Expedient routes to 4,4-dialkyl- 5-methylene-1,3-oxazolines

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Dedicated to Academician Boris Trofimov on his 65th birthday
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Abstract
Tertiary alkynols with benzonitrile cyclize in the presence of acids to give 4,4-dialkyl-5-methylene-2-phenyl-1,3-oxazolines. Aliphatic nitriles and tertiary acetylenic alcohols are transformed, through intermediate acetylenic amides, which undergo ring-closure upon heating with solid alkali, to 2-alkyl-4,4-dialkyl-5-methylene-1,3-oxazolines.

Keywords: Tertiary acetylenic alcohols, nitriles, acetylenic amides, 5-methylene-1,3-oxazolines, amido-ketones

Introduction

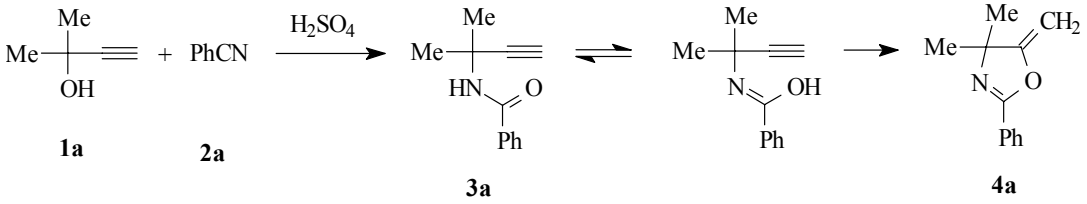
Recent investigations[1–11] have shown that 1,3-oxazolines (4,5-dihydro-oxazoles or 2-oxazolines) are potential ligands for the design of metal complex catalysts which are widely used in oxidation, polymerization, hydrogenation, hydrosilylation, and C–C bond formation (by Diels–Alder and Heck reactions). The asymmetric catalysis employing enantiomerically pure oxazoline ligands has been developed intensively during the last fifteen years.[1] Additionally, 1,3-oxazolines are well known as fuel and oil additives, antistatic agents for polyolefins and textiles, corrosion inhibitors, polyvinyl chloride stabilizers, rubber plasticizers, photosensitizers, antipyrenes, curing agents, etc.[12] Attractive representatives of the oxazoline family are the 5-methylene derivatives, owing to the presence of the double bond in their structure, which is capable of further modification.

According to patents,[13–16] 5-methylene-1,3-oxazolines can be prepared by cyclization of propargyl amides, although the conditions were not well disclosed. Two specific groups of the methylene-1,3-oxazolines, namely, 2-(2-aminophenyl)-4,4-dimethyl-5-methylene-4*H*-oxazoles and 3,3-disubstituted-2-methyleneoxazolo[2,3*b*]quin-5(3*H*)-ones, have been synthesized from isatoic anhydride and propargyl amines through the corresponding 2-amino-*N*-(1,1-disubstituted-propynyl) benzamides.[17] A recent publication[18] describes the catalytic cyclization of propargyl amides with aryl halides, leading to 5-methylene-1,3-oxazoles and -oxazolines, substituted at the methylene position, upon prolonged heating in the presence of Pd catalysts and bases.

Results and Discussion

We have developed a novel synthesis of 5-methylene-1,3-oxazolines directly from acetylenic alcohols and nitriles. Some propargyl amides being intermediates of this reaction were synthesized before.[19,20] Herein, we briefly report the results obtained.

The reaction of 2-methyl-3-butyn-2-ol **1a** with benzonitrile **2a** in the presence of concentrated sulfuric acid affords 4,4-dimethyl-5-methylene-2-phenyl-1,3-oxazoline **4a**, via the intermediate propargyl amide **3a**, in 80% yield.



1a **2a** **3a** **4a**

To evaluate the scope of this synthesis we have studied the reaction of the acetylenic alcohols **1** with other nitriles **2** in the presence of sulfuric acid (Table 1). 5-Methylene-1,3-oxazolines are easily detected even at a trace level by two doublets of the methylene group at 4.1–4.8 ppm (1H NMR of the reaction products).

