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Formation of N-Heterocycles from 1,1-Diethoxy-5-hydroxyalk-3-yn-2-ones

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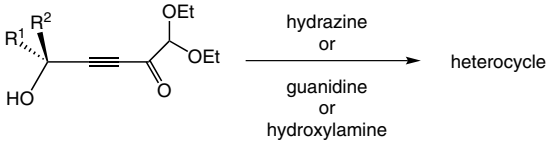

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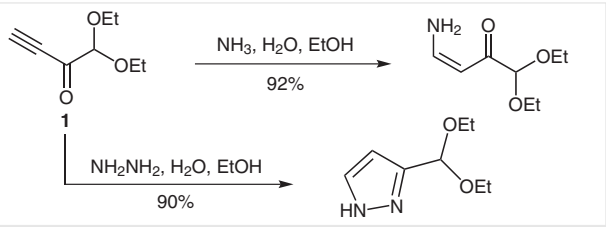
Abstract When treated with hydrazine, guanidine, and hydroxylamine, 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones undergo Michael addition and give the corresponding β,β-disubstituted α,β-unsaturated olefinic ketones, which are unstable and undergo secondary reactions to form heterocyclic compounds. Hydrazine affords 3,5-disubstituted pyrazoles and hydroxylamine 5-hydroxy-4,5-dihydroisoxazoles in very good yields. Guanidine, however, furnishes complex reaction mixtures, which include the corresponding 2-aminopyrimidines. These results show that cyclization involves attack of the ketone moiety by the bisnucleophile reactive terminal group and not the hydroxyl group present in the starting material.

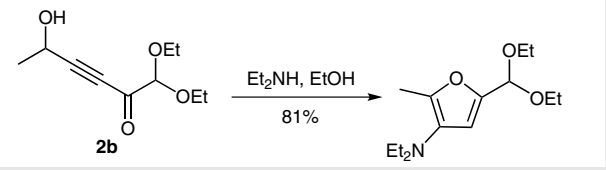
Key words α,β-unsaturated alkynones, hydrazine, guanidine, hydroxylamine, Michael addition, pyrazole, dihydroisoxazole, pyrimidine

Conjugated alkynones have become important intermediates in organic synthesis in recent years.[1–5] One reason is that such compounds react with nucleophiles in a Michael fashion and afford α,β-unsaturated alkenones as primary products, another is that the primary products may undergo subsequent reactions and form interesting compounds by secondary transformations.[5–7]

The outcome in a given case depends on the nature of the nucleophile and the properties of any additional reactive moiety present in the right position in the unsaturated ketone. The importance of these factors is illustrated by the outcome of reactions with two acetylenes, 1,1-diethoxybut-3-yn-2-one (**1**) and 1,1-diethoxy-5-hydroxyhex-3-yn-2-one (**2b**). When **1** is reacted with ammonia, the final product is (*Z*)-4-amino-1,1-diethoxybut-3-en-2-one, but when the nucleophile is switched to hydrazine, a bisnucleophile, the primary product reacts intramolecularly and furnishes 3-diethoxymethyl-1*H*-pyrazole (Scheme 1).[5] Ketone **2b**, however, contains one reactive group more than **1**, that is, an OH group, and when **2b** was treated with diethylamine the OH group reacts with the carbonyl group in the primary product and furnishes 4-diethylamino-2-diethoxymethyl-5-methylfuran (Scheme 2).[8]



Scheme 1

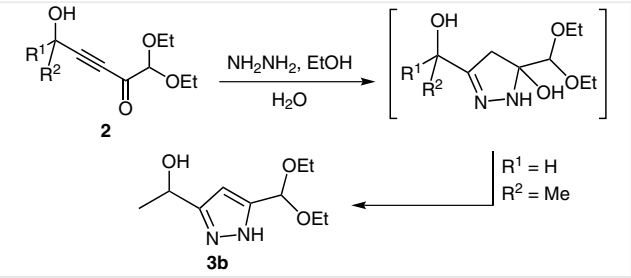


Scheme 2

What would happen if **2b** were treated with hydrazine or another bisnucleophile instead of a simple amine is, however, not obvious. The first step is supposed to be a conjugate addition leading to the corresponding β-substituted γ-hydroxy α,β-unsaturated olefinic ketone, but what the stereochemistry is going to become depends to a large extent on the hydrogen-bonding ability of the nucleophile residue relative to that of the OH group. If the OH and carbonyl groups end up *Z* to each other, a furan is expected, if not another heterocycle is anticipated. In principle, a third option is the formation of products due to intermolecular reactions, but from the results depicted in Schemes 1 and 2 that is unlikely.[5] Thus, the ultimate outcome is really determined by the competition in the first step. In order to get

some insight into this competition, **2b** and its analogues **2a** and **2c**–**e** have been reacted with three bisnucleophiles that are known to add very well to **1**, namely, hydrazine, guanidine, and hydroxylamine,[5,6] and the results obtained are reported here.

