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M. THEVIS, G. OPFERMANN, O. KRUG, W. SCHÄNZER:
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Synthesis of Stably Deuterated Ephedrines and Theobromine Promoted by *N*-Methyl-*N*-Trimethylsilyltrifluoroacetamide

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Abstract

Isotope dilution mass spectrometry has successfully been employed in numerous fields of analytical chemistry. Ever since, the synthesis and mass spectrometric characterization of stably labeled analogues to target analytes is of great interest, in particular when quantitative results are required, e.g. theobromine in case of equine urine samples or ephedrine in human urine samples. Deuterated theobromine, ephedrine as well as p-hydroxypseudoephedrine were prepared by incubation of respective starting material with *N*-methyl-*N*-trimethylsilyl-trifluoroacetamide and iodomethane-d_3. Initial *N*-acetylation of corresponding phenyl propanolamines was performed to avoid multiple methylation, and alkaline hydrolysis of acetyl and trimethylsilyl functions yielded the desired products. While classical methylation reactions employing alkyl halides in the presence of a base suffered from slow progress, the use of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide and alkyl halide accelerated the alkylation significantly. In order to elucidate this particular mechanism of methylation, phenylethyl-amine was derivatized and alkylated as a model compound under various conditions providing information on the influences of acetyl residues, benzylic hydroxyl functions and derivatization-related enolization on the general alkylation reaction. *N*-Trifluoroacetylation entailed severe deceleration of the alkylation reaction, while the presence or absence of a benzylic hydroxyl function proved to be not essential. With the introduction of a deuterated acetyl group into the phenyethylamine, enolization activity was monitored indicating that keto-enol-tautomerism of the amide function is involved in the methylation mechanism. A rearrangement based on an intermediate six-member ring structure with a trimethylsilyl-enol-ether is proposed giving rise to a leaving group of trimethyliodosilane and the desired monomethylated product.

For details, please refer to:

M. Thevis et al. *Rapid Commun Mass Spectrom* **2004**, *18*: 1553-1560

M. Thevis et al. *Eur J Mass Spectrom* **2004**, *10*: 673-681.