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FLUORINATION OF METHIONINE AND METHIONYLGLYCINE DERIVATIVES WITH XENON DIFLUORIDE*

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SUMMARY

A mild procedure for the fluorination of methionine and methionylglycine derivatives is described. Fluorination with xenon difluoride occurs at -20 to 20°C within 20-30 minutes in 70-90% yield, exclusively at the methylthio position. The products were characterized by elemental analysis, fluorine, proton and carbon NMR spectroscopy.

RESULTS AND DISCUSSION

The selective introduction of fluorine-19 or fluorine-18 labels into organic and biomolecules as probes for mechanistic and metabolic studies is still somewhat limited by the availability of effective fluorinating agents. The finding that XeF_2 is suitable for the α-fluorination of sulfides [1,2], combined with the recent preparation of fluorine-18 XeF_2 [3], suggests that XeF_2 might be useful for the labelling of other alkylthio derivatives and we wish to report a convenient method of fluorination of methionine and methionylglycine derivatives.

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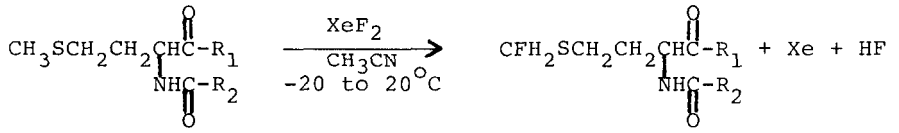

Ia-Id IIa-IId

a R_1=OCH_3 R_2=CF_3

b R_1=$OC_6H_4(p\text{-}NO_2)$ R_2=CF_3

c R_1=$OC_6H_4(p\text{-}NO_2)$ R_2=$OC(CH_3)_3$

d R_1=$NHCH_2C(O)OCH_2CH_3$ R_2=$OCH_2C_6H_5$

Fluorination with xenon difluoride produces the fluoromethionine (IIa-IIc) and fluoromethionylglycine (IId) derivatives, as well as xenon gas and hydrogen fluoride. In a typical reaction, N-carbobenzoxy-L-methionylglycine ethyl ester (Id) (0.43 mmol) in acetonitrile (1 mL) in a syringe was injected onto a solution of xenon difluoride (0.45 mmol) in acetonitrile (0.5 mL) in a Teflon bottle with a rubber cap at -20°C. Xenon gas evolved on warming the sample to room temperature and the reaction, as conveniently monitored by the rise of the syringe plunger, was complete within 20-30 min. At the completion of the reaction, HF was destroyed by the addition of $(Me_3Si)_2NH$ [4] (Safety note: Although no violent reactions were encountered in this work, the technique of destroying excess HF with $(Me_3Si)_2NH$ is potentially hazardous because XeF_2 reacts explosively with some silicon-nitrogen compounds [5]). Removal of volatile material under vacuum left behind a solid which was recrystallized from benzene and petroleum ether, washed with cold toluene and dried under vacuum to give a white solid, identified as IId, mp 99-100°C. Analysis [6]: Found: C, 52.82; H, 6.03; N, 7.22%. $C_{17}H_{23}FO_5N_2S$ requires C, 52.83; H, 6.00; N, 7.25%. A similar procedure was used for the preparation of compounds IIa-IIc.

The NMR spectral properties of the CFH_2S- group in IIa-IId are very similar to those of the CFH_2S- group in simple monofluoroalkyl sulfides [2]. For the CFH_2S- group, δ_H 5.2-5.3 ppm (IIa-IId), δ_F -184 ppm (IId), $^2J_{HF}$ 52.4-53.1 Hz (IIa-IId),

$^4J_{FH}$ 2.4 Hz (IIc), δ_C 88.9 ppm (IId), and $^1J_{CF}$ 209.6 Hz (IId). NMR examination showed that products IIa-IId were formed in yields of 70-90%, but no evidence was found for the formation of products with CF_2HS- or CH_3SCFH- substituents.

The stability of IIa-IId was briefly investigated and, in general, the thermal stability appeared comparable to that of the non-fluorinated starting compounds. A recrystallized sample of IId was kept in a sealed tube at 0°C for 3 months without sign of decomposition. Under aqueous NaOH or Et_3N conditions, the CFH_2S- group remained intact, as judged by NMR, but aqueous or non-aqueous solutions of HF, HCl or CF_3COOH produced decomposition with loss of the fluoride signal in the NMR spectrum.

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