The study started by treating **2b** with hydrazine, which is known to give pyrazoles when reacted with simple conjugated acetylenic ketones.[5,6] Exploratory experiments, performed at room temperature and monitored by TLC and ^{1}H NMR, revealed that **2b** gave two products in a ratio, which varied with the reaction time in such a way that it was clear that the primary product was unstable and was gradually converted to a more stable secondary product. This was confirmed when the products were isolated; the stable product turned out to be 5-diethoxymethyl-3-(1-hydroxyethyl)pyrazole (**3b**) whereas the unstable compound was believed to be 5-diethoxymethyl-5-hydroxy-3-(1-hydroxyethyl)-4,5-dihydro-1*H*-pyrazole (Scheme 3) because it decomposed fairly quickly and furnished **3b** and water.[9] Apparently, the OH group cannot compete with the hydrazino moiety for the position *Z* to the carbonyl group in the addition reaction, and subsequent condensation leads to the formation of a pyrazole derivative.



Scheme 3

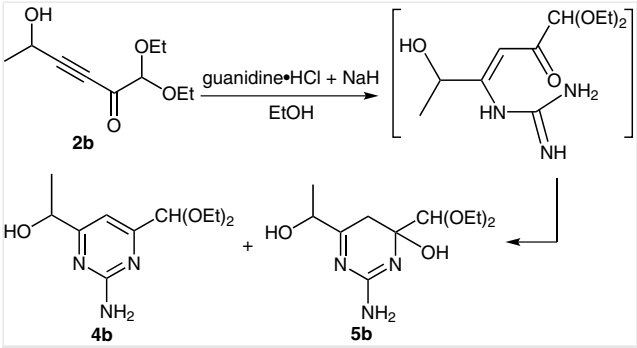
Based on these findings, the reactions of **2** with hydrazine were carried out above room temperature (40 °C) and under these conditions, some 16–18 hours were required to consume all the starting material. In most cases, the corresponding pyrazole **3** was obtained in good yield (>80%); in fact the only exception was 5-diethoxymethyl-3-(hydroxy)(phenyl)methyl-1*H*-pyrazole (**3d**), which was obtained from **2d** in 65% yield only (Table 1). In all cases, the conjugate addition obviously must have furnished the corresponding β-hydrazino-γ-hydroxy α,β-unsaturated olefinic ketone with *Z* stereochemistry.

The formation of 3,5-disubstituted pyrazole derivatives **3** in high yields is interesting because such pyrazoles have been shown to form useful complexes with some transition metals.[10] The 1-hydroxyalkyl group is instrumental when P- and S-ligands are going to be incorporated, and by converting the acetal group in position 3 to the corresponding aldehyde other ligands can subsequently be introduced. This approach to expand the scope of pyrazole ligands will be investigated in due course.

Table 1 Synthesis of 5-Diethoxymethyl-1*H*-pyrazoles **3** from **2** and Hydrazine

2	R^1, R^2	3	Isolated yield (%)
2a	H, H	**3a**	94
2b	H, Me	**3b**	94
2c	H, *i*-Pr	**3c**	80
2d	H, Ph	**3d**	65
2e	Me, Me	**3e**	89

Based on the results obtained for hydrazine, it was expected that also guanidine would afford the primary product with the *Z*-isomer and ultimately the corresponding 2-aminopyrimidine **4**. However, this expectation was only partly fulfilled due to formation of a number of by-products, of which one could be isolated in a couple of cases. The best result was obtained when 1,1-diethoxy-5-hydroxyhex-3-yn-2-one (**2b**) was reacted and gave 2-amino-6-diethoxymethyl-4-(1-hydroxyethyl)pyrimidine (**4b**) in 48% yield along with 30% of 2-amino-6-diethoxymethyl-5,6-dihydro-4-(1-hydroxyethyl)-6-pyrimidinol (**5b**) (Scheme 4).



Scheme 4

Attempts to improve the yield by extending the reaction time and/or running the reaction at higher temperatures did not help; instead the number and total yield of by-products increased. The best results, summarized in Table 2, are indeed disappointing considering the fact that 2-amino-4-diethoxymethylpyrimidine was isolated in 95% yield when **1** was reacted with guanidine for just 45 minutes at room temperature.[5]

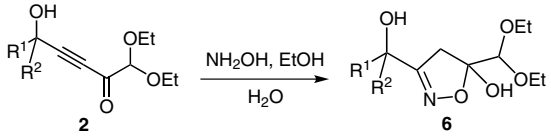
Unlike hydrazine and guanidine, hydroxylamine does not give aromatic heterocycles at all when reacted with **2** under similar conditions. In every case, the only product was a derivative of 5-diethoxymethyl-5-hydroxy-3-hydroxymethyl-4,5-dihydroisoxazole (**6**), which was easily isolated in better than 80% yield (Table 3).

