C–H Arylation of Thiophenes with Aryl Bromides by a Parts-per-Million Loading of a Palladium NNC-Pincer Complex

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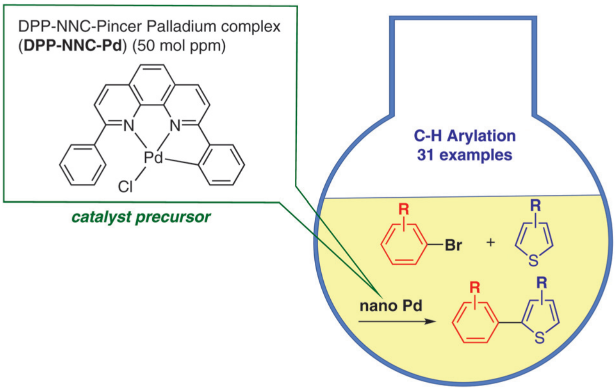

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Abstract A palladium NNC-pincer complex efficiently catalyzed the direct arylation of thiophene derivatives with extremely low palladium loadings of the order of parts per million. Thus, the reaction of various thiophenes with aryl bromides in the presence of 25–100 mol ppm of chlorido[(2-phenyl-κ-*C*^{2})-9-phenyl-1,10-phenanthroline-κ^2-*N*,*N′*]palladium(II) NNC-pincer complex, K_2CO_3, and pivalic acid in *N*,*N*-dimethylacetamide afforded the corresponding 2- or 5-arylated thiophenes in good to excellent yields. A combination of the present C–H arylation and Hiyama coupling with the same NNC-pincer complex provides an efficient synthesis of unsymmetrical 2,5-thiophenes with catalyst loadings at mol ppm levels.

Key words C–H functionalization, arylation, palladium catalysis, pincer complexes, thiophenes, Hiyama coupling

Transition-metal catalysis plays an important role in the synthesis of many valuable pharmaceuticals, agrochemicals, functional materials, and other substances.[1] In most transition-metal-catalyzed organic reactions, mole percent loadings of catalysts are required to obtain the desired products in reasonable yields within acceptable reaction times. As a result, there is potential for contamination of target compounds by metal species. Metal contaminants are usually problematic in practical applications and have to be removed because of their potential toxicity to living species or their ability to impair the performance of organic functional materials.[2,3] Moreover, depletion of global resources of noble metals is another problem that needs to be resolved. Decreasing the catalyst loading provides a simple and straightforward solution to these problems. Therefore, the development of highly active transition-metal catalysts that operate at extremely low metal loadings (mol ppm to ppb levels) has become a topic of interest in organic synthesis.[4–7]

Arylthiophenes are important heterocyclic motifs present in many organic electronics materials[8] and biologically active compounds.[9] In 1990, Ohta and co-workers reported a straightforward direct arylation of several heterocycles, including thiophenes and 1-benzothiophenes, by treatment with aryl halides in the presence of a palladium catalyst.[10] This method avoids the need for prior functionalization of substrates, as required in conventional cross-coupling reactions. Following Ohta's report, many catalytic systems have been developed for the C–H arylation of thiophenes and related heterocycles.[11] Despite this impressive progress, the documented catalytic systems typically require a 1–10 mol% loading of the catalyst to achieve a good yield of the arylated product.[11,12] Efforts have been made to develop suitable catalytic systems for possible use at lower metal loadings.[13,14] For example, Douchet and co-workers achieved a phosphine-free C–H arylation of thiophenes with aryl bromides by using $Pd(OAc)_2$ as a catalyst.[14] However, only one example of a high yield has been achieved by using a catalyst loading of less than 0.01 mol% (100 mol ppm); however, a stoichiometric excess of base was required to afford a high yield of the arylated products. To the best of our knowledge, there have been no previous reports of a catalytic system for C–H arylation of thiophenes that operate at a catalyst loading of less than a 100 mol ppm level with a broad substrate tolerance.

