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OXOALKYLATION OF PYRAZINE BY 1-METHYLCYCLOALKANOLS UPON MECHANICAL ACTIVATION

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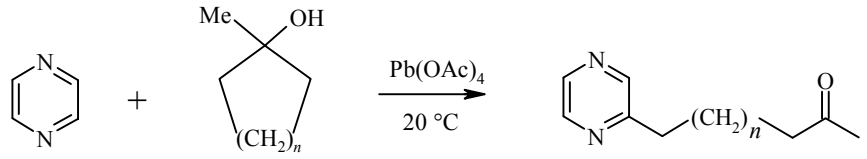
Solid-phase reactions and reactions in the absence of solvent have recently attracted considerable attention [1, 2].

We have already shown that the solid-phase reaction of protonated pyridine and 4-picoline with tertiary cyclic alcohols, which proceeds by the action of $Pb(OAc)_4$, leads to the products of the oxoalkylation of these heterocyclic compounds in high yield [3]. However, the oxoalkylation of pyrazine could not be achieved under analogous conditions.



1 **2a,b** **3a,b**

a $n = 1$; **b** $n = 2$

In the present work, a new approach is described for the synthesis of 2-(oxoalkyl)pyrazines (Table 1) based on the reaction of pyrazine **1**, 1-methylcycloalkanols **2a**,**b**, and $Pb(OAc)_2$ upon mechanical activation in a heterogeneous system with the absence of solvent.

The results of the oxoalkylation of pyrazine in acetic acid as the solvent without mechanical activation, i.e., under the usual conditions for reactions with $Pb(OAc)_4$ in a homogeneous system, are also given in Table 1 for comparison [4].

Our major conclusion is that the conversion of cycloalkanols **2a**,**b**, the yield of oxoalkylation products **3a**,**b**, and the selectivity of formation of these products are much higher in the case of the mechanical activation than in the liquid-phase variant of this reaction. When a small amount of acetic acid (0.5 mol/mol pyrazine) is added to the reagents, the conversion, yield, and selectivity are even further increased. The reaction does not proceed in the absence of solvent without mechanical activation.

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TABLE 1. Oxoalkylation of Pyrazine by 1-Methylcyclobutanol (**2a**) and 1-Methylcyclopentanol (**2b**) by the Action of $Pb(OAc)_4$

Cycloalkanol	**1**:**2**:$Pb(OAc)_2$:AcOH Molar Ratio*	Conversion of **2a,b**, %*[2]	Yield of **3a,b**, %*[3]
2a	6 : 1 : 1.5 : 0	85	84/99
2a	6 : 1 : 2 : 0	92	92/100
2a	6 : 1 : 2 : 3	96	96/100
2a	6 : 1 : 1.5*[4]	70	38/54 [4]
2b	6 : 1 : 1.5 : 0	35	33/95
2b	6 : 1 : 2 : 0	40	37/92
2b	6 : 1 : 2 : 3	64	59/92
2b	6 : 1 : 2*[4]	35	25/73

* The amount of cycloalkanol **2** was 0.5 mmol.
*[2] The conversion of $Pb(OAc)_4$ was 100%.
*[3] Reaction in 10 ml AcOH at 80°C.
*[4] Yield relative to starting **2**/to amount of **2** consumed.

General Method for the Oxoalkylation. The mechanical activation of the reaction mixture (1-2 g total mass) consisting of pyrazine **1**, cycloalkanol **2**, $Pb(OAc)_4$, and acetic acid was carried out in a vibrational mill with frequency 12 Hz and amplitude 11 mm in a hermetically-sealed ~80-cm^3 steel reactor. Steel balls with 12.3 mm diameter and ~150 g total mass were used as the activation packing. The mechanical action was carried out for 4 h. The mixture was then treated with ether and chloroform. The combined extracts were washed with 3% hydrochloric acid and aqueous $NaHCO_3$ and dried over Na_2SO_4. Filtration and evaporation gave product **3**.

2-(4-Oxopentyl)pyrazine (3a); bp 62-63°C (15 mm Hg). IR spectrum (neat), ν, cm^{-1}: 1720 (C=O). ^{13}C NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 23.02, 34.33 and 42.55 (CH_2), 29.93 (CH_3), 142.30, 144.00, and 144.55 ($C_{(3)}$, $C_{(5)}$, $C_{(6)}$), 156.93 ($C_{(2)}$), 208.12 (C=O). The ^1H NMR spectrum was identical to that described for this product in our previous work [4].

2-(5-Oxohexyl)pyrazine (3b); bp 67-69°C (15 mm Hg). IR spectrum (neat), ν, cm^{-1}: 1715 (C=O). ^1H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm, *J* (Hz): 2.01-2.09 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2CO$); 2.13 (3H, s, CH_3CO); 2.48 (2H, t, *J* = 3.45, CH_2CO); 2.82 (2H, t, *J* = 3.64, $C\underline{H}_2CH_2CH_2CH_2CO$); 8.39 and 8.48 (2H, d, *J* = 1.21, d, *J* = 0.94, 5-, 6-H); 8.46 (1H, s, 3-H). ^{13}C NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 23.12, 23.45, 34.53 and 42.66 (CH_2), 29.82 (CH_3), 142.11, 143.98 and 144.45 ($C_{(3)}$, $C_{(5)}$ and $C_{(6)}$), 156.93 ($C_{(2)}$), 208.10 (C=O). Mass spectrum, *m/z*: 178 $[M]^+$. Found, %: C 67.38; H 7.88; N 15.80. $C_{10}H_{14}N_2O$. Calculated, %: C 67.41; H 7.86; N 15.73.

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