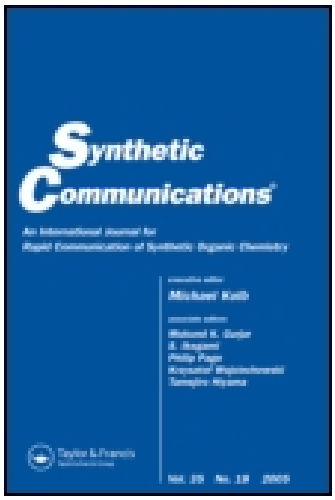

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New Straightforward Quinoline Synthesis from the Mannich Reaction of α-Ketohydrazones

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New Straightforward Quinoline Synthesis from the Mannich Reaction of α-Ketohydrazones

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ABSTRACT

The addition of α-ketohydrazones to 2-acetamidobenzaldehyde proceeds efficiently in the presence of *N*-benzylpiperazine to afford in good to high yields the expected Mannich adducts; these are easily converted to quinoline derivatives under acidic conditions in a new Azo–Friedländer reaction.

Key Words: Azo–Friedländer reaction; Quinoline; Mannich reaction; α-Ketohydrazone.

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INTRODUCTION

Among the various heterocyclic compounds used in medical chemistry, the quinoline derivatives have a long tradition of biologically relevant compounds with such activities as cardiovascular, bactericidal or antimalarial.[1]

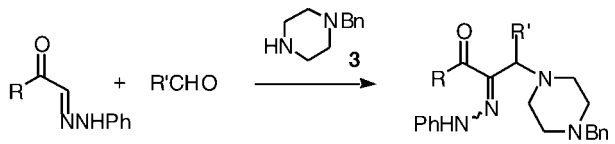
Synthesis of the heterocyclic core most often use aniline derivatives as starting materials. In the classical Friedländer synthesis, the quinoline system is formed by an aldol reaction between protected 2-aminobenzaldehyde and various ketones followed by cyclisation.[2] The selectivity problems encountered in the final cyclisation have stimulated some recent improvements such as the use of α-ketophosphonates.[3,4] Despite their first preparation at the end of the nineteenth century, new synthetic approaches for their preparation will still be needed to meet the demand for new biologically active quinolines.

Following our ongoing interest in hydrazone chemistry, we recently described a Mannich coupling of α-ketohydrazones with aldehydes in the presence of *N*-benzylpiperazine.[5] This coupling reaction initially limited to formaldehyde (Keil and Ried reaction)[6] proved in our hand to be successful with a wide range of aldehydes (Sch. 1).

If efficient with protected 2-aminobenzaldehyde, we imagined that this coupling reaction could give an easy access to quinolines.

RESULTS AND DISCUSSION

When a 2 M solution of 2-acetamidobenzaldehyde **1a** (prepared in two steps from 2-aminobenzyl alcohol) in toluene was heated at 80°C with hydrazone **2a** and *N*-benzylpiperazine, the expected Mannich adduct **4a** was obtained in a 93% isolated yield. Hydrazone **2b** behaved similarly to give **4b** with the same yield (Sch. 2). Deprotection of the *N*-acetyl group of **4a** and **4b** was easily performed as usual in hot aqueous hydrochloric acid solutions; to our delight, under these conditions, deprotection, cyclisation and elimination



Scheme 1.

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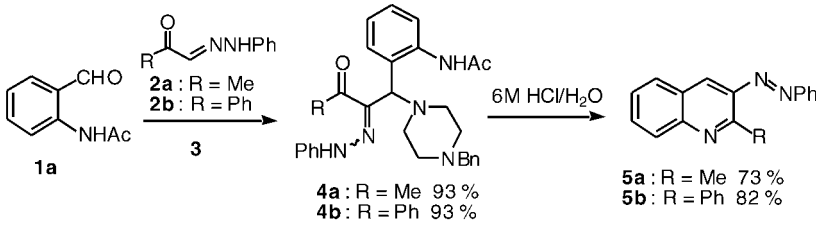


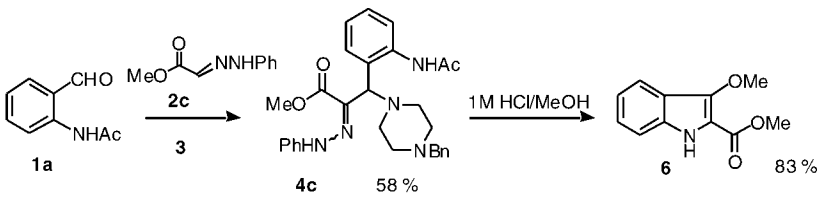
Scheme 2.

of the *N*-benzylpiperazine were carried out in a single step giving the quinolines **5a** and **5b** in good yield (Sch. 2).