Our group has been interested in the development of highly active catalysts that can operate with metal loadings at mol ppm to mol ppb levels.[13c,15,16] We recently reported an allylic arylation of aryl acetates,[16a] as well as Heck[16b] and Hiyama[16c] reactions, by using mol ppm to mol ppb loadings of the palladium NNC-pincer complex DPP-NNC Pd (Figure 1), which afforded the corresponding products in high yields. In a continuation of our studies on efficient palladium catalysis at mol ppm to mol ppb loadings, we now report a highly efficient C–H arylation of thiophenes with

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aryl bromides in the presence of DPP-NNC Pd. The reaction proceeds smoothly in the presence of only 25–100 mol ppm of palladium to give the arylated products in up to 99% yield.

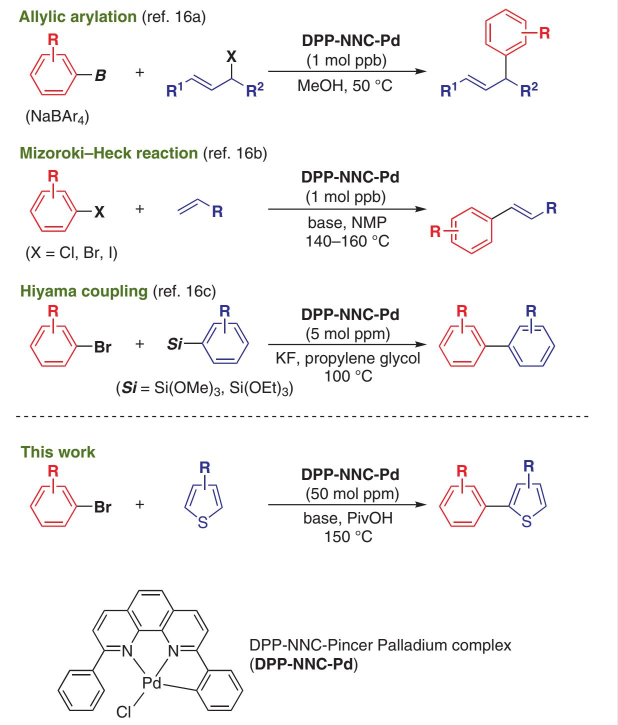
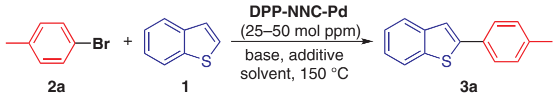


Figure 1 Reactions at ppb to ppm catalyst loadings with an NNC-pincer palladium complex

We began by investigating the reaction of 1-benzothiophene (**1**) with 4-bromotoluene (**2a**) as model substrates. After systematic optimization (Table 1), the desired arylated product **3a** was obtained in 94% GC yield by using 50 mol ppm of DPP-NNC Pd in the presence of 0.5 equivalents of K_2CO_3 and 30 mol% of pivalic acid (PivOH) (Table 1, entry 1). The catalyst loading could be further decreased to 25 mol ppm, although a slightly lower yield of **3a** was obtained (entry 2). The effects of various bases were evaluated, and the choice of base was found to be crucial for the efficiency of the reaction (entries 3–11). In contrast to K_2CO_3, other weak bases (Na_2CO_3, Cs_2CO_3, KOAc, and NaOAc) gave inferior results. Similarly, a low yield of **3a** was obtained when a strong base (KOH, NaOH, LiOH, *t*-BuOK, or K_3PO_4) was used. The choice of solvent was also crucial for the efficiency of this C–H arylation reaction. DMF or NMP could be used as the solvent, albeit with slightly lower yields of **3a** (69% and 81%, respectively; entries 12 and 13). When the reaction was conducted in DMSO or xylenes, no reaction occurred (entries 14 and 15). Other acid additives (AcOH, BzOH, or $MesCO_2H$) gave lower yields of the desired product **3a** than that obtained with PivOH (entries 16–18 vs. entry 1). When control experiments were conducted, no reaction was detected in the absence of DPP-NNC Pd, K_2CO_3, or PivOH, demonstrating the crucial role of each of these components in the catalytic system (entries 19–21).

