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Iron sulfide clusters for annulation of 2-nitrobenzonitriles and benzylamines toward synthesis of 2-aryl-4-quinazolinones

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ABSTRACT

A method for coupling of benzylamines and 2-nitrobenzonitriles is herein reported. Reactions proceeded in the presence of $FeCl_3$, elemental sulfur, urea, DABCO (1,4-diazabicyclo[2.2.2]octane) base, and DMF solvent. The conditions were compatible with both electron-donating and electron-withdrawing substituents. This tactic appears to be the first method to use a first-row transition metal to promote the synthesis of 2-aryl-4-quinazolinones from commercially available 2-nitrobenzonitriles.

Introduction

Given that the iron sulfide clusters are often found in biological studies [1,2], the catalytic systems have attracted substantial attention toward redox transformations over the last decade [3-6]. Most of those available methods do not require the use of expensive, high-molecular-weight ligands with regard to using first row transition metals for catalytic condensations. Notable examples have been devoted to the Fe/S-promoted electron transfer that is attributed to nitro (-NO_2) functionality.

Despite certain successes, general methods for synthesis of six-membered *N*-heterocycles are still rare. In our continuing efforts towards the combination of iron and main group elements for synthesis of heterocycles [7,8], herein we report our attempts to obtain 2-aryl-4-quinazolinones via an Fe/S-mediated annulation of 2-nitrobenzonitriles and benzylamines.

As one of the quintessential six-membered *N*-heterocycles, quinazolinones have been targeted with respect to a plethora of synthetic methods. Known methods often utilize *ortho*-substituted anilines [9-11]. Perhaps it would be more step-economical if the corresponding nitroarenes are used, thus pre-functionalized reduction will be thwarted. It should be noted that only one example for coupling of 2-nitrobenzonitriles and benzyl alcohols to afford quinazolinones in the presence of heterogeneous catalyst Au/TiO_2 was known [12]. We hypothesized that the use of benzylamines should be appropriate to an Fe/S-promoted six-electron transfer involving nitroarenes [13], thus affording an imine intermediate. Cyclization of the ensuing species with a proximal nitrogen nucleophile (etc. *ortho* to -NO_2 group) would afford the targeted quinazolinones. This requirement was met in 2-nitrobenzonitriles. Consequently, the method herein would present a rare example for using first-row transition metals to promote the

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transformation of 2-nitrobenzonitriles toward the synthesis of 2-aryl-4-quinazolinones.

Experimental

Chemicals were commercially obtained from Sigma Aldrich, Acros, Bidepharm, and directly used unless further noted. An exemplary experiment regarding optimization studies should be as follows: to a 5 mL vial equipped with a magnetic stir bar was charged with 2-nitrobenzonitrile 1a (44.4 mg, 0.3 mmol), benzylamine hydrochloride 2a (13.4 mg, 0.1 mmol), DABCO (11.2 mg, 0.1 mmol), elemental sulfur (6.4 mg, 0.1 mmol), $FeCl_3.6H_2O$ (13.5 mg, 0.05 mmol), urea (6.0 mg, 0.1 mmol), and DMF (0.2 mL). The vial was placed into a preheated bath at 140 °C for 16 h. Upon completion, the mixture was cooled to room temperature, charged with diphenyl ether (17 mg, 0.1 mmol), then diluted with ethyl acetate (EtOAc, 2 mL). Aliquots of the ensuing mixture was mixed with brine (1 mL), then further extracted with EtOAc (2 mL x 2). After dried over Na_2SO_4, filtered, and concentrated, the mixture was analyzed with regard to GC yield. The analyses were performed on a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 µm). For isolated yields, the crude mixture was diluted with EtOAc (10 mL). The organic phase was washed with brine (3 mL x 3), dried over Na_2SO_4, filtered, and concentrated. Further crystallization with acetone/ethanol mixture would afford 2-phenyl-4(3*H*)-quinazolinone 3aa as a light yellow solid. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 500 spectrometer using residual solvent peak as a reference.

