Novel Synthesis of Bihetaryl Compounds

Nagatoshi Nishiwaki,* Keiko Yamashita, Mayumi Azuma, Tomoko Adachi, Mina Tamura, Masahiro Ariga*
Department of Chemistry, Osaka Kyoin University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan
Fax +81(729)783398; E-mail: ariga@cc.osaka-kyoiku.ac.jp
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Abstract: The ring transformation of nitropyrimidinone 1 with acetoophenone derivatives 2 affords two kinds of azaheterocyclic compounds, 4-phenylpyrimidines 3 and 3-nitro-6-phenyl-2-pyridones 4. On the basis of the relationship between electronic properties of the substituent and ratios of products, a plausible reaction mechanism is provided. Furthermore, the present reaction could be applied to heterocyclic ketones giving bihetaryl compounds.

Key words: ring transformation, nitropyridine, pyrimidine, bihetaryl compounds

The ring transformation has been employed as one of the effective methodologies for preparation of functionalized systems.1 Electron-deficient compounds having a good leaving group are often used as the substrate for this reaction, and we have studied ring transformations using dinitropyridones2 and related nitro compounds.3 Among them, 3-methyl-5-nitropyrimidin-4(3H)-one (1) is found to be an excellent substrate leading to several kinds of polyfunctionalized azaheterocyclic compounds. In reactions of nitropyrimidinone 1 with 1,3-dicarbonyl compounds under basic conditions, 2-pyridones,4 4-pyridones5 and 4-aminopyridines6 can be readily prepared. Furthermore, simple ketones are also usable in this reaction. When pyrimidinone 1 is allowed to react with ketones in the presence of ammonium acetate as the nitrogen source, two kinds of ring transformations competitively proceed to give 4,5-disubstituted pyrimidines 3 and 5,6-disubstituted 3-nitro-2-pyridones 4 (Scheme 1).7 Pyrimidinone 1 behaves as the synthetic equivalent of activated diformylamine in the former case, and behaves as that of α-nitroformylacetic in the latter case. Since both pyrimidine and 3-nitro-2-pyridone skeletons are often found in biologically active compounds and synthetic intermediates of medicines,8 synthesis of either product on demand provides a new methodology for this field.

In the present paper, the control of these ring transformations is studied, in which electronic properties of ketones are focused by use of substituted acetoophenones 2 (R = H), and a plausible reaction mechanism is newly provided. Furthermore, a new preparative method for bihetaryl compounds is represented.

The ring transformation of pyrimidinone 1 with acetoophenone 2a afforded equal amounts of pyrimidine 3a8d and pyridine 4a8 in an excellent total yield (Table 1, run 1).

When six p-substituted acetoophenones 2b–g were used as the substrate (runs 2–7), ring transformations effectively proceeded except for the reaction using 2b, which was somewhat complicated with side reactions caused by the amino group. The ratios of 3:4 were markedly varied with electronic properties of the substituent on the benzene ring. While pyridones 4 were mainly produced in reactions of 1 with electron-rich ketones 2b–e, the ratio of 3:4 was inverted in the case of electron-poor ketone 2g. 3-Nitroacetophenone (2h) showed similar reactivity to afford pyrimidine 3h13 as the major product (run 8), however no reaction was observed upon treatment of 1 with 2-nitro derivative 2i because of steric hindrance besides strong electron-withdrawing ability of the nitro group (run 9). These results reveal that diminished electron density on the carbonyl group is influential for the lower reactivity and the formation of large amounts of 3. On the other hand, all four methoxycacetophenones 2d and 2j–l effectively caused the ring transformation to afford corresponding products in good yields (runs 4 and 10–12). It is noteworthy that the reactivity of these ketones is almost the same, although 3-methoxy group only behaves as the electron-withdrawing group for the carbonyl group. Hence, the electron density on the benzene ring seems more influential rather than that on the carbonyl group in cases of electron-rich ketones. A plausible mechanism is reconsidered on the basis of above experimental results, which is different from supposed one in our previous paper (Scheme 2).7

