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Preparation of Nitriles from Carboxylic Acids: A New, Synthetically Useful Example of the Smiles Rearrangement[1]

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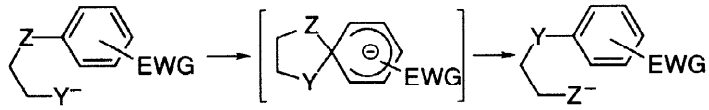
Abstract: Reaction of 2,4-dinitrobenzenesulfonamide with acyl chlorides in the presence of excess triethylamine produces the corresponding nitrile in good to fair yields. Mechanistic studies indicate that the reaction proceeds via a Smiles rearrangement of the initially formed *N*-(2,4-dinitrobenzenesulfonyl)amide to form the nitrile, 2,4-dinitrophenol and sulfur dioxide.

INTRODUCTION

The Smiles rearrangement represents a class of intramolecular nucleophilic aromatic substitution reactions in which a tethered nucleophile, Y, displaces an aromatic electrophile, Z (Scheme 1).[2] A variety of Y and Z groups have been reported.[3-5] The nucleophilic group in this rearrangement has included alcohols, phenols, amines, amides and sulfonamides. The leaving group is often an ether, sulfide, sulfoxide or sulfone. Despite the variety of possible substrates, the Smiles rearrangement has been incorporated into only a few synthetic strategies. The most successful application has been the base-promoted conversion of phenoxyacetamides to *N*-(hydroxyacetyl)anilines.[6-12] The scarcity of practical applications based on this rearrangement may be due to limitations imposed by the nature of the electron-deficient aryl group, particularly since the aryl and Y groups remain bonded in the product. Herein, we report a new variation of the Smiles rearrangement in which an *N*-(2,4-dinitrobenzenesulfonyl)amide undergoes rearrangement to give a nitrile, 2,4-dinitrophenol and sulfur dioxide.



Scheme 1. Schematic representation of the Smiles rearrangement.

As part of the development of new ionophores for the efficient and selective complexation and separation of metal cations,[13-16] we are investigating *N*-(X)sulfonyl carboxamide lariat ethers **1** in which X is an alkyl, perfluoroalkyl or aryl group. Our initial studies involved a series of compounds in which R was *n*-decyl and X was a methyl, trifluoromethyl, phenyl or 4-nitrophenyl group.[17] These compounds were found to be highly selective for Na^+ in the competitive solvent extraction of alkali-metal cations from aqueous solution into

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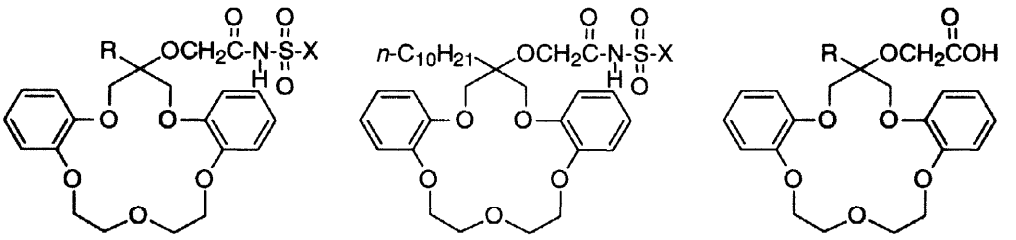
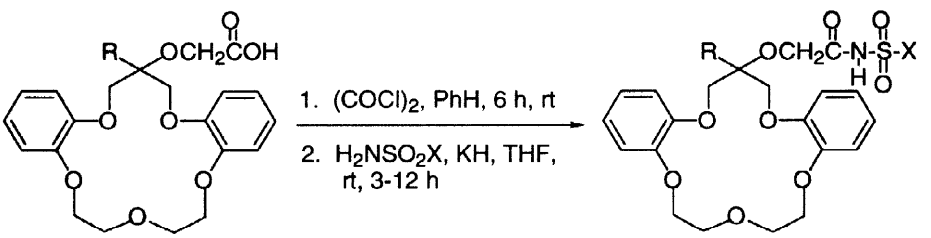


1 2, X = CF_3 3, X = 2,4-$(NO_2)_2C_6H_3$ 4

chloroform.[17] The most efficient extractant was *N*-(trifluoromethyl)sulfonyl *sym*-(decyl)dibenzo-16-crown-5-oxyacetamide (**2**). Hence, it was of interest to prepare other lariat ethers that possess highly electron-deficient sulfonyl groups, *e.g.*, compound **3**.

