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CYCLIZATION OF N-(1,1-DIMETHYL-2-PROPYNYL)ACETAMIDE TO 2,2,3,5,5,6-HEXAMETHYL-2,5-DIHYDROPYRAZINE

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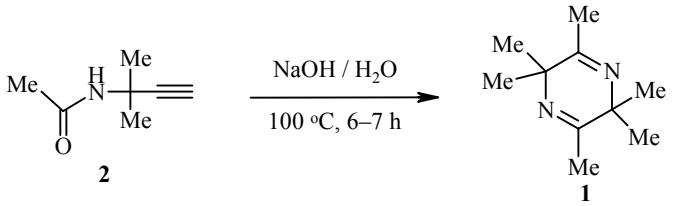
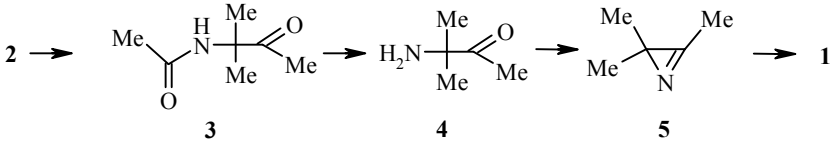
Dihydropyrazines, which feature as intermediates in the synthesis of pyrazines, are generally unstable compounds usually obtained by the intermolecular condensation of amino ketones [1]. 2,2,3,5,5,6-Hexamethyl-2,5-dihydropyrazine (**1**), which is one of the few stable representatives of this class, is synthesized by the hydration of acetylenic amines or amides [2-4], sometimes with the use of mercury catalysts [3, 4]. However, in these studies, dihydropyrazine **1** was isolated only as hydrates. Unhydrated dihydropyrazine **1** was obtained through not readily available trimethyl-2-chloroxirane [5] or an unusual compound, dimethyl-2,4-diazabicyclo[3.1.0]hexan-3-one [6].

We have found that N-(1,1-dimethyl-2-propynyl)acetamide (**2**) is readily converted in 15% aq. NaOH into dihydropyrazine **1** in 90% yield.



2 **1**

This cyclization probably proceeds through 2-methyl-3-oxo-2-butylacetamide (**3**), amino ketone **4**, and trimethyl-2-azirine (**5**):



2 **3** **4** **5** **1**

We have reported the hydration of amide **2** to give amido ketone **3** was observed under aquathermolysis conditions in a separate communication [7]. The formation of azirine **5** was confirmed by GC/MS (M = 83). It is interesting that only the base-catalyzed cyclization of amide **2** to give 2,4,4-trimethyl-5-methylene-1,3-oxazoline has been reported until now [8].

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This preparative version of propargylamide cyclization is the simplest pathway to hexaalkyl-2,5-dihydropyrazines.

The ^{1}H and ^{13}C NMR spectra of dihydropyrazine **1** at 400 and 100 MHz, respectively, were taken on a Bruker DPX-400 spectrometer in $CDCl_3$. The IR spectra were taken on a Hewlett-Packard HP 5971A mass spectrometer at 70 eV with a mass selective detector and HP 5890 chromatograph using a 25-m SPB-1 column packed with SE-30 as the liquid phase. The injection temperature was 250°C. The column temperature was raised from 70 to 250°C at a rate of 20°C/min.

2,2,3,5,5,6-Hexamethyl-2,5-dihydropyrazine (1). A sample of amide **2** (1.0 g, 8 mmol) in 15% aq. NaOH (10 ml) was heated at reflux for 6-7 h. A moist white mass melting at ~35-50°C formed within the condenser. Drying this mass at ~3 mm Hg for 10 min gave 0.6 g (90%) dihydropyrazine as white crystals; mp 66°C (hexane). ^{1}H NMR spectrum, δ, ppm: 2.00 (Me), 1.29 (Me_2). IR spectrum, ν, cm^{-1} (KBr): 2966, 2970, 2928, 2868, 1656 (C=N), 1541, 1462, 1435, 1368, 1356, 1305, 1219, 1164, 1153, 1130, 1041, 1021, 993, 937, 874, 740, 658, 611, 598, 551, 500. ^{13}C NMR spectrum, δ, ppm: 168.73 (C=N), 55.63 (C–N), 28.10 (Me_2), 22.27 (Me). Mass spectrum, *m/z* (*I*, %): 166 [M], 125 (40), 110 (100), 95 (3), 83 (10), 69 (41), 53 (8), 55 (55), 39 (18). Found, %: C 72.25; H 10.86; N 16.79. $C_{10}H_{18}N_2$. Calculated, %: C 72.29; H 10.91; N 16.85.

Trimethyl-2-azirine 5. Mass spectrum, *m/z* (*I*, %): 85 [M + 2] (2), 84 [M + 1] (54), 83 [M] (2), 68 (7), 66 (100), 50 (13), 48 (33), 46 (58).

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