Table 1 C–H Arylation of 1-Benzothiophene with a DPP-NNC Palladium Complex: Optimization of Reaction Conditions[a]



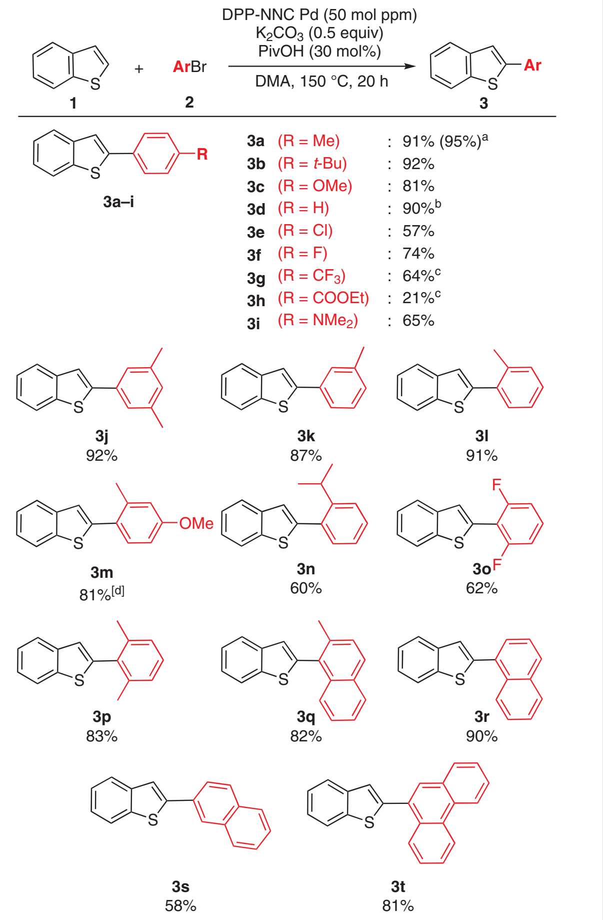
2a **1** **3a**

Entry	Catalyst (mol ppm)	Base	Additive	Solvent	Yield[b] (%)
1	50	K_2CO_3	PivOH	DMA	94 (91)[c]
2	25	K_2CO_3	PivOH	DMA	71
3	50	Na_2CO_3	PivOH	DMA	13
4	50	Cs_2CO_3	PivOH	DMA	6
5	50	KOAc	PivOH	DMA	18
6	50	NaOAc	PivOH	DMA	12
7	50	KOH	PivOH	DMA	28
8	50	NaOH	PivOH	DMA	2
9	50	LiOH	PivOH	DMA	3
10	50	*t*-BuOK	PivOH	DMA	17
11	50	K_3PO_4	PivOH	DMA	42
12	50	K_2CO_3	PivOH	DMF	69
13	50	K_2CO_3	PivOH	NMP	81
14	50	K_2CO_3	PivOH	DMSO	n.r.[d]
15	50	K_2CO_3	PivOH	xylenes	n.r.
16	50	K_2CO_3	AcOH	DMA	19
17	50	K_2CO_3	$PhCO_2H$	DMA	8
18	50	K_2CO_3	$MesCO_2H$	DMA	62
19	–	K_2CO_3	PivOH	DMA	n.r.
20	50	–	PivOH	DMA	n.r.
21	50	K_2CO_3	–	DMA	n.r.

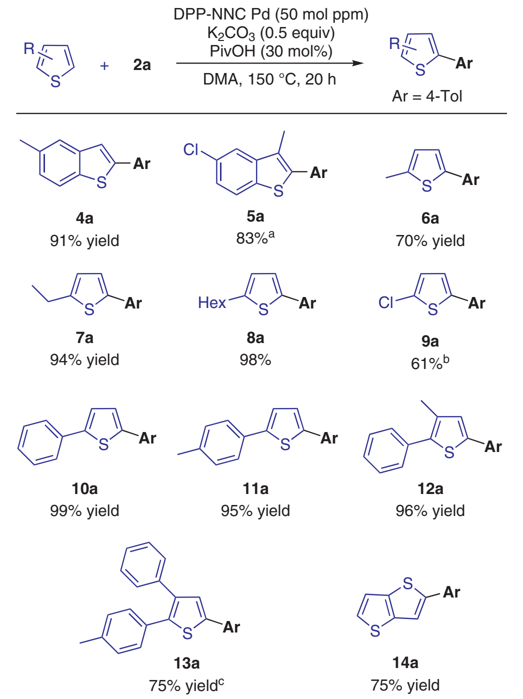
[a] Reaction conditions: **1** (2 equiv, 2 mmol), **2a** (1 equiv, 1 mmol), base (0.5 equiv, 0.5 mmol), PivOH (30 mol%, 0.3 mmol), DPP-NNC-Pd (25–50 mol ppm; 2.5×10^{-5} to 5×10^{-5} mmol), solvent (0.5 M), stirring, 150 °C, 20 h, under N_2.
[b] GC yield with mesitylene as internal standard.
[c] Isolated yield.
[d] n.r. = no reaction.

