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An Improved Preparation of 3,5-Bis(trifluoromethyl)acetophenone and Safety Considerations in the Preparation of 3,5-Bis(trifluoromethyl)phenyl Grignard Reagent

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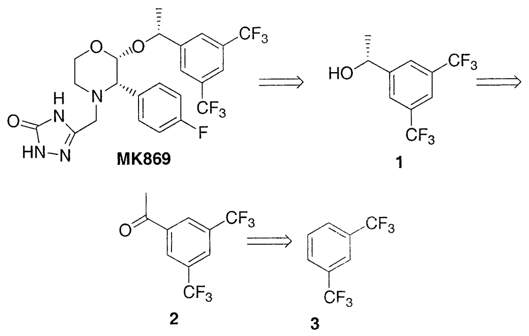
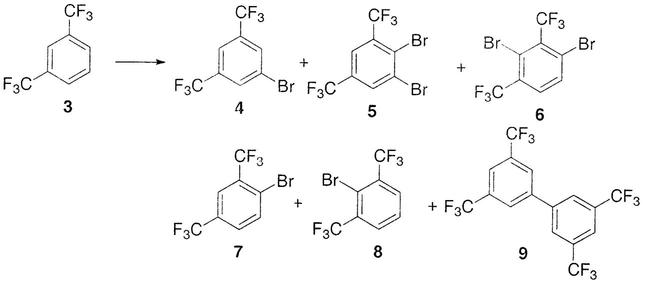
Abstract: An improved and efficient bromination of 3,5-bis(trifluoromethyl)benzene was developed. A safe and reliable preparation of the potentially explosive 3,5-bis(trifluoromethyl)phenyl Grignard and 3-trifluoromethylphenyl Grignard reagents, from the precursor bromides, is described. Reaction System Screening Tool (RSST) and Differential Thermal Analysis (DTA) studies suggest these trifluoromethylphenyl Grignard reagents can detonate on loss of solvent contact or upon moderate heating. When prepared and handled according to the methods described herein, these Grignard reagents can be safely prepared and carried on to advanced intermediates.

The novel neurokinin 1 receptor antagonist MK869 has shown clinical efficacy in the treatment of depression and chemotherapy-induced emesis.[1] As part of a program directed toward the synthesis of MK869, we required a practical synthesis of chiral benzyl alcohol **1**.[1a,2] It was envisioned that **1** could be obtained by a chiral reduction of 3,5-bis(trifluoromethyl)acetophenone **2**.[1a] Acetophenone **2** could in turn arise from 3,5-bis(trifluoromethyl)benzene **3** by a highly regioselective bromination followed by coupling of the corresponding Grignard reagent with Ac$_2$O. In this note we describe a highly regioselective bromination of **3**, a safe and scalable preparation of the corresponding Grignard reagent **10**, as well as its conversion to **2**, and present key safety considerations associated with the highly reactive and potentially explosive trifluoromethylphenyl Grignard reagents.

SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Bromination of 1,3-Bis(trifluoromethyl)benzene (3)



Literature methods for the bromination of **3** to give bromide **4** utilize either *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH) in concentrated sulfuric acid or trifluoroacetic acid.[3] The yields are quoted in the 90% range for bromide **4** with bis-brominated (**5** and **6**) and isomeric byproducts (**7**, **8**, and **9**) amounting to 5–10 mol %[3] as the byproducts (Scheme 2). Attempts to reproduce these procedures gave inconsistent results with significant amounts (>30 mol %) of byproducts **5**–**9**, later determined to result from inadequate mixing of the biphasic bromination reaction mixture.

To circumvent the selectivity issues, the use of cosolvents to solubilize both the starting materials and products was examined. Addition of acetic acid to a sulfuric acid slurry of **3** and DBH resulted in increased reaction selectivity for bromide **4** (>98%). Similar effects were also observed when using NBS in HOAc/H$_2$SO$_4$ mixtures to brominate **3**. When using HOAc/H$_2$SO$_4$ mixtures in the DBH system, bis-bromination of **3**, producing bromides **5** and **6,** was observed only after **3** was completely consumed. In HOAc/H$_2$SO$_4$ mixtures, little if any bis-bromination occurred after **3** was com-

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[†] Department of Process Research.

