Liquid-Phase Decarboxylation of Aromatic Haloformates: A New Access to Chloro- and Fluoroaromatics

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The treatment of phenyl chloroformates **1** with a Lewis acid in the liquid phase resulted in decarboxylation to the corresponding chloroaromatics **2**. Fluoroaromatic compounds were synthesized from phenylchloroformates **1** through a sequential fluorination/decarboxylation in the liquid phase by treatment with excess anhydrous hydrogen fluoride under mild conditions. In all cases, yields were increased by performing the reaction in 1,2,4-trichlorobenzene, which is inert to Friedel−Crafts reactions.

Introduction

There is increasing demand for selectively halogenated aromatic compounds due to their increasing incorporation in agrochemicals, pharmaceuticals, and liquid crystals.[1] Chloroaromatics are generally accessible through direct chlorination of aromatic compounds[2] or from the corresponding amine through diazotization.[3] Selectively fluorinated aromatic compounds are not generally accessible through direct fluorination[4] and are synthesized by halogen exchange[5] or from the corresponding amines by Balz−Schiemann-type reactions.[6]

Limitations of these classical processes have led to considerable interest in new synthetic routes to halogenated aromatic compounds. The decarboxylation of aryl chloroformates and aryl fluoroformates to the corresponding halogenated aromatic has received much attention due to the low cost of the starting materials and the potential versatility of this process. Although it is well documented that aliphatic fluoro- and chloroformates can be converted to the corresponding alkyl halides in solution,[7] under similar conditions no halogenated aromatic compounds were obtained from aryl haloformates.[8a] Christe and Pavlath first demonstrated that this reaction can be selectively performed in the gas phase.[8] However, the required conditions (700−800 °C, Pt gauze) are too extreme for an industrial application. More efficient catalysts have resulted in decarboxylation temperatures in the range of 300−350 °C;[9,10] however, these processes suffer from catalyst degeneration with time.

We report here studies of the liquid-phase decarboxylation of aryl chloroformates and the fluorodecarboxylation of aryl chloroformates with anhydrous HF.[11]

Table 1. Lewis Acid-Catalyzed Decarboxylation of 2,6-Dimethylphenyl Chloroformate to 2,6-Dimethylchlorobenzene at 200 °C

entry	Lewis acid	mol %	reaction time (h)	conversion (%)	yield[a] (%)
1	$AlCl_3$	2.0	2.0	93	74
2	$AlBr_3$	2.6	4.0	29	27
3	$FeCl_3$	2.7	4.0	50	40
4	BF_3	3.0	8.0	0	0
5	γ-Al_2O_3	20	60	96	28
6	$TiCl_4$	3.0	24	0	0
7	$SnCl_4$	3.0	24	0	0
8	$SbCl_5$	3.0	24	0	0

[a] Isolated yield

Results and Discussion

Synthesis of Chloroaromatics. The treatment of 2,6-dimethylphenyl chloroformate with $AlCl_3$ (2 mol %) followed by heating to 200 °C resulted in a smooth decarboxylation to give the corresponding 2,6-dimethylchlorobenzene in good yield (Table 1, entry 1). The success of this reaction prompted us to investigate the efficiency of other Lewis acids as catalysts of this reaction (Table 1).[11] $AlCl_3$, $AlBr_3$, and $FeCl_3$ are all good catalysts for this reaction, with the strongest Lewis acid $AlCl_3$ being the most efficient.[12] Although boron trifluoride is an efficient catalyst for the conversion of alkyl chloro-

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(1) Becker, A. *Inventory of Industrial Fluoro- Biochemicals*; Editions Eyrolles: Paris, 1996.

(2) *Houben-Weyl, Methoden der Organischen Chemie band V/3*; Georg Thieme Verlag: Stuttgart, 1962.

(3) Harthman, W. W.; Berthen, M. R. *Org. Synth.* **1955**, *3*, 79−81.

(4) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; John Wiley & Sons: New York, 1976; pp 46−48.

(5) Langlois, B.; Gilbert, L.; Forat, G. *Ind. Chem. Libr.* **1996**, *8*, 244−291.

