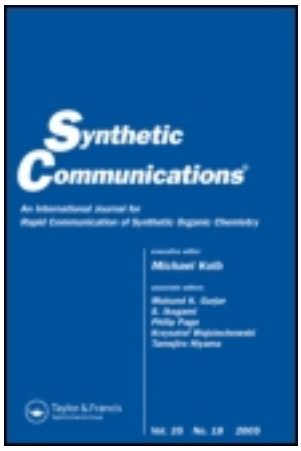

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Syntheses and Characterizations of Imidazole-4,5-diacylhydrazones

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Syntheses and Characterizations of Imidazole-4,5-diacylhydrazones

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ABSTRACT

Tartaric acid was transformed into imidazole-4,5-dicarboxylic acids **2**, then via esterification, hydrazinolysis, condensation with aromatic aldehyde in glacial acetic acid to furnish seven title compounds in about 24% overall yield.

Key Words: Tartaric acid; Imidazole-4,5-dicarboxylic acid; Imidazole-4,5-diacylhydrazone.

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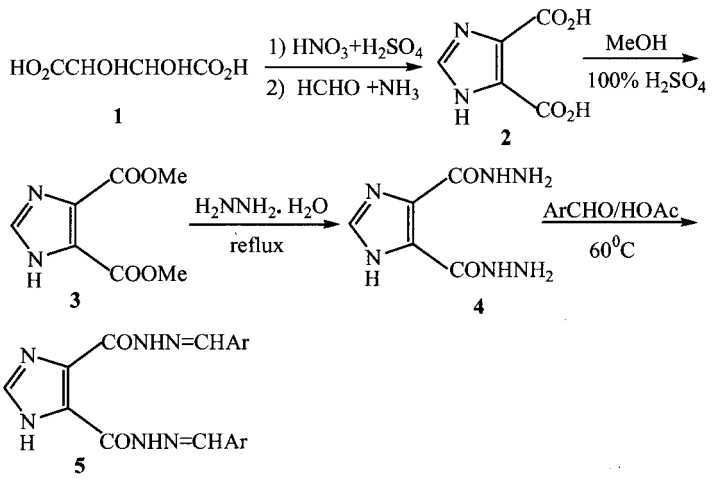
Imidazoles are widely distributed in nature, and known as ''biocatalyst'' and ''biological ligand.'' They play a vital role in life activities.[1] Schiff bases containing polyfunctional groups have not only produced stable metal complexes, but these ligands and their metal complexes also have a significant role in the domains of stereochemistry, model systems of biochemical interest, drugs, herbicides and fungicides, catalysis, stabilizers, polymers, pigments and dyes, etc.[2] One type of Schiff base, acylhydrazones and their metal complexes possess excellent insecticidal,[3] antimicrobial[3–7] and genotoxic activities.[7] Most acylhydrazones were synthesized by extensive reflux of a solution of acylhydrazine and an aromatic aldehyde. Recently we reported a practical and convenient synthesis of thiophene-2,5-diacylhydrazones. The key step is the reaction of thiophene-2,5-dicarboxylic acid dihydrazide with an aromatic aldehyde in glacial acetic acid for several minutes.[8] Here we wish to report a fast and efficient synthesis of imidazole-4,5-diacylhydrazones **5** (Sch. 1).

The molar ratio between ester and hydrazine reagents affected the formation of imidazole-4,5-dicarboxylic acid dihydrazide **(4)**. At a molar ratio of 1:4, the reaction was incomplete even after 6 h. In our experiments, we used a 1:8 (ester:hydrazine ratio).



1 **2** **3** **4** **5**

5a Ar = Ph-, **5b** Ar = *o*-HOC_6H_4, **5c** Ar = furyl, **5d** Ar = *m*-$O_2NC_6H_4$, **5e** Ar = PhCH=CH-, **5f** Ar = *p*-$CH_3OC_6H_4$, **5g** Ar = 3-CH_3O-4-HO-C_6H_4

Scheme 1.

The condensation of imidazole-4,5-dicarboxylic acid dihydrazide **(4)** with aromatic aldehyde in glacial acetic acid was completed in several minutes. This fast reaction is supposed due to the differences in solubility between acylhydrazine **4** and the reaction intermediates (amino alcohols), and between the intermediates and diacylhydrazones **5**.[8] Acetic acid is a poor solvent for **4** and most diacylhydrazones **5** (besides **5a** which is partially soluble in hot acetic acid). With the addition of aldehyde, dihydrazide **4** reacted with it and formed the soluble intermediate. By quickly eliminating two molecules of water from amino alcohols, diacylhydrazone **5** were precipitated.

In summary, we have described a fast and efficient synthesis for imidazole-4,5-diacylhydrazones **5**: condensation of imidazole-4,5-dicarboxylic acid dihydrazide with aromatic aldehydes in glacial acetic acid for several minutes. This method offers high yield with mild reaction conditions, short reaction time, and simple work-up.

