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New Entry for Synthesis of *N*-Acylhydrazones, Pyridazinones, and 1,3,4-Oxadiazin-6-ones from α-Amino Acid Esters

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Versatile electrophiles *N*-acylhydrazones are synthesized *via* diazotization, reduction, and acylation of α-amino acid esters. Reduction of diazo esters with *L*-selectride® or tributylphosphine affords the corresponding hydrazones in good yields. Both reducing agents give *anti*-hydrazones as the major product although the reactivity of each reductant is slightly different. The resulting hydrazones are acylated to give *N*-acylhydrazones, which are subjected to further reactions to give 1,3,4-oxadiazin-6-ones that serve as useful synthetic intermediates for the Diels–Alder reaction.

Key words α-diazo ester; hydrazone; *N*-acylhydrazone; 1,3,4-oxadiazin-6-one; pyridazinone

N-Acylhydrazones are utilized as versatile electrophiles in many reactions.[1] For example, the reduction of *N*-acylhydrazones gives *N′*-alkyl-*N*-acylhydrazines, and if the reduction of *N*-acylhydrazones proceeds enantio- or diastereoselectively, chiral amines are obtained after cleavage of the N–N bond. The Mannich-type reaction of *N*-acylhydrazones with ester enolates gives α-amino carbonyl compounds, and allylation of *N*-acylhydrazones gives homoallylic amines. In our series of investigations on the reactivities and utility of α-diazo esters, which are easily obtainable from corresponding α-amino acid esters,[2,3] we found that lithium reagents that act as nucleophiles simply attack the edge of the diazo group of α-diazo esters to give *N*-alkyl or *N*-arylhydrazones in good yields.[4,5] In this paper, we describe the reaction of α-diazo esters with hydride or phosphine reagent as a nucleophile to afford hydrazones. The obtained hydrazones are acylated to give *N*-acylhydrazones, which function as versatile electrophiles in many reactions, and these are followed by their derivatization to 1,3,4-oxadiazin-6-ones, which are good dienes for the Diels–Alder reaction.

Results and Discussion

The reduction of ethyl 2-diazo-3-phenylpropanoate **1a**, which was derived from phenylalanine ethyl ester as a starting material, with several hydride reagents gave hydrazone **2a**. Sodium borohydride ($NaBH_4$) reduction of **1a** gave **2a** in moderate yield, as previously reported.[5] Potassium tri-*sec*-butylborohydride and lithium tri-*sec*-butylborohydride (*K*-selectride® and *L*-selectride®) were next examined and the results are listed in Table 1. Lithium triethylborohydride (super-Hydride®) was also examined according to the literature[6] and **2a** was obtained in fairly good yield. Of these hydride reagents, *L*-selectride® gave the best yield (84%). In another trial, diisobutylaluminum hydride (DIBAL-H) was examined, but it gave only a complex mixture in both CH_2Cl_2 and toluene.

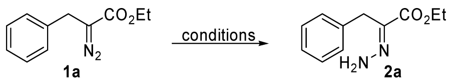
According to the Staudinger reaction, the phosphine attacks the terminal nitrogen of the azide to form iminophosphorane.[7] There are several examples of the reduction of the diazo group of β-oxo-α-diazo esters with phosphine reagents.[8—12] When diazo ester **1a** was treated with triphenylphosphine or tributylphosphine, each phosphine gave desired hydrazone **2a**, with tributylphosphine giving the best results (93%) among the reagents used (Table 1).

The reduction of **1a** with hydride reagents gave the *anti*-isomer **2a** as the sole product, while phosphines gave a small amount of *syn*-isomer **2a′** along with **2a** as the major product. These isomers are easily separated by silica gel column chromatography (the *syn*-isomer was less polar, eluent : hexane/ethyl acetate=10/1). The stereochemistry of the isomers was determined from the chemical shifts in the ^{1}H-NMR spectra.[4,13] The signal for the terminal hydrogen on the *syn*-hydrazone amine appeared at a lower field than that for the *anti*-isomer due to hydrogen bonding with the ester carbonyl group.

Next, the reduction of several diazo esters prepared according to a previously reported procedure[2—4] was examined with *L*-selectride® and tributylphosphine. In all cases, tributylphosphine gave better results, as shown in Table 2.