The fact that hydroxylamine does not give aromatic products whereas hydrazine and guanidine do is interesting. These results clearly indicate that the aromaticity of

Table 2 Synthesis of 2-Amino-6-diethoxymethylpyrimidines **4** from **2** and Guanidine

2	R^1, R^2	Isolated yield (%)	
		4	5
2a	H, H	26	21
2b	H, Me	48	30
2c	H, *i*-Pr	30	0
2d	H, Ph	trace	0
2e	Me, Me	24	0

Table 3 Synthesis of 5-Diethoxymethyl-5-hydroxy-4,5-dihydroisoxazoles **6** from **2** and Hydroxylamine



2 6

2	R^1, R^2	6	Isolated yield (%)
2a	H, H	**2a**	85
2b	H, Me	**2b**	88
2c	H, *i*-Pr	**2c**	82
2e	Me, Me	**2e**	87

isoxazoles is significantly less than that of pyrazoles and pyrimidines, and this is in complete accordance with empirical resonance energy values reported by Katritzky et al.[11] Dehydration of 2-isoxazoline **6** to form the corresponding isoxazole should therefore not be a favored reaction and this was indeed what was observed. When **6a** and **6b** were refluxed in aqueous acetone under acidic conditions (Dowex 50W) no product was detected (TLC and NMR) even after 11 hours, and 2-isoxazolines were recovered in quantitative yield. And when water elimination was attempted from **6b** by azeotropic distillation in the presence of Dowex 50W only some of it reacted and gave a reaction mixture, which contained mainly unreacted 2-isoxazoline and from which no pure products were obtained.[12]

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 IR spectrophotometer, in most cases with the compound as a film between two NaCl plates. Standard abbreviations for denoting the intensities were used. NMR spectra were run on a Bruker Spectrospin DMX 400. Chemical shifts are reported downfield from TMS, the coupling constants are given in Hz, and standard abbreviations were used for denoting the multiplicities. TLC analyses of the reaction mixtures were performed with silica gel (60 F_{254}) on aluminum sheets with mixtures of EtOAc and isomeric hexanes as the mobile phase. Flash chromatography was carried out with silica gel (230–400 mesh) as the stationary phase with mixtures of EtOAc and isomeric hexanes as the mobile phase. The eluent composition is given for each of the isolations described below. Mass spectra were obtained on a JEOL AccuTOF T100GC spectrometer operated in the DART+ mode at 10–15 eV.

3,3,4,4-Tetraethoxybut-3-yn-2-one (**1**) was synthesized as described in the literature. This was used to prepare the 5-substituted 1,1-diethoxy-5-hydroxypent-3-yn-2-ones **2a**–**f** following published procedures.[3,5,7] The spectroscopic data were in agreement with those reported in the literature.

3,5-Disubstituted 1*H*-pyrazoles 3 by Reaction of 2 with Hydrazine; General Procedure

The unsaturated ketone **2** (5.00 mmol) was dissolved in absolute EtOH (25.0 mL) and a 55% aq solution of hydrazine (0.3 g, 5.1 mmol) was slowly added to the stirred solution. The reaction mixture was heated to 40 °C and left stirring overnight. The EtOH was removed on a rotary evaporator and the crude product was purified using gradient flash chromatography with a mixture of hexanes, EtOAc, and MeOH to give the 3,5-disubstituted 1*H*-pyrazoles **3a**–**e**.

5-Diethoxymethyl-3-hydroxymethyl-1*H*-pyrazole (3a)

The unsaturated ketone **2a** (0.93 g, 4.99 mmol) was reacted with a 55% aq solution of hydrazine (0.30 g, 5.1 mmol) for 16 h. The title compound **3a** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as an orange-red oil; yield: 0.94 g (94%).

IR (ATR): 3592–3056 (br), 3143 (m), 3106 (m), 3028 (w), 2974 (s), 2930 (m), 2876 (m), 1632 (w), 1573 (w), 1444 (w), 1390 (w), 1371 (w), 1324 (m), 1291 (w), 1141 (s), 1096 (s), 1047 (s), 994 (s), 910 (m), 805 (s), 759 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.25 (m, 6 H), 3.52–3.74 (m, 4 H), 4.68 (s, 2 H), 5.61 (s, 1 H), 6.24 (s, 1 H); signals due to the OH and NH groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (2 C), 56.7, 61.3 (2 C), 96.9, 101.9, 146.9, 148.0.