(6) (a) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186−1190. (b) Osswald, P. Scherer, German Patent 600,706, 1934. (c) Fern, R. L.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1950**, *72*, 4809−4811.

(7) (a) Weickmann, A. German Patent 857,350, 1949. (b) Eilingsfeld, H.; Seefelder, M.; Weidiner, H. *Angew. Chem.* **1960**, *72*, 836−845. (c) Nakanisihi, S.; Myers, T. C. Jensen *J. Am. Chem. Soc.* **1955**, *77*, 3099−3100. (d) Nakanisihi, S.; Myers, T. C. Jensen *J. Am. Chem. Soc.* **1955**, *77*, 5033−5034. (e) US Patent 4,814,524, 1989. (f) Clinch, P. W.; Hudson, H. R. *J. Chem. Soc. B* **1971**, 747−745.

(8) (a) Christe, K. O.; Pavlath, A. E. *J. Org. Chem.* **1965**, *30*, 3170−3173. (b) Christe, K. O.; Pavlath, A. E. *J. Org. Chem.* **1965**, *30*, 4104−4107. (c) Christe, K. O.; Pavlath, A. E. *J. Org. Chem.* **1966**, *31*, 559−561. (d) Christe, K. O.; Pavlath, A. E. U.S. Patent 3,283,018, 1966.

(9) (a) Aston, D. P.; Ryan, A.; Webster, B. F.; Wolfindale, B. A. *J. Fluorine Chem.* **1985**, 263−274. (b) Aston, D. P.; Ryan, A.; Webster, B. F.; Wolfindale, B. A. European Patent 0,118,241, 1984. (c) Aston, D. P.; Ryan, A.; Webster, B. F.; Wolfindale, B. A. U.S. Patent 4,745,235.

(10) Garcia, H.; Gilbert, L.; Perrod, M. C.; Ratton, S.; Rochin, C. *Ind. Chem. Libr.* **1996**, *8*, 301−312.

(11) (a) Lui, N.; Bielefeldt, D.; Marhold, A. U.S. Patent US 5,306,849, 1994. (b) Lui, N.; Marhold. A. German Patent DEA 4415777. (c) Lui, N, Rock, M. H. German Patent DEA 19642868.

(12) Olah, G. A. *Friedel−Crafts and related reactions*; Interscience Publishers: New York, 1963; Vol. 1.

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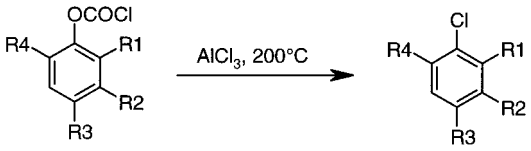
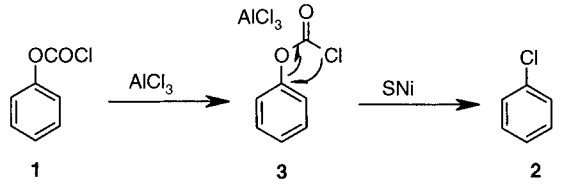
Table 2. $AlCl_3$ (2 mol %)-Catalyzed Decarboxylation of Aromatic Chloroformates to the Corresponding Chlorobenzenes at 200 °C



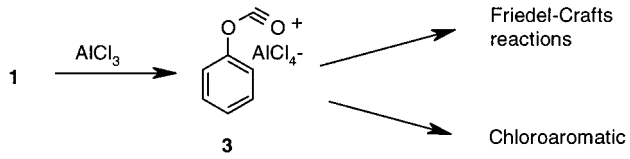
entry	R1	R2	R3	R4	solvent	yield[a] (%)
1	CH_3			CH_3		74
2	CH_3			CH_3	trichlorobenzene[b]	95
3	CH_3		CH_3	CH_3		72
4	CH_3		CH_3	CH_3	trichlorobenzene[b]	75
5	CH_3		CH_3			20
6	CH_3		CH_3		trichlorobenzene[b]	45
7	CH_3	CH_3			trichlorobenzene[b]	60
8	isopropyl					20

[a] Isolated yield. [b] 1,2,4-Trichlorobenzene.

