



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

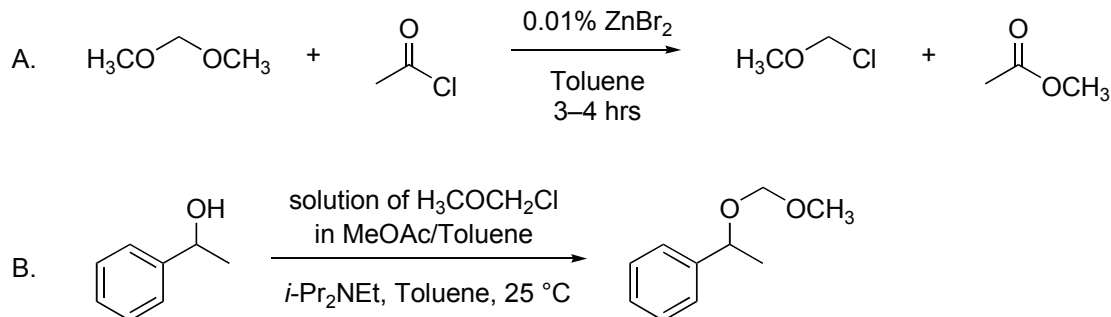
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

**SYNTHESIS OF ALPHA-HALO ETHERS FROM SYMMETRIC  
ACETALS AND *in situ* METHOXYMETHYLATION OF AN  
ALCOHOL**

**[1-Methoxymethoxy-1-phenylethane]**



Submitted by Martin Berliner<sup>1</sup> and Katherine Belecki.  
Checked by William D. Paquette and Peter Wipf.<sup>2</sup>

### 1. Procedure

*CAUTION: Chloromethyl methyl ether is an OSHA registered carcinogen and is listed as an extremely hazardous substance by the EPA and the European Community. Other  $\alpha$ -halo ethers are likely to be carcinogenic. Exercise due caution to minimize handling of these compounds.*

*A. Chloromethyl methyl ether as a solution in toluene.* A three-necked 500-mL flask is fitted with a magnetic stirbar, thermometer, reflux condenser with nitrogen inlet, and addition funnel (Note 1). The vessel is charged with dimethoxymethane (22.1 mL, 250 mmol, 1 equiv) (Note 2), toluene (66 mL, 3 volumes) (Notes 3, 4) and ZnBr<sub>2</sub> (5.6 mg, 0.01 mol%) (Notes 5, 6). The zinc bromide dissolves shortly after addition. Acetyl chloride (17.8 mL, 250 mmol, 1 equiv) (Note 7) is placed in the addition funnel and then introduced into the reaction mixture at a constant rate over 5–15 minutes (Note 8). The addition funnel is rinsed with a minimum volume of toluene (5 mL) directly into the reaction mixture. The reaction self-heats slowly to 40–45 °C and then cools to ambient temperature over 2–3 h, at which time the exchange reaction is typically complete (Note 9). This clear, colorless solution of chloromethyl methyl ether in toluene is employed directly in the subsequent step without further manipulation (Note 10).

*B. 1-Methoxymethyl-1-phenylethane.* The reaction flask containing a toluene solution of chloromethyl methyl ether (250 mmol, 1.5 equiv) prepared above is immersed in a cold water bath and the contents cooled to 5–10 °C.  $\alpha$ -Phenethyl alcohol (20 mL, 166 mmol, 1 equiv) is charged to the addition funnel and added in one portion (Note 11). Diisopropylethylamine (36.0 mL, 208 mmol, 1.25 equiv) is charged to the addition funnel and added to the reaction mixture dropwise over 30 min (Notes 12, 13). The internal temperature of the mixture is maintained below 25 °C during and immediately after the amine addition, and once heat evolution has ceased, the reaction mixture is allowed to come to ambient temperature and then stirred for 12 h. At this time the starting material is consumed (Note 14). The orange solution is diluted with ethyl acetate (100 mL) and a saturated aqueous  $\text{NH}_4\text{Cl}$  solution (100 mL), and the biphasic mixture stirred vigorously for a minimum of five minutes to ensure all residual chloromethyl methyl ether is decomposed (Note 15). The layers are separated and the resulting clear, colorless organic layer is washed once with water (100 mL), once with brine (100 mL), dried with  $\text{MgSO}_4$  and concentrated by rotary evaporation to a clear, colorless oil (Note 16). The material is transferred to a 50-mL round-bottomed flask equipped with a magnetic stirbar and a short-path distillation head. The product is purified by distillation, collecting a single fraction (bp 60–63 °C, 0.5 mmHg) of 1-methoxymethoxy-1-phenylethane as a clear, colorless oil (26.2 g, 157 mmol, 95% yield) (Notes 17, 18, 19).