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[1] (a) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, M. A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; Mcnamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2003. (b) Navari, R.; Reinhardt, R. R.; Gralla, R. J.; Kris, M. G.; Hesketh, P. J.; Khojasteh, A.; Kindler, H.; Grote, T. H.; Pendergrass, K.; Grunberg, S. M.; Carides, A. D.; Gertz, B. J. *N. Engl. J. Med.* **1999**, *340*, 190. (c) Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science* **1998**, *281*, 1640.

[2] (a) Zhao, M. M.; McNamara, J. M.; Ho, G-.H.; Emerson, K. M.; Song, Z. J.; Tschaen, D. M.; Brands, K. M. J.; Dolling, U.-H.; Grabowski, E. J. J. *J. Org. Chem.* **2002**, *67*, 6743. (b) Pye, P. J.; Rossen, K.; Weissman, S. A.; Maliakal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *Chem. Eur. J.* **2002,** *8*, 1372.

[3] (a) Porwisiak, J.; Schlosser, M. *Chem. Ber.* **1996**, *129*, 233. (b) Kunshenko, B. V.; Omarov, V. O.; Muratov, N. N.; Mikhailevskii, S. M.; Yagupol'skii, L. M. *Zh. Org. Khim.* **1991**, *27*, 125. (c) Larionova, Y. A.; Ponomarev, A. I.; Klebanskii, A. L.; Zaitsev, N. B.; Kol'tsov, A. I.; Motsarev, G. V.; Rozenberg, V. R. *Zh. Prikl. Khim.* **1973**, *46*, 2012. (d) Furumata, T. Central Glass Company, Ltd., JP 9067297-A2 [J09067297] 97.03.11; filing date 08/28/95. (e) Suzuki, H. Nissan Chemical Industries, Ltd., Japan, JP 9169673-A2 [J09169673] 97.06.30 Heisei; filing date 12/22/95.

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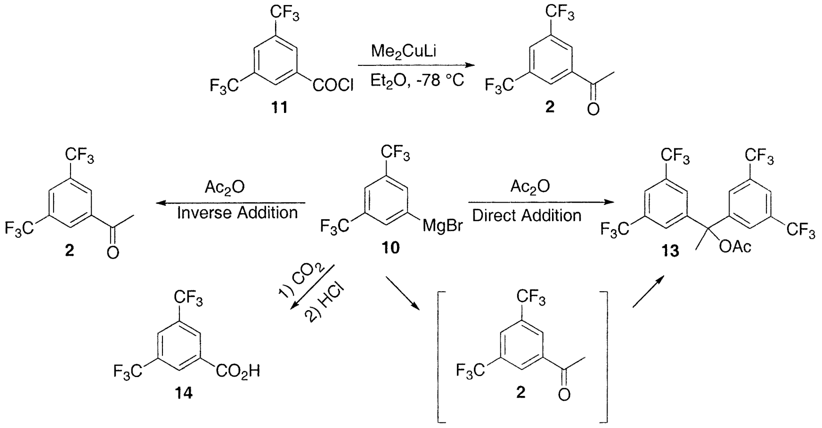
SCHEME 3. Preparation of Acetophenone 2 and Acid 14



pletely consumed. The optimum conditions (6.5:1 (v:v) H_2SO_4:HOAc, 0.54 equiv of DBH, 45 °C) routinely gave **4** in 99% isolated yield and 98% purity without distillation or chromatography.