Scheme 1



Scheme 2

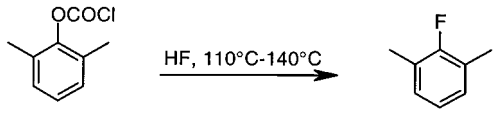


formates to the corresponding alkyl chlorides,[7d] no reaction in the case of aryl chloroformates was observed (Table 1, entry 4). Long reaction times and high concentrations of γ-Al_2O_3 were required to catalyze this reaction with low yields of the desired 1-chloro-2,6-dimethylbenzene formed. The low yields may be due to hydrolysis of the chloroformate to the corresponding phenol.

To assess the scope and limitations of the reaction, the decarboxylation of a series of aryl chloroformates in the presence of $AlCl_3$ was investigated (Table 2). Aryl chloroformates with alkyl substituents in the 2- and 6-positions smoothly decarboxylated to the desired chlorinated aromatic (Table 2, entries 1 and 3). However, when the 2- and 6-positions were not both occupied by a methyl group, the yield was reduced with the formation of unidentified high boiling products (Table 2, entry 5).

Treatment of aryl chloroformates with $AlCl_3$ can proceed by two different processes. The first is the formation of the chloroaromatic through an internal nucleophilic substitution (S_ni) involving activation by the $AlCl_3$ through coordination to the aryl chloroformate (Scheme 1). The second involves the formation a cation of $Ar-O-CO^+$ type **3**, which can then undergo Friedel–Crafts reactions[13] or decomposition, in which chlorine is intramolecularly delivered to give the desired chloroaromatic (Scheme 2). Which process predominates will depend on the relative stabilities of the $ArOCO^+$ **3** and aryl cations for a given aryl formate.

Table 3. Decarboxylation of 2,6-Dimethylphenyl Chloroformate to 2,6-Dimethylfluorobenzene in the Presence of Hydrofluoric Acid



entry	HF:chloroformate	*T* (°C)	time (min)	yield[a] (%)
1	4.6	110	180	11[b]
2	18.4	130	180	51
3	30.6	140	90	69
4	36.8	130	180	68.9

[a] Isolated yield. [b] 2,6-Dimethylphenyl fluoroformate (68%) was the major product.

In the case of 2,6-dimethylphenyl chloroformate, the predominant process is the S_ni to give the desired chloroaromatic in good yield. However, when only one substituent is present *ortho* to the chloroformate moiety, the Friedel–Crafts reactions predominate resulting in a low yield of the desired chloroaromatic (Table 2, entries 5 and 8).

To reduce undesirable Friedel–Crafts reactions, the process was carried out in an inert solvent. The solvent of choice was the high-boiling 1,2,4-trichlorobenzene, which is sufficiently deactivated to Friedel-Craft reactions, and in all cases, yields were improved (Table 2, entries 2, 4, and 6).

Synthesis of Fluoroaromatics

When 2,6-dimethylphenyl fluoroformate, which is readily available by fluorination of the corresponding chloroformate with KF/18-crown-6 in dichloromethane,[14] was treated with SbF_5, the desired fluoroaromatic was isolated in 40% yield.

Chloroformates can also be fluorinated by anhydrous hydrogen fluoride in an autoclave at temperatures above 80 °C. If conditions could be found where in addition to being a fluorinating agent, HF acts as a catalyst for the decarboxylation of aromatic fluoroformates, the synthesis of fluoroaromatics, without the isolation of the intermediate fluoroformates, would be possible. Different ratios of HF/2,6-dimethylphenyl chloroformate were heated in a sealed vessel at different temperatures (Table 3). The fluorodecarboxylation of the in situ formed 2,6-dimethylphenyl fluoroformate was found to occur under surprisingly mild conditions (110–140 °C) without the formation of chlorobenzene or phenols.