## 2. Notes

1. The success of the reaction does not depend on having previously dried the glassware.
2. Dimethoxymethane was obtained from Acros Organics at 99.5+% purity and used as received. The submitters used dimethoxymethane, obtained from Aldrich Chemical Co. at 99% purity, as received.
3. ACS grade toluene was employed without additional purification. A similar grade of dichloromethane, dichloroethane and alkyl acetate esters (i.e. ethyl acetate, isopropyl acetate) can be substituted for toluene with no change in reaction behavior or yield.
4. Although the reaction can be conducted neat, the authors strongly recommend using a co-solvent to mitigate the strongly exothermic nature of the process. The volume of solvent employed in this reaction was chosen to

provide a good balance of reaction rate and thermal control. If less solvent is employed, active cooling should be utilized to keep the reaction temperature below 45 °C.

5. Zinc bromide (anhydrous powder, 98+%) was obtained from Acros Organics and used as received.

6. For small- and medium-scale reactions with dimethoxymethane, such small amounts of catalyst are required that the authors found it easiest to dispense the correct amount of catalyst from standard solutions of ZnBr<sub>2</sub> in dimethoxymethane (20–50 mg/mL).

7. The submitters obtained acetyl chloride from Aldrich Chemical Co. and Acros Organics at 97–99% purity and used it as received.

8. The reaction temperature increases slightly upon addition of acetyl chloride; the reaction is not dose controlled at this temperature. For a dose-controlled addition, the submitters recommend pre-heating the solvent/acetal/catalyst solution to 40 °C before dropwise addition of the halogenating agent, since the catalyzed exchange reaction is very rapid once the temperature exceeds 40 °C.

9. A small amount of the reaction mixture (20 mL) is dissolved in 0.6 mL of CDCl<sub>3</sub> for the analysis. The ratio of AcCl (δ 2.6 ppm):MeOAc (δ 2.0 ppm) is utilized to evaluate reaction progress as a small excess of dimethoxymethane is usually present once the exchange is complete (typical ratio MeOAc:AcCl ≥ 99:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.44 (s, 2 H, MOMCl), 3.64 (s, 3 H, MeOAc), 3.49 (s, 3 H, MOMCl), 2.03 (s, 3 H, MeOAc). *In situ* IR can also be employed to monitor reaction progress without requiring sampling of the reaction contents.

10. The solution of MOMCl in toluene prepared using this stoichiometry have a density of 0.91 g/mL, are approx 2.1 M (18% w/w), and are stable for months if adequately sealed.

11. No heat evolution is observed during the addition.

12. Addition of the amine base results in a strong and extended exotherm as the reaction proceeds. In the absence of external cooling the reaction temperature can exceed 60 °C.

13. The order of addition of the amine and alcohol can be interchanged without affecting the purity or yield of the product. The following procedure is suggested: The solution of MOMCl is cooled to 10 °C and the base is added, slowly at first, keeping the internal temperature below 25 °C. Alcohol is added in one portion and the solution allowed to warm to ambient

temperature and stirred until complete. Workup is as described in the main procedure.