HRMS (DART): *m*/*z* calcd for $C_7H_{11}N_2O_2^+$ [M – EtO]$^+$: 155.08205; found: 155.08212.

5-Diethoxymethyl-3-(1-hydroxyethyl)-1*H*-pyrazole (3b)

The unsaturated ketone **2b** (1.02 g, 5.09 mmol) was reacted with a 55% aq solution of hydrazine (0.3 g, 5.1 mmol) for 18 h. The title compound **3b** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as an orange-red oil; yield: 1.03 g (94%).

IR (ATR): 3577–3059 (br), 3143 (m), 3102 (m), 2974 (s), 2930 (m), 2882 (m), 1664 (w), 1571 (w), 1479 (w), 1445 (w), 1371 (m), 1322 (m), 1277 (m), 1149 (s), 1088 (s), 1050 (s), 991 (s), 892 (m), 804 (s), 735 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.25 (m, 6 H), 1.53 (d, *J* = 6.5 Hz, 3 H), 3.52–3.74 (m, 4 H), 4.97 (q, *J* = 6.5 Hz, 1 H), 5.60 (s, 1 H), 6.21 (s, 1 H); signals due to the OH and NH groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (2 C), 23.2, 61.4 (2 C), 63.4, 96.9, 100.2, 146.8, 152.6.

MS (EI+): *m*/*z* (%) = 169.1 (100, M^+ – OEt).

HRMS (DART): *m*/*z* calcd for $C_{10}H_{19}N_2O_3^+$ [M + H]$^+$: 215.13856; found: 215.13155.

5-Diethoxymethyl-3-(1-hydroxy-2-methylpropyl)-1*H*-pyrazole (3c)

The unsaturated ketone **2c** (0.46 g, 2.02 mmol) was reacted with hydrazine (0.12 g, 2.06 mmol) for 16 h. The title compound **7c** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as a yellow to orange solid; yield: 0.39 g (80%). The obtained solid was recrystallized from hexane; mp 58–60 °C.

IR (ATR): 3595–3059 (br), 3141 (m), 3102 (m), 3028 (w), 2972 (s), 2930 (m), 2872 (m), 1707 (w), 1563 (w), 1469 (w), 1445 (w), 1384 (m), 1368 (m), 1323 (m), 1270 (w), 1148 (m), 1117 (s), 1094 (s), 1050 (s), 1010 (s), 910 (m), 805 (m), 736 (m), 702 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 6 H), 1.97–2.05 (m, 1 H), 3.53–3.68 (m, 4 H), 4.55 (d, *J* = 6 Hz, 1 H), 5.62 (s, 1 H), 6.18 (s, 1 H); signals due to the OH and NH groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (2 C), 17.9, 18.8, 34.4, 61.2, 61.3, 73.0, 96.9, 101.0, 146.8, 150.6.

HRMS (DART): *m*/*z* calcd for $C_{12}H_{23}N_2O_3^+$ $[M + H]^+$: 243.17086; found 243.16509.

5-Diethoxymethyl-3-(hydroxy)(phenyl)methyl-1*H*-pyrazole (3d)

The unsaturated ketone **2d** (0.523 g, 1.99 mmol) was reacted with a 55% aq solution of hydrazine (0.12 g, 2.06 mmol) for 16 h. The title compound **3d** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as an orange oil; yield: 0.36 g (65%).

IR (ATR): 3592–3048 (br), 3143 (m), 3104 (m), 3063 (m), 3028 (m), 2974 (s), 2932 (m), 2881 (m), 1663 (w), 1603 (w), 1565 (w), 1493 (w), 1479 (w), 1452 (m), 1391 (w), 1371 (w), 1323 (m), 1139 (s), 1096 (s), 1045 (s), 1021 (s), 984 (s), 911 (m), 804 (s), 698 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (dt, *J* = 7.0, 1.1 Hz, 6 H), 5.43–3.66 (m, 4 H), 5.48 (s, 1 H), 5.83 (s, 1 H), 6.00 (s, 1 H), 7.22–7.36 (m, 5 H); signals due to the OH and NH groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (2 C), 61.3 (2 C), 69.7, 96.6, 101.9, 126.7 (2 C), 127.7, 128.4 (2 C), 142.4, 146.3, 151.6.

MS (EI+): *m*/*z* (%) = 231.2 (100, M^+ – OEt).

HRMS (DART): *m*/*z* calcd for $C_{15}H_{21}N_2O_3^+$ $[M + H]^+$: 277.15521; found: 277.15892.

3-Diethoxymethyl-5-(1-hydroxy-1-methylethyl)-1*H*-pyrazole (3e)

The unsaturated ketone **2e** (0.22 g, 1.03 mmol) was reacted with a 55% aq solution of hydrazine (0.062 g, 1.06 mmol) for 18 h. The title compound **3e** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as a yellow semi-solid; yield: 0.21 g (89%).