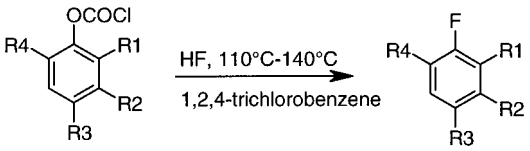
When the reaction was carried out at low HF/substrate ratios, the major product was the fluoroformate. The optimal ratio was 30:1 for the formation of 2,6-dimethylfluorobenzene, with excess HF being recovered. Anhydrous HF has a low solubility in aromatic compounds, and this reaction occurs in a two-phase system. Thus, to achieve sufficient concentrations of HF in the organic phase, a large molar excess is required.

This process was investigated for a series of aromatic chloroformates in 1,2,4-trichlorobenzene as the solvent (Table 4). The addition of solvent resulted in an increase in yield for 1-fluoro-2,6-dimethylbenzene from 69% to 90%. In general, the yields were good with no chloroaromatics or phenols being detected.

(13) Coppock, W. H. *J. Org. Chem.* **1957**, *22*, 325–326.

(14) Dang, V. A.; Olofson, R. A. *J. Org. Chem.* **1990**, *55*, 1847–1851

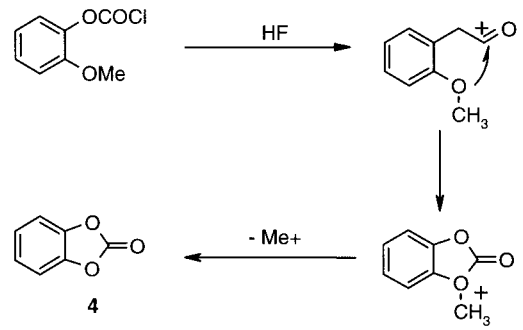
Table 4. Decarboxylation of Aromatic Chloroformates in HF and 1,2,4-Trichlorobenzene to the Corresponding Fluorobenzenes



entry	R1	R2	R3	R4	*T* (°C)	yield[a] (%)
1	CH_3		CH_3	CH_3	110	72
2	CH_3	CH_3			110	0[b]
3	CH_3	CH_3			150	76
4	CH_3			CH_3	140	90
5	CH_3		CH_3		150	70
6	CH_3		Br	CH_3	200	0

[a] Isolated yield. [b] The corresponding fluoroformate was isolated in greater than 90% yield.

Scheme 3



The first step of the reaction is fluorination of the phenylchloroformate by the HF, indicated by the isolation of 2,3-dimethylphenylfluoroformate as the sole product from the treatment of the corresponding chloroformate at 100 °C (Table 4, entry 2). The temperature required for the decarboxylation of the fluoroformate is dependent on the nature, number, and position of substituents. The more alkyl substituents present, the lower the decarboxylation temperature. For example, there is a 30 °C difference between the decarboxylation temperature of 2,4,6-trimethyl- and 2,6-dimethylphenyl formate (Table 4, entries 1 and 2). The difference in the decarboxylation temperature between 2,3- and 2,6-dimethylphenyl formate indicates that substituents in the 2 and 6 positions have the greatest effect on the decarboxylation temperature. When an electron-withdrawing substituent such as a bromine atom is present, the stability of the phenyl fluoroformate is such that decarboxylation does not occur below 200 °C, the practical limit of our procedure (Table 4, entry 6). Finally, the treatment of 2-methoxyphenyl chloroformate with HF under identical conditions did not give the desired fluorinated aromatic compound, but instead benzo[1,3]dioxol-2-one (**4**) (Scheme 3).

Experimental Section

NMR spectra were performed in $CDCl_3$ solution on a Bruker AC 200 and ARX 400 (^1H, 200 or 400 MHz; ^{19}F, 188 or 376 MHz). Chemical shifts are reported in ppm relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. GC analysis was performed on capillary columns SE30, 10 or 25 m. All reagents were used as supplied, without further purification.

Synthesis of Aryl Chloroformates. 2,6-Dimethylphenyl chloroformate,[15a] 2,4,6-trimethylphenyl chloroformate,[15b] 2,4-dimethylphenyl chloroformate,[15c] 2,3-diimethylphenyl chloroformate,[15d] and 2-isopropylphenyl chloroformate[15e] were prepared from the corresponding phenols by literature procedures.

