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LETTERS
TO THE EDITOR

Environmentally Friendly One-Pot Synthesis of Substituted Thiazoles and Thiazolylpyrazoles

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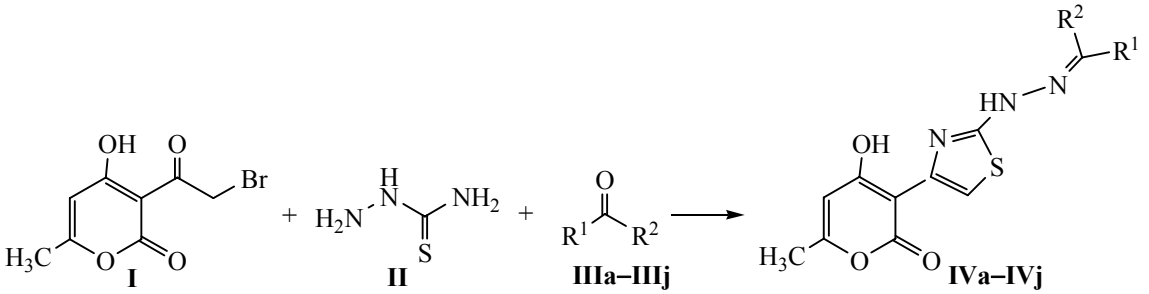
Over the past several years chemists have been trying to develop new synthetic routes to widely used organic compounds from readily available starting materials, reagents, and reaction conditions that reduce risks to the humans and environment. Heterocycles are widely used in the development of modern pharmaceuticals, therefore this is one of the reasons why continuous efforts are directed towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (dehydroacetic acid) is a convenient starting material, and its derivatives find wide application in the synthesis of heterocyclic compounds [1–4]. Some 4-hydroxy-2-pyrans have also been tested as anticoagulant agents [5]. The nitrogen and sulfur heterocyclic systems are very interesting because of their physicochemical properties with relevance to the design of new drugs. The compounds containing a thiazole ring play a prominent role in nature as they are found in numerous biologically active compounds. Thiazole ring systems are known to possess various pharmacological properties such as anti-tubercular [6], antifungal [7], analgesic [8], and anticancer activity [9]. Pyrazoles have emerged as a group of compounds possessing a broad spectrum of useful medicinal properties such as herbicides, fungicides, and analgesics activities [10–11]. The Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, antifungal, and antitumor activity [12–18].

In view of various biological activities of thiazoles, Schiff bases, and pyrazoles our current studies are focused on the development of new routes to the synthesis of thiazoles and thiazolylpyrazoles incorporating pyran moiety. So we have developed a practical, solvent-free, one-pot method for the synthesis of the title compounds.

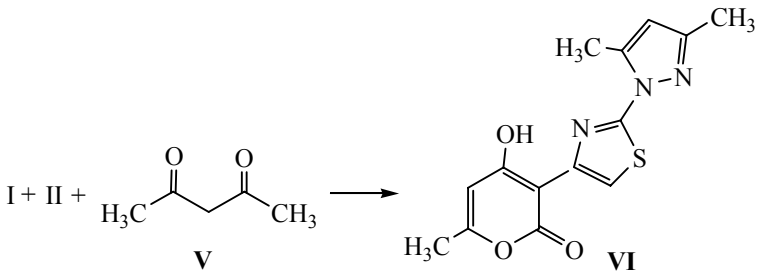
The multicomponent reactions are one-pot processes, in which more than two reagents directly get converted into their products. The multicomponent reactions play an important role in modern organic chemistry, because they generally exhibit higher selectivity as well as produce fewer by-products compared to the classic multistep synthesis. Furthermore, in many cases the multicomponent reactions are easy to perform, inexpensive, quick, consume less energy, and involve simple experimental procedures.

As a part of our continuing work on the synthesis of new heterocyclic systems [19–24], a facile and convenient approach was developed for the synthesis of various 4-hydroxy-3-[2-(*N*′-substituted hydrazino) thiazol-4-yl]-6-methylpyran-2-one and 4-hydroxy-6-methyl-3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl]-2*H*-pyran-2-one derivatives. The reaction of an equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **I**, thiosemicarbazide **II**, carbonyl compound **III,** or acetyl acetone **V** while stirring at room temperature for 10 min results in the title compounds **IV** or **VI**.