Elimination of *N*-benzylpiperazine from these Mannich adducts was performed previously in our group under alkylating conditions (1,2-dibromoethane) to generate transient azoalkenes trapped in situ by various nucleophiles;[7] in this case, final aromatisation to quinoline ensures easy elimination of piperazine. Though hydrazo-noester analogue **2c** gave a successful Mannich coupling with aldehyde **1a**, the resulting hydrazone **4c** gave a complex mixture under treatment with aqueous hydrochloric acid. **4c** was finally cleanly converted to indole **6** when treated with an excess of HCl in hot MeOH (Sch. 3). This new indole synthesis is however of lower synthetic value as similar indoles are more easily prepared from malonate derivatives.[8]

In contrast to this indole formation, the new quinoline synthesis brings a valuable access to 2-alkyl-3-amino derivatives. Our procedure coupled with the Japp–Klingemann reaction[8] allows a straightforward formation of various 2-alkyl derivatives as shown by the preparation of quinoline **5c** from ethyl acetoacetate without any purification of synthetic intermediates in a 25% unoptimized overall yield (Sch. 4).

The use of formylating reactions of aniline analogues also allows structural variations on the starting aldehyde **1a**. Naphthyridine **5d**, for instance, was obtained in low yields from 2-aminopyridine. Though the application of a *tert*-butyloxycarbonyl protecting group allowed easy



Scheme 3.

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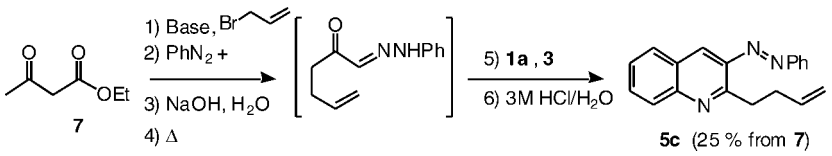


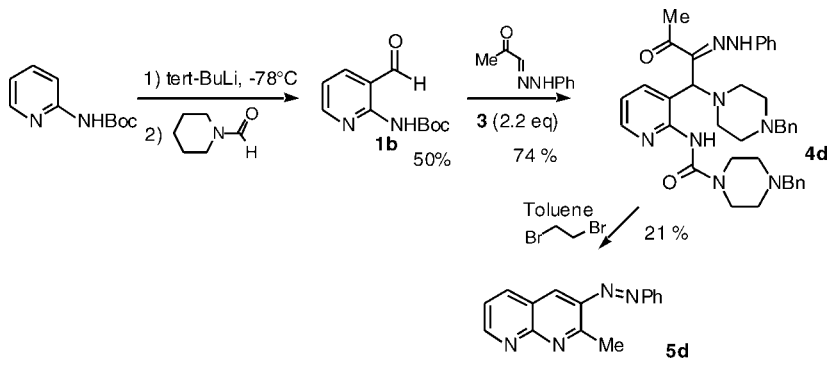
Scheme 4.

formylation, it was in this case associated with problems in the Mannich coupling and cyclisation [BOC is displaced during the reaction and two equivalents of *N*-benzylpiperazine are needed, cyclisation of the resulting carbamate is only observed in low yield under 1,2-dibromoethane alkylation (Sch. 5)].

This work is a new demonstration of the synthetic interest of umpolung reactions involving hydrazones.[10–14] This new heterocyclic synthesis gives a general access to 3-azoquinoline derivatives; easily converted into amino group through reduction, the azo function could be further used to construct more complex quinoline derivatives by nucleophilic attack on the 4 heterocyclic position.[19] These features as well as other applications of umpolung reactions of *N*-arylhydrazones are still under study in our research group.

EXPERIMENTAL

^{1}H and ^{13}C NMR were recorded on an Bruker Advance 400 (400 MHz) spectrometer using chloroform-d as a solvent. IR spectra were recorded on a Perkin–Elmer 299 using a CaF_2 cell. Melting points were obtained on a



Scheme 5.

