ACYL TRANSFER CATALYSIS WITH 1,2,4-TRIAZOLE ANION

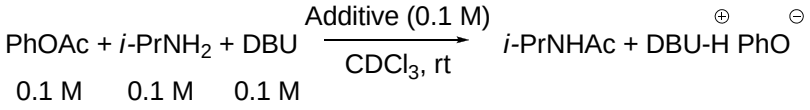
Xing Yang and Vladimir B. Birman*

A contribution from the Department of Chemistry, Washington University, Campus Box 1134, One Brookings Drive, Saint Louis, Missouri 63130

SUPPORTING INFORMATION.

1. General. All reagents and solvents were obtained commercially and used as received. Stock solutions were prepared in volumetric flasks of specified volume by dissolving reagents in a solvent and bringing the volume to the mark. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Unity 300 MHz Varian spectrometer. Flash column chromatography was performed over ICN Ecochrom silica gel (32-63 μm).

2. Catalytic activity screen

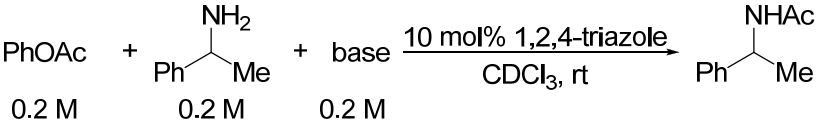


*Stock solution **A**:* 0.20 M phenyl acetate (126 μL, 1.00 mmol) and 0.20 M isopropylamine (86 μL, 1.00 mmol) in 5.0 mL of $CDCl_3$.

*Stock solution **B**:* 0.20 M DBU (60 μL, 0.40 mmol) and 0.20 M additive (0.40 mmol **1**, **8**-**21**, or none for the blank) in 2.0 mL of $CDCl_3$.

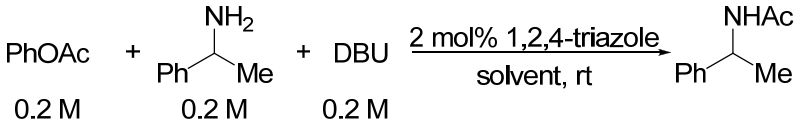
The test was carried out by mixing 0.50 mL aliquots of stock solutions **A** and **B** at room temperature and monitoring reaction progress by ^{1}H NMR. The time required to reach 50% conversion of isopropylamine into N-isopropylacetamide was recorded as $t_{1/2}$ in Table 1. In those cases when the conversion was lower than 50% after 3 days, $t_{1/2}$ was not determined.

3. Influence of base



Phenyl acetate (25 μL, 0.20 mmol), α–phenethylamine (25 μL, 0.20 mmol) and 0.20 mmol of a base (30 μL of DBU, or 28 μL of NEt_3, or none for the blank) were added successively to 1.0 mL of 0.02 M stock solution of 1,2,4-triazole in $CDCl_3$ at room temperature. The reaction was progress monitored by ^{1}H NMR. The % conversion of α–phenethylamine into N-phenethylacetamide was recorded in Figure 3.

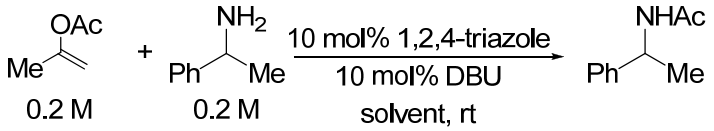
4. Influence of solvents on the aminolysis of phenyl acetate



*Stock solution **C:*** 0.20 M 1,2,4-triazole (0.40 mmol, 28 mg) and 0.20 M DBU (0. 40 mmol, 60 μL) in 2 mL of $CDCl_3$.
*Stock solution **D**:* 0.20 M phenyl acetate (50 μL, 0.40 mmol), 0.20 M α–phenethylamine (51 μL, 0.40 mmol) and 0.20 M DBU (0. 40 mmol, 60 μL) in 2.0 mL of a deuterated solvent (chloroform-d, acetonitrile-d_3, benzene-d_6, DMSO-d_6 or THF-d_8.

The test was carried out by adding 20 μL of Stock solution **C** into 1.0 mL of Stock solution **D** and monitoring the conversion of α–phenethylamine into N-phenethylacetamide by ^{1}H NMR at 10 min, 30 min, 1 h, 2 h, 6 h, and 24 h. The data were plotted in Figure 4.

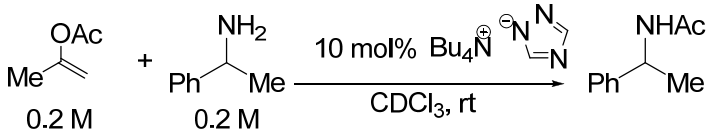
5. Influence of solvents on the aminolysis of isopropenyl acetate



*Stock solution **E**:* 0.40 M 1,2,4-triazole (0.80 mmol, 55 mg) and 0.40 M DBU (0. 80 mmol, 120 μL) in 2 mL of $CDCl_3$.
*Stock solution **F**:* 0.20 M isopropenyl acetate (44 μL, 0.40 mmol) and 0.20 M α–phenethylamine (51 μL, 0.40 mmol) in 2.0 mL of a deuterated solvent (chloroform-d, acetonitrile-d_3, benzene-d_6, DMSO-d_6 or THF-d_8).

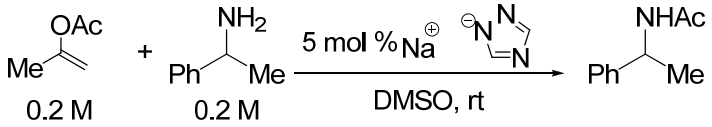
The test was carried out by adding 50 μL of Stock solution **E** into 1.0 mL of Stock solution **F** and monitoring the conversion of α–phenethylamine into N-phenethylacetamide by ^{1}H NMR at 10 min, 30 min, 1 h, 2 h, 6 h, and 24 h. The data were plotted in Figure 5.

6. Catalytic activity of tetrabutylammonium triazolide.



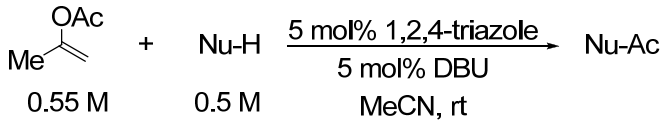
Catalyst reparation: A modified procedure found in a patent[1] was followed. A mixture of powdered solid NaOH (0.40 g, 10 mmol) and triazole (0.69 g, 10 mmol) in 5 mL of methanol was stirred for 30 min at room temperature. Solid Bu_4NBr (3.22 g, 10 mmol) was added and the stirring continued for 2 h. After addition of 100 mL of anhydrous Et_2O, NaBr precipitated and was filtered off. The filtrate was concentrated to dryness and held under high vacuum overnight.
Catalytic activity test: A 50 μL aliquot of 0.40 M solution of tetrabutylammonium triazolide in $CDCl_3$ was added to 1.0 mL of stock solution **F** (in $CDCl_3$) and the reaction progress was monitored by ^{1}H NMR. until 50% conversion (4.0 h). A control experiment with DBU triazolide reached 50% conversion in 5.5 h.

7. Catalytic activity of sodium triazolide.



Catalyst reparation: A mixture of NaOH (10 mmol, 0.40 g) and 1,2,4-triazole (10 mmol, 0.69 g) in 5 mL of MeOH was stirred overnight and then evaporated to dryness. The evaporation residue was dried azeotropically with toluene and then kept overnight under high vacuum.
Catalytic activity test: A 50 μL aliquot of 0.20 M solution of sodium triazolide in DMSO-d6 was added to 1.0 mL of stock solution **F** (in DMSO-d6) and the reaction progress was monitored by ^{1}H NMR. until 50% conversion (12 min). A control experiment with DBU triazolide reached 50% conversion in 45 min.

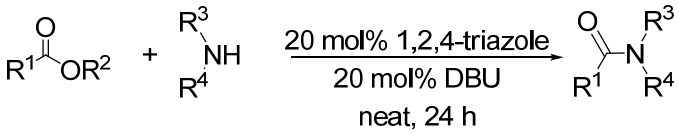
8. Preparative scale acetylation of substrates with isopropenyl acetate



General procedure: 2.0 mL of freshly prepared stock solution of 1,2,4-triazole (0.025 M) and DBU (0.025 M) in acetonitrile was added to 1.0 mmol of a substrate, followed by isopropenyl acetate (1.1 mmol, 121 μL). After 10 h at room temperature, the solvent was removed under reduced pressure and the residue was diluted with Et_2O and passed through a plug of silica gel to give pure product upon concentration. Purification of acetanilide required the use of 2:1 Et_2O-hexane mixture as eluent. The results are summarized in Figure 7.