Reaction of **1a**, 3-methyl-1-pentyn-3-ol **1b,** or 1-ethynylcyclohexanol **1c** with aliphatic nitriles such as acetonitrile **2b** or valeronitrile **2c** furnishes the corresponding propargyl amides **3b–f**. It is amazing that the well-known Ritter reaction was seemingly tried only once with tertiary acetylenic alcohols,[19] and consequently the real potential of this straightforward entry to propargyl amides remained obscured. The reaction is likely to involve the addition of carbocations **5** to nitriles **2** leading to cations **6**, which further add water. The subsequent treatment with an alkali gives the 5-methylene-1,3-oxazolines **4**.

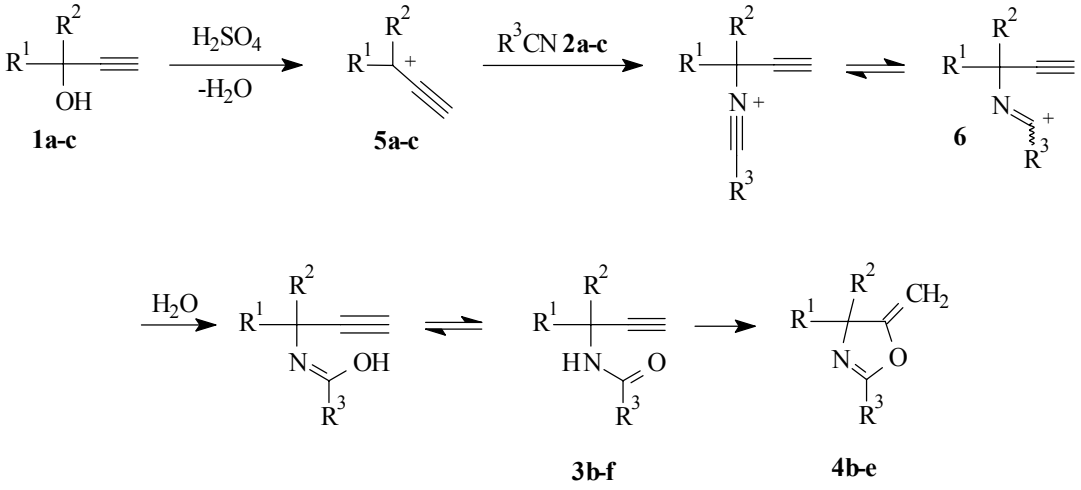
The modest yields of **3e** may be due to steric hindrances and insufficient stability of the starting alkynol **1c** under the reaction conditions. Indeed, a substantial amount of side 1-acetylcyclohex-1-ene **7**) is formed as a result of the Rupe rearrangement.[19,21] With benzonitrile, **2a**, 1-ethynylcyclohexanol gives a mixture of products composed of *N*-(1-

ethynylcyclohexyl)benzamide **3e**, oxazoline **4e** and ketone **7** in 3:1:8 ratio (by ^{1}H-NMR) (Table 1).

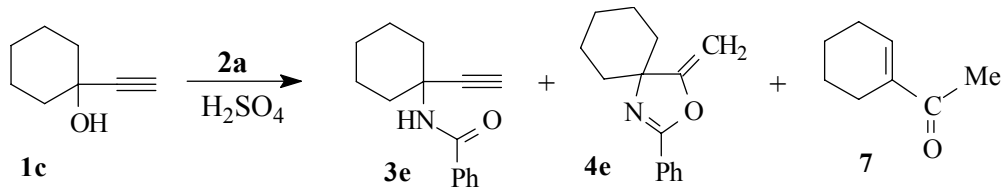
Table 1. Reaction of acetylenic alcohols **1** with nitriles **2**: effects of the reaction conditions and reactant structure

