Condensation Reactions of Aryl Acyloins with Ureas in Ethylene Glycol

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Received August 4, 1994

4,5-Diaryl-4-imidazolin-2-ones were prepared in good yield by heating aryl acyloins with ureas in ethylene glycol for 0.5-2 hours. 4,4'-Dimethoxybenzoin and 2,2'-pyridoin gave 4-oxazolin-2-one derivatives in addition to 4-imidazolin-2-ones.

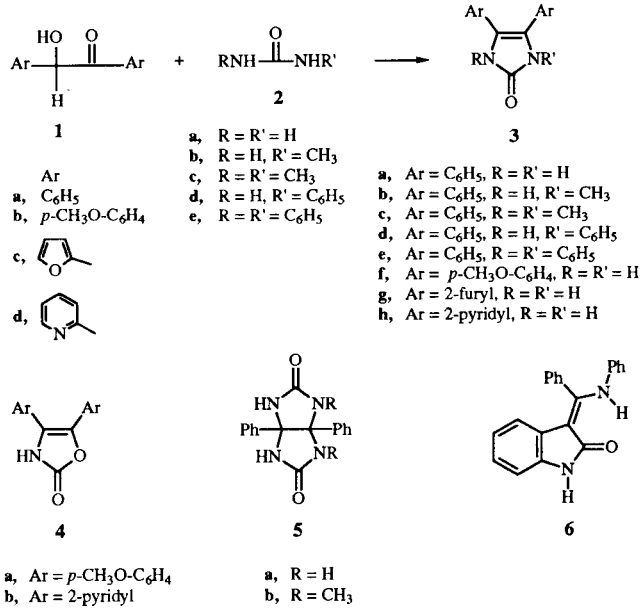
J. Heterocyclic Chem., **31**, 1653 (1994).

Condensation reactions of acyloins **1** with ureas **2** seem to be the most straight-forward procedure for preparation of 4-imidazolin-2-one **3** derivatives [1,2]. Typical reaction conditions are refluxing a mixture of an acyloin and urea in acetic acid for 6-7 hours. However, the work-up procedure is lengthy and the yield seems to be poor when the reaction scale is smaller (0.01 mole instead of 1 mole). Alternatively, a mixture of **1a**, **2a**, and sodium bisulfate was heated at 150-170° to give **3a** in 83% yield [3]. In contrast, heating **1a** with **2a** and 85% formic acid for 3 hours at 180-185° gave 4,5-diphenylimidazole in 65% yield [4]. Butler and Hussain reported the formation of 3a,7a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (**5a**) when benzoin (**1a**) and urea (**2a**) were refluxed in benzene in the presence of trifluoroacetic acid [5]. The bicyclic compound **5a** was also obtained when benzil was treated under similar reaction conditions [6]. Therefore, the formation of **5a** was attributed to easy oxidation of benzoin to benzil. A similar bicyclic compound, **5b**, was formed when **1a** and methylurea (**2b**) reacted under similar conditions. 1,3-Dimethylurea (**2c**), however, did not react with **1a** [5]. Phenylurea (**2d**) reacted with **1a** in acetic acid to form **3d** (43%) and an indoline compound **6** (yield not given) [7]. However, formation of only **3d** (21%) was reported in another case [8]. Heating 2,2'-pyridoin (**1d**) and **2a** in acetic acid for 6 hours gave both a 4-imidazolin-2-one (**3h**, 7%) and a 4-oxazolin-2-one **4b** (17%) [9].

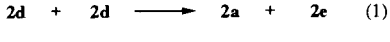
In the course of our extensive investigation of the reactions of 5-membered heterocyclic aromatic compounds we attempted to prepare 4,5-bis(2-furyl)-4-imidazolin-2-one (**3g**) by following the typical procedure [1,2], but only 17% of the desired product could be isolated. This led us to re-examine the reactions of benzoins and ureas and we now report a much more convenient procedure for the synthesis of 4-imidazolin-2-one derivatives **3**.

Results and Discussion.

The key feature of our method is the use of ethylene glycol as the solvent and heating at 180° for 0.5-2 hours. The products usually precipitated upon cooling the reaction mixtures. The solvent and unreacted urea could be removed easily by washing with water and the unreacted benzoin could be removed readily by washing with ether. In case no precipitate formed, water was added and then the mixture was extracted with chloroform. The products were recrystallized from ethanol and the yields were 70-98%.



In contrast to the report of the formation of **3d** and **6** from **1a** and **2d** in acetic acid [7], **3a** was isolated as the major product (70%) and **2e** as the minor one (25%) when **1a** and **2d** were heated in ethylene glycol at 180° for 1 hour. Formation of **3a** and **2e** could be explained if a disproportionation reaction takes place as shown in Equation 1.