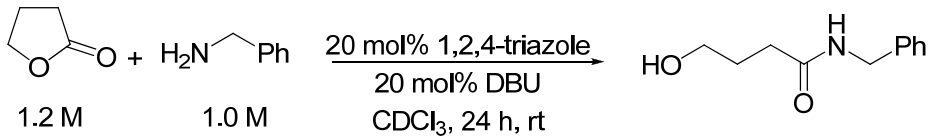
Enantiomeric purity of amides obtained from *(R)*-phenylglycine methyl ester and *(S)*-phenylalanine methyl ester was determined by chiral stationary phase HPLC using CHIRALCEL OD-H and CHIRALPAK AD-H analytical columns, respectively, (4.6x150 mm, Chiral Technologies, Inc.) with isopropanol/hexane eluent at 1 mL/min flow rate.

9. Aminolysis of unactivated acyclic esters[2]



General procedure: A reaction mixture consisting of an ester (1.2 mmol), an amine (1.0 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and DBU (30 μL, 0.20 mmol) was stirred at a specified temperature for 24 h and then applied directly to a silica gel chromatographic column and eluted with Et_2O.

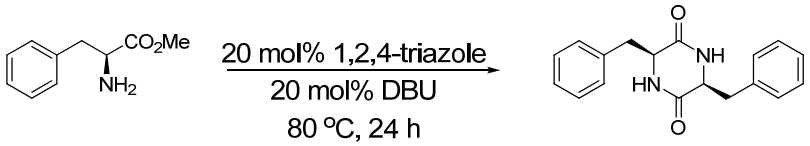
10. Aminolysis of γ–butyrolactone



A solution of γ–butyrolactone (1.2 mmol), benzylamine (1.0 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and DBU (30 μL, 0.20 mmol) in 1.0 mL of $CDCl_3$ was stirred at room temperature for 24

h, concentrated and chromatographed with EtOAc-Et_2O 1:3 to give 125 mg (84% yield) of N-benzyl- γ–hydroxybutyramide.

11. Cyclocondensation of (L)-Phenylalanine methyl ester.



Commercially available (L)-phenylalanine methyl ester hydrochloride was converted into the free base by treating it with aqueous K_2CO_3 and extracting the mixture with CH_2Cl_2. A mixture of this material (180 mg, 1.0 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and DBU (30 μL, 0.20 mmol) was heated without stirring in a vial placed in an 90 °C oil bath. After 3 h, the initially liquid mixture solidified completely. After 24 h, ^{1}H NMR analysis of the crude reaction mixture (in $CF3CO_2D$) indicated essentially complete conversion to the expected product as a 95:5 mixture of *cis*- and *trans*-diastereomers. The solid mixture was broken up and suspended in 25 mL of hot ethanol. After cooling to rt, the suspension was filtered and the white powdery precipitate was rinsed with ethanol to give 116 mg (79% yield) of the product (97:3 *cis*-*trans* ratio).

---

[1] Sturm, E.; Eckhardt, W.; Gloor, B.; Nyfeler, R. US Patent 4,259,505, 1981.

[2] All reaction products obtained in this study have been previously reported. References to commercially unavailable compounds are provided below.

(a) **Methyl N-acetylphenylglycinate:** Fadnavis, N. W.; Reddy, N. P.; Bhalerao, U. T. *J. Org. Chem.* **1989**, *54*, 3218.

(b) **N-benzyl-octanamide:** Rolfe, A.; Probst, D. A.; Volp, K. A.; Omar, I.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785.

(c) **N-benzyl-isobutyramide:** Bosch, I.; González, A.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 5638.

(d) **N-benzyl-lactamide:** Savinov, S. N.; Austin, D. J. *Org. Lett.* **2002**, *4*,1415.

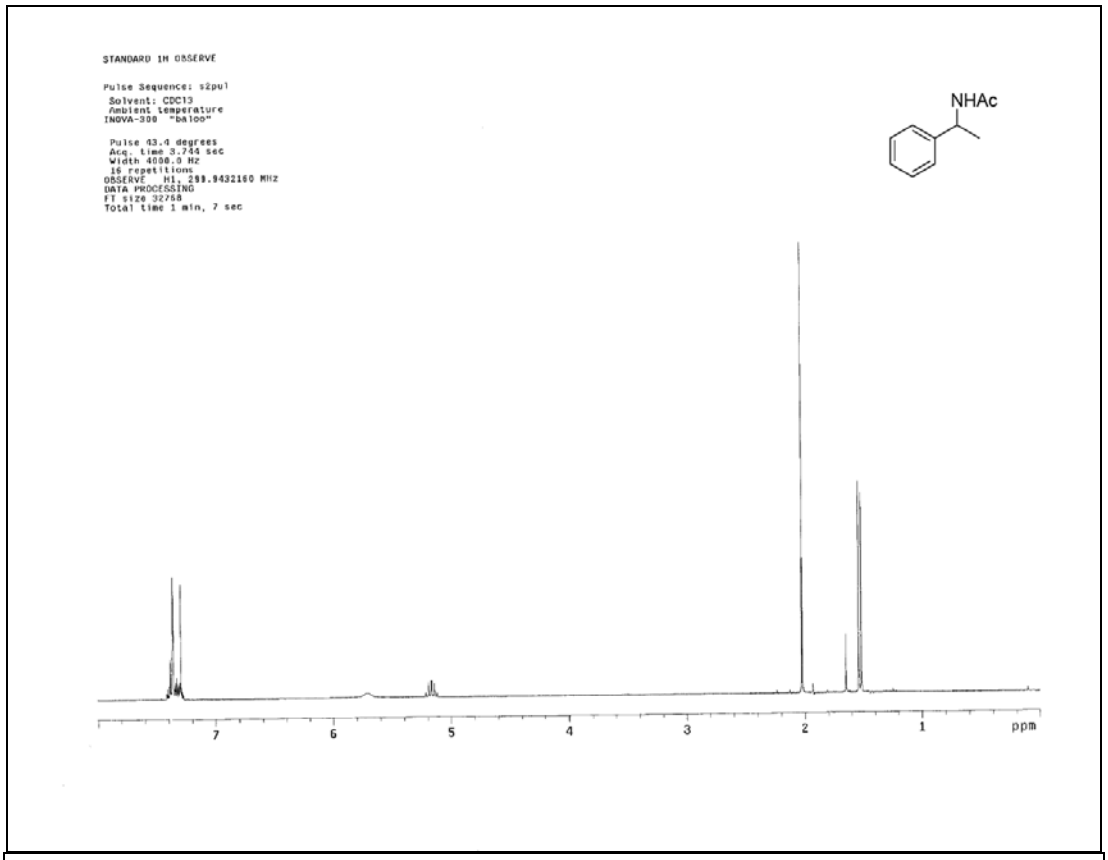
(e) **N-benzyl-4-hydroxybutanamide:** Decker, M.; Nguyen, T. T. H.; Lehmann, J. *Tetrahedron* **2004,** *60*, 4567.

