoline 13c. Mp 206–207 °C; δ_H (CDCl$_3$) 2.50 (s, 3H), 7.35 (dd, 1H, J = 4.4, 8.5), 7.39 (d, 2H, J = 8.0), 7.52 (m, 3H), 7.70 (d, 2H, J = 8.0), 7.80 (dd, 2H, J = 1.5, 7.3), 8.01 (d, 1H, J = 9.5), 8.06 (d, 1H, J = 9.52), 8.54 (d, 1H, J = 8.5), 8.85 (d, 1H, J = 4.4); δ_C (CDCl$_3$) 21.5, 114.7, 116.8, 121.5, 123.4, 123.9 (2C), 127.6, 129.4 (2C), 129.5 (2C), 129.6 (2C), 130.3, 130.8, 131.1, 138.0, 138.7, 139.4, 146.3, 148.1, 148.6; *m*/*z* (EI) 335 (M^+, 100%), 334 (49), 319 (8), 167 (23); ν_{max} (KBr)/cm^{-1} 1597, 1522, 1503, 1393, 1134, 965, 808, 770, 694 (Found: C, 82.30; H, 5.25; N, 12.57. $C_{23}H_{17}N_3$ requires C, 82.36; H, 5.11; N, 12.53%).

3-(4-Fluorophenyl)[1,2,4]triazino[6,5-*f*]quinoline 11b. Mp 161–163 °C; δ_H (CDCl$_3$) 7.30 (d, 2H, J = 8.8), 7.83 (dd, 1H, J = 4.4, 8.4), 8.15 (d, 1H, J = 9.2), 8.50 (d, 1H, J = 9.2), 8.82 (d, 2H, J = 8.8), 9.18 (dd, 1H, J = 1.6, 4.4), 9.77 (dd, 1H, J = 1.6, 8.4); δ_C (CDCl$_3$) 116.1 (2C), 123.9, 125.2, 129.5, 130.9 (2C), 131.9, 139.7, 142.6, 143.9, 148.7, 152.9, 161.1, 164.1, 166.6; *m*/*z* (CI) 277 (M^+ + 1, 100%), 251 (22), 190 (30); ν_{max} (KBr)/cm^{-1} 1599, 1514, 1450, 1391, 1225, 1157, 1053, 853, 768, 596, 550 (Found: C, 69.47; H, 3.32; N, 20.21. $C_{16}H_9FN_4$ requires C, 69.56; H, 3.28; N, 20.28%).

3-(4-Chlorophenyl)[1,2,4]triazino[6,5-*f*]quinoline 11c. Mp 254–255 °C; δ_H (CDCl$_3$) 7.59 (d, 2H, J = 8.0), 7.83 (dd, 1H, J = 4.4, 8.4), 8.15 (d, 1H, J = 9.2), 8.50 (d, 1H, J = 9.2), 8.75 (d, 2H, J = 8.0), 9.18 (dd, 1H, J = 1.6, 8.4), 9.77 (dd, 1H, J = 1.6, 8.4); δ_C (CDCl$_3$) 123.1, 123.2, 123.9, 124.3, 128.2 (2C), 128.9, 129.3, 130.0 (2C), 130.5, 130.8, 132.0, 138.2, 139.7, 153.0; *m*/*z* (CI) 295 (M^+ + 2, 3.3%), 293 (M^+, 10.7) 266 (27), 264 (82), 132 (34), 127 (100); ν_{max} (KBr)/cm^{-1} 1561, 1381, 1343, 1263, 1090, 1067, 1015, 835, 810, 785, 409. This compound was difficult to obtain in a form completely free from **10c**.

3-Phenyl[1,2,4]triazino[6,5-*f*]quinoline 11d. Mp 178–179 °C; δ_H (CDCl$_3$) 7.55–7.65 (m, 3H), 7.81 (dd, 1H, J = 4.4, 8.4), 8.44 (d, 1H, J = 10.0), 8.62 (dd, 2H, J = 1.6, 7.2), 8.67 (dd, 1H, J = 10.0), 9.19 (dd, 1H, J = 1.6, 4.4), 9.69 (dd, 1H, J = 1.6, 8.4); δ_C (DMSO-d_6) 123.5, 124.4, 128.0 (2C), 128.5 (2C), 129.0, 131.0, 131.2, 134.7, 139.1, 141.9, 143.5, 148.0, 152.4, 160.9; *m*/*z* (CI) 259 (M^+ + 1, 100%), 149 (27); ν_{max} (KBr)/cm^{-1} 1583, 1516, 1435, 1389, 1345, 1277, 1196, 1053, 1022, 855, 804, 748, 694, 550 (Found: C, 73.88; H, 4.02; N, 21.48. $C_{16}H_{10}N_4$ requires C, 74.40; H, 3.90; N, 21.69%).