Reactants, g (mmol)		H_2SO_4, g (mmol)	Temperature, °C	Yield of product, %
1a, 4.2 (50)	**2a**, 14.1 (137)	5.5 (55)[a]	0	**4a**, 80
1a, 5.5 (66)	**2b**, 2.7 (66)	6.0 (60)	5–10	**3b**, 38
1a, 11.0 (130)	**2b**, 21.6 (530)	12.0 (120)	-20 : -15	**3b**, 54
1a, 11.0 (130)	**2b**, 21.6 (530)	12.0 (120)	-40 : -35	**3b**, 49
1a, 11.0 (130)	**2b**, 54.0 (1320)	12.0 (120)	-20 : -15	**3b**, 49
1a, 1.7 (20)	**2b**, 3.1 (76)	1.0 (20)[b]	-70	**3b**, 49
1a, 4.2 (50)	**2c**, 16.6 (200)	6.0 (60)	-20	**3c**, 25
1b, 19.4 (200)	**2b**, 32.6 (800)	18.0 (180)	-20	**3d**, 23
1c, 6.2 (50)	**2a**, 14.0 (137)	6.0 (60)	0	**3e**, ~25[c]
1c, 1.0 (8)	**2b**, 4.0 (97)	3.7 (38)	-20	**3f**, 20
1c, 3.1 (25)	**2b**, 2.7 (67)	12.0 (120)[d]	0	**3f**, 20
1c, 16.0 (130)	**2b**, 17.0 (416)	12.0 (120)	-20	**3f**, 27

[a] 1 g of Ac_2O was added. [b] Oleum was used instead of sulfuric acid. [c] A mixture of **3e**, **4d** and **7** (3:1:8). [d] 0.5 g of Ac_2O was added.

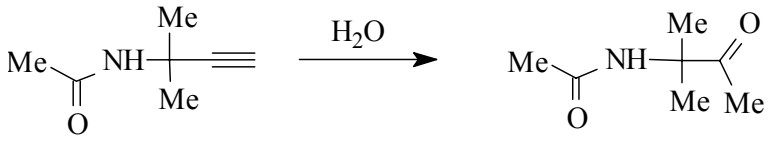


1a (R^1=R^2=Me); **1b** (R^1=Me, R^2=Et); **1c** [R^1–R^2=$(CH_2)_5$]; **2a** (R^3=Ph); **2b** (R^3=Me); **2c** (R^3=Bu); **3b** (R^1=R^2=R^3=Me); **3c** (R^1=R^2=Me, R^3=Bu); **3d** (R^1= R^3=Me, R^2=Et); **3e** [R^1–R^2= $(CH_2)_5$, R^3=Ph]; **3f** [R^1–R^2 =$(CH_2)_5$, R^3= e]; **4b** (R^1=R^2=R^3=Me); **4c** (R^1=R^3=Me, R^2=Et); **4d** [R^1–R^2=$(CH_2)_5$, R^3=Me]; **4e** [R^1–R^2=$(CH_2)_5$, R_3=Ph]; **5a** (R^1=R^2=Me); **5b** (R^1=Me, R^2=Et); **5c** [R^1–R^2=$(CH_2)_5$]



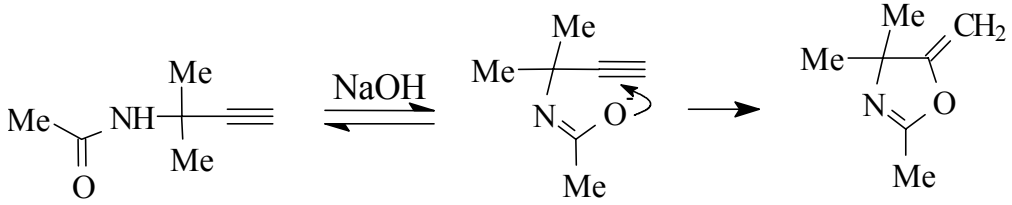
Substituents in the alkynols **1** and nitriles **2** have a strong effect on the cyclization ability of the intermediate propargyl amides **3**. In this case, the ring-closure proceeds during the work-up of the reaction mixture with aqueous alkali. In attempts to isolate the aromatic propargyl amide **3a** diverse work-ups were employed, including neutralization with aqueous alkali or ammonia, and drying of the organic layer with K_2CO_3 or $MgSO_4$, but in all the cases only the corresponding 1,3-oxazoline **4a** was isolated.

Amide **3b** is stable towards acids: heating it (50–95°C) in aqueous H_2SO_4 (5–45%) for 1–6 h resulted just in partial resinification and the release of traces of the starting alkynol **1a**. At 150°C, non-catalyzed hydration of the amide **3b** to 2-methyl-3-oxo-2-butylacetamide **8** occurs in 59% yield (autoclave, 1 h).



