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Ultrasound-assisted synthesis of azlactone and its reactions with nucleophiles

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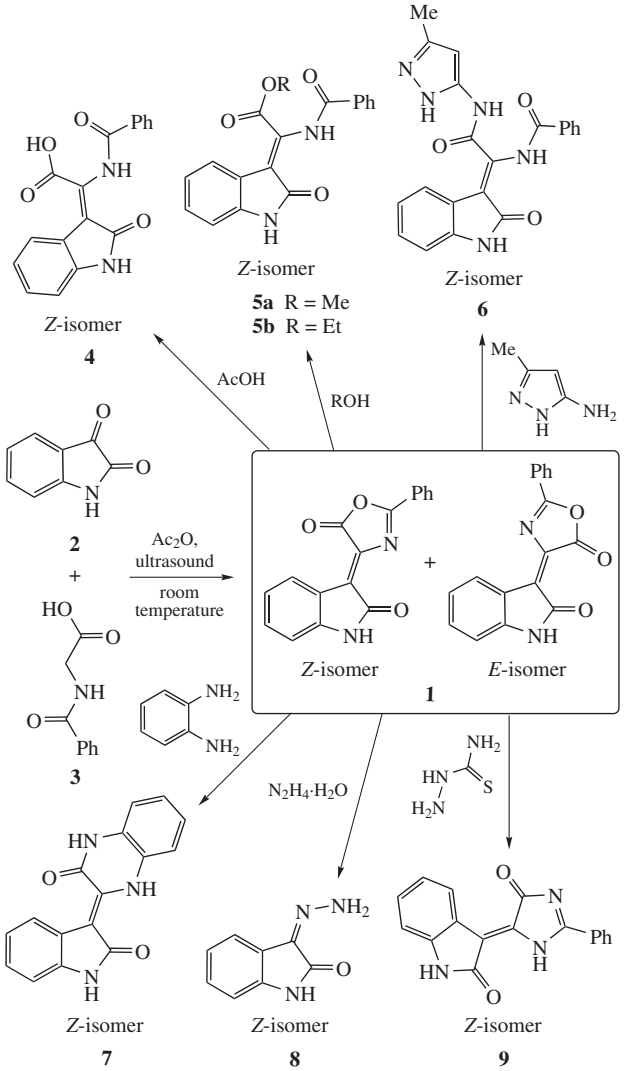
4-(2-Oxoindolin-3-ylidene)-2-phenyl-5(4*H*)-oxazolone (azlactone) was synthesized as a mixture of *E*- and *Z*-isomers by ultrasound-assisted Erlenmeyer–Plöchl reaction between isatin and *N*-benzoylglycine. Treatment of azlactone with nucleophiles causes opening of its oxazolone moiety.

4-Substituted 2-phenyl-5-(4)-oxazolones (azlactones) are highly demanded building blocks for the synthesis of various biologically active compounds, including potential anti-cancer agents.[1] The most important route for their preparation is the Erlenmeyer–Plöchl reaction[2] comprising condensation of carbonyl compounds with hippuric acid (*N*-benzoylglycine). Thermal[3] or microwave[4] activation of this condensation are reported. On the other hand, indolin-2-one moiety is one of the most important structure subunits in the modern medicinal chemistry.[5–7]

Surprisingly, 2,3-dioxindole (isatin) is not studied enough as the carbonyl counterpart in the Erlenmeyer–Plöchl reaction. Therefore, the structure and chemical properties of the thus obtained product should be clarified.[8]

Herein, we report on the efficient synthesis of azlactone **1** and some its reactions leading to its oxazolone ring transformations (Scheme 1). Previously, the synthesis of *N*-acetyl derivative of compound **1** under thermal activation was reported.[8] However, after deacetylation the yield of azlactone **1** did not exceed 45%. In our experiments, sonication of the reactants **2** and **3** raised the yield of product **1** to 95%.† This procedure is the first successful application of ultrasound to promote Erlenmeyer–Plöchl reaction (see Scheme 1).

Due to the exocyclic double bond between 3-position of oxindole moiety and 4-position of oxazolone ring, structure **1** can be either 4-*Z* or 4-*E* isomer. In our experiments, it was formed in a ratio of 2:1, respectively. This isomerism was also observed when thermal activation was applied to the reactants **2** + **3**. However, this fact was not noted earlier. The preferred formation of *Z*-isomer can be explained by the mutual repulsion of the oxindole and oxazolone moieties carbonyl groups in the *E*-isomer mole-



