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for the Preparation
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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.

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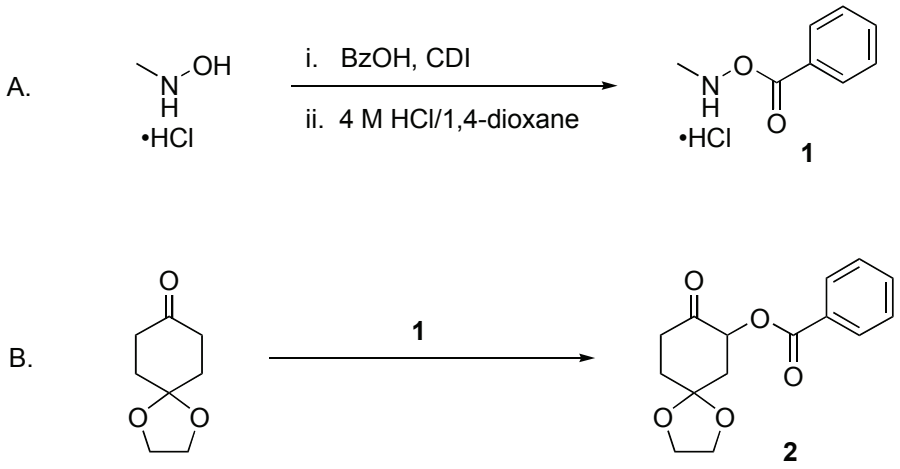
A PRACTICAL PROCEDURE FOR CARBONYL α-OXIDATION: SYNTHESIS OF (2-BENZOYLOXY)-1,4-CYCLOHEXANEDIONE *MONO*-ETHYLENE KETAL



Submitted by Teyrnon C. Jones and Nicholas C. O. Tomkinson.[1]
Checked by Kalyani Patil and Peter Wipf.[2]

1. Procedure

A. N-Methyl-O-benzoylhydroxylamine hydrochloride **1** (Note 1). Benzoic acid (18.32 g, 150.0 mmol, 1 eq.) (Note 2) is placed in an open single-necked 500-mL round-bottomed flask equipped with a large magnetic stirrer and dissolved in 200 mL of methylene chloride (Note 3). This clear solution is cooled to 0 °C in an ice-water bath before the controlled addition of carbonyldiimidazole (24.32 g, 150.0 mmol, 1 equiv.) over a period of five min (Note 4). The ice bath is removed and the resultant yellow solution is stirred at ambient temperature until all effervescence has ceased (15 minutes). After this period, *N*-methylhydroxylamine hydrochloride (15.87 g, 190.0 mmol, 1.27 equiv.) is added in one portion to the reaction mixture and stirring is continued for a further 40 min at 25 °C. The reaction broth is diluted with 100 mL of methylene chloride, transferred to a 1-L separatory funnel and washed sequentially with cold (0 °C) 1 M hydrochloric acid (300 mL) (Note 5) and saturated sodium hydrogen carbonate solution (300 mL). The organic layer is separated, dried using sodium sulfate (40 g), filtered through a Büchner funnel and concentrated to dryness in a 500-mL round-bottomed flask on a rotary evaporator (25 °C, 20 mmHg). Diethyl ether (200 mL) is added to the resulting liquid followed by 4 M HCl in dioxane (75

mL, 0.30 mol, 2 equiv.) (Note 6). After 30 minutes, the solid precipitate is collected in a Büchner funnel (Note 7), washed with 100 mL of ice-cold diethyl ether and dried under high vacuum (0.5 mmHg) for 8 h to give *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **1** as a white microcrystalline solid (17.45 g, 62%) (Note 8) that is used in Step B without further purification (Note 9).

