Organic Chemistry

Pivaloylpyruvic acid as a new acylating reagent for amines

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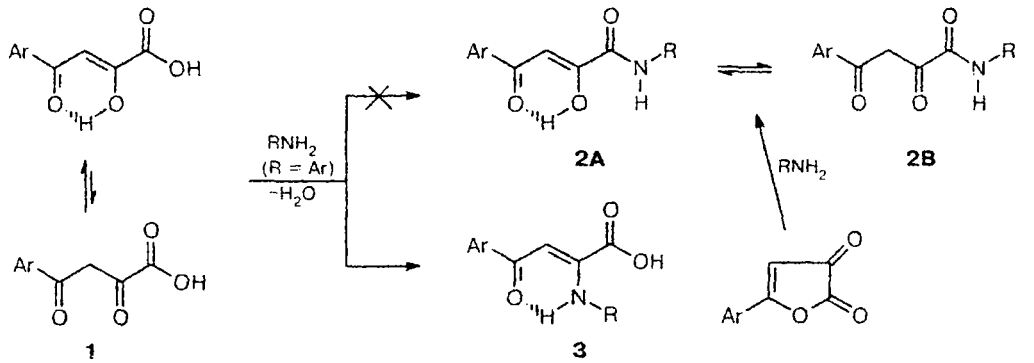
Pivaloylpyruvic acid is an efficient reagent for preparative acylation of amines. A method for the synthesis of substituted pivaloylpyruvamides with domination of (*Z*)-β-keto-enol tautomer is proposed. The structure of pivaloylpyruvic acid and its amides, as well as the specific features of the reaction of pivaloylpyruvic acid with amines, are discussed.

Key words: pivaloylpyruvic acid, reaction with amines, substituted pivaloylpyruvamides.

It is known[1,2] that noncatalyzed reactions of carboxylic acids with amines under mild conditions usually result in the corresponding ammonium carboxylates rather than in amides. Previously,[3–5] it was found that aroylpyruvic acids (**1**) react with arylamines to give, instead of aroylpyruvamides **2** (R = Ar), α-imino derivatives, namely, 4-aryl-2-arylamino-4-oxobut-2-enoic acids (**3**) (Scheme 1).

While studying the nucleophilic transformations of acylpyruvic acids, we found out that the reactions of

Scheme 1



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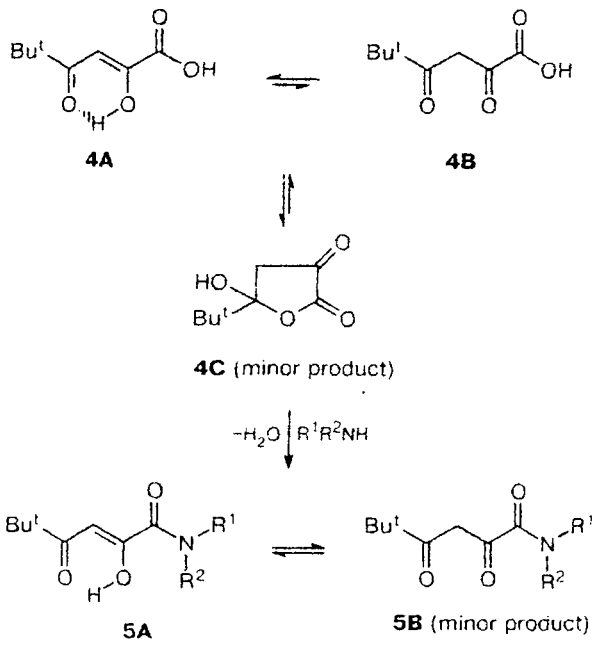
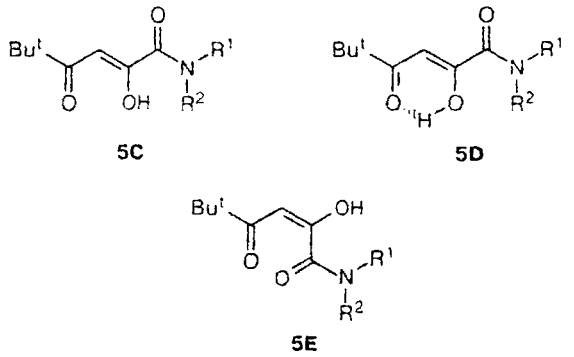
pivaloylpyruvic acid (**4**)[6–8] with alkyl-, aryl-, or hetarylamines under unusually mild conditions (room temperature and no catalyst) yield substituted pivaloylpyruvamides **5a–g** (Scheme 2).

