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Novel approach to arylhydrazones, the precursor for Fischer indole synthesis, via diazo esters derived from α-amino acid esters

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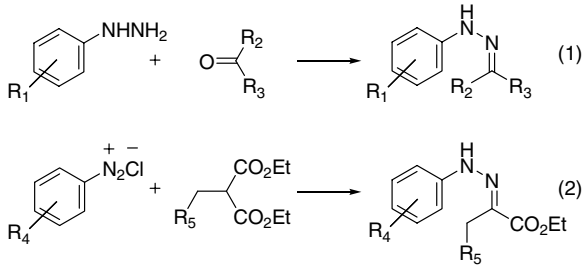
Abstract—A novel method for synthesizing arylhydrazones, the precursor for Fischer indole synthesis, using aryllithium reagents and α-diazo esters that are easily obtained from α-amino acid esters, is described.

Indole compounds have important biological activities. For example, melatonin and indole-3-propionic acid (IPA) reduce reactive oxygen species that cause cellular damage and prevent death of neurons exposed to amyloid β-proteins, the agent responsible for Alzheimer's disease.[1] Some indole derivatives function as dopamine agonists and/or selective serotonin reuptake inhibitors (SSRIs), the latter being a class of anti-depressants.[2] Acemetacin[3] and indometacin[4] are clinically used as anti-inflammatory drugs and fluvastatin sodium[5] is a well-known HMG-CoA reductase inhibitor. During the course of our investigations on the synthesis of low molecular weight compounds for use as anti-aging drugs, we developed a novel method for synthesizing arylhydrazones, the precursor for Fischer indole synthesis.

Many methods for synthesizing indole derivatives have so far been developed.[6] Although Fischer indole synthesis is a classic one, it is still a good tool for synthesizing bioactive compounds. There are two ways to prepare arylhydrazones: the condensation of carbonyl compound with arylhydrazine (Scheme 1 (1)) and the Japp–Klingemann reaction[7] between an arenediazonium salt and a malonic acid derivative (Scheme 1 (2)). We report herein a novel method for synthesizing a variety of arylhydrazones from α-diazo esters.

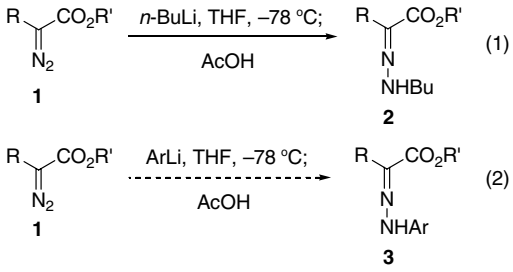
Takamura et al. reported the reaction of α-substituted-α-diazo esters **1** with some bases and found that when



Scheme 1. Methods for synthesizing arylhydrazone.

1 was treated with *n*-BuLi in THF at −78 °C, the reagent acted as a nucleophile rather than a base to give hydrazone **2**[8] (Scheme 2 (1)). Therefore, we expected that arylhydrazone **3**, the precursor for Fischer indole synthesis, would be obtained when **1** was reacted with aryllithium reagent (Scheme 2 (2)).

First, **4a**, which was obtained by the diazotization of ethyl phenylalaninate,[9] was treated with 1 equiv of



Scheme 2. Reaction of α-diazo esters with lithium reagents.

Keywords: Fischer indole synthesis; Arylhydrazone; α-Diazo ester.
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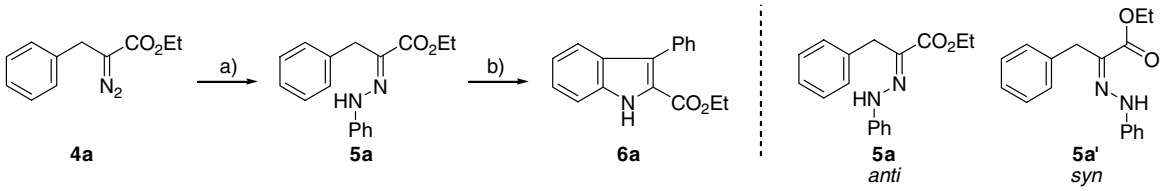
phenyllithium in THF at −68 °C for 20 min. The reaction mixture was neutralized with acetic acid and purified by silica gel column chromatography to give *anti*-hydrazone **5a** in 86% yield together with trace amounts of minor *syn* product **5a′**.[10] The stereochemistry of the hydrazone was assigned according to a reported procedure using NMR analysis.[11] As the reaction was exothermic, it was necessary to keep the reaction temperature below −60 °C to prevent decrease in yield. Grignard reagent was also used as a nucleophile for this reaction. To a cooled solution (−68 °C) of **4a** in THF was added 1 equiv of phenylmagnesium bromide. The reaction proceeded smoothly but more slowly than the phenyllithium case. The yield was almost the same (86%) and the stereochemistry of the major product was also *anti*. Next, hydrazone **5a** was subjected to Fischer indole synthesis according to the reported method.[12] Hydrazone **5a** was treated with thionyl chloride in ethanol for 40 min at 80 °C in a sealed tube, and the reaction mixture was worked up and purified by silica gel column chromatography to give the desired indole **6a** in good yield (95%)[13] (Scheme 3).

