Investigation of the Reaction of *o*-Aminonitriles with Ketones: A New Modification of Friedländer Reaction and Structures of Its Products

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Abstract: A new modification of the Friedländer reaction is described and the new byproduct obtained from the reaction of *o*-aminonitriles and ketones was found to be 2,3-dihydroquinazolin-4(1*H*)-one. The mechanism probably involved the formation of an intermediate oxazine, via the Pinner reaction and its transformation into new products via the Dimroth rearrangement.

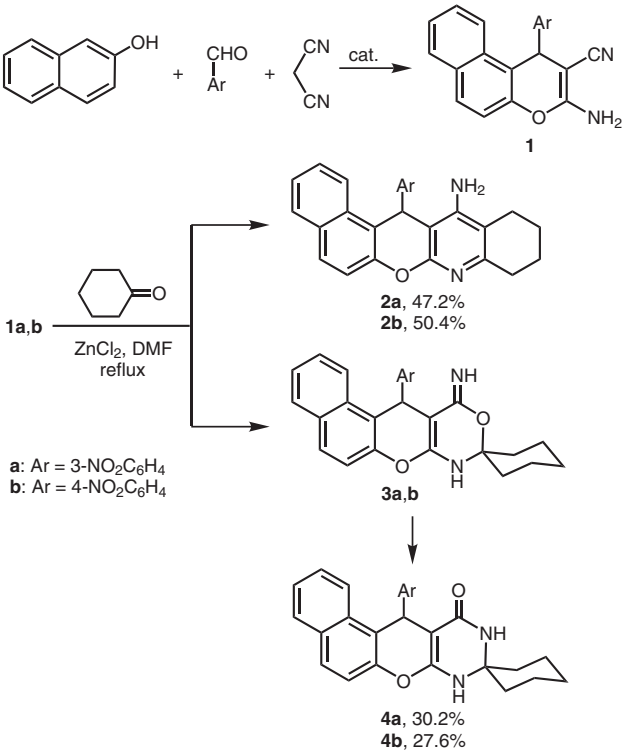
Key words: Friedländer reactions, cyclizations, spiro compounds, rearrangements, molecular recognition

Aromatic *o*-aminonitriles are versatile synthons[1] for the synthesis of quinolines,[2] pyrimidines,[3] quinazolines,[4] quinazolinones,[5] quinazolinediones,[6] and other fused nitrogen-containing heterocycles. The classical Friedländer annulation involving the cyclocondensation of an *o*-aminobenzonitrile with a carbonyl compound possessing a reactive α-methylene group is a straightforward method for the synthesis of quinoline skeleton compounds.[7]

Tacrine (9-amino-1,2,3,4-tetrahydroacridine, commercially named THA),[8] which is currently one of the major approved drugs for treatment of mild to moderate Alzheimer's disease, is obtained by Friedländer-type cyclocondensation of *o*-aminobenzonitrile with cyclohexanone. Because of the serious toxicity of THA, a large number of its derivatives and analogues have been synthesized through this kind of reaction.[9] Recently, during our synthetic study of THA derivatives, a new conversion was found that proceeded along with the normal Friedländer annulation. The structure of the new product, which was obtained from the reaction of *o*-aminonitriles and cyclohexanone under refluxing in the presence of anhydrous $ZnCl_2$, was assigned as spiropyrimidinones (Scheme 1).

A subsequent study of the reaction of aromatic *o*-aminobenzonitriles with ketones in our laboratory gave similar results. Thus, additional experiments based on both the mechanism of this new conversion and the structures of products were carried out. Herein, we report the results of our findings.