Scheme 2



5: $R^1 = R^2 = Et$ (**a**), $R^2 = H$, $R^1 = PhCH_2$ (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 2-$MeOCOC_6H_4$ (**e**), 2-pyridyl (**f**), 2-thiazolyl (**g**)

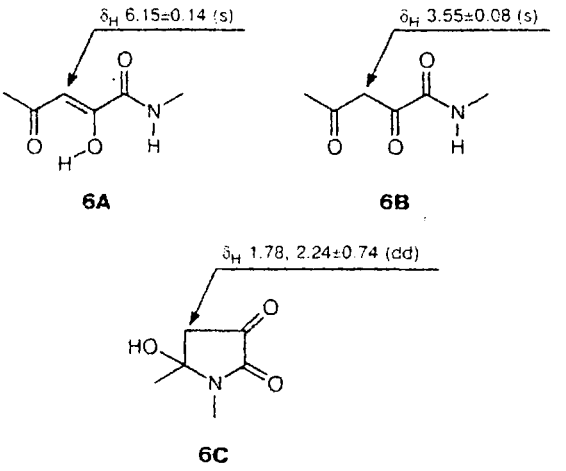
Spectral data for the compounds **5** synthesized are in satisfactory agreement with the parameters of the well-known *N*-arylaroylpyruvamides **2** (R = Ar).[9,10] Thus, the IR spectra of amides **5a–e** show, along with the absorption band at 1665–1676 cm^{-1} (characteristic of an amide carbonyl group), a broad low-frequency band at 1540–1612 cm^{-1} corresponding to the C=O stretching vibrations in the 1,3-dione fragment, which indicates the presence of an OH chelate ((*Z*)-isomers **5**) closed *via* an —O—H···O=C< intramolecular hydrogen bond (IMHB).[10] The ^1H NMR spectra of pivaloylpyruvamides **5** in DMSO-d_6 exhibit doublets for the proton-containing groups and a large difference in the shifts of the signals for the methine C(3)H protons, as compared to the relevant spectra in CCl_4 and $CDCl_3$. This suggests that these amides can exist in DMSO in two solvate forms, *viz.*, a nonassociated form (**5C**) without IMHB in the 1,3-keto-enol fragment and an associated one (**5D**), in which the enol OH proton is involved in OH-chelation. The fact that the spectra recorded in CCl_4 and $CDCl_3$ do not exhibit doubling of proton signals indicates the absence of a second possible (*E*)-isomer (**5E**).



In addition, the ^1H NMR spectra of compounds **5** often contain, along with a signal for the C(3)H methine proton at δ 5.47–6.72, a singlet at δ 3.78–4.08 corresponding to two CH_2 protons. This pattern suggests the presence of both the keto-enol (**5A**) and minor 1,3-dione tautomer (**5B**), whose content ranges from 10 to 27% (see Scheme 2). While interpreting the ^1H NMR spectra, note that a marker signal for the C(3)H methine proton in model aroylpyruvamides **2** (δ 6.70–7.26 in DMSO-d_6)[10,11] is shifted downfield (on average, by 0.9 ppm) on account of conjugation with the 4-aryl fragment.

