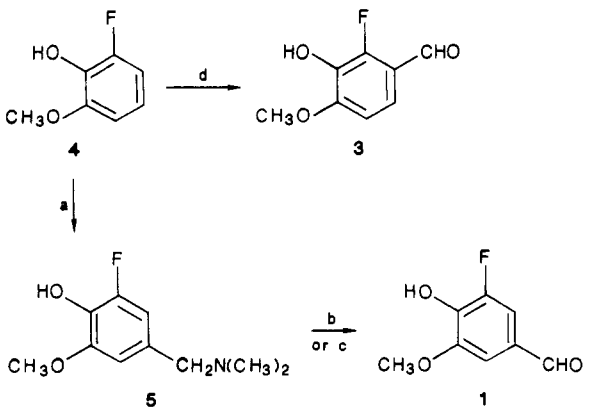
Scheme I[a]



[a] (a) 37% CH_2O, 40% $(CH_3)_2NH$; (b) HMTA, HOAc; (c) 1. CH_2I; 2. HMTA, HOAc/H_2O; (d) HMTA, TFA.

amine.[7] Treatment of **4** with formaldehyde and *N,N*-dimethylamine afforded, *N,N*-dimethyl-3-methoxy-4-hydroxy-5-fluorobenzylamine (**5**, 95%) as the sole regioisomer. A standard method for the conversion of tertiary amines into aldehydes involves a transamination with HMTA, followed by hydrolysis.[8] Treatment of **5** with HMTA in acetic acid gave a 20% yield of **1**. In order to increase the yield, we sought a better leaving group. Treatment of **5** with methyl iodide, followed by reaction with HMTA in a 50% aqueous acetic acid and hydrolysis with concentrated HCl, afforded **1** in 91% yield, after purification.

In summary, we have developed new pathways for the formation of both 2-fluoroisovanillin and 5-fluorovanillin from a common intermediate. Each step of the reaction sequence can be scaled up and involves a modest to very good yield of the product. We also report a new method for the formation of benzaldehydes via a transamination and hydrolysis of quaternary salts of *N,N*-dimethylbenzylamines.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 spectrophotometer. The ^1H and ^{19}F NMR were recorded on a Bruker HX-90E or a IBM 270 spectrometer with tetramethylsilane as the internal standard for ^1H NMR and hexafluorobenzene as the external standard for ^{19}F NMR. The mass spectra were obtained at the Ohio State University Chemical Instrument Center, by use of a Kratos MS-30 mass spectrometer. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN. TLC was performed on silica gel 60 F precoated aluminum-backed plated from EM Reagents. Column chromatography was performed on silica gel 60, 70–230 mesh, from EM Reagents. Flash chromatography was performed on flash silica gel 60, 230–400 mesh, from EM Reagents. All organic solvents were appropriately dried prior to use.

2-Fluoro-3-hydroxy-4-methoxybenzaldehyde (3). To a heated solution (80 °C) of hexamethylenetetraamine (HMTA) (2.8 g, 20 mmol) in trifluoroacetic acid (10 mL) was added dropwise over a 50-min period 2-fluoro-6-methoxyphenol[2] (1.42 g, 10 mmol) in TFA (10 mL). The mixture was heated for an additional 1 h and concentrated, and H_2O (50 mL) was added. The mixture was stirred for 10 min and solid potassium carbonate was added until the solution was neutral. The mixture was stirred for 20 min and extracted with ether (3 × 50 mL), washed with H_2O (3 × 50 mL), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure to give 1.4 g (75%) of **3** which was purified by sublimation (113 °C) to give 1.1 g (63%) of pure **3**; mp 180–181 °C (lit.[5,6] mp 180–195 °C).

