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- N-METHYLTYRAMINE AND N,O-DIMETHYLTYRAMINE SYNTHESIS VIA INTERMEDIATE 4-METHOXYPHENYL-N-METHYLTHIOACETAMIDE

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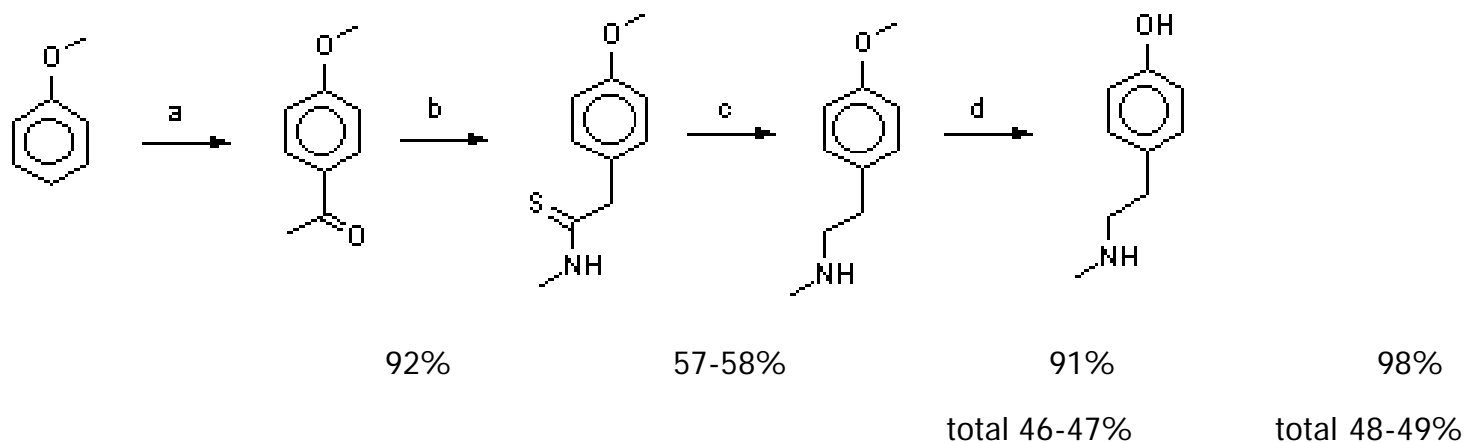
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N-Methyltyramine and its alkyl or benzyl ethers are common intermediate products in the syntheses of narwedine, and galanthamine alkaloids [1-8]. They are usually produced from the corresponding arylacetamides by lithium aluminium hydride reduction. In order to avoid application of inflammable lithium aluminium hydride bulgarian scientists have transformed arylacetamide to arylthioacetamide with phosphorus (V) sulfide with following reduction of arylthioacetamide with complex sodium borohydride - nickel or cobalt chloride agents [7, 8].

Here we present a new short way route to N-methyltyramine and its ethers via the corresponding aryl-N-methylthioacetamides, shown at the scheme 1 at the example of N-methyltyramine and N,O-dimethyltyramine synthesis.

Scheme 1.



a) H_3CCOBr , AlCl_3 , $\text{ClCH}_2\text{CH}_2\text{Cl}$.

b) $\text{H}_3\text{CNH}_2 \cdot \text{HCl}$, S_8 , $\text{H}_3\text{CCO}_2\text{Na}$, $(\text{H}_3\text{C})_2\text{NCHO}$, 115°C , 3h.

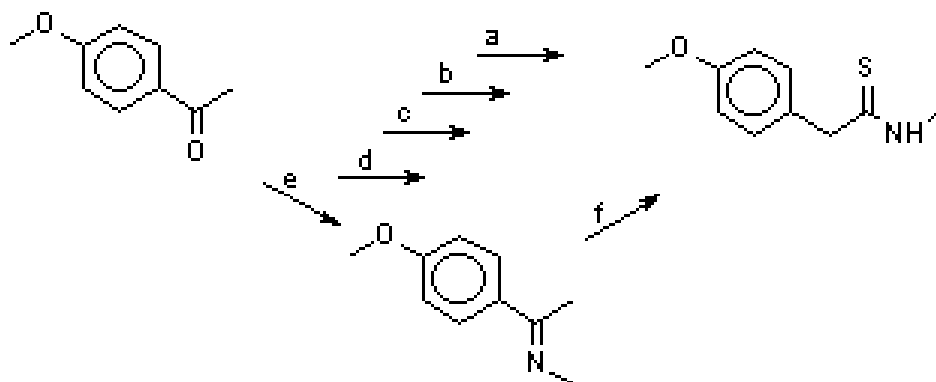
c) Zn (dust) and 36% HCl(aq.) in ethanol

d) 36% HCl(aq.), refluxion

Anisole was smoothly acetylated in a classical conditions [9] with acetyl bromide and aluminium chloride in dichloroethane to produce 4-methoxyacetophenone in 92% yield.