Such ^1H NMR chemical shifts of the signals for the CH and CH_2 groups in compounds **5** satisfactorily correlate with the theoretical spectral parameters calculated for model chain tautomeric structures **6A** and **6B** with the use of an ACD/Labs® PC program (Scheme 3).

Scheme 3



A possible cyclic structure of 5-hydroxypyrrolidine-2,3-dione (**6C**) is unambiguously excluded because a characteristic signal for two coupling geminal CH_2 protons in position 4 of the ring (two doublets of the AB

system) is absent in the ^{1}H NMR spectra of amides **5** (see Scheme 3).

When tested for the enol OH group in a color reaction with 10% $FeCl_3$ in ethanol, the resulting amides **5** show characteristic dark red color.

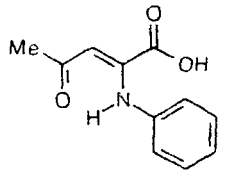
Like biologically active aroylpyruvamides **2**,[10–12] pivaloylpyruvamides **5** exhibit bacteriostatic and pronounced analgesic effects.

The unusual pathway of the reaction is probably due to the fact that acid **4C** reacts with amines in a tautomeric cyclic form so that an amine as a nucleophile attacks its lactone carbonyl group to cause ring opening (see Scheme 2).

It should be noted that pivaloylpyruvic acid **4**, according to its ^{1}H NMR spectrum recorded in DMSO-d_6, consist of three tautomers, namely, **4A** (71%), **4B** (24%), and **4C** (5%). Such a spectral pattern is not contradictory to the previous data on the presence of some prototropic forms in solutions of their analogs, aroylpyruvic acids.[12,13]

Thus, we discovered an easy way of acylation of amines with a carboxylic acid capable of reacting in the equilibrium lactone form. According to our data, pivaloylpyruvic acid **4** can be used to introduce the pivaloylpyruvoyl fragment into various NH-nucleophiles.

We believe (this assumption is now being defined more precisely) that the ability to form amides in reactions with amines is characteristic only of pivaloylpyruvic acid **4** rather than of the whole series of alkanoylpyruvic acids. Thus, judging from scarce literature data published more than fifty years ago, alkyl acetylpyruvates react with ammonia, aniline, or *N*-methylaniline to give the corresponding acetylpyruvamides,[14–17] while the reaction of acetylpyruvic acid itself with aniline yields 4-oxo-2-(phenylamino)pent-2-enoic acid (**7**),[14] as in a reaction with aroylpyruvic acids (see Scheme 1).



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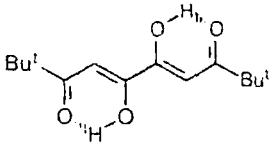

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The starting pivaloylpyruvic acid **4** can be prepared by mild hydrolysis of ethyl pivaloylpyruvate in a basic medium[6,7] or by the Claisen condensation as reported in a brief communication[8] (without detailed description of the procedure). We synthesized pivaloylpyruvic acid **4** by the reaction of diethyl oxalate with a twofold excess of pinacolin[8] in the presence of an excess of sodium methoxide. The latter was used to prevent the formation of methyl pivaloylpyruvate, because the Claisen reaction in the presence of excess base is well known to give acylpyruvic acids[12,18,19] rather than their esters. A condensation by-product was the known 5,6-dihydroxy-2,2,9,9-tetramethyldeca-4,6-diene-3,8-dione (**8**)[20,21] in low yield (2%).