B. (2-Benzoyloxy)-1,4-cyclohexanedione (mono)ethylene ketal **2**. An open 25-mL single-necked round-bottomed flask (Note 10) equipped with a magnetic stirring bar is charged at ambient temperature with 1,4-cyclohexanedione mono-ethylene ketal (4.68 g, 30.0 mmol, 1 equiv.) (Note 11) and dimethyl sulfoxide (7.5 mL). *N*-Methyl-*O*-benzoyl-hydroxylamine hydrochloride **1** (5.63 g, 30.0 mmol, 1 equiv., as prepared above) is added to the flask over a period of 15 min (Note 12) and the reaction mixture is stirred for 1 h (Note 13). The solution is subsequently poured into 300 mL of ethyl acetate and transferred to a 1-L separatory funnel where it is washed with 250 mL of water. The layers are separated and retained: the organic layer is washed further with two 250 mL portions of water, which are discarded; and the original aqueous layer is washed with two 100 mL portions of ethyl acetate which are added to the original organic layer. The combined organic fractions are dried using magnesium sulfate (25 g), filtered through a Büchner funnel and concentrated on a rotary evaporator (40 °C, 20 mmHg) to give a brown solid as a crude product (Note 14). The crude solid is transferred to a 25-mL Erlenmeyer flask and dissolved in 5 mL of hot (80 °C) isopropyl alcohol, then allowed to slowly cool to room temperature. The resultant solid is collected in a Büchner funnel and sequentially washed with ice-cold isopropyl alcohol (50 mL) and ice-cold 35-60 petroleum ether (50 mL) (Note 11) before being dried under high vacuum (0.5 mmHg) for 8 h to yield (2-benzoyloxy)-1,4-cyclohexanedione mono-ethylene ketal **2** (Note 15) as pale yellow needles (6.38 g, 77%) (Note 16).

2. Notes

1. Procedure A is a modification of the method of Geffken: Geffken, D. *Chem*. *Ber*. **1986**, *119*, 744.

2. Benzoic acid (99+%), carbonyldiimidazole, *N*-methylhydroxylamine hydrochloride (98%), and 4 M hydrochloric acid in 1,4-dioxane were obtained from Aldrich Chemical Company, Inc.

Methylene chloride and diethyl ether were obtained from Fisher Scientific Ltd. Submitters purchased benzoic acid (98%) from Avocado Research Chemicals Ltd. and carbonyldiimidazole (97%) from Lancaster Synthesis Ltd. All chemicals were used as received.

3. There was no need to oven-dry the vessels used in the reaction, and all steps were carried out in flasks open to the atmosphere.

4. The reaction produced carbon dioxide gas, resulting in vigorous effervescence.

5. The hydrochloric acid was prepared by dilution of 12 M hydrochloric acid purchased from EMD Chemicals Inc.

6. The submitters generated hydrochloride acid gas from a slow addition of sulfuric acid to ammonium chloride and bubbled the gas directly into the diethyl ether solution.

7. Filtration should be carried out in a fume hood as the mother liquor contains dissolved hydrogen chloride.

8. The checkers performed the reaction also at 50%, 25%, and 10% scale. The yields ranged from 58-62%.

9. Physical properties and spectral data for **1** are as follows: mp 135–137 °C; IR (nujol) 2923, 1770, 1599, 1475, 1260 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^6) δ: 2.90 (s, 3 H), 7.57 (t, J = 7.8 Hz, 2 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.95 (d, J = 7.2 Hz, 2 H), 11.38 (brs, 2 H); ^{13}C NMR (75 MHz, DMSO-d^6) δ: 36.7, 126.4, 129.6, 129.8, 135.1, 163.7; MS (EI) *m/z* (rel intensity) 151 ($[M\text{-}HCl]^+$, 11), 136 (25), 123 (24), 122 (87), 107 (8), 106 (70), 105 (56); HRMS (EI) calculated for $C_8H_9NO_2$ 151.0633, found 151.0631; Anal. calcd. for $C_8H_{10}NO_2Cl$ C, 51.2, H, 5.4, N, 7.5, Cl, 18.9; found C, 51.3, H, 5.5, N, 7.5, Cl, 18.9.