3-Amino-1-phenyl-1*H*-benzo[*f*]chromene-2-arbonitriles **1**, the starting materials for this work, were conveniently synthesized from a three-component reaction using commercial β-napathanol, aldehyde and malononitrile using a standard methodology reported by Sakurai.[10] Cyclization of **1** with cyclohexanone in DMF in the presence of anhydrous $ZnCl_2$ under reflux gave two different compounds. One was the expected quinoline **2** (tacrine analogues) obtained from the normal Friedländer condensation, and the other was the 'unexpected' spiro compound **4** obtained from the new annulation. Compounds **2** gave satisfactory analytical and spectroscopic data in agreement with their postulated structures.[11] As for the new conversion products, their structures were assigned to be spiropyrimidinone derivatives **4**, not oxazines **3**. High resolution mass spectrometry of **4a** suggested an elemental composition of $C_{26}H_{23}N_3O_4$ for its molecular ion and its IR spectrum showed two strong bands in the range of 3186–3239 cm^{-1} due to NH absorptions, and one strong band at 1659 cm^{-1} due to C=O absorption. In the ^{13}C NMR spectrum, the signals of two quaternary carbons, C2 and C4, resonated at δ = 165.5 and 67.1 ppm, respectively. And their chemical shifts were coincident with those of similar compounds in the literature (Figure 1).[12]



Scheme 1 Reaction of *o*-aminonitriles with cyclohexanone

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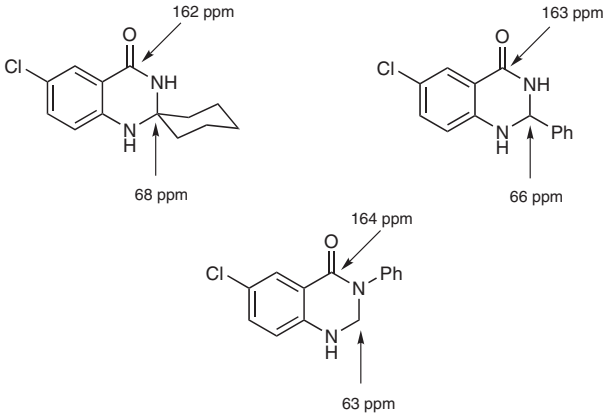


Figure 1 ^{13}C NMR spectroscopic data of known compounds

To unambiguously confirm the structure of compound **4a**, yellow single crystals of **4a** were grown from a solution of tetrahydrofuran by slow evaporation at room temperature and its X-ray diffraction data were collected.[13] The molecular structure of **4a** (Figure 2) further confirmed the spiropyrimidinone structure. Two molecules of **4a** were linked by two N(2)–H(2)…O(6) and N(5)–H(5) …O(2) hydrogen bonds, together with two tetrahydrofuran molecules to form a triclinic crystal structure. A similar structure was also found for compound **4b** (Figure 3).[13]

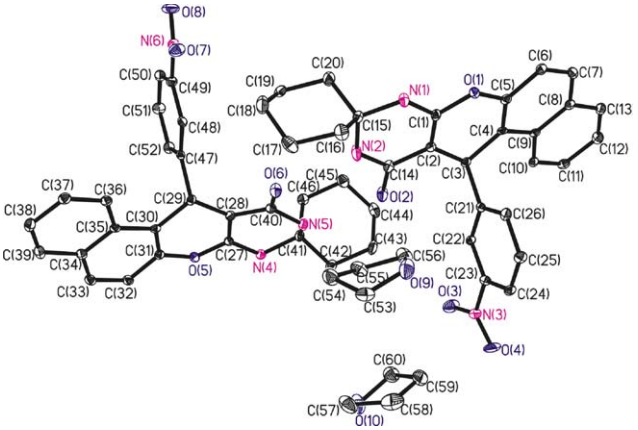
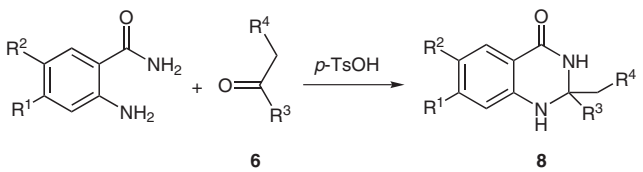


Figure 2 Crystal structure of compound **4a**

In addition, a confirmation study was carried out to further confirm our assignments of the new conversion products. Hence, compounds **8** were independently synthesized via the reaction of *o*-aminobenzamide and ketone **6** in the presence of the catalyst *p*-TsOH (Scheme 2). They exhibited the same spectroscopic data as the products prepared from the Friedländer reaction.