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ring is substituted with electron-withdrawing group, the more electrophilic carbonyl group A is predominantly aminated to give enamine 6. The following intramolecular attack of the amino group occurs at the less hindered 2-position to furnish bicyclic intermediate 7 from which nitroacetamide is eliminated affording pyrimidine 3. On the other hand, the carbonyl group B is more readily aminated when electron-rich ketone is employed. The amino group of 8 attacks the carbonyl A to yield pyridone 4 via the bicyclic intermediate 9. In consideration of the result for the reaction using 3-methoxyacetophenone 2j, attractive interaction between two rings in adduct 5 might facilitate the reaction of ammonium ion with two carbonyl groups as shown in Figure 1 which results in predominant formation of pyridone 4.

Figure 1 Adduct intermediate of 1 and 2j.

The ratio of 3:4 was influenced by electronic properties of the substituent in a series of reactions of pyrimidinone 1 with acetophenones 2a–l. This observation prompted us to study application of the present reaction to heterocyclic ketones 2m–s. We considered pyrimidine derivatives would be mainly formed in reactions using electron-deficient heterocyclic ketones 2m–o, and pyridone derivative would be obtained in those using electron-sufficient het-

<table>
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<th>Run</th>
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<th>G′</th>
<th>Yield (%)</th>
<th>Ratio of 3:4</th>
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<td>l</td>
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Scheme 2 A plausible mechanism for two ring transformations.

ecroyclic ones 2p–s. Although almost equal amounts of 3m<sup>11</sup> and 4m were furnished in the reaction with 3-acetylpyridine (2m) (Table 2, run 1), pyridylpyrimidines 3n<sup>12</sup> and 3o<sup>15</sup> were predominantly formed in cases of 2n and 2o having a more electron-poor acetyl group (runs 2 and 3). When electron-sufficient heterocyclic ketones 2p–s were employed as substrates, exclusive formation of pyridones 4p–r was realized to our expectation (runs 4–9).

In summary, the possibility to control two ring transformations was shown from the viewpoint of electronic properties of ketones. Pyridylpyrimidines 3m–o and pyridones substituted with a five-membered ring 4p–s could be actually prepared as a result of application of tendency that was observed in reactions using acetophenones 2a–l. Hence, the present ring transformation provides a new methodology in synthetic chemistry of polyfunctionalized heterocyclic compounds, which are not easily prepared by alternative procedures.

The melting points were determined on a Yanaco micro-melting-points apparatus, and are uncorrected. All the reagents and solvents were commercially available and used as received. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured on a Bruker DPX-400 at 400 MHz and at 100 MHz with TMS as an internal standard. <sup>13</sup>C NMR assignments (s, d and q) were made from DEPT experiments. IR spectra were recorded on a Horiba FT-200 IR spectrometer. Elemental microanalyses were performed using a Yanaco MT-3 CHN recorder. Since pyrimidines 3 are hygroscopic, it was difficult to obtain satisfactory analytical data.
3-Methyl-5-nitro-4(3H)-pyrimidinone (1)
Pyrimidin-4(3H)-one (2.00 g, 18.2 mmol) was gradually dissolved into cold 18 M H$_2$SO$_4$ (18 mL, 324 mmol), and then fuming HNO$_3$ (d = 1.52, 2.4 mL, 57.8 mmol) was added. After heating the mixture at 100 °C for 7 h, it was poured onto ice. The pH of the mixture was adjusted to 5, and it was extracted with CHCl$_3$ (3×100 mL). The organic layer was dried (MgSO$_4$), and concentrated under reduced pressure giving crude nitropyrimidinone 1 (2.4 g) as a yellow solid. Further purification was performed with recrystallization from EtOH to afford 1 (2.19 g, 78%) as yellow needles.