10. There was no need to oven-dry the reaction flask, and the reaction was carried out open to the atmosphere.

11. 1,4-Cyclohexanedione mono-ethylene ketal (97%) was obtained from Aldrich Chemical Company, Inc. Dimethyl sulfoxide (99.9%) was obtained from Fisher Scientific Ltd. Isopropyl alcohol and 35-60 petroleum ether was obtained from J. T. Baker Chemical Co. Submitters used dimethyl sulfoxide (99%) purchased from Aldrich Chemical Company, Inc., and, isopropyl alcohol and 40-60 petroleum ether purchased from Fisher Scientific Ltd. All chemicals were used as received.

12. It was noted that this reaction was exothermic. Measuring of the internal reaction temperature with a thermometer showed that during the addition of **1** the temperature rose to a maximum of 70 °C.

13. The progress of the reaction was monitored by TLC analysis on EMD Silicagel 60 F_{254} 0.25 mm silica plates, using 50% ethyl acetate/35-60 petroleum ether as eluent and visualising with potassium permanganate solution. The ketone starting material had an R_f = 0.37 and the oxidized product had an R_f = 0.51.

14. Occasionally, the crude product was obtained as a brown oil. In these cases the oil may solidify on standing or can be induced to crystallize by the addition of a small amount of 35-60 petroleum ether, which was subsequently removed by rotary evaporation.

15. The checkers performed the reaction also at 50%, 25%, and 10% scale. The yields ranged from 78-81%.

16. Physical properties and spectral data for **2** are as follows: mp 114-116 °C; IR (dichloromethane) 2964, 1720, 1451, 1274, 1111, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.01–2.12 (m, 2 H), 2.27 (t, *J* = 12.8 Hz, 1 H), 2.45–2.51 (m, 2 H), 2.80 (dt, *J* = 14.2, 6.6 Hz, 1 H), 4.04–4.13 (m, 4 H), 5.68 (q, *J* = 6.6 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 8.08 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.5, 35.8, 40.3, 64.9, 65.0, 73.6, 107.3, 128.4, 129.5, 129.8, 133.2, 165.3, 203.3; MS (EI) *m/z* (rel intensity) 276 (M^+, 16), 219 (25), 171 (22), 155 (23), 126 (16), 122 (20), 115 (12), 105 (100); HRMS (EI) calculated for $C_{15}H_{16}O_5$ 276.0997, found 276.1000; Anal. calcd. for $C_{15}H_{16}O_5$ C, 65.2, H, 5.8; found C, 65.1, H, 5.8.

3. Discussion

α-Oxyacylated carbonyl compounds are important functional groups present in many natural products, pharmaceuticals and synthetic intermediates of broad utility. Shi and coworkers have reported the catalytic asymmetric introduction of the oxybenzoyl group α- to ketone carbonyl groups by the low temperature epoxidation of preformed enol esters followed by rearrangement under acidic conditions, which furnishes products in good yields and excellent enantioselectivity.[3] The preparation of α-acetoxy ketones catalyzed by iodobenzene via a hypervalent iodine intermediate has also been described.[4] Despite the effectiveness of this method, it has not been extended to aldehyde substrates and is only effective for the introduction of acetoxy groups. Discrimination between primary and non-sterically encumbered secondary carbon centers is also poor using this method.

The procedure described above provides a very practical alternative for the α-acyloxylation of carbonyl compounds. The reagents are bench stable and react under mild conditions with both aldehydes and ketones in good yields. Not only do these reagents avoid air-sensitive intermediates and therefore obviate the need for purified solvents and specialized equipment; but the reagents display a remarkable functional group tolerance and useful chemo- and regioselectivity.

N-Methyl-*O*-benzoylhydroxylamine hydrochloride **1** is a general reagent for the oxygenation of both aldehydes and ketones.[5] The related *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochloride **3** allows the chemoselective α-oxybenzoylation of aldehyde substrates in good to excellent yield, since it is completely inert to ketones.[6] Both classes of reagents can be used for the introduction of the oxyacyl group of choice by simple modification of the carboxylic acid used in the reagent synthesis. Representative examples for the α-functionalization of aldehydes and ketones by *N*-alkyl-*O*-acylhydroxylamine hydrochlorides are given in Tables 1 and 2.