Scheme 2 Synthesis of compounds **8**

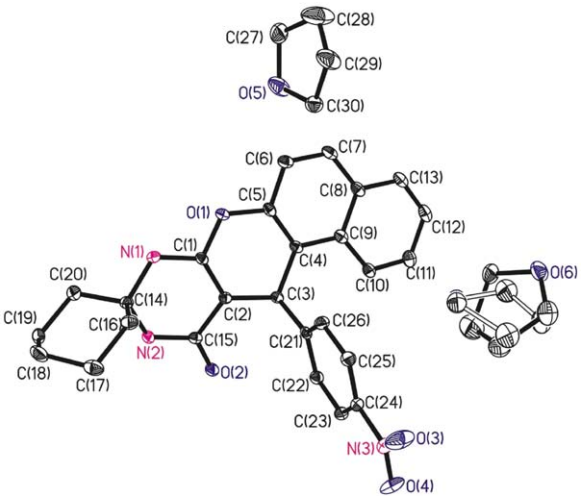
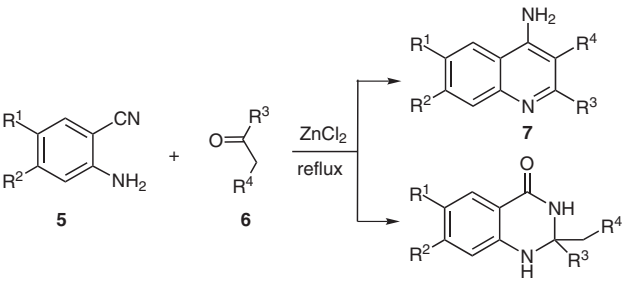


Figure 3 Crystal structure of compound **4b**

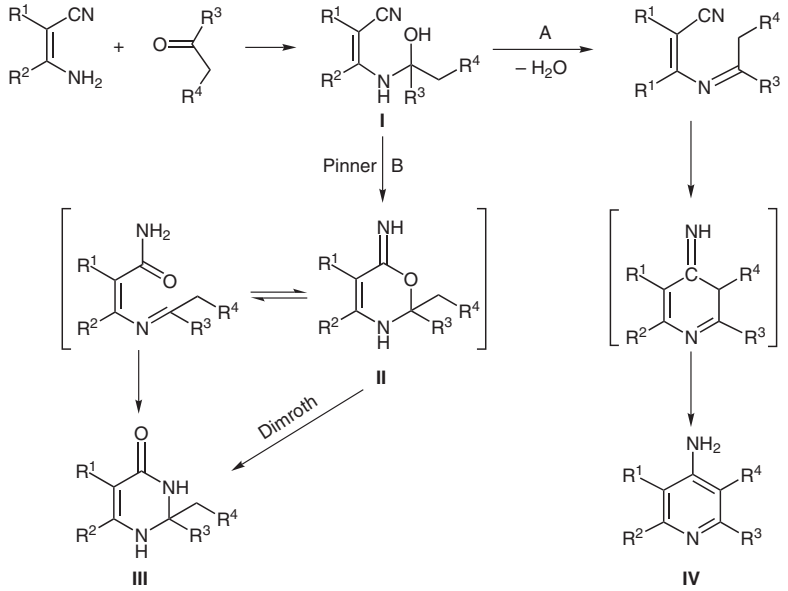
Encouraged by these results, we then reinvestigated the reaction of aromatic *o*-aminonitriles **5** with various ketones **6**. The results are summarized in Table 1. As shown in Table 1, all the data suggested a high generality of the new conversion. Various ketones reacted with substituted *o*-aminobenzonitriles in the presence of $ZnCl_2$ to give two heterocycles: a quinoline built up through the normal Friedländer reaction, and a quinazolinone produced via