A plausible mechanism of this reaction can be described as follows. The bromine atom of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one is replaced by the sulfur atom of thiosemicarbazide to yield an open-chain α-thioketone followed by trans-protonating into 4-hydroxythiazoline derivative. It subsequently undergoes the dehydration to give *in situ* 2-hydrazinothiazole derivative followed by condensation with various carbonyl compounds to give the



III, **IV**, $R^1 = R^2 =$ Me (**a**); $R^1 =$ Me, $R^2 =$ Ph (**b**); $R^1 =$ Me, $R^2 = p$-tolyl (**c**); $R^1 =$ Me, $R^2 = p$-anisyl (**d**); $R^1 =$ Me, $R^2 =$ Et (**e**); $R^1 = R^2 =$ cyclohexylidene (**f**); $R^1 =$ H, $R^2 =$ Ph (**g**); $R^1 =$ H, $R^2 = o$-hydroxyphenyl (**h**); $R^1 =$ H, $R^2 = p$-tolyl (**i**); $R^1 =$ H, $R^2 = p$-anisyl (**j**).



final product **IV**. This is in accordance with the modified Hantzsch thiazole synthesis. Probably in the synthesis of thiazole first the thiosemicarbazide **II** undergoes condensation with 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **I** with a loss of water and HBr molecules to give the corresponding cyclic product. Further, the latter undergoes condensation with acetyl acetone to give the target product.

The structure of the compounds obtained was proved by the IR and NMR spectroscopy. Thus, the IR spectrum of compound **IVb** contains the absorption bands at 1731 and 3367 cm^{-1} originating from the lactone and hydroxy group of pyran ring, respectively. In the ^1H NMR spectrum of **IVb** there are characteristic singlets of the CH_3-moiety of the pyran ring at δ 2.24 ppm, of the C^5H proton of the pyran ring at δ 6.23 ppm and of the thiazole proton at δ 7.81 ppm. The ^1H NMR spectrum of **VI** contains the corresponding singlet signals at δ 2.22 (CH_3, pyran), 2.27 and 2.62 (CH_3, pyrazole), 6.30 (pyran and pyrazole rings), 7.89 ppm (thiazole). The remaining protons were observed in the expected regions.

In conclusion, we developed a simple, rapid, efficient, and green method of the synthesis of a variety of thiazoles and thiazolylpyrazole derivatives via the three-component reaction in the one-pot procedure. This method does not involve the use of the volatile organic solvents and thus is an environmentally friendly process.

All the reagents and solvents were pure, purchased from commercial sources, and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one was prepared by the literature procedure [25].

The IR spectra were recorded on a Thermo Nicolet Nexus 670 instrument from KBr pellets. The ^1H NMR spectra were registered on a Bruker WM-400 spectrometer using TMS as an internal reference. The mass spectra (ESI-MS) were taken on a Perkin Elmer SCIEX API- 2000 instrument at 12.5 eV. The melting points were determined in open capillaries with a Cintex melting point apparatus (Mumbai, India) and were uncorrected. The CHNS-analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds obtained was monitored by TLC.

General procedure for the synthesis of 4-hydroxy-3-[2-(*N*′-substituted-hydrazino)thiazol-4-yl]-6-methylpyran-2-one (IVa–IVj). A mixture of 1 mmol of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **I**, 1 mmol of thiosemicarbazide **II,** and 1 mmol of the corresponding carbonyl compound **III** was stirred at room temperature for about 10 min. The solids obtained were filtered off, washed with water, and recrystallized from ethanol.

4-Hydroxy-3-[2-(*N*′-isopropylidenehydrazino)-thiazol-4-yl]-6-methylpyran-2-one (IVa). Yield 0.25 g (92%), mp 182–184°C, pale yellow crystals. IR

spectrum, ν, cm^{-1}: 1717 (C=O, lactone), 3251 (NH), 3370 (OH). ^1H NMR spectrum, δ, ppm: 1.96 s (6H, CH_3), 2.23 s (3H, CH_3), 6.20 s (1H, CH^5, pyran), 7.31 s (1H, thiazole), 11.11 s (1H, NH), 14.57 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 17.9, 19.3, 24.7, 93.8, 101.1, 103.3, 140.8, 152.9, 161.7, 162.0, 168.0, 168.6. Mass spectrum, *m*/*z*: 278 $[M + H]^+$. Found, %: C 51.5; H 4.63; N 15.12. $C_{12}H_{13}N_3O_3S$. Calculated, %: C 51.60; H 4.69; N 15.04.

4-Hydroxy-6-methyl-3-{2-[*N*′-(1-phenylethylidene)-hydrazino]thiazol-4-yl}pyran-2-one (IVb). Yield 0.27 g (80%), mp 197–199°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1731 (C=O, lactone), 3247 (NH), 3367 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.35 s (3H, CH_3), 6.23 s (1H, C^5H, pyran), 7.39–7.46 m (5H, Ph), 7.81 s (1H, thiazole), 11.57 s (1H, NH), 14.50 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 14.2, 19.3, 94.1, 101.1, 104.0, 125.8, 128.4, 129.1, 137.3, 142.2, 148.5, 161.5, 161.9, 168.2, 168.5. Mass spectrum, *m*/*z*: 340 $[M + H]^+$. Found, %: C 59.85; H 4.40; N 13.26. $C_{17}H_{15}N_3O_3S$. Calculated, %: C 59.81; H 4.43; N 12.31.