TABLE 1

α-Oxybenzoylation of Aldehydes and Ketones using *N*-Methyl-*O*-Benzoylhydroxylamine Hydrochloride (**1**)

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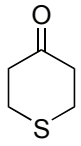
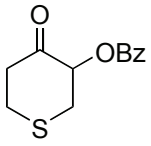
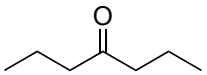
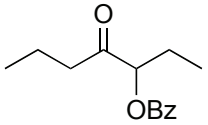
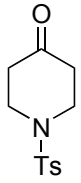
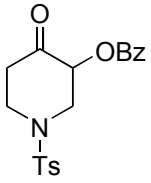
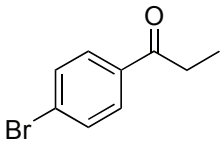
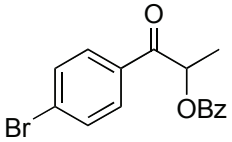
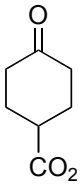
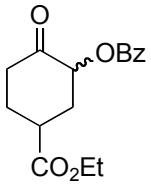
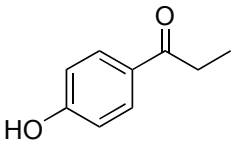
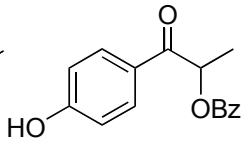
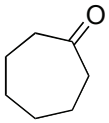
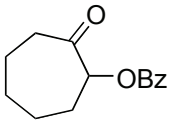
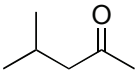
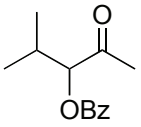
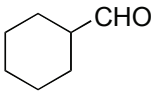
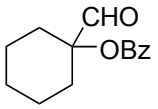
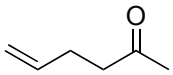
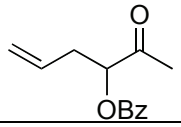
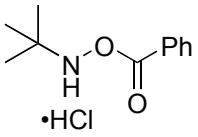
1			75[a]	6			90[b]
2			74[a]	7			82[c]
3			75[a]	8			85[c]
4			69[a]	9			73[b]
5			74[a]	10			81[b]

[a] DMSO, rt, 4-24 h, 1 equiv. **1**; [b] DMSO, 50 °C, 24 h, 1 equiv. **1**; [c] DMSO, 50 °C, 48 h, 2 equiv. **1**



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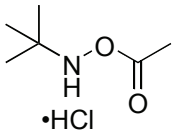

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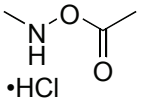

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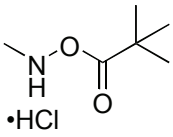

6

TABLE 2

α-Acyloxylaton of Carbonyl Compounds using *N*-Alkyl-*O*-Acyl Hydroxylamine Hydrochlorides (**3-6**)

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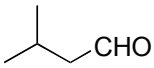
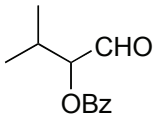
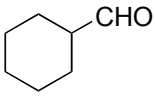
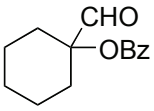
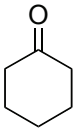
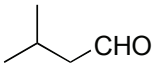
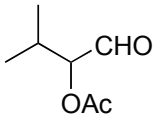
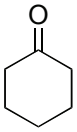
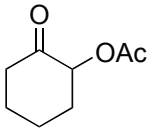
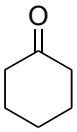
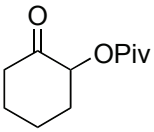
1	**3**			79[a]
2	**3**			82[a]
3	**3**		None	0[a]
4	**4**			72[a]
5	**5**			67[b]
6	**6**			69

[a] THF/H_2O (9:1), 50 °C, 24 h; [b] DMSO, rt, 24 h

1. School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK; tomkinsonnc@cardiff.ac.uk.

2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA; pwipf@pitt.edu.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Benzoic acid; (65-85-0)