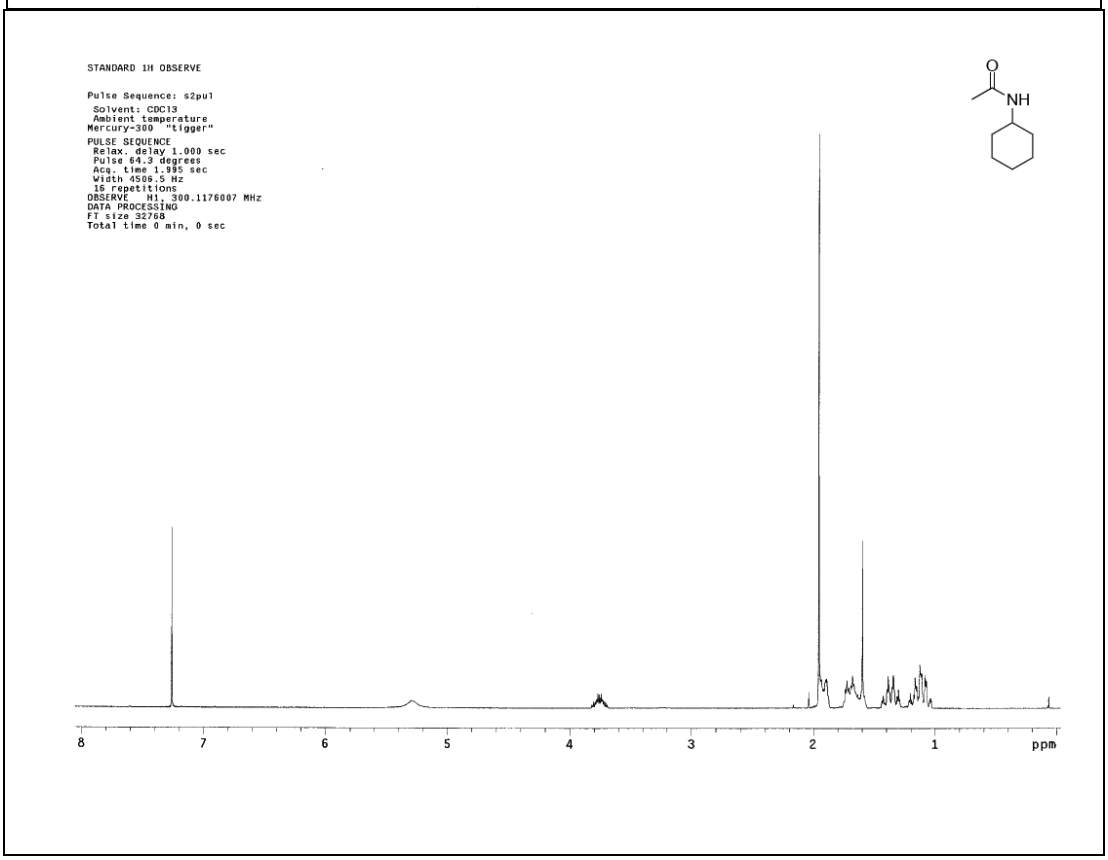
(f) **N-cyclohexyl-octanamide:** Lücking, U.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J. Jr. *J. Am. Chem. Soc.* **2000**, *122*, 8880.

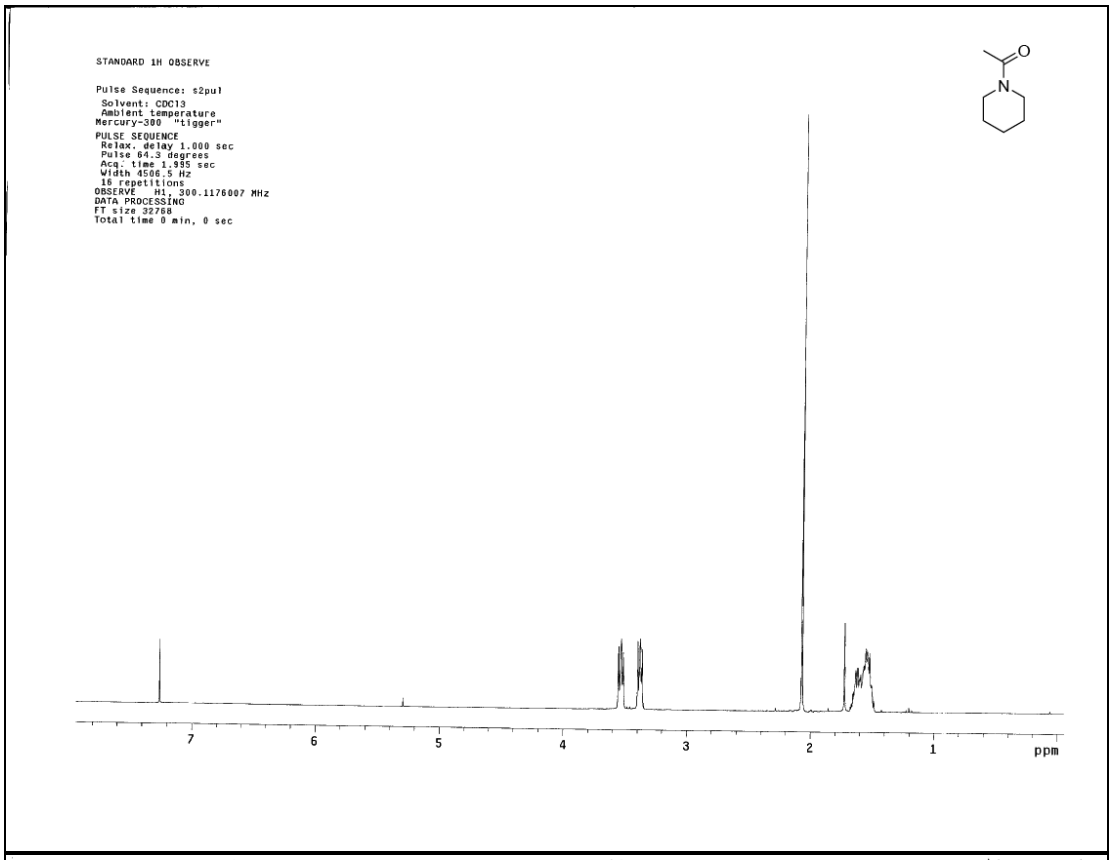
(g) **N-α̃-phenethyl-octanamide:** Souto-Bachiller, F.; Bates, G. S.; Masamune, S. J. *Chem. Soc., Chem. Commun.* **1976,** 719.

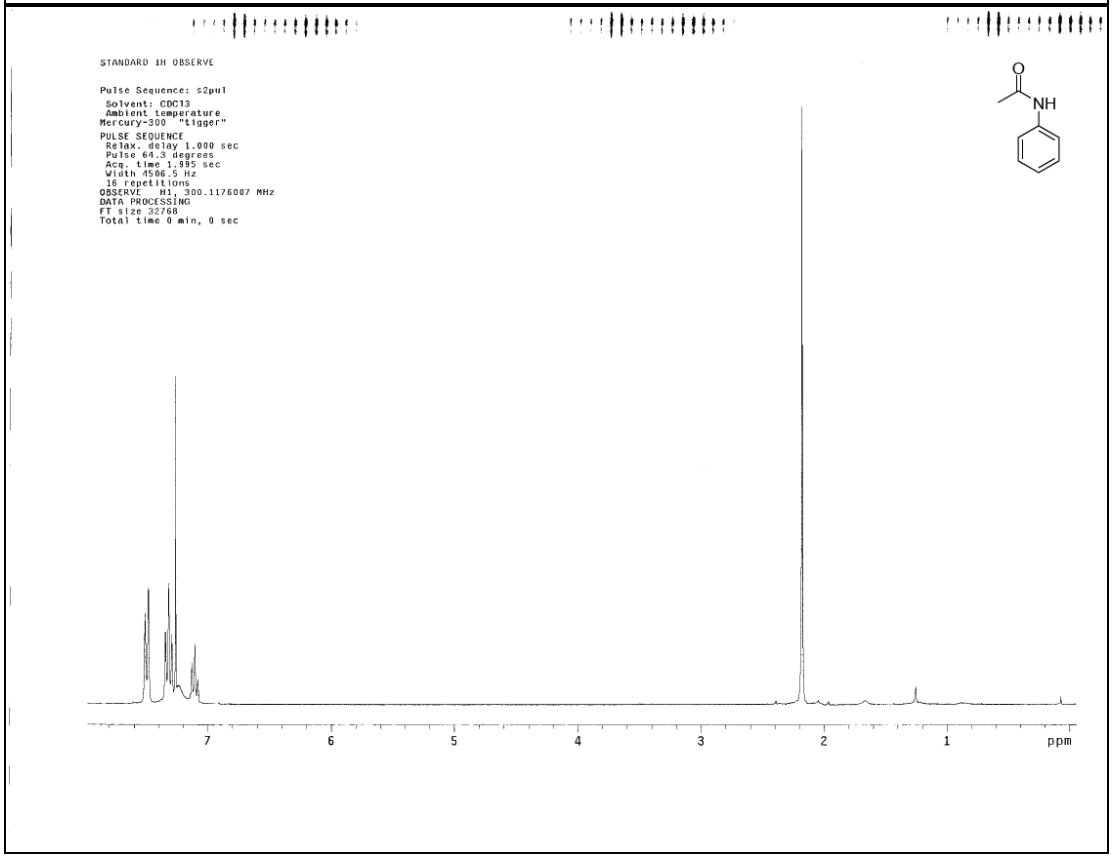
(h) **N-octanoylpiperidine:** Jensen, A. E.; Knochel, P.*J. Org. Chem.*, **2002**, *67*, 79.