***N,N*-Dimethyl-3-hydroxy-4-methoxy-5-fluorobenzylamine (5).** 2-Fluoro-6-methoxyphenol[2] (10 g, 70 mmol) was added to a solution of 40% dimethylamine (15 g, 124 mmol) and 37% formaldehyde (9 mL, 124 mmol) in absolute ethanol (70 mL). The mixture was heated at reflux for 2 h, cooled, and concentrated under reduced pressure to give a solid. The solid was triturated with ether (100 mL) to give 13.2 g of **5** (95%); mp 140–142 °C; IR (KBr) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 6.56–6.68 (m, 2 H, 2 × ArH), 3.74 (s, 3 H, $ArOCH_3$), 3.35 (s, 2 H, $ArCH_2N$), 2.24 (s, 6 H, $N(CH_3)_2$).

Anal. Calcd for $C_{10}H_{14}FNO_2$: C, 59.67; H, 4.50; N, 7.73. Found: C, 59.37; H, 4.35; N, 7.68.

3-Methoxy-4-hydroxy-5-fluorobenzaldehyde (1). Iodomethane (40 mL) was added to a solution of *N,N*-dimethyl-3-methoxy-4-hydroxy-5-fluorobenzylamine (**5**) (4 g, 20 mmol) in $CHCl_3$ (200 mL). The mixture was stirred at 25 °C for 18 h and filtered to give 7.8 g of a white solid. Without further purification, the solid was heated to 120 °C in HOAc (20 mL) and H_2O (20 mL). At that time, HMTA (12 g, 30 mmol) was added to the reaction mixture. The mixture was stirred at 120 °C for 2 h and concentrated HCl (5 mL) was added. The mixture was heated an additional 5 min, cooled, and extracted with ether (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL), dried with $MgSO_4$, and evaporated under reduced pressure to give 3.12 g (91%) of **1** which was purified by sublimation: mp 113–114 °C (lit.[1] mp 113–114 °C); ^1H NMR ($CDCl_3$) δ 9.8 (d, 1 H, J_{HF} = 1.3 Hz, CHO), 7.3 (m, 2 H, ArH), 6.1 (b, 1 H, OH), 4.0 (s, 3 H, OCH_3); ^{19}F NMR ($CDCl_3$) δ − 138.47.

Acknowledgment. We thank the NIH for financial support (GM29358 and HL22533) and Mr. Jack Fowble for NMR spectra on the 270-MHz instrument.

Registry No. **1**, 79418-78-3; **3**, 79418-73-8; **5**, 103905-49-3; 2-fluoro-6-methoxyphenol, 73943-41-6.

(7) Zaugg, H. E. *Synthesis* **1984**, 85.
(8) Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* **1979**, 161.

An Improved Synthesis of 4-Fluoroveratrole. Efficient Route to 6-Fluoroveratraldehyde and 6-Fluoro-D,L-DOPA

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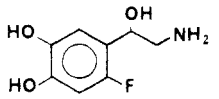
Fluorinated analogues of catecholamines and amino acids have received recent attention as pharmacological tools and as mechanistic probes and biological tracers.[1] For example, the utility of 6-fluoronorepinephrine (6FNE) (**1**) as a specific α-adrenergic agonist has been demonstrated in several studies of both central and peripheral systems.[2] The study of the pharmacology of 6-fluoro-D,L-DOPA (6FDOPA) (**2**) has increased importance due to the potential of ^{18}F-labeled 6FDOPA as a scanning agent in positron emission transaxial tomography.[3] Both of these analogues, as well as other 6-fluoro analogues of amines and metabolites related to DOPA, have been synthesized from a common precursor, 6-fluoroveratraldehyde (**3**).[4,5] Our previous synthesis of **3** was based on our