EXPERIMENTAL

General Considerations

All reagents were obtained from commercial suppliers. Liquid reagents and solvents were purified by standard procedures shortly before use. Melting points were obtained by using a WRS-IA melting point apparatus and uncorrected.

All elemental analyses were performed by Carlo Erba model 1106 analyzer. ^{1}H NMR spectra were recorded on a Varian INOVA 500 MHz spectrometer in DMSO-d_6. Infrared spectra were recorded on a Nicolet ESP 360 FT-IR spectrometer as KBr pellets.

1H-Imidazole-4,5-dicarboxylic acid (2) was synthesized according to the literature,[9] white solid, m.p. 278–280°C (decomposition), yield 40% (lit. 43–48%, m.p. 280°C).

Dimethyl 1H-imidazole-4,5-dicarboxylate (3) was synthesized with modified procedures of literature.[10] After neutralizing with calcium carbonate, the mixture was filtered, the filtrate was put into the refrigerator and allowed to stand overnight. The mixture was filtered, the solid was dried and recrystallized from methanol to furnish a white solid, m.p. 200–202°C, yield 70%. (lit. 200–203°C, yield 72%[10]).

1H-Imidazole-4,5-dicarboxylic acid dihydrazide (4). To a flask containing 1.5 g (8.2 mmol) of dimethyl 1H-imidazole-4,5-dicarboxylate

28 mL of methanol was added. The mixture was refluxed until all imidazole-4,5-dicarboxylate had dissolved. 2.96 mL of 80% hydrazine hydrate (76.6 mmol) was added, the mixture was heated to reflux for 3 h, cooled to r.t. and filtered. The crude product was recrystallized from water to give 1.75 g (95%) of **4** as a white solid, m.p. > 300°C.

Imidazole-4,5-diacylhydrazone (5). To a flask were added 0.184 g (1 mmol) of imidazole-4,5-dicarboxylic acid dihydrazide and 10 mL of glacial acetic acid. The stirred mixture was heated in a water bath. Then, 2 mmol of aromatic aldehyde was added at 60°C. With the addition of aldehyde, dihydrazide **4** dissolved and a clear solution was obtained before a solid precipitated very quickly. When the reaction was complete (several minutes, monitored by TLC), the mixture was cooled and filtered. The solid was washed with ethanol, then with water until the washings were neutral (for **5a** and **5d**, first washed with hexane and acetic acid, then washed with ethanol and water). The crude product was purified by recrystallization from DMF-water (**5a** also can be recrystallized from glacial acetic acid), then dried (**5c** and **5d** are easily oxidized, therefore must be dried and kept under vacuum and room temperature).

DMF and DMSO are good solvents for compound **5**.

There are three characteristic absorption bands in IR of acylhydrazone **5**. The bands at 1656–1667 cm^{-1}, 1554–1561 cm^{-1} and 1255–1302 cm^{-1} are assigned as $\nu_{C=O}$ (amide I), $\nu_{C=N}$ (amide II) and $\nu_{C\text{-}N}$ (amide III) modes respectively. The imidazole ring-skeletal vibration (~1550 cm^{-1}) overlaps with amide II. Two protons at ~14.2 and ~12.0 ppm were assigned as –CONH–; two protons at ~8.50 ppm were assigned as –N=CH–, because there are cis and trans isomers in acylhydrazones and $\delta_{cis} > \delta_{trans}$. The proton at 8.0 ppm was assigned as 2-imidazole-H, a characteristic peak of imidazole nucleus.

5a. White solid, yield 86%, m.p. > 300°C, R_f (AcOEt/EtOH = 1:1) = 0.86. Anal. calcd. for $C_{19}H_{16}O_2N_6$ C, 63.33; H, 4.44; N, 23.33. Found: C, 63.27; H, 4.35; N, 23.23. IR (ν): 3130 (s, N-H), 1661 (s, C=O), 1556 (s, mixed C=N and imidazole ring-skeletal vibration), 1291 (m, C-N). ^{1}H NMR: δ 14.29 (1H, s, –CO-NH–), 13.67 (1H, s, 1-imidazole-H), 12.07 (1H, s, –CO-NH–), 8.67 (1H, s, –N=CH–), 8.45 (1H, s, –N=CH–), 8.03 (1H, s, 2-imidazole-H), 7.4–7.8 (10H, m, Ph).

5b. Pale yellow crystal, yield >99%, m.p. > 300°C, R_f (HOAc/AcOEt = 1:20) = 0.70. Anal. calcd. for $C_{19}H_{16}O_4N_6$ C, 58.16; H, 4.08; N, 21.43. Found: C, 57.93; H, 3.92; N, 21.28. IR (ν): 3150 (s, N-H), 1657 (s, C=O), 1558 (s, mixed C=N and imidazole ring-skeletal vibration), 1276 (m, C-N). ^{1}H NMR δ 14.27 (1H, s, –CO-NH–), 13.71 (1H, s, 1-imidazole-H), 12.40 (1H, s, –CO-NH–), 11.11, 11.05 (2H,

s, –OH), 8.89 (1H, s, –N=CH–), 8.61 (1H, s, –N=CH–), 8.06 (1H, s, 2-imidazole-H), 6.9–7.7 (8H, m, Ph).