Carbonyldiimidazole: 1*H*-Imidazole, 1,1'-carbonylbis-; (530-62-1)

N-Methylhydroxylamine hydrochloride: Methanamine, *N*-hydroxy-, hydrochloride; (4229-44-1)

N-Methyl-*O*-benzoylhydroxylamine hydrochloride: Methanamine, *N*-(benzoyloxy)-, hydrochloride; **(**27130-46-7)

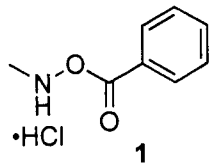
1,4-cyclohexanedione mono-ethylene ketal: 1,4-Dioxaspiro[4.5]decan-8-one; **(**4746-97-8)

(2-Benzoyloxy)-1,4-cyclohexanedione (mono)ethylene ketal: 1,4-Dioxaspiro[4.5]decan-8-one, 7-(benzoyloxy)-; (872312-37-3)

Nick Tomkinson was born in St Andrews, Scotland in 1969. He studied Chemistry at The University of Sheffield and received his BSc in 1992. His Ph.D. studies were under the supervision of Dr. D. Neville Jones and Professor Jim Anderson investigating asymmetric synthesis with unsaturated sulfur compounds. Postdoctoral studies on Nuclear Receptors were undertaken with Dr. Tim Willson at GlaxoSmithKline, Research Triangle Park, North Carolina (1996-1998). Nick was appointed to the staff at Cardiff University in 1999 and in 2004 was awarded an EPSRC Advanced Research Fellowship.

Teyrnon Jones was born in 1978 and raised in Anglesey, North Wales. He received his MChem from The University of Sheffield in 2000, and following completion of his undergraduate studies chose to remain at Sheffield to research new applications of germanium-linked solid-phase organic synthesis in the laboratory of Dr. Alan Spivey. Subsequent to the award of his Ph.D. in 2004, an interest in metal-free synthesis and organocatalysis lead to a successful two-year postdoctoral collaboration with Dr. Nick Tomkinson at Cardiff University developing new practical methods for carbonyl α-oxygenation. He is currently senior scientist in Medicinal Chemistry at AstraZeneca, Loughborough UK, working in the respiratory and inflammation therapeutic area.

Kalyani Patil obtained her B.Sc. (1998) in Chemistry from the University of Mumbai, India. She completed her M.Sc. in 2000 from the Indian Institute of Technology, Bombay under the guidance of Professor Sujata Bhat. Her M.Sc. thesis involved the synthesis of dienones for applications in the synthesis of bioactive molecules. She then moved to North Dakota State University to pursue her Ph.D. under the supervision of Professor Mukund Sibi, where her research was focused on the synthesis of β-amino acids via free radical chemistry. After completion of her Ph.D. in 2005 she joined the group of Professor Peter Wipf at the University of Pittsburgh as a postdoctoral research associate and is currently working on the synthesis of the tetracyclic core of viridin.



1

BRUKER

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SWH	18115.941 Hz
FIDRES	0.276427 Hz
AQ	1.8088436 sec
RG	912.3
DW	27.600 usec
DE	6.00 usec
TE	300.0 K
D1	10.00000000 sec
d11	0.03000000 sec
DELTA	9.89999962 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	9.00 usec
PL1	1.80 dB
SFO1	75.5381641 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	92.00 usec
PL2	0.00 dB
PL12	20.00 dB
PL13	20.00 dB
SFO2	300.3812015 MHz

F2 - Processing parameters

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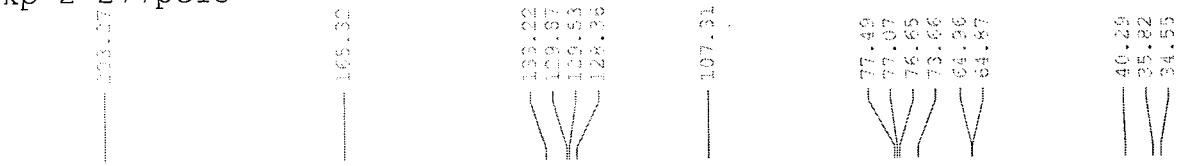
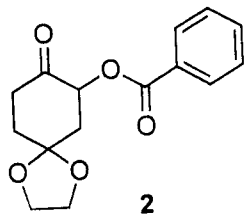
GB	0
PC	1.40