(1) Kirk, K. L.; Creveling, C. R. *Med. Res. Rev.* **1984**, *4*, 189.
(2) Cantacuzene, D.; Kirk, K. L.; McCulloh, D. H.; Creveling, C. R. *Science (Washington, D.C.)* **1978**, *204*, 1217.
(3) Garnett, E. S.; Firnau, G.; Nahmias, C. *Nature (London)* **1983**, *305*, 137.
(4) Kirk, K. L.; Cantacuzene, D.; Nimiktitpisan, Y.; McCulloh, D.; Padgett, W.; Daly, J. W.; Creveling, C. R. *J. Med. Chem.* **1979**, *22*, 1493.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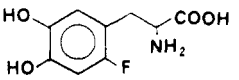
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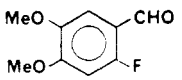
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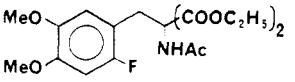
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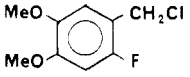
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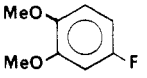
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photochemical variant of the Schiemann reaction.[4] However, this procedure is inconvenient if large-scale preparation is required. Herein we report alternative approaches to **3** and to diethyl 2-acetamido-2-(4,5-dimethoxy-2-fluorobenzyl)malonate (**4**) through 4-(chloromethyl)-5-fluoroveratrole (**5**), the latter two compounds being key intermediates in our reported synthesis of 6FDOPA.[5] These new routes feature an improved synthesis of 4-fluoroveratrole (**6**) followed by regioselective formylation or chloromethylation to produce **3** and **5**, respectively.

Our earlier attempts to gain access to the 4,5-dihydroxy-2-fluoro aromatic substitution pattern from 4-fluorocatechol derivatives had proved unrewarding. Ingraham et al.[6] synthesized 3- and 4-fluoroveratroles by treatment of the corresponding aminoveratrole in hydrochloric acid with sodium nitrite, followed by addition of a specific amount of fluoroboric acid solution and subsequent thermal decomposition of the isolated diazonium tetrafluoroborate.[7] In our hands, this procedure gave inconsistent results, particularly with respect to isolation of the diazonium tetrafluoroborate. Poor solubility of this aniline in the small volume of hydrochloric acid used in the procedure was an obvious complication. However, an increase in the volume of hydrochloric acid resulted essentially in complete failure of the procedure. We found also that maintenance of low temperature during the sodium nitrite addition to the aminoveratrole suspension was difficult and tedious.

We now report that diazotization of 4-aminoveratrole in methanol and fluoroboric acid solution, using *n*-butyl nitrite as the source of nitrous acid,[8] leads consistently to good yields of veratrole-4-diazonium tetrafluoroborate. In addition to improved yields, the procedure is operationally extremely convenient. Thermal decomposition of the isolated salt and flash distillation of the product as it forms gives 4-fluoroveratrole in yields of 40% to 50% (based on 4-aminoveratrole) after purification.

Formylation of 4-fluoroveratrole was carried out by using the procedure of Gross et al.[9] Thus, titanium tetrachloride catalyzed alkylation of **6** with α,α-dichloromethyl methyl ether, followed by acidic aqueous workup, produced 6-fluoroveratraldehyde as the only detectable aromatic aldehyde, identical with authentic material prepared previously.[4] Chloromethylation of **6** (HCl gas, formaldehyde, acetic acid)[10] gave **5**. Without further purification, this material was alkylated with the sodium salt of diethyl acetamidomalonate to give **4**, identical with previously prepared authentic material.[5]

The availability of convenient routes to these synthetic intermediates assures ready access to adequate supplies of 6FDOPA, 6FNE, and to other analogues in this important series.

Experimental Section

Reagents and solvent were commercial materials. All melting points, determined with a Thomas-Hoover capillary apparatus, are uncorrected.

4-Fluoroveratrole (6). A solution of 25 g (160 mmol) of 4-aminoveratrole (Aldrich Chemical Corp.) in 100 mL of methanol and 100 mL of 50% fluoroboric acid in a 1-L beaker was cooled to 0 °C in an ice–salt bath. To the magnetically stirred solution was added dropwise 24.6 mL (270 mmol) of *n*-butyl nitrite (Aldrich), at such a rate that the temperature of the solution did not exceed 5 °C. The dark solution was stirred for an additional hour at 0 °C and then was diluted with 600 mL of ether to give an immediate precipitate. After storage at 0–5 °C for 1 h, the purplish white crystals were collected by filtration. Washing with cold ether and drying in a desiccator under vacuum for 12 h gave 34.3 g (136 mmol, 83%) of veratrole-4-diazonium tetrafluoroborate, decomposition temperature 116–119 °C (lit.[11] 123 °C), used in the next step without further purification.