Results and discussion

The condensation of 2-nitrobenzonitrile (1a) and benzylamine hydrochloride (2a) was firstly investigated (Figure 1). The reaction conditions were optimized with respect to bases, NH_3 surrogates, iron salts, and solvents.

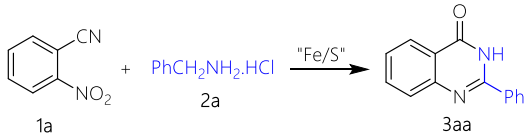

Figure 1: Fe/S clusters for annulation of 2-nitrobenzonitrile and benzylamine hydrochloride

The annulation to afford the quinazolinone 3aa was studied regarding different bases. The results are shown in Figure 2. It should be noted that no product was observed in absence of base. The condensation afforded 40% yield of 3aa if *N*-methylmorpholine (NMM) base was used. Running the reaction with an analogous base *N*,*N*'-dimethylpiperazine (NDMP) gave a nearly identical yield of 3aa. The use of 1,4-diazabicyclo[2.2.2]octane (DABCO) base was suitable, affording 3aa in 69% yield. Acyclic, tertiary amines such as *N*,*N*-diisopropylethylamine (DIPEA) were not suitable for the condensation.

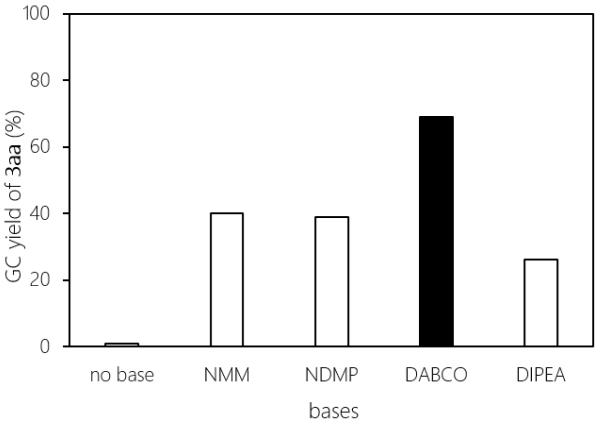

Figure 2: Effect of bases on yield of quinazolinone 3aa

During the investigation, we have noticed that a certain amount of urea was crucial for obtaining the 2-phenyl-4(3*H*)-quinazolinone 3aa in high yields. Such an effect of urea regarding the transformation of *ortho*-substituted nitroarenes, presumably as a NH_3 surrogate, has been reported [13].

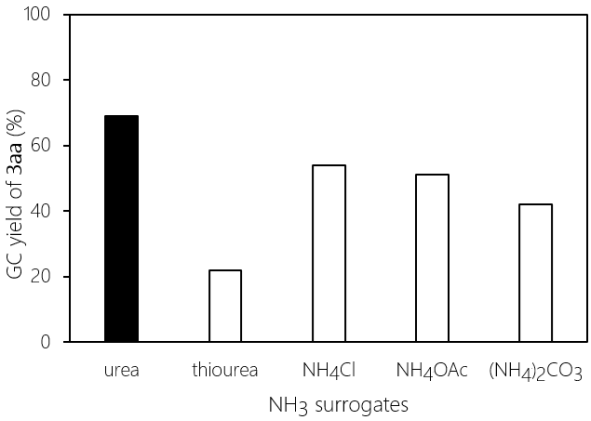

Figure 3: Effect of NH_3 surrogates on yield of quinazolinone 3aa

To examine the unique role of urea for this condensation, some ammonium salts as well as an analogous thiourea were attempted. The results are shown in Figure 3. Yields of the desired quinazolinone were moderate regardless of the counterions of ammonium salts. Meanwhile, thiourea was inferior to

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urea, as only 22% yield of 3aa was obtained. The result herein was consistent with that reported with regard to the choice of urea as a NH_3 surrogate [13]. Notably, 12% yield of 3aa was obtained if urea was omitted.

The condensation of 2-nitrobenzonitrile (1a) and benzylamine hydrochloride (2a) was next studied with respect to iron salts. The result is shown in Figure 4. Iron(III) chloride was superior to iron(III) salts of sulfate and nitrate. Use of $Fe(acac)_3$ gave 23% yield of 3aa. Iron oxides such as Fe_3O_4 and Fe_2O_3 could be used, albeit affording the desired quinazolinone in lower yields.