IR (ATR): 3584–3006 (br), 3137 (m), 3100 (m), 2974 (s), 2930 (m), 2878 (m), 1683 (m), 1457 (m), 1377 (m), 1364 (m), 1327 (m), 1281 (m), 1207 (m), 1153 (s), 1116 (s), 1090 (s), 1050 (s), 995 (s), 961 (s), 909 (m), 845 (m), 807 (m), 770 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 6 H), 1.54 (s, 6 H), 3.48–3.64 (m, 4 H), 5.54 (s, 1 H), 6.13 (s, 1 H); signals due to the OH and NH groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (2 C), 30.8 (2 C), 61.3 (2 C), 69.1, 97.1, 99.5, 147.5, 155.2.

MS (EI+): *m*/*z* (%) = 183.2 (45, $[M – OEt]^+$).

HRMS (DART): *m*/*z* calcd for $C_{11}H_{21}N_2O_3^+$ $[M + H]^+$: 229.15521; found: 229.14924.

2,4,6-Trisubstituted Pyrimidines 4 by Reaction of 2 with Guanidine; General Procedure

A 60% suspension of NaH in mineral oil (0.046 g, 1.15 mmol) was dissolved in EtOH (2.50 mL) and left stirring for 15 min before guanidine hydrochloride (0.105 g, 1.10 mmol) dissolved in EtOH (1.0 mL) was added to the solution. After stirring for 30 min, the unsaturated ketone **2** (1.00 mmol) was added to the solution with some additional EtOH (1.5 mL). The reaction mixture was left stirring overnight at r.t. The solvent was removed on a rotary evaporator and the residue was dissolved in CH_2Cl_2 (10 mL), and H_2O was added (10 mL). The organic layer was separated from the aqueous phase and the aqueous phase was then extracted with CH_2Cl_2(3 × 8 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator. The crude product was purified using gradient flash chromatography with a mixture of hexanes, EtOAc, and MeOH to give a 2,4,6-trisubstituted pyrimidine **4** and in two cases also a 6-pyrimidinol **5**.

2-Amino-6-diethoxymethyl-4-hydroxymethylpyrimidine (4a) and 2-Amino-6-diethoxymethyl-5,6-dihydro-4-hydroxymethyl-6-pyrimidinol (5a)

The unsaturated ketone **2a** (0.93 g, 4.99 mmol) was reacted with guanidine hydrochloride (0.48 g, 5.02 mmol) for 15 h. The crude product was purified by gradient flash chromatography ([hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] affording pyrimidine **4a** as a yellowish solid, which was recrystallized from EtOH; yield: 0.30 g (26%): Further, the pyrimidinol derivative **5a** was isolated as a slightly yellow liquid; yield: 0.26 g (21%).

4a

Mp 120–123 °C.

IR (ATR): 3438 (m), 3304 (m), 3280–2990 (br), 2971 (s), 3929 (m), 2887 (s), 2840 (m), 1641 (s), 1568 (s), 1478 (m), 1456 (m), 1436 (m), 1392 (m), 1375 (m), 1347 (m), 1324 (m), 1308 (m), 1233 (m), 1125 (s), 1102 (s), 1056 (s), 1032 (s), 1006 (m), 981 (m), 952 (m), 905 (m), 848 (m), 836 (m), 809 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 6 H), 3.41 (br s, 1 H, OH), 3.55–3.71 (m, 4 H), 4.61 (s, 2 H), 5.12 (br s, 2 H, NH_2), 5.22 (s, 1 H), 6.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2 (2 C), 62.0 (2 C), 63.5, 100.9, 104.6, 162.5, 167.4, 170.2.

MS (DART): *m*/*z* (%) = 228 (100, $[M + H]^+$).

HRMS (DART): *m*/z calcd for $C_{10}H_{18}N_3O_3^+$ $[M + H]^+$: 228.13482; found: 228.13457.

5a (Mixture of Diastereomers)

IR (ATR): 3597–3313 (br), 2974 (s), 3931 (m), 2883 (m), 1482 (w), 1444 (m), 1391 (w), 1368 (w), 1274 (w), 1235 (w), 1158 (s), 1109 (s), 1051 (s), 1006 (s), 970 (s), 945 (s), 908 (m), 848 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.25 (m, 6 H), 2.15 (d, *J* = 13.4 Hz, 1 H), 2.37 (d, *J* = 13.4 Hz, 1 H), 3.44–3.82 (m, 4 H), 3.79 (d, *J* = 9.3 Hz, 1 H), 4.06 (d, *J* = 9.3 Hz, 1 H), 4.38 (s, 1 H); signals due to the OH and NH_2 groups were not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.42, 15.45, 15.48, 42.0, 58.0, 58.4, 64.6, 64.9, 72.1, 103.6, 105.8, 108.3.