In the earlier work, lariat ether *N*-(X)sulfonyl oxyacetamides **1** were prepared from the corresponding oxyacetic acids **4**[18] as shown in Scheme 2. The carboxylic acid was first converted into its acyl chloride by treatment with oxalyl chloride in benzene. A sulfonamide was reacted with KH in THF at room temperature followed by the acyl chloride which gave, after an appropriate workup, the desired *N*-(X)sulfonyl carboxamide. Surprisingly, when this reaction was attempted using 2,4-dinitrobenzenesulfonamide (DNBSA), lariat ether **3** could not be isolated from the product mixture. However, when triethylamine (TEA) was used as the base, lariat ether **3**[19] was obtained in low yield (<25 %) and the corresponding nitrile was isolated as the major product in 52% yield. In light of this unexpected result, a more thorough investigation of the reactions of acyl chlorides with DNBSA and base was undertaken.[20]



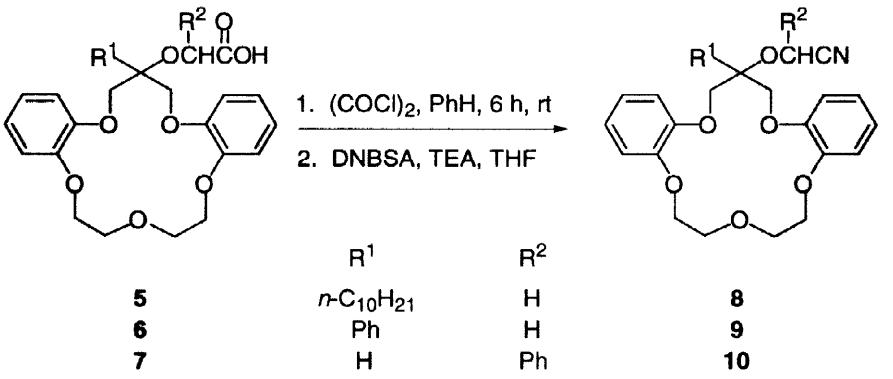
Scheme 2. Synthesis of N-sulfonylcarboxamide lariat ethers.

RESULTS AND DISCUSSION

Lariat ether carboxylic acids **5-7** (Scheme 3) were converted into the corresponding acid chlorides which were subsequently reacted with DNBSA in the presence of TEA in THF under different conditions (Table 1). Anisoyl chloride, 1-naphthylacetyl chloride, benzoyl chloride and octanoyl chloride, representative acyl chlorides without cyclic polyether units, were also reacted with DNBSA in the presence of TEA.

As shown in Table 1, when the reaction was conducted at reflux, a higher yield of nitrile product was isolated than for reaction at room temperature (compare entry 2 with 3, and entry 4 with 5). No starting material was recovered from reactions conducted at room temperature or at reflux. As judged by the TLC of the crude reaction mixture, the reactions conducted at reflux appear to have fewer side products than those performed at room temperature.

Generally, the reaction of an acyl chloride with DNBSA and TEA in refluxing THF produced a 75-77% yield of the corresponding nitrile. The nitrile yield appeared to be insensitive to structural variations in the



	R^1	R^2	
5	n-$C_{10}H_{21}$	H	**8**
6	Ph	H	**9**
7	H	Ph	**10**

Scheme 3. Synthesis of lariat ether nitriles.

Table 1. Conditions and Yields for Reactions of Acyl Chlorides with DNBSA and TEA in THF.

