Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability

Gauri S. Lal,* Guido P. Pez, Reno J. Pesaresi and Frank M. Prozonic

Air Products and Chemicals Inc, 7201, Hamilton Boulevard, Allentown, PA 18195-1501, USA.
E-mail: lalgs@apci.com

Received (in Corvallis, OR, USA) 2nd November 1998, Accepted 7th December 1998

Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor™) is effective for the conversion of alcohols to alkyl fluorides, aldehydes/ketones to the corresponding *gem*-difluorides and also for the transformation of carboxylic acids to their trifluoromethyl derivatives; it is a less thermally sensitive, broader-spectrum alternative to the traditional dialkylaminosulfur trifluoride (DAST) deoxofluorination reagents.

In view of the importance of organofluorine compounds in the pharmaceutical and agrochemical industries, efforts aimed at the development of simple, safe and efficient methods for their synthesis have escalated in recent years.[1–5] The conversion of carbon–oxygen to carbon–fluorine bonds by nucleophilic fluorinating sources (deoxofluorination) represents one such technique which has been widely used for the selective introduction of fluorine into organic molecules.[6] This transformation has been accomplished routinely with the dialkylaminosulfur trifluorides, such as DAST (NEt_2SF_3), for laboratory scale reactions.[7] However, utilization of DAST for larger scale applications has been limited by its well known thermal instability.[8,9] DAST and related dialkylaminosulfur trifluorides are said to undergo catastrophic decomposition (explosion or detonation) with gas evolution on heating to >90 °C.[10]

We now report on bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) **1**, a new deoxofluorinating agent which is a less thermally sensitive and very effective alternative to DAST. It permits the facile conversion of alcohols to alkyl fluorides, aldehydes/ketones to the corresponding *gem*-difluorides, and also the transformation of carboxylic acids to the corresponding trifluoromethyl derivatives with, in some cases, superior performance to DAST.

Deoxo-Fluor reagent is obtained in a manner analogous to that of DAST[9] by reacting the *N*-trimethylsilyl derivative of bis(2-methoxyethyl)amine with SF_4 in Et_2O at -30 °C. The crude product is distilled (60 °C, 0.1 mmHg) to afford a light yellow oil in 70% yield [$\delta_H(CDCl_3)$ 3.5 (t, 4H), 3.15 (t, 4H), 3.05 (s, 6H); $\delta_F(CDCl_3)$ 55 (s, br, 2F), 28 (s, br, 1F]. A comparison of the thermal stability of Deoxo-Fluor and DAST, as determined by differential scanning calorimetry (DSC), is illustrated in Fig. 1. While the onset of decomposition is almost the same for both compounds (~ 140 °C), DAST degrades much more rapidly and with somewhat larger heat evolution (1700 *vs.* 1100 J g^{-1} for **1**). Deoxo-Fluor showed a much more gradual exotherm over a wider temperature range. These preliminary results indicate that the latter should be safer to use than DAST on a larger, practical scale.

The broad applicability of **1** for the deoxofluorination of organic substrates is illustrated by its reaction chemistry, as shown in Table 1. Primary, secondary and tertiary alcohols react at relatively low temperatures (-78 °C to ambient), giving moderate to excellent yields of the corresponding alkyl fluorides. Fluorination of the anomeric hydroxy group of the sugar was particularly effective, giving the desired compound in 95% yield. The fluorination of aldehydes and ketones con-

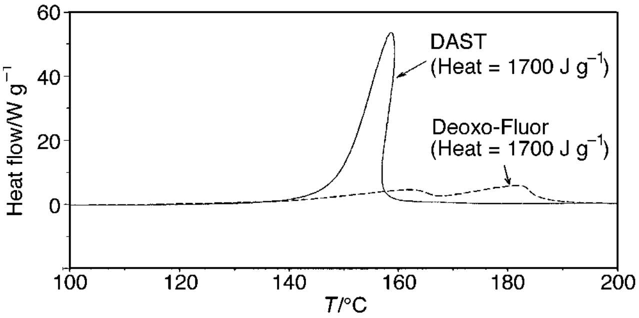
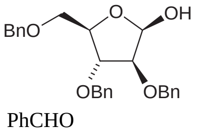
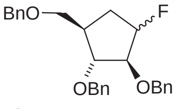


Fig. 1 DSC plots for the thermal decomposition of DAST and Deoxo-Fluor **1** (ref. 13). Samples were in hermetically sealed gold pans; scan rate 10 °C min^{-1}.