With optimized reaction conditions in hand, we examined the scope of the aryl bromide reactant (Scheme 1). Various aryl bromides **2** with a range of electronic and steric properties reacted with 1-benzothiophene (**1**) under the standard conditions to give the corresponding 2-aryl-1-benzothiophenes **3** in good to excellent yields. Aryl bromides with an electron-donating group such as methyl, *tert*-butyl, or methoxy in the *para*-position reacted well to afford the corresponding 2-aryl-1- benzothiophenes **3a–c** in excellent yields. Further decreasing the catalyst loading to 25 mol ppm was possible, as **3a** was isolated in 95% yield by using 25 mol ppm of DPP-NNC Pd with a prolonged reaction time of 30 hours. 2-Phenyl-1-benzothiophene (**3d**) was isolated in 90% yield from the reaction of bromobenzene. Aryl bromides with an electron-withdrawing chloro, fluoro, or trifluoromethyl group in the *para*-position were tolerated and afforded good yields of the corresponding products **3e**–**g**. Other functional groups such as ester and amine were also tolerated in this reaction (**3h** and **3i**). Aryl bromides with *meta* or *ortho* functional groups reacted with 1-benzothiophene (**1**) to give **3j**–**p**[17,18] in good to excellent yields. Interestingly, 2,5-dimethylbenzyl bromide and 2-methyl-1-bromonaphthalene, which have a high steric hindrance, also reacted well with 1-benzothiophene to give **3p** and **3q**, respectively, in yields of 83 and 82%. Bicyclic and tricyclic aryl bromides such as 1- or 2-bromonaphthalene and 9-bromophenanthrene were also well tolerated, giving the corresponding products **3r**–**t** in good to excellent yields.

The scope of substrates was further evaluated by treating 4-bromotoluene (**2a**) with various types of thiophenes (Scheme 2). Functionalized 1-benzothiophenes such as 5-methyl- or 5-chloro-3-methyl-1-benzothiophenes were well tolerated and afforded the corresponding arylated products **4a** and **5a** in yields of 91 and 83%, respectively. 2-Alkylthiophenes with alkyl chains of various lengths were smoothly arylated at the C5 position to give the corresponding products **6a**–**8a** in yields of 70–98%. The lower yield of **6a** might be associated with the low boiling point of the starting material, 2-methylthiophene.[19] The reaction also tolerated the use of 2-chlorothiophene as a substrate to afford the arylated product **9a** in moderate yield. The resulting product **9a** should be amenable to further arylation at the C2 position of the thiophene ring through various cross-coupling reactions such as the Suzuki–Miyaura reaction. 2-Phenyl- and 2-(4-methylphenyl)thiophene reacted well with 4-bromotoluene to give the corresponding arylated products **10a** and **11a** in yields of 99 and 95%, respectively. The reaction also tolerated a 2,3-disubstituted thiophene, giving product **12a** in 96% isolated yield. Under slightly modified reaction conditions, 3-phenylthiophene gave the 2,5-diarylated product **13a** in 75% isolated yield, along with small amounts of the corresponding 2- and 5-monoarylated products. Interestingly, when thieno[3,2-*b*]thiophene was used, the 2-arylated product **14a** was obtained as the sole product in 75% yield.