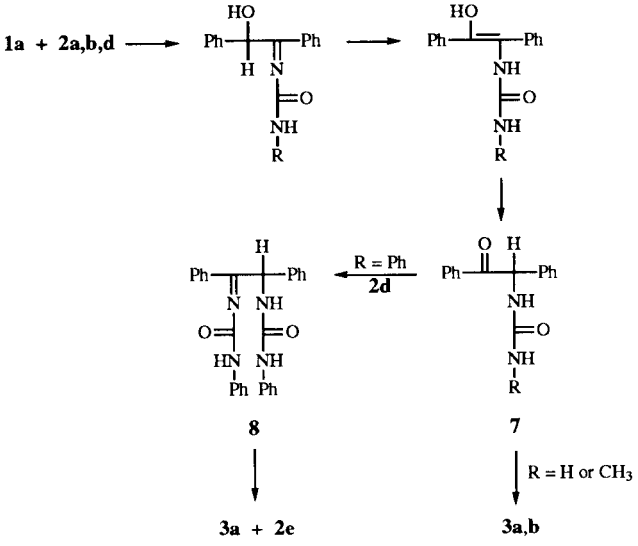


However, **2d** did not change even after it was heated at reflux temperature in ethylene glycol for 5 hours. Therefore, formation of **2a** in the course of the reaction of **1a** and **2d** can be ruled out.

Methylurea (**2b**), on the other hand, gave only **3b** under similar conditions. These contrasting results from **2b** and **2d** may be explained by a mechanism such as shown in Scheme 1. Once an intermediate such as **7** is formed it may undergo intramolecular cyclization when R is

methyl. However, the cyclization may not be feasible if R is phenyl for steric and electronic reasons. In this case, **7** will react with a second molecule of **2d** to form **8**. A disproportionation reaction could take place with **8**, giving **3a** and **2e**.

Scheme 1

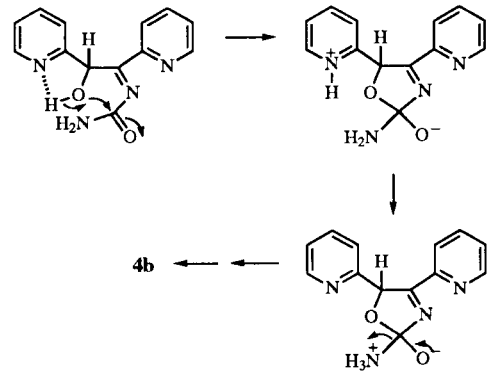


4,4'-Dimethoxybenzoin gave a mixture of **3f** and an oxazolone compound **4a**. The nmr spectrum of the crude product indicated a compositional ratio of 9:1. Recrystallization of the mixture from ethanol gave **3f** (75%), which was analytically pure, but the filtrate contained a mixture of **3f** and **4a**. It was not easy to purify **4a** by fractional crystallization, so a column chromatography method was used to obtain an analytical sample of **4a**. Formation of **4a** may have been possible because of the electron-releasing effect of the *p*-methoxy group, making the α-oxygen atom of **7** more electron-rich, which would facilitate attack of the oxygen atom at the amide carbon atom.

The yield of **3g** was only 17% when 2,2'-furoin (**1c**) was heated at reflux with **2a** in acetic acid for 7 hours. The low yield may be due to the decomposition of **1c** in acidic solution. On the other hand, heating **1c** and **2a** in ethylene glycol for 2 hours gave a nearly quantitative yield of **3g**. The structure of **3g** could be readily established by its spectral and elemental analyses. The symmetric nature of the structure was confirmed by three groups of one-proton peaks in ^{1}H nmr spectrum at δ 6.58, 6.79, and 7.72 and a one-proton singlet at δ 10.55, which correspond to the 3-, 4-, and 5-furyl-H and one N-H, respectively. The presence of only five peaks at δ 107.6, 110.3, 112.1, 142.8 and 144.6 ppm and one at 153.8 ppm (N-CO-N) in the ^{13}C nmr spectrum also supports the symmetrically substituted 4-imidazolin-2-one structure.

Unlike the cases of benzoin and 2,2'-furoin, the reaction mixture of 2,2'-pyridoin (**1d**) and urea (**2a**) in ethylene glycol after heating at reflux temperature for 1 hour did not give any precipitate. The deep red solution was mixed with water and then extracted with chloroform. Compounds **3h** and **4b** were isolated from the extract in 30% and 45% yields, respectively. It is interesting to confirm the formation of an oxazolinone-type skeleton which had previously been formed only under acetic acid conditions [5]. Apparently, the major product of this condensation reaction is a 4-oxazolin-2-one, regardless of the reaction medium. The basic nitrogen of the pyridine may assist the attack of the α-hydroxyl oxygen on the carbonyl carbon atom by pulling off the hydroxyl proton as shown in Scheme 2. A similar type of assistance cannot be expected with furoin because the oxygen atom in the furan ring is not sufficiently basic.