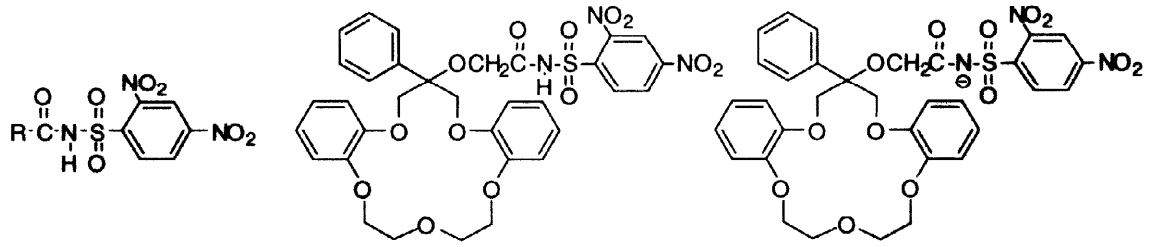
entry	acyl chloride precursor[a]	time (h)	temp	DNBSA (equiv.)	product	yield (%)
1	**5**	24	rt	2.0	**8**	52
2	**6**	36	rt	2.0	**9**	40
3	**6**	24	reflux	1.2	**9**	77
4	**7**	96	rt	1.2	**10**	50
5	**7**	24	reflux	1.1	**10**	77
6	anisoyl chloride[b]	24	reflux	1.1	4-methoxy-benzonitrile	76
7	2-naphthylacetyl chloride[b]	48	reflux	1.1	2-naphthyl-acetonitrile	75
8	benzoyl chloride[b]	24	reflux	1.1	benzonitrile	25
9	octanoyl chloride[b]	24	reflux	1.1	heptanenitrile	14

[a]The acyl chloride was not purified before use. [b]The commercially available acyl chloride was utilized.

substrate. However, the yields of benzonitrile and heptanenitrile were disappointingly low and initial attempts to improve the yields of these reactions were unsuccessful. At present, it is unclear if these yields represent a fundamental limitation to this reaction.

This reaction sequence may represent a viable synthetic method for the conversion of a carboxylic acid into the analogous nitrile under mild conditions, particularly since only a limited number of methods for converting carboxyl groups into nitriles are available. Of these methods, only the dehydration of amides to give nitriles has met with some simple and elegant methods.[21] The reported procedures for converting carboxylic acids into nitriles, on the other hand, generally require strong reagents and high temperatures or pressures.[22-24] Only a very limited number of methods have been published for the preparation of nitriles from the corresponding carboxylic acids under relatively mild conditions.[20,25]

At this point, a renewed effort was undertaken to obtain the anticipated intermediate **11**. The *N*-(2,4-dinitrophenyl)sulfonyl oxyacetamide lariat ether **12** was obtained in 76% yield by reacting the acyl chloride derived from carboxylic acid **6** with DNBSA and KH in THF at 0 °C.



11 **12** **13**

The behavior of sulfonamide **12** in the presence of different bases was investigated by ^{1}H NMR spectroscopy. Ratios of the starting material and its reaction products were determined by integration of their acetyl-methylene signals. Results are presented in Figure 1 for the reaction of **12** with pyridine, K_2CO_3, TEA and tetramethylammonium hydroxide pentahydrate (TMAOH) in $CDCl_3$ at 50 °C.

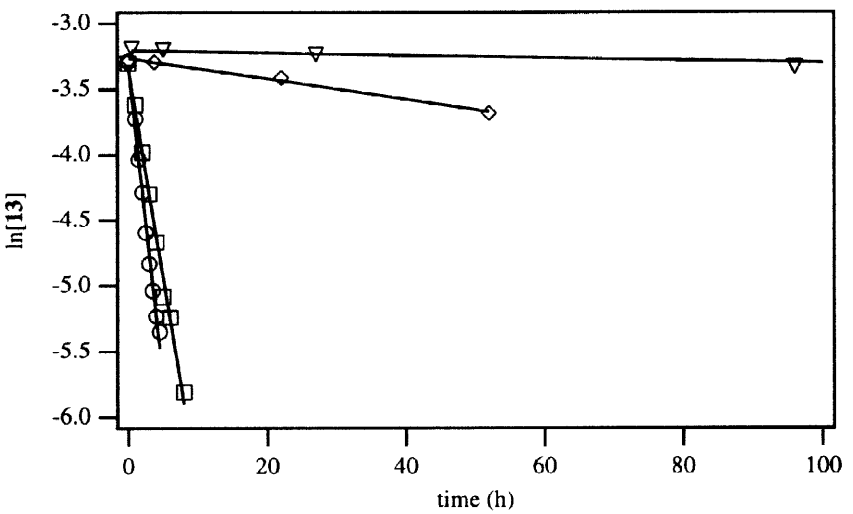


Figure 1. Plot of **[13]** as a function of time when treated with base in $CDCl_3$ at 50 °C. Reaction conditions: [▽]—$[\mathbf{12}]_o$ = 41 mM, $[\text{pyridine}]_o$ = 82 mM; (◊)—$[\mathbf{12}]_o$ = 38 mM, initial mass of K_2CO_3 = 7.7 mg (2 mole equiv.); (□)—$[\mathbf{12}]_o$ = 37 mM, initial mass of TMAOH = 13.8 mg (2.7 mole equiv.); (O)—$[\mathbf{12}]_o$ = 37 mM, $[\text{TEA}]_o$ = 100 mM.