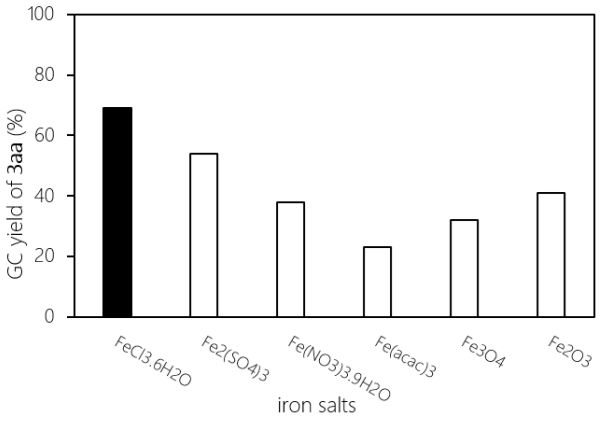

Figure 4: Effect of iron salts on yield of quinazolinone 3aa

After extensive screening of further reaction conditions, a summary of the amount of reagents was obtained as that shown in Figure 5. It should be noted that 2-nitrobenzonitrile 1a should be used in excess, with 3 equivalents, compared to benzylamine hydrochloride 2a. The annulation also utilized 50 mol% $FeCl_3.6H_2O$, 1 equivalent of DABCO, 2 equivalents of elemental sulfur, and 1 equivalent of urea. The reaction was carried out at 140 ℃ for 20 h. Running the reaction in DMF solvent (0.2 mL for 0.1 mmol of 1a) furnished 3aa in 84% yield. Other amide-based solvents such as DMAc and NMP afforded the product in lower yields. Use of DMSO solvent gave 3aa in 25% yield. As such, DMF should be the solvent of choice.

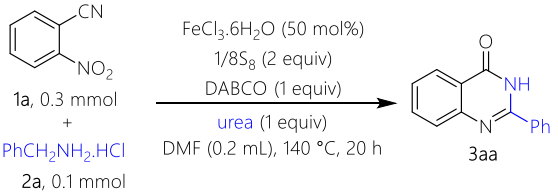

Figure 5: Standard conditions for synthesis of quinazolinone 3aa

Isolation of the desired quinazolinone 3aa was attempted in a 0.1 mmol run. The product, as a light yellow solid, was then obtained in 75% yield. The structure of 3aa was further confirmed by ^1H and ^{13}C NMR spectra. The results were as follows: ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 11.32 (s, 1H), 8.36 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.25 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.88 – 7.82 (m, 2H), 7.62 – 7.61 (m, 3H), 7.55 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 163.7, 151.7, 149.5, 134.9, 132.8, 131.7, 129.1, 128.0, 127.4, 126.8, 126.4, 120.9.

In comparison with the previous study [14], the possible mechanism was proposed as that shown in Figure 6. It should be noted that the formation of intermediates such as 4 or 5 could be observed by GC-MS. Urea was envisaged to play a pivotal role in the transformation of cyano group to amide group [13]. Meanwhile, DABCO presumably was in charge of the last oxidation to afford the desired quinazolinone [15].

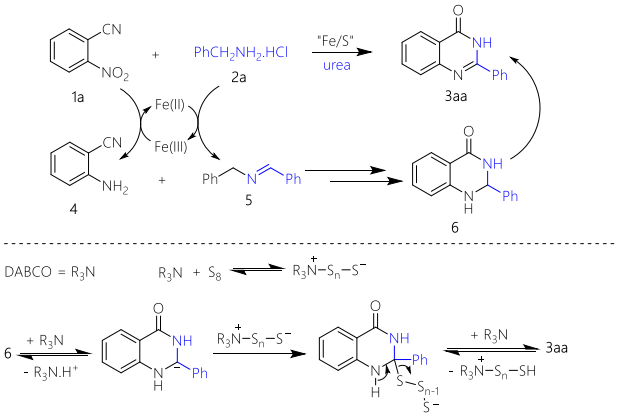

Figure 6: Possible mechanism

Scope of the reaction with respect to benzylamines was next examined. The result is shown in Table 1. It could be observed that derivatives bearing either electron-rich (entries 1, 2, and 4) or electron-poor (entry 3) substituents were competent substrates.