4-Hydroxy-6-methyl-3-{2-[*N*′-(1-*p*-tolylethylidene)-hydrazino]thiazol-4-yl}pyran-2-one(IVc). Yield 0.28 g (80%), mp 237–239°C, pale yellow crystals. IR spectrum, ν, cm^{-1}:1727 (C=O, lactone), 3248 (NH), 3377 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.32 s (3H, CH_3), 2.33 s (3H, CH_3), 6.22 s (1H, C^5H, pyran), 7.25 d (2H, Ph, *J*8.0 Hz), 7.41 s (1H, thiazole), 7.70 d (2H, Ph, *J* 8.0 Hz), 11.50 s (1H, NH), 14.90 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 14.2, 19.3, 20.8, 93.9, 101.1, 104.0, 125.8, 129.0, 134.5, 138.8, 141.5, 148.9, 161.6, 161.9, 168.0, 168.5. Mass spectrum, *m*/*z*: 356 $[M + H]^+$. Found, %: C 60.78; H 4.78; N 11.76. $C_{18}H_{17}N_3O_3S$. Calculated, %: C 60.83; H 4.82; N 11.82.

4-Hydroxy-3-(2-{*N*′-[1-4-methoxyphenyl)ethyl-idene]hydrazino}thiazol-4-yl)-6-methyl-pyran-2-one (IVd). Yield 0.30 g (82%), mp 232–234°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1728 (C=O, lactone), 3263 (NH), 3370 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.31 s (3H, CH_3), 3.80 s (3H, OCH_3), 6.22 s (1H, C^5H, pyran), 6.99 d (2H, Ph, *J* 8.8 Hz), 7.40 s (1H, thiazole), 7.75 d (2H, Ph, *J* 8.8 Hz), 11.47 s (1H, NH), 14.87 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 14.1, 19.3, 55.2, 94.2, 101.1, 103.6, 113.8, 127.3, 129.8, 142.5, 148.3, 160.1, 161.5, 161.8, 168.3, 168.5. Mass spectrum, *m*/*z*: 372 $[M + H]^+$. Found, %: C 58.26; H 4.56; N 11.34. $C_{18}H_{17}N_3O_4S$. Calculated, %: C 58.21; H 4.61; N 11.31.

3-[2-(*N*′-*sec*-Butylidenehydrazino]thiazol-4-yl]-4-hydroxy-6-methylpyran-2-one(IVe). Yield 0.23 g (80%), mp 216–218°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1721 (C=O, lactone), 3261 (NH), 3392 (OH). ^1H NMR spectrum, δ, ppm: 1.06 t (3H, CH_3, *J* 7.6 Hz), 1.94 s (3H, CH_3), 2.23 s (3H, CH_3), 2.29 q (2H, CH_2, *J* 7.6 Hz), 6.20 s (1H, C^5H, pyran), 7.33 s (1H, thiazole), 11.22 s (1H, NH), 14.82 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 10.3, 16.7, 19.3, 31.0, 93.5, 101.0, 103.5, 139.7, 156.9, 161.8, 162.1, 168.0, 168.6. Mass spectrum, *m*/*z*: 293 $[M + H]^+$. Found, %: C 53.18; H 5.10; N 14.27. $C_{13}H_{15}N_3O_3S$. Calculated, %: C 53.23; H 5.15; N 14.32.

3-[2-(*N*′-Cyclohexylidenehydrazino]thiazol-4-yl]-4-hydroxy-6-methylpyran-2-one (IVf). Yield 0.25 g (81%), mp 256–258°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1737 (C=O, lactone), 3252 (NH) and 3420 (OH). ^1H NMR spectrum, δ, ppm: 1.60–1.63 m (6H, $3CH_2$, cyclohexyl), 2.23 s (3H, CH_3), 2.27–2.29 m (2H, CH_2), 2.43–2.46 m (2H, CH_2, cyclohexyl), 6.21 s (1H, C^5H, pyran), 7.33 s (1H, thiazole), 11.50 s (1H, NH), 14.77 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.4, 24.8, 25.5, 26.7, 27.7, 34.6, 93.0, 100.9, 104.0, 137.9, 160.1, 162.0, 162.4, 167.7, 168.6. Mass spectrum, *m*/*z*: 320 $[M + H]^+$. Found, %: C 56.37; H 5.32; N 13.12. $C_{15}H_{17}N_3O_3S$. Calculated, %: C 56.41; H 5.37; N 13.16.