Scheme 2



EXPERIMENTAL

Melting points were determined on a MEL-TEMP apparatus and uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer and the ultraviolet-visible (uv) spectra were recorded on a Hitachi U-3200 double beam spectrometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Bruker 300 MHz spectrometer, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Electron-impact mass spectra (ms) were obtained by Kratos MS 2S RFA spectrometer. Elemental analyses were performed by the M-H-W Laboratories, Phoenix, AZ.

Materials.

Aryl acyloins **1a-d**, ureas **2a-e**, and ethylene glycol were all commercial materials and used as delivered.

4,5-Diphenyl-4-imidazolin-2-one (**3a**).

An Illustrative Procedure.

A mixture of **1a** (1.0 g, 4.7 mmoles) and **2a** (1.0 g, 17 mmoles) in ethylene glycol (10 ml) was heated in an oil bath at 180° for 1 hour with stirring. After cooling to room temperature and standing for a few hours the solid was collected by filtration and washed with diethyl ether. The pale yellow solid was recrys-

tallized from ethanol to give 0.78 g (70%) of **3a** as a white solid, mp >287° (lit [10] 323°); ir (potassium bromide): 3200 (m, NH), 3030 (m, C=C-H), 1683 (vs, C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.20-7.37 (m, 5 H, C_6H_5), 10.53 (s, 1 H, NH); uv (ethanol): λ_{max} (ε) 307 (13200), 277 (3500), 260 (12100), 255 infl (11200), 247 (12300), 242 infl (12000); ms: m/z (%) 236 (100, M^+), 104 (58), 77 (30).

Anal. Calcd. for $C_{15}H_{12}N_2O$ (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.22; H, 5.08; N, 11.90.

1-Methyl-4,5-diphenyl-4-indolin-2-one (**3b**).

This compound had mp >285° (lit [11] 290°); ir (potassium bromide): 3120 (w, NH), 3025 (m, C=C-H), 2900 (m, CH_3), 1662 (s, C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.94 (s, 3 H, NCH_3), 7.11-7.47 (m, 10 H, C_6H_5), 10.79 (s, 1H, NH); uv (ethanol): λ_{max} (ε) 301 (11900), 283 infl (9500), 248 (7300), 218 infl (17500); ms: m/z (%) 250 (100, M^+), 245 (15), 104 (70), 77 (60).

Anal. Calcd. for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.74; H, 5.82; N, 10.95.

1,3-Dimethyl-4,5-diphenyl-4-imidazolin-2-one (**3c**).

This compound had mp 185-187°; ir (potassium bromide): 3056 (m, C=C-H), 2937 (m, CH_3), 1680 (vs, C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.22 (s, 3 H, NCH_3), 7.24-7.29 (m, 5 H, C_6H_5); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 28.9, 121.1, 127.8, 128.4, 129.1, 130.0, 153.6; uv (ethanol): λ_{max} (ε) 295 (9400), 284 infl (9000), 242 infl (5500); ms: m/z (%) 264 (100, M^+), 249 (15, M^+ - CH_3), 207 (15), 118 (18), 77 (15).

Anal. Calcd. for $C_{17}H_{16}N_2O$ (264.33): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.30; H, 6.33; N, 10.79.

4,5-Bis(4-methoxyphenyl)-4-imidazolin-2-one (**3f**) and 4,5-Bis(4-methoxyphenyl)-4-oxazolin-2-one (**4a**).

A mixture of **1b** (1.0 g, 4.5 mmoles) and **2a** (1.0 g, 17 mmoles) in ethylene glycol (5 ml) was heated at 180° and then cooled to room temperature. The precipitate was collected by filtration and recrystallized from ethanol to give **3f** (0.75 g, 75%), mp 150-152°; ir (potassium bromide): 3300-2700 (ms, NH), 1680 (vs, C=O), 1600 (s, C=C), 1240 (s), 1180 (s), 1030 (s), 835 (s) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.73 (s, 3 H, OCH_3), an AB pattern centered at 6.87 and 7.22 (4 H, C_6H_4, J = 8.50 Hz), 10.50 (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 55.6, 114.5, 117.2, 123.3, 128.7, 154.5, 158.7; uv (ethanol): λ_{max} (ε) 312 (18200), 280 (5300), 260 (14400); ms: m/z (%) 296 (100, M^+), 281 (25), 134 (55), 107 (20).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (296.33): C, 68.91; H, 5.44; N, 9.45: Found: C, 68.80; H, 5.50; N, 9.27.