Scheme 1

† Hippuric acid **3** (9.49 g, 53 mmol) and isatin **2** (7.8 g, 53 mmol) in 25 ml of acetic anhydride were sonicated at 40 °C for 90 min (TLC control). After completion of the reaction, the mixture was filtered and the precipitate was washed with 100 ml of sodium bicarbonate solution (5%) and recrystallized from acetonitrile to afford product **1** as a mixture of *Z*- and *E*-isomers (2:1). Reddish brown powder, 14.6 g (95%), mp 224–226 °C (lit.,[8] mp 235 °C). MS (EI, 70 eV) *m*/*z*: 290 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.79 (s, 0.31H), 10.68 (s, 0.69H), 8.66 (d, 0.31H, *J* 7.9 Hz), 8.42 (d, 0.69H, *J* 7.7 Hz), 8.27–8.17 (m, 2×0.69H), 8.13 (d, 2×0.31H, *J* 7.7 Hz), 7.79–7.75 (m, 1H), 7.68–7.63 (m, 2H), 7.39–7.34 (m, 1H), 7.09–7.01 (m, 1H), 6.85 (t, 1H, *J* 7.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.0, 166.7, 165.9, 165.5, 160.8, 159.1, 145.2, 145.0, 141.8, 139.7, 135.0, 134.7, 133.8, 132.8, 129.9, 129.1, 129.0, 128.8, 127.9, 125.2, 125.1, 123.0, 122.9, 122.1, 121.9, 110.3, 110.1. Found (%): C, 70.37; H, 3.39; N, 9.61. Calc. for $C_{17}H_{10}N_2O_3$ (%): C, 70.34; H, 3.47; N, 9.65.

cule of azlactone **1**. This hypothesis was confirmed by computational methods.‡

(*Z*)-2-Benzamido-2-(2-oxoindolin-3-ylidene)acetic acid **4** and its esters **5a**,**b** were formed from azlactone **1** *via* oxazolone moiety cleavage by heating in acetic acid or alkanols, respectively (Scheme 1).

The formation of azolopyrimidinones was described for reaction of 4-benzylidene azlactone with aminoazoles.[9] However, only heterocyclic amides of *N*-benzoyl-2-(2-oxoindolin-3-ylidene)-2-aminoacetic acid can be formed. In our investigations, reaction of azlactone **1** with 5-amino-3-methylpyrazole was provided as an example, amide **6** being obtained in a good yield (similarly to the case with anilines[10]).

Compounds **4**, **5a**,**b** and **6** were formed only as *Z*-isomers from a mixture *E*,*Z*-**1**.§ Apparently, these *Z*-isomers were stabilized by intramolecular hydrogen bond between the carbonyl oxygen in the oxindole moiety and the benzamide NH group.

3-(2-Oxoindolin-3-ylidene)-3,4-dihydroquinoxalin-2(1*H*)-one **7** identical to the described previously[11] was formed in the reaction of 1,2-diaminobenzene with azlactone **1**. In this case, the benzamide moiety in the molecule **1** was cleaved. Product **7** was obtained in excellent yield as the *Z*-isomer only. Similar transformation was proposed earlier for the classical Erlenmeyer reaction of 4-benzylidene azlactone.[12]

Treatment of lactone **1** with hydrazine-hydrate gave (*Z*)-3-hydrazonoindolin-2-one **8** as the product of oxazolone ring opening. When thiosemicarbazide was used as the nucleophile, formal replacement of cycle oxygen by nitrogen was observed, and (*Z*)-3-[4-oxo-2-phenyl-1*H*-imidazol-5(4*H*)-ylidene]indolin-2-one **9** was isolated in a moderate yield.

In summary, the ultrasound-assisted Erlenmeyer–Plöchl reaction between hippuric acid and isatin made azlactone available, which may promote its further studying in the fields of heterocyclic and medicinal chemistry.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.09.016.

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‡ For the computational data, see Online Supplementary Materials.

§ *A typical procedure of oxazolone ring opening.* A solution of 200 mg (0.67 mmol) of compound **1** in 10 ml of acetic acid or corresponding alcohol was refluxed for 1 h, then the solid product was filtered off.

For **4**: yellow needles, 195 mg (92%), mp > 300 °C. MS (EI, 70 eV) *m*/*z*: 308 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.86 (s, 1H), 11.28 (s, 1H), 8.01 (d, 2H, *J* 7.7 Hz), 7.68 (d, 1H, *J* 7.7 Hz), 7.61 (t, 2H, *J* 7.7 Hz), 7.29 (d, 1H, *J* 7.4 Hz), 7.14 (t, 1H, *J* 7.4 Hz), 7.08–6.92 (m, 2H), 3.32 (s, 1H, H_2O exchange). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.7, 167.4, 162.0, 139.7, 137.1, 134.0, 133.3, 130.2, 129.0, 128.7, 128.4, 121.9, 121.2, 118.8, 110.9. Found (%): C, 66.27; H, 3.90; N, 9.01. Calc. for $C_{17}H_{12}N_2O_4$ (%): C, 66.23; H, 3.92; N, 9.09.

For **5a**: yellow needles, 180 mg (78%), mp 217–218 °C. MS (EI, 70 eV) *m*/*z*: 322 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.70 (s, 1H), 11.21 (s, 1H), 7.96 (d, 2H, *J* 7.4 Hz), 7.65 (d, 1H, *J* 7.4 Hz), 7.58 (t, 2H, *J* 7.4 Hz), 7.25 (d, 1H, *J* 7.4 Hz), 7.17 (t, 1H, *J* 7.4 Hz), 7.06–6.91 (m, 2H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.0, 164.7, 162.8, 139.8, 137.7, 133.8, 133.2, 129.9, 129.1, 128.7, 128.1, 122.3, 121.5, 119.2, 111.7, 52.4. Found (%): C, 67.17; H, 4.39; N, 8.71. Calc. for $C_{18}H_{14}N_2O_4$ (%): C, 67.07; H, 4.38; N, 8.69.

For characteristics of compounds **5b**, **6**–**9**, see Online Supplementary Materials.