14. Analysis is by HPLC. Starting material  $t_R$  4.46 min, product  $t_R$  7.25 min. Agilent Zorbax® SB-C8 column 4.6 x 150 mm, 2 mL/min flow, using acetonitrile and 0.1% HClO<sub>4</sub>/H<sub>2</sub>O as the eluent. The following gradient profile is used: 2 min isocratic (10:90, organic:aqueous), ramp to 90:10 (organic:aqueous) over 6 min, then 2 min isocratic at 90:10 (organic:aqueous). Analysis can also be done by TLC (5:1, hexanes:EtOAc;  $\alpha$ -phenethyl alcohol,  $R_f$ = 0.13; 1-methoxy-1-phenylethane,  $R_f$ = 0.5).

15. The quench is mildly exothermic as residual MOMCl decomposes. Typically all remaining  $\alpha$ -chloro ether has been quenched five minutes after addition of the aqueous solution. Water and saturated carbonate solutions are also effective for quenching the reaction.

16. Typical mass of crude product is 27 g (98% yield) with purity >95%.

17. The submitters observed yields from 77–80%. Some decomposition of the product occurs during extended batch distillation, resulting in decreased yields. This is not observed when the purification is conducted on small scale in a Kugelrohr apparatus, or when a chromatographic purification is employed.

18. The checkers obtained a yield of 90% (12.5 g) on half-scale.

19. Physical data for the product:  $R_f$  0.5 (5:1, hexanes:EtOAc). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.49 (d,  $J$  = 6.6 Hz, 3 H), 3.39 (s, 3 H), 4.55 (d,  $J$  = 6.9 Hz, 1 H), 4.59 (d,  $J$  = 6.6 Hz, 1 H), 4.76 (q,  $J$  = 6.6 Hz, 1 H), 7.27–7.37 (m, 5 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 23.6, 55.3, 73.7, 94.0, 126.3, 127.5, 128.4, 143.2. IR (neat, cm<sup>-1</sup>): 2976, 2931, 2887, 1451, 1155, 1099, 1036, 919, 759, 700. Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: C, 72.26; H, 8.49. Found: C, 72.22; H, 8.64.

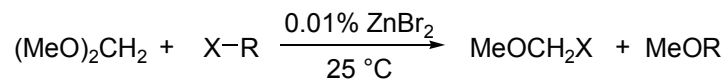
### Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

### 3. Discussion

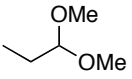
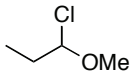
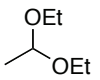

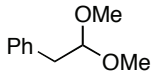
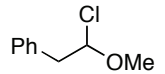
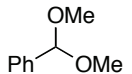
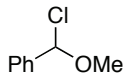
Chloromethyl methyl ether (MOMCl) and other  $\alpha$ -halo ethers are versatile reagents for protecting a variety of functional groups<sup>3</sup> and as precursors of carbenes, electrophiles and  $\alpha$ -stannyl ethers that have wide use in organic synthesis.<sup>4</sup> This procedure describes an improved method for the generation of  $\alpha$ -halo ethers from symmetric aliphatic acetals, including MOMCl and higher substituted analogs.<sup>5</sup> The original preparation of MOMCl in this series<sup>6</sup> and current commercial preparations utilize the reaction between methanol, formaldehyde and hydrogen chloride and produce substantial amounts of the very highly carcinogenic bis(chloromethyl) ether which cannot be readily separated by distillation. More recent procedures<sup>7</sup> have employed the exchange reaction between dimethoxymethane and a halide donor catalyzed by protic acid; these minimize formation of bis(chloromethyl)ether and are preferred to the original preparation. These methods employ different halide sources and different acid catalysts, but all require extended (2–24 hours or more) reflux to effect full exchange, and due to the high vapor pressure of the reactants and products, efficient condensers are required to minimize material loss.