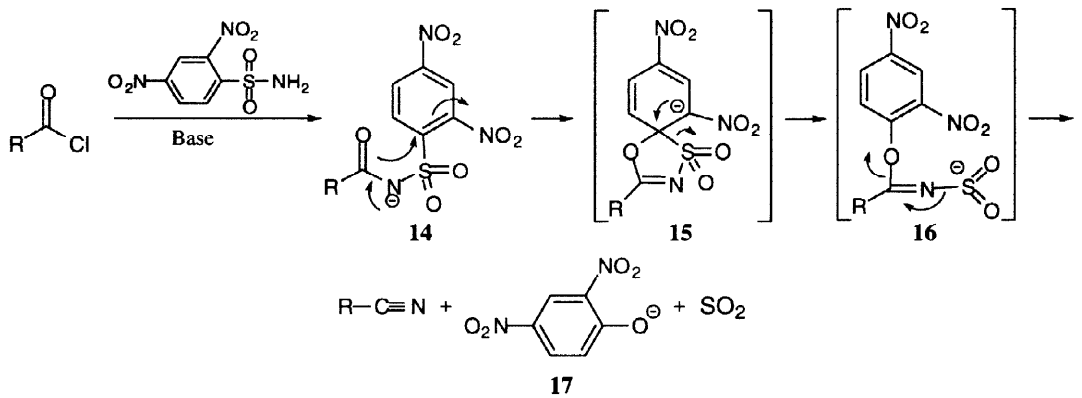
When the base was pyridine, anion **13** appeared to be formed as a tight ion pair as inferred from the broadened and shifted NMR signals. This species was essentially unreactive. On the other hand, treatment of chloroform solutions of **12** with K_2CO_3, TEA or TMAOH gave sharp NMR peaks for **13** whose disappearance was a first-order process. The rate at which **13** disappeared was noted to be markedly influenced by the identity of the base which was utilized in its generation. Thus, the potassium salt of **13** disappeared only slowly. However, the acetyl-methylene proton signal in **13** was rapidly converted into that for nitrile **9** when the counter ion was a triethylammonium or tetramethylammonium cation. One possible explanation for this behavior is that charge localization by ion pair formation in anion **13** inhibits its transformation into the nitrile product. When

the initial concentrations of **12** and TEA were doubled, the rate of disappearance on **13** increased by a factor of two which is also consistent with a first-order decomposition of **13** in the rate-limiting step.

These NMR studies also allowed us to unambiguously identify 2,4-dinitrophenoxide (**17**)[26] as a product of the reaction. Integration of the NMR signals for **17** revealed that it was formed at the same rate as **9**. In the NMR spectra, anions **13** and **17** were the only species observed that contained the 2,4-dinitrophenyl moiety.

Treatment of other *N*-(X)sulfonyl lariat ether carboxamides [X = trifluoromethyl, 2-nitrophenyl, 4-nitrophenyl, perfluorophenyl, and 3-(trifluoromethy)phenyl][17] with TMAOH in $CDCl_3$ at 50 °C gave no nitrile products. Inspection of their ^1H NMR spectra over a period of 10 days indicated the exclusive presence the *N*-sulfonyl amide anion. These observations indicated that the 2,4-dinitrophenyl unit is directly involved in the reaction pathway.

Based on these studies, a mechanism for the formation of the nitrile from the reaction of an acyl chloride with DNBSA and base is proposed (Scheme 4). The key step in this mechanism involves a Smiles rearrangement. Anion **14** is proposed to cyclize to form a spirobicyclic intermediate **15** which then opens to give **16**. α-Elimination of the sulfenate anion leads directly to the observed products.



Scheme 4. Proposed mechanism for the reaction of acyl chlorides with DNSA to form nitriles.

In conclusion, we have shown that acyl chlorides can be converted into the corresponding nitriles in good yields by reaction with 2,4-dinitrobenzenesulfonamide and TEA in THF. This method may allow carboxylic acids to be converted into nitriles under mild conditions in the presence of other functional groups.