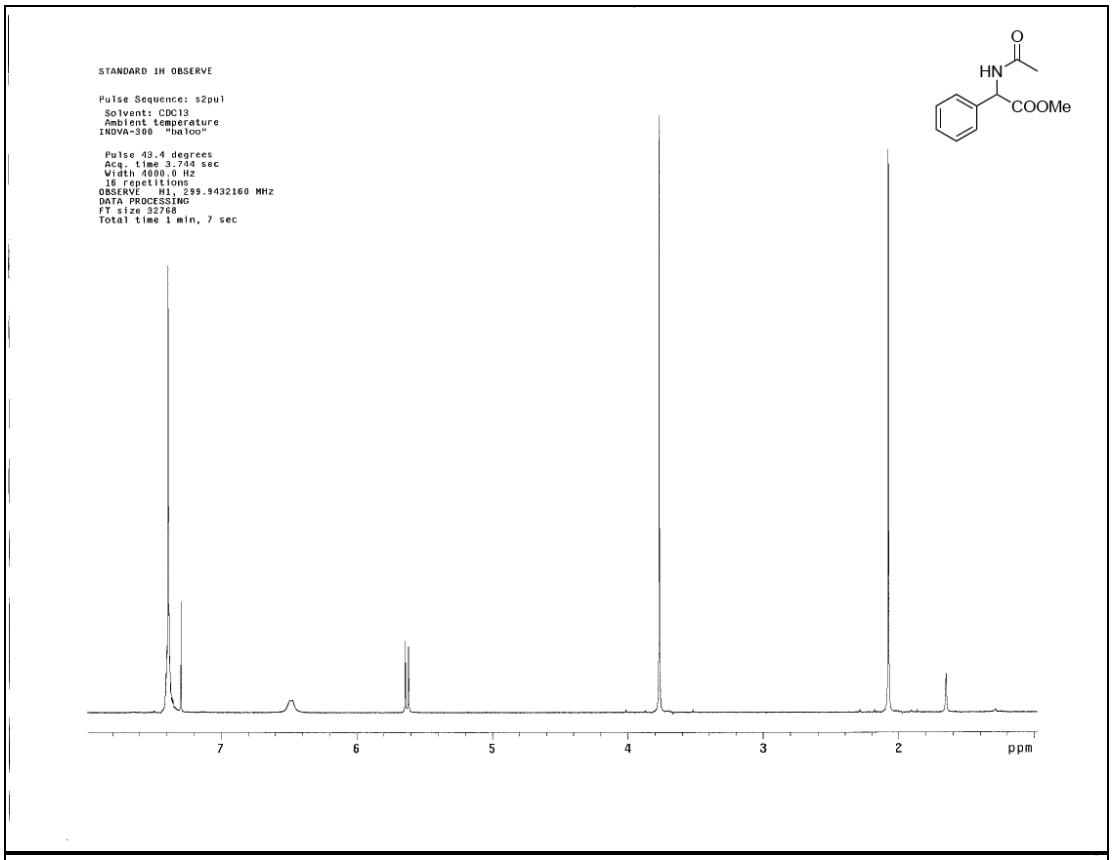
(i) ***cis*-3,6-dibenzylpiperazine-2,5-dione (cyclo-Phe-Phe):** Donkor, I. O.; Sanders, M. L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2647.