Synthesis of Bihetaryl Compounds by Ring Transformation Reaction; General Procedure
To a solution of pyrimidinone 1 (155 mg, 1.0 mmol) in MeOH (20 mL) were added acetophenone derivative 2 (2.00 mmol) and NH$_2$OAc (154 mg, 2.0 mmol) and the mixture was refluxed for 2 d. During the reaction, 3-nitro-2-pyridine 4 precipitated, and the precipitates were collected by filtration. After concentration of the filtrate, the residue was extracted with benzene to give almost pure pyrimidone 3, and further purification was performed on treatment with column chromatography on silica gel.

6-(4-Acetamino phenyl)-3-nitro-2-pyridine (4b)
Red powder, mp 234–240 °C (dec.).
IR (Nujol): 3471, 3375, 1605, 1524, 1380 cm$^{-1}$.
$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ = 2.23 (s, 3 H), 7.55 (br s, 2 H), 7.69 (d, J = 5.4 Hz, 1 H), 8.08 (d, J = 8.7 Hz, 2 H), 8.74 (d, J = 5.4 Hz, 1 H), 9.24 (s, 1 H).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ = 30.6 (q), 56.0 (s), 116.3 (d), 118.8 (d), 127.6 (d), 130.1 (s), 157.6 (d), 158.6 (d), 162.0 (s), 168.7 (s).

6-(4-Acetylaminophenyl)-3-nitro-2-pyridine (4c)
Yellow powder; mp 260–268 °C (dec.).
IR (Nujol): 1678, 1556, 1377 cm$^{-1}$.
$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ = 2.09 (s, 3 H), 6.72 (br s, 1 H), 7.73 (d, J = 8.8 Hz, 2 H), 7.83 (d, J = 8.8 Hz, 2 H), 8.50 (d, J = 8.3 Hz, 1 H), 10.3 (s, 1 H), 12.9 (s, 1 H).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ = 24.1 (q), 102.0 (d), 118.7 (d), 123.8 (s), 128.2 (s), 128.6 (d), 138.3 (s), 140.3 (d), 142.4 (s), 155.1 (s), 168.9 (s).
Anal. Calcd for C$_{18}$H$_{12}$N$_3$O$_5$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.02; H, 4.18; N, 15.22.

6-(4-Methoxyphenyl)-3-nitro-2-pyridine (4d)
Yellow needles; mp 278–279 °C.
IR (Nujol): 1684, 1558, 1370 cm$^{-1}$.
$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ = 3.85 (s, 3 H), 6.73–6.75 (br s, 1 H), 7.10 (d, J = 8.9 Hz, 2 H), 7.85 (d, J = 8.9 Hz, 2 H), 8.48 (d, J = 8.2 Hz, 1 H), 14.6–14.7 (br s, 1 H).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ = 55.6 (q), 102.4 (d), 114.5 (d), 124.0 (s), 129.7 (d), 134.4 (s), 140.3 (d), 154.7 (s), 155.7 (s), 162.0 (s).
Anal. Calcd for C$_{15}$H$_{14}$N$_3$O$_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.65; H, 4.06; N, 11.23.

6-(4-Methylphenyl)-3-nitro-2-pyridine (4e)
Yellow needles; mp 195–196 °C.
IR (Nujol): 1680, 1516, 1350 cm$^{-1}$.
$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ = 2.38 (s, 3 H), 6.75 (d, J = 8.2 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H), 8.49 (d, J = 8.2 Hz, 1 H), 13.0–13.1 (br s, 1 H).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ = 21.0 (q), 102.9 (d), 127.7 (d), 129.0 (s), 129.6 (d), 135.2 (s), 140.2 (d), 141.8 (s), 154.6 (s), 155.4 (s).
Anal. Calcd for C$_{16}$H$_{16}$N$_3$O$_4$: C, 62.61; H, 4.38; N, 12.17. Found: C, 63.01; H, 4.30; N, 12.28.