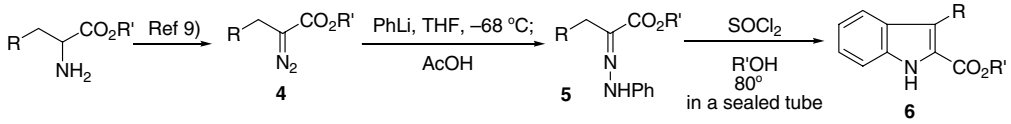
This reaction was then applied to other amino acid esters that have a methylene group adjacent to the α-carbon. The results are summarized in Table 1.

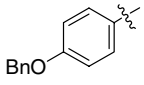
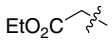
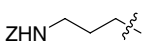
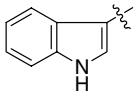
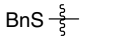
Diazo esters **4a**–**h** were easily obtained according to a known method.[9] The diazo esters were reacted with phenyllithium to give corresponding hydrazones **5a**–**h**



Scheme 3. Reagents and conditions: (a) PhLi (1.0 equiv), THF, −68 °C; AcOH, 86%; (b) $SOCl_2$, EtOH, 80 °C in a sealed tube, 95%.

Table 1. Yields of indole synthesis from α-diazo esters



Amino acid	R	R′	4	5	6
Phenylalanine		Et	**4a**, 93%	**5a**, 86% (86%)[a]	**6a**, 95%
Leucine		Et	**4b**, 94%	**5b**, 67%	**6b**, 86%[c]
Tyrosine		Me	**4c**, 97%	**5c**, 72%	**6c**, 70%
Methionine		Me	**4d**, 85%	**5d**, 79%	**6d**, 59%
Glutamic acid		Et	**4e**, 73%	**5e**, —[b]	**6e**, 47%[d]
Lysine		Me	**4f**, 89%	**5f**, 88%[b]	**6f**, 78%
Tryptophan		Me	**4g**, 51%	**5g**, 82%	—
S-Bn-Cysteine		Et	**4h**, 80%	**5h**, 97%	**6h**, 67%

[a] The result of the reaction with PhMgBr.
[b] 2 equiv of PhLi was used.
[c] The reaction was performed at 100 °C.
[d] Isolation yield for two steps.

in good yields. Even glutamic acid and lysine derivatives (**4e** and **4f**) having acidic proton in the molecule gave hydrazones **5e** and **5f**, respectively, in good yields. However, in the case of the diazo compound derived from aspartic acid ester, the reaction gave a complex mixture. From NMR analysis, the stereochemistry of all the hydrazones was confirmed to be *anti*. Hydrazones **5a**–**h** were subjected to the indole cyclization reaction. Most substrates gave the desired indoles in moderate to good yields. The cyclization reaction of **5b** hardly proceeded at 80 °C, whereas **6b** was obtained in 86% yield when **5b** was cyclized at 100 °C. Only tryptophan derivative **5g** did not give any product.

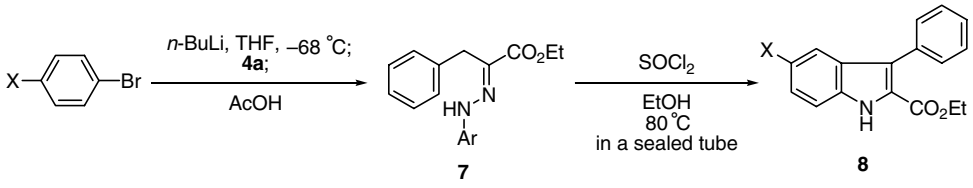
It became clear that many diazo esters derived from α-amino acid esters could be converted into the corresponding indoles. The diversity of aryllithium reagents was next examined. If aryllithium reagents generated in situ could react with diazo esters, the application of this reaction would be extended because commercially available aryllithium reagents are limited. For that purpose, 4-substituted aryl bromides (1.5 equiv) were treated with *n*-BuLi (1.5 equiv) in THF at −68 °C to produce aryllithium reagents and to the mixture was added diazo compound **4a** (1.0 equiv) (scheme in Table 2). The lithiation of aryl bromides and the subsequent nucleophilic attack of the lithium reagents on diazo compound **4a** proceeded successfully (Table 2).