3b **8**

Using the amide of **3b** as an example, the behavior of tertiary propargyl amides in the presence of NaOH with or without solvent has been studied (Table 2). In most cases, 5-methylene-2,4,4-trimethyl-1,3-oxazoline **4b** was formed in 37–96% yield, depending on the reaction conditions.



3b **4b**

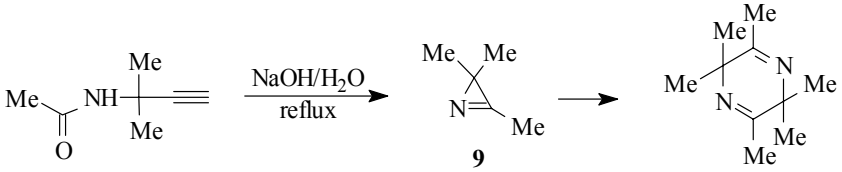
Table 2. Conditions for base-catalyzed cyclization of *N*-(1,1-dimethyl-2-propynyl)acetamide **(3b)**

Solvent	NaOH,	Temperature,	Time,	Yield of **4b**,

	%	°C	h	%
None	40	~130	0.1	96
None	4	~130	0.1	86
H_2O	14	98	7	90[a]
Toluene	4	20	3	37
Toluene	4	110	0.5	87
Benzene	4	80	3	71
DMSO	4[b]	20	0.1	~90

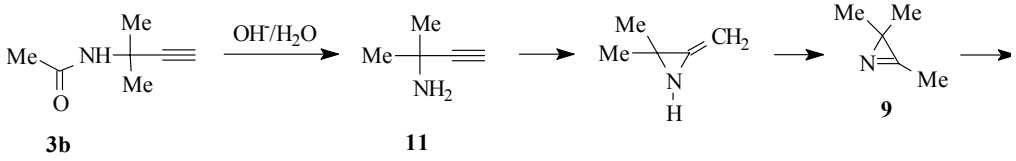
[a] 2,3,3,5,6,6-Hexamethyl-2,5-dihydropyrazine **10**. [b] KOH.

In a diluted (15%) aqueous solution of NaOH, amide **3b** undergoes hydrolysis to form 2,3,3,5,6,6-hexamethyl-2,5-dihydropyrazine, **10**, in 90% yield (Table 2) via the intermediate azirine **9**.



3b **9** **10**

Formation of trimethyl-2-azirine **9** has been proved by mass spectrometry and GLC. Apparently, a precursor of the compounds **9** and **10** is the acetylenic amine **11** which undergoes the ring-closure.



3b **11** **9**

The amides **3** represent protected acetylenic amines of the type **11**, which are of particular interest for the synthesis of pharmacologically active compounds.[22,23] Therefore, a search for preparatively acceptable conditions for removing the acetyl protecting group is a challenging synthetic task. Amazingly, the known methods for deacylation of amides,[24] such as aminolysis, hydrazinolysis and hydroxylaminolysis (in addition to the above alkaline and acidic hydrolysis) proved to be inefficient here. In the aminolysis of amide **3b** with ethanolamine, dibutylamine, dioctylamine, morpholine, aniline (50–100°C, 0.5–7 h), as well as in hydrazinolysis (60°C, 3 h) and in hydroxylaminolysis (80°C, 3 h), the initial amide **3b** was recovered, and trace amounts

(1–2%) of alkynol **1a** were sometimes detected. Deprotection also failed upon heating (50–100°C, 1–5 h) the amide **3b** with amido compounds, such as urea, guanidine and semicarbazide.

Under anhydrous conditions in the presence of solid NaOH, amide **3b** cyclizes smoothly to the oxazoline **4b** (Table 2). High, up to quantitative, yields of **4b** are reached by distilling it off from the reaction mixture (Table 2). In a superbase system, KOH–DMSO, the reaction accelerates so much that it is finished in ~5–6 min at room temperature.