2,6-Dimethyl-4-bromophenyl Chloroformate. The title compound was prepared from 2,6-dimethyl-4-bromophenol by a method analogous to the previously described synthesis of 2,6-dimethylphenyl chloroformate[15b] in 63% yield upon recrystallization from hexanes/diethyl ether (9:1) (mp = 55−56 °C;^1H NMR δ 2.25 (s, 6H, $2CH_3$), 7.1 (3H, H-aromatic)).

Decarboxylation of 2,6-Dimethylphenyl Chloroformate: General Procedure. Anhydrous Lewis acid (2−20 mol %) was added to 2,6-dimethylphenyl chloroformate (**1**) (46.1 g, 0.25 mol) and then heated at 200 °C for the stated time. The reaction mixture was then allowed to cool to room temperature and then poured onto ice and extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil that was purified by vacuum distillation to give the pure 1-chloro-2,6-dimethylchlorobenzene: bp 70−74 °C/5 mbar; NMR data were in agreement with published data.[16a]

Decarboxylation of Aryl Chloroformates without Solvent: General Procedure. Anhydrous aluminum chloride (0.006 mol) was added to the phenyl chloroformate (**1**) (0.27 mol) and then heated to 200 °C. Above 180 °C, the evolution of carbon dioxide commenced and heating was continued until the evolution stopped (ca. 210 min). The reaction mixture was worked up as described above. All NMR data were in agreement with published data: 1-chloro-2,4,6-trimethylbenzene,[16b] 2,4-dimethylchlorobenzene,[16c] 1-chloro-2,3-dimethylbenzene,[16d] and 1-chloro-2-isopropylbenzene.[16e]

Decarboxylation of Aryl Chloroformates in 1,2,4-Trichlorobenzene. General Procedure. Anhydrous aluminum chloride (0.05 mol) was added to a solution of the phenyl chloroformate **1** (2.5 mol) in 1,2,4-trichlorobenzene (600 mL) and then heated to 200 °C. Above 180 °C, the evolution of carbon dioxide commenced, and heating was continued until the evolution stopped (210 min). The mixture was worked up as above.

Synthesis of 2,6-Dimethylphenyl Fluoroformate. Anhydrous potassium fluoride (50 g, 0.86 mol) was added portionwise to a stirred solution of 2,6-dimethylphenyl chloroformate (100 g, 0.54 mol) and 18-crown-6 (7 g, 0.26 mol) in dichloromethane (250 mL) at room temperature. After 5 h, the suspension was filtered, and the resulting solution was then evaporated under reduced pressure to give a colorless oil that was purified by vacuum distillation to give the pure 2,6-dimethylphenyl fluoroformate (bp 59−63 °C/16 mbar) in 80% yield: IR (neat) 1842 cm^{-1}; ^{19}F NMR δ 16.4; ^1H NMR δ 2.25 (s, 6H, 2 CH_3), 7.1 (3H, H-aromatic).

Synthesis of 2,6-Dimethylfluorobenzene by the SbF_5-Catalyzed Decarboxylation of 2,6-Dimethylphenyl Fluoroformate. A stirred mixture of anhydrous SbF_5 (17.6 g, 0.059 mol) and 2,6-dimethylphenyl fluoroformate (100 g, 0.59 mol) was heated to 185 °C. Above 180 °C, the evolution of carbon dioxide commenced, and heating was continued until the evolution stopped (180 min). The reaction mixture was then allowed to cool to room temperature and then poured onto ice and extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a black oil that was purified by vacuum distillation to give the pure 1-chloro-2,6-dimethylfluorobenzene: bp = 80−82 °C/20 mBar; NMR data were in agreement with published data.[16a]

(15) (a) Pattison, V. A.; Colson, J. G.; Carr, R. L. K. *J. Org. Chem.* **1968**, *33*, 1084−1087. (b) Zabik, M. J.; Schuetz, R. D. *J. Org. Chem.* **1967**, 32, 300−307. (c) Pickard, R. H.; Littlebury, W. O. *J. Chem. Soc.* **1907**, *91*, 302−307. (d) Barnes, J. H. *J. Pharm. Pharmacol.* **1961**, *13*, 39−48. (e) Altner, W.; Meisert, E.; Rockstroh, G. German Patent 1,117,589, 1961; *Chem. Abstr.* **1962**, *57*, 11106d.