The filtrate was purified by flash chromatography (silica gel, benzene) to give 0.05 g (5%) of **4a** as a white solid, mp 203-205°; ir (potassium bromide): 3350 (ms, NH), 1710 (vs, C=O) 1120 (s, C-O), 810 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.77 (s, 3 H) and 3.85 (s, 3 H, OCH_3), two AB patterns centered at 6.92, 7.10, 7.48 and 7.97 (total 8 H, C_6H_4, J = 8.50 Hz), 11.80 (s, 1 H, NH); uv (ethanol): λ_{max} (ε) 325 (19000), 270 (8700), 256 infl (13800); ms: m/z (%) 297 (60), 297 (100), 134 (77), 107 (50).

Anal. Calcd. for $C_{17}H_{15}NO_4$ (297.31): C, 68.68; H, 5.09; N, 4.71: Found: C, 68.84; H, 4.83; N, 4.95.

4,5-Bis(2-furyl)-4-imidazolin-2-one (**3g**).

This compound had mp 283°; ir (potassium bromide): 3420 (br, NH), 3128 (m), 1693 (vs, C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.58 (dd, 1 H, 4'-H, J = 1.84 and 3.42 Hz), 6.79 (d, 1 H, 3'-H, J = 3.34 Hz), 7.72 (d, 1 H, 5'-H, J = 1.75 Hz), 10.55 (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 107.6, 110.3, 112.1, 142.8, 144.6, 153.8; uv (ethanol): λ_{max} (ε) 344 infl (12300), 331 (17100), 324 infl (16300), 264 infl (3800), 237 (21200); ms: m/z (%) 216 (100, M^+), 187 (30), 95 (25), 94 (25).

Anal. Calcd. for $C_{11}H_8N_2O_3$ (216.20): C, 61.11; H, 3.73; N, 12.96. Found: C, 61.12; H, 4.03; N, 12.82.

4,5-Bis(2-pyridyl)-4-imidazolin-2-one (**3h**) and 4,5-Di(2-pyridyl)-4-oxazolin-2-one (**4b**).

A mixture of **1d** (1.0 g, 4.7 mmoles) and **2a** (1.0 g, 17 mmoles) in ethylene glycol (10 ml) was heated at 180° for 1 hour. After cooling, the dark red solution was added to 30 ml of water and extracted with chloroform (3 x 30 ml). The extract was evaporated to dryness and the residue was crystallized from ethanol to give 0.35 g of **4b** (35%), mp 215-216° (lit [5] 215°); ir (potassium bromide): 3245 (m, NH), 1725 (vs, C=O), 1633 (ms), 1546 (s), 1507 (vs), 755 (m) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.71 (dd, 1 H, J = 6.84 and 6.90 Hz), 7.28 (dd, 1 H, J = 6.50 and 4.77 Hz), 7.48 (m, 1 H), 7.93 (m, 1 H), 8.06 (d, 1 H, J = 7.17 Hz), 8.31 (apparent d, 2 H, J = 7.71 Hz), and 8.67 (d, 1 H, J = 4.17 Hz, all pyridyl-H), 11.71 (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 112.6, 118.4, 118.5, 122.1, 122.1, 124.7, 125.6, 131.4, 137.2, 147.9, 147.9, 160.0; uv (ethanol): λ_{max} (ε) 447 (23200), 309 infl (1200), 273 (8600), 262 infl (8100), 237 infl (9500); ms: m/z (%) 239 (80, M^+), 105 (58), 79 (100).

Anal. Calcd. for $C_{13}H_9N_3O_2$ (239.24): C, 65.27; H, 3.79; N, 17.56: Found: C, 65.73; H, 4.00; N, 17.55.

The filtrate gave **3h** (0.20 g, 20%) after two recrystallizations from ethanol, mp 245-246° (lit [9] 241.5°); ir (potassium bromide): 3300 (m, NH), 1685 (vs, C=O), 1600 (s), 780 (m) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.29 (s, 1 H, 3'-H), 7.73 (d, 1 H, 5'-H, J = 6.50 Hz), 7.76 (d, 1 H, 4'-H, J = 6.50 Hz), and 8.56 (s, 1 H, 6'-H, all pyridyl-H), 10.56 (s, 1 H, NH); ^{13}C nmr 121.1, 122.5, 122.6, 137.1, 149.1, 149.3, 153.7; uv (ethanol): λ_{max} (ε) 337 (20700), 272 infl (8000), 230 infl (18200), 217 (20900); ms: m/z (%) 239 (5), 238 (12, M^+), 237 (27), 195 (20), 106 (100), 78 (20).

Anal. Calcd. for $C_{13}H_{10}N_4O$ (238.25): C, 65.54; H, 4.23; N, 23.52: Found: C, 65.41; H, 4.50; N, 23.27.

Acknowledgments.

We thank professor Wayland E. Noland and Miss Carolyn Choo of the University of Minnesota for helpful discussion and manuscript preparation. We gratefully acknowledge the Ministry of Education for financial support through a Basic Research Center Program (BSRI-90-303) and the Research Center for New Biomaterials in Agriculture.

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