Conclusions

While tertiary alkynols cyclize with aromatic nitriles and acids directly to 2-aryl-5-methylene-1,3-oxazolines, aliphatic nitriles under similar conditions form acetylenic amides **3**, which selectively transform to 2-alkyl-5-methylene-1,3-oxazolines upon heating with alkali under anhydrous conditions.

Experimental Section

General Procedures. ^{1}H- and ^{13}C- NMR spectra were recorded on a Bruker DPX 400 spectrometer in $CDCl_3$, with HMDS as an internal standard. IR spectra were run on a Bruker IFS 25 instrument. Chromatographic analysis was performed using a gas chromatograph "M 3700" equipped with 3×2000 mm columns filled with Chromaton AW HMDS with 15% of liquid phase DC-550. GC/MS analysis was carried out using a Hewlett-Packard HP 5971A instrument (70 eV, mass-selective detector), HP 5890 chromatograph, SPB-1 column (liquid phase SE-30), column length of 25 m, vaporizer temperature 250 °C, column temperature 70–280 °C, temperature increase rate of 20°C/min.

The alkynols **1a–c** were synthesized from ketones and acetylene by the Favorsky reaction in the KOH–DMSO system,[25] and commercial grade nitriles **2a–c**, DMSO (~0.4% H_2O), H_2SO_4 (98%), NaOH (< 2% H_2O), KOH (~15% H_2O) were used.

Synthesis of 2-aryl-5-methylene-1,3-oxazolines (typical procedure). To a mixture of a tertiary alkynol (50 mmol) and benzonitrile (136 mmol), cooled to 0°C, a mixture of 3 mL of sulfuric acid and 1 mL of acetic anhydride is added dropwise for 30 min under stirring. The reaction mixture is further stirred for 30 min at 0°C and allowed to stay 20 h at room temperature. After that the mixture is decomposed with ice, neutralized with aqueous ammonia, extracted with diethyl ether, and the extract is dried over anhydrous K_2CO_3. After removal of the ether, the corresponding oxazoline is isolated from the mixture by column chromatography (alumina, hexane).

4,4-Dimethyl-5-methylene-2-phenyl-1,3-oxazoline (4a). Colorless liquid (80%), μ_D^{20} 1.539; IR (cm^{-1}, neat): 3112 w, 3091 w, 3067 m, 3034 w (ν $=CH_2$, ν $C=C-H_{aryl}$), 1695 for 2-(2-

aminophenyl)-4,4-dimethyl-5-methylene-4*H*-oxazole; [17] 2974 s, 2928 m, 2865 m (ν CH_3); 1696 s (ν C=C); 1650 vs. (ν C=N), 1640 for 2-(2-aminophenyl)-4,4-dimethyl-5-methyleneoxazoline;[17] 1603 m, 1580 m, 1495 m (ν, benzene ring); 1451 s, 1388 m (δ CH_3); 1294 s (ν C-N); 1188 s, 1056 s (ν C-O); 1321 s, 1075 m, 1024 s (ν C-C_{aryl}); 826 s (δ CH_2); 779 s, 695 *vs.* (γ C-H_{aryl}) cm^{-1}; ^{1}H NMR: δ 7.97–7.42 (m, 5H, benzene ring protons), 4.74 d and 4.23 d (4H, =CH_2, ^2J = 2.81 Hz, 2.7 Hz for 2-(2-aminophenyl)-4,4-dimethyl-5-methyleneoxazoline[17]), 1.43 (s, 3H, Me_2); ^{13}C NMR δ 168.00 (C=CH_2), 159.90 (C=N), 131.69, 128.50, 128.17, 127.07 (benzene ring carbons), 82.35 (=CH_2), 69.13 (CMe_2), 29.80 (Me_2). Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.06; H, 6.92; N, 7.61%.

5-Methylene-2-phenyl-4-spirocyclohexane-1,3-oxazoline (4e). The product is obtained in a mixture with **3e** and **7** (Table 1). ^{1}H NMR: δ 7.87–7.39 (m, 5H, phenyl ring protons), 4.72 d and 4.22 d (4H, =CH_2, ^2J = 2.84 Hz), 2.15–1.61 (m, 10H, cyclohexane ring protons).