Table 1 Reaction of *o*-Aminobenzonitriles with Ketones[a]



Entry	R^1	R^2	R^3, R^4	Time (h)	Yield (%)[b] of **7**	Yield (%)[b] of **8**
a	H	Cl	R^3, R^4 = $(CH_2)_4$	1.5	17	69
b	H	NO_2	R^3, R^4 = $(CH_2)_3$	1	15	71
c	H	NO_2	R^3 = Me R^4 = Et	1	12	75
d	H	NO_2	R^3 = Me R^4 = Me_2CH	1	trace	76
e	Cl	H	R^3 = Me R^4 = Et	1.5	trace	70
f	Cl	H	R^3 = Me R^4 = Me_2CH	1.5	trace	65
g	Cl	H	R^3 = Me, R^4 = 4-$MeOC_6H_4$	1.5	trace	66

[a] All reactions were carried out using **5** (6 mmol), **6** (4 mL), $ZnCl_2$ (6 mmol), and DMF (8 mL).
[b] Isolated yield.



Scheme 3 Proposed mechanism

the new conversion route. The results also showed that *o*-aminobenzonitriles **5** having strong electron-withdrawing substituents on the aromatic ring were cyclized with ketones to give the corresponding quinolines **7** in lower yields but quinazolinones **8** in better yields than other *o*-aminobenzonitriles. This probably suggests that electron-withdrawing groups on the aromatic ring facilitate the new conversion. In addition, different ketones could be employed but had not much influence on the yield of product **8**.

On the basis of these observations, a possible mechanism was proposed (Scheme 3). The formation of pyridine ring compound **IV** takes place via normal Friedländer reaction (**A**), while the new modification may proceed via a different route (**B**) after the key intermediate **I** is formed by addition of the amino group of the *o*-aminonitrile onto the carbonyl of the cyclohexanone. The hydroxyl group of intermediate **I** then attacks the nitrile group (i.e. Pinner reaction[14]) to afford a benzoxazine **II**, which subsequently rearranges to give the new conversion product **III** (Dimroth rearrangement[15]). We called this new conversion as the PDF pathway.[16]

In summary, a new modification of Friedländer annulation for the cyclization of *o*-aminonitriles with ketones in the presence of $ZnCl_2$ was described, and the structures of the conversion products were confirmed as quinazolinone derivatives. Further studies to extend the scope of this new conversion and to fully understand its mechanism are in progress.

Acknowledgment

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(11) **Typical Procedure for Preparation of Products 2 and 4**: *o*-Aminonitrile **1** (1.5 mmol), cyclohexanone (1.7 mmol), anhyd zinc chloride (1.6 mmol) and DMF (10 mL) were added into a 50-mL flask. The reaction mixture was refluxed for 2 h (monitored by TLC). Then the mixture was diluted with H_2O and titrated to pH 12–13 by 20% NaOH. After filtration, the solid was dissolved in THF, the organic phase obtained was combined with the extracted component of filtrate (using EtOAc) and evaporated in vacuo, and then chromatographed (Merck, 200–300 mesh, EtOAc–PE, 1:2) to afford product **2** and **4**.

Selected data for compounds **2**, **4** and **8**:

14-(3-Nitrophenyl)-9,10,11,12-tetrahydro-14*H*-naphtho[1′,2′:5,6]pyrano[2,3-*b*]quinolin-13-amine (2a): yellow solid; mp 287–289 °C. IR (KBr): 3450, 3364, 2935, 1640, 1607, 1573, 1523, 1445, 1348, 1232 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$): δ = 1.80–1.86 (m, 4 H, CH_2), 2.28–2.42 (m, 2 H, CH_2), 2.82 (m, 2 H, CH_2), 4.42 (s, 2 H, NH_2), 5.76 (s, 1 H, CH), 7.34–7.40 (q, *J* = 8.0 Hz, 2 H, ArH), 7.46–7.51 (m, *J* = 8.0 Hz, 2 H, ArH), 7.72 (d, *J* = 7.9 Hz, 1 H, ArH), 7.79 (t, *J* = 7.9 Hz, 2 H, ArH), 7.98 (m, *J* = 2.0, 8.0 Hz, 2 H, ArH), 8.38 (t, *J* = 2.0 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.4, 22.9, 32.4, 37.9, 99.3, 113.2, 114.9, 118.5, 121.8, 122.1 (2 × C), 124.3, 127.1, 128.9, 129.8, 129.9, 130.5, 130.8, 134.3, 145.6, 148.0, 149.0, 150.3, 154.5, 154.8. MS (ESI): *m*/*z* = 424.3 [M + H^+]. Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.60; H, 5.05; N, 9.75.