With bromide **4** in hand, we turned our attention to the synthesis of acetophenone **2**. Preparation of acetophenone **2** has been described in the literature and involved the addition of dimethyl copper lithium to acid chloride **11** in ethereal solvent at −78 °C.[4] This method was unsatisfactory for large-scale synthesis due to the cryogenics. A simpler approach to acetophenone **2** involved the direct acetylation of Grignard **10**.[5]

An experimental review of the various methods of Grignard formation was undertaken. Grignard initiation of bromide **4** in THF began within 5 min at room temperature with use of a slight excess of either Mg granules or dust. The reaction could also be initiated with granules or dust at 0 °C, although initiation frequently required up to an hour. This lower initiation temperature allowed for a greater safety margin in the event of an accidental over-addition of bromide **4**, which can result in an uncontrollable exothermic reaction with the potential for detonation.[6] Interestingly, Grignard reagent **10** did not form when using Mg turnings, even with the coaxing of activating agents.[7] We found Knochel's procedure for the low-temperature halogen−magnesium exchange (THF, 0 °C, 1.1 equiv of *i*-PrMgBr, 30 min) to be the best method for the preparation of trifluoromethylphenyl Grignard reagents.[8] Unlike the transmetalation reaction, Knochel's halogen−magnesium exchange showed no propensity toward runaway reactions. The exchange reaction was rapid (<1 h) and suitable for multi-kilogram scale-up. Formation of Grignard reagent **10** was effectively monitored by the conversion to acid **14** on treatment with CO_2. The lithiation of **3** (*t*-BuLi, THP, −20 °C) was generally nonselective and gave mixtures of products on treatment with either Ac_2O or CO_2.[9]

With Grignard reagent **10** in hand, the reaction conditions for conversion to acetophenone **2** were examined. Addition of acetic anhydride to a freshly prepared solution of **10** gave bis-adduct **13** as the exclusive product.[10] On the other hand, addition of Grignard reagent **10** to an excess of acetic anhydride gave acetophenone **2** in 90% isolated yield.

During the course of these Grignard studies, literature references mentioning detonations of trifluoromethylphenyl Grignard reagents surfaced.[11] Pfizer scientists reported a violent explosion of 3-(trifluoromethyl)phenylmagnesium bromide (**15**) resulting in extensive laboratory damage.[12] Another report mentioned the detonation of 4-(trifluoromethyl)phenylmagnesium bromide (**16**) resulting in destruction of a factory and loss of life.[6a] The chemical community is in need of a possible explanation of these explosions, as well as in need of a safe and reliable preparation of these valuable reagents, particularly in light of the fact that the trifluoromethylphenyl moiety is frequently encountered in pharmaceutical drugs,[1a,13] catalysts,[14] and synthetic intermediates.[15]

A series of Grignard reagents (**10**, **15**, **16**, **17**, **18**, and **19**) was prepared with excess Mg dust and subjected to

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[4] Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**, *53*, 4647.

[5] Newman, M.; Smith, A. *J. Org. Chem.* **1948**, *13*, 592.

[6] (a) Ashby, E. C.; Al-Fekri, D. M. *J. Organomet. Chem.* **1990**, *390*, 275. (b) Jones, M. C. *Plant/Oper. Prog.* **1989**, *8*, 200.

[7] Raston, C. L.; Salem, G. Preparation and Use of Grignard and Group II Organometallics in Organic Synthesis. In *The Chemistry of the Metal−Carbon Bond. The Use of Organometallic Compounds in Organic Synthesis*; Hartley, F. R., Ed.; John Wiley and Sons Ltd.: New York, 1987; Vol. 4, pp 163−306.

[8] Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449.

[9] Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett* **1990**, 747.

[10] Commercially available from Maybridge Chemical Company, Ltd.