EXPERIMENTAL

General. Infrared spectra were recorded with a Perkin Elmer 1600 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained with IBM AF-200 and AF-300 spectrometers and chemical shifts are reported downfield from TMS. Mass spectra were obtained with a Hewlett Packard 5995 mass spectrometer using a 70 ev ionization beam with samples introduced by direct insertion. Elemental analyses were performed by Desert Analytics Laboratory of Tucson, Arizona.

2,4-Dinitrobenzenesulfonamide: Solid 2,4-dinitrobenzenesulfonyl chloride was added to aqueous NH_4OH solution in an ice bath and the resulting mixture was stirred at 0 °C for 3 h. The resulting dark red solution was acidified to pH 3 by the dropwise addition of concentrated HCl to give a pale yellow solid and a

dark yellow solution. The precipitate was filtered, washed with water and dried *in vacuo* to give the desired product as a pale yellow solid in 60-80% yield.[27]

General Procedure for Conversion of Carboxylic Acids into the Corresponding Nitriles. Oxalyl chloride (0.60 mL, 6.20 mmol) was added to a mixture of the carboxylic acid (1.0 mmol) in benzene (25 mL). The mixture was stirred at room temperature under nitrogen for 6 h and evaporated *in vacuo*. The acid chloride was dissolved in THF (15 mL) and a solution of DNBSA (0.30 g, 1.2 mmol) and TEA (1.4 mL, 16 mmol) in dry THF (10 mL) was added. The resulting orange mixture was refluxed under nitrogen for 24 h. EtOAc (50 mL) was added and the resulting solution was washed with 1 N HCl (2 X 25 mL) and 10% aq K_2CO_3 (2 X 25 mL). The dark organic solution was dried over $MgSO_4$ and evaporated *in vacuo* to give a red residue which was purified by column chromatography.

[*sym*-(Decyl)dibenzo-16-crown-5-oxy]acetonitrile (8): Carboxylic acid **5** (1.82 mmol) was converted into nitrile **8** with the modification that reaction of the acyl chloride with DNBSA and TEA in THF was conducted at room temp for 72 h. Compound **8** was obtained as a white solid in 50% yield by column chromatography on alumina with CH_2Cl_2 as eluent followed by recrystallization from Et_2O, mp 105-106 °C. IR (deposit from $CHCl_3$ solution on a NaCl plate): 2924, 2853, 1596, 1500, 1454, 1256 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, 3H, 7.0 Hz), 1.20-1.51 (m, 16H), 1.90 (br t, 2H), 3.89-3.93 (m, 4H), 4.01 (d, 2H, 10.5 Hz), 4.15-4.20 (m, 4H), 4.50 (d, 2H, 10.5 Hz), 5.01 (s, 2H), 6.82-7.00 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.6, 23.4, 29.2, 29.5, 30.1, 31.8, 33.4, 51.3, 67.0, 69.5, 72.0, 80.3, 112.6, 117.5, 118.2, 121.0, 123.0, 147.7, 150.1. MS (DIP-EI) *m/e* 525.3. Anal. calcd for $C_{31}H_{45}NO_7 \cdot 0.1CHCl_3$: C, 69.60; H, 8.10; N, 2.61. Found: C, 69.82; H, 8.09; N, 2.61.

[*sym*-(Phenyl)dibenzo-16-crown-5-oxy]acetonitrile (9): Carboxylic acid **6** (1.04 mmol) was converted into nitrile **9** in 77% yield after chromatography on silica gel with EtOAc/hexanes (1:2) as eluent as a white solid, mp 164-165 °C. IR (deposit from $CHCl_3$ solution on a NaCl plate): 3062, 2874, 1595, 1499, 1452, 1256 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.96-4.20 (m, 8H), 4.49 (d, 2H, 10.4 Hz), 4.62 (d, 2H, 10.4 Hz), 4.65 (s, 2H), 6.81-7.01 (m, 8H), 7.32-7.51 (m, 3H), 7.70-7.81 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.44, 67.30, 69.73, 83.07, 113.0, 117.7, 121.2, 123.2, 127.2, 128.1, 128.4, 137.8, 147.6, 150.2. Anal. calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90. Found: C, 70.54; H, 5.78.