A 500-mL, round-bottomed flask was charged with 34.4 g (136 mmol) of the diazonium fluoroborate and connected to a vacuum adaptor and 50-mL receiving flask by way of a wide U-tube. The receiving flask was packed in dry ice, the pressure was reduced by using a water aspirator, and the diazonium salt was heated with a Bunsen burner. The rate of decomposition was controlled by gently waving the flame under the flask such that gas evolution was evident, but not vigorous. As the decomposition proceeded, evolution of boron trifluoride was evident by white fumes. The product was flash distilled as it formed by gently heating the U-tube. The distillate was dissolved in 120 mL of ether and the solution was washed three times with 25 mL of 10% sodium hydroxide solution and once with water. After drying (sodium sulfate), removal of solvent and distillation gave 10.1 g (50%) of pure 4-fluoroveratrole, bp 120–123 °C, 45 mm (lit.[7] by 98 °C, 14 mm). This procedure has been repeated several times without incident, and the yields have ranged from 40% to 50%, based on 4-aminoveratrole.

6-Fluoroveratraldehyde (3). A solution of 8.4 g (54 mmol) of **6** in 55 mL of anhydrous methylene chloride under argon and cooled to ice-bath temperature was treated dropwise over 0.5 h with 9.5 mL (15.6 g, 87 mmol) of titanium tetrachloride in 20 mL of anhydrous methylene chloride (Aldrich Chemical Corp.). To the resulting bright red solution was added dropwise over 15 min 6.48 g (56 mmol) of α,α-dichloromethyl methyl ether in 15 mL of anhydrous methylene chloride. The solution was stirred for 0.5 h at ice-bath temperature and then allowed to warm to room temperature and stirred for an additional 4 h. The emerald green solution was then poured into 200 g of cracked ice, resulting in a white precipitate. The methylene chloride layer was separated, and the aqueous layer and solids were extracted three times with 75 mL of ether. The combined organic fractions were washed three times with 50 mL of 10% sodium bicarbonate and once with brine. After drying (sodium sulfate), the solvent was removed to give, after recrystallization from ethyl acetate and petroleum ether, 5.9 g (60%) of **3**, mp 94–96 °C (lit.[4] mp 94–96 °C).

4-(Chloromethyl)-5-fluoroveratrole (5). Hydrogen chloride gas was bubbled slowly through a solution of 10 g (64.1 mmol) of **6** in 25 mL of acetic acid and 10 mL of 37.4% formalin solution. The temperature was maintained below 30 °C by use of an ice

(5) Creveling, C. R.; Kirk, K. L. *Biochem. Biophys. Res. Commun.* **1985**, *130*, 1123.
(6) Corse, J.; Ingraham, L. L. *J. Org. Chem.* **1951**, *18*, 1345.
(7) Smith, L. E.; Haller, H. L. *J. Am. Chem. Soc.* **1934**, *56*, 237.
(8) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1977; Vol. B, p 275.
(9) Gross, H.; Reiche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308.
(10) Ladd, D. C.; Weinstock, J. *J. Org. Chem.* **1981**, *46*, 203.
(11) Smith, L. E.; Hallet, H. L. *J. Am. Chem. Soc.* **1934**, *56*, 237.

bath. After approximately 1 h the temperature of the solution began to fall and the cooling bath was removed. The gas flow was continued for an additional 1 h, and the reaction mixture was then poured into 200 mL of water. The aqueous solution was extracted three times with 100 mL of ether. The ether layer was washed three times with 25 mL of water and dried (sodium sulfate). Evaporation of solvent and drying in vacuo over sodium hydroxide (to remove acetic acid) gave 11.2 g (55.8 mmol, 98%) of **5**, mp 50–51 °C (from ether/petroleum ether). The unrecrystallized product is of sufficient purity for the next stage. NMR ($CDCl_3$): δ 6.84 (d, J_{HF}^{meta} = 7.4 Hz, ArH-3), 6.63 (d, J_{HF}^{ortho} = 11.0 Hz, ArH-6), 4.61 (d, J_{HF} = 1.6 Hz, CH_2Cl), 3.89 (s, OCH_3), 3.87 (s, OCH_3).