6-(4-Chlorophenyl)pyrimidine (3f)
Yellow powder (eluted with EtOH; mp 221–224 °C).
IR (Nujol): 3471, 3375, 1605, 1524, 1380 cm$^{-1}$.
$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ = 7.63 (d, J = 8.5 Hz, 2 H), 8.12 (d, J = 5.4 Hz, 1 H), 8.24 (d, J = 8.5 Hz, 2 H), 8.89 (d, J = 5.4 Hz, 1 H), 9.26 (s, 1 H).
$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ = 117.1 (d), 128.7 (d), 129.0 (d), 134.7 (s), 135.1 (s), 155.8 (d), 158.7 (d), 161.3 (s).
Anal. Calcd for C$_{13}$H$_{11}$N$_3$Cl: C, 63.01; H, 3.70; N, 14.70. Found: C, 62.80; H, 3.31; N, 14.84.

6-(4-Chlorophenyl)-3-nitro-2-pyridine (4f)
Yellow powder; mp 275–280 °C (dec.).
IR (Nujol): 1687, 1558, 1353 cm$^{-1}$.

Table 2 Synthesis of Bihetaryl Compounds

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<td>n 44$^{14}$</td>
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<td>2</td>
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3-Nitro-6-(4-nitrophenyl)-2-pyridone (4g)
Yellow powder; mp 272–285 °C (dec.).

1H NMR (DMSO-d6, 400 MHz): δ = 6.82 (s, 1 H), 7.27 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 8.5 Hz, 2 H), 8.51 (d, J = 8.1 Hz, 1 H), 13.0–13.1 (br s, 1 H).

13C NMR (DMSO-d6, 100 MHz): δ = 128.9 (d), 129.6 (d), 136.3 (s), 139.8 (d), 155.3 (s). The concentration of the sample was not enough for observation of all of signals because of low solubility of 4g, and four signals were not detected.


3-Nitro-6-(4-nitrophenyl)-2-pyridone (4h)
Yellow powder; mp 241–242 °C.

1H NMR (DMSO-d6, 400 MHz): δ = 6.82–7.1 (br s, 1 H), 8.1–8.2 (br s, 2 H), 8.36 (d, J = 8.7 Hz, 2 H), 8.53 (d, J = 8.0 Hz, 1 H), 13.1–13.2 (br s, 1 H).


3-Nitro-6-(3-nitrophenyl)-2-pyridone (4h)
Yellow powder; mp 241–242 °C.

1H NMR (CDCl3, 400 MHz): δ = 7.05 (br s, 1 H), 7.85 (dd, J = 8.0, 8.1 Hz, 1 H), 8.30 (d, J = 8.1 Hz, 1 H), 8.40 (dd, J = 8.0, 1.5 Hz, 1 H), 8.53 (J = 8.1 Hz, 1 H), 8.72 (s, 1 H), 13.2 (s, 1 H).

13C NMR (DMSO-d6, 100 MHz): δ = 112.4 (d), 122.9 (d), 125.8 (d), 129.6 (s), 130.8 (d), 134.4 (d), 139.6 (s), 142.2 (s), 145.5 (s), 148.2 (d), 155.5 (s).

4-(3-Methoxyphenyl)pyrimidine (3j)
Yellow oil (eluted with CHCl3–EtOAc, 1:1).

IR (neat): 1458, 1024 cm–1.

1H NMR (CDCl3, 400 MHz): δ = 3.91 (s, 3 H), 7.06 (d, J = 5.4 Hz, 1 H), 7.4–7.7 (m, 4 H), 8.05 (d, J = 8.1 Hz, 1 H), 13.0 (br s, 1 H).

13C NMR (CDCl3, 100 MHz): δ = 55.3 (q), 112.1 (d), 117.2 (d), 117.3 (d), 119.5 (d), 130.1 (d), 137.8 (s), 157.3 (d), 158.9 (d), 160.2 (d), 163.9 (s).

6-(3-Methoxyphenyl)-3-nitro-2-pyridone (4j)
Yellow powder; mp 252–253 °C.