The anion of α-carbon of **9′**, which was formed by the addition of aryllithium to the diazo moiety, stabilized the ester carbonyl to give enolate **9** as shown in Scheme 4, and the ester survived despite the existence of excess aryllithium species. However, when the nitrile group was substituted on the *para*-position of phenyllithium, the excess lithiated compound further reacted with the ester moiety of **7o** to give **7o′** in 28% yield together with the desired **7o** in 46% yield.

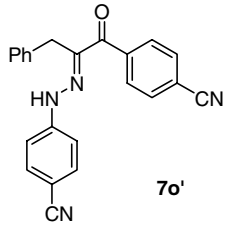
All hydrazones **7i**–**o** were converted into the corresponding indoles **8i**–**o**. The reaction time was dependent on the electron density of the aromatic ring. In most cases (**5a**–**h**, **7i**–**l**), the cyclization was completed within 1 h, but when an electron-withdrawing group (**7m**–**o**) was substituted on the aromatic ring, the reaction time became longer. In the case of **7o**, 23% of the starting material was recovered even after heating at 80 °C for 3 h.

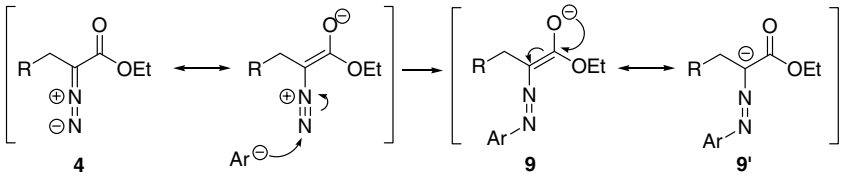
In summary, we developed a novel method for synthesizing various aryl hydrazones, the precursor for Fischer

Table 2. Yields of indole derivatives



X	7	8
OMe	**7i**, 79%	**8i**, 92%
Me	**7j**, 77%	**8j**, 82%
n-Bu	**7k**, 74%	**8k**, 92%
t-Bu	**7l**, 78%	**8l**, 83%
Br	**7m**, 69%	**8m**, 81%
CF_3	**7n**, 76%	**8n**, 76%
CN	**7o**, 46%	**8o**, 49%





Scheme 4. Reaction mechanism of diazo ester and aryllithium.

indole synthesis, from α-substituted-α-diazo esters **1**. Utilizing the diazo compounds derived from various α-amino acid esters and aromatic bromides having appropriate substituents, structurally complicated indoles can be easily synthesized in short steps by this method.

Acknowledgments

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10. Typical experimental procedure for **5**: Diazo ester **4a** (204 mg, 1 mmol) was dissolved in THF (10 ml) and stirred at −68 °C under nitrogen atmosphere. To this solution was slowly added phenyllithium (0.48 ml, 2.1 M in Bu_2O). The reaction mixture was stirred for 20 min at the same temperature, neutralized with acetic acid (0.06 ml, 1 mmol), diluted with an aqueous saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 5/1) to give **5a** as pale yellow crystals (242 mg, 86%). Recrystallization from isopropylether afforded slightly yellow crystals, mp (88–89 °C) (lit.;[14] 89 °C, lit.;[11] 92–94 °C). Data for **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.29–7.20 (m, 7H), 7.06 (m, 1H), 6.91 (m, 1H), 4.31 (q, $J = 7.2$ Hz, 2H), 3.98 (s, 2H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.33, 142.87, 135.00, 133.59, 129.08, 129.04, 127.85, 126.93, 122.04, 113.90, 61.23, 30.87, 14.20; IR (KBr) 3300, 3244, 1701, 1669 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368, found 282.1360.
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13. Typical experimental procedure for **6**: Ethanol (1.1 ml) was cooled in an ice bath and thionyl chloride (0.08 ml, 1.1 mmol) was added dropwise. This solution was poured into hydrazone **5a** (30.0 mg, 0.106 mmol) in a sealed tube. The reaction solution was stirred at 80 °C for 40 min, cooled, diluted with chloroform, and neutralized with an aqueous saturated $NaHCO_3$ solution. The separated water phase was further extracted with chloroform twice and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 9/1) to give **6a** as pale yellow crystals (26.7 mg, 95%). Recrystallization from ethanol afforded slightly yellow crystals, mp (137–138 °C) (lit.;[14] 137–138 °C). Data for **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.34 (s, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.55 (m, 2H), 7.45–7.31 (m, 5H), 7.13 (m, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 1.22 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.22, 135.78, 133.53, 130.62, 127.86, 127.67, 127.11, 125.69, 124.16, 122.74, 121.67, 120.76, 111.72, 60.88, 13.96; IR (KBr) 3344, 1668, 1252 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{15}NO_2$ (M^+) 265.1103, found 265.1103.
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