Diethyl 2-Acetamido-2-(4,5-dimethoxy-2-fluorobenzyl)-malonate (4). Alkylation of 11 g (53.8 mmol) of **5** with the sodium salt of diethyl acetamidomalonate as described previously[5] gave, after recrystallization from aqueous ethanol, 17.1 g (44.4 mmol, 82.5%) of **4**: mp 140–142 °C (lit.[5] mp 136–138 °C); NMR (CD_3OD) δ 6.72 (d, J_{HF}^{ortho} = 11.1 Hz, ArH-3), 6.53 (d, J_{HF}^{meta} = 7.0 Hz, ArH-6), 4.89 (s, $ArCH_2$), 4.21 (m, OCH_2CH_3), 3.79 (s, OCH_3), 3.75 (s, OCH_3), 4.98 (s, $COCH_3$), 1.26 (t, J = 7.0 Hz, OCH_2CH_3).

Acknowledgment. D.C.F. was supported by NIH Grant No. F32AM07530.

Registry No. **2**, 102034-49-1; **3**, 71924-62-4; **4**, 102034-51-5; **5**, 91407-48-6; **6**, 398-62-9; 6-fluoronorepinephrine, 86820-21-5; 4-aminoveratrole, 6315-89-5; veratrole-4-diazonium tetrafluoroborate, 450-57-7; α,α-dichloromethyl ether, 4885-02-3; diethyl acetamidomalonate sodium salt, 1068-90-2.

A Convenient Preparation of 5-Alkyl-4-carbalkoxy-1,2,3-thiadiazoles

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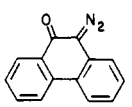
Received April 14, 1986

In connection with ongoing projects, preparation of 5-alkyl-4-carbalkoxy-1,2,3-thiadiazoles[1] was required. The reaction of the α-diazo β-ketoester **1** with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**2**) or 2,4-bis(4-phenoxyphenyl-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**3**) was envisioned as a direct entry to 1,2,3-thiadiazole **4** (eq 1—see Table I).

It has been described in the literature[2] that α-diazo thiocarbonyl compounds, such as **5**, could readily be cyclized to the 1,2,3-thiadiazole **6**. Substituted 1,2,3-thiadiazoles were also prepared from α-diazo ketones via their thioketone intermediates using Lawesson's reagent **2**.[3] However, it has been pointed out that only molecules possessing a rigid cis diazo ketone geometry could be converted to the 1,2,3-thiadiazoles. Thus, compound **7** was converted to **8**, whereas **9** did not yield the corresponding thiadiazole **10**.

5 **6**

As Cava and Levinson's suggestion was based on a single example and also the fact that **5** could readily be converted



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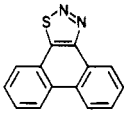

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to the corresponding thiadiazole, it was decided to evaluate the reaction of diazo dicarbonyl compounds with both thionating reagents **2** and **3**. The results of this investigation are reported in this paper.