3-(3-Methylphenyl)[1,2,4]triazino[6,5-*f*]quinoline 11e. Mp 178–180 °C; δ_H (CDCl$_3$) 2.54 (s, 3H), 7.43 (d, 1H, J = 7.2), 7.51 (t, 1H, J = 7.2), 7.82 (dd, 1H, J = 4.4, 8.2), 8.16 (d, 1H, J = 9.6), 8.49 (d, 1H, J = 9.6), 8.61 (m, 2H), 9.17 (dd, 1H, J = 1.6, 4.4), 9.78 (dd, 1H, J = 1.6, 8.2); δ_C (CDCl$_3$) 24.6, 117.7, 119.9, 124.3, 125.9, 129.9, 131.9, 132.6, 134.6, 135.2, 139.0, 142.7, 143.9, 148.6, 152.8, 162.1, 168.3; *m*/*z* (CI) 273 (M^+ + 1, 100%), 244 (5), 117 (6); ν_{max} (KBr)/cm^{-1} 1591, 1514, 1462, 1389, 1343, 1296, 1240, 1181, 1152, 1057, 806, 775, 696 (Found: C, 74.84; H, 4.50; N, 20.46. $C_{17}H_{12}N_4$ requires C, 74.98; H, 4.44; N, 20.58%).

3-(4-Methylphenyl)[1,2,4]triazino[6,5-*f*]quinoline 11f. Mp 199–201 °C; δ_H (CDCl$_3$) 2.50 (s, 3H), 7.43 (d, 2H, J = 8.2), 7.81 (dd, 1H, J = 4.4, 8.4), 8.15 (d, 1H, J = 9.0), 8.48 (d, 1H, J = 9.0), 8.69 (d, 2H, J = 8.2), 9.16 (dd, 1H, J = 1.6, 4.4), 9.77 (dd, 1H, J = 1.6, 8.4); δ_C (CDCl$_3$) 21.6, 118.5, 122.3, 122.9, 123.2, 128.5, 128.7 (2C), 129.5 (2C), 132.5, 135.3, 139.5, 142.2, 149.3, 154.0, 156.8; *m*/*z* (CI) 273 (M^++1, 100%), 245 (2), 136 (4), 135 (4); ν_{max} (KBr)/cm^{-1} 1609, 1580, 1507, 1427, 1397, 1345, 1317, 1263, 1188, 1065, 847, 818, 542 (Found: C, 74.85; H, 4.50; N, 20.45. $C_{17}H_{12}N_4$ requires C, 74.98; H, 4.44; N, 20.58%).

3-(4-Methoxyphenyl)[1,2,4]triazino[6,5-*f*]quinoline 11g. Mp 237–238 °C; δ_H (DMSO-d_6) 3.80 (s, 3H), 7.02 (d, 2H, J = 8.8), 7.44 (d, 1H, J = 9.4), 7.61 (d, 2H, J = 8.8), 7.65 (dd, 1H, J = 3.8, 8.8), 8.07 (d, 1H, J = 9.4), 9.00 (d, 1H, J = 3.8), 9.32 (d, 1H, J = 8.8); δ_C (CDCl$_3$) 55.4, 114.2 (2C), 114.6, 120.1, 121.0, 125.1, 127.0, 129.0, 130.1 (2C), 132.1, 139.1, 147.4, 153.2, 161.0, 162.0; *m*/*z* (CI) 289 (M^+ + 1, 100%), 263 (14), 190 (32), 136 (41); ν_{max} (KBr)/cm^{-1} 1603, 1507, 1474, 1432, 1406, 1333, 1229, 1254, 1177, 1026, 831, 540, 442. This compound crystallized from EtOH–dichloromethane as fine plates, which retained part of the solvent even after drying under vacuum over $CaCl_2$.

Synthesis of N^2-(nitroaryl) derivatives of 4-methylbenzaldehyde hydrazones 9f and 12d. Typical procedure

To a mixture of 6-nitroquinoline **6** (0.30 g, 1.7 mmol), NaH (0.29 g, 7.0 mmol) and DMF (15 mL) cooled to −10 °C were added 4-methylbenzaldehyde hydrazone **9f** (0.27 g, 2.0 mmol) and CuCl (10 mol%). The resulting deep purple solution was stirred at this temperature for 3 h and then diluted with water (50 mL). The aqueous phase was extracted with EtOAc (50 mL × 3) and the combined extracts were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using a mixture of EtOAc and hexane (1 : 3 to 1 : 1) as the eluent to obtain the N^2-(6-nitroquinolin-5-yl) derivative of **9f** (0.073 g, 14%).

