Supporting Information

Chlorotrimethylsilane activation of acylcyanamides for the synthesis of mono-*N*-acylguanidines.

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1. General Experimental Considerations:

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using flame-dried glassware. Diisopropylamine, triethylamine, and *N*,*N*-diisopropylethylamine were distilled from CaH_2 immediately prior to use. Dichloromethane tetrahydrofuran, diethylether, toluene, and dimethylformamide were degassed with argon and passed through a solvent purification system containing either alumina or molecular sieves. *P*-Anisidine was recrystallized from hexanes/chloroform and then hexanes/ethyl acetate prior to use.

Yields were calculated for material judged homogeneous by thin-layer chromatography and ^{1}H NMR. Thin-layer chromatography was performed on silica plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an ethanolic solution of 12-molybdophosphoric acid, *p*-anisaldehyde, or $KMnO_4$. Flash column chromatography was performed with slurry-packed silica gel with solvents indicated in glass columns. ^{1}HNMR spectra were recorded at 300, 400, or 500 MHz as indicated. The chemical shifts (δ) of proton resonances are reported relative to $CHCl_3$, DMSO-d_5, HOD, or HD_2COD using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constant(s) (*J* in Hz), integral].[1,2] ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak.[1] Infrared spectra were recorded on an IR spectrometer fitted with a SmartOrbit sample system. All absorptions are reported in cm^{-1} relative to polystyrene. Mass spectra were obtained by ESI/APCI for LRMS or ESI/APCI-TOF for HRMS.

[1] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**; *62*(21); 7512-7515.
[2] Hoye, T.R.; Hansen, P.R.; Vyvyan, J.R. *J. Org. Chem.* **1994**; *59*(15); 4096-4103.

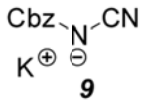
2. ^{1}H and ^{13}C NMR spectra for compounds 9, 8a-k:

RELI272-KCBZCN-DMSO-500MHz

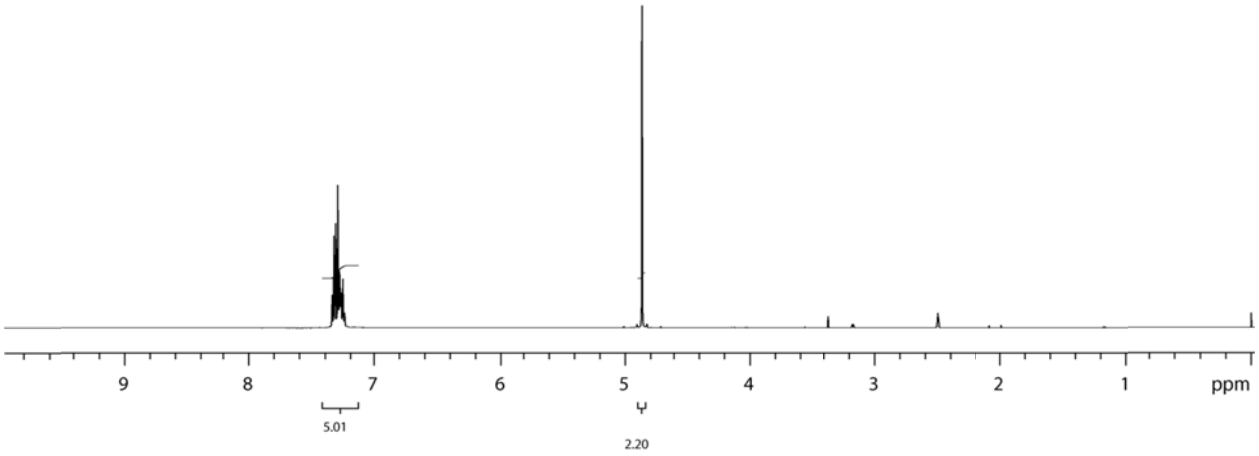
Pulse Sequence: s2pul

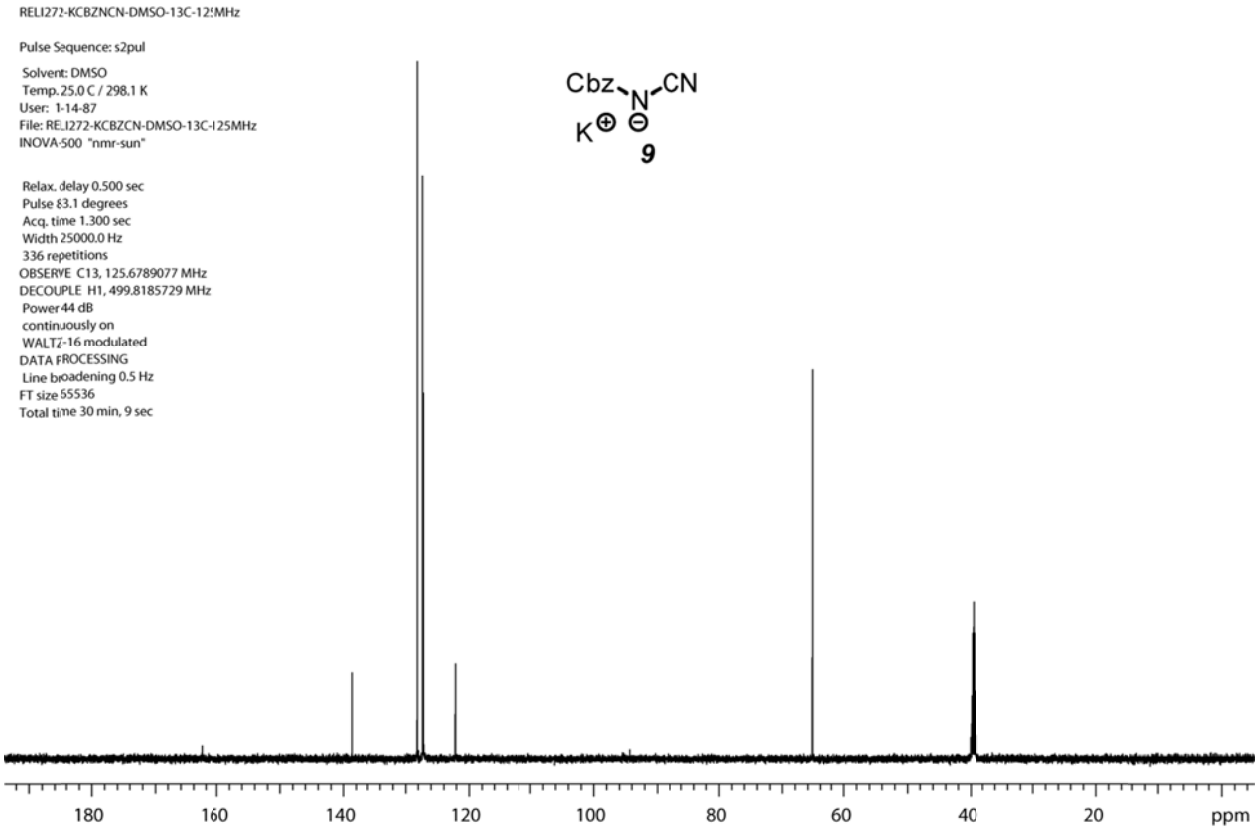
Solvent: DMSO
Temp. 25.0 C / 298.1 K
File: RELI272-KCBZCN-DMSO-500MHz
INOVA-500 "nmr-sun"

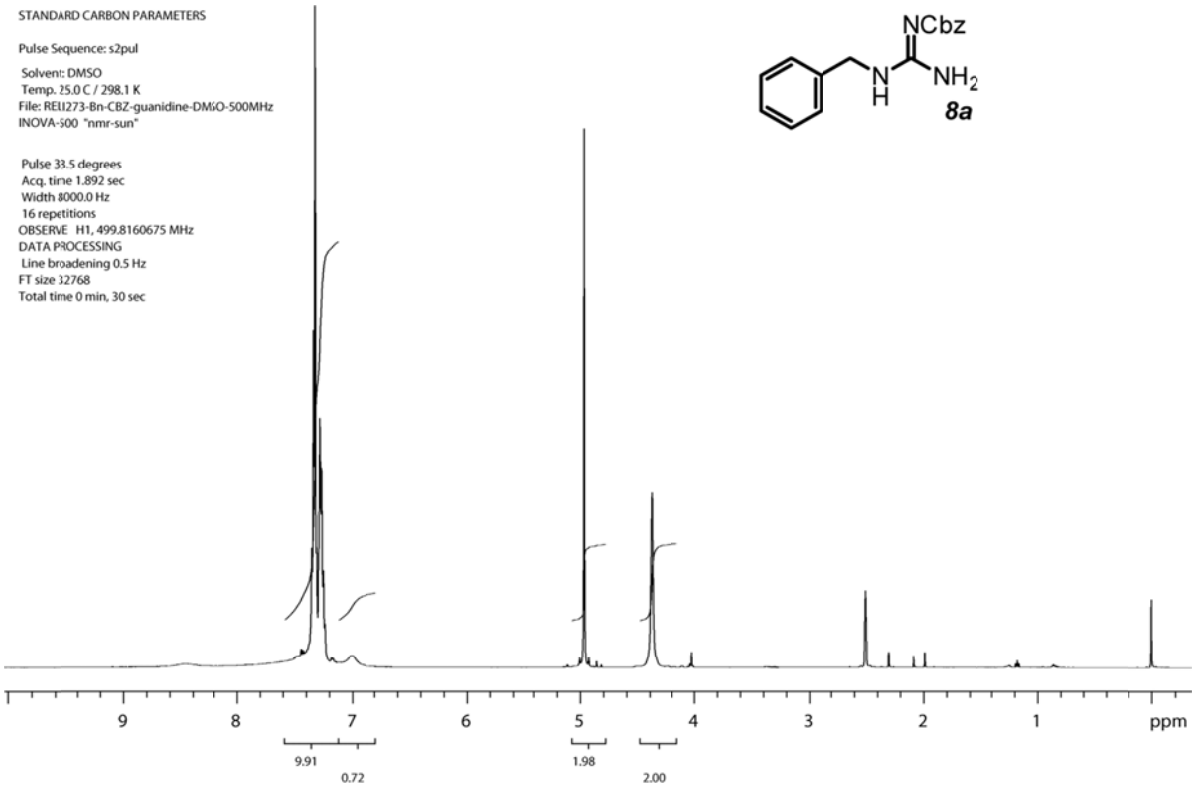
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.8160682 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 30 sec