The present method utilizes catalytic zinc(II) salts (0.001 to 0.01 mol%) to accelerate the exchange reaction between halide donors and acetals. Reactions typically are complete in one to four hours irrespective of the scale of the preparation (mmol through mole scale) without the need for external heating. A range of zinc(II) salts can be utilized, with  $\text{Zn}(\text{OTf})_2$ ,  $\text{ZnBr}_2$  and  $\text{Zn}(\text{OAc})_2$  being the easiest to manipulate. Acid halides and thionyl chloride (but not thionyl bromide) are effective as the halide source (Table 1). A variety of symmetric aliphatic acetals participate in the reaction to give synthetically useful  $\alpha$ -halo ethers (Table 2). The solutions of  $\alpha$ -halo ethers are employed without isolation in base-mediated reactions where the presence of the ester by-product does not interfere, including alkylations of acids, alcohols, phenols and stabilized enolates under the usual conditions (Table 3). Since  $\alpha$ -halo ethers are hazardous (some are carcinogenic; others are possible carcinogens), this procedure illustrates a convenient on-demand synthesis and use of these reagents without isolation or unnecessary handling. The improved safety of this telescoped procedure addresses concerns of both academic and industrial chemists who are under increasing pressure to reduce laboratory hazards.

**Table 1.** Halogen Sources

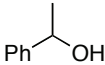
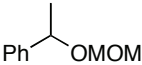
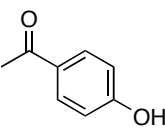
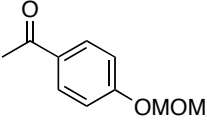
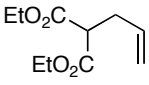
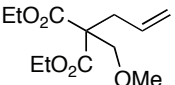
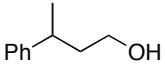
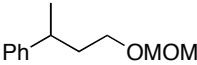
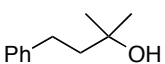
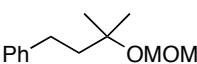
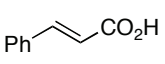
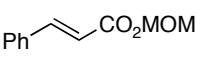
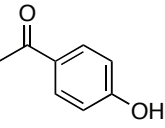
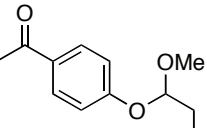
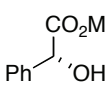
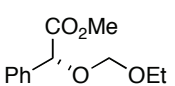
Entry	Halide Source	Equiv required	Time
1	(COCl) <sub>2</sub>	0.5	< 5 min
2	RCOCl	1.0	30 min
3	SOCl <sub>2</sub>	0.5	30 min
4	CH <sub>3</sub> COBr	1.0	45 min

**Table 2.** Acetals Employed in the Exchange Reaction

Entry	Acetal	$\alpha$ -Halo Ether	Halide Source	Catalyst	Time <sup>a</sup>
1	(EtO) <sub>2</sub> CH <sub>2</sub>	EtOCH <sub>2</sub> Cl	AcCl	ZnBr <sub>2</sub>	4 hr
2			(COCl) <sub>2</sub>	Zn(OTf) <sub>2</sub>	1 hr
3			AcCl	ZnBr <sub>2</sub>	1 hr
4			AcCl	Zn(OTf) <sub>2</sub>	30 min
5			AcCl	Zn(OTf) <sub>2</sub>	30 min

(a) Time to completion of exchange reaction by NMR spectroscopy.

**Table 3:** Alkylation Reactions of In Situ Generated  $\alpha$ -Halo Ethers<sup>a</sup>

Entry	Starting Material	Product	Yield <sup>b</sup> (%)
1			92
2			86
3 <sup>c</sup>			80
4			92
5			92
6	PhCO <sub>2</sub> H	PhCO <sub>2</sub> MOM	92
7			96
8			93
9			85

(a) Reactions are conducted on 10–20 mmol scale with 1.5–2.0 equivalents of  $\alpha$ -halo ether and 1.25 equivalents of *i*-Pr<sub>2</sub>NEt in toluene for 12–16 hours followed by a standard aqueous workup as described in this procedure. (b) Yield of purified product. (c) Malonate anion was prepared using NaH in THF followed by addition to a MOMCl solution prepared in toluene.