***N*^{2}-Methyl-*N*^{1}-(4-methylbenzylidene)-*N*^{2}-(6-nitroquinolin-5-yl)hydrazine 14.** Mp 225–227 °C; δ_H (CDCl$_3$) 2.33 (s, 3H), 3.56

(s, 3H), 7.14 (d, 2H, J = 7.9), 7.43 (d, 2H, J = 7.9), 7.55 (dd, 1H, J = 4.1, 8.5), 7.61 (s, 1H), 8.00 (d, 1H, J = 8.4), 8.03 (d, 1H, J = 8.4), 8.53 (dd, 1H, J = 1.2, 8.5), 9.03 (dd, 1H, J = 1.2, 4.1); δ_C ($CDCl_3$) 39.9, 41.3, 123.6, 125.3, 125.5, 127.1 (2C), 128.6 (2C), 130.2, 132.5, 132.8, 134.5, 136.5, 138.1, 138.6, 140.7, 143.3; *m*/*z* (EI) 320 (M^+, 100%), 274 (36), 259 (22); ν_{max} (KBr)/cm^{-1} 1599, 1532, 1478, 1393, 1356, 1316, 1065, 897, 843, 812, 777, 519 (Found: C, 67.20; H, 5.06; N, 17.35. $C_{18}H_{16}N_4O_2$ requires C, 67.49; H, 5.03; N, 17.49%).

N^1-(4-Methylbenzylidene)-N^2-(6-nitroquinolin-5-yl)hydrazine 17. Mp 191–192 °C; δ_H ($CDCl_3$) 2.42 (s, 3H), 7.28 (d, 2H, J = 8.4), 7.47 (dd, 1H, J = 4.4, 8.8), 7.49 (d, 1H, J = 9.6), 7.63 (d, 2H, J = 8.4), 8.39 (d, 1H, J = 9.6), 8.98 (dd, 1H, J = 1.2, 4.4), 9.86 (dd, 1H, J = 1.2, 8.8), 12.64 (s, 1H); δ_C ($CDCl_3$) 22.21, 120.3, 122.0, 124.1, 125.8, 126.5 (2C), 128.1 (2C), 129.0, 130.6, 138.2, 139.8, 141.2, 146.8, 148.3, 152.3; *m*/*z* (CI) 307 (M^+ + 1, 100%), 247 (22), 190 (27); ν_{max} (KBr)/cm^{-1} 3121 (NH), 1609, 1512, 1460, 1408, 1370, 1279, 1233, 1171, 1144, 1098, 804, 772, 669, 511 (Found: C, 66.36; H, 4.65, N, 18.04. $C_{17}H_{14}N_4O_2$ requires C, 66.66; H, 4.61; N, 18.29%).

N^1-(2,4-Dinitrophenyl)-N^2-(4-methylbenzylidene)hydrazine 22a. Mp 203–204 °C; δ_H ($CDCl_3$) 2.39 (s, 3H), 7.12 (d, 1H, J = 9.2), 7.22 (d, 2H, J = 8.0), 7.59 (d, 2H, J = 8.0), 7.79 (s, 1H), 8.02 (br, 1H), 8.15–8.20 (m, 2H); δ_C ($CDCl_3$) 21.6, 116.8, 123.5, 127.6 (2C), 129.8 (2C), 130.0, 130.4, 138.1, 141.6, 144.8, 148.0, 148.1; *m*/*z* (EI) 300 (M^+, 68%), 152 (38), 121 (100); ν_{max} (KBr)/cm^{-1} 3287 (NH), 1618, 1586, 1507, 1422, 1331, 1136, 1084 (Found: C, 55.96; H, 4.07; N, 18.27. $C_{14}H_{12}N_4O_4$ requires C, 56.00; H, 4.03; N, 18.66%).