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Reichert apparatus and are uncorrected. Mass spectra were obtained on a MS 50 spectrometer. Chromatography was performed using Merck silica gel or Aldrich activated neutral aluminum oxide (Brockmann I). Analytical TLC was performed using 0.25 mm Merck Kieselgel 60 P254 precoated silica gel plates. All solvents are reagent grade. Aldehydes **1a**,[20] **2a**[21] and hydrazones **2a**,[18] **2b**,[19] **2c**[20] were prepared according reported procedures.

Preparation of Mannich adducts 4a–d. To a solution of starting hydrazones **2a–c** (2 mmol) in 1 mL of toluene at room temperature were added aldehyde **1a–b** (2.2 mmol), and *N*-benzylpiperazine (2.2 mmol). The resulting mixture was heated at 80°C for 8 hours. Solvents were evaporated, and the crude purified by flash chromatography on silica gel with Et_2O/petroleum ether (PE) The following compounds were obtained.

***N*-{2-[1-(4-Benzyl-piperazin-1-yl)-3-oxo-2-(phenyl-hydrazono)-butyl]-phenyl}-acetamide (4a)**. Yield 93%. Brown oil. R_f: 0.60 (Et_2O/PE, 50 : 50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.11 (s, 1H, NH-Ph), 9.51 (s, 1H, NH-Ac), 7.84 (dd, $J = 8.1$, 0.8 Hz, 1H), 7.56 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.42 (t, $J = 7.9$ Hz, 2H), 7.35–7.25 (m, 8H, Har), 7.10 (t, $J = 7.4$ Hz, 2H), 5.02 (s, 1H), 3.58 (d, $J = 13.0$ Hz, 1H), 3.54 (d, $J = 13.0$ Hz, 1H), 2.90–2.73 (m, 4H), 2.46 (s, 3H, Me–C═O), 2.37 (td, $J = 11.4$, 2.0 Hz, 1H), 2.34 (s, 3H, NH–CO-Me), 2.20 (td, $J = 11.4$, 2.0 Hz, 2H), 1.94 (td, $J = 11.4$, 2.0 Hz, 1H).^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 200.2, 169.3 (C_q, HN–C═O), 143.2, 138.5, 137.8, 136.4, 130.0, 129.7, 129.5, 128.9, 128.7, 127.6, 127.3, 126.1, 125.9, 123.3, 114.5, 63.2, 63.1, 53.8, 53.6, 52.8, 51.4, 25.0 (CH_3, NHAc), 24.6 (CH_3, Me–C═O). IR (CCl_4, CaF_2) ν (cm^{-1}): 3317, 2810, 1698, 1650, 1602, 1554, 1453, 1367, 1296, 1264, 1231, 1003. Mass (ID ICP NH3) m/z 484 (MH^+), 307, 249, 178. Exact Mass (CI, CH_4) m/z calculated: 484.2713; found: 484.2705 (MH^+).

***N*-{2-[1-(4-Benzyl-piperazin-1-yl)-3-oxo-3-phenyl-2-(phenylhydrazono)-propyl]-phenyl}-acetamide (4b)**. Yield 93%. Brown solid M.p. 95–97°C. R_f: 0.60 (Et_2O/PE, 50 : 50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.44 (s, 1H, NH-Ph), 9.64 (s, 1H, NH-Ac), 7.86 (d, $J = 10.9$ Hz, 2H), 7.84 (d, $J = 7.4$ Hz, 2H), 7.66–7.64 (m, 1H), 7.56–7.52 (m, 1H), 7.44 (t, $J = 7.4$ Hz, 2H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.35–7.27 (m, 6H), 7.16–7.11 (m, 3H), 7.09 (t, $J = 7.3$ Hz, 1H), 5.23 (s, 1H), 3.60 (d, $J = 13.0$ Hz, 1H), 3.54 (d, $J = 13.0$ Hz, 1H), 3.00–2.93 (m, 2H), 2.89–2.86 (m, 1H), 2.82–2.80 (m, 1H), 2.53–2.48 (m, 1H), 2.39 (s, 3H, O═C–Me), 2.30–2.22 (m, 2H), 2.07–2.02 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 194.3, 169.4, 143.3, 138.5, 138.0, 137.8, 136.6, 132.0, 131.1, 130.1, 129.5, 129.0, 128.7, 127.9, 127.8, 127.4, 126.4, 126.2, 123.4, 114.7, 64.4, 63.1, 53.9, 53.6, 53.1, 51.4, 24.8 (O═C–CH_3). IR (CCl_4, CaF_2) ν (cm^{-1}): 3325, 3064, 3030, 2940, 2810, 1698, 1548, 1452, 1296, 1238. Mass (ID ICP NH3) m/z 545 ($M^{+\cdot}$), 369, 310, 178. Micro analysis: found: C 74.91, H 6.63, calculated: C 74.84, H 6.47.