9




RELI272-KCBZNCN-DMSO-13C-125MHz
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: RELI272-KCBZCN-DMSO-13C-125MHz
INOVA-500 "nmr-sun"
Relax. delay 0.500 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
336 repetitions
OBSERVE C13, 125.6789077 MHz
DECOUPLE H1, 499.8185729 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec
Cbz
N
CN
K
9
180
160
140
120
100
80
60
40
20
ppm


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 25.0 C / 298.1 K
File: RELI273-Bn-CBZ-guanidine-DMSO-500MHz
INOVA-500 "nmr-sun"
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.8160675 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 0 min, 30 sec
NCbz
NH2
N
H
8a
9
8
7
6
5
4
3
2
1
ppm
9.91
0.72
1.98
2.00

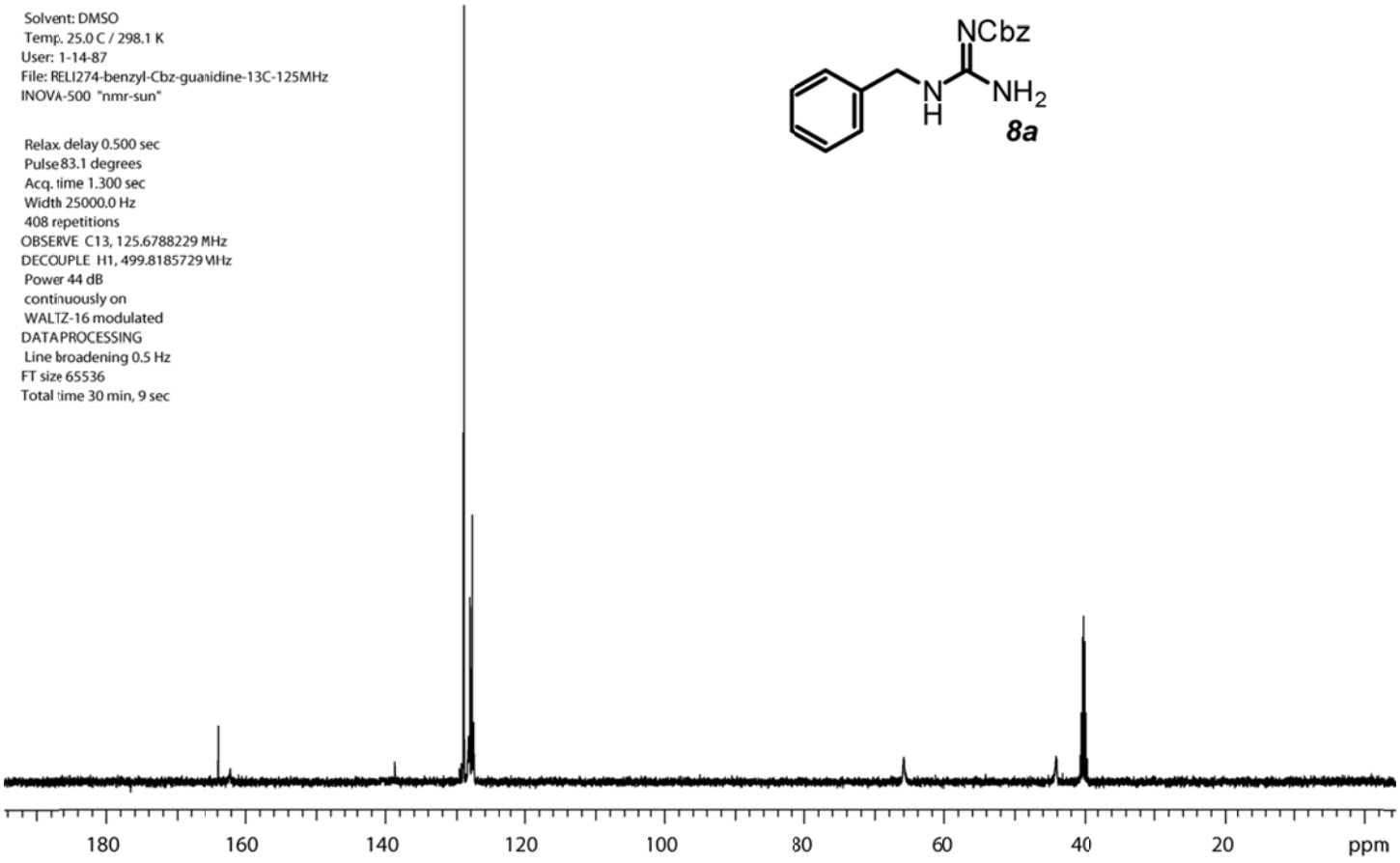
RELI274-benzyl-CBz-guanidine-13C-125MHz

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: RELI274-benzyl-Cbz-guanidine-13C-125MHz
INOVA-500 "nmr-sun"

Relax. delay 0.500 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
408 repetitions
OBSERVE C13, 125.6788229 MHz
DECOUPLE H1, 499.8185729 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec

8a

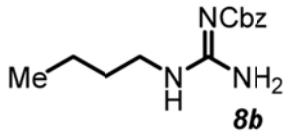


RELI275-nBu-CBZ-guanidine-1H-500MHz

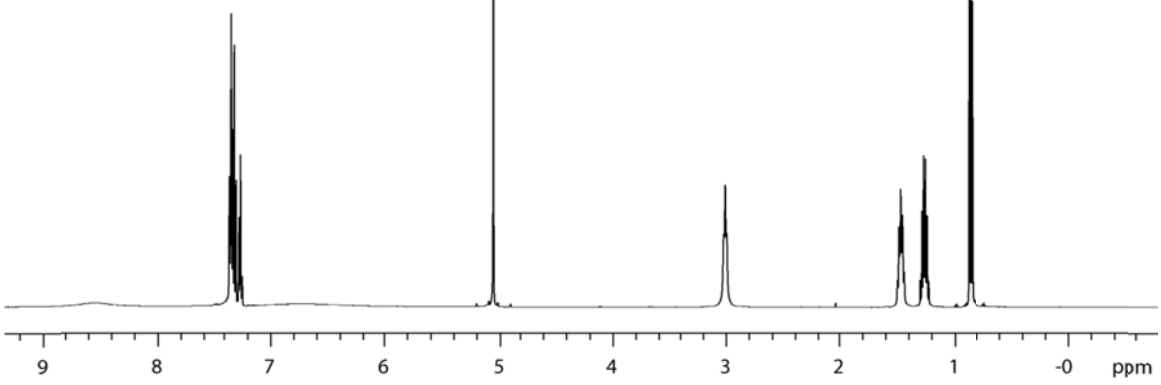
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: RELI275-nBu-CBZ-guanidine-1H-500MHz
INOVA-500 "nmr-sun"

Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec



8b

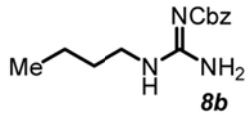


RELI275-nBuCBZ-guanidine-13C-125MHz

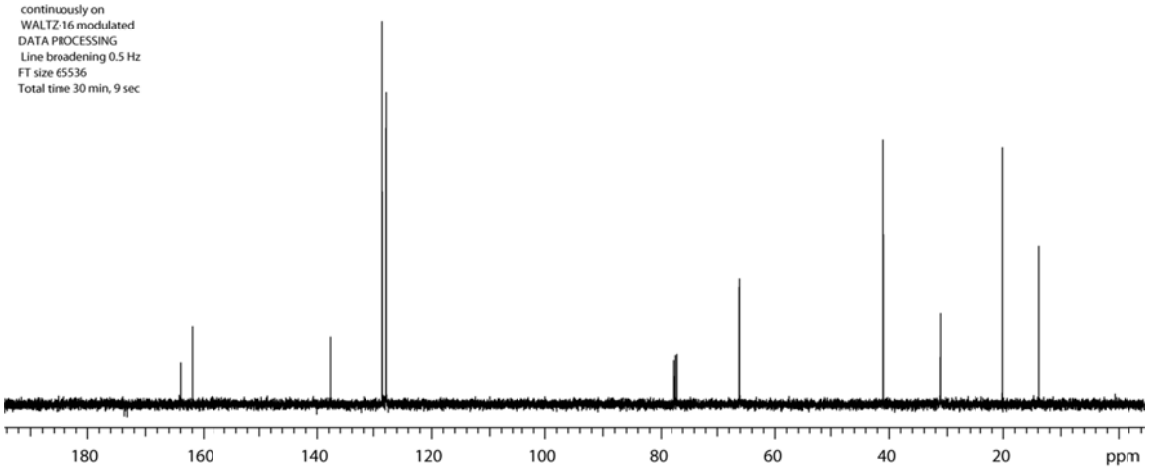
Pulse Sequence: s2pul

Solvent CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: RELI275-nBu-CBz-guanidine-13C-125MHz
INOVA-500 "nmr-sun"

Relax. delay 0.500 sec
Pulse 81.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
79 repetitions
OBSERVE C13, 125.6782367 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec



8b

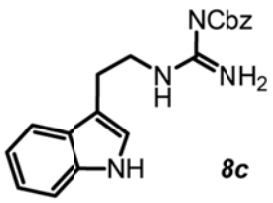


JM-01-096
HNMR-CD3OD
500MHz
12-23-10

Pulse Sequence: s2pul

Solvent: cd3od
Temp. 25.0 C / 298.1 K
File: JM-01-096-HNMR-CD3OD-pure-500MHz
INOVA-500 "nmr-sun"

Pulse 34.2 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
152 repetitions
OBSERVE H1, 499.8156752 MHz
DATA PROCESSING
FT size 32768
Total time 31 min, 40 sec



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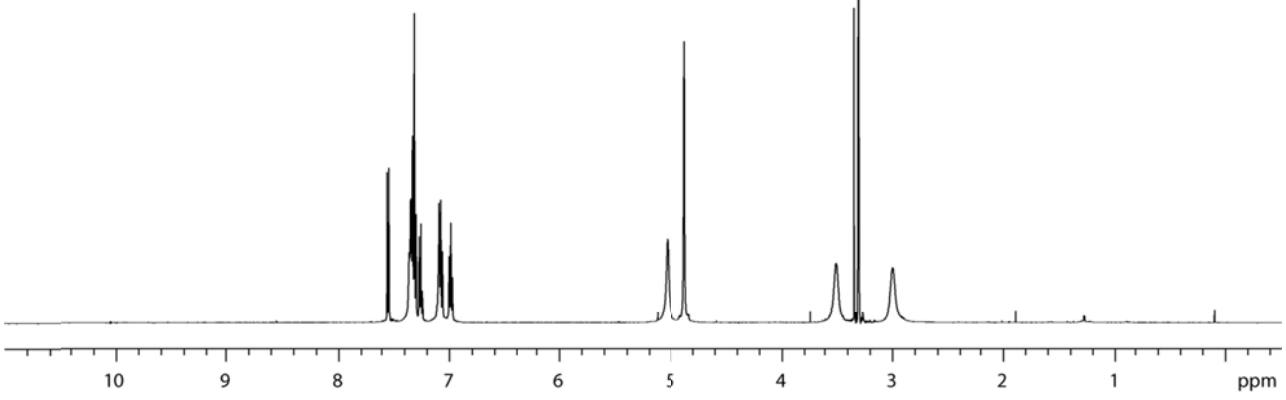


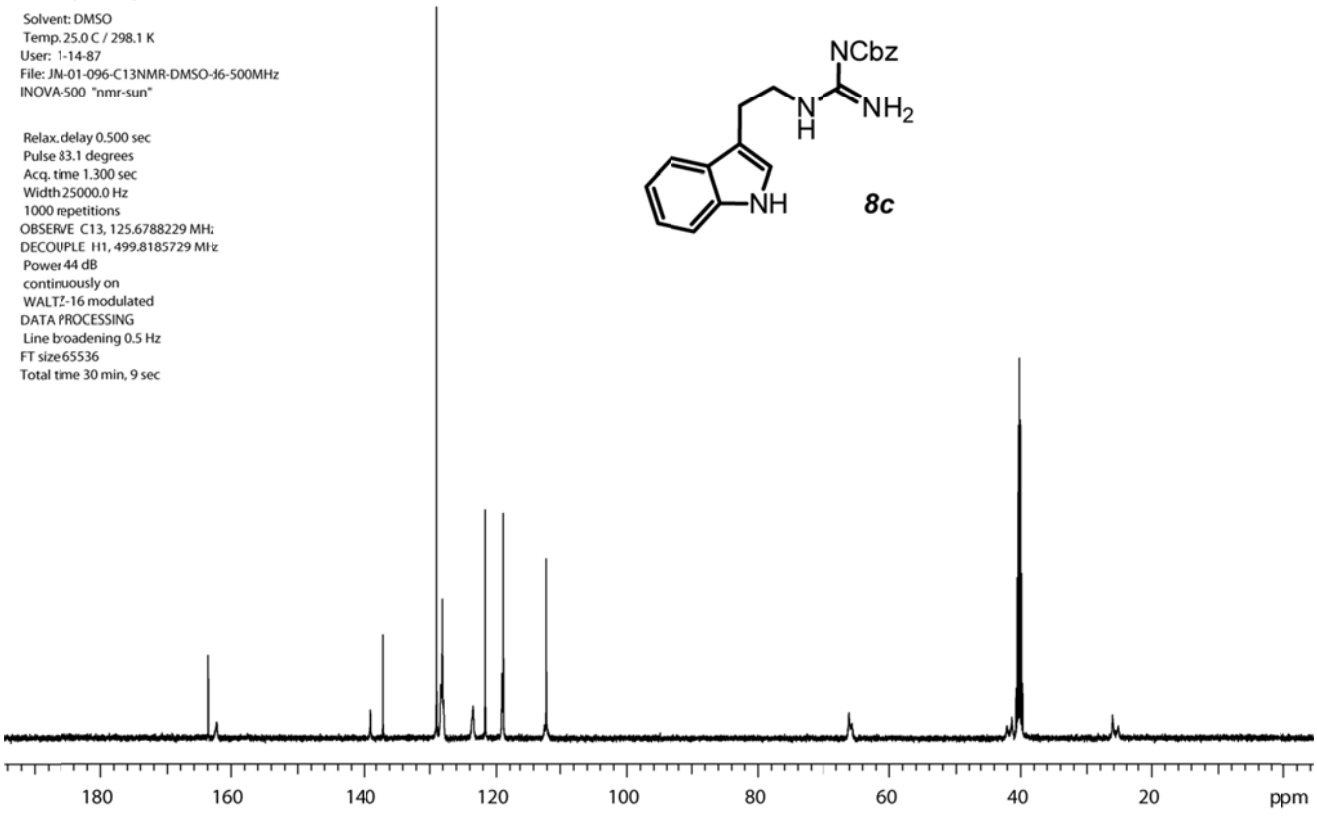
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: JM-01-096-C13NMR-DMSO-d6-500MHz
INOVA-500 "nmr-sun"

Relax. delay 0.500 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
1000 repetitions
OBSERVE C13, 125.6788229 MHz
DECOUPLE H1, 499.8185729 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec

8c

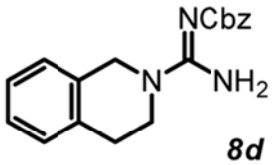


RELI274-tetrahydroisoquinolise-guanidine

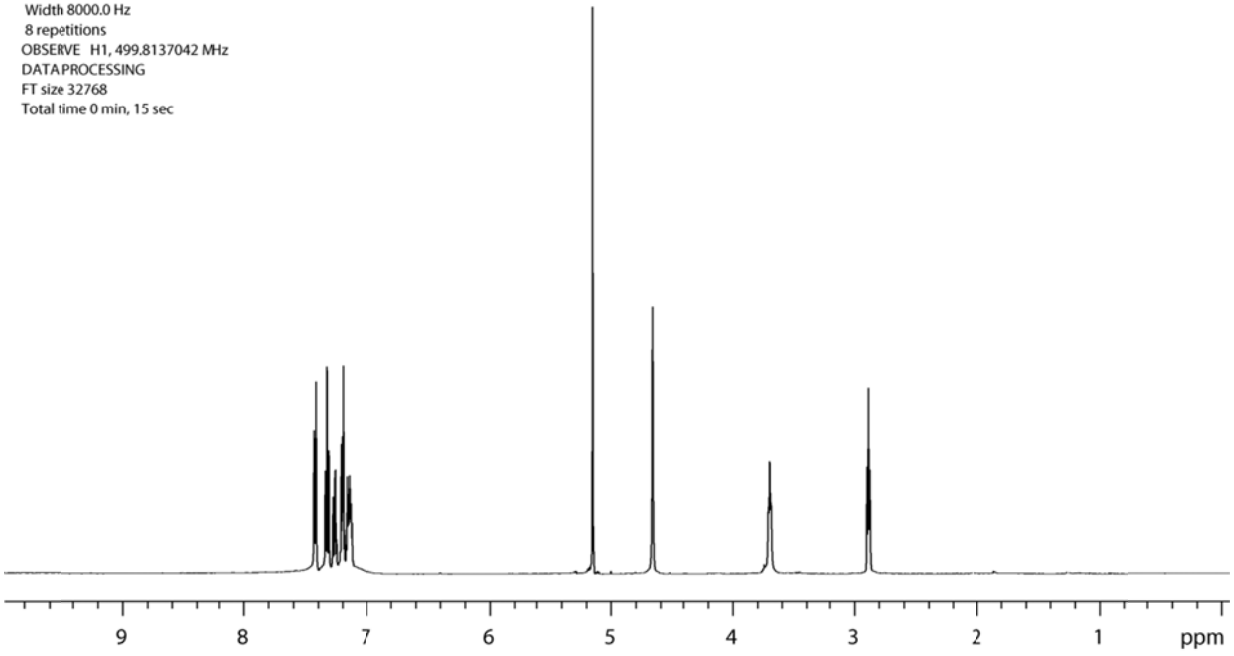
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: RELI274-tetrahydroisoquinoline
INOVA-500 "nmr-sun"

Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec



8d

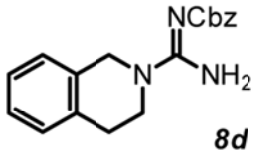


RELI274-tetrahydroisoquinoline-guanidine-13C-125MHz

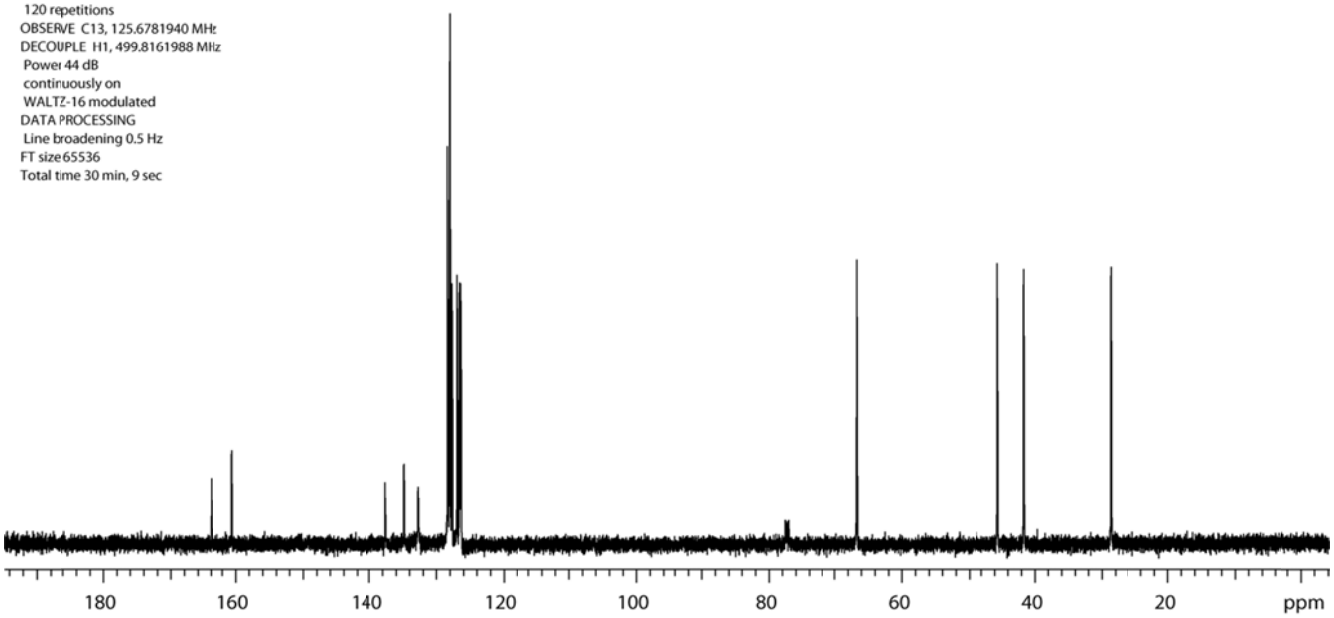
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: RELI274-tetrahydroisoquinoline-guanidine-13C-125MHz
INOVA-500 "nmr-sun"

Relax.delay 0.500 sec
Pulse 33.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
120 repetitions
OBSERVE C13, 125.6781940 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec



8d

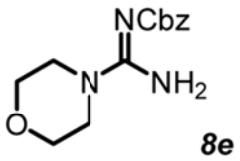


RELII226-TMS-Guanylation

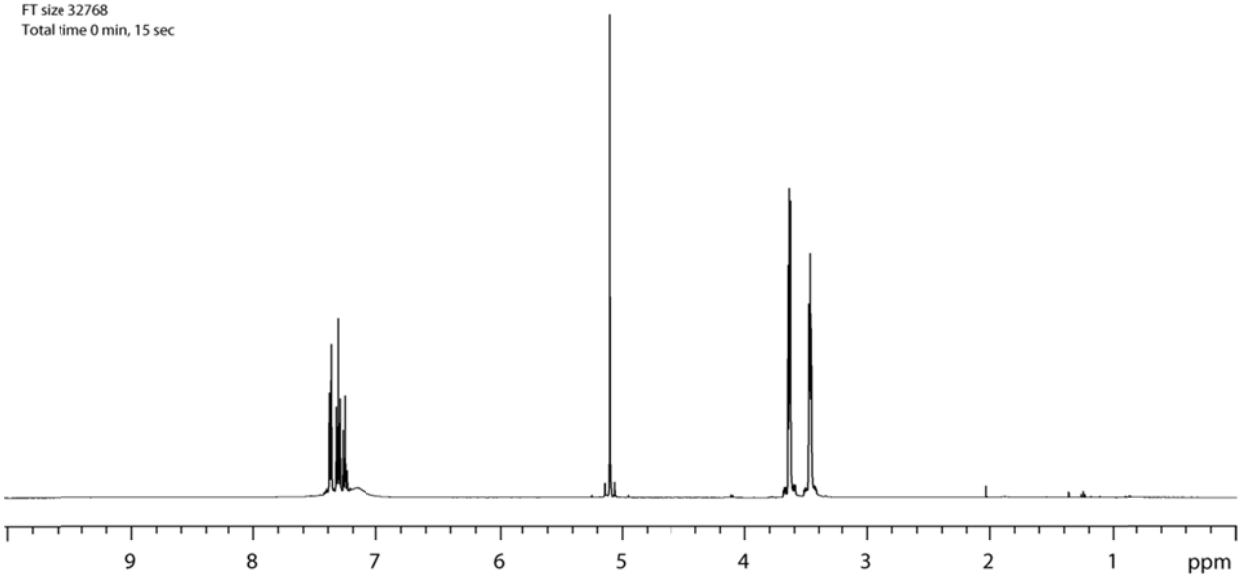
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
File: RELI226-TMS-Guanylation
INOVA-500 "nmr-sun"

Pulse 34.2 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec



8e

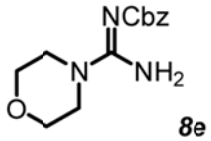


RELI226-TMS-GUANYLATION

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
User: 1-14-87
File: RELI226-TMS-guanylation-C13
INOVA-500 "nmr-sun"

Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
128 repetitions
OBSERVE C13, 125.6782382 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min, 29 sec



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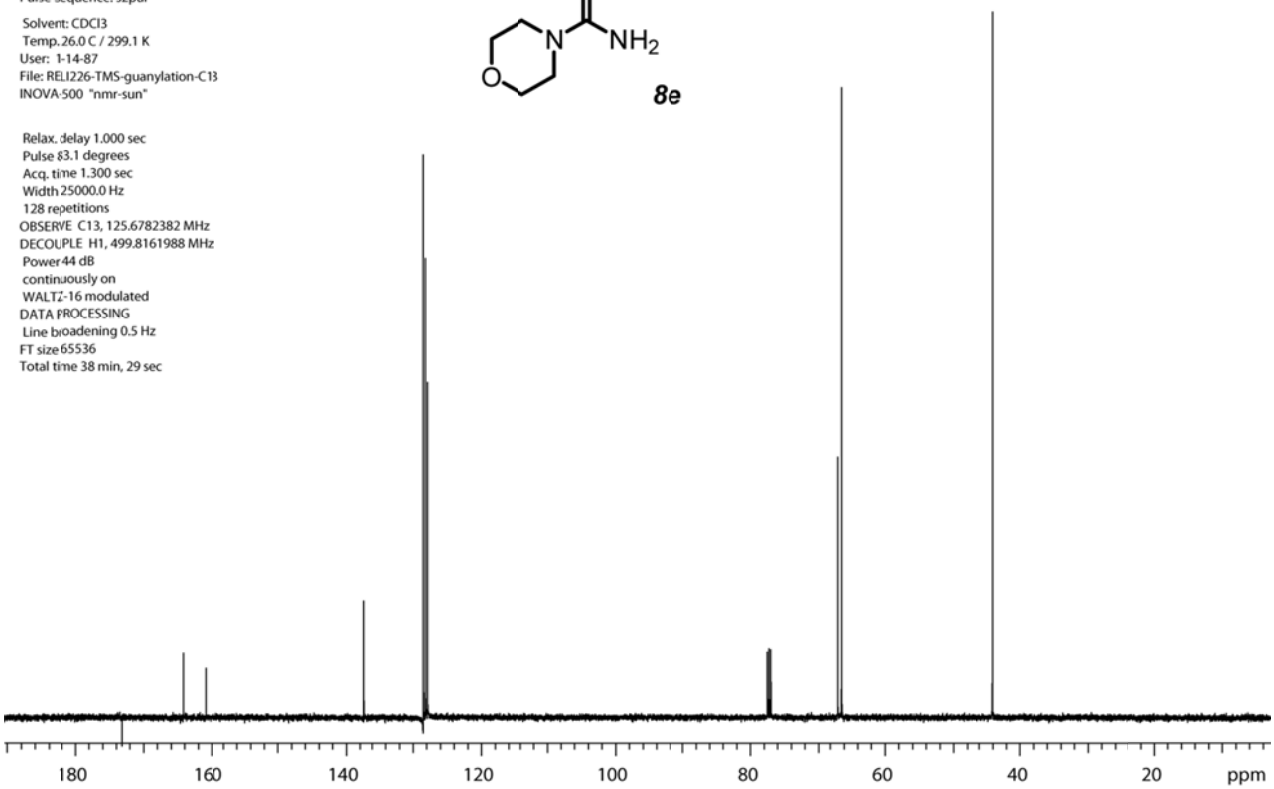