As shown in entries 1–4 (Table I), treatment of the α-diazo β-ketoester **1** (R = CH_3, Et; R′ = allyl) with 0.6 equiv of either **2** or **3** in refluxing benzene or THF, respectively, resulted in good to excellent yield of 1,2,3-thiadiazoles (76–94%).[4] Under these conditions both Lawesson's reagent[5] **2** and the more soluble 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide[6] (**3**) reacted smoothly.[7] This procedure differs from Wolff's synthesis where ammonium hydrogen sulfide was used as thionating agent.[8,9]

The relative importance of steric hindrance[10] in the course of the reaction was examined in entries 5–7. The presence of a bulkier substituent adjacent to the ketone function required more forcing conditions. For example, substrate **1** (R = cyclopentyl; R′ = allyl) required a reaction time of 7 h under standard reaction conditions (entry 5). The bulkier diazo ketoester (R = *tert*-butyl; R′ = allyl) when refluxed for 20 h in THF gave the desired product in only 20% yield (entry 6).[11] However, when DME was used as a solvent, a 77% yield of the desired thiadiazole was obtained after 3.5 h (entry 7).

The modification of the ester side chain in **1** allows a quick entry to a variety of 5-alkyl-4-carbalkoxy-1,2,3-thiadiazoles (entries 8–11). Treatment of **1** (R = Et; R′ = CH_3, $CH_2CH_2Si(CH_3)_3$, benzyl, *tert*-butyl) with **3** under standard reaction conditions afforded the corresponding thiadiazole **4** in excellent yield.[12] These compounds can be readily transformed to the parent carboxylic acid **4** (R = Et; R′ = H) for further synthetic elaboration.[13]

In view of the above facile preparation of a variety of 5-alkyl-4-carbalkoxy-1,2,3-thiadiazoles, it was felt that conformationally unrestricted diazo ketones may also be

(1) The chemistry of 1,2,3-thiadiazoles has recently been reviewed; see: Thomas, E. W. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Volume Ed.; Katritzky, A. R., Rees, C. W.; Series Eds.; Pergamon Press: London, 1984; Vol. 6, Part 4B, Chapter 4.24, p 447.

(2) (a) Regitz, M.; Liedhegener, A. *Justus Liebigs Ann. Chem.* **1967**, *710*, 118. (b) For a similar observation, see: Hinz, W.; Just, G. *Synth. Commun.* **1986**, 917.

(3) Levinson, M. I.; Cava, M. P. *Heterocycles* **1982**, *19*, 241.

(4) The more general synthesis of 1,2,3-thiadiazoles reported by Hurd and Mori where a hydrazone is treated with $SOCl_2$ is an interesting alternative to prepare 5-alkyl-4-carbalkoxy-1,2,3-thiadiazoles, although in some cases yields have been found to be irreproducible (Daris, J. P., Bristol-Myers, A.I. research, Candiac, private communication, 1985). See: (a) Hurd, C. D.; Mori R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359. (b) Shafiee, A. *J. Heterocycl. Chem.* **1976**, *13*, 301.

(5) A review on Lawesson's reagent has been published; see: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(6) For the application and the preparation of **3**, see: (a) Sauve, G.; Rao, V. S.; Lajoie, G.; Belleau, B. *Can. J. Chem.* **1985**, *63*, 3089. (b) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815 and references cited therein.

(7) As expected the ester carbonyl was unreactive toward either of the thionating reagents.

(8) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129; **1904**, *333*, 1.

(9) For cases where Wolff's synthesis has been applied, see: (a) Wieland, H.; Bloch, S. *Chem. Ber.* **1906**, *39*, 1488. (b) Staudinger, H.; Becker, J.; Hinzel, H. *Chem. Ber.* **1916**, *49*, 1978, (c) Peet, N. P.; Sunder, S. *J. Heterocycl. Chem.* **1975**, *12*, 1191.

(10) The steric bulk effect could be felt either during the conversion of the C=O to C=S group or as steric compression between the groups around the C=C bond during the product-controlled formation of the final compound.

(11) The longer reaction time may give rise to consumption of **3** in side reactions, see: Pedersen, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293.

(12) Detection of any of the presumably initially formed diazo thiocarbonyl compounds failed. For a similar observation, see ref 3.

(13) (a) See ref 4b and references cited therein. (b) Green, T. W. *Protective Groups in Organic Syntheses*; Wiley-Interscience: New York, 1981; Chapter 5, pp 152–192 and references cited therein.

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