[(±)-*sym*-Dibenzo-16-crown-5-oxy]phenylacetonitrile (10). Carboxylic acid **7** (2.08 mmol) afforded nitrile **10** in 77% yield after chromatography on silica gel with EtOAc/hexanes (1:2) as eluent to provide a white solid, mp 43-45 °C. IR (deposit from $CHCl_3$ solution on a NaCl plate): 3060, 2927, 2873, 1596, 1499, 1453, 1258 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.87-4.13 (m, 4H), 4.15-4.34 (m, 7H), 4.56-4.60 (m, 2H), 5.98 (s, 1H), 6.84-7.02 (m, 8H), 7.34-7.48 (m, 3H), 7.61-7.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.46, 67.77, 69.54, 69.61, 70.62, 71.08, 73.40, 113.1, 113.5, 117.3, 118.2, 119.8, 121.2, 121.4, 122.8, 123.8, 127.5, 129.0, 129.7, 134.2, 147.8, 148.2, 149.8, 150.8. Anal. calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.23; H, 5.93; N, 3.01.

***N*-(2,4-Dinitrophenyl)sulfonyl *sym*-(Phenyl)dibenzo-16-crown-5-oxyacetamide (12).** Oxalyl chloride (1.10 mL, 12.5 mmol) was added to a mixture of carboxylic acid **6** (1.00 g, 2.08 mmol) in

benzene (25 mL). The mixture was stirred at room temp under nitrogen for 6 h and evaporated *in vacuo*. The resultant acyl chloride was dissolved in dry THF (15 mL) and added to a mixture of pentane-washed KH (1.19 g, 10.4 mmol) and DNBSA (0.62 g, 2.50 mmol) in dry THF (25 mL). The dark red mixture was stirred at 0 °C under nitrogen for 0.5 h and water was carefully added to destroy the residual KH. After EtOAc (50 mL) was added, the organic phase was separated and washed with 10% aq K_2CO_3 (3 X 25 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a red residue. The residue was washed with hexanes and chromatographed on alumina with CH_2Cl_2-> CH_3OH/CH_2Cl_2 (1:49) as eluent to give a yellow solid which was washed with Et_2O then dissolved in $CHCl_3$ and washed with 1 N HCl (50 mL). Evaporation of the $CHCl_3$ *in vacuo* gave 1.12 g (76%) of **12** as a dark yellow solid, mp 119-120 °C. IR (deposit from $CHCl_3$ solution on a NaCl plate): 3330, 3098, 2927, 2874, 1738, 1595, 1552, 1538, 1498, 1452, 1412, 1347, 1255 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.82-4.14 (m, 8H), 4.12 (d, 10.6 Hz, 2H), 4.73 (d, 10.6 Hz, 2H), 5.10 (s, 2H), 6.59-6.91 (m, 8H), 7.41-7.68 (m, 5H), 8.12 (d, 2.2 Hz, 1H), 8.35 (dd, 8.6 Hz, 2.2 Hz, 1H), 8.51 (d, 8.6 Hz, 1H), 9.98 (br-s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.38, 66.89, 69.24, 70.82, 72.85, 82.00, 111.7, 117.2, 120.0, 120.9, 123.2, 125.8, 125.9, 128.2, 128.7, 134.0, 136.8, 139.1, 147.0, 147.8, 150.0, 150.1, 170.0. Anal. calcd for $C_{33}H_{31}N_3O_{13}S•0.75CHCl_3$: C, 50.91; H, 4.02; N, 5.28. Found: C, 50.76; H, 3.73; N, 5.23.

NMR Studies. The NMR experiments with substrate **12** were conducted at 50 °C in the pre-heated probe of an IBM AF-300 spectrometer. An organic-soluble base was added directly to a solution of **12** in $CDCl_3$. Alternatively, a solution of **12** in $CDCl_3$ was contacted with an excess of a heterogeneous base for 1 minute and then filtered directly into the NMR tube. The contents of the NMR tube were briefly mixed and the NMR spectrum was recorded as a function of time. Once inserted into the probe, the NMR tube was not removed from the spectrometer for the duration of the experiment.

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19. Compound **3** was identified on the basis of its ^{1}H and ^{13}C NMR spectra, as well as its IR spectrum. This compound was unstable towards purification by chromatography and we were unable to obtain satisfactory elemental analysis for it.
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