Experimental

The IR spectra of compounds **4**, **5**, and **8** were recorded on UR-20 and Specord M-80 spectrometers (Vaseline oil). The ^{1}H NMR spectra of compounds **4** and **5** were recorded on RYa-2310 (60 MHz), Gemini-200 (200 MHz), and Bruker AC-300 (300.13 MHz) instruments in DMSO-d_6, CCl_4, and $CDCl_3$ with Me_4Si or HMDS as the internal standard. The ^{13}C NMR spectra of amides **5** were recorded on JEOL EX-90A FT-NMR (22.30 MHz) and Gemini-200 (50.29 MHz) spectrometers in DMSO-d_6 and $CDCl_3$. The course of the reactions was monitored and the purity of compounds was checked by TLC on Silufol UV-254® plates in a benzene—ether—acetone system (10 : 9 : 1); spots were visualized with iodine vapors. The mass spectra (EI) of compounds **4** and **5** were recorded on a Kratos MS-30 spectrometer (United Kingdom) (direct inlet of a sample into the ion source, emission current 1 A, ionizing voltage 70 eV, evaporator temperature 100—180 °C). A PC program designed to plot ^{1}H NMR spectra was provided by ACD/Labs® Software (Toronto, Canada, http://www.acdlabs.com).

Methanol was preliminarily dehydrated by distillation with sodium.

(*Z*)-2-Hydroxy-5,5-dimethyl-4-oxohex-2-enoic (pivaloylpyruvic) acid (4). Sodium (9.2 g, 0.4 mol) was added portionwise to 100 mL of anhydrous methanol. The methanol was then removed, and anhydrous diethyl ether (150 mL) was added to the dry sodium methoxide. A mixture of diethyl oxalate (29.2 g, 0.2 mol) and pinacolin (40.0 g, 0.4 mol) was added with cooling and stirring to the resulting suspension. The day after, the stirred precipitate of sodium enolate was treated with hot water (40 mL) and with conc. HCl in small portions to pH 3—4. The solvent was removed, and the dry residue was recrystallized from CCl_4 or a toluene—hexane mixture (1 : 1) to give acid **4** as colorless needles. Yield 24.60 g (71%), m.p. 55—56 °C (*cf.* Ref. 6: m.p. 60 °C; Ref. 7: m.p. 64 °C). IR, ν/cm^{-1}: 3455—3510 (COO<u>H</u>); 1675—1708 (<u>C</u>OOH); 1615—1622, 1580—1590 (C=O$_{chelate}$, C=C); 1458, 1372, 1293, 1257, 1138, 1115 (enol form **4A** in crystals). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.20 (s, 9 H, Bu^t); 6.62 (s, 1 H, CH) (100% of enol form **4A**). ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 1.02 (s, 9 H, Bu^t, **4C** (5%)); 1.08 (s, 9 H, Bu^t, **4B** (24%)); 1.17 (s, 9 H, Bu^t, **4A** (71%)); 2.90, 3.38 (both d, 2 H, CH_2, **4C**); 4.06 (s, 1 H, CH_2, **4B**); 5.42 (s, 1 H, OH, **4C**); 6.50 (s, 1 H, CH, **4A**); 13.90—14.30 (br.s, 2 H, 2 OH, —COOH, **4A** and **4B**). MS, m/z (I_{rel} (%)): 172 $[M]^+$ (30), 144 $[M - CO]^+$ or $[Bu^tCOCH_2COOH]^+$ (20), 128 $[M - CO_2]^+$ (8), 127 $[M - CO_2 - H]^+$ or $[Bu^tCOCH_2{-}C{\equiv}O]^+$ (81), 116 $[M - 2\,CO]^+$ (34), 115 (8), 111 (8), 88 (21), 83 (12), 69 $[O{=}C{-}CH{=}C{=}O]^+$ (40), 60 (5), 57 $[Me_2CH{-}CH_2]^+$ (100), 55 (11), 45 (13), 44 (20), 43 (62), 42 (21), 41 (57), 40 (32), 39 (25) (peaks with I_{rel} > 5% are included only). Found (%): C, 56.24; H, 6.73. $C_8H_{12}O_4$. Calculated (%): C, 55.81; H, 7.02. Molecular weight: 172.18.

Crystallization from the mother liquor gave 5,6-dihydroxy-2,2,9,9-tetramethyldeca-4,6-diene-3,8-dione (**8**) (1.30 g, 2%), m.p. 85—86 °C (from EtOH) (*cf.* Ref. 20: m.p. 98 °C). IR, ν/cm^{-1}: 1605; 1580—1545 (C=O$_{chelate}$, C=C); 1530; 1458. The ^{1}H NMR spectra (in $CDCl_3$ and DMSO-d_6) of compound **8** are available from Ref. 21.