kp-2-277pc13





2

BRUKER

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TD	65536
SOLVENT	CDCl3
NS	3408
DS	4
SWH	18115.941 Hz
FIDRES	0.276427 Hz
AQ	1.8088436 sec
RG	11585.2
DW	27.600 usec
DE	6.00 usec
TE	300.0 K
D1	10.00000000 sec
d11	0.03000000 sec
DELTA	9.89999962 sec
TD0	1

======== CHANNEL f1 ========

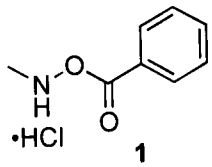
NUC1	13C
P1	9.00 usec
PL1	1.80 dB
SFO1	75.5381641 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	92.00 usec
PL2	0.00 dB
PL12	20.00 dB
PL13	20.00 dB
SFO2	300.3812015 MHz

F2 - Processing parameters

SI	65536
SF	75.5306110 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



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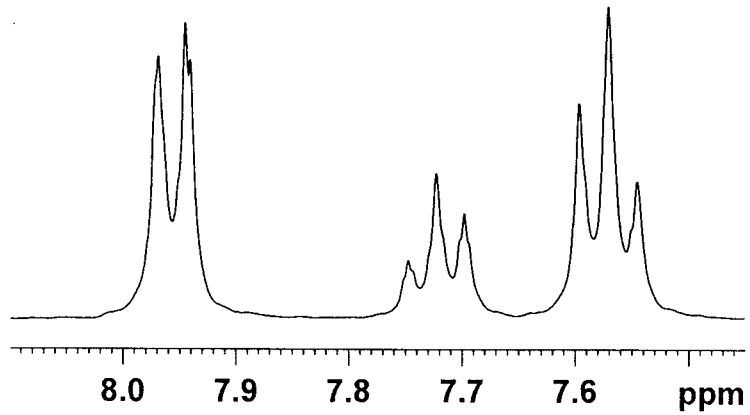