Synthesis of amides 3b–3d (typical procedure). Into a flask, equipped with magnetic stirrer, thermometer and dropping funnel, 12.0 g (120 mmol) of H_2SO_4 is placed, then 132 mmol of a nitrile **2a**, **2b** or **2c** is added dropwise at 5 °C. The reaction mixture is cooled to –20°C and 130 mmol of an alkynol **1a**, **1b** or **1c** in 396 mmol of the same nitrile is added dropwise for 2.5 h. After 15 h the reaction mixture is decomposed with crushed ice and neutralized with 40% aqueous NaOH at -10–0°C. The organic layer is separated and the aqueous layer is extracted with diethyl ether, and the combined extracts dried over K_2CO_3. After removal of the solvents, the crude amide is recrystallized from an appropriate solvent.

***N*-(1,1-Dimethyl-2-propynyl)acetamide (3b).** Light-yellow crystals (54%), mp 100–101°C (hexane) [Lit.[19] mp 103–104.5°C (di-isopropyl ether)]; IR (cm^{-1}, KBr): 3292 sh. (ν ≡C-H); 3267 s, 3202 m (ν N-H); 3069 m (overtone of amide-II); 3002 m, 2984 m, 2973 m, 2938 m, 2855 m (ν CH_3); 2111 w (ν C≡C); 1652 s (amide-I); 1549 s (amide-II); 1302 m (ν C-N); 1225 m, 1192 m, 1173 m (ν -C-C-) cm^{-1}; ^{1}H NMR: δ 5.78 (br. s, 1H, NH), 2.29 (s, 1H, ≡CH), 1.95 (s, 3H, Me), 1.63 (s, 6H, Me_2); ^{13}C NMR: δ 168.97 (C=O), 87.30 (C≡CH), 69.11 (C≡CH), 47.59 (C-Me_2), 28.90 (Me_2), 24.03 (Me). Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.47; H, 9.17; N, 10.78%.

***N*-(1,1-Dimethyl-2-propynyl)valeramide (3c).** Light-yellow crystals (25%), mp 75–76°C (hexane), [Lit.[19] 78–79°C (hexane)]; IR (cm^{-1}, KBr): 3324 s (ν N-H); 3281 sh. (ν ≡CH); 3221 s (ν N-H); 3069 m (overtone of amide-II); 2982 m, 2961 s, 2930 s, 2872 m (ν CH_2, ν CH_3); 2110 w (ν C≡C); 1644 vs. (amide-I), 1546 s (amide-II); 1454 m (δ CH_2); 1227 m, 1189 m, 1169 m, 1097 m (ν -C-C-) cm^{-1}; ^{1}H NMR: δ 5.94 (br. s, 1H, NH), 2.31 (s, 1H, ≡CH), 2.14 (t, 2H, CH_2C=O), 1.62 (s, 6H, Me_2), 1.60 (m, 2H, CH_2CH_2C=O), 1.34 (q, 2H, MeCH_2), 0.90 (t, 3H, Me). ^{13}C NMR: δ 172.44 (C=O), 87.54 (C≡CH), 69.00 (C≡CH), 47.46 (CMe_2), 47.46 (CH_2C=O), 29.07 (Me_2), 27.74 (CH_2CH_2C=O), 22.39 (MeCH_2), 13.87 (Me). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.70; H, 11.02; N, 8.36%.

***N*-(1-Ethyl-1-methyl-2-propynyl)acetamide (3d).** Colorless liquid (23%), bp 120°C (15 mm Hg), η_D^{20} 1.4695. IR (neat, cm^{-1}): 3298 sh. (ν, ≡C-H); 3264 s, 3064 m (overtone of amide-II);

2977 m, 2938 m, 2881 m (ν, CH_3), 2113 w (ν, C≡C), 1654 s (amide-I); 1547 s (amide-II); 1443 m, 1371 m, 1303 m (ν, C-N); 1225 m, 1202 m, 1192 m, 1179 m (ν, -C-C-) cm^{-1}; ^{1}H NMR: δ ^{1}H NMR (*δ*, ppm): 5.79 br. s (1H, NH); 2.28 s (1H, C≡CH); 1.98 m, [1H, CH_2Me], 1.74 m [1H, CH_2Me], 1.93 t [3H, CH_2Me]; 1.89 s [3H, MeC(O)]; 1.54 s (3H, Me); ^{13}C NMR: δ 169.24 (C=O), 86.24 (C≡CH), 70.26 (C≡CH), 52.05 (CEtMe), 32.94 [CH_2Me], 26.34 (MeC=O), 24.07 (Me), 8.75 [CH_2Me]. Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.10; H, 9.38; N, 10.02%.