Pivaloylpyruvamides (5a—e) (general procedure). A solution of a corresponding alkyl-, aryl-, or hetarylamine (7.8 mmol) in 15—20 mL of EtOH or CCl_4 was added with stirring to a solution of pivaloylpyruvic acid **4** (1.35 g, 7.8 mmol) in

20—30 mL of EtOH or CCl_4. The reaction mixture was left at ~20 °C for ~24 h. The precipitate that formed was filtered off and recrystallized from EtOH, dioxane, or a toluene—hexane mixture (2 : 1).

***N,N*-Diethylpivaloylpyruvamide (5a).** Yield 1.63 g (92%), m.p. 120—121 °C. ^{1}H NMR (60 MHz, $CDCl_3$), δ: 1.21 (s, 9 H, Bu^t); 1.30 (t, 6 H, 2 CH_3 in 2 Et); 3.04 (q, 4 H, 2 CH_2 in 2 Et); 4.06 (s, 2 H, C(3)H_2, **5B** (12%)); 6.67 (s, 1 H, C(3)H, **5A** (88%)). ^{1}H NMR (200 MHz, DMSO-d_6), δ: 1.16 (s, 9 H, Bu^t); 1.23 (t, 6 H, 2 CH_3 in 2 Et); 2.85 (q, 4 H, 2 CH_2 in 2 Et); 3.78 (s, 2 H, C(3)H_2, **5B** (27%)); 5.77 (s, 1 H, C(3)H, **5A** (73%)). ^{13}C NMR (22.30 MHz, DMSO-d_6), δ: 10.9 (CH_3 in Et); 25.7 (CH_3 in Bu^t); 27.3 ($\underline{C}Me_3$); 37.7 (C(3)H_2, **5B**); 41.2, 42.4 (CH_2 in Et); 95.7 (C(3)H); 163.2 (=C(OH)—); 165.5 ($Bu^t\underline{C}O$); 182.3 ($\underline{C}ONEt_2$). Found (%): C, 63.29; H, 9.47; N, 6.33. $C_{12}H_{21}NO_3$. Calculated (%): C, 63.41; H, 9.31; N, 6.16.

***N*-Benzylpivaloylpyruvamide (5b).** Yield 1.35 g (66%), m.p. 133—134 °C (decomp.). IR, ν/cm^{-1}: 3284 (CO$\underline{N}$H); 1665 ($\underline{C}$ONH); 1540—1610 ($CO_{chelate}$). ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.15 (s, 9 H, Bu^t); 4.47 (d, 2 H, $\underline{CH_2}$Ph, J = 3.8 Hz); 5.57 (s, 1 H, C(3)H); 7.28—7.39 (m, 5 H, C_6H_5); 7.93 (s, 1 H, NH). ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 1.07 (s, 9 H, Bu^t); 1.12 (s, 9 H, Bu^t); 4.56 (d, 2 H, $\underline{CH_2}$Ph); 4.61 (d, 2 H, $\underline{CH_2}$Ph); 5.47 (s, 1 H, C(3)H, **5C** (46%)); 5.62 (s, 1 H, C(3)H, **5D** (54%)); 7.27—7.38 (m, 10 H, 2 C_6H_5); 9.18 (s, 1 H, NH); 10.43 (s, 1 H, NH). ^{13}C NMR (50.29 MHz, $CDCl_3$), δ: 27.8 (CH_3 in Bu^t); 47.9 ($\underline{C}Me_3$); 76.6 (CH_2); 91.0 (CH); 127.5, 128.4, 129.1 (C in Ph); 154.3 (=C(OH)—); 162.2 ($Bu^t\underline{C}O$); 205.0 ($\underline{C}O$—NH). MS, m/z (I_{rel} (%)): 261 [M]$^+$ (5), 204 [M − Me_2CH—CH_2]$^+$ (17), 126 [Bu^tCO—CH=C=O]$^+$ (4), 92 (9), 91 [$PhCH_2$]$^+$ (100), 69 [O=C—CH=C=O]$^+$ (3), 65 (12), 57 [Me_2CH—CH_2]$^+$ (9), 41 (12), 39 (8) (peaks with I_{rel} > 3% are included only). Found (%): C, 69.31; H, 7.68; N, 5.12. $C_{15}H_{19}NO_3$. Calculated (%): C, 68.94; H, 7.33; N, 5.36.