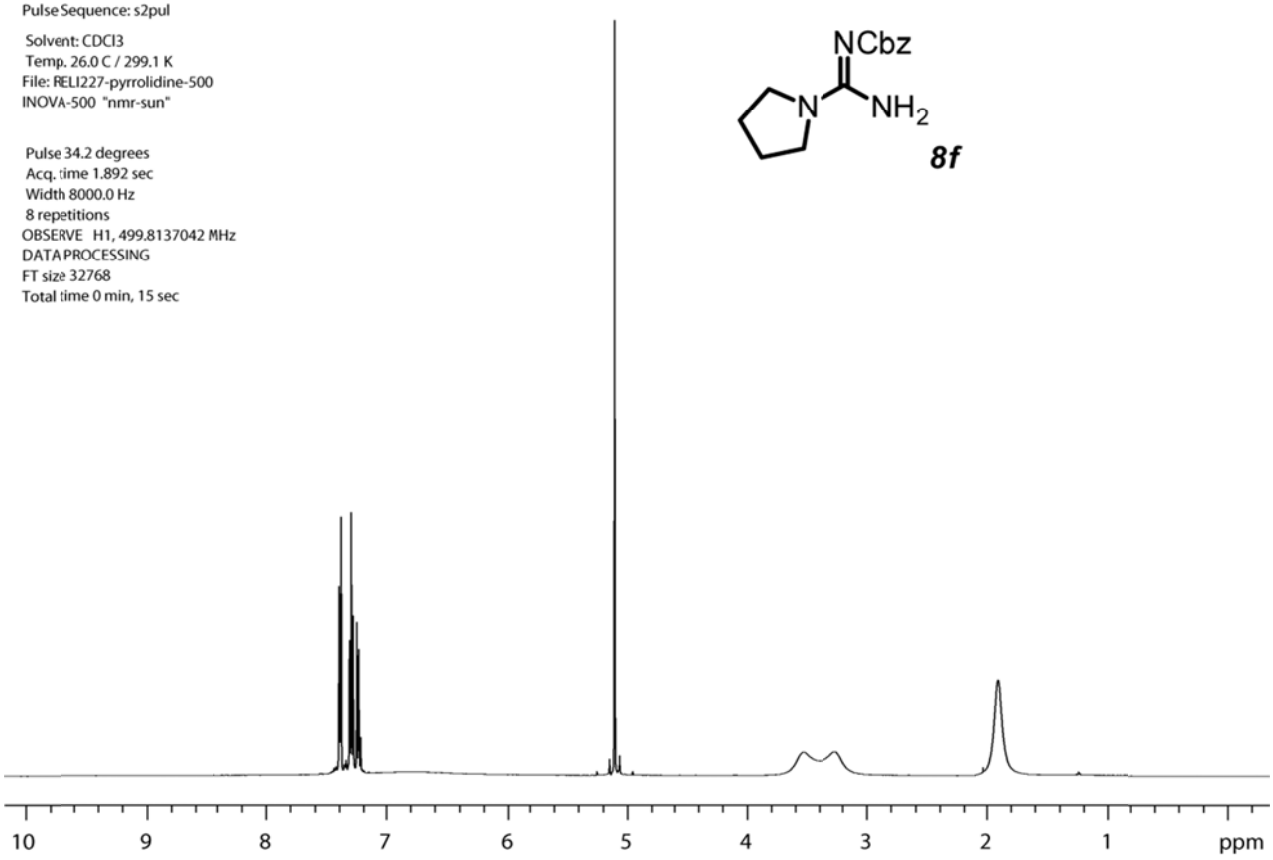
RELI227-pyrrolidine

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
File: RELI227-pyrrolidine-500
INOVA-500 "nmr-sun"

Pulse 34.2 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec

8f

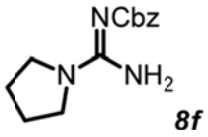


RELI227-pyrrolidine-C13-100MH:

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
Operator: rlooper
File: RELI227-pyrrolidine-C13-100MHZ
INOVA-500 "nmr-sun"

Relax. delay 1.000 sec
Pulse 111.4 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
336 repetitions
OBSERVE C13, 100.5578177 MHz
DECOUPLE H1, 399.9135467 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 37 min, 41 sec



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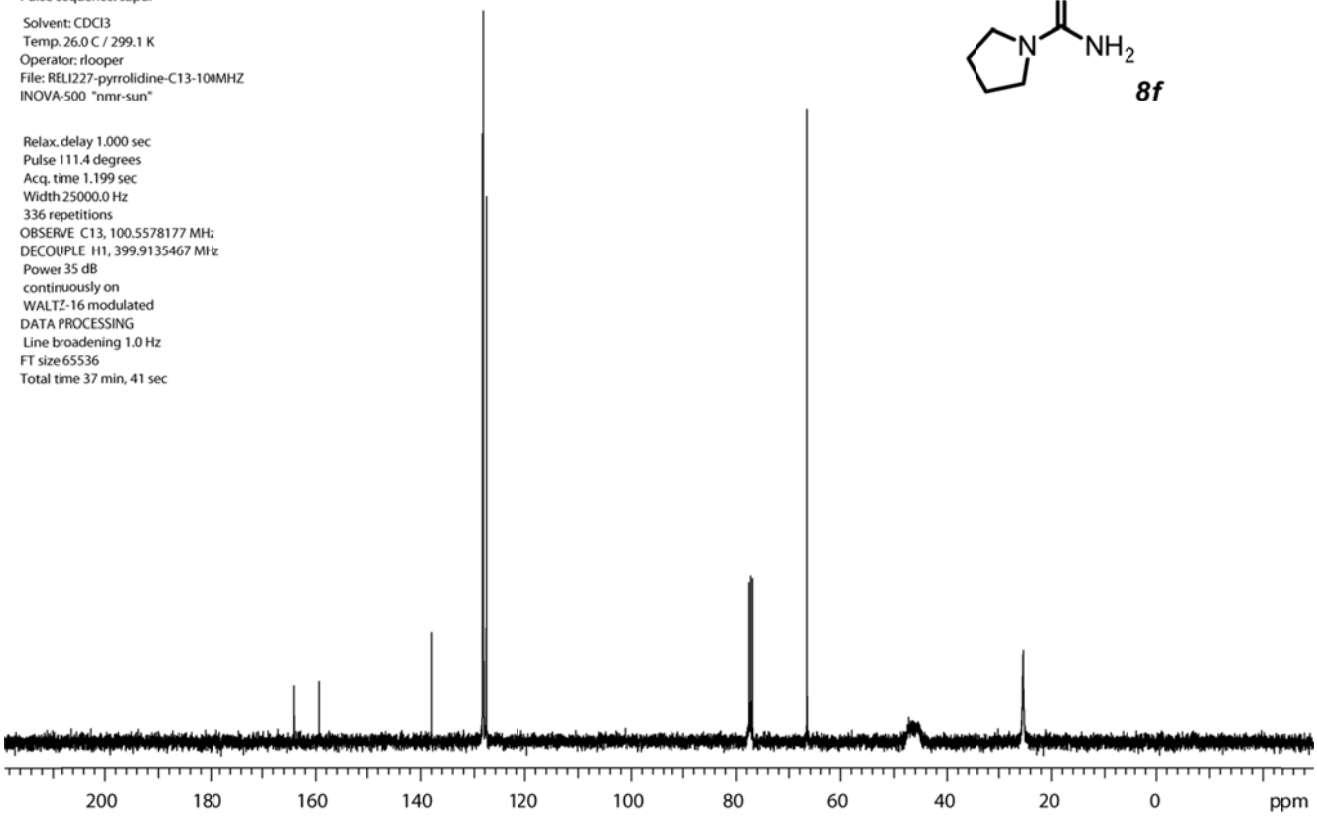


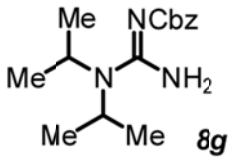
RELI227-Diisopropyl-guanylation

Archive directory: /home/nmr/vnmr1/vnmrsys/data
File: RELI227-Diisopropylamine-1H

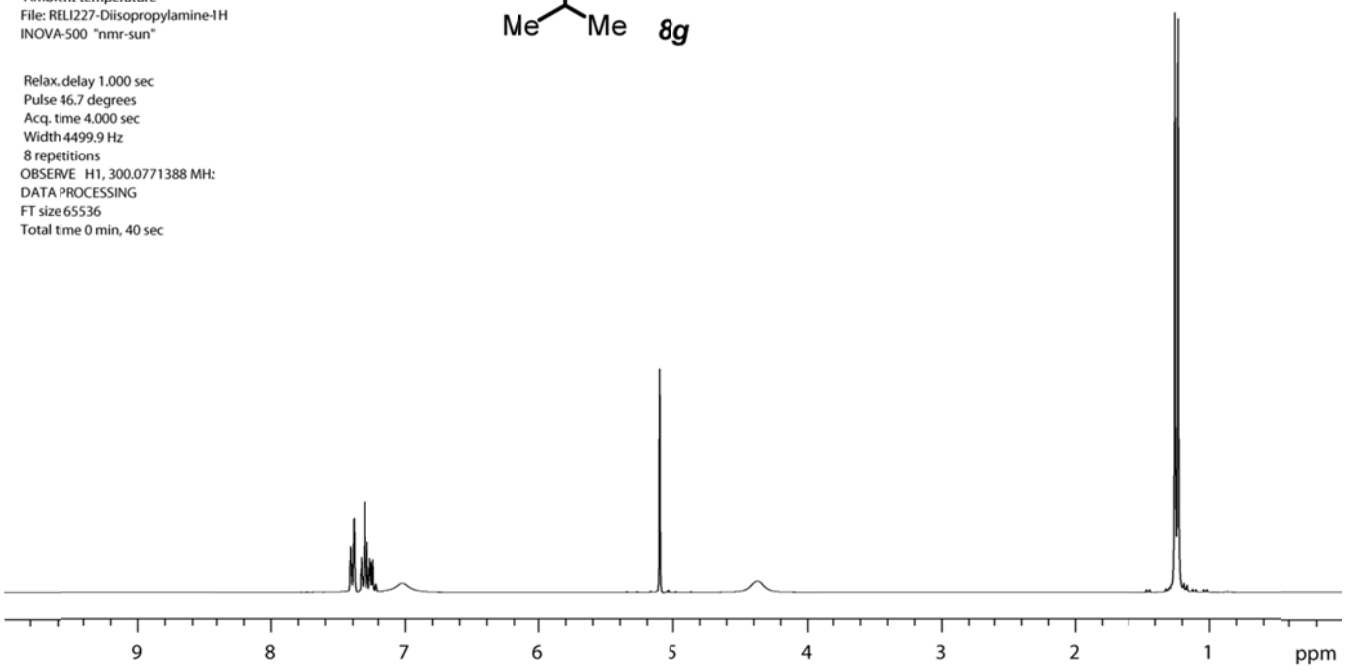
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: RELI227-Diisopropylamine-1H
INOVA-500 "nmr-sun"