When diazo ester **1e**, which was derived from glutamic acid ester, was reduced with tributylphosphine, an interesting transformation was observed. Whereas the reduction of **1e** with *L*-selectride® gave usual hydrazone **2e**, that with tributylphosphine gave cyclized compound **3e** in 77% yield. The presumed mechanism of the transformation from **1e** to **3e** is shown in Fig. 1. This cyclization was not observed in the case of diazo ester **1i** derived from aspartic acid ester. Compound **3e** has a pyridazinone structure. Pyridazinone derivatives having a cyclic amino acid moiety are utilized to control the conformation of peptides.[14,15] In addition, they

Table 1. Reduction of α-Diazo Ester **1a** to Hydrazone **2a** with Hydride Reagents or Phosphine Reagents



Conditions					Yield (%)
Reagent	eq	Solv.	Temp (°C)	Time (h)	
$NaBH_4$	5.0	EtOH	0 °C to rt	5	57
K-Selectride®	1.0	THF	−68	0.5	61
L-Selectride®	1.0	THF	−68	0.5	84
Super-Hydride®	1.0	THF	−68	0.7	72
PPh_3	3.0	*i*-Pr_2O	rt	6	50
PBu_3	3.0	*i*-Pr_2O	rt	3.5	93

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exhibit bronchodilatory, cardiotonic, anti-inflammatory, and platelet aggregation activities.[16,17] Treatment of the glutamic acid derivatives with tributylphosphine could be a new approach to synthesizing this type of compound.

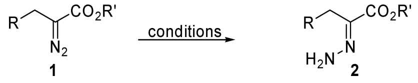
The hydrazones thus obtained were subjected to acylation. Treatment of **2a** with acetyl chloride (1.4 eq) and pyridine (1.8 eq) in THF gave desired *anti*-acetylhydrazone **4a** in 94% yield along with *syn*-isomer **4a′** in 4% yield (Fig. 2). This reaction was completed within 15 min; prolonging the reaction induced isomerization through which the yield of *syn*-isomer **4a′** was increased. Phenylacetyl chloride was also used and the results are shown in Table 3.

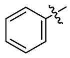
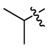
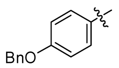
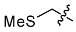
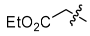
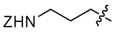
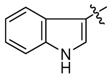
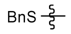
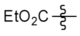
Isomerization also occurred when *anti*-acetylhydrazone **4a** was treated with anhydrous camphor sulfonic acid (CSA) in toluene at 110 °C, giving the *syn*-isomer **4a′** in 77% yield. These isomers were easily separated by silica gel column chromatography (eluent: hexane/ethyl acetate=4/1). Isomerization of hydrazone **2a** with calcium chloride gave **2a′** in 46% yield and **2a** was recovered in 50% yield. Acetylation of *syn*-hydrazone **2a′** gave *syn*-acetylhydrazone **4a′** in 95% yield.

Next, the *syn*-*N*-acylhydrazones thus obtained were converted into 1,3,4-oxadiazin-6-one derivatives, the precursors of the Diels–Alder reaction (Fig. 3).[18]

Diazo ester **1j** derived from phenylglycine methyl ester was reduced to hydrazones **2j** and **2j′** with tributylphosphine. *Anti*-hydrazone **2j** was acylated with phenylacetyl chloride and then isomerized under acidic conditions. The resulting *syn*-acylhydrazone **4j′** was hydrolyzed to *syn*-acylhydrazone carboxylic acid **5j′**. The spectral data of **5j′** are consistent with the reported one.[19] Finally, **5j′** was subjected to cyclization with DCC to give **6j**. This procedure could be applied to other diazo esters. For example, **2a** was converted into **6a**, as shown in Fig. 4. The 1,3,4-oxadiazin-6-one (**6a**) obtained seems to react with oxygen: the compounds gradually decomposed when exposed to air. Therefore, the solvents should be distilled with benzophenone ketyl, the workup should be done under nitrogen stream, and the compounds

Table 2. Reduction of Diazo Esters



Amino acid	R	R′	Prod.	*L*-Selectride® (%)	PBu$_3$ (*anti*/*syn* %)
Phenylalanine		Et	**2a**	84	93/2
Leucine		Et	**2b**	71	73
O-Bn-tyrosine		Me	**2c**	80	90
Methionine		Me	**2d**	54	88
Glutamic acid		Et	**2e**	78	77/6[a]
Lysine		Me	**2f**	81	93/6
Tryptophan		Me	**2g**	80	95/2
S-Bn-cysteine		Et	**2h**	63	93/3
Aspartic acid		Et	**2i**	69	80

[a] Product **3e** was obtained in 77% yield along with *syn*-hydrazone **2e′** in 6% yield.