Table 1 Fluorination of model compounds with the Deoxo-Fluor reagent **1**

Substrate	**1**/equiv.	Solvent	*T*/°C	*t*/h	Product	Yield (%)
$PhCH_2CH_2OH$	1.1	CH_2Cl_2	room temp.	16	$PhCH_2CH_2F$	85
$MeCH(OH)CO_2Et$	1.1	CH_2Cl_2	room temp.	3	$MeCHFCO_2Et$	73
$Me_2C(OH)CO_2Et$	1.1	CH_2Cl_2	room temp.	8	Me_2CFCO_2Et	89
	1.1	CH_2Cl_2	0	0.5		95[a]
PhCHO	1.7	CH_2Cl_2	reflux	16	$PhCHF_2$	95
4-*tert*-butylcyclohexanone	1.7	CH_2Cl_2	room temp.	16	1-*tert*-butyl-4,4-difluorocyclohexane	85
$PhOCH_2COMe$	1.7	CH_2Cl_2	room temp.	16	$PhOCH_2CF_2Me$	98
PhCOMe	1.5	neat	85	16	$PhCF_2Me$	92
$PhCO_2H$	1.1	CH_2Cl_2	0	0.5	PhCOF	96
$Me(CH_2)_8CO_2H$	1.1	CH_2Cl_2	0	0.5	$Me(CH_2)_8COF$	96
PhCOF	2.0	neat	85	48	$PhCF_3$	58
$Me(CH_2)_8COF$	2.0	neat	85	48	$Me(CH_2)_8CF_3$	63

[a] Ratio α : β = 9 : 91.

ducted in CH_2Cl_2 at room temperature in the presence of 0.1 equiv. of HF, generated *in situ* with added EtOH, afforded excellent yields of the corresponding *gem*-difluoro products from both aliphatic and aromatic carbonyl compounds. The relatively greater thermal stability of **1** was exploited for the fluorination of electron-deficient ketones and carboxylic acids, which are traditionally less reactive substrates. As illustrated in Table 1, **1** reacted readily with carboxylic acids, giving acyl fluorides. These were subsequently converted to the trifluoromethyl derivatives on heating for an extended period in the neat reagent at 90 °C. DAST has not been generally employed for the fluorination of carboxylic acids and we are only aware of one report of such an application.[11]

The broad-spectrum reactivity of the Deoxo-Fluor reagent coupled with its potentially greater margin of safety in use and commercial availability[12]should lead to its widespread application for the synthesis of specialty organofluorine compounds. Detailed studies of its thermal behavior and reactivity with a wider range of functional groups are in progress.

Notes and references

1 J. T. Welch and S. Eshwarakrishan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991.

2 R. Filler and K. Kirk, *Biological Properties of Fluorinated Compounds*, A. J. Elliott, *Fluorinated Pharmaceuticals* and R. W. Lang, *Fluorinated Agrochemicals* in *Chemistry of Organic Fluorine Compounds II*, ed. M. Hudlicky and A. E. Pavlath, ACS Monograph 187, American Chemical Society, Washington, DC, 1995.

3 D. Cartwright, *Recent Developments in Fluorine-Containing Agrochemicals*, in *Organofluorine Chemistry, Principles and Commercial Applications*, ed. R. E. Banks, B. E, Smart and J. C. Tatlow, Plenum, New York, 1994.

4 R. Filler, in *Organofluorine Compounds in Medicinal and Biomedicinal Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, The Nederlands, 1993.

5 *New Fluorinating Agents in Organic Synthesis*, ed. L. German and S. Zemskov, Springer-Verlag, Heidelberg, New York, 1989.

6 M. Hudlicky, *Fluorination with Diethylaminosulfur Trifluoride and related Aminosulfuranes*, in *Org. React.*,, 1988, **25**, 513.

7 W. J. Middleton, *J. Org. Chem*., 1975, **40**, 574.

8 J. Cochran, *Chem. Eng. News*, 1979, **57**, 4.

9 W. J. Middleton, *Chem. Eng. News*, 1979, **57**, 43.

10 P. A. Messina, K. C. Mange and W. J. Middleton, *J. Fluorine Chem*., 1989, **42**, 137.

11 $PhCF_3$ was reportedly produced in 50% yield by heating *in situ* prepared PhCOF with excess DAST in diglyme for 20 h at 80 °C: W. J. Middleton, *US Pat.* 3,914,265 (1975).

12 From Aldrich Chemical Co, Milwaukee, WI 53201 and Air Products and Chemicals, Inc. 7201 Hamilton Boulevard, Allentown, PA, USA 18195-1501.

13 The exotherm peak for DAST appears skewed, as the sample heats faster than the furnace, then cools to readjust to the temperature program.

Communication 8/08517J

Typeset and printed by Black Bear Press Limited, Cambridge, England