[11] (a) Broeke, J.; Deelman, B.-J.; Koten, G. *Tetrahedron. Lett.* **2001**, *42*, 8085−8087. (b) Beck, C.; Park, Y.-J.; Crabtree, R. *Chem. Commun.* **1998**, 693. (c) Pinho, P.; Guijarro, D.; Andersson, P. *Tetrahedron* **1998**, *54*, 7897. (d) Kaul, F.; Puchta, G.; Schneider, H.; Grosche, M.; Mihalios, D.; Herrmann, W. *J. Organomet. Chem.* **2001**, *621*, 184. (e) Li, N.-S.; Yu, S.; Kabalka, G. *J. Organomet. Chem.* **1997**, *531*, 101. (f) Doctorvich, F.; Deshpande, A.; Ashby, E. *Tetrahedron* **1994**, *50*, 5945.

[12] Appleby, I. C. *Chem. Ind.* **1971**, 120.

[13] (a) Riachi, N. J.; Arora, P. K.; Sayre, L. M.; Harik, S. I. *J. Neurochem.* **1988**, 1319. (b) Houlihan, W. J.; Gogerty, J. H.; Ryan, E. A.; Schmitt, G. *J. Med. Chem.* **28**, *28*, 1985. (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*: John Wiley & Sons: New York, 1991; p 246. (d) Desai, R. C.; Cicala, P.; Meurer, L. C.; Finke, P. E. *Tetrahedron Lett.* **2002**, *43*, 4569. (e) Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I. W.; Dormer, P. G.; Welch, J. W.; Hillier, M. C.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5993.

[14] Kaul, F. A. R.; Puchta, G. T.; Schneider, H.; Grosche, M.; Mihalios, D.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *621*, 184.

[15] (a) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897. (b) Broeke, J.; Deelman, B.-J.; Koten, G. *Tetrahedron Lett.* **2001**, *42*, 8085−8087.

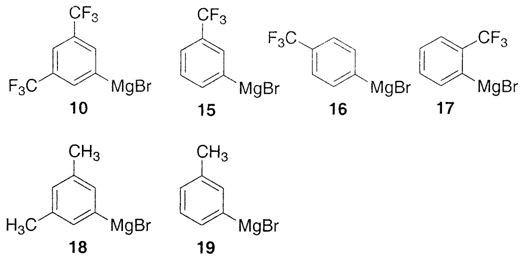

FIGURE 1. Grignard reagents tested by RSST and DTA analysis.

both Differential Thermal Analysis (DTA)[16] and Reactive System Screening Tool (RSST)[17] testing in an effort to determine the role of the trifluoromethyl group on aryl Grignard stability. While tolyl Grignards **18** and **19** exhibited no exothermic activity under the RSST and DTA testing conditions, Grignard reagents **10**, **15**, **16**, and **17** all exhibited significant exothermic activity on RSST and DTA analysis. Further, the RSST and DTA results suggest that once an exothermic reaction initiates for these compounds, it can lead to an uncontrollable reaction leading to potential for explosion. Ashby,[6a] in studies on the reaction of benzotrihalides with Mg, states that benzotribromides and benzotrichlorides are unstable in the presence of Mg above −40 °C. He states that these two trihalides react with Mg to form a phenylhalocarbene that reacts with the Grignard reagent resulting in a plethora of byproducts. Ashby suggests that since the benzotrichlorides and benzotribromides can react with Mg, benzotrifluorides may behave similarly, although offering no direct evidence.

Intrigued by the vast differences in exothermic activity of tolyl Grignards **18** and **19** versus trifluoromethylphenyl Grignards **10**, **15**, **16**, and **17**, several experiments were designed to determine if a highly activated form of Mg might account for the unusual exothermic nature of these trifluoromethylphenyl Grignards. In one experiment, Grignard **10** was prepared with excess Mg dust and then filtered through a 10-μm filter to remove the excess Mg. Grignard reagent **10** prepared under these conditions exhibited no exothermic activity on RSST and DTA analysis. In a second experiment, Grignard **10** was prepared with Mg dust and 25 mol % excess of bromide **4**. The excess bromide served to consume all Mg in the reaction mixture ensuring that no excess Mg would be present once the Grignard reagent had formed completely. Examination of this Grignard by RSST and DTA analysis showed no exothermic activity. In a third experiment, Grignard **10** was prepared via the Mg free Knochel protocol and showed no exothermic properties on RSST and DTA testing. The experiments described above demonstrate that exothermic activity is observed only when these Grignards are tested with excess Mg present.