***N*-(1-Ethynylcyclohexyl)acetamide (3f).** Yield 27%, mp 149°C (toluene), Lit.[19] 151.5–152°C (toluene); IR (cm^{-1}, KBr): 3346 s (ν N-H); 3312 sh (ν ≡CH); 3217 s (ν N-H); 3065 w (overtone of amide–II); 2984 s, 2927 s, 2859 s (ν CH_3, ν CH_2); 2109 w (ν C≡C), 1649 vs (amide-I); 1540 s (amide–II); 1451 m (δ CH_2) cm^{-1}; ^{1}H NMR 5.53 (br. s, 1H, NH), 2.39 (s, 1H, ≡CH), 2.15–1.61 (m, 10 H, cyclohexane ring protons), 1.96 (s, 3H, Me); ^{13}C NMR 169.34 (C=O), 85.71 (C≡CH), 71.30 (C≡CH), 51.71 (C-1, cyclohexane ring carbon), 36.94 (C-2, cyclohexane ring carbon), 25.32 (Me), 24.18 (C-4, cyclohexane ring carbon), 22.47 (C-3, cyclohexane ring carbon); Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.41; H, 9.27; N, 8.53%.

Synthesis of 2-alkyl-5-methylene-1,3-oxazolines (typical procedure). A mixture of 8 mmol of an acetylenic amide and 10 mmol of powdered NaOH is distilled (at 130°C for the amide **3b**), and the corresponding oxazoline is collected.

5-Methylene-2,4,4-trimethyl-1,3-oxazoline (4b). Yield 96%, bp 115°C, η_D^{20} 1.4380; IR (cm^{-1}, neat): 3115 w, 3012 w (ν $=CH_2$); 2976 s, 2930 s, 2866 m (ν CH_3); 1700–1670 s, br (ν C=C, ν C=N); 1456 s, 1387 s [δ $(CH_3)_2$]; 1435 s, 1361 s (δ C-CH_3); 1256 s (ν C-N); 1190 s, 1132 s (ν C-O); 824 s (δ $=CH_2$) cm^{-1}; ^{1}H: δ NMR 4.54 d and 4.11 d (4H, $=CH_2$, ^2J = 2.54 Hz), 2.03 (s, 3H, Me), 1.30 (s, 6H, Me_2); ^{13}C NMR: δ 168.17 (C=CH_2), 160.61 (C=N), 81.37 ($=CH_2$), 68.45 (CMe_2), 29.42 (Me_2), 13.95 (Me); Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 65.87; H; 8.93; N, 10.82%.

2,4-Dimethyl-4-ethyl-5-methylene-1,3-oxazoline (4c). Yield 87%, bp 142–143°C, η_D^{20} 1.4410; IR (neat, cm^{-1}): 3114 w (ν, $=CH_2$); 2976 s, 2929 s, 2856 m (ν, Me, CH_2); 1700–1660 s, br (ν, C=C, ν, C=N); 1453 s, 1437 s, 1384 s (δ, Me); 1262 s (ν, C-N); 1182 s, 1127 s (ν, C-O); 823 s (δ, $=CH_2$) cm^{-1}; ^{1}H: δ NMR 4.05 d and 4.60 d (2H, $=CH_2$, ^2J = 2.64), 2.05 s (3H, Me-C=N), 1.46 m and 1.71 m (2H, CH_2-Me), 1.29 s (3H, Me), 0.76 t (3H, Me-CH_2); ^{13}C NMR: δ 166.30 (C=CH_2), 160.35 (C=N), 81.77 ($=CH_2$), 71.90 (C-Me), 34.33 (CH_2-Me), 28.00 (Me), 13.52 (Me-C=N), 7.85 (Me-CH_2); Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.77; H; 9.72; N, 10.12%.