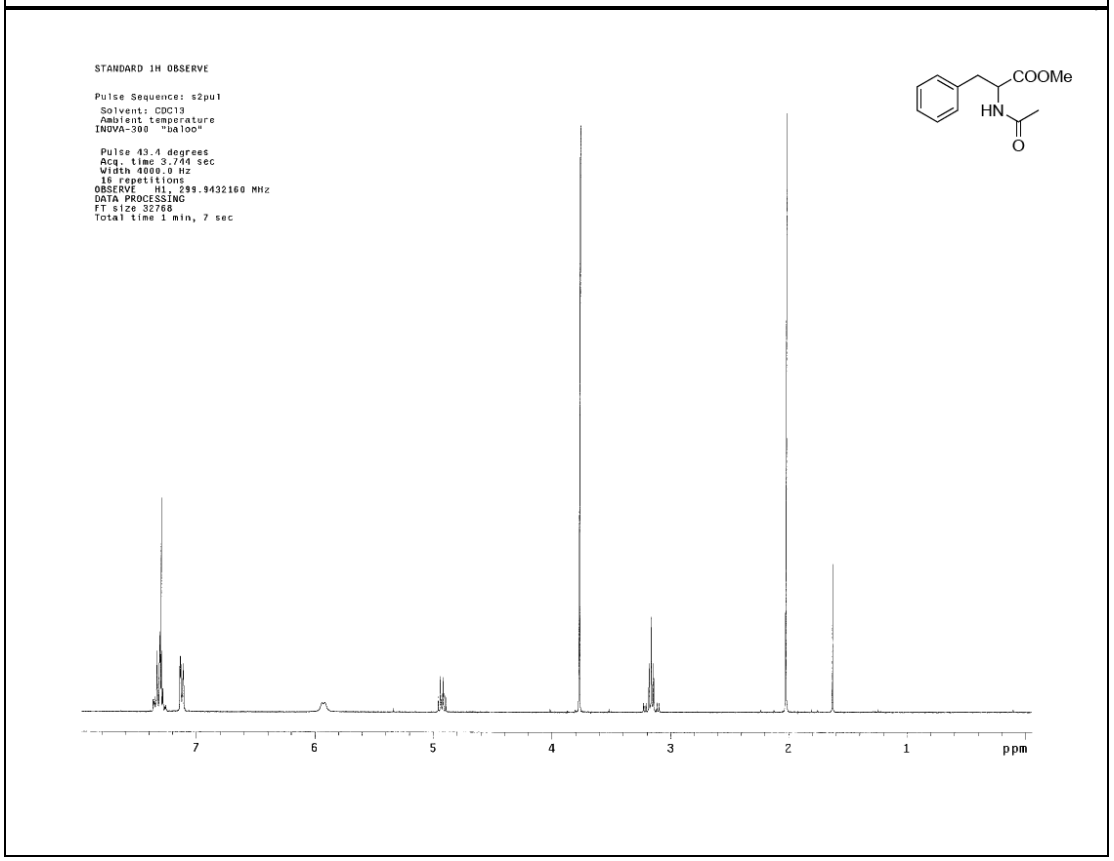

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
NHAc
7
6
5
4
3
2
1
ppm

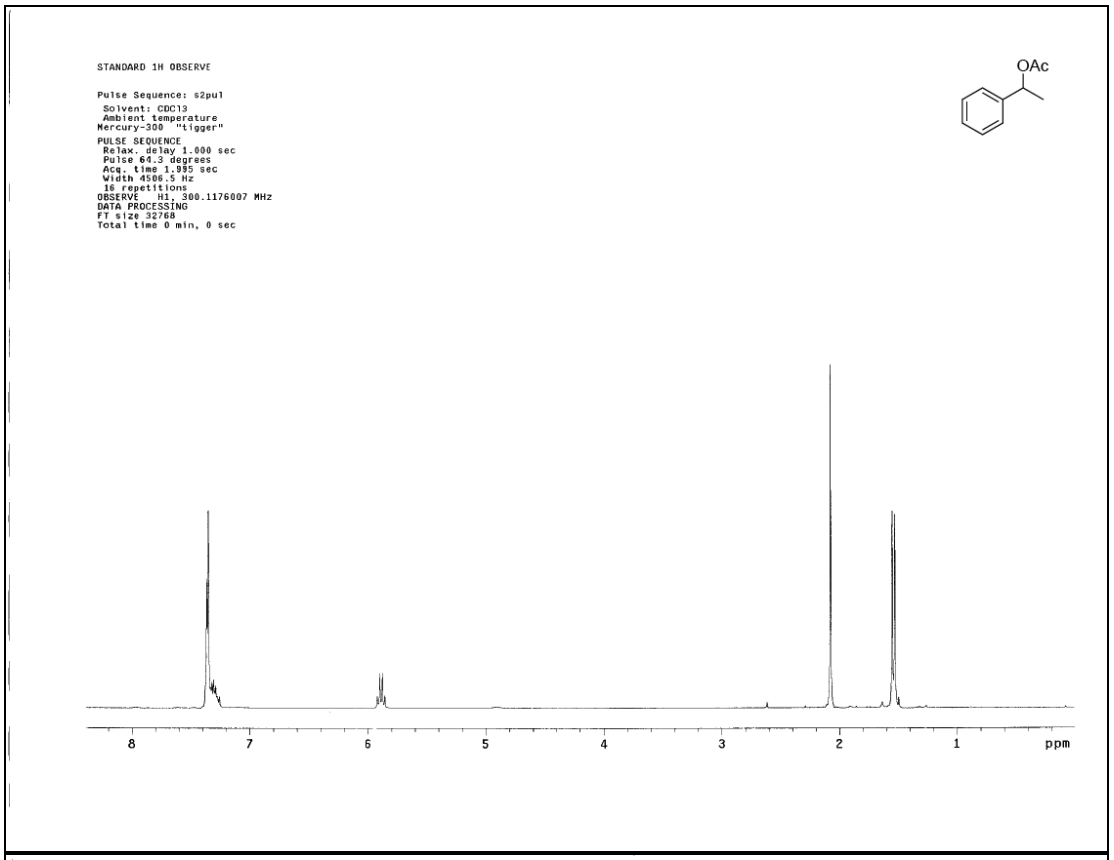

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
O
NH
8
7
6
5
4
3
2
1
ppm

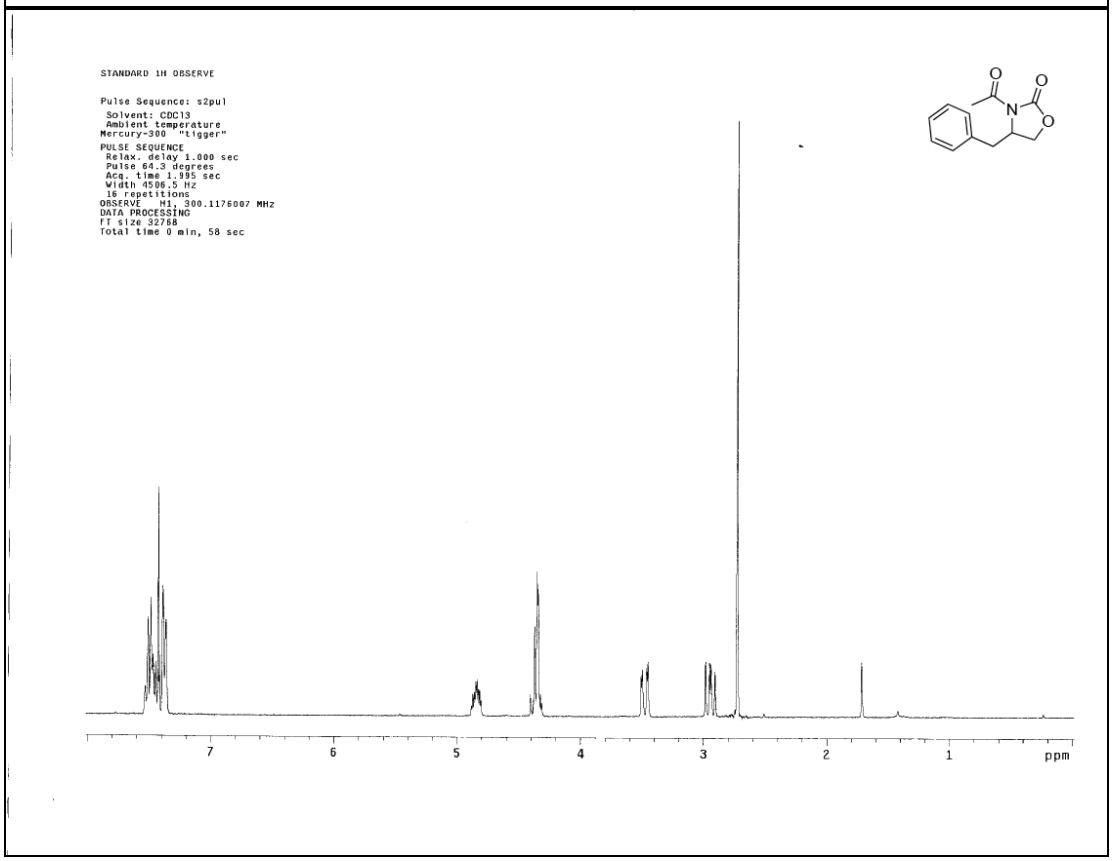

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
O
N
7
6
5
4
3
2
1
ppm