Finally, the stability of **10** and **15** was evaluated in both THF and Et_2O. DTA studies suggest that trifluoromethylphenyl Grignards **10** and **15** are substantially more stable in THF than in Et_2O, making THF the solvent of choice when working with these reagents. The DTA data also indicate that once these Grignards lose contact with solvent, a severe exothermic reaction can occur.

Detonations associated with formation of trifluoromethylphenyl Grignards may be attributed to loss of contact with solvent, as evidenced by DTA analysis, runaway exothermic side reactions, and potentially the presence of a highly activated form of Mg. By carefully controlling these factors, trifluoromethylphenyl Grignards can be reproducibly and safely prepared on large scale. The Knochel procedure should be used whenever possible. If these reagents are generated from Mg, the reaction should be done in THF, and well below reflux, since loss of solvent contact can cause a runaway exothermic reaction. By carefully adhering to the guidelines described herein, Grignards **10**, **15**, **16**, and **17** can be reproducibly prepared with greatly reduced risk.

Experimental Section

General Procedure. All reagents were purchased from commercial sources and used without further purification. Toluene and THF solvents were dried overnight over activated 3 Å molecular sieves prior to use. Unless otherwise stated, all reactions were carried out under a N_2 atmosphere. RSST data were collected on a Reactive Systems Screening Tool from Fauske and Associates. All RSST data were collected with use of a 2 °C/min gradient from 25 to 350 °C with a 15 psi nitrogen backpressure (closed cup). Open cup DTA data were collected on a T.A. Instruments 2920, using 4 mm open glass sample tubes. All HPLC analyses were carried out on a 4.6 mm × 250 mm Zorbax RX C8 5-μm column. The solvent composition was 35:65 0.1% H_3PO_4 (aq):acetonitrile. The flow rate was 1 mL/min. All reactions were monitored at 195 nm.

3,5-Bis(trifluoromethyl)bromobenzene (4). To a neat solution of 2.14 kg (2.32 L, 15 mol) of 1,3-bis(trifluoromethyl)benzene (**3**) at 5 °C was added 660 mL of glacial acetic acid. Concentrated sulfuric acid (4.26 L) was then added. The mixture was recooled to 10 °C and 2.31 kg (8.08 mol) of 1,3-dibromo-5,5-dimethylhydantoin was slowly added to the vigorously stirred mixture. The reaction mixture was then heated at 45 °C for 4 h, cooled to 2 °C, and slowly poured into 7.5 L of cold water. After the solution was stirred vigorously for 10 min, the colored lower organic layer was separated and washed with 2.25 L of NaOH (5 N) to give 4.3 kg (94%) of a clear, colorless oil. ^1H NMR/^{13}C NMR data were consistent with that for material purchased from Aldrich.

3,5-Bis(trifluoromethyl)phenylmagnesium Bromide 10 (Method 1). A slurry of 475 g (22.6 mol) of magnesium granules in 10.5 L of THF was heated to 35 °C. To the slurry was added 4.08 kg (14.0 mol) of bromide **4** over a 4-h period such that the reaction temperature was maintained between 30 and 35 °C. After complete bromide addition, the dark brown solution was heated at 30 °C for 1 h at which time an HPLC assay indicated complete Grignard formation.

3,5-Bis(trifluoromethyl)phenylmagnesium Chloride 10 (Method 2). A 2 M room-temperature solution of *i*-PrMgCl (55 mL, 110 mmol) was added over a 30-min period to a −10 °C solution of bromide **4** (29.3 g, 100 mmol) in 50 mL of anhydrous

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[16] DTA measures heat flows and temperature changes resulting from a transition in a material as a function of temperature and time. These measurements provide key chemical and physical information regarding endothermic or exothermic processes. For more information see: *Handbook of Thermal Analysis and Calorimetry*: *Principles and Practice*; Brown, M. E., Ed.; Elsevier Science B.V.: Amsterdam, The Netherlands, 1998.