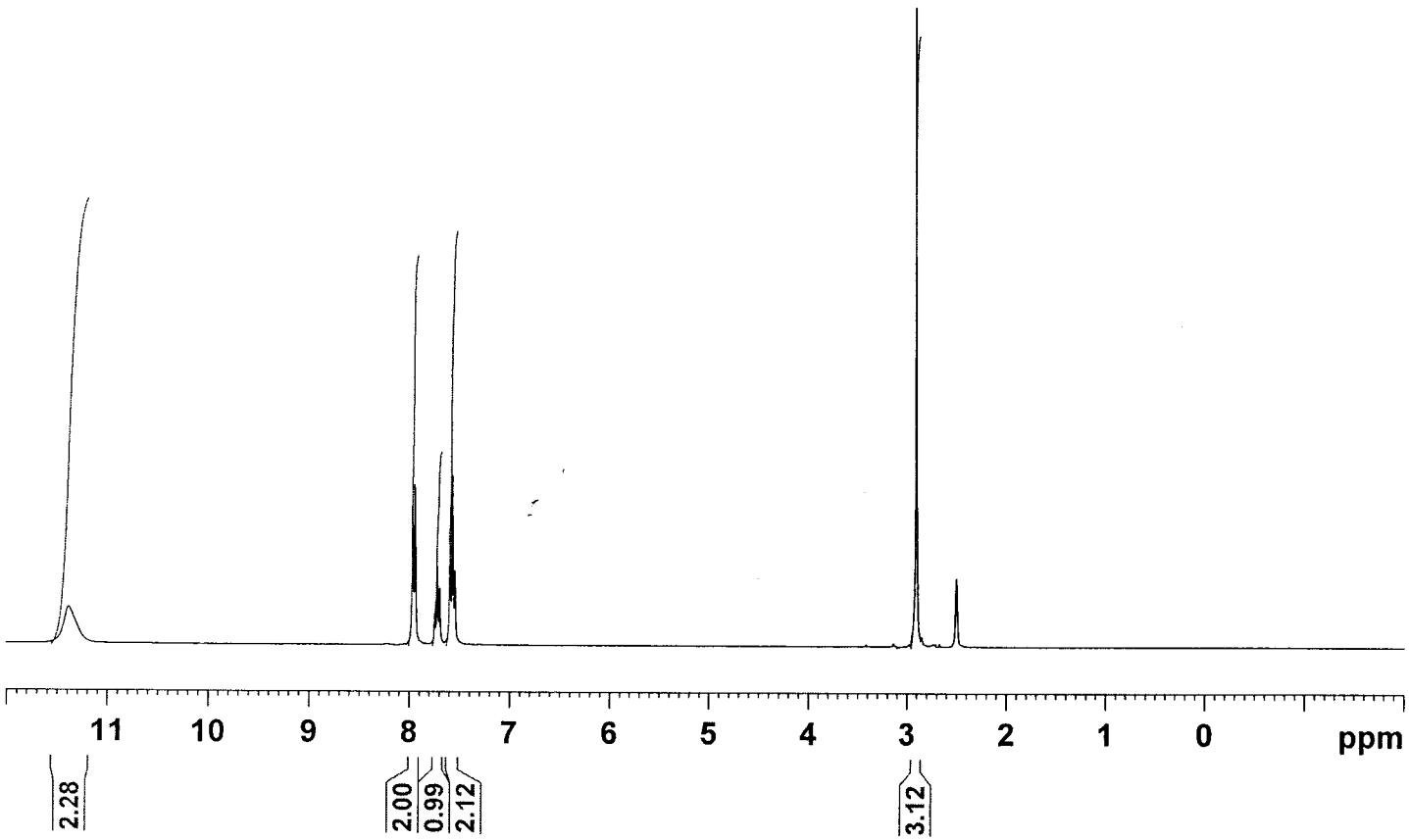


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PROCNO                     1

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SOLVENT                DMSO
NS                        4
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FIDRES             0.094893 Hz
AQ                 5.2691445 sec
RG                     143.7
DW                   80.400 usec
DE                    6.00 usec
TE                   300.0 K
D1              2.00000000 sec
TD0                       1

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

F2 - Processing parameters
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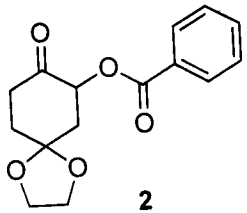

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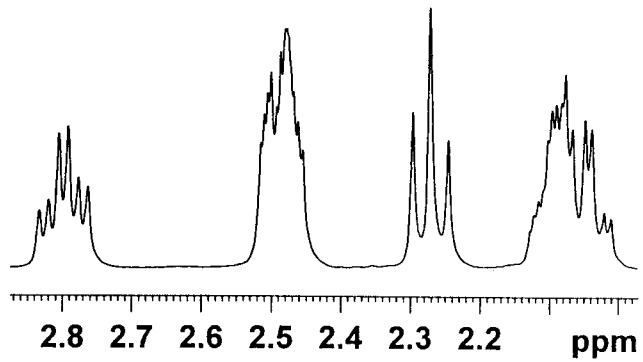