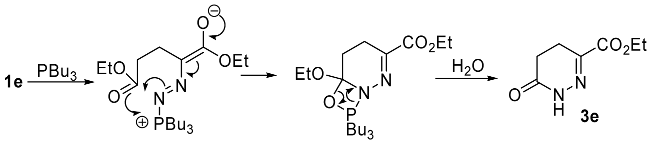


Fig. 1. Presumed Mechanism of Transformation from **1e** to **3e**

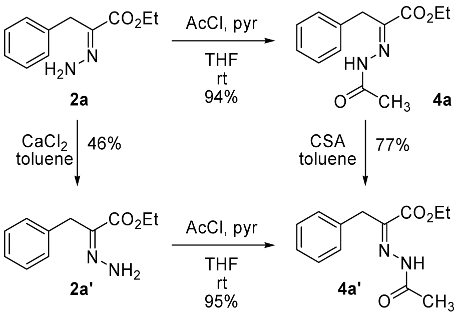
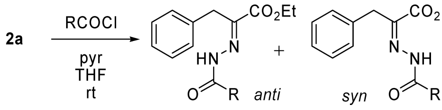


Fig. 2. Acetylation and Isomerization of *anti*-Hydrazone **2a** to *syn*-Acetylhydrazone **4a′**

Table 3. Acylation of Hydrazone **2a**



R	Time (min)	Yield (%)	
		anti	*syn*
Me	10	94	4
PhCH$_2$	60	94	5

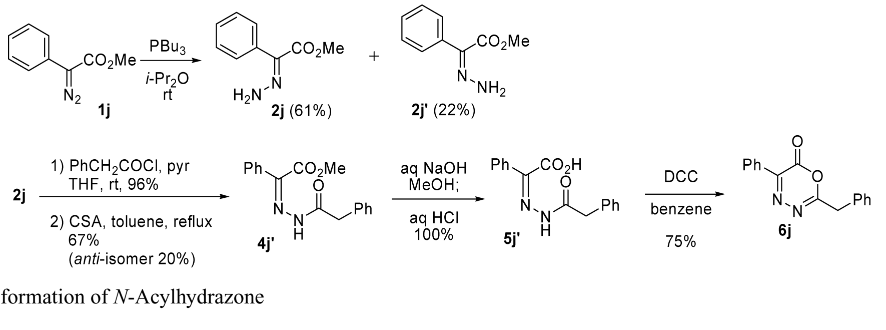


Fig. 3. Example of Transformation of *N*-Acylhydrazone

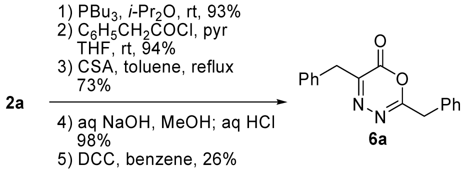


Fig. 4. Synthesis of **6a**

must be stored in a freezer filled with nitrogen.

Conclusion

In summary, we presented here a novel synthetic route to *N*-acylhydrazones, pyridazinone compounds, and 1,3,4-oxadiazin-6-ones from α-amino acid esters.

Experimental

^{1}H and ^{13}C spectra were recorded on a JEOL JNM-ECX-400 spectrometer. Chemical shifts were expressed in δ ppm with tetramethylsilane as an internal reference for ^{1}H-NMR and the carbon signal of the corresponding solvent for ^{13}C-NMR. IR spectra were recorded on a JASCO FT/IR-4100. Mass spectra were recorded on a JEOL JMS-GCmateII. Melting points were measured on a Yanaco MP-500P micro melting point apparatus and are not corrected. THF was distilled from benzophenone ketyl just prior to use.