***N*-(4-Tolyl)pivaloylpyruvamide (5c).** Yield 1.0 g (48%), m.p. 106—107 °C (decomp.). ^{1}H NMR (60 MHz, DMSO-d_6), δ: 0.97 (s, 9 H, Bu^t); 1.12 (s, 9 H, Bu^t); 2.28 (s, 6 H, 2 Me); 4.08 (s, 2 H, C(3)H_2, **5B** (20%)); 5.82 (s, 1 H, C(3)H, **5C** (49%)); 6.28 (s, 1 H, C(3)H, **5D** (51%)); 6.88—7.40 (m, 8 H, 2 C_6H_4); 8.28 (s, 1 H, NH); 11.68 (s, 1 H, NH). Found (%): C, 68.77; H, 7.59; N, 5.50. $C_{15}H_{19}NO_3$. Calculated (%): C, 68.94; H, 7.33; N, 5.36.

***N*-(4-Methoxyphenyl)pivaloylpyruvamide (5d).** Yield 1.60 g (74%), m.p. 124—125 °C (decomp.). IR, ν/cm^{-1}: 3204 (CO$\underline{N}$H); 1676 ($\underline{C}$ONH); 1580—1612 ($CO_{chelate}$). ^{1}H NMR (60 MHz, CCl_4), δ: 1.13 (s, 9 H, Bu^t); 3.80 (s, 3 H, MeO); 6.03 (s, 1 H, C(3)H); 6.85—7.30 (m, 4 H, C_6H_4); 9.18 (br.s, 1 H, NH). ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.15 (s, 9 H, Bu^t); 3.86 (s, 3 H, MeO); 6.09 (s, 1 H, C(3)H); 6.99, 7.03, 7.21, 7.25 (all s, 4 H, C_6H_4); 8.99 (s, 1 H, NH). ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 1.02 (s, 9 H, Bu^t); 1.18 (s, 9 H, Bu^t); 3.76 (s, 3 H, MeO); 3.79 (s, 3 H, MeO); 5.68 (s, 1 H, C(3)H, **5C** (76%)); 6.02 (s, 1 H, C(3)H, **5D** (24%)); 6.87—7.23 (m, 8 H, 2 C_6H_4); 9.72 (s, 1 H, NH); 11.58 (s, 1 H, NH). ^{13}C NMR (50.29 MHz, $CDCl_3$), δ: 27.5 (CH_3 in Bu^t); 41.9 ($\underline{C}Me_3$); 55.3 (MeO); 91.3 (CH); 114.1, 115.0, 123.1, 125.7, 128.7 (C in C_6H_4); 158.8 (=C(OH)—); 162.3 (Bu^t—$\underline{C}O$); 205.4 ($\underline{C}O$—NH). Found (%): C, 65.23; H, 7.30; N, 4.94. $C_{15}H_{19}NO_4$. Calculated (%): C, 64.97; H, 6.91; N, 5.05.