8,9,12-Trihydro-9,9-pentamethylene-12-(3-nitrophenyl)-11*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11 (10*H*)-one (4a): yellow solid; mp 275–278 °C. IR (KBr): 3187, 2937, 1659, 1630, 1527, 1349, 1227 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.22 (m, 1 H, CH_2), 1.38 (m, 4 H, CH_2), 1.66 (m, 4 H, CH_2), 1.76 (m, 1 H, CH_2), 5.76 (s, 1 H, CH), 7.23 (s, 1 H, NH), 7.43–7.52 (m, *J* = 7.8 Hz, 4 H, ArH), 7.58 (s, 1 H, NH), 7.63 (d, *J* = 7.8 Hz, 1 H, ArH), 7.96 (m, *J* = 1.8, 7.8 Hz, 4 H, ArH), 8.12 (t, *J* = 1.8 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.7, 21.1, 24.7, 34.3, 36.0, 36.3, 67.1, 81.6, 116.9, 117.0, 121.1, 121.9, 123.3, 125.0, 127.4, 128.6, 129.6, 129.9, 130.6, 130.8, 134.1, 147.6, 147.7, 148.8, 154.8, 165.5. MS (ESI): *m*/*z* = 442.3 [M + H^+]. Anal. Calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52. Found: C, 70.45; H, 5.22; N, 9.61.

6-Chloro-2,2-pentamethylene-1,2-dihydroquinazolin-4 (3*H*)-one (8a): light yellow solid; mp 232–233 °C. IR (KBr): 3358, 3173, 2934, 2855, 1643, 1612, 1493, 825 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.23–1.73 (m, 10 H, CH_2), 6.63 (dd, *J* = 2.0, 8.0 Hz, 1 H, ArH), 6.86 (d, *J* = 2.0 Hz, 1 H, ArH), 6.90 (s, 1 H, NH), 7.54 (d, *J* = 8.0 Hz, 1 H, ArH), 8.05 (s, 1 H, NH). MS (ESI): *m*/*z* (%) = 264.2 (100) [M + H^+]. Anal. Calcd for $C_{13}H_{15}ClN_2O$ (252.1): C, 62.28; H, 6.03; N, 14.14. Found: C, 62.19; H, 5.92; N, 14.11.

2,2-Butamethylene-6-nitro-1,2-dihydroquinazolin-4 (3*H*)-one (8b): mp 281–283 °C. IR (KBr): 3319, 3180, 2912, 1672, 1619, 1534, 1310 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.67–1.88 (m, 8 H, C_4H_8), 6.82 (d, *J* = 8.0 Hz, 1 H, ArH), 8.10 (dd, *J* = 2.4, 8.0 Hz, 1 H, ArH), 8.30 (s, 1 H, NH), 8.42 (d, *J* = 2.4 Hz, 1 H, ArH), 8.56 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ = 21.90 (2 × C), 40.15 (2 × C), 77.32, 112.31, 114.14, 124.11, 128.62, 136.68, 151.63, 161.21. MS (ESI): *m*/*z* (%) = 248.2 (100) [M + H^+]. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.33; H, 5.31; N, 17.08.

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(13) CCDC 660416 (**4a**) and CCDC 667600(**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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(16) This new conversion is abbreviated as PDF conversion, which means a new conversion from Pinner to Dimroth rearrangement in the Friedländer reaction.