(16) (a) Jenneskens, L. W.; De Wolf, W. H.; Bickelhaupt, F. *Synthesis* **1985**, 647−649. (b) Brown, F.; Bruyne, J. M. A.; Gross, P. *J. Am. Chem. Soc.* **1934**, *56*, 1−93. (c) Socrates, G.; Adlard, M. W. *J. Chem. Soc B*, **1971**, 733−736. (d) Hopff, H.; Gallegra, P. *Helv. Chim. Acta* **1968**, *51*, 253−260. (e) Beak, P.; Trancik, R. J.; Simpson, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 5073−5086.

Decarboxylation of 2,6-Dimethylphenyl Chloroformate in Anhydrous Hydrogen Fluoride. General Procedure. 2,6-Dimethylphenyl chloroformate (184.5 g, 1 mol) was added dropwise to anhydrous hydrogen fluoride (HF) (4.6−36.8 mol) at 0 °C in a stainless steel laboratory autoclave (2 L). Once the addition was complete, the autoclave was sealed and heated at the required temperature for 90 min, with the formed gases being released at 26 bar. The autoclave was then allowed to cool to room temperature, and the excess HF was recovered by distillation. The remaining reaction mixture was poured onto ice and extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brown oil that was purified by vacuum distillation to give 1-fluoro-2,6-dimethylbenzene: NMR data were in agreement with published data.[17a]

Decarboxylation of Phenyl Chloroformates with Anhydrous Hydrogen Fluoride in 1,2,4-Trichlorobenzene. General Procedure. To a mixture of 1,2,4-trichlorobenzene (600 mL) and anhydrous HF (400 mL) in a stainless steel laboratory autoclave (2 L) at 0 °C was added the phenyl chloroformate (2.5 mol) dropwise. Once the addition was complete, the autoclave was sealed and heated at the required temperature for 360 min, with the formed gases (HCl and CO_2) being released at 26 bar. The autoclave was then allowed to cool to room temperature, and the excess HF was recovered by distillation. The remaining reaction mixture was poured onto ice and extracted with dichloromethane (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brown oil that was purified by vacuum distillation. All ^1H and ^{19}F NMR data were in agreement with published data: 1-fluoro-2,4,6-trimethylbenzene,[17b] 1-fluoro-2,4-dimethylbenzene,[17c] and 1-fluoro-2,3-dimethylbenzene.[17d]

Benzo[1,3]dioxol-2-one. To a mixture of 1,2,4-trichlorobenzene (300 mL) and anhydrous HF (200 mL) in a stainless steel laboratory autoclave (1 L) at 0 °C was added 2-methoxyphenyl chloroformate (233 g, 1.25 mol) dropwise. Once the addition was complete, the autoclave was sealed and heated at the required temperature for 360 min, with the excess gases (HCl and a little CO_2) being released at 26 bar. The autoclave was then allowed to cool to room temperature, and the excess HF was recovered by distillation. The remaining reaction mixture was poured onto ice and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a brown solid that was recrystallized from toluene to give benzo[1,3]dioxol-2-one: mp 117−120 °C; ^1H NMR data were in agreement with published data.[18]

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(17) (a) Nasir, M. S.; Cohen, I. C.; Karlin, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 2482−2494. (b) De Meio, G.; Morgen, J.; Pinhey, J. T. *Tetrahedron* **1993**, *49*, 8129−8139. (c) Schieh, T. C.; Feit, E. D.; Chernick, C. L.; Yang, N. C. *J. Org. Chem.* **1967**, *32*, 300−307. (d) Sket, B.; Zupan, M. *J. Org. Chem.* **1978**, *43*, 835−837.

(18) Fountain, K. R.; Pierschbacher, M. *J. Org. Chem.* **1976**, *41*, 2039−2042.