MS (DART): *m*/*z* (%) = 229 (100, $[M + H – H_2O]^+$).

HRMS (DART): *m*/*z* calcd for $C_{10}H_{19}N_3O_3^+$ $[M + H – HO]^+$: 229.14264; found: 229.14367.

2-Amino-6-diethoxymethyl-4-(1-hydroxyethyl)pyrimidine (4b) and 2-Amino-6-diethoxymethyl-5,6-dihydro-4-(1-hydroxyethyl)-6-pyrimidinol (5b)

The unsaturated ketone **2b** (0.60 g, 3.00 mmol) was reacted with guanidine hydrochloride (0.34 g, 3.60 mmol) for 17 h. The crude product was purified by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] affording pyrimidine **4b** as a pale yellow solid, which was recrystallized from EtOH; yield: 0.35 g (48%). Further, the pyrimidinol derivative **5b** was isolated as as a colorless liquid; yield: 0.23 g (30%).

4b

Mp 94–95 °C.

IR (ATR): 3314 (s), 3184 (s), 2975 (s), 3930 (s), 2930 (m), 2840 (m), 1637 (m), 1563 (s), 1469 (m), 1443 (m), 1401 (m), 1384 (m), 1328 (m), 1300 (m), 1218 (w), 1165 (m), 1125 (s), 1056 (s), 1032 (s), 1005 (m), 952 (m), 909 (m), 876 (m), 851 (m), 831 (m), 801 (m), 785 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.8 Hz, 6 H), 1.46 (d, *J* = 6.6 Hz, 3 H), 3.55–3.71 (m, 4 H), 3.96 (br s, 1 H, OH), 4.69 (q, *J* = 6.6 Hz, 1 H), 5.21 (br s, 2 H, NH_2), 5.22 (s, 1 H), 6.84 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 (2 C), 23.3, 61.8, 61.9, 68.6, 100.8, 103.7, 162.5, 167.5, 174.1.

MS (DART+): *m*/*z* (%) = 242 (100, $[M + H]^+$).

HRMS (DART+): *m*/*z* calcd for $C_{11}H_{20}N_3O_3^+$ $[M + H]^+$: 242.15047; found: 242.15145.

5b (Mixture of Diastereomers)

IR (ATR): 3595–3335 (br), 2975 (s), 3932 (m), 2883 (m), 1482 (w), 1444 (m), 1390 (m), 1326 (m), 1286 (w), 1157 (s), 1112 (s), 1050 (s), 987 (s), 917 (m), 853 (m), 734 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.30 (m, 9 H), 1.61 (s, 1 H, NH/OH), 2.09 and 2.23 (2 d in an approximate ratio of 2:1, *J* = 13.1 and 13.9 Hz, respectively, 1 H), 2.41 and 2.45 (2 d in an approximate ratio of 2:1, *J* = 13.1 and 13.9 Hz, respectively, 1 H), 3.42–3.82 (m, 4 H), 4.06 (s, 1 H, NH/OH), 4.11 and 4.36 (2 q in an approximate ratio of 1:2, *J* = 6.6 and 6.5 Hz, respectively, 1 H), 4.31 (s, 1 H, NH/OH), 4.38 (s, 1 H); signals due to OH or NH_2 protons were not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.05, 15.09, 15.13, 15.2, 15.3, 17.2, 17.7, 39.6, 40.3, 56.8, 57.2, 58.2, 58.8, 64.3, 64.9, 65.0, 77.9, 79.4, 103.3, 103.6, 103.9, 104.0, 107.6, 108.4.

MS (DART+): *m*/*z* (%) = 215 (100, $[M + H - OEt]^+$).

HRMS (DART+): *m*/*z* calcd for $C_9H_{17}N_3O_3^+$ $[M + H - OEt]^+$: 215.12699; found: 215.12602.

2-Amino-6-diethoxymethyl-4-(1-hydroxy-2-methylpropyl)pyrimidine (4c)

The unsaturated ketone **2c** (0.24 g, 1.05 mmol) was reacted with guanidine hydrochloride (0.12 g, 1.26 mmol) for 3 h. The title compound **4c** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as a yellow solid after recrystallization from EtOAc; yield: 0.086 g (30%); mp 120–121 °C.