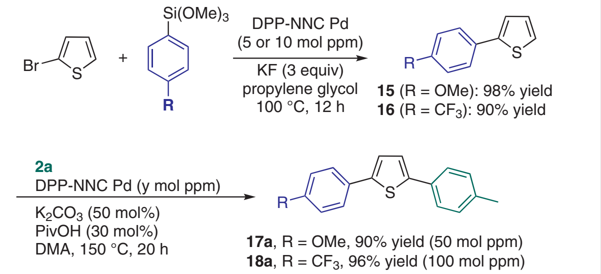


Scheme 1 Scope of the aryl bromide. *Reagents and0 conditions*: **3** (2 mmol), **2** (1 mmol), DPP-NNC Pd (50 mol ppm; 5 × 10^{-5} mmol), K_2CO_3 (0.5 mmol), PivOH (0.3 mmol), DMA (2.0 mL), 150 °C, 20 h. [a] DPP-NNC Pd (100 mol ppm). [b] DPP-NNC Pd (25 mol ppm), 30 h. [c] DPP-NNC Pd (75 mol ppm).



Scheme 2 Scope of thiophenes. *Reagents and conditions*: thiophene (2 mmol), **2a** (1 mmol), DPP-NNC Pd (50 mol ppm; 5 × 10^{-5} mmol), K_2CO_3 (0.5 mmol), PivOH (0.3 mmol), DMA (2.0 mL), 150 °C, 20 h. [a] DPP-NNC Pd (100 mol ppm). [b] NMR yield with 1,1,2,2-tetrachloroethane as internal standard. [c] *Reagents and conditions*: 3-phenyl-2-(4-tolyl)thiophene (1 mmol), **2a** (2.2 mmol), DPP-NNC Pd (100 mol ppm; 10 × 10^{-5} mmol), K_2CO_3 (1 mmol), PivOH (0.6 mmol), DMA (2.0 mL), 150 °C, 20 h.

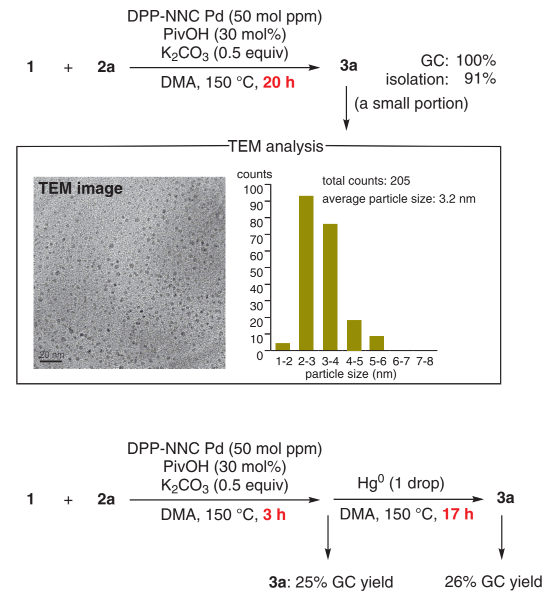
A combination of the present catalytic system with our previously reported Hiyama reaction proved to be an effective method for the synthesis of unsymmetrical 2,5-diarylthiophenes (Scheme 3). Starting from 2-bromothiophene, Hiyama coupling with arylsilanes gave the corresponding 2-arylthiophenes **15** and **16** in excellent yields. Treatment of the resulting 2-arylthiophenes with 4-bromotoluene (**2a**) under the present reaction conditions afforded the desired unsymmetrical 2,5-diarylthiophenes **17a** and **18a** in excellent yields. It is noteworthy that both reactions were performed by using the same palladium NNC-pincer complex, and that only a mol ppm loading of palladium was required.



Scheme 3 Synthesis of unsymmetrical 2,5-diarylthiophenes with a mol ppm loading of DPP-NNC Pd by sequential Hiyama and C–H arylation reactions

When a transmission electron microscopy (TEM) analysis of the reaction mixture of **1** and **2a** was conducted after completion of the reaction [Scheme 4 (top)], palladium nanoparticles with an average diameter of 3.2 nm were observed. Furthermore, a mercury amalgamation test showed that the catalytic activity was inhibited by the addition of mercury to the reaction mixture [Scheme 4 (bottom)]. These results indicated that palladium nanoparticles are involved in the catalytic cycle. In a previous study we found that palladium nanoparticles were formed in equilibrium with monomeric palladium species, and that the monomeric palladium species acted as the actual highly catalytically active species that permitted the coupling reactions to proceed at mol ppm levels of palladium.[15g,16b] The same monomeric palladium species might be also formed in the present reaction, and might be responsible for the high catalytic activity.