N^1-(4-Methylbenzylidene)-N^2-(4-nitrophenyl)hydrazine 22b. Mp 236–238 °C; δ_H ($CDCl_3$) 2.39 (s, 3H), 7.12 (d, 2H, J = 8.8), 7.22 (d, 2H, J = 8.0), 7.59 (d, 2H, J = 8.0), 7.78 (s, 1H), 7.99 (br, 1H), 8.18 (d, 2H, J = 8.8); δ_C ($CDCl_3$) 13.5, 110.8 (2C), 112.4 (2C), 125.4 (2C), 125.9, 127.0 (2C), 127.5, 128.7, 130.3, 131.4; *m*/*z* (EI) 255 (M^+, 100%), 240 (3), 225 (4), 208 (13); ν_{max} (KBr)/cm^{-1} 3258 (NH), 1610, 1595, 1495, 1480, 1300, 1275, 1173, 1107, 837, 818, 750, 513 (Found: C, 65.82; H, 5.15; N, 16.46. $C_{14}H_{13}N_3O_2$ requires C, 65.87; H, 5.13; N, 16.46%).

Synthesis of 3-aryl-1*H*-indazoles 16. Typical procedure

A mixture of 1,3-dinitrobenzene **15a** (0.29 g, 1.7 mmol) and NaH (0.29 g, 7.0 mmol) in DMF (15 mL) was cooled to −10 °C and 4-nitrobenzaldehyde hydrazone **9a** (0.33 g, 2.0 mmol) was added in one portion. The resulting deep purple solution was stirred at this temperature for 12 h and then diluted with water (50 mL). The aqueous mixture was extracted with EtOAc (50 mL × 3) and the combined extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel using a mixture of EtOAc and hexane (1 : 5 to 1 : 1) as the solvent to give 3-aryl-1*H*-indazole **16a** as a light brown powder (0.18 g, 37%).

5-Nitro-3-(4-nitrophenyl)-1*H*-indazole 16a. Mp 210–212 °C; δ_H (DMSO-d_6) 7.71 (m, 3H), 8.07 (d, 1H, J = 8.0), 8.14 (d, 1H, J = 8.0), 8.31 (d, 2H, J = 8.5), 14.38 (s, 1H); δ_C (DMSO-d_6) 117.8, 119.1, 122.9 (3C), 126.2, 130.0 (2C), 140.8, 141.7, 141.8, 143.2, 146.8; *m*/*z* (EI) 284 (M^+, 100%), 254 (18), 208 (50), 179 (44), 152 (43); ν_{max} (KBr)/cm^{-1} 3349 (NH), 1599, 1516, 1346, 1326, 1105, 988, 858, 795, 733, 704 (Found: C, 54.88; H, 2.94; N, 19.44. $C_{13}H_8N_4O_4$ requires C, 54.93; H, 2.80; N, 19.71%).

6-Chloro-3-(4-nitrophenyl)-1*H*-indazole 16b. Mp 203–204 °C; δ_H ($CDCl_3$) 7.45 (dd, 1H, J = 1.8, 8.8), 7.52 (d, 1H, J = 8.8), 8.02 (d, 1H, J = 1.8), 8.14 (d, 2H, J = 8.8), 8.39 (d, 2H, J = 8.8), 10.34 (s, 1H); δ_C (DMSO-d_6) 112.8, 119.6, 120.9, 124.2 (2C), 126.6, 126.9, 127.4 (2C), 139.5, 140.3, 140.8, 146.5; *m*/*z* (EI) 274 (M^+, 21%), 273 (100), 243 (32), 192 (32), 164 (37); ν_{max} (KBr)/cm^{-1} 3245 (NH), 1599, 1518, 1478, 1346, 1316, 1109, 922, 856, 789, 718 (Found: C, 57.14; H, 3.08; N, 15.51. $C_{13}H_8ClN_3O_2$ requires C, 57.05; H, 2.95; N, 15.35%).

6-Nitro-3-(4-nitrophenyl)-1*H*-indazole 16c. Mp >300 °C; δ_H (DMSO-d_6) 7.27 (d, 2H, J = 8.8), 7.99 (d, 2H, J = 8.8), 8.13 (s, 1H), 8.18 (d, 1H, J = 9.2), 8.27 (d, 1H, J = 9.2), 11.65 (s, 1H); δ_C (DMSO-d_6) 112.0 (2C), 124.1, 124.4, 126.1 (2C), 127.1, 127.9, 139.0, 139.3, 141.2, 147.0, 150.0; *m*/*z* (EI) 284 (M^+, 100%), 254 (26), 192 (40), 164 (42); ν_{max} (KBr)/cm^{-1} 3374 (NH), 1603, 1526, 1470, 1348, 1319, 1111, 1074, 858, 814, 789, 750, 698 (Found: C, 54.77; H, 3.35; N, 19.34. $C_{13}H_8N_4O_4$ requires C, 54.93; H, 2.84; N, 19.71%).

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