IR (ATR): 3426 (m), 3294 (m), 3270–3000 (br), 2967 (m), 3930 (m), 2881 (s), 1630 (s), 1563 (s), 1470 (m), 1403 (m), 1370 (m), 1317 (s), 1252 (w), 1227 (w), 1125 (s), 1056 (s), 1014 (s), 983 (m), 924 (w), 901 (w), 871 (m), 841 (m), 783 (m), 730 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 6 H), 1.97–2.05 (m, 1 H), 3.53–3.68 (m, 4 H), 3.90 (br s, 1 H, OH), 4.40 (d, *J* = 3.6 Hz, 1 H), 5.22 (s, 1 H), 5.34 (br s, 2 H, NH_2), 6.79 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (2 C), 15.8, 19.7, 34.5, 62.0 (2 C), 76.6, 101.0, 105.4, 162.2, 167.2, 172.3.

MS (DART+): *m*/*z* (%) = 270 (100, $[M + H]^+$).

HRMS (DART+): *m*/*z* calcd for $C_{13}H_{24}N_3O_3^+$ $[M + H]^+$: 270.18177; found: 270.18313.

2-Amino-6-diethoxymethyl-4-(1-hydroxyisopropyl)pyrimidine (4e)

The unsaturated ketone **2e** (0.22 g, 1.03 mmol) was reacted with guanidine hydrochloride (0.16 g, 1.67 mmol) for 15 h. The title compound **4e** was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as a yellow solid, which was recrystallized from EtOH; yield: 0.064 g (24%), mp 80–83 °C.

IR (ATR): 3362 (m), 3311 (m), 3184 (m), 2976 (m), 3927 (m), 2878 (m), 1638 (m), 1567 (s), 1455 (m), 1444 (m), 1381 (m), 1357 (m), 1330 (m), 1313 (m), 1177 (s), 1023(s), 1054 (s), 1025 (s), 982 (m), 967 (m), 944 (m), 900 (w), 852 (m), 821 (m), 804 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 6 H), 1.46 (s, 6 H), 3.55–3.70 (m, 4 H), 4.56 (br s, 1 H, OH), 5.21 (s, 1 H), 5.33 (br s, 2 H, NH_2), 6.89 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (2 C), 30.0 (2 C), 62.3 (2 C), 71.6, 101.3, 103.0, 162.0, 168.0, 176.8.

MS (EI+): *m*/*z* (%) = 211.2 (45, $[M + H - OEt]^+$).

HRMS (DART+): *m*/*z* calcd for $C_{12}H_{22}N_3O_3^+$ $[M + H]^+$: 256.18177; found: 256.18313.

4,5-Dihydroisoxazoles 6 by Reaction of 2 with Hydroxylamine; General Procedure

The unsaturated ketone **2** (1.00 mmol) was dissolved in EtOH (5.0 mL) and a 50 wt% aq solution of hydroxylamine (0.07 g, 1.06 mmol) was slowly added to the solution. The reaction mixture was stirred at r.t. for 1.5 h. The EtOH was removed on a rotary evaporator and the crude product was purified using gradient flash chromatography with a mixture of hexanes, EtOH, and MeOH to give the 3,5-disubstituted 4,5-dihydroisoxazoles **6**.

5-Diethoxymethyl-5-hydroxy-3-hydroxymethyl-4,5-dihydroisoxazole (6a)

The unsaturated ketone **2a** (0.93 g, 4.94 mmol) was reacted with a 50 wt% aq solution of hydroxylamine (0.34 g, 5.15 mmol). The title compound was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as an orange liquid; yield: 0.92 g (85%).

IR (ATR): 3629–3020 (br), 2977 (m), 3932 (m), 2881 (m), 1628 (w), 1446 (m), 1410 (m), 1372 (m), 1334 (m), 1198 (m), 1164 (m), 1056 (s), 998 (s), 896 (s), 862 (s), 820 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.28 (m, 6 H), 2.96 (d, *J* = 18.2 Hz, 1 H), 3.23 (d, *J* = 18.2 Hz, 1 H), 3.59–3.85 (m, 4 H), 4.40 (d, *J* = 14.4 Hz, 1 H), 4.43 (d, *J* = 14.4 Hz, 1 H), 4.58 (s, 1 H); signals due to the OH groups were missing.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (2 C), 42.0, 57.8, 64.7, 64.8, 102.0, 107.7, 160.1.

HRMS (DART+): *m*/*z* calcd for $C_9H_{18}NO_5^+$ $[M + H]^+$: 219.11850; found: 220.11842.

5-Diethoxymethyl-5-hydroxy-3-(1-hydroxyethyl)-4,5-dihydroisoxazole (6b)

The unsaturated ketone **2b** (1.05 g, 5.24 mmol) was reacted with a 50 wt% aq solution of hydroxylamine (0.34 g, 5.15 mmol) and **6b** was isolated as an inseparable mixture of diastereomers by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15) as a yellow liquid; yield: 1.06 g (88%).