1. Chemical Research and Development, Pfizer Global Research and Development, Groton, CT 06340, *martin.a.berliner@pfizer.com*.
2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA.
3. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
4. For a review, see: Benneche, T. *Synthesis* **1995**, 1 and references therein.
5. Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618.



6. Marvel, C. S.; Porter, P. K. *Organic Syntheses*; John Wiley & Sons: New York, 1941. Coll. Vol. I, p. 377.
7. With HCl: (a) Weinstock, L.M.; Karady, S.; Sletzing, M. US 3,972,947 (*Chem. Abstr* **1976**, 85, 142633) (b) Amato, J. S.; Karady, S.; Sletzing, M.; Weinstock, L. M. *Synthesis* **1979**, 970. (c) Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem.* **1994**, 59, 6499. With H<sub>2</sub>SO<sub>4</sub>: (d) Chong, J. M.; Shen, L. *Synth. Commun.* **1998**, 28, 2801. (e) Williams, A. G. WO 02/059070 A1 (*Chem. Abstr.* **2002**, 137, 124930). (f) Reggelin, M.; Doerr, S. *Synlett* **2004**, 1117. By other methods: (g) Stadlwieser, J. *Synthesis* **1985**, 490. (h) Jones, M. *Synthesis* **1984**, 9, 727.

## Appendix

### Chemical Abstracts Nomenclature; (Registry Number)

Dimethoxymethane; (109-87-5)

Zinc bromide; (7699-45-8)

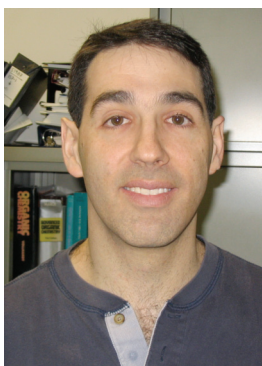
Acetyl chloride; (75-36-5)

Chloromethyl methyl ether: Methane, chloromethoxy-; (107-30-2)

$\alpha$ -Phenethyl alcohol: Benzenemethanol,  $\alpha$ -methyl-; (98-85-1)

Diisopropylethylamine: 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)-; (7087-68-5)

1-Methoxymethoxy-1-phenylethane: Benzene, [1-(methoxymethoxy)ethyl]-; (94073-86-6)



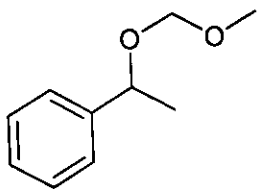
Marty Berliner was born in Denver, Colorado in 1968. He received a B.S. in Physics from Harvey Mudd College in 1990 and then switched fields to organic chemistry in graduate school, where he earned a Ph.D. with Tarek Sammakia (University of Colorado, Boulder) developing the asymmetric Diels-Alder reaction of oxocarbenium ions (1996). Following postdoctoral research with David Williams at Indiana University, he joined Pfizer in 1999 and is currently a senior principal scientist in the early candidate group in Chemical Research and Development.



Katherine Belecki was born in Silver Spring, Maryland, in 1979. After completing her B.A. in Chemistry at Williams College in 2001, she spent two years working with Dr. Marty Berliner in the early development and discovery support group at Pfizer. She is currently pursuing a doctorate degree in the lab of Dr. Craig Townsend at the Johns Hopkins University in Baltimore, investigating biosynthetic pathways of polyketide natural products.



William D. Paquette received his B.S. degree at the University of New Hampshire in 2000 and performed research under Prof. Charles Zercher. He then obtained his Ph.D. in 2006 from the University of Notre Dame with Prof. Richard E. Taylor. His graduate research focused on studies toward the total synthesis of 20-deoxyapoptolidin. At Notre Dame, he developed unique methodology to construct contiguous (*E*)-trisubstituted olefins utilizing a thionyl chloride-induced rearrangement. Currently, he is conducting postdoctoral research under the supervision of Prof. Peter Wipf at the University of Pittsburgh on the synthesis of novel phosphatase inhibitors as well as the natural product wortmannin.