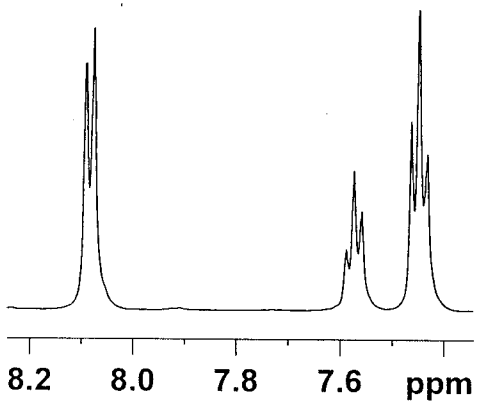

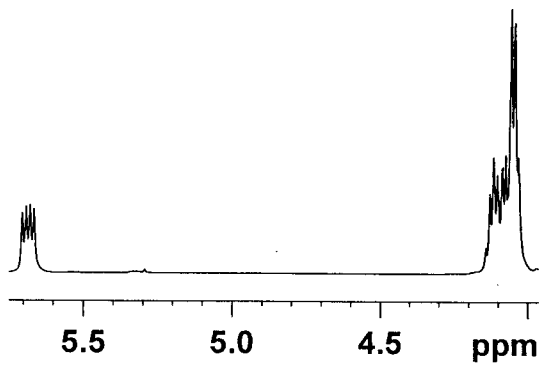

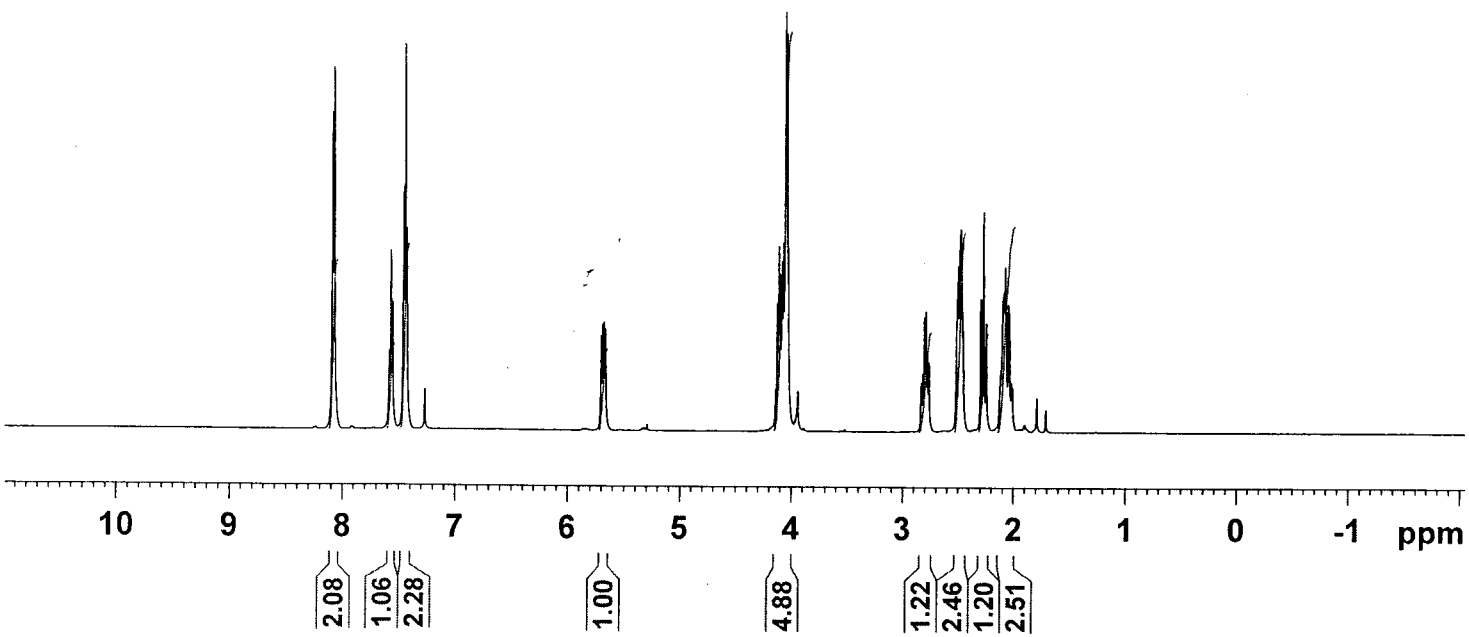


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FIDRES         0.157632 Hz
AQ             3.1719923 sec
RG                    16
DW               48.400 usec
DE                6.00 usec
TE                297.2 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
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PL1                0.00 dB
SFO1        500.1330885 MHz

F2 - Processing parameters
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SF          500.1300077 MHz
WDW                   EM
SSB                    0
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