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3-(2-Acetylaminophenyl)-3-(4-benzylpiperazin-1-yl)-2-(phenylhydrazono)-propionic acid methyl ester (4c). Yield 58%. Brown solid. M.p. 155–157°C. R_f: 0.25 (EtOAc/PE, 60 : 40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.30 (s, 1H, NHPh), 11.19 (s, 1H, NHAc), 8.50 (dd, $J = 8.2$, 0.8 Hz, 1H), 7.35–7.24 (m, 8H), 7.20–7.15 (m, 3H), 7.03 (tt, $J = 7.4$, 1.0 Hz, 1H), 9.67 (td, $J = 7.5$, 1.2 Hz, 1H), 4.72 (s, 1H), 3.83 (s, 3H, OMe), 3.58 (s, 2H), 2.80–2.50 (brs, 8H), 2.14 (s, 3H, O═C–CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.6 (C_q, C═O), 163.9, 143.3, 138.8, 138.0, 130.5, 129.8, 129.6, 128.8, 128.7, 127.6 (CHar), 126.0, 125.3, 123.3, 123.2, 120.6, 114.7, 70.3, 63.3, 54.0, 52.2 (CH_3, OMe), 51.4, 25.9 (CH_3, O═C–Me). IR (CCl_4, CaF_2) ν (cm^{-1}): 3062, 3030, 2952, 2810, 2766, 1692, 1603,1591, 1536, 1445, 1290, 1227, 1169, 1132, 1004. Mass (ID ICP NH3) m/z 500 (MH^+), 323, 265, 178. Micro analysis: found: C 69.32, H 6.71, calculated: C 69.72, H 6.66.

4-Benzylpiperazine-1-carboxylic acid {3-[1-(4-benzylpiperazin-1-yl)-3-oxo-2-(phenylhydrazono)-butyl]-pyridin-2-yl}-amide (4d). Was obtained as a brown oil (yield 74%) after 4 hr heating using 2.2 eq. of *N*-benzylpiperazine and purified on silica gel (EtOH/CH_2Cl_2). R_f: 0.45 (EtOH/CH_2Cl_2, 5 : 95). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.14 (s, 1H, NHPh), 8.90 (s, 1H, NH–C═O), 8.46 (dd, $J = 4.7$, 1.7 Hz, 1H), 7.84 (dd, $J = 7.8$, 1.7 Hz, 1H) 7.43–7.23 (m, 14H), 7.10 (t, $J = 7.4$ Hz, 1H), 6.99 (dd, $J = 7.8$, 4.7 Hz, 1H), 4.98 (s, 1H), 3.80–3.66 (m, 4H), 3.60 (m, 2H), 3.54 (s, 2H), 2.89–2.54 (m, 8H), 2.41 (s, 3H, CH_3–C═O), 2.39–2.05 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.9, 155.1, 151.3, 149.3, 143.1, 138.4, 138.3, 137.8, 136.2, 130.1, 129.6, 129.4, 128.7, 127.7, 127.6, 125.4, 123.4, 120.5, 114.4, 63.4, 63.4, 63.0, 53.7, 53.5, 53.3, 52.9, 51.3, 24.9 (CH_3–C═O). IR (CCl_4, CaF_2) ν (cm^{-1}): 3334, 2934, 2809, 1676, 1555, 1495, 1233, 1003. Mass (ID ICP NH3) m/z 378, 296, 246, 207, 178, 95. HRMS (FAB): Calc 645.3665; Found 645.3662 (MH^+).