2-Methyl-5-methylene-4-spirocyclohexane-1,3-oxazoline (4d). The product is obtained in a mixture with **3d** (1:1) upon heating (100 °C) of 0.5 g (3 mmol) of amide **3d** with 0.1 g (2.5 mmol) of NaOH for 30 min in ~50% yield (^{1}H NMR). ^{1}H NMR: δ 4.56 d and 4.11 d (4H, $=CH_2$, ^2J = 2.68 Hz), 2.15–1.61 (m, 10H, cyclohexane ring protons), 2.06 (s, 3H, Me). The synthesis of **4d** was described in ref. 26, with the bp of 69 °C (4 mm Hg) given as the only characteristic.

Hydration of N-(1,1-dimethyl-2-propynyl)acetamide (3b). A solution of 0.50 g (4 mmol) of amide **3b** in 50 mL of water is heated in an autoclave at 150°C during 1 h. After cooling the reaction mixture is extracted with diethyl ether, dried over anhydrous K_2CO_3, the solvent is removed to give 0.34 g (59% yield) of amido-ketone **8**.

2-Methyl-3-oxo-2-butylacetamide (8). White crystals, mp 100–101 °C (hexane), Lit.[27] 109–111°C; IR (cm^{-1}, KBr): 3273 s, 3202 m (ν N-H); 3067 w (overtone of amide-II); 2984 m, 2938 m, 2855 m (ν CH_3); 1715 s (ν C=O); 1643 vs (amide-I); 1546 vs (amide–II); 1305 m (ν C-N); 1218 m, 1128 m (ν -C-C-) cm^{-1}. ^{1}H NMR: δ 6.55 (br. s, 1H, NH), 2.18 (s, 3H, Me-N), 1.98 (s, 3H, Me-C=O), 1.46 (s, 6H, Me_2); ^{13}C NMR: δ 209.23 (Me-C=O), 170.17 (N-C=O), 61.00 (CMe_2), 23.68 Me_2), 23.52 [N-(C=O)-Me], 23.52 [C-(C=O)-Me]. Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 59.61; H, 9.27; N, 9.98.

Alkaline hydrolysis of amide (3b). A mixture of 1.00 g (8 mmol) of amide **3b** and 10 mL of 15% aqueous solution of NaOH is refluxed for ~6 h. A low-melting (~35–50 °C) white mass is collected in a condenser. The ratio **9**:**10** is ≈ 1:4 (GLC). m/z (%): 84 [$(M+H)^+$, 54]; 68 [$(M-Me)^+$, 7]; 66 [$(M-NH_3)^{+\bullet}$, 100]; 50 (13), 48 (33), 46 (58); the retention time is 3.4 min. After vacuum drying (~3 mm Hg, 10 min) 0.6 g (90% yield) of the dihydropyrazine **10** is obtained.

2,3,3,5,6,6-Hexamethyl-2,5-dihydropyrazine (10). White crystals, mp 66°C, Lit.[28] 65°C; IR (cm^{-1}, KBr): 2970 s, 2928 m, 2870 m (ν CH_3); 1656 vs, 1641 s (ν C=N); 1462 m, 1434 m, 1368 m, 1356 m (δ CH_3); 1219 m, 1164 m, 1153 m, 1130 m (ν ring); 938 w, 874 m (ν C-C); 657 m [(ρ + ω) CH_3]; 500 m (δ ring) cm^{-1}; ^{1}H NMR: δ 2.00 (s, 3H, Me), 1.29 (s, 6H, Me_2); ^{13}C NMR: δ 168.73 (C=N), 55.63 (C-N), 28.10 (Me_2), 22.27 (Me). m/z (%): 166 ($M^{+\bullet}$, 7); 125 [$(M-MeCN)^{+\bullet}$, 40]; 110 [$(M-Me_2CN)^+$, 100]; 83 [$(M-Me_2CN-HCN)^+$, 10]; 69 [$(M-Me_2CN-MeCN)^+$, 41]; 42 [$(C_3H_6)^{+\bullet}$, 53]; 41 [$(C_3H_5)^+$, 37]; retention time is 7.3 min. Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 69.71; H, 10.78; N, 16.30%.

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