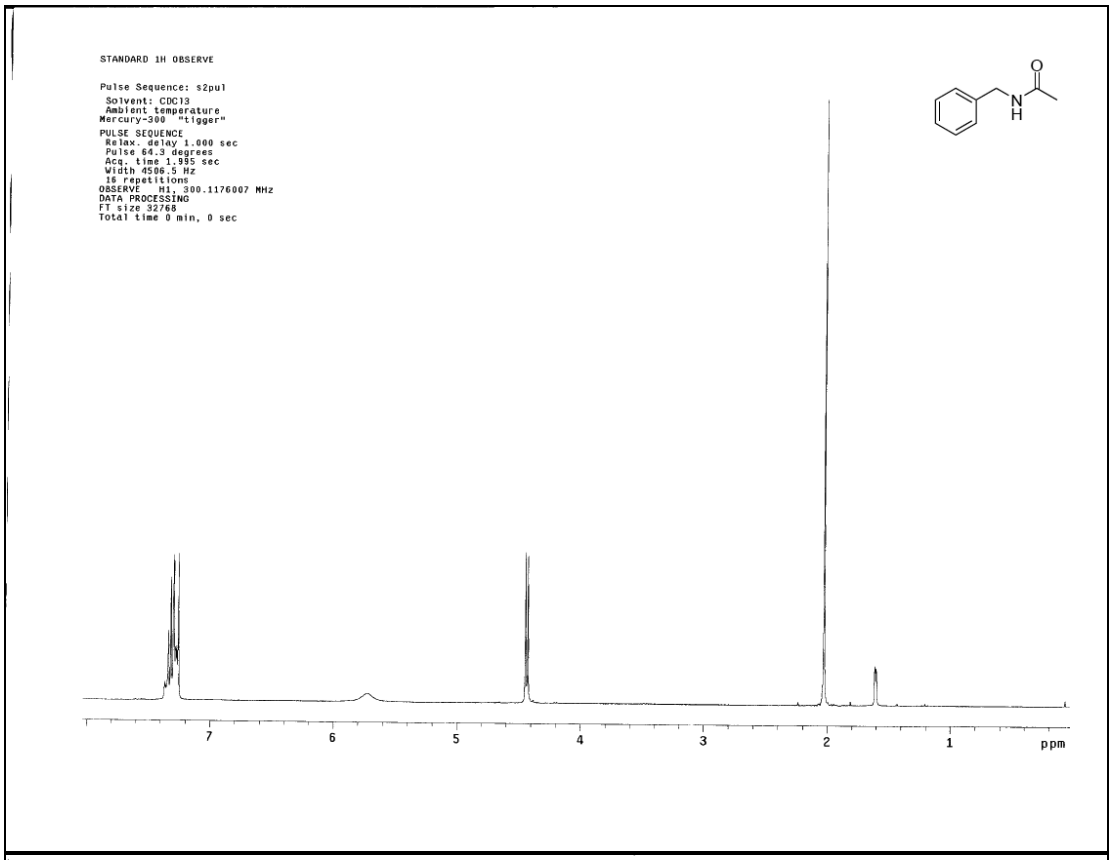

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
O
NH
7
6
5
4
3
2
1
ppm

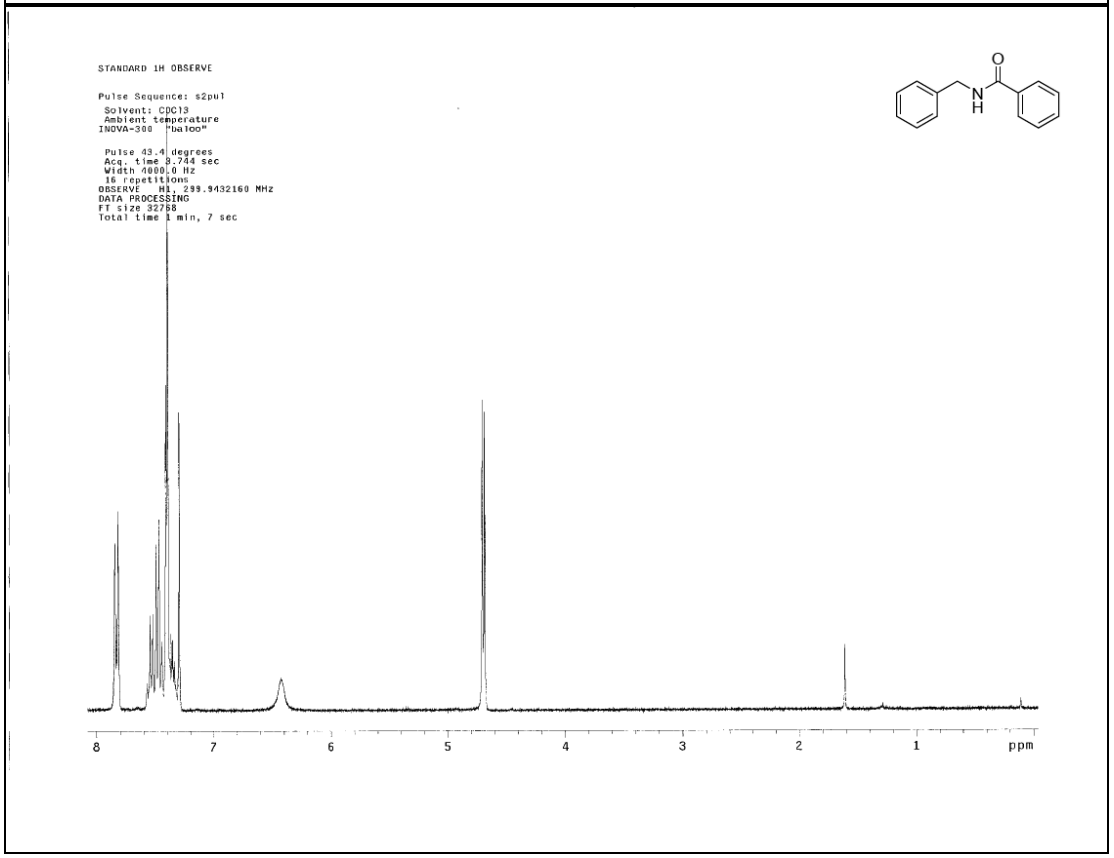

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
HN
COOMe
7
6
5
4
3
2
ppm

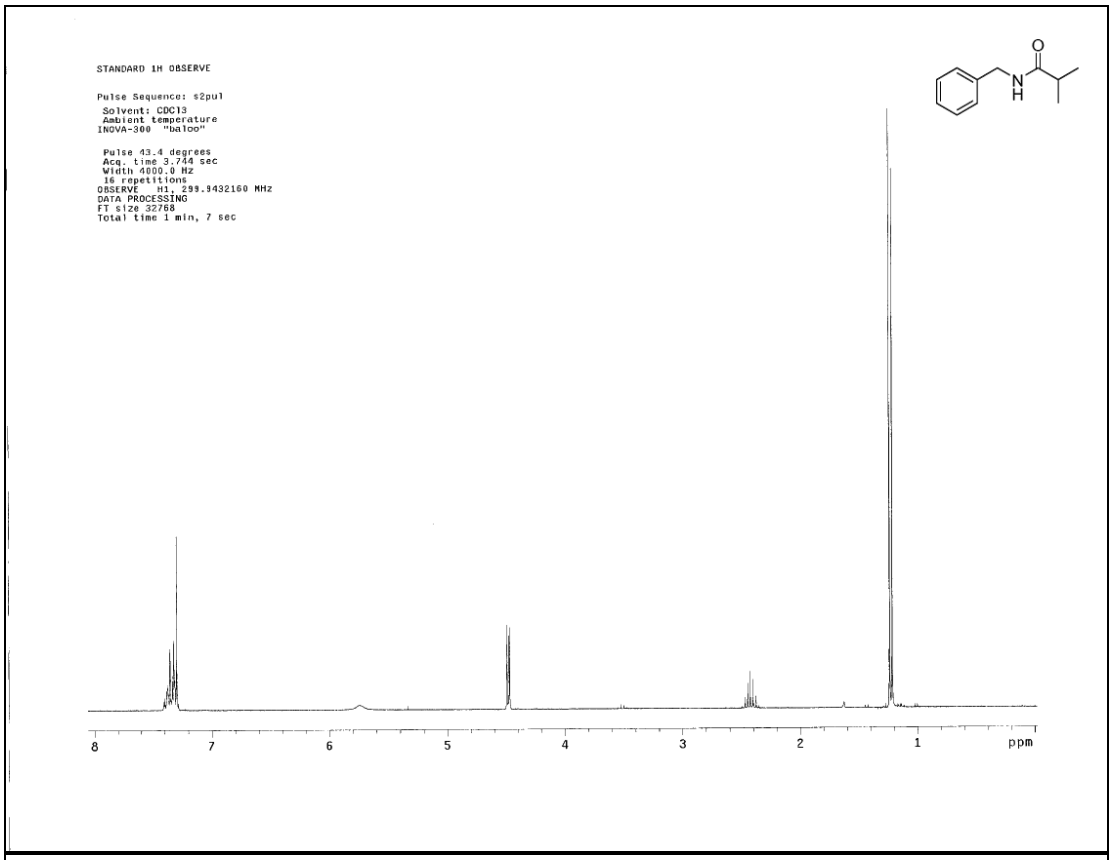

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
COOMe
HN
O
7
6
5
4
3
2
1
ppm