Cyclization Procedures

(2-Methyl-quinolin-3-yl)-phenyldiazene (5a). A solution of 1.00 g (2.07 mmol, 1.0 eq.) of Mannich adduct **4a** in HCl 6M (5 mL) was heated at 80°C for 40 mn. The mixture was cooled to 0°C, and quenched with NaOH. Et_2O was added, and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel with Et_2O/PE (30%) gave 373 mg (73%) of compound **5a** as an orange solid M.p. 95–96°C (cyclohexane). R_f: 0.70 (EtOAc/PE, 40 : 60). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (s, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 7.94–7.91 (m, 2H), 7.83 (d, $J = 8.1$ Hz,

1H), 7.66 (t, $J = 8.1$ Hz, 1H), 7.52–7.42 (m, 4H), 3.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 158.9, 153.3, 149.2, 145.1, 132.0, 130.9, 130.0, 129.6, 128.9, 127.6, 126.8, 123.6, 120.9, 22.4. IR (CCl_4, CaF_2) ν (cm^{-1}): 3065, 2960, 2923, 2859, 1612, 1585, 1453, 1411, 1369, 1184, 1147. Mass (ID ICP NH3) m/z 248 (MH^+), 190. Micro analysis: found: C 77.88, H 5.29, calculated: C 77.71, H 5.30. Analogously the following compounds were obtained:

Phenyl-(2-phenyl-quinolin-3-yl)-diazene (5b). Yield 82%. Orange solid. M.p. 118–120°C (cyclohexane). R_f: 0.80 (EtOAc/PE, 60 : 40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.27 (d, 1H, $J = 8.5$ Hz), 8.00 (d, 1H, $J = 8.0$ Hz), 7.94–7.90 (m, 4H), 7.81 (ddd, $J = 8.5$, Hz, 1H), 7.60 (ddd, $J = 8.0$, 7.1, 1.0 Hz, 1H), 7.56–7.50 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 157.9, 153.2, 149.4, 144.9, 140.0, 132.0, 131.6 (CHar), 131.2, 130.0, 129.9, 129.7, 129.3, 128.3, 122.4, 127.5, 123.9, 122.4. IR (thin film): 3057, 1715, 1613, 1586, 1545, 1484, 1450, 1416, 1369, 1247, 1186, 1152, 1131, 1070. (ID ICP NH3) m/z 310 (MH^+). Micro analysis: found: C 81.81, H 4.92, calculated: C 81.53, H 4.89.

3-Methoxy-1*H*-indole-2-carboxylic acid methyl ester (6). To a solution of HCl 1M in ethanol (9.0 mL) was added 115 mg (0.23 mmol, 1.0 eq.) of hydrazone **4c**. The resulting mixture was heated at 80°C for 40 min, then cooled to 0°C and quenched with NaOH. Et_2O was added, and the aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel with EtOAc/PE (10%) gave 39 mg (83%) of indole **6**[21] as a pale solid M.p. 102–104°C (Lit[21] m.p. 106°C). R_f: 0.45 (EtOAc/PE, 40 : 60). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H, NH), 7.80 (dd, $J = 8.2$, 0.8 Hz, 1H), 7.37–7.31 (m, 2H), 7.13 (ddd, $J = 8.2$, 5.6, 2.3 Hz, 1H), 4.17 (s, 3H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.4, 145.4, 134.8, 126.6, 120.8, 120.7, 120.4, 114.6, 112.6, 62.8, 52.4. IR (CCl_4, CaF_2) ν (cm^{-1}): 3461, 3336, 2952, 1726, 1698, 1474, 1338, 1252, 1004. Mass (ID ICP NH3) m/z 223 ($M + NH_4^+$), 206 (MH^+). Micro analysis: found: C 64.34, H 5.69, calculated: C 64.38, H 5.40.