5c. Pale yellow crystal, yield 83%, m.p. 277–279°C (decomposition), R_f (HOAc/AcOEt = 1:20) = 0.65. Anal. calcd. for $C_{15}H_{12}O_4N_6$ C, 52.94; H, 3.53; N, 24.71. Found: C, 52.76; H, 3.43; N, 24.63. IR (ν) 3131 (s, N-H), 1661 (s, C=O), 1558 (s, mixed C=N and imidazole ring-skeletal vibration), 1282 (m, C-N). ^{1}H NMR δ 14.29 (1H, s, –CO-NH–), 13.66 (1H, s, 1-imidazole-H), 12.12 (1H, s, –CO-NH–), 8.56 (1H, s, –N=CH–), 8.28 (1H, s, –N=CH–), 8.6-7.9 (6H, m, furan), 8.01 (1H, s, 2-imidazole-H).

5d. White crystal, yield 90%, m.p. > 300°C, R_f (HOAc/AcOEt = 1:20) = 0.66. Anal. calcd. for $C_{19}H_{14}O_6N_8$ C, 50.67; H, 3.11; N, 24.89. Found: C, 50.52; H, 3.09; N, 24.73. IR (ν) 3251 (m, N-H), 1667 (s, C=O), 1559 (s, mixed C=N and imidazole ring-skeletal vibration), 1299 (m, C-N). ^{1}H NMR δ 14.25 (1H, s, –CO-NH–), 13.74 (1H, s, 1-imidazole-H), 12.40 (1H, s, –CO-NH–), 8.72 (1H, s, –N=CH–), 8.60 (1H, s, –N=CH–), 8.06 (1H, s, 2-imidazole-H), 7.7–8.3 (8H, m, Ph).

5e. Yellow crystal, yield 96%, m.p. 274–275°C (decomposition). R_f (HOAc/EtOAc = 1:20) = 0.72. Anal. calcd. for $C_{23}H_{20}O_2N_6$ C, 66.99; H, 4.85; N, 20.39. Found: 66.72; H, 4.61; N, 20.17. IR (ν) 3269 (m, N-H), 1659 (s, C=O), 1554 (s, mixed C=N and imidazole ring-skeletal vibration), 1302 (m, C-N). ^{1}H NMR δ 14.24 (1H, s, –CO-NH–), 13.65 (1H, s, 1-imidazole-H), 12.00 (1H, s, –CO-NH–), 8.46 (1H, d, J = 8 Hz, –N=CH–), 8.15 (1H, d, J = 9 Hz, –N=CH–), 8.01 (1H, s, 2-imidazole-H), 7.0–7.7 (14H, m, PhCH=CH–).

5f. Yellow crystal, yield 91%, m.p. 263°C. R_f (HOAc/EtOAc = 1:20) = 0.64. Anal. calcd. for $C_{21}H_{20}O_4N_6$ C, 60.00; H, 4.76; N, 20.00. Found: C, 59.84; H, 4.63; N, 19.72. IR (ν) 3123 (m, N-H), 1657 (s, C=O), 1561 (s, mixed C=N and imidazole ring-skeletal vibration), 1255 (s, C-N). ^{1}H NMR δ 14.24 (1H, s, –CO-NH–), 13.60 (1H, s, 1-imidazole-H), 11.91 (1H, s, CO-NH-), 8.61 (1H, s, –N=CH–), 8.35 (1H, s, –N=CH–), 8.06 (1H, s, 2-imidazole-H), 7.0–8.0 (8H, m, Ph), 3.83 (6H, s, –OCH_3).

5g. Yellow crystal, yield 92%, m.p. > 300°C. R_f (HOAc/EtOAc) = 0.78. Anal. calcd. for $C_{21}H_{20}O_6N_6$ C, 55.75; H, 4.42; N, 18.58. Found: C, 55.66; H, 4.37; N, 18.47. IR (ν) 3173 (s, N-H), 1656 (s, C=O), 1559 (s, mixed C=N and imidazole ring-skeletal vibration), 1283 (s, C-N). ^{1}H NMR δ 14.20 (1H, s, –CO-NH–), 13.56 (1H, s, 1-imidazole-H), 11.83 (1H, s, –CO-NH–), 9.50, 9.46 (2H, s, –OH), 8.54 (1H, s, –N=CH–), 8.28 (1H, s, –N=CH–), 8.07 (1H, s, 2-imidazole-H), 6.9–7.4 (6H, m, Ar), 3.84 (6H, s, –OCH_3).

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