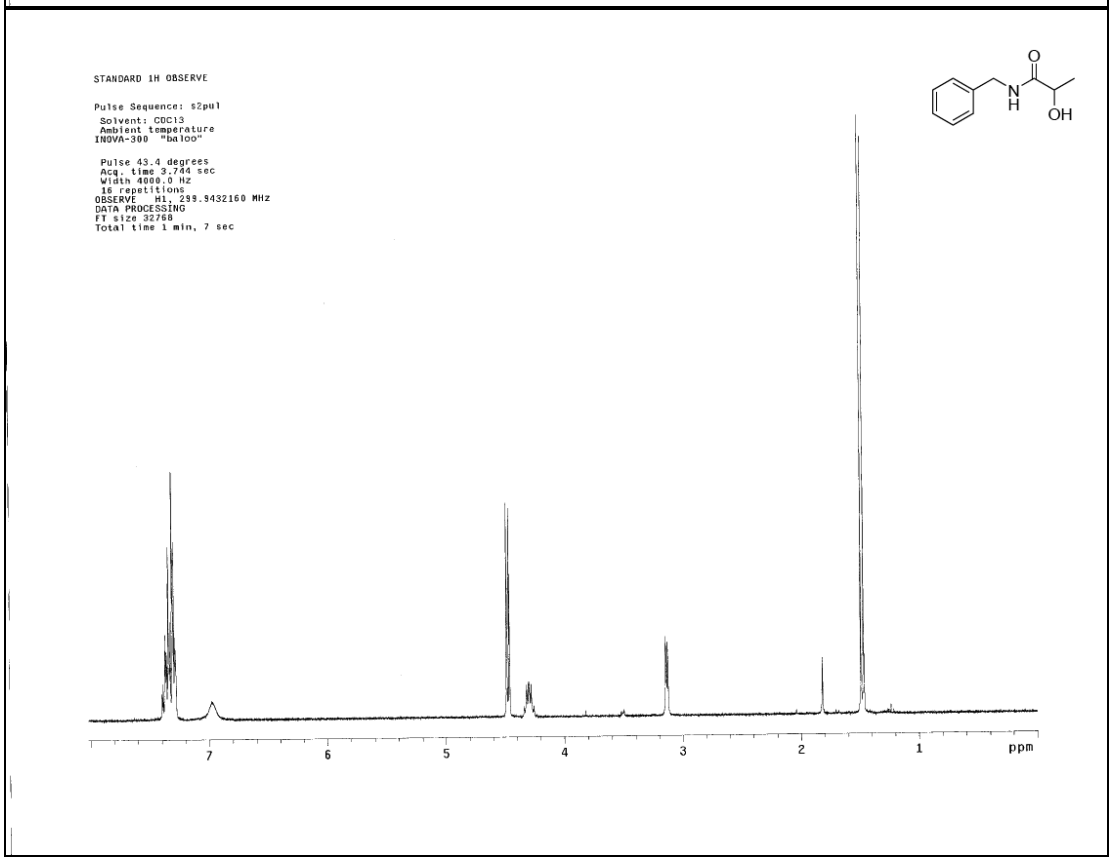

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
OAc
8
7
6
5
4
3
2
1
ppm

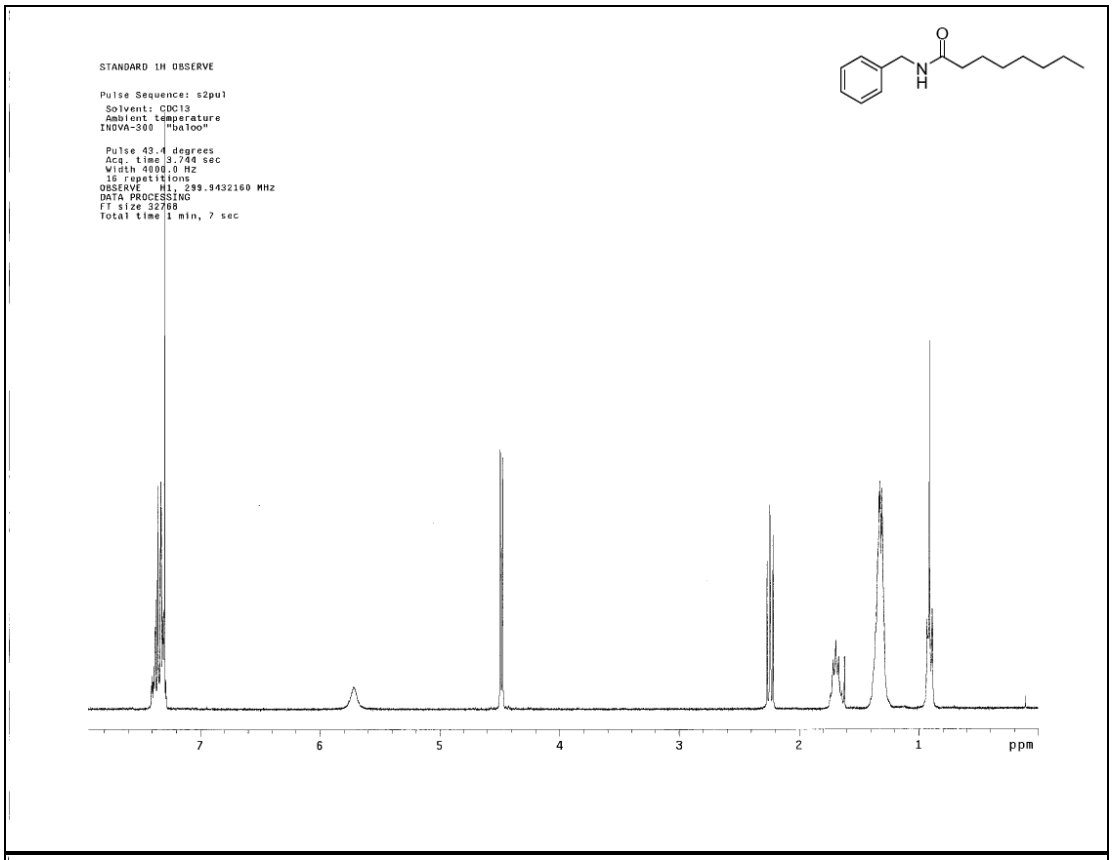

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
O
O
N
O
7
6
5
4
3
2
1
ppm

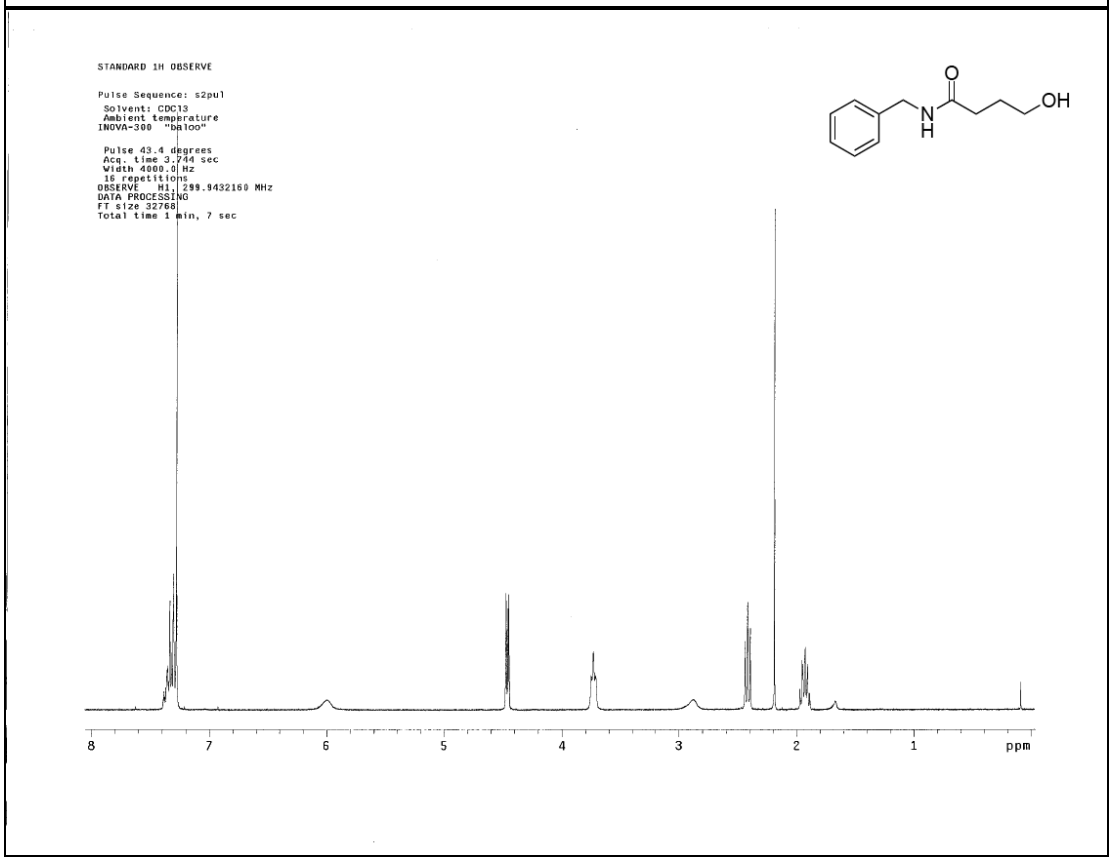

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
O
N
H
7
6
5
4
3
2
1
ppm

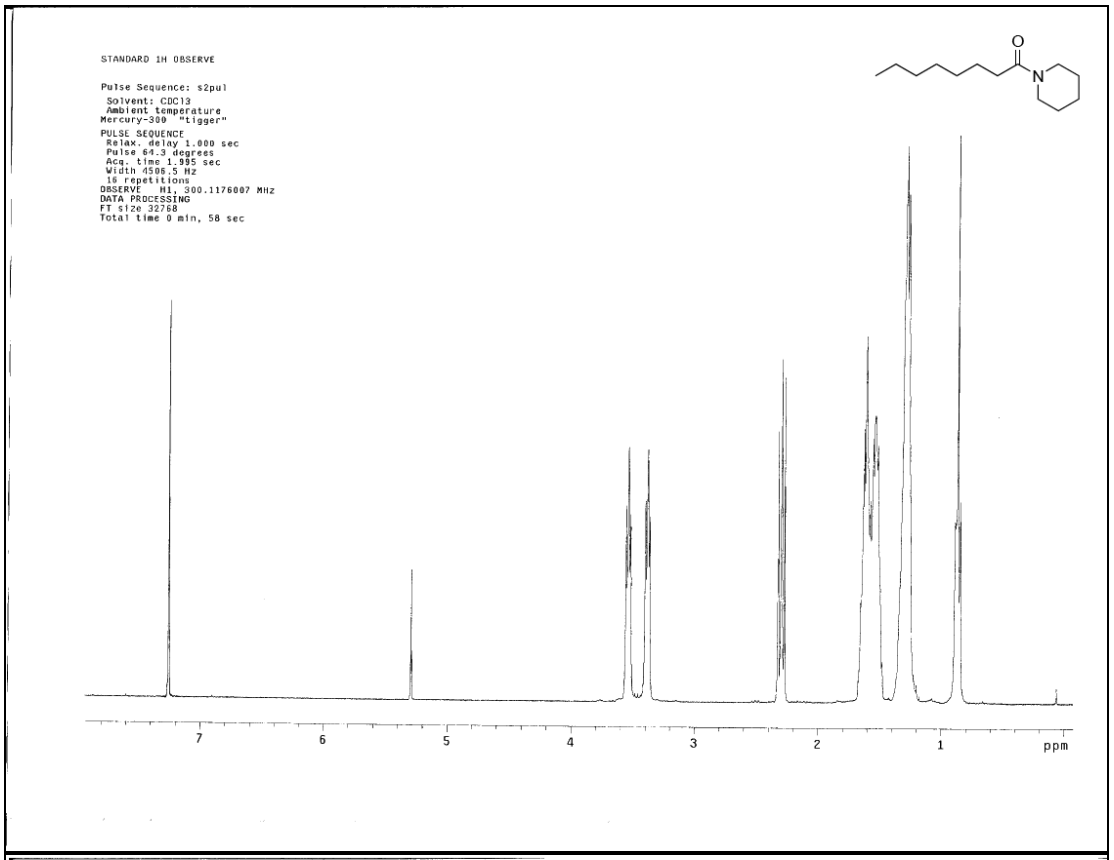

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 8.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
O
N
H
8
7
6
5
4
3
2
1
ppm

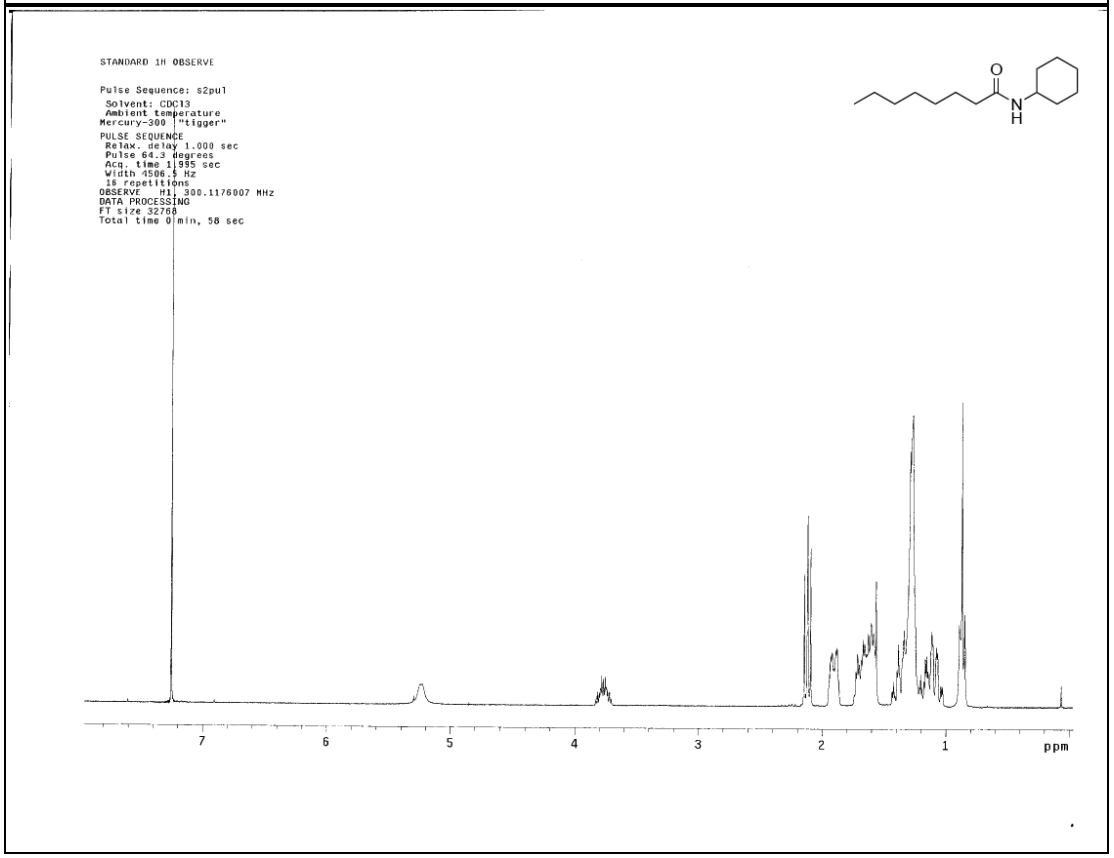

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
O
N
H
8
7
6
5
4
3
2
1
ppm

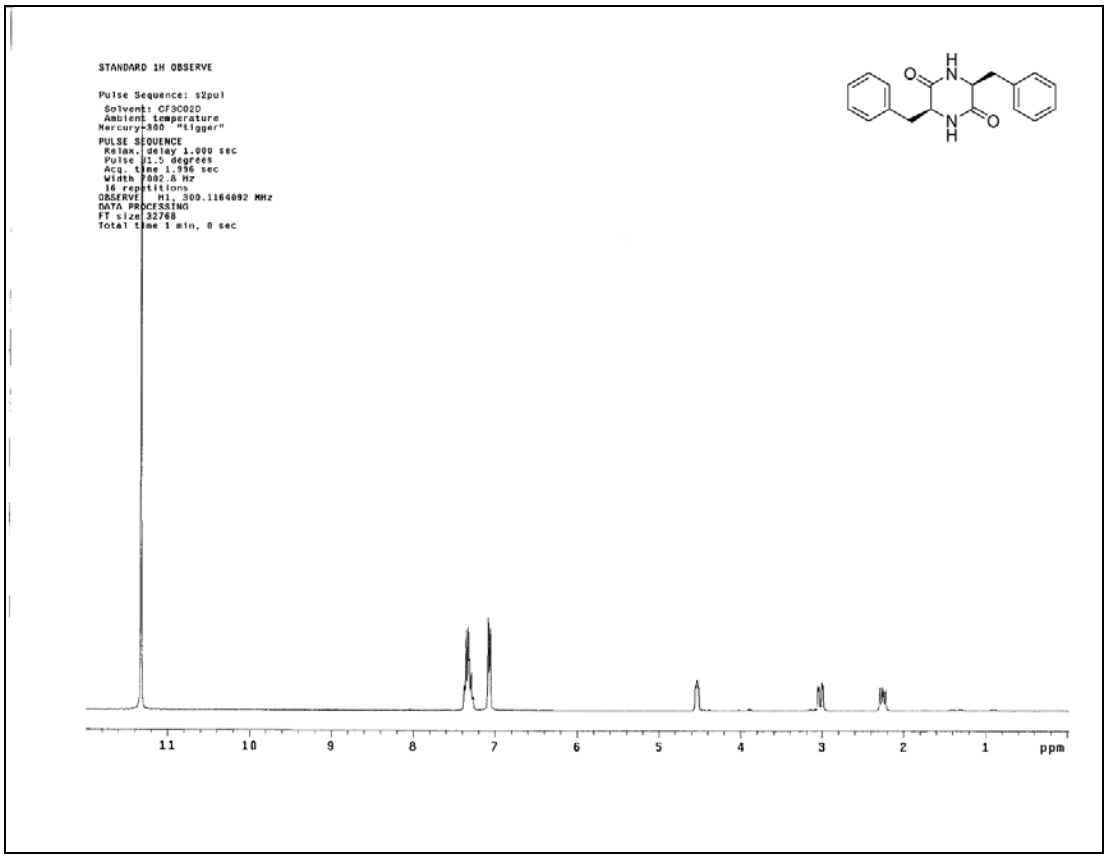

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
O
N
H
OH
7
6
5
4
3
2
1
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
O
N
H
7
6
5
4
3
2
1
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-300 "baloo"
Pulse 43.4 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9432160 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 7 sec
O
N
H
OH
8
7
6
5
4
3
2
1
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
O
N
7
6
5
4
3
2
1
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 64.3 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.1176007 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 58 sec
O
N
H
7
6
5
4
3
2
1
ppm


STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CF3CO2D
Ambient temperature
Mercury+300 "tigger"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 1.996 sec
Width 7002.8 Hz
16 repetitions
OBSERVE H1, 300.1164092 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
O
N
H
N
H
O
11
10
9
8
7
6
5
4
3
2
1
ppm