[17] RSST is a calorimeter that is used to identify a potential hazard in a chemical process. The data provide information on the rate of pressure and rate of temperature rise, in response to controlled heating. RSST data represent the worst case scenario of what could happen in the event of a runaway reaction. For more information see: Fauske, H. K.; Clare, G. H.; Creed, M. T. *RSST: Laboratory Tool for Characterizing Chemical Systems*; International Symposium on Runaway Reactions; CCPS: Cambridge, MA, March 1989; AIChE: New York; pp 367−371.

THF, such that the reaction temperature never exceeded −5 °C. The mixture was stirred at −10 °C for 1 h, at which time an HPLC assay indicated complete Grignard formation.

3,5-Bis(trifluoromethyl)acetophenone (2). A solution of 14.0 mol of Grignard **10** (prepared by either method 1 or method 2) in 10.5 L of THF was transferred over 2 h, via cannula, into a neat −15 °C solution of 5.0 L of acetic anhydride. The dark brown mixture was stirred for 15 min at 0 °C. Water (10.5 L) was then added over 2 h, and the resulting mixture was stirred at 60 °C for an additional 15 min to ensure complete hydrolysis of residual acetic anhydride. After the solution was cooled to 15 °C, the phases were separated and the organic layer was diluted with 8.0 L of MTBE. The diluted organic layer was vigorously stirred at 15 °C, and 5N NaOH was added dropwise until the pH of the aqueous phase reached 7.1. The layers were separated and the organic phase was washed with 1.5 L of saturated aqueous $NaHCO_3$ and 1 L of brine. The solvent was removed under reduced pressure. Mineral oil (250 mL) was added to the crude product to serve as a distillation aid. The resulting mixture was distilled in vacuo (57 Torr; distillate collected at 90−125 °C) to give 2.88 kg (88%) of acetophenone **2** as a clear colorless oil. ^{1}H NMR/^{13}C NMR data were consistent with that for material purchased from Aldrich.

3,5-Bis(trifluoromethyl)benzoic Acid (14). A solution of 100 mmol of Grignard **10** (prepared by either method 1 or method 2) in 105 mL of THF was transferred via cannula to a CO_2 pressure bottle. The Grignard reaction vessel was rinsed with 50 mL of THF. The material was cooled to −45 °C under a N_2 atmosphere and briefly degassed in vacuuo. The mixture was then treated with CO_2 (20 psi) and the slurry was vigorously stirred at −45 °C for 1 h. The brown mixture was warmed to 0 °C, care being taken to maintain the CO_2 pressure at a safe level by venting with N_2. To the 0 °C mixture was added 200 mL of aqueous HCl (1 N). The biphasic mixture was vigorously stirred for 20 min, and the layers separated. The aqueous layer was washed with 200 mL of toluene. The combined organic layer was concentrated under reduced pressure to a volume of 250 mL. The concentrate was then extracted with 200 mL of 5% aqueous Na_2CO_3. The turbid aqueous layer (pH 9.5) was filtered through Celite. Concentrated HCl was added to the filtrate to adjust the pH to 2.0. The resulting slurry was stirred at room temperature for 1 h. The flocculent white solid was filtered and washed with water. The product was dried overnight at 35 °C to provide 24.1 g (94%) of **14** as a white crystalline solid. ^{1}H NMR/^{13}C NMR data were consistent with that from material purchased from Aldrich.

Acknowledgment. We thank Dr. Jeffrey T. Kuethe, of Merck and Co., Inc, for careful review of the manuscript.

Supporting Information Available: RSST and DTA data for compounds **10**, **15**, **16**, **17**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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