3-[2-(*N*′-Benzylidenehydrazino]thiazol-4-yl]-4-hydroxy-6-methylpyran-2-one (IVg). Yield 0.25 g (77%), mp 227–229°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1728 (C=O, lactone), 3217 (NH), 3431 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 6.22 s (1H, C^5H, pyran), 7.41–7.47 m (5H, Ph; 1H, thiazole), 8.08 s (1H, CH=N), 12.47 s (1H, NH), 14.88 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 16.3, 99.9, 128.4, 128.5, 129.0, 129.1, 152.3, 156.5, 161.1, 162.1, 162.8, 163.9, 166.7, 193.2. Mass spectrum, *m*/*z*: 328 $[M + H]^+$. Found, %: C 58.65; H 3.96; N 12.80. $C_{16}H_{13}N_3O_3S$. Calculated, %: C 58.70; H 4.00; N 12.84.

4-Hydroxy-3-{2-[*N*′-(2-hydroxybenzylidene)hyd-razino]thiazol-4-yl}-6-methylpyran-2-one (IVh). Yield 0.29 g (87%), mp 243–245°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1707 (C=O, lactone), 3207 (NH), 3370 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 6.23 s (1H, C^5H, pyran), 6.85–6.92 m (4H, Ph), 7.33 s (1H, thiazole), 8.06 s (1H, CH=N), 11.32 s (1H, NH), 14.82 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.8, 94.9, 101.4, 104.0, 116.5, 116.6, 119.7, 120.2, 126.7, 131.5, 143.4, 156.6, 161.8, 162.4, 167.3, 168.8. Mass spectrum, *m*/*z*: 342 $[M + H]^+$.

Found, %: C 55.93; H 3.78; N 12.20. $C_{16}H_{13}N_3O_4S$. Calculated, %: C 55.97; H 3.82; N 12.24.

4-Hydroxy-6-methyl-3-{2-[*N*′-(4-methylbenzylidene)-hydrazino]thiazol-4-yl}pyran-2-one (IVi). Yield 0.27 g (80%), mp 237–239°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1717 (C=O, lactone), 3242 (NH), 3366 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.34 s (3H, CH_3), 6.22 s (1H, C^5H, pyran), 7.26 d (2H, Ph, *J* 8.0 Hz), 7.41 s (1H, thiazole), 7.59 d (2H, Ph, *J* 8.0 Hz), 8.05 s (1H, CH=N), 12.42 s (1H, NH), 14.82 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.4, 21.0, 94.0, 100.9, 104.0, 126.6, 129.4, 129.6, 131.1, 134.0, 139.7, 144.2, 161.5, 162.1, 167.0, 168.4, 192.6. Mass spectrum, *m*/*z*: 342 $[M + H]^+$. Found, %: C 59.77; H 4.40; N 12.28. $C_{17}H_{15}N_3O_3S$. Calculated, %: C 59.81; H 4.43; N 12.31.

4-Hydroxy-3-{2-[*N*′-(4-methoxybenzylidene)hydrazino]thiazol-4-yl}-6-methylpyran-2-one (IVj). Yield 0.27 g (78%), mp 273–275°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1712 (C=O, lactone), 3234 (NH), 3438 (OH). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 2.31 s (3H, CH_3), 3.80 s (3H, OCH_3), 6.21 s (1H, C^5H, pyran), 7.13 d (2H, Ph, *J* 8.4 Hz), 7.39 s (1H, thiazole), 7.64 d (2H, Ph, *J* 8.0 Hz), 8.03 s (1H, CH=N), 11.22 s (1H, NH), 14.82 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 19.5, 55.3, 99.5, 113.7, 114.4, 129.1, 130.4, 131.3, 160.7, 161.7, 162.2, 163.8, 163.9, 164.2, 191.2. Mass spectrum, *m*/*z*: 358 $[M + H]^+$. Found, %: C 57.10; H 4.20; N 11.71. $C_{17}H_{15}N_3O_4S$. Calculated, %: C 57.13; H 4.23; N 11.76.

4-Hydroxy-6-methyl-3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl]-2*H*-pyran-2-one(VI). A mixture of 1 mmol of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **I**, 1 mmol of thiosemicarbazide **II,** and 1 mmol of acetyl acetone **V** was stirred at room temperature for about 10 min. The solid obtained was filtered off, washed with water, and recrystallized from ethanol. Yield 0.26 g (88%), mp 217–219°C, pale yellow crystals. IR spectrum, ν, cm^{-1}: 1727 (C=O, lactone), 3437 (OH). ^1H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 2.27 s (3H, CH_3), 2.62 s (3H, CH_3), 6.20 s (1H, C^5H, pyran; 1H, pyrazole), 7.95 s (1H, thiazole), 13.27 s (1H, OH). Mass spectrum, *m*/*z*: 303 $[M + H]^+$. Found, %: C 55.40; H 4.28; N 13.81. $C_{14}H_{13}N_3O_3S$. Calculated, %: C 55.43; H 4.32; N 13.85.

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