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94.00

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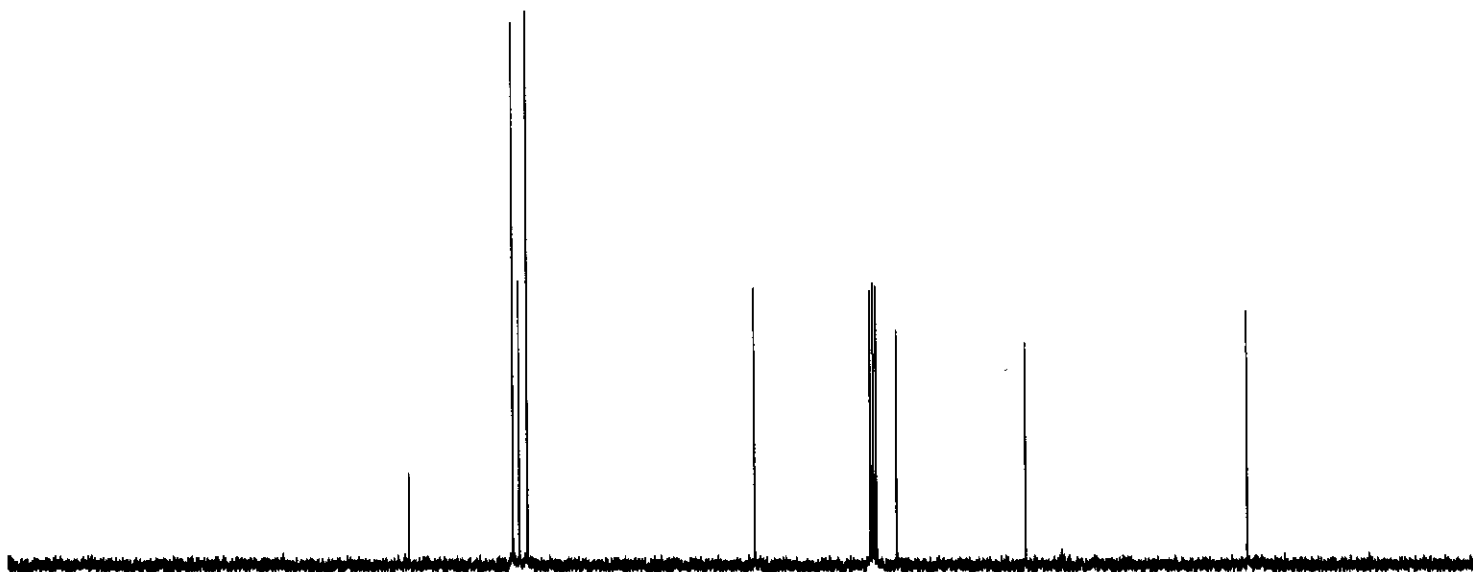
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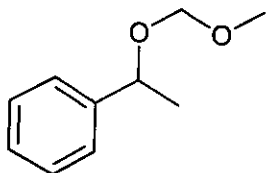
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 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



180 160 140 120 100 80 60 40 20 ppm



Current Data Parameters  
 NAME wdp1011 orgsyn prep at 100%  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20060525  
 Time\_ 23.56  
 INSTRUM spect  
 PROBHD 5 mm DUL 1H-13  
 PULPROG zg  
 TD 65536  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 6218.905 Hz  
 FIDRES 0.094893 Hz  
 AQ 5.2691445 sec  
 RG 256  
 DW 80.400 usec  
 DE 6.00 usec  
 TE 300.0 K  
 D1 2.00000000 sec  
 TDO 1

===== CHANNEL f1 =====  
 NUC1 1H  
 P1 9.00 usec  
 PL1 1.00 dB  
 SFO1 300.3818550 MHz

F2 - Processing parameters  
 SI 32768  
 SF 300.3799996 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