IR (ATR): 3620–3067 (br), 2976 (m), 3930 (m), 2884 (m), 1622 (w), 1446 (m), 1398 (m), 1371 (m), 1323 (m), 1202 (m), 1165 (m), 1059 (s), 984 (s), 895 (s), 854 (s), 815 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.14 (m, 6 H), 1.25 and 1.30 (2 d in an approximate 3:2 ratio, *J* = 6.6 Hz, 3 H), 2.79 and 2.82 (2 d in an approximate 2:3 ratio, *J* = 18.0 Hz, 1 H), 3.15 (d, *J* = 18.0 Hz, 1 H), 3.40 and 4.30 (2 br s, 1 H, OH), 3.50–3.70 (m, 4 H), 4.42 and 4.44 (2 s, 1 H), 4.50 and 4.59 (2 q in an approximate 2:3 ratio, *J* = 6.4 Hz, 1 H), 5.25 and 5.51 (2 br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 15.1, 20.4, 20.5, 19.5, 40.9, 63.1, 63.6, 64.3, 64.4, 64.5, 64.7, 101.8, 107.4, 107.5, 162.9, 163.0.

MS (DART+): *m*/*z* (%) = 234 (100, $[M + H]^+$).

HRMS (DART+): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{20}NO_5^+$: 234.13415; found 234.13423.

5-Diethoxymethyl-5-hydroxy-3-(1-hydroxy-2-methylpropyl)-4,5-dihydroisoxazole (6c)

The unsaturated ketone **2c** (0.23 g, 1.01 mmol) was reacted with a 50 wt% aq solution of hydroxylamine (0.07 g, 1.06 mmol). The title compound was isolated as an inseparable mixture of diastereomers by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc (85:15)] as a white solid, which was recrystallized from EtOAc; yield: 0.22 g (82%); mp 88–90 °C.

IR (ATR): 3511–3210 (br), 2976 (m), 2959 (m), 3933 (m), 2875 (m), 1622 (w), 1472 (m), 1447 (w), 1409 (m), 1370 (w), 1338 (m), 1241 (w), 1217 (m), 1164 (m), 1106 (m), 1069 (s), 1049 (s), 1028 (s), 1005 (s), 923 (w), 873 (s), 830 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84, 0.95, 0.99, and 1.03 (4 d in an approximate 2:1:1:2 ratio, *J* = 6.8 Hz, 6 H), 1.17–1.27 (m, 6 H), 1.76–1.91 (m, 1 H), 2.83, 2.98, 3.17, and 3.21 (4 d in an approximate 1:2:2:1 ratio, *J* = 18.4, 18.0, 18.0, and 18.4 Hz, 2 H), 3.51 (br s, 1 H, OH), 3.55–3.82 (m, 4 H), 4.22 (d, *J* = 6.8 Hz, 1 H), 4.53 and 4.57 (2 s in an approximate ratio of 2:1, 1 H), 4.23 and 4.86 (2 br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.31, 15.35, 17.5, 18.4, 18.6, 32.1, 32.4, 40.2, 41.5, 64.4, 64.7, 64.9, 65.0, 73.0, 73.2, 102.1, 107.3, 107.7, 161.8, 162.1.

HRMS (DART+): *m*/*z* calcd for $C_{12}H_{24}NO_5^+$ $[M + H]^+$: 234.13415; found: 234.13423.

5-Diethoxymethyl-5-hydroxy-3-(1-hydroxyisopropyl)-4,5-dihydroisoxazole (6e)

The unsaturated ketone **2e** (0.22 g, 1.03 mmol) was reacted with a 50 wt% aq solution of hydroxylamine (0.07 g, 1.06 mmol). The title compound was isolated by gradient flash chromatography [hexanes–EtOAc (70:30), EtOAc–MeOH (85:15)] as a yellow solid, which was recrystallized from EtOAc; yield: 0.22 g (87%); mp 60–62 °C.

IR (ATR): 3553–3198 (br), 2976 (m), 2932 (m), 3933 (m), 2902 (w), 2886 (m), 1617 (w), 1456 (m), 1372 (m), 1330 (m), 1254 (m), 1223 (m), 1176 (m), 1063 (s), 1008 (s), 995 (m), 962 (m), 923 (m), 876 (s), 831 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.23 (m, 6 H), 1.40 (s, 3 H), 1.46 (s, 3 H), 2.95 (2 d, *J* = 18.2 Hz, 1 H), 3.23 (2 d, *J* = 18.2 Hz, 1 H), 3.57–3.79 (m, 4 H), 4.52 (s, 1 H); signals due to the OH groups were missing.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3 (2 C), 27.9, 28.0, 41.0, 64.4, 64.8, 69.4, 102.0, 107.9, 165.3.

HRMS (DART+): *m*/*z* calcd for $C_{11}H_{22}NO_5^+$ $[M + H]^+$: 248.14980; found: 248. 14965.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378898.

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