In summary, we have reported a highly efficient C–H arylation of thiophenes with aryl bromides by using an extremely low loading of a palladium NNC-pincer complex. The present reaction system permits the arylation of various thiophenes with aryl bromides to afford 2- or 5-arylated thiophenes in good to excellent yields by using only 25–100 mol ppm of DPP-NNC Pd.



Scheme 4 TEM analysis (top) and an amalgamation test (bottom)

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707213.

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(17) **C–H Arylation of 1-Benzothiophene (1); General Procedure**
A Schlenk tube containing a magnetic stirrer bar was charged with 1-benzothiophene (**1**; 2 mmol), the appropriate aryl bromide **2** (1 mmol), K_2CO_3 (0.5 mmol), pivalic acid (0.3 mmol), a 0.5 mM solution of DPP-NNC in anhyd DMA (100 µL; 5 $\times 10^{-5}$ mmol Pd), and anhyd DMA (1.9 mL). The resulting mixture was degassed and stirred vigorously at 150 °C under N_2 for 20 h. The mixture was then cooled to r.t., diluted with EtOAc, transferred to a separatory funnel, and washed with water (×3). The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the resulting residue was purified by chromatography (silica gel, hexane/AcOEt).

(18) **2-(2,6-Dimethylphenyl)benzo[*b*]thiophene (3j)**
White solid; yield: 218 mg (92%). ^{1}H NMR (396 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3 Hz, 1 H), 7.75 (d, *J* = 7.1 Hz, 1 H), 7.52 (s, 1 H), 7.36–7.24 (m, 4 H), 6.98 (s, 1 H), 2.37 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 140.7, 139.4, 138.5, 134.1, 130.1, 124.4, 124.3, 124.1, 123.5, 122.2, 119.2, 21.26. HRMS (FAB): *m/z* [M$^+$] calcd for $C_{16}H_{14}S$: 238.0816; found: 238.0823.

2-(2-Isopropylphenyl)benzo[*b*]thiophene (3n)
Colorless oil; yield: 152 mg (60%). ^{1}H NMR (396 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.9 Hz, 1 H), 7.79 (d, *J* = 7.1 Hz, 1 H), 7.42–7.31 (m, 5 H), 7.22–7.20 (m, 1 H), 7.18 (s, 1 H), 3.38–3.31 (m, 1 H), 1.22 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 143.3, 140.3, 140.0, 133.0, 131.0, 129.0, 125.7, 125.4, 124.3, 124.0, 123.4, 123.1, 122.0, 29.7, 24.4. EI-MS: *m/z* = 252 [M$^+$]. HRMS (FAB): *m/z* [M$^+$] calcd for $C_{17}H_{16}S$: 252.0973; found: 252.0961.

2-(2,6-Difluorophenyl)benzo[*b*]thiophene (3o)
White solid; yield: 152 mg (62%). ^{1}H NMR (396 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 2 H), 7.74 (s, 1 H), 7.38–7.35 (m, 2 H), 7.31–7.25 (m, 1 H), 7.10–7.00 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (dd, *J* = 252.9, 6.8 Hz), 140.3 (t, *J* = 2.9 Hz), 139.2, 129.7 (t, *J* = 2.8 Hz), 129.2 (t, *J* = 10.5 Hz), 126.2 (t, *J* = 5.7 Hz), 124.8, 124.3, 123.9, 121.8, 112.1 (q, *J* = 17.2 Hz), 111.9 (dd, *J* = 24.9, 1.9 Hz). EI-MS: *m/z* = 246 [M$^+$]. HRMS (FAB): *m/z* [M$^+$] calcd for $C_{14}H_8F_2S$: 246.0315; found: 246.0323.

(19) King, W. J.; Nord, F. F. *J. Org. Chem.* **1949**, *14*, 638.