General Procedure for Reduction with *L*-Selectride® Diazo ester **1a** (204 mg, 1 mmol) was dissolved in THF (9 ml) and stirred at −68 °C under nitrogen atmosphere. To this solution was slowly added *L*-selectride® (1.0 ml, 1.0 M in THF). The reaction mixture was stirred for 20 min at the same temperature, diluted with saturated NH$_4$Cl solution and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 2/1) to give **2a** as pale yellow crystals (172.9 mg, 84%).

General Procedure for Reduction with Tributylphosphine Diazo ester **1a** (427 mg, 2.09 mmol) was dissolved in i-Pr$_2$O (2.1 ml) and stirred at rt under nitrogen atmosphere. To this solution was added tributylphosphine (1.57 ml, 6.27 mmol). The reaction mixture was stirred for 150 min at the same temperature, diluted with ethyl acetate (30 ml) and washed with saturated NaHCO$_3$ solution and brine. The organic phase was dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 10/1 to 1/1) to give **2a** (401.5 mg, 93%) and **2a′** (10.1 mg, 2%).

Spectral Data of **2a** and **2a′**: **2a**: mp 49—50 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 7.32—7.20 (m, 5H), 6.05 (s, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.90 (s, 2H), 1.37 (t, J=7.2 Hz, 3H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 165.16, 137.98, 134.82, 128.96, 128.00, 126.85, 61.40, 30.39, 14.29; IR (KBr) 3386, 1698, 1559 cm^{-1}; HR-MS (EI) Calcd for C$_{11}$H$_{14}$N$_2$O$_2$ (M$^+$) 206.1055, Found 206.1053; **2a′**: mp 67—68 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 8.17 (s, 2H), 7.29—7.18 (m, 5H), 4.14 (q, J=7.2 Hz, 2H), 3.70 (s, 2H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 162.73, 139.23, 130.38, 128.84, 128.13, 126.07, 60.20, 39.48, 13.98; IR (KBr) 3455, 1693, 1676, 1576, 1540, 1211 cm^{-1}; HR-MS (EI) Calcd for C$_{11}$H$_{14}$N$_2$O$_2$ (M$^+$) 206.1055, Found 206.1065.

Spectral Data of **3e**: mp 133—134 °C; ^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 9.10 (s, 1H), 4.36 (q, J=7.2 Hz, 2H), 2.93 (t, J=8.4 Hz, 2H), 2.57 (t, J=8.4 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 166.88, 162.94, 142.89, 62.20, 25.69, 21.02, 14.11; IR (KBr) 1713, 1624, 1288, 1202 cm^{-1}; HR-MS (EI) Calcd for C$_7$H$_{10}$N$_2$O$_3$ (M$^+$) 170.0691, Found 170.0692.

General Procedure for 1,3,4-Oxadiazine-6-ones To a stirred solution of **5j′** (1.13 g, 4.0 mmol) in absolute benzene (20 ml) was added a solution of DCC (1.07 g, 5.2 mmol) in absolute benzene (2 ml) under N$_2$, and the whole mixture was stirred at rt for 90 min and then filtered. The filtrate and washings were evaporated to dryness to give a crystalline yellow solid, which was triturated with absolute ether to give **6j** (0.79 g, 2.98 mmol, 75%) as light yellow needles.

Spectral Data of **6j**: ^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 8.20 (m, 2H), 7.54—7.30 (m, 8H), 4.01 (s, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 161.34, 153.33, 148.11, 132.79, 132.06, 130.62, 129.31, 129.02, 129.00, 128.55, 127.93, 39.52; IR (KBr) 1766, 1578, 1135 cm^{-1}; HR-MS (EI) Calcd for C$_{16}$H$_{12}$N$_2$O$_2$ (M$^+$) 264.0899, Found 264.0931.

Spectral Data of **6a**: ^{1}H-NMR (CDCl$_3$, 400 MHz) δ: 7.37—7.24 (m, 10H), 4.07 (s, 2H), 3.89 (s, 2H); ^{13}C-NMR (CDCl$_3$, 100 MHz) δ: 161.40, 157.58, 148.71, 134.16, 132.69, 129.52, 129.28, 128.93, 128.70, 127.86, 127.37, 39.48, 37.60; IR (KBr) 1766, 1606, 1494, 1453, 1419 cm^{-1}; HR-MS (EI) Calcd for C$_{17}$H$_{14}$N$_2$O$_2$ (M$^+$) 278.1055, Found 278.1066.

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