(2-But-3-enyl-quinolin-3-yl)-phenyldiazene (5c). To a stirred solution of LDA (50 mmol, 2.0 eq.), prepared from diisopropylamine (7 mL, 50 mmol, 2.0 eq.) and *n*-BuLi (50 mmol, 2.0 eq.), in dry THF (50 mL), was added ethyl acetoacetate (3.2 ml, 25.0 mmol, 1.0 eq.) at 0°C. After 30 mn, allyl bromide (2.2 mL, 25 mmol, 1.0 eq.) was added and the resulting solution was stirred for an additional 30 mn at 0°C, then at room temperature overnight, followed by addition of acetic acid (2.8 mL, 50 mmol, 2.0 eq.), ether and water. Organic layers were extracted with ether, washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give the crude keto ester (3.9 g, 75% crude yield) as a colorless oil. To a solution of this ester in ethanol (25 mL, 1M) was added

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sodium acetate (6.2 g, 3 eq.) followed by a controlled (the temperature should be kept under 10°C) addition of a phenyl diazonium chloride water solution (prepared from 25 mmol of aniline, HCl and $NaNO_2$ in water). The resulting solution was brought to pH = 7, ethanol was evaporated under reduced pressure and the resulting solution extracted with CH_2Cl_2. After evaporation of the solvents, the crude hydrazone was diluted in MeOH and H_2O (25 mL of each), and sodium hydroxide (3.0 g, 75 mmol, 3.0 eq.) was added. The resulting solution was stirred overnight at room temperature, the solution was brought to pH 7 with HCL (1M) and the solvents were evaporated. The solid mixture was then heated under argon 1h30 at 150°C. To the crude hydrazone was added toluene (12 ml), *N*-(2-formylphenyl)-acetamide **1a** (4.1 g, 25 mmol) and *N*-benzylpiperazine (4.7 mL, 27 mmol, 1.1 eq) and the resulting mixture heated under argon at 80°C for 8 hours. After evaporation of the solvent, a 2M water solution of HCl (200 mL) was added and the mixture heated at 80°C for 2 hours. Neutralisation with NaOH, extraction with Et_2O and flash chromatography on silica gel (Et_2O/PE 10/90) gave quinoline **5d** (2.2 g, 25%). Orange solid. M.p. 72–74°C (petroleum ether). R_f: 0.35 (Et_2O/PE, 10 : 90). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 8.02 (d, $J = 8.1$ Hz, 1H), 7.93–7.89 (m, 2H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.65 (td, $J = 8.1$, 1.2 Hz, 1H), 7.50–7.40 (m, 4H, Har), 5.92 (ddt, $J = 17.0$, 10.2, 6.7 Hz, 1H), 5.02 (dd, $J = 17.0$, 1.4 Hz, 1H), 4.91 (dd, $J = 10.2$, 1.4 Hz, 1H), 3.50 (t, $J = 7.9$ Hz, 2H), 2.62–2.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 161.6, 153.3, 149.4, 144.7, 138.5, 132.0, 130.9, 130.1, 129.6, 129.2, 127.6, 126.9, 123.6, 121.1, 115.4, 35.1, 34.6. IR (CCl_4, CaF_2) ν (cm^{-1}): 3066, 2929, 1640, 1617, 1591, 1561, 1496, 1153, 1131. Mass (ID ICP NH3) m/z 287 (M), 195. Micro analysis: found: C 79.61, H 6.11, calculated: C 79.41, H 5.96.

(2-Methyl-[1,8]naphthyridin-3-yl)-phenyldiazene (5d). To a solution of 283 mg (0.439 mmol, 1.0 eq.) of Mannich adduct **4d** in 1.0 mL of toluene at room temperature was added 75 μL (0.88 mmol, 2.0 eq.) of 1,2-dibromoethane. The resulting mixture was heated to reflux under argon for 4 h. H_2O was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $NaSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel with 10% EtOAc/CH_2Cl_2, gave 23 mg (21%) of naphthyridine **5d** as a pale yellow solid along with 11% of starting material. M.p. 106–108°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (dd, $J = 4.2$, 1.9 Hz, 1H), 8.29 (dd, $J = 8.1$, 1.9 Hz, 1H), 8.26 (s, 1H), 8.02–7.99 (m, 2H), 7.60–7.55 (m, 3H), 7.48 (dd, $J = 8.1$, 4.2 Hz, 1H), 3.17 (3H, Me). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.8, 156.9, 154.5, 153.2, 145.5, 139.1, 132.4, 129.7, 123.8, 122.5, 122.0, 120.9, 22.9 (CH_3, Me). IR (CCl_4, CaF_2) ν (cm^{-1}): 2926, 2354, 1605, 1553, 1490, 1467, 1264, 1151. Mass (ID ICP NH3) m/z 249 (MH^+). HRMS (CI, CH_4) calc 249.1140, found 249.1143.

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