IR (Nujol): 1473, 1232, 1039 cm–1.

1H NMR (CDCl3, 400 MHz): δ = 3.91 (s, 3 H), 7.06 (d, J = 5.4 Hz, 1 H), 7.4–7.7 (m, 4 H), 8.05 (d, J = 8.1 Hz, 1 H), 13.0 (br s, 1 H).

13C NMR (CDCl3, 100 MHz): δ = 55.3 (q), 112.1 (d), 117.6 (s), 120.0 (d), 125.3 (d), 130.1 (d), 132.8 (s), 140.1 (d), 153.9 (s), 155.1 (s), 159.4 (s).


4-(2-Methoxyphenyl)pyrimidine (3k)
Yellow oil (eluted with CHCl3–EtOAc, 1:1).

IR (Nujol): 1473, 1232, 1039 cm–1.

1H NMR (CDCl3, 400 MHz): δ = 3.91 (s, 3 H), 7.06 (d, J = 5.4 Hz, 1 H), 7.4–7.7 (m, 4 H), 8.05 (d, J = 8.1 Hz, 1 H), 13.0 (br s, 1 H).

13C NMR (CDCl3, 100 MHz): δ = 55.3 (q), 112.1 (d), 117.6 (s), 120.0 (d), 125.3 (d), 130.1 (d), 132.8 (s), 140.1 (d), 153.9 (s), 155.1 (s), 159.4 (s).


4-(2-Methoxyphenyl)pyrimidine (3k)
Yellow oil (eluted with CHCl3–EtOAc, 1:1).

IR (Nujol): 1458, 1024 cm–1.

1H NMR (CDCl3, 400 MHz): δ = 3.91 (s, 3 H), 7.06 (d, J = 5.4 Hz, 1 H), 7.11 (dd, J = 7.5, 7.4 Hz, 1 H), 7.45 (dd, J = 7.5, 5.4, 1.7 Hz, 1 H), 7.96 (d, J = 5.4 Hz, 1 H), 7.99 (dd, J = 7.4, 1.7 Hz, 1 H), 8.70 (J = 5.3 Hz, 1 H), 9.27 (s, 1 H).

13C NMR (CDCl3, 100 MHz): δ = 55.5 (q), 111.4 (d), 121.1 (d), 121.9 (d), 125.8 (s), 130.9 (d), 131.9 (d), 155.2 (d), 157.8 (s), 158.6 (d), 162.6 (s).

Anal. Calcd for C10H7N3O3: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.75; H, 5.32; N, 14.81.
3-Nitro-6-(2-pyridyl)-2-pyridone (4o)
The presence of small amount of 4o was confirmed by 1H NMR spectroscopy.

1H NMR (DMSO-d6, 400 MHz): δ = 7.20–7.5 (br s, 1 H), 7.61 (dd, J = 7.5, 7.4 Hz, 1 H), 8.05 (dd, J = 7.8, 7.5 Hz, 1 H), 8.25 (d, J = 7.8 Hz, 1 H), 8.57 (d, J = 7.4 Hz, 1 H), 8.78 (d, J = 4.4 Hz, 1 H), 12.5 (br s, 1 H).

3-Nitro-6-(2-pyryldiyl)-2-pyridone (4p)
Brown solid; mp 210–215 °C (dec.).

IR (Nujol): 3300, 1670, 1558, 1377 cm–1.

3-Nitro-6-(3-pyryldiyl)-2-pyridone (4q)
Orange powder; mp 274–280 °C (dec.).

IR (Nujol): 3000, 1671, 1558, 1377 cm–1.

3-Nitro-6-(2-thienyl)-2-pyridone (4r)
Yellow needles; mp 250–256 °C (dec.).

IR (Nujol): 1672, 1530, 1377 cm–1.

6-(2-Furyl)-3-nitro-2-pyridone (4s)
Yellow powder; mp 241–245 °C (dec.).

IR (Nujol): 1664, 1537, 1377 cm–1.

References