Phenylacetic acid thioamides are usually synthesized by the Willgerodt-Kindler reaction from the corresponding substituted acetophenones, amines, and sulfur. We have studied several alternative routes to the 4-methoxyphenyl-N-methylthioacetamide synthesis shown at the scheme 2.

Scheme 2.



a) H_3CNH_2 , S_8 , $170\text{-}180^\circ\text{C}$, 3h (yield 10,4%, and 21,9% by-product amide).

b) $\text{H}_3\text{CNH}_2 \cdot \text{HCl}$, S_8 , $\text{H}_3\text{CCO}_2\text{Na}$, $(\text{H}_3\text{C})_2\text{NCHO}$, 115°C , 3h (yield 58,4%).

c) $\text{H}_3\text{CNH}_2 \cdot \text{HCl}$, S_8 , $\text{N}(\text{C}_2\text{H}_5)_3$, $4\text{-H}_3\text{CC}_6\text{H}_4\text{SO}_3\text{H} \cdot \text{H}_2\text{O}$, $(\text{H}_3\text{C})_2\text{NCHO}$, 75°C , 72h (yield 57%)

d) H_3CNHCHO , S_8 , 190°C , 20h (yield 35%).

e) $\text{H}_3\text{CNH}_2 \cdot \text{HCl}$, Na_2CO_3 , CaO , $\text{N}(\text{C}_2\text{H}_5)_3$, -7°C (isolated mixture imine : ketone 77:23 (^1H NMR) formed, used for the next stage without separation).

f) S_8 , $\text{N}(\text{C}_2\text{H}_5)_3$, $(\text{H}_3\text{C})_2\text{NCHO}$, 70°C (total yield on two stages 21,5%).

The best results were produced according to routes b and c.

The key thioamide was isolated chromatographically on alumina or silica gel.

In classical conditions of the Willgerodt-Kindler reaction in the sealed tube [10] the desired thioamide was obtained in only 10.4% yield, while the corresponding by-product amide was also isolated in 21.9% yield. In order to avoid the application of high pressure, two-stage synthesis was carried out via intermediate 4-methoxyacetophenone methylimine [11] by method [12, 13] in 21.5% total yield.

Earlier proposed method of carrying out the Willgerodt-Kindler reaction with volatile lower secondary amines, e. g. dimethylamine, using its hydrochloride and sodium acetate in dimethyl formamide at $100\text{-}110^\circ\text{C}$ and atmospheric pressure was developed [14].

We have used a similar method for lower primary amine. Thus methylamine hydrochloride, 4-methoxyacetophenone, sulfur, and a base in dimethyl formamide at $60\text{-}110^\circ\text{C}$ and atmospheric pressure

gave the desired thioamide in 57-58% yield.

An other route of 4-methoxyphenyl-N-methylthioacetamide synthesis on heating the mixture of 4-methoxyacetophenone, N-methylformamide and sulfur at 170-180°C at atmospheric pressure according to the method [15] 35% yield was achieved.

4-Methoxyphenyl-N-methylthioacetamide is a new compound, forming colorless crystals, m. p. 89-91°C (from ethanol or from diethyl ether) [16].

We have elaborated for the thioamide obtained a new simple and efficient method of reduction with zinc dust and hydrochloric acid in ethanolic solution. N,O-Dimethyltyramine was obtained in 91% yield, which was converted to its hydrochloride, m.p. 179-181°C (from ethanol), (lit. m.p. 181-182°C [17]).

O-Demethylation of N,O-dimethyltyramine to N-methyltyramine was carried out according to earlier described method for N-acetylated compound [18] by refluxing with concentrated hydrochloric acid in the oil bath heated to 170-175°C. The yield was 98%, m. p. 146-149°C (from ethanol with a small amount of hydrochloric acid), lit. m. p. 148.5°C [18].

The total yield of N-methyltyramine was 46-47% on four-stage synthesis and the total yield of N,O-dimethyltyramine was 48-49% in three-stage synthesis starting from anisole.

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- [16] Elemental analysis, %: found: C 61.87; H 6.99; N 7.00; for C₁₀H₁₃NOS, M=195.28, calculated: C 61.51, H 6.71, N 7.17.
- MS (m/z), (%): (M+2)⁺ 197 (46.1), (M+1)⁺ 196 (60.4), M⁺ 195 (96.4), M⁺⁺ 97.5 (46.3), 180 (30.9), 164 (65.5), 149 (41.9), 147 (40.0), 140 (42.0), 121 (100), 107 (61.8), 77 (51.9).
- ¹H-NMR (CCl₄-CDCl₃), (p.p.m.): 3.05 and 3.09 (2s., 3H, CH₃N, S-cis- and S-trans- forms), 3.78 (s., 3H, CH₃O), 3.97 (s., 2H, CH₂), 6.81 (d., 2H) and 7.12 (d., 2H) (para-C₆H₄).
- UV (ethanol), (nm) (extinction): 210 (11420), 225(sh.); 266 (10190).
- IR (nujol), (cm⁻¹): 3210, 1600, 1520, 1505, 1300, 1230, 1185, 1175, 1060, 1020, 825, 810, 760, 600, 540, 510.
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