Reaction conditions: 2-nitrobenzonitriles (0.3 mmol), benzylamine hydrochloride (0.1 mmol), $FeCl_3.6H_2O$ (0.05 mmol), elemental sulfur (0.2 mmol), DABCO (0.1 mmol), urea (0.1 mmol), at 140 °C for 20 h. Yields are isolated yields. [a] 4-Methoxybenzyl amine (0.1 mmol) was used.

Structural identification of the 2-aryl-4(3*H*)-quinazolinones was confirmed by NMR spectra. The results are as follows:

- 7-Methyl-2-phenylquinazolin-4(3*H*)-one (entry 1, Table 1): ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 11.54 (s, 1H), 8.34 – 8.18 (m, 3H), 7.66 (s, 1H), 7.65 – 7.55 (m, 3H),

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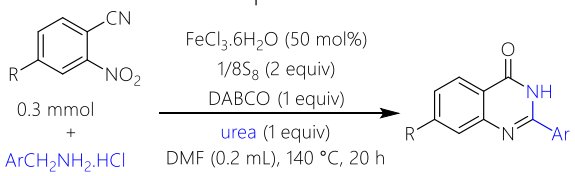
7.35 (d, *J* = 8.1 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 163.7, 151.8, 149.6, 146.0, 132.9, 131.6, 129.0, 128.4, 127.8, 127.4, 126.2, 118.4, 22.0.

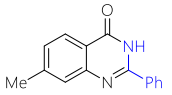
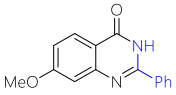
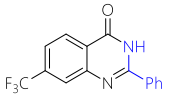
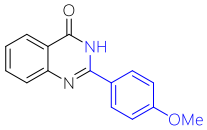
- 7-Methoxy-2-phenylquinazolin-4(3*H*)-one (entry 2, Table 1): ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.31 (s, 1H), 8.15 – 8.14 (m, 3H), 7.52 – 7.51 (m, 3H), 7.19 – 7.16 (m, 1H), 7.02 – 7.0 (m, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 165.1, 163.2, 152.5, 151.8, 132.8, 131.7, 129.1, 127.9, 127.4, 117.1, 114.3, 108.5, 55.7.

- 7-Trifluoromethoxy-2-phenylquinazolin-4(3*H*)-one (entry 3, Table 1): ^{1}H NMR (500 MHz, DMSO-*d*$_6$, ppm) δ 12.81 (s, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.23 – 8.18 (m, 2H), 8.05 (d, *J* = 1.8 Hz, 1H), 7.81 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.57 (dd, *J* = 8.3, 6.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, ppm) due to low solubility, only possible peaks are listed. δ 161.4, 154.0, 134.1, 132.3, 131.8, 128.6, 127.9, 127.7, 124.6, 123.8, 122.4, 122.15, 122.13.

- 2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (entry 4, Table 1): ^{1}H NMR (500 MHz, DMSO-*d*$_6$, ppm) δ 12.12 (s, 1H), 8.15 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.83 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.61 – 7.47 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, ppm) δ 161.7, 157.6, 152.7, 149.5, 134.8, 132.7, 130.9, 127.9, 127.1, 126.3, 123.1, 121.5, 120.9, 112.4, 56.3.

Table 1: Scope of the reaction



Entry	R	Ar	products	yield (%)
1	Me	Ph		52
2	MeO	Ph		56
3	CF_3	Ph		75
4[a]	H	4-MeC_6H_4		51

Conclusion

In conclusion, we have developed a method for Fe/S clusters promoted annulation of commercially available 2-nitrobenzonitriles and benzylamines. The conditions were compatible with functionalities such as methyl, methoxy, and trifluoromethyl groups. Our tactic herein would offer a somewhat convenient pathway to afford substituted quinazolinones from nitroarene precursors.

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