Relax.delay 1.000 sec
Pulse 46.7 degrees
Acq. time 4.000 sec
Width 4499.9 Hz
8 repetitions
OBSERVE H1, 300.0771388 MH:
DATA PROCESSING
FT size 65536
Total time 0 min, 40 sec



8g

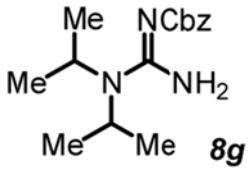


RELI227-Diisopropylamine-guanylation-C13-75

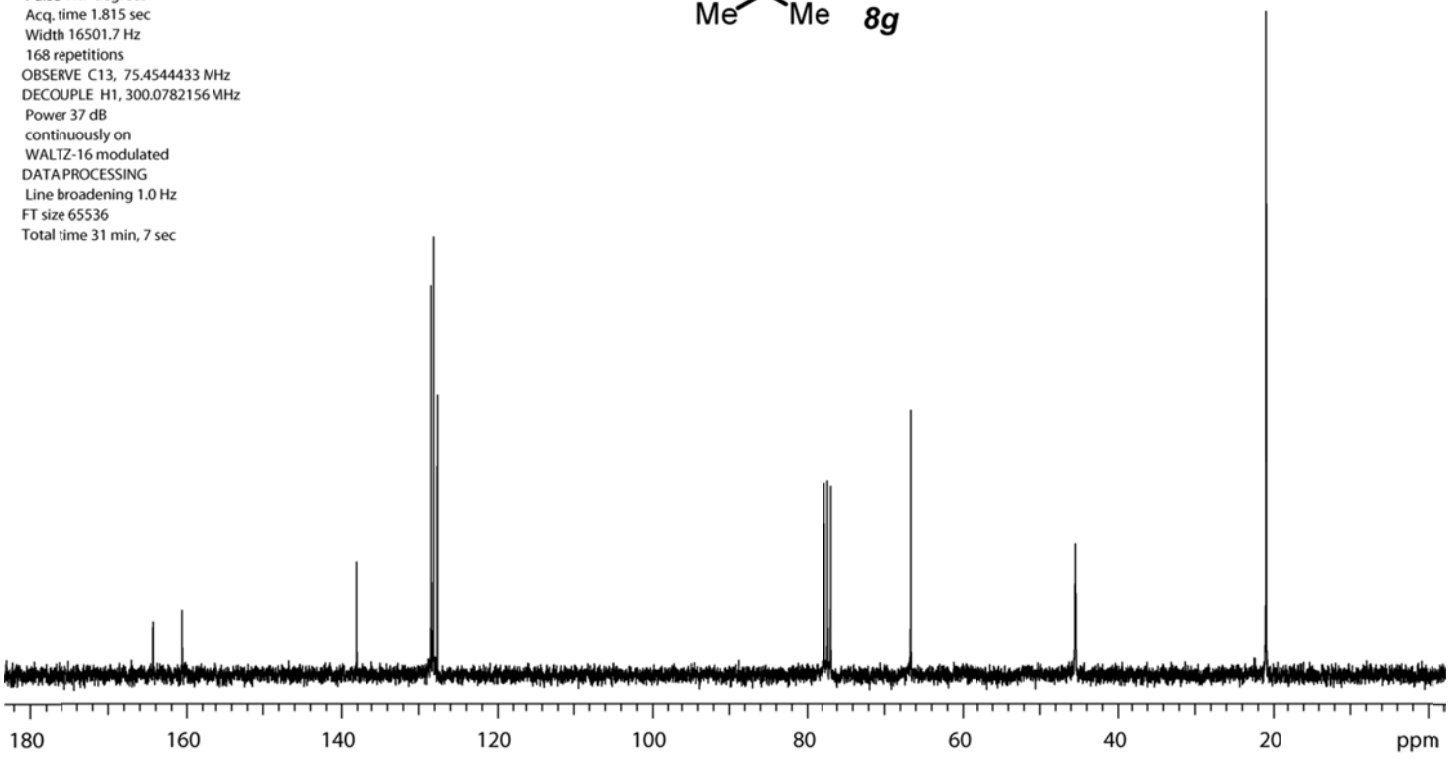
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: RELI227-Diisopropylamire-C13-75
INOVA-500 "nmr-sun"

Pulse 41.7 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
168 repetitions
OBSERVE C13, 75.4544433 MHz
DECOUPLE H1, 300.0782156 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 31 min, 7 sec



8g



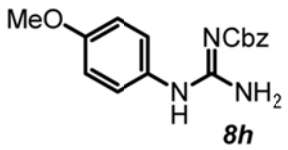
RELI227-Anisidine-guanylation

Archive directory: /home/nmr/vnmr1/vnmrsys/data
File: RELI227-anisidine-1H-300

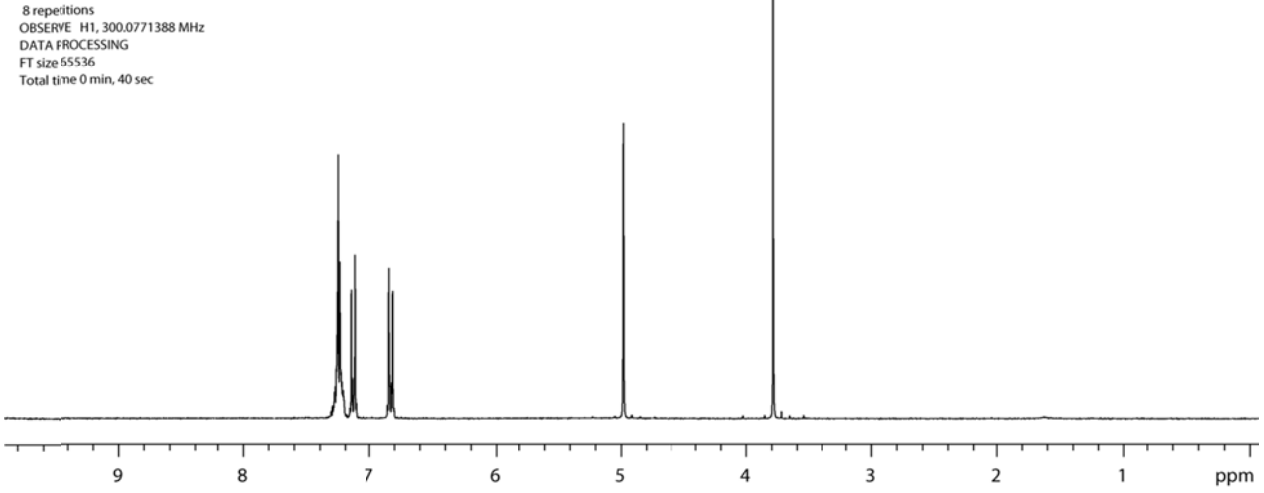
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: RE..I227-anisidine-1H-300
INOVA-500 "nmr-sun"

Relax. delay 1.000 sec
Pulse 46.7 degrees
Acq. time 4.000 sec
Width 4499.9 Hz
8 repetitions
OBSERVE H1, 300.0771388 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 40 sec