Methyl *N*-pivaloylpyruvoylanthranilate (5e). Yield 1.15 g (48%), m.p. 150—151 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 1.03 (s, 9 H, Bu^t); 1.18 (s, 9 H, Bu^t); 3.91 (s, 6 H, 2 MeO); 6.06 (s, 1 H, C(3)H, **5C** (29%)); 6.72 (s, 1 H, C(3)H, **5D** (71%)); 6.92—8.03 (m, 8 H, 2 C_6H_4); 10.13 (s, 1 H, NH); 12.12 (s, 1 H, NH). MS, m/z (I_{rel} (%)): 305 [M]$^+$ (8), 249 (10), 248 [M − Me_2CH—CH_2]$^+$ (63), 216 (26), 204 (8), 202 (37), 188 (7), 172 (24), 170 [M − 2-MeOCOC_6H_4]$^+$ (29), 158 (40), 145 (12), 144 (38), 143 (10), 135 [2-MeOCOC_6H_4]$^+$ (12), 132 (10), 119 [O=C—C_6H_4—NH]$^+$ (11), 117 (8), 116 (19), 115 (10), 105 (7), 92 (18), 91 (13), 89 (19), 77 [Ph]$^+$ (23), 76 (12), 69 [O=C—CH=C=O]$^+$ (13), 65 (12), 63 (11), 58 (8), 57 [Me_2CH—CH_2]$^+$ (54), 56 (12), 55 (15), 51 (13), 50 (13), 44 (100), 43 (27), 40 (83), 39 (36) (peaks with I_{rel} > 5% are included only). Found (%): C, 63.12; H, 6.50; N, 4.74. $C_{16}H_{19}NO_5$. Calculated (%): C, 62.94; H, 6.27; N, 4.59.

***N*-(2′-Pyridyl)pivaloylpyruvamide (5f).** Yield 1.34 g (69%), m.p. 143—144 °C (decomp.). ^{1}H NMR (200 MHz, DMSO-d_6), δ: 1.15 (s, 9 H, Bu^t); 3.97 (s, 2 H, C(3)H_2, **5B** (10%)); 6.31 (s, 1 H, C(3)H, **5A** (90%)); 7.20 (br.s, 1 H, NH); 6.64, 7.59, 7.90 (all s, 4 H, C_5H_4N). MS, m/z (I_{rel} (%)): 144 (10), 127 [Bu^tCO—CH_2—C≡O]$^+$ (66), 116 (30), 114 (9), 110 (10), 95 (11), 94 [$C_5H_4NNH_2$]$^+$ (92), 93 (10), 88 (15), 85 (7), 83 (15), 81 (10), 71 (17), 69 [O=C—CH=C=O]$^+$ (66), 68 (13), 67 (90), 66 (26), 65 (8), 60 (10), 57 [Me_2CH—CH_2]$^+$ (100) (peaks with I_{rel} > 5% are included only; the peak of a molecular ion is absent). Found (%): C, 62.60; H, 6.93; N, 11.05. $C_{13}H_{16}N_2O_3$. Calculated (%): C, 62.89; H, 6.49; N, 11.38.

***N*-(2′-Thiazolyl)pivaloylpyruvamide (5g).** Yield 1.43 g (72%), m.p. 137—138 °C (decomp.). ^{1}H NMR (200 MHz, DMSO-d_6), δ: 1.14 (s, 9 H, Bu^t); 6.45 (s, 1 H, C(3)H); 6.61, 7.02 (both d, 2 H, C(4′)H, C(5′)H, J = 2.6 Hz); 7.90 (br.s, 1 H, NH); 12.20 (br.s, 1 H, OH). ^{13}C NMR (50.29 MHz, DMSO-d_6), δ: 26.4 (CH_3 in Bu^t); 41.0 ($\underline{C}Me_3$); 97.1 (C(3)H); 106.7, 135.9 (C(4′) and C(5′)); 164.0 (=C(OH)—); 169.7 ($Bu^t\underline{C}O$); 207.9 ($\underline{C}O$—NH). Found (%): C, 52.23; H, 5.71; N, 11.26. $C_{11}H_{14}N_2O_3S$. Calculated (%): C, 51.95; H, 5.55; N, 11.01.

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