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One-pot synthesis of (5-alkyl-1,2,4-oxadiazol-3-yl)benzoic acids

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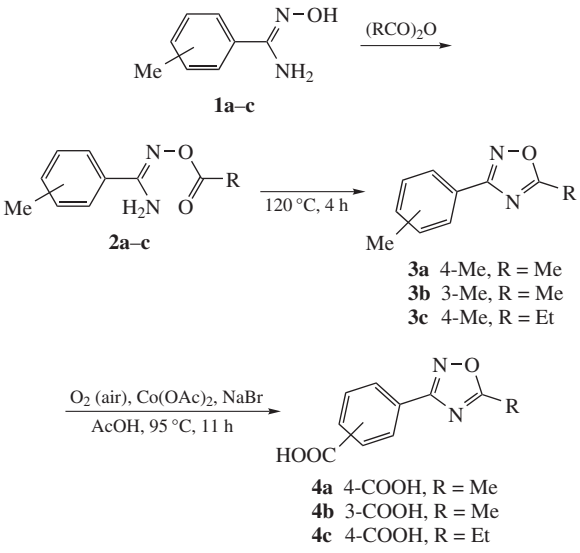
Heterocyclization of toluic acid amidoximes with acetic or propionic anhydrides affords 5-alkyl-3-tolyl-1,2,4-oxadiazoles, whose air oxidation in the same vessel gives (5-alkyl-1,2,4-oxadiazol-3-yl)benzoic acids.

The development of new methods for the synthesis of 4- and 3-(5-R-1,2,4-oxadiazol-3-yl)benzoic acids is of considerable importance for pharmaceutical and medical chemistry because these acids and their derivatives are the antagonists of $\alpha_{IIb}\beta_3$[1] integrin and D_3 dopamine receptors,[2,3] the inhibitors of cathepsin K[4,5] and the agonists of retinoic acid receptors (pan-RAR),[6] and they are used for the treatment of mucoviscidosis and muscular dystrophy (Duchenne–Greisinger disease).[7]

The known syntheses of such carboxylic acids include the formation of the 1,2,4-oxadiazole system from reactants containing an alkoxycarbonyl group followed by hydrolysis.[1–7] A study of the effect of different solvents showed that 3-phenyl-5-alkyl-1,2,4-oxadiazoles can be prepared from carboxylic acid amidoximes and anhydrides in acetic acid in good yields.[8] Earlier, we found that 5-(cyclo)alkyl-1,2,4-oxadiazoles are stable to the action of oxidizing agents in acidic media.[9] At the same time, the methyl group in 3-tolyl-1,2,4-oxadiazole is readily oxidized to the carboxyl one in acidic medium.[10] Since both of these reactions can be performed in acidic medium, we combined them into the consecutive one-pot procedure (Scheme 1).



Scheme 1

The completeness of the cyclization of amidoxime ester **2** into 1,2,4-oxadiazole **3** is a crucial factor for performing the one-pot synthesis. At the stage of oxidation, the unreacted *O*-acylamidoximes **2** are converted into tere- or isophthalic acid. This decreases the yield of the target compounds and considerably complicates their isolation and purification. The developed synthesis conditions made it possible to obtain acids **4a–c** † in 89– 95% yields based on the initial amidoximes **1a–c**.

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† The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) in DMSO-d_6 solutions with TMS as internal standard. The mass spectra were measured on a Perkin-Elmer Clarus 500 GC/MS instrument with electron ionization. The HRMS spectra were measured on a Bruker microTOF instrument with electrospray ionization (ESI).

(5-Alkyl-1,2,4-oxadiazol-3-yl)benzoic acids **4a–c**. Amidoxime **1a–c** (15 mmol) was dissolved in anhydride $(RCO)_2O$ (10 mmol). The reaction mass was heated to boiling (~120 °C) and kept at this temperature for 4 h. Then, it was cooled and diluted with 40 ml of glacial acetic acid, and 1 mmol of cobalt acetate and 1 mmol of sodium bromide were added. The mixture was heated to 95 °C, and air was supplied with stirring. At the end of the oxidation, acetic acid was distilled off under reduced pressure; the residue was cooled to room temperature, and the precipitate of compounds **4a–c** was filtered off.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid **4a**: yield 90%, mp 274 °C. ^{1}H NMR, δ: 2.70 (s, 3H), 8.11 (s, 4H), 13.26 (s, 1H). ^{13}C NMR, δ: 11.91, 126.99, 129.98, 133.10, 166.51, 166.92, 177.68. MS, *m/z*: 204 [M$^+$] (78), 187 (3), 163 (100), 146 (31), 118 (14), 102 (5), 90 (9), 88 (9). HRMS (ESI), *m/z*: 205.0608 [M+H]$^+$ (calc. for $C_{10}H_9N_2O_3$, *m/z*: 205.0609). Found (%): C, 58.66; H, 4.00; N, 13.63. Calc. for $C_{10}H_8N_2O_3$ (%): C, 58.82; H, 3.92; N, 13.78.

3-(5-Methyl-1,2,4-oxadiazol-3-yl)benzoic acid **4b**: yield 89%, mp 226–227 °C. ^{1}H NMR, δ: 2.70 (s, 3H), 7.71 (t, 1H, *J* 7.8 Hz), 8.14 (d, 2H, *J* 7.8 Hz), 8.22 (d, 1H, *J* 7.8 Hz), 8.55 (s, 1H), 13.27 (s, 1H). ^{13}C NMR, δ: 11.91, 126.57, 127.48, 129.62, 130.78, 131.63, 131.86, 166.41, 166.91, 177.68. MS, *m/z*: 204 [M$^+$] (77), 187 (2), 163 (100), 146 (15), 118 (25), 102 (6), 90 (10), 88 (9), 76 (6), 75 (6), 63 (6), 62 (6), 51 (9), 50 (7), 43 (31). HRMS (ESI), *m/z*: [M+H]$^+$ 205.0608 (calc. for $C_{10}H_9N_2O_3$, *m/z*: 205.0609). Found (%): C, 58.75; H, 3.85; N, 13.58. Calc. for $C_{10}H_8N_2O_3$ (%): C, 58.82; H, 3.92; N, 13.78.

4-(5-Ethyl-1,2,4-oxadiazol-3-yl)benzoic acid **4c**: yield 95%, mp 200–201 °C. ^{1}H NMR, δ: 1.37 (t, 3H, *J* 7.6 Hz), 3.04 (m, 2H), 8.13 (s, 4H), 9.80 (s, 1H). ^{13}C NMR, δ: 10.3, 19.6, 127.1, 130.1, 133.3, 144.6, 166.6, 166.9, 181.5. MS, *m/z*: 218 [M$^+$] (100), 163 (97), 146 (20), 130 (6), 118 (6). HRMS (ESI), *m/z*: [M+H]$^+$ 219.0764 (calc. for $C_{11}H_{11}N_2O_3$, *m/z*: 219.0770). Found (%): C, 59.55; H, 4.68; N, 12.35. Calc. for $C_{11}H_{11}N_2O_3$ (%): C, 60.55; H, 4.59; N, 12.84.

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