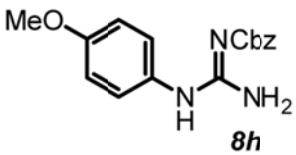


8h

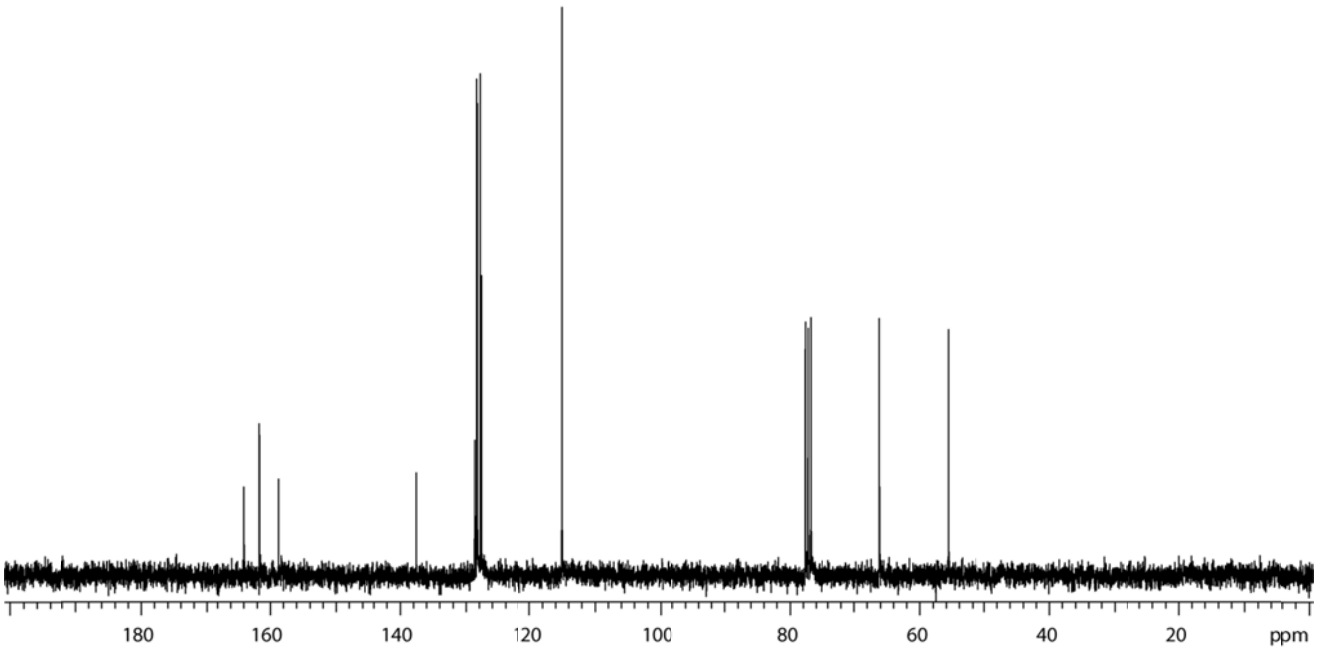


RELI227-Anisidine-guanylation

Pulse Sequence: s2pul



8h

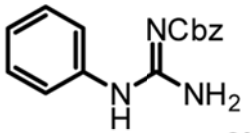


JM-01-105
HNMR-CDCl3
500MHz
06-02-11

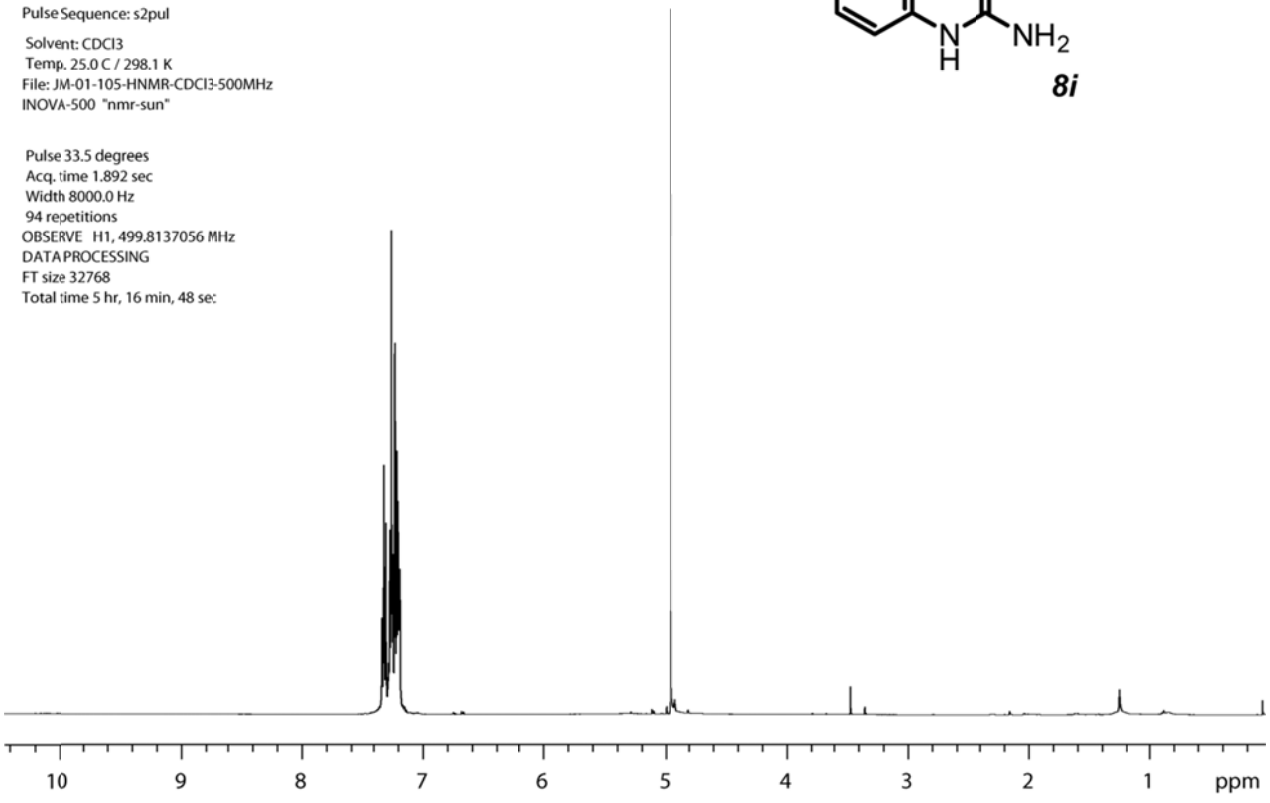
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: JM-01-105-HNMR-CDCl3-500MHz
INOVA-500 "nmr-sun"

Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
94 repetitions
OBSERVE H1, 499.8137056 MHz
DATA PROCESSING
FT size 32768
Total time 5 hr, 16 min, 48 sec



8i

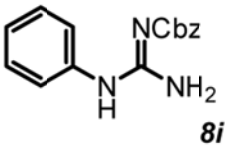


STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: JM-01-105-C13NMR-CDCl3-500MHz
INOVA-500 "nmr-sun"

Relax.delay 1.000 sec
Pulse 33.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
316 repetitions
OBSERVE C13, 125.6782321 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 6 hr, 24 min, 53 sec



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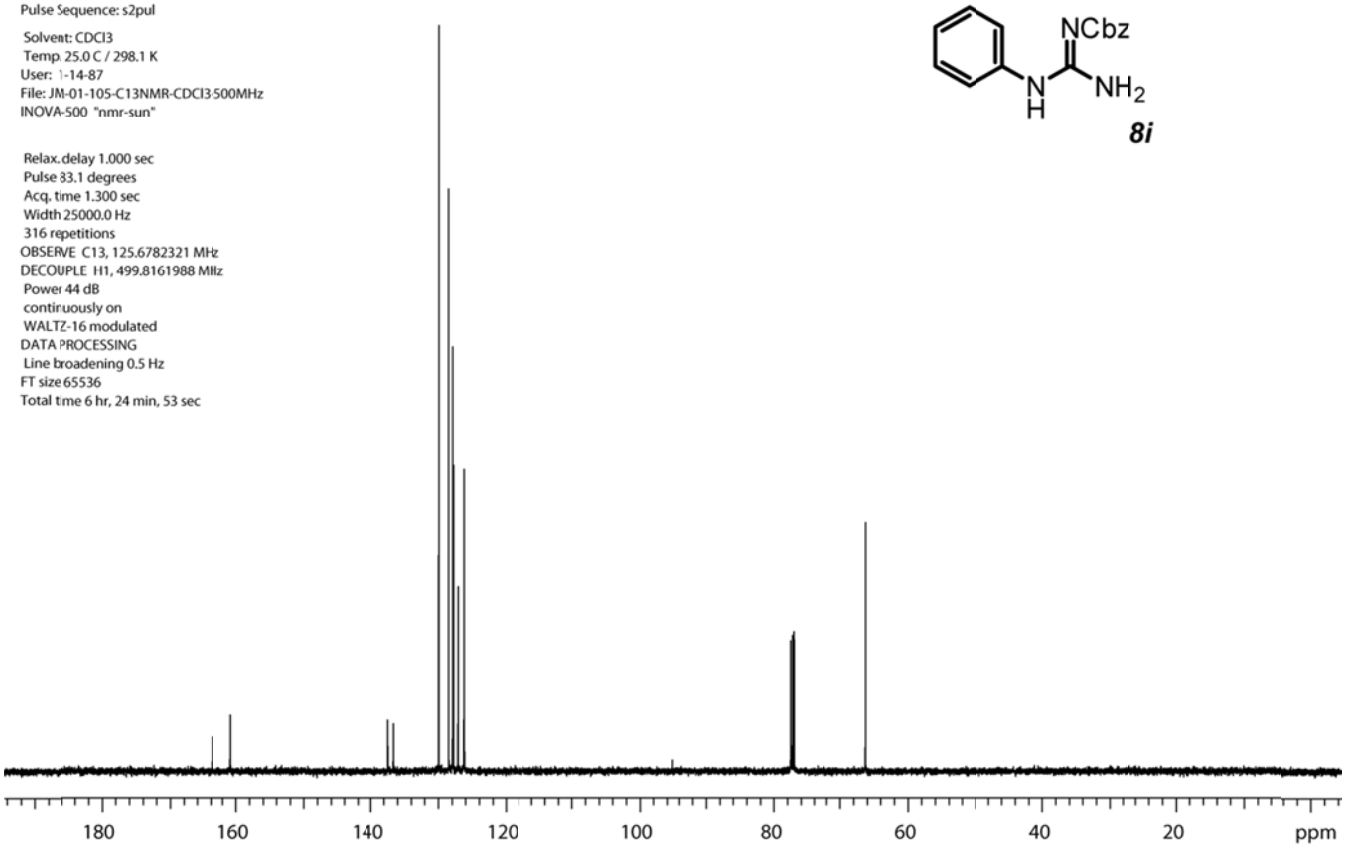
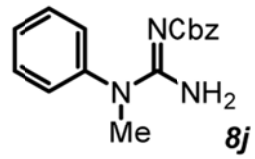


RELI227-N-Me-aniline

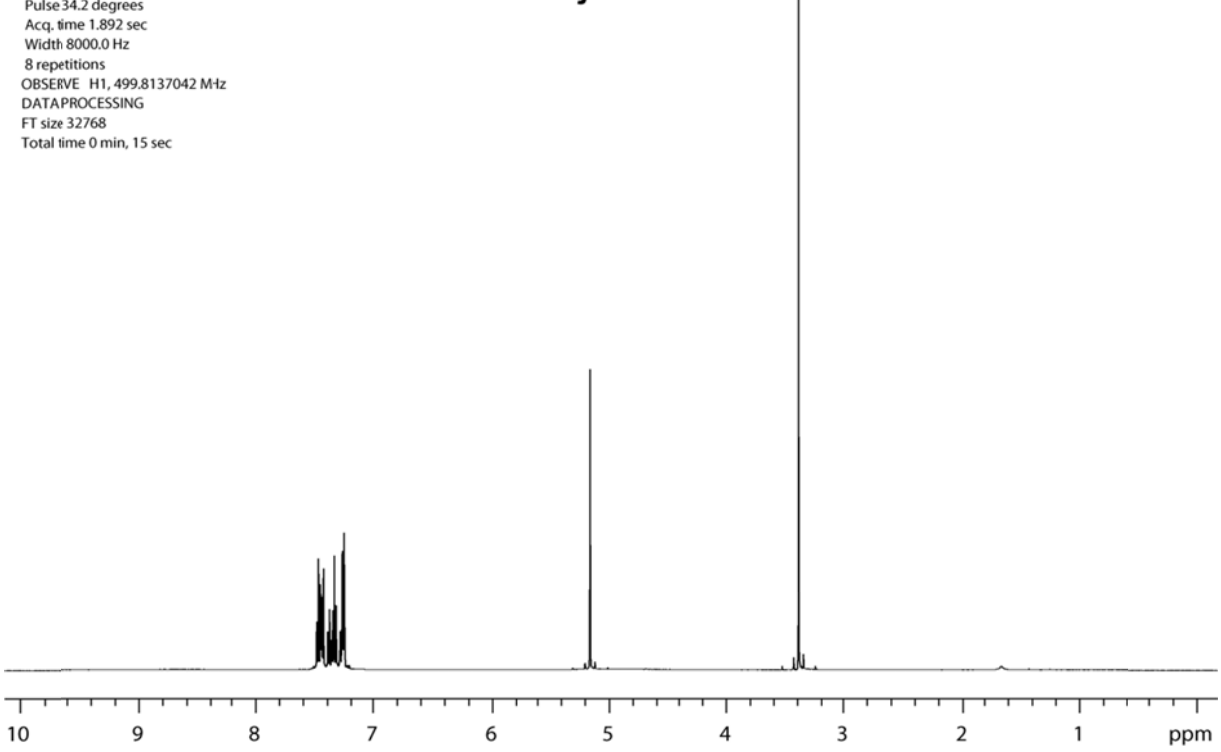
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
File: RELI227-N-Me-aniline-500
INOVA-500 "nmr-sun"

Pulse 34.2 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 15 sec



8j



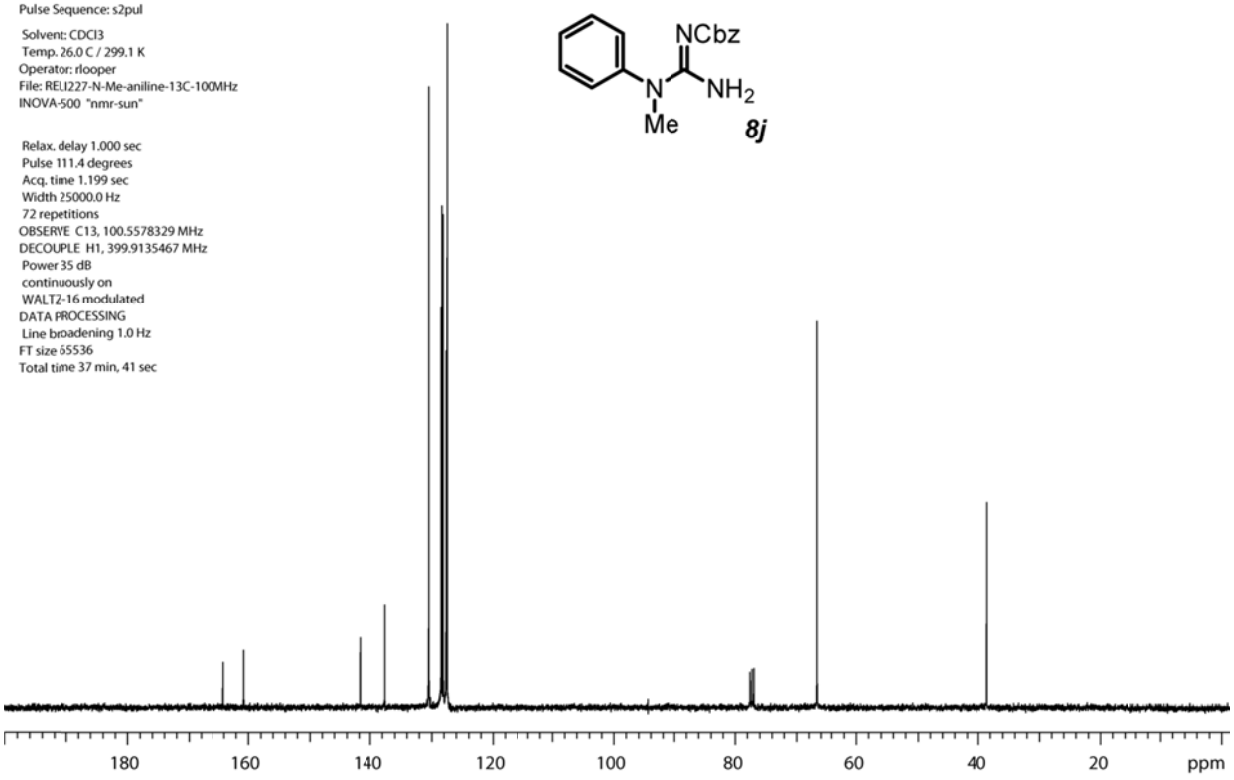
RELI227-N-Me-aniline-13C-100MHz

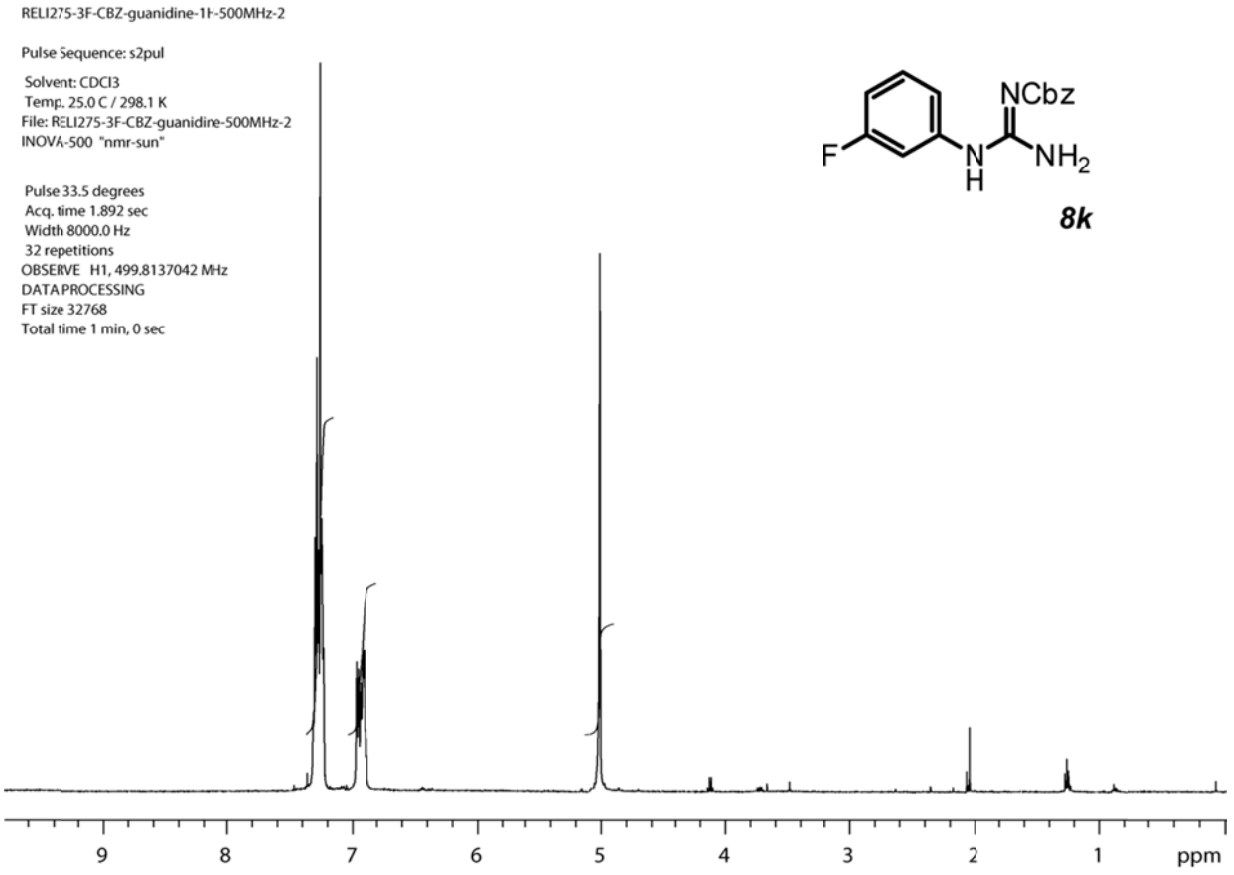
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 26.0 C / 299.1 K
Operator: rlooper
File: RELI227-N-Me-aniline-13C-100MHz
INOVA-500 "nmr-sun"

Relax. delay 1.000 sec
Pulse 111.4 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
72 repetitions
OBSERVE C13, 100.5578329 MHz
DECOUPLE H1, 399.9135467 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 37 min, 41 sec

8j

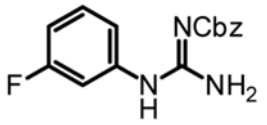



RELI275-3F-CBZ-guanidine-1H-500MHz-2
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: RELI275-3F-CBZ-guanidine-500MHz-2
INOVA-500 "nmr-sun"
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.8137042 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 0 sec
F
N
H
NCbz
NH2
8k
9
8
7
6
5
4
3
2
1
ppm

RELI275-3F-CBZ-guanidine-13C-125MHz

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: RELI275-3F-CBZ-guanidine-13C-125MHz
INOVA-500 "nmr-sun"

Relax.delay 0.500 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
612 repetitions
OBSERVE